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# Indolizine Derivatives. X. Cyclization of 3-(2-Pyridyl)methylene-2,4-pentanediones and Ethyl 3-Oxo-2-(2-pyridyl)methylene-butanoates Substituted in the Pyridine Ring

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A study has been made of the cyclization, in acetic anhydride, of 3-(2-pyridyl)methylene-2,4-pentanediones *2a, b, d* and ethyl 3-oxo-2-(2-pyridyl)methylenebutanoates *3a, c–f* carrying methyl, methoxy or methoxycarbonyl groups in the 4- and/or 6-position of the pyridine ring: The 2-pyridylvinyldicarbonyl compound *3c*, unsubstituted in the 6-position, and the 2-quinoline analog *9* produce an acetoxy indolizine (*5c* and *10b*) and an indolizine that requires a reduction step for its formation (*5b* and *10a*). The 6-methyl-2-pyridylvinyldicarbonyl compounds *2a, d* and *3a, d, e* give rise to 5-acetoxymethylindolizines *4d, e* and *5d–f*. The 2-pyridylvinyldicarbonyl compounds *2b* and *3f* carrying a larger, inert substituent (methoxycarbonyl or methoxy) in the 6-position do not change in boiling acetic anhydride.

In Part VII it was shown that cyclization of parent 2-pyridylvinyldicarbonyl compounds (the Knoevenagel condensation products of 2-pyridinecarbaldehyde and 1,3-diketones or 1,3-keto esters) in an acid anhydride provides a versatile route to various indolizines substituted in the pyrrole moiety.[1]

To test the generality of this interesting cyclization and explore the reaction mechanism, several 2-pyridylvinyldicarbonyl compounds, suitably substituted in the pyridine ring, were exposed to hot acetic anhydride. The substituents chosen were methyl, methoxy and methoxycarbonyl in the 4- and/or 6-position. The reaction of a parent 2-quinoline analog was also examined.

The results are described here, along with the preparation of the new starting 2-pyridylvinyldicarbonyl compounds.

## RESULTS

The substituted 2-pyridylvinyldicarbonyl compounds *2a, b, d* and *3a, c–f* needed as starting materials were prepared according to known condensations[1] of similarly substituted 2-pyridinecarbaldehydes *1a–f* and 2,4-pentanedione or ethyl 3-oxobutanoate. The cyclizations of *2a, b, d, 3a, c–f* and the 2-quinoline analog *9*, as well as purifications of the products, were performed as described for parent 2-pyridylvinyldicarbonyl compounds.[1] The structures of the new 2-pyridylvinyldicarbonyl compounds and indolizines were determined in a straightforward way by means of spectral properties (UV, IR, $^1$H NMR and MS). Relevant spectral data for comparison have been published in the earlier papers of this series.[1–3]

The cyclization mode, in acetic anhydride, of the 6-methyl-2-pyridylvinyldicarbonyl compounds *2a, d* and *3a, d, e* differed considerably from that observed[1] for the parent compounds, the acetoxymethylindolizines *4d, e* and *5d–f*, respectively, being virtually the sole products. The $^1$H NMR spectrum of these indolizine products exhibits a methylene singlet at about $\delta$ 5.3 in deuteriochloroform which remains a singlet in trifluoroacetic acid ($\delta = 5.70$ for *4d*). At the same time a methyl singlet ($\delta = 3.03$ for *4d* in deuteriochloroform) is split into a doublet ($\delta = 1.86$ in trifluoroacetic acid) due to protonation in position 3 ($\delta = 6.13$, one proton

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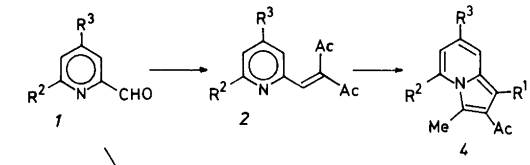
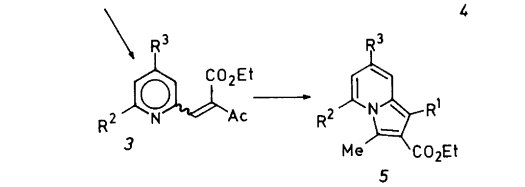
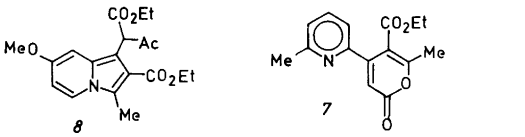
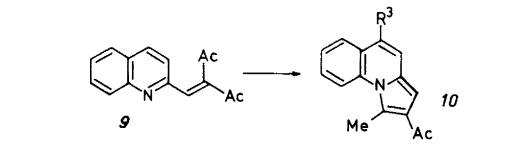




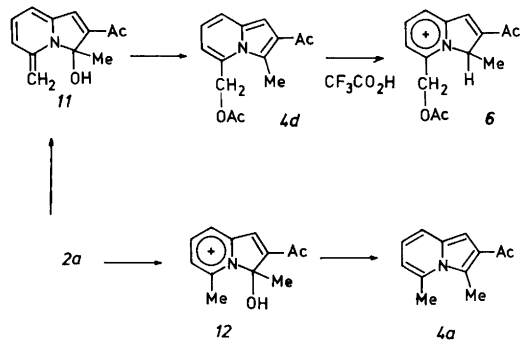




| | $R^1$ | $R^2$ | $R^3$ |
|---|---|---|---|
| Compounds *1*, *2* and *3* | | | |
| *a* | – | Me | H |
| *b* | – | $CO_2Me$ | H |
| *c* | – | H | OMe |
| *d* | – | Me | Me |
| *e* | – | Me | OMe |
| *f* | – | OMe | OMe |
| Compounds *4* and *5* | | | |
| *a* | H | Me | H |
| *b* | H | H | OMe |
| *c* | OAc | H | OMe |
| *d* | H | $CH_2OAc$ | H |
| *e* | H | $CH_2OAc$ | Me |
| *f* | H | $CH_2OAc$ | OMe |
| Compound *10* | | | |
| *a* | – | – | H |
| *b* | – | – | OAc |

quartet) as depicted in formula *6*. This proves the acetoxymethyl group to be situated in position 5 and not in position 3.

No indolizines carrying an acetoxy group in position 1 were encountered in the case of 6-methylsubstrates. Only very small amounts of



reduced indolizine products (for example, in the reactions of *2a* and *3a*) were observed (TLC). In the cyclization of *2a* a small amount of the indolizine *4a* was isolated and identified by $^1H$ NMR spectroscopy. A similarly small amount of an oxidized product, the 4-(2-pyridyl)-2-pyrone *7*, was isolated only in the reaction of *3a*. When the 6-position of 2-pyridylvinyldicarbonyl compounds carries a larger, inert group, such as methoxy or methoxycarbonyl, the cyclization into an indolizine system is entirely prevented. Despite prolonged heating of *2b* or *3f* in acetic anhydride only the starting materials could be isolated. In the case of the keto ester *3f* a mixture of the *E*- and *Z*-isomer was the product.

The 4-methoxy-2-pyridylvinyldicarbonyl compound *3c* gave the 1-acetoxyindolizine *5c* and the indolizine *5b*, which requires a reduction step for its formation. When a condensation mixture of 4-methoxy-2-pyridinecarbaldehyde (*1c*) and ethyl 3-oxobutanoate was treated with acetic anhydride, a mixture of the indolizines *5b*, *c* and *8* was obtained.

The 2-quinolylvinyldiketone *9* behaved similarly, giving the pyrroloquinolines *10a*, *b*. The site of acetoxy attack was this time, exceptionally, the γ-position of the pyridine part and not the pyrrole ring carbon. In the $^1H$ NMR spectrum of *10b* two singlets which are due to protons 1 and 10 are observed.

## DISCUSSION

The cyclization of the 2-pyridylvinyldicarbonyl compounds unsubstituted in position 6 (*3c*) or carrying a "small" substituent in this position (*9*), occurs in a similar way to the cyclization of the parent 2-pyridylvinyldicarbonyl compounds.[1] The

formation of the indolizine *8* can be explained as cyclization of the Michael-addition product of the 2-pyridylvinylketo ester *3c* and ethyl 3-oxobutanoate. The carbon 9 as the exceptional point of acetoxy attack in the cyclization of the 2-quinolylvinyldiketone *9* to give *10b* is in accordance with the known reactivity of the quinoline γ-position.

The various and differing cyclization modes of the substituted 2-pyridylvinyldicarbonyl compounds *2a, b, d* and *3a, d–f* demonstrate that formation of the indolizine ring system by closing the pyrrole part through attack of the pyridine nitrogen on a side-chain carbonyl is sensitive in regard to steric hindrance. A too large group at position 6, such as methoxy in *3f* and methoxycarbonyl in *2b*, entirely prevents the reaction. It would seem that the electronic properties of the substituents in the pyridine ring do not play an important role, because the 6-methoxy group of *3f* should even further the cyclization reaction. However *3f* is as inert as the 6-methoxycarbonyl substrate *2b*.

In the case of 6-methyl-2-pyridylvinyldicarbonyl compounds *2a, d* and *3a, d, e*, this methyl carbon is the preferential point of acetoxy attack. The formation of an intermediate 5-methyleneindolizine species, for example *11* from *2a*, probably through an intramolecular proton shift, is suggested. The cyclization of these 6-methyl-2-pyridylvinyldicarbonyl compounds is relatively slow with very low tar formation as compared with all corresponding cyclizations giving the indolizine nucleus.[1-3] It seems clear that 1-acetoxyindolizines, such as *5c* or *10b*, and probably the products of reduced nature, such as *4a, 5a, b* and *10a*, are formed through a bicyclic pyridinium compound, which in the case of *4a* is formulated as *12*.

The formation of reduced indolizine products (*4a, 5a, b* and *10a*) from 4- or 6-substituted 2-pyridylvinyldicarbonyl compounds, although in minor amount in the case of 6-methyl substrates, argues against positions 4 or 6 as the point of a redox reactions.

There are still ambiguities concerning this and related redox processes although reasonable mechanisms could be drawn up.[1,2] Examinations of similar cyclizations of 2-pyridylvinyldicarbonyl compounds substituted in position α to the pyridine ring are now pertinent.

## EXPERIMENTAL

The general conditions of related cyclizations, as well as separation procedures and instruments used, have been described in the earlier papers of this series.[1,2]

### Preparation of substituted 2-pyridinecarbaldehydes

The 2-pyridinecarbaldehydes *1a–f* were prepared according to known sequences, adapted for a rational preparation of the compounds as a group: *1a*,[4] *1b*,[4] *1c*,[6] *1e*[5] and *1f*,[7] the *N*-oxides of 2-methyl-, 2,6-dimethyl- and 2,4,6-trimethylpyridines being needed as starting materials.

### Preparation of the 2-pyridylvinyldicarbonyl compounds *1a, b, d, 3a, c–f* and *9*

*General procedure.* To the 2-pyridinecarbaldehyde (0.10 mol) and 2,4-pentanedione or ethyl 3-oxobutanoate (0.10 mol) 0.5 g of piperidine was added with shaking at 20 °C. The reaction progress was followed by $^1$H NMR spectroscopy. When completed (2–10 h) the oily or semi-solid product mixture was treated with methanol (*ca.* 50 ml). The respective condensation product *2a, b, d* or *3a, c–f* was obtained in a crystalline state after cooling and filtration. In the case of *9* dehydration was best accomplished by dissolving in concentrated $H_2SO_4$ (20 ml, 2 h) and neutralizing with $NaHCO_3$. Each 2-pyridylvinyldicarbonyl compound was purified by recrystallization from MeOH.

*2a.* Yield 70 %, m.p. 69 °C. Anal. $C_{12}H_{13}NO_2$: C, H, N. IR: 1700 (*cis* Ac), 1655 (*trans* Ac) $cm^{-1}$. $^1$H NMR: δ 2.50 (3H s, 6-Me), 2.48 (3H s, *cis* Ac), 2.42 (3H s, *trans* Ac).

*2b.* Yield 80 %, m.p. 97 °C. Anal. $C_{13}H_{13}NO_4$: C, H, N. IR: 1720 (ester), 1705 (*cis* Ac), 1660 (*trans* Ac) $cm^{-1}$. $^1$H NMR: δ 2.52 (3H s, *cis* Ac), 2.37 (3H s, *trans* Ac).

*2d.* Yield 65 %, m.p. 81 °C. Anal. $C_{13}H_{15}NO_2$: C, H, N.

*3a*[9] (*Z*-form). Yield 80 %, m.p. 72 °C. IR: 1730 (ester), 1655 (Ac) $cm^{-1}$. $^1$H NMR: δ 4.40 (2H q), 2.52 (3H s, 6-Me), 2.42 (3H s, Ac).

*3c*[9] (*Z*-form). Yield 75 %, m.p. 114 °C.

*3d* (*Z*-form). Yield 80 %, m.p. 91 °C. Anal. $C_{14}H_{17}NO_3$: C, H, N. IR: 1735 (ester), 1655 (Ac) $cm^{-1}$.

*3e* (*E*-form). Yield 50 %, m.p. 111 °C. Anal. $C_{14}H_{17}NO_4$: C, H, N. IR: 1700 (broad, Ac and ester) $cm^{-1}$. $^1$H NMR: δ 4.28 (2H q), 2.52 (3H s, Ac), 2.46 (3H s, 6-Me).

*3e* (*Z*-form). IR: 1735 (ester), 1660 (Ac) $cm^{-1}$ measured from a *E*/*Z*-mixture before recrystallization.

*3f* (*E*-form). Yield 60 %, m.p. 112 °C. Anal. $C_{14}H_{17}NO_5$: C, H, N. IR: 1700 (broad, Ac and ester) $cm^{-1}$. $^1H$ NMR: $\delta$ 4.30 (2H q), 2.51 (3H s, Ac).

*3f* (*Z*-form). $^1H$ NMR: $\delta$ 4.36 (2H q), 2.40 (3H s, Ac) measured from product mixture of an attempted cyclization.

*9*. Yield 90 %, m.p. 144 °C.[8]

## Cyclizations of the 2-pyridylvinyldicarbonyl compounds *2 a, b, d, 3 a, c–f* and *9*

*General procedure.* The 2-pyridylvinyldicarbonyl substrate (0.05–0.10 mol) was heated in excess of acetic anhydride (20 ml) until most of the starting material had disappeared (TLC). After the reaction all volatile materials were removed *in vacuo*. The residue was fractionated, when necessary by CC,[1,2] and the components purified by recrystallization from light petroleum (b.p. 40–60 °C).

*Cyclization of 2a.* The reaction at 120 °C (2 h) gave *4a*, yield 2 %, m.p. 86 °C. Anal. $C_{12}H_{13}NO$: C, H, N. $^1H$ NMR: $\delta$ 3.03 (3 H, s, C-3 Me), 2.76 (3 H, s, C-5 Me), 2.34 (3 H, s, Ac); *4d*, yield 36 %, m.p. 106 °C. Anal. $C_{14}H_{15}NO_3$: C, H, N. MS, *m/e* (%): 245 (87, M), 230 (4), 202 (13), 187 (16), 186 (100, M–OAc), 185 (14), 160 (33, 186-$H_2C_2$), 144 (27), 143 (31), 142 (33), 130 (12). $^1H$ NMR: $\delta$ 7.23 (1 H, dd, H-8), 6.71 (1 H, s, H-1), 6.6–6.3 (2 H, m, H-6 and H-7), 5.36 (2 H, s, $CH_2$), 3.03 (3 H, s, C-3 Me), 2.48 (3 H, s, Ac), 2.08 (3 H, s, OAc). IR: 1730 (ester), 1655 (ketone) $cm^{-1}$. UV, $\lambda_{max}$ (nm) and log $\varepsilon$: 407 (sh, 3.08), 385 (3.28), 372 (3.27), 352 (sh, 3.15), 300 (sh, 3.04), 268 (sh, 3.74), 248 (4.38), 244 (sh, 4.37). At 70 °C (10 h) the yield of *4d* was 64 %.

*Cyclization of 2b.* At 140 °C (50 h) recovered *2b ca.* 90 %.

*Cyclization of 2d.* At 70 °C (10 h) *2d* gave *4e*, yield 72 %, m.p. 110 °C. Anal. $C_{15}H_{17}NO_3$: C, H, N. $^1$HNMR: $\delta$ 6.96 (1 H, broad s, H-8), 6.49 (1 H, s, H-1), 6.32 (1 H, broad s, H-6). 5.32 (2 H, s, $CH_2$), 2.96 (3 H, s, C-3 Me), 2.43 (3 H, s, Ac), 2.26 (3 H, broad s, C-7 Me), 2.05 (3 H, s, OAc).

*Cyclization of 3a.* The reaction at 130 °C (20 h) gave *5d*, yield 69 %, m.p. 78 °C. Anal. $C_{15}H_{17}NO_4$: C, H, N. MS, $^1H$ NMR: $\delta$ 5.25 (2 H, s), *m/e*: 275 (M). IR: 1725 (C-5 acetate), 1690 (C-2 ester) $cm^{-1}$; the pyrone *7*, yield 3 %, m.p. 105 °C. Anal. $C_{15}H_{15}NO_4$: C, H, N. MS, *m/e*: 273 (M). $^1H$ NMR: $\delta$ 7.53 (1 H, t, H-4′), 7.29 (1 H, d, H-3′), 7.06 (1 H, d, H-5′), 6.14 (1 H, s, H-3), 3.91 (2 H, q), 2.48 (3 H, s, C-6′ Me), 2.39 (3 H, s, C-6 Me), 0.92 (3 H, t). IR: 1725 and 1700 (ester and 2-pyrone) $cm^{-1}$. At 140 °C (1 h) 33 % of *5d* was isolated; recovered *3a ca.* 40 %.

*Cyclization of 3c.* The reaction at 110 °C (1 h) gave *5b*, yield 27 %, m.p. 84 °C. Anal. $C_{13}H_{15}NO_3$: C, H, N. MS, *m/e*: 233 (M). $^1H$ NMR: $\delta$ 7.42 (1 H, d, *J* 7.2 Hz, H-5), 6.32 (1 H, broad s, H-8), 6.30 (1 H s, H-1), 6.16 (1 H, dd, *J* 7.2 and 2.6 Hz, H-6), 4.24 (2 H, q), 3.70 (3 H, s, C-7 OMe), 2.62 (3 H, s, C-3 Me), 1.34 (3 H, t); *5c*, yield 32 %, m.p. 135 °C. Anal. $C_{15}H_{17}NO_5$: C, H, N. MS, *m/e* (%): 291 (24, M), 249 (38, M–$CH_2$=C=O), 248 (5, M–Ac), 246 (7), 204 (19), 203 (100, 249–EtOH), 202 (57), 175 (53, 203–CO), 147 (42), 136 (10, 248–MeC≡$CCO_2$Et), 108 (36), 67 (12), 43 (22). IR: 1750 (C-1 acetate) 1685 (C-2 ester) $cm^{-1}$.

*Cyclization in the presence of* $AcCH_2CO_2Et$. At 130 °C (2 h) the condensation mixture of *1c* and $AcCH_2CO_2Et$ gave *5b* (10 %), *5c* (16 %) and *8*, yield 28 %, m.p. 107 °C. Anal. $C_{19}H_{23}NO_6$: C, H, N. MS, *m/e*: 361 (M). $^1H$ NMR: $\delta$ 13.02 (1 H, s), 4.12 (2 H, q), 1.74 (3 H, s), 1.11 (3 H, t) due to C-1 $AcCHCO_2Et$. IR: 1690 (esters), 1645 (ketone) $cm^{-1}$.

*Cyclization of 3d.* The reaction at 130 °C (20 h) gave *5e*, yield 66 %, m.p. 93 °C. Anal. $C_{16}H_{19}NO_4$: C, H, N. MS, *m/e*: 289 (M). $^1H$ NMR: $\delta$ 5.23 (2 H, s). IR: 1725 (acetate), 1685 (ester) $cm^{-1}$. At 140 °C (1 h) 30 % of *5e* was isolated; recovered *3d ca.* 40 %.

*Cyclization of 3e.* The reaction at 130 °C (20 h) gave *5f*, yield 75 %, m.p. 124 °C. Anal. $C_{16}H_{19}NO_5$: C, H, N. $^1H$ NMR: $\delta$ 6.49 (1 H, s, H-1), 6.33 (1 H, d, *J* 2.5 Hz, H-8), 6.25 (1 H, d, *J* 2.5 Hz, H-6), 5.31 (2 H, s, $CH_2$), 4.25 (2 H, q), 3.74 (3 H, s, C-7 OMe), 2.97 (3 H, s, C-3 Me), 2.06 (3 H, s, OAc), 1.32 (3 H, t).

*Cyclization of 3f.* At 140 °C (50 h) recovered *3f* (90 %) as *ca.* 1:1 *E*/*Z*-mixture.

*Cyclization of 9.* The reaction at 100 °C (1 h) gave *10a*, yield 24 %, m.p. 103 °C. Anal. $C_{15}H_{13}NO$: C, H, N. MS, *m/e*: 223 (M). $^1H$ NMR: $\delta$ 8.29 (1 H, broad d, *J* 7.5 Hz, H-5), 7.08 (1 H, d, *J* 9.5 Hz, H-10), 6.77 (1 H, d, *J* 9.5 Hz, H-9), 6.66 (1 H, s, H-1), 3.17 (3 H, s, C-3 Me), 2.44 (3 H, s, Ac); *10b*, yield, 40 %, m.p. 179 °C. Anal. $C_{17}H_{15}NO_3$: C, H, N. MS, *m/e*: 281 (M). $^1H$ NMR: $\delta$ 7.06 (1 H, s, H-10), 6.79 (1 H, s, H-1). IR: 1755 (acetate), 1665 (ketone) $cm^{-1}$.

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