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Indolizine Derivatives. VIII. 3-Acyloxyindolizines *via* Cyclization of Diethyl 2-Pyridylmethylenemalonate

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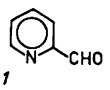
In boiling acetic anhydride the cyclization of diethyl 2-pyridylmethylenemalonate (*3*) gives ethyl 3-acetoxy-2-ethoxycarbonyl-1-indolizineacetate (*4*) in high yield. Use of [2-^{13}C]-labelled acetic anhydride affords 3-[2-^{13}C] acetoxy-1-[2-^{13}C] acetate enriched *4* (*4'*), suggesting that cyclization of the intermediate addition product of *3* and acetic anhydride occurs at the ester carbonyl group and involves an intramolecular ethoxy shift. Propionic anhydride yields diethyl 2-methyl-3-propionyloxy-1-indolizinemalonate (*9*) through reaction at the anhydride carbonyl.

Similar cyclizations in the presence of 1,3-dicarbonyl species gave pyrrolo[2,1,5-*cd*] indolizines *via* 3-acyloxyindolizines.

The cyclizations of 2-(2-pyridyl)methylene-1,3-diketones and -1,3-keto esters in acid anhydrides to yield 2-acylindolizines through reaction of the ketone carbonyl were discussed in Part VII of this series.[1] On the other hand, it was recently reported that the Perkin reaction of 2-pyridinecarbaldehyde (*1*) in the presence of diethyl malonate gives the indolizinemalonate *2*.[2] The next logical step was to study the reaction of 2-(2-pyridyl)methylene-1,3-diesters with an acid anhydride.



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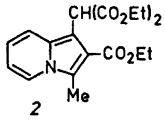

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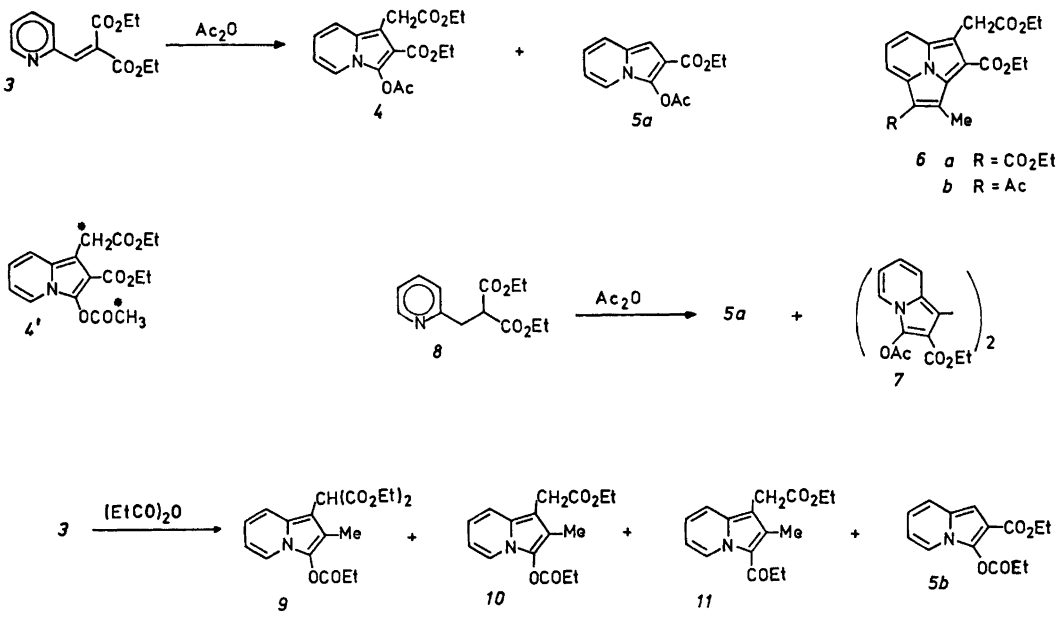
Thus, the present paper deals with the cyclization of diethyl 2-pyridylmethylenemalonate (*3*) with acetic and propionic anhydrides, as well as its reaction in the presence of some 1,3-dicarbonyl compounds. These novel conversions furnishing 3-acyloxyindolizines are described in detail. 3-Acyloxyindolizines can be used as starting materials in a versatile synthesis of the pyrrolo[2,1,5-*cd*]indolizine nucleus.[3] The reaction of *3* with ^{13}C-labelled acetic anhydride to solve the origin of the carbon atoms of the C-1 acetate group of *4* and to settle the question about the migrating group is included. The mechanisms are discussed.

Cyclization products

Diethyl 2-pyridylmethylenemalonate (*3*) showed no reaction with acetic anhydride below 100 °C, whereas at reflux temperature it was converted into the indolizineacetic ester *4* in 80 % yield. Some of the indolizine *5a* was also isolated (Scheme 1). The structure of *4* (like other new indolizine derivatives below) was assigned by comparison of its spectral data (UV, IR, NMR, MS) with those of related indolizines.[1,4] Thus, *4* was shown to be 1,2,3-trisubstituted indolizineacetic acid derivative (^{1}H NMR) and a 2-indolizinecarboxylic ester (UV, IR). Further, the formation of the cycloaddition compounds *6a* and *6b* from *4* with ethyl acetoacetate or 2,4-pentanedione, respectively, supported the presence of a 3-acyloxyindolizine partial structure.[3,4] The ^{13}C NMR spectrum of *4* was in accord with its formula. Cyclization of *3* with acetic anhydride/[2-^{13}C]-acetic acid gave the corresponding 3-[2-^{13}C]-acetoxy-1-[2-^{13}C]acetate enriched *4* (*4'*) as verified by ^{13}C NMR spectroscopy. The indolizine *5a* was the product, along with the dimer *7*, when diethyl 2-pyridylmethylmalonate (*8*) was treated with boiling acetic anhydride.



Scheme 1.

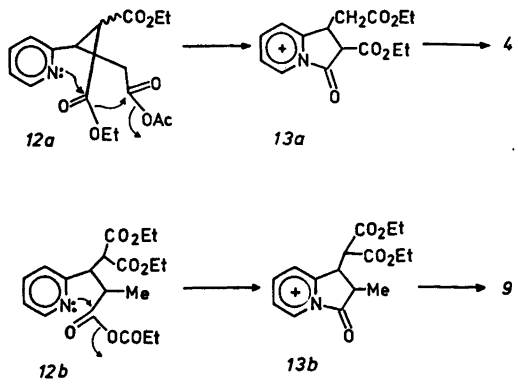
With propionic anhydride the diester *3* gave the indolizinemalonate *9* in 70 % yield at 130 °C. In refluxing propionic anhydride *3* was cyclized to a mixture of the indolizineesters *9*, *10*, *11* and *5b*, the malonate *9* being in slight majority (30 %). Heating *9* in propionic anhydride containing 20 % of propionic acid afforded a mixture of *10*, *11* and unchanged *9*.

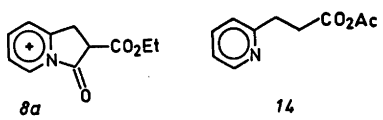
The diester *3* did not react with benzoic anhydride. Cyclization of *3* with acetic anhydride in the presence of ethyl acetoacetate gave the pyrrolo[2,1,5-*cd*]indolizine *6a* as the end product *via* *4* (TLC). 2,4-Pentanedione afforded similarly the pyrrolo[2,1,5-*cd*]indolizine *6b*, whereas acetic anhydride/diethyl malonate did not convert *3* further than to *4*.

Treatment of the diester *3* with acetic anhydride/potassium acetate in the presence of diethyl malonate gave the indolizinemalonate *2*, which has been shown to be the main product of the Perkin reaction of the aldehyde *1* in the presence of diethyl malonate.[2]

Mechanistical sequences

The formation of 2-acylindolizines from 2-(2-pyridyl)methylene-1,3-keto esters and acid anhydrides takes place exclusively *via* an intramolecular nucleophilic attack of the ring nitrogen atom on the side-chain ketone carbonyl group.[1] Hence, 2-(2-pyridyl)methylene-1,3-diesters would be expected to be quite unreactive. However, nucleophilic addition of acetic and propionic anhydrides probably changes diethyl 2-pyridylmethylenemalonate (*3*) into the intermediates *12a* and *12b*, respectively, which are able to undergo cyclizations. The reason for *3* remaining unchanged when heated with benzoic anhydride would be that no intermediate analogous to *12a* and *12b* can be formed.





8a *14*

The saturated diester *8* cyclizes only reluctantly, probably *via 8a*, to give *5a*,[5] the yield being moderate at its best. The much more facile cyclization of *12a* is readily understandable as being due to the simultaneous intramolecular transesterification (ethoxy shift) furnishing *4 via 13a*. This is strongly supported by isolation of the ^{13}C-labelled indolizine *4'* when *3* was treated with [2-^{13}C]-enriched acetic anhydride. Another, foreseeable possibility[3] involving the attack of the ring nitrogen on the anhydride carbonyl group and migration of one of the ethoxycarbonyl groups is out of the question.

Interestingly, cyclization of *12b* takes a different course, namely as a reaction at the anhydride carbonyl group to *9 via 13b*, although the saturated anhydride *14*[4] will not react at all in boiling acetic anhydride. At the present it is difficult to explain the divergent reactions of *3* with acetic and propionic anhydrides. Presumably, the methyl substituent prevents *12b* to attain the conformation essential for the attack on the ester carbonyl, while sterically enhancing conversion into *13b*, with *9* as the sole product.

The formation of *5a*, *5b* from *3*, and *11* from *9*, require a reduction step, occurring probably *via* a route proposed earlier for some analogous transformations,[1,4] as exemplified for the case of formation of *11* from *10 via 15* and *16*.

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.[1,4] The ^{13}C NMR spectra were measured for solutions in $CDCl_3$ with a JEOL JNM FX60 spectrometer through cooperation of Dr. E. Kantolahti at the laboratories of Kemira Oy.

Diethyl 2-pyridylmethylenemalonate (3).[6] From diethyl malonate (16.0 g, 0.10 mol) and 2-pyridinecarbaldehyde (10.7 g, 0.10 mol). Aldol formation catalyzed by 0.5 ml of $(Et)_2NH$ was accomplished at 20 °C within 2.5 h. Heating this aldol product in Ac_2O (50 ml) at 100 °C for 1 h effected the dehydration. Evaporation and recrystallization gave the malonate *3*, 19.5 g (78 %), m.p. (MeOH) 48 °C. Alternatively, the aldol was heated neat at 110 °C for 2 h to yield 82 % of *3*.

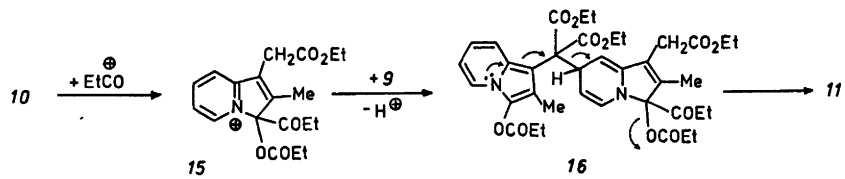
General procedure for cyclizations. The pyridyldiester was heated in an excess of acid anhydride (1/10, mol/mol), temperature and time given. After the reaction all volatile materials were removed *in vacuo*. The residue was fractionated, when necessary, by CC and the components purified by recrystallization from light petroleum (b.p. 40–60 °C) if not stated otherwise.

3 *with* Ac_2O. At refluxing temperature (5 h) *3* gave: *ethyl 3-acetoxy-2-indolizinecarboxylate* (*5a*),[5] yield 4 %, m.p. 77 °C; *ethyl 3-acetoxy-2-ethoxycarbonyl-1-indolizineacetate* (*4*), yield 78 %, m.p. 85 °C. Anal. $C_{17}H_{19}NO_6$: C, H, N. IR: 1780 (s), 1725 (s), 1715 (s), 1700 (s), 1690 (s) cm^{-1}. ^1H NMR: δ 7.47 (1 H, broad d, J 7 Hz), 7.26 (1 H, broad d, J 9 Hz), 6.70–6.20 (2 H, m), 4.22 (2 H, q), 4.02 (2 H, q), 3.91 (2 H, s), 2.38 (3 H, s), 1.32 (3 H, t), 1.20 (3 H, t). ^{13}C NMR: δ 14.2 ($2\times CH_3-CH_2-$), 20.3 (CH_3CO_2-), 30.6 ($Ar-CH_2-CO_2-$), 59.8 and 60.4 ($2\times CH_3CH_2-$), 104.2 and 105.6 (C-1 or C-2), 112.2, 117.0, 117.6 and 119.0 (C-5, C-6, C-7 or C-8), 125.2 (C-8a), 129.8 (C-3), 163.2, 167.5 and 171.1 ($3\times -CO-O-$). MS, *m/e*: 333 (M).

3 *with* $Ac_2O/2$-^{13}C *acetic acid.* To the preheated mixture of Ac_2O (30 ml) and [2-^{13}C]-acetic acid (1.0 ml, 90 %) 2.50 g (0.010 mol) of *3* was added and boiled for 4 h to afford 1.33 g (40 %) of *4'*. ^{13}C NMR: the peaks at δ 20.3 and 30.6 enriched (*ca.* five-fold as compared with those of *4*).

8 *with* Ac_2O. Heating *8*[5] (from *3* with H_2-Pd/C) with Ac_2O gave the indolizine *5a*[5] (22 %) and *diethyl 3,3'-diacetoxy-1,1'-biindolizine-2,2'-dicarboxylate* (*7*), yield 5 %, m.p. (light petroleum b.p. 40–60 °C/AcOEt) 177 °C. Anal. $C_{26}H_{24}N_2O_8$: C, H, N. MS, *m/e*: 492 (10, M).

3 *with* Ac_2O *and* Ac_2CH_2. *3* (5.0 g, 0.020 mol) and Ac_2CH_2 (3.0 g, 0.030 mol) were refluxed in Ac_2O (100 ml) for 15 h to give after aqueous work-up and recrystallization *ethyl 4-acetyl-2-ethoxycarbonyl-3-methyl-1-pyrrolo*[*2,1,5-cd*]*indolizineacetate* (*6b*), yield 3.6 g (51 %), m.p. (EtOH) 148 °C. Anal. $C_{20}H_{21}NO_5$: C, H, N.



^{1}H NMR: δ 8.32 (1 H, broad d, J 7 Hz), 7.90 (2 H, m), 4.49 (2 H, q), 4.40 (2 H, s), 4.18 (2 H, q), 3.16 (3 H, s), 2.81 (3 H, s), 1.47 (3 H, t), 1.25 (3 H, t).

3 *with* Ac_2O *and* $AcCH_2CO_2Et$. Similarly as above there was obtained *ethyl 2,4-diethoxycarbonyl-3-methyl-1-pyrrolo*[*2,1,5*-cd]*indolizineacetate* (*6a*), yield 24 %, m.p. (EtOH) 167 °C. Anal. $C_{21}H_{23}NO_6$: C, H, N.

3 *with* $(EtCO)_2O$. The reaction at reflux temperature (5 h) gave the following mixture: *ethyl 3-propionyloxy-2-indolizinecarboxylate* (*5b*), yield 5 %, m.p. 53 °C. Anal. $C_{14}H_{15}NO_4$: C, H, N; *ethyl 2-methyl-3-propionyloxy-1-indolizineacetate* (*10*), yield 21 %, m.p. 61 °C. Anal. $C_{16}H_{19}NO_4$: C, H, N. ^{1}H NMR: δ 3.57 (2 H, s), 2.11 (3 H, s); *diethyl-2-methyl-3-propionyloxy-1-indolizinemalonate* (*9*), yield 28 %, m.p. 81 °C. Anal. $C_{19}H_{23}NO_6$: C, H, N. ^{1}H NMR: δ 4.72 (1 H, s), 2.10 (3 H, s); *ethyl 2-methyl-3-propionyl-1-indolizineacetate* (*11*), yield 7 %, m.p. 70 °C. Anal. $C_{16}H_{19}NO_3$: C, H, N. IR: 1730 (s), 1720 (s), 1615 (s), 1605 (s) cm^{-1}. ^{1}H NMR: δ 9.93 (1 H, ddd, J 6.7, 1.2 and 1.0 Hz), 3.53 (2 H, s), 2.49 (3 H, s). The reaction at 130 °C (2.5 h) gave *9* in 72 % yield. Treatment of *9* with $(EtCO)_2O/EtCO_2H$ (1/8/2, mol/mol/mol) at 140 °C for 3 h afforded the following mixture: *9* (40 %), *10* (35 %) and *11* (5 %).

3 *with* $Ac_2O/KOAc$ *and* $CH_2(CO_2Et)_2$. 2.5 g of *3*, 3.2 g of $CH_2(CO_2Et)_2$ and 30 g of KOAc in 100 ml of Ac_2O were kept at 120 °C for 1 h producing after aqueous work-up and CC *diethyl 2-ethoxycarbonyl-3-methyl-1-indolizinemalonate* (*2*), yield 26 %, m.p. 72 °C. Anal. $C_{19}H_{23}NO_6$: C, H, N. ^{1}H NMR: δ 4.31 (1 H, s), 2.58 (3 H, s).

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