Indolizine Derivatives. VII. Indolizines *via* Cyclizations of 2-(2-Pyridyl)methylene-1,3-diketones and -1,3-Keto Esters

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The reaction of 3-(2-pyridyl)methylene-2,4-pentanedione with acetic anhydride gives at 60° 1-(1-acetoxy-3-methyl-2-indolizinyl)ethanone (**3a**) or, in the presence of 2,4-pentanedione, 3-(2-acetyl-3-methyl-7-indolizinyl)-2,4-pentanedione (**7a**) in good yield. In refluxing acetic anhydride, 1-(3-methyl-2-indolizinyl)ethanone (**4a**) is the main product. In refluxing dimethyl sulfoxide the cycloaddition product, 3-[2-acetyl-3-(2-pyridyl)-1-indolizinyl)]-2,4-pentanedione (**6**), is obtained. Ethyl 2-(2-pyridyl)methylene-3-oxobutanoate and ethyl 2-(2-pyridyl)methylene-3-oxo-3-phenylpropanoate behave analogously. The stereochemistry of the keto esters has a marked influence on the course of cyclization. The mechanisms are discussed.

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In a preliminary paper (1) it was reported that the Perkin reaction of 2-pyridinecarbaldehyde (**1**) in the presence of 1,3-dicarbonyl compounds, such as 2,4-pentanedione or ethyl acetoacetate, gives rise to 2-carbonyl-substituted indolizines. It was also shown that the indolizines were formed *via* the corresponding condensation products, **2a** and **2b** (or **2c**), respectively. This paper presents the details of this work as well as the cyclizations of the condensations products **2a-d** in acetic, propionic and benzoic anhydride or in dimethyl sulfoxide as a novel synthetic route to indolizines. The mechanisms of the various transformations are also discussed.

The structures of the new compounds were assigned on the basis of the spectral data (uv, ir, nmr, MS), and by comparison with the spectra of related compounds (2,3). Of particular importance for the placement of the substituents of indolizines is the fact that δ-values of the protons attached to carbons 5 and 8 increase, when the substituents at carbons 3 and 1, respectively, are in the order: alkyl or acyloxy, phenyl, 2-pyridyl, acyl (ester or ketone), *cf.*, Table I. A further general rule of importance is the presence of a peak at m/e = 106 in the mass spectra of 1-acyloxyindolizines (the pyridine moiety unsubstituted).

Cyclizations of 3-(2-Pyridyl)methylene-2,4-pentanedione (**2a**).

When the diketone **2a** was treated with an excess of acetic anhydride at 40-100°, the indolizine **3a** was obtained in high yield. Some of the indolizine **4a**, the formation of which must involve a reduction step, and the dihydroindolizine **5a** were also isolated. The elemental analysis and mass spectrum of the latter (**5a**) revealed its composition to correspond to **2a** + acetic anhydride. Its ir (omitting the saturated ester functions, 1740 and 1730 cm^{-1}) and uv spectra are in all essentials the same as those of substituted 3-acylpyrroles, 1660 cm^{-1} and 289 nm

1

2

	R^1	R^2	Configuration
a	Ac	Me	
b	CO_2Et	Me	*E*
c	CO_2Et	Me	*Z*
d	CO_2Et	Ph	*Z*

3

a, R = Me
b, R = Et
c, R = Ph

4

a, R = Me
b, R = CHO

5

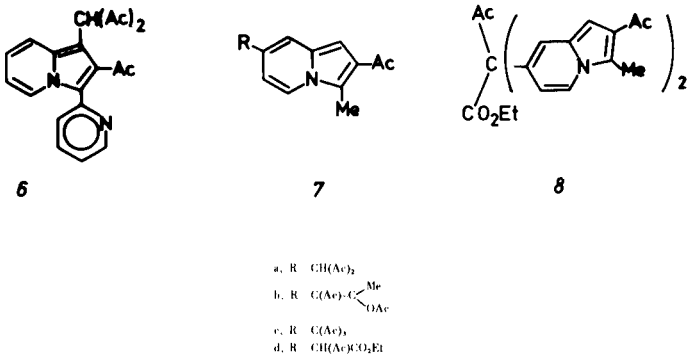
a, R = Ac
b, R = CO_2Et

(log ϵ = 4.15). The coupling constant of 1.6 Hz between the protons attached to carbons 5 and 6 suggests that **5a** has the *trans*-configuration.

At temperatures of 110-140°, the indolizine **4a** became the main product (40% at 130°). Some **3a** and considerable amounts of resineous material were also formed.

Propionic or benzoic anhydride and **2a** gave, among other products, the 1-acyloxyindolizines **3b** or **3c**, respectively. The latter (**3c**) was also formed in the oxidation of **4a** with dibenzoyl peroxide, along with **2a** and **4b**.

The reaction using equivalent amounts of **2a** and acetic anhydride produced, in addition to **3a** and **4a**, the cycloaddition product **6** (1 H, s at δ 16.85, enol form), which was obtained as the sole indolizine product when **2a** was boiled in dimethyl sulfoxide for 2 hours. Heating **2a** neat for 5 minutes at 160° produced a lot of tar but also some **4a** and **6**. The reaction of **2a** (1 mole with an excess of acetic anhydride) in the presence of 2,4-pentanedione (1 mole) below 100° gave the 7-substituted indolizine **7a** (1 H, s at δ 16.55, enol form) in 80% yield. Prolonged



heating of **7a** with acetic anhydride or reactions at temperatures higher than 100° yielded the *O*-acetylated derivative **7b** (both geometric isomers). The *C*-acetylated derivative **7c** was obtained from **2a** and 2,4-pentanedione with acetic anhydride/potassium acetate. The Perkin reaction of **1** in the presence of 2,4-pentanedione gave rise to a mixture of 2-indolizinylethanones (**3a**, **4a**, **7a-c**) and clearly proceeds through the normal condensation product **2a**.

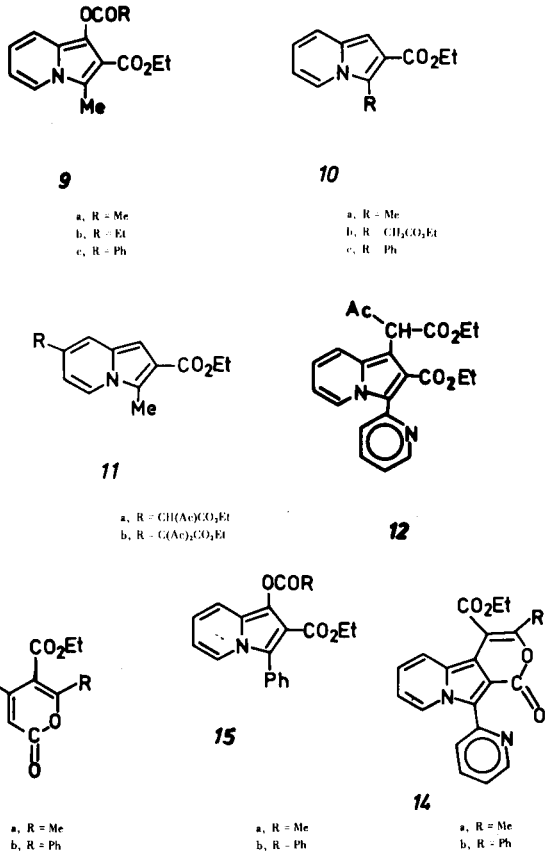
The reaction of **2a** in the presence of ethyl acetoacetate gave the indolizine derivatives **7d** and/or **8** depending on the ratio of the reactants. The latter (**8**) was also formed from **2a** with **7d**.

Cyclizations of Ethyl 2-(2-Pyridyl)methylene-3-oxobutanoate (**2b** and **2c**).

The keto ester stereoisomers **2b** and **2c** could be obtained in a pure state. However, heating neat just above their melting points, or in solution, converted them into a mixture of both isomers.

The *E*-isomer, **2b**, gave the ethyl 2-indolizinecarboxylates **9a-c**, **10a**, **11a-b**, **12** and the dihydroindolizine **5b**, analogously (at corresponding temperatures) to **2a**. The *Z*-isomer, **2c**, reacted much slower than **2b** and somewhat more **10a** but less **9a** and **11a** was produced from **2c** than from **2b**. In addition to the indolizines, some of the pyridyl-2-pyrone **13a** was formed from both **2b** and **2c** with acetic anhydride above 100°, and the indolizinopyranone **14a** from **2c** with benzoic anhydride. The indolizine **9a** was also formed in the acylative cyclization of ethyl 3-oxo-3-(2-pyridyl)propanoate (a further reaction requiring a reduction step).

The Perkin reaction of **1** in the presence of ethyl acetoacetate gave a mixture of **9a**, **10a** and **11a-b**, and in the presence of diethyl acetonedicarboxylate **10a-b**.



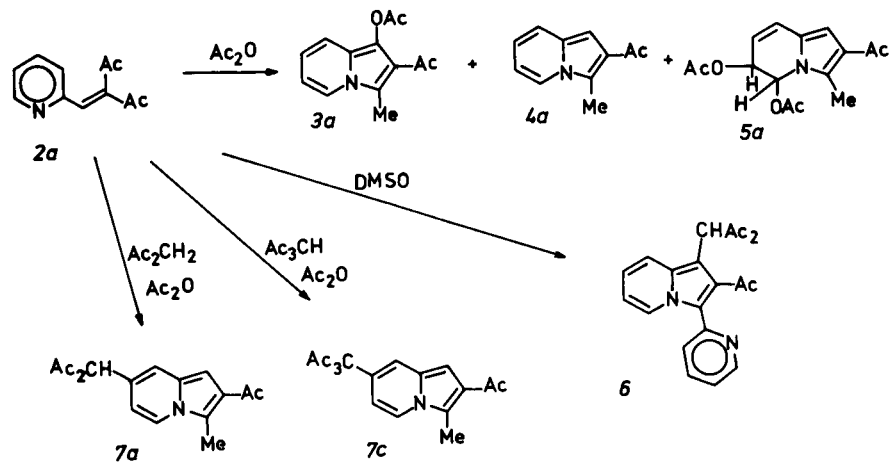
Cyclizations of Ethyl 2-(2-Pyridyl)methylene-3-oxo-3-phenylpropanoate (**2d**).

The reaction of the keto ester **2d** with acetic anhydride gave a mixture of the indolizines **10c** and **15a**, along with the pyrone **13b**. Similarly, the indolizines **10c** and **15b** were obtained from **2d** with benzoic anhydride, accompanied by small amounts of the indolizinopyranone **14b**.

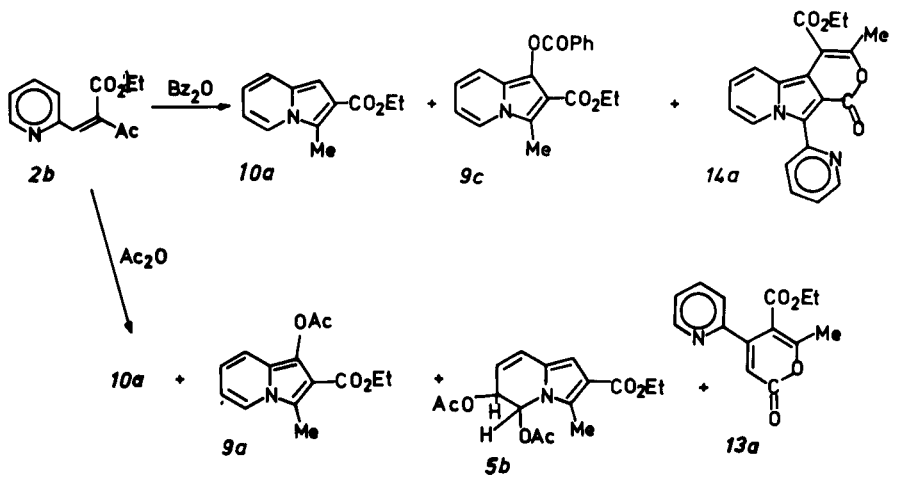
Formation of the Cyclization Products.

The cyclizations of 2-(2-pyridyl)methylene-1,3-diketones and -1,3-keto esters producing the indolizine nucleus

Scheme 1a



Scheme 1b



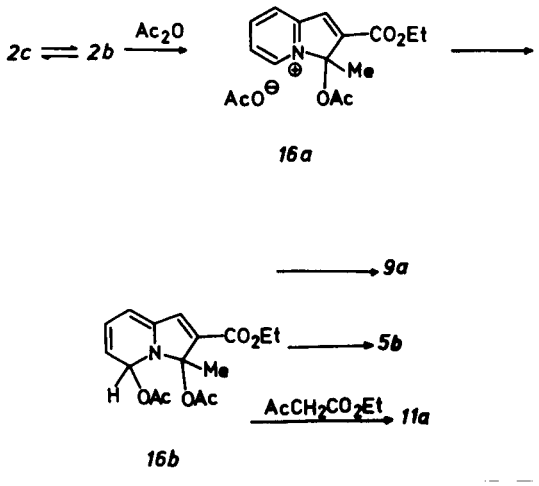
take place exclusively *via* an intramolecular nucleophilic attack of the ring nitrogen atom on the side-chain ketone carbonyl group.

Products of the Unchanged Oxidation Level.

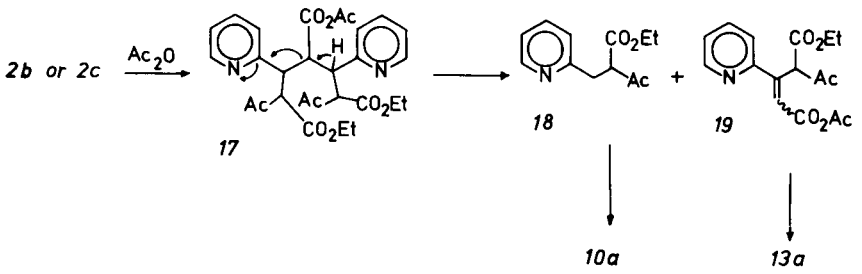
The fact that **2b** (a *cis*-2-pyridylvinyl ketone) with acetic anhydride more readily gives cyclization products of the same oxidation level (**5b, 9a, 11a**) than **2c** (a *trans*-2-pyridylvinyl ketone) indicates reaction through the intermediates **16a** and **16b** (Scheme 2). The absence of the aromatic indolizine products carrying a substituent at C-5 is obviously due to *peri*-effect. The formation and stability of the dihydroindolizine **5b** (*trans*-isomer) is probably due to slow *cis*-elimination of acetic acid and the presence of a stable pyrrole moiety.

The formations of the indolizines **3a-c, 7a-d, 8, 9b-c, 11b** and **15a-b** and the dihydroindolizine **5a** are similarly explained.

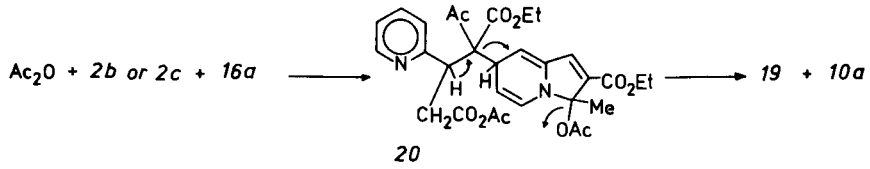
Scheme 2



Scheme 3



Scheme 4



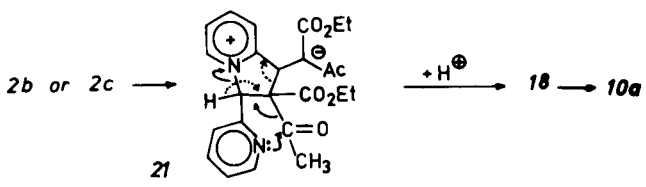
Reduction and Oxidation Products.

The formation of the products requiring a reduction step: **4a** from **2a**, **10a** from **2b** (or **2c**) and **10c** from **2d** with acetic anhydride but not with benzoic anhydride, may occur as a double Michael-aodition of the acid anhydride to the pyrididylmethylene-1,3-dicarbonyl compound **2**, the subsequent redox-cleavage (2) being followed by cyclization. The isolation of the pyrones **13a-b** (oxidation products) gives support for this mechanism as exemplified in Scheme 3.

However, two other reasonable sequences can be considered, exemplified by the formation of **10a** (Scheme 4 and 5). The sequence, **2b** (or **2c**) + **16a** → **20** → **10a**, is supported by the ready attack of β-dicarbonyl species on **2b** (or **2c**) to yield, *e.g.*, **11a**, and by the formation of **10c** from **2d** and benzoic anhydride. When **10c** is formed, BzO^- first attacks **2d**.

The sequence, **2b** (or **2c**) → **21** → **18** → **10a**, is very probable in the absence of an acid anhydride but may also be involved when acid anhydride is present. Especially, the formation of **10c** from **2d** and benzoic anhydride may proceed through the corresponding cycloaddition intermediate.

Scheme 5



The oxidation products compatible with the above mechanisms should be 2-pyridylacetylenes or their equivalents. Such substances are highly reactive, (4) and would resinify under the conditions used (**19** is an exception).

In boiling dimethyl sulfoxide the cycloaddition product **21** is not cleaved but oxidized to **12**. The pyridylindolizines **6** and **14a-b** are assumed to be formed through analogous intermediates.

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 (2,3).

Preparation of 2-(2-Pyridyl)methylene-1,3-dicarbonyl Compounds (**2a-d**).

Owing to the obscurities in the literature preparations and properties, the syntheses of 2-(2-pyridyl)methylene-1,3-dicarbonyl compounds **2a-d** are here described in some details.

The Diketone **2a**.

To 2,4-pentanedione (0.10 mole) and 2-pyridinecarbaldehyde (**1**) (0.10 mole), 0.5 g. of piperidine was added with shaking at 20°. After *ca.* 2 hours, the condensation reaction was complete (nmr). The oily product was dissolved in cold methanol (100 ml.). At -15° the crystalline **2a** (5) separated, 13 g. (69%), m.p. 70°; ir: 1700 (s), 1650 (s) cm^{-1}.

The Keto Ester **2c**.

To ethyl acetoacetate (0.10 mole) and 0.10 mole of **1**, 0.5 g. of piperidine was added with shaking at 20°. After *ca.* 10 hours, the crystalline product was freed from dark impurities by washing with cold methanol to yield **2c** (6,7), 12.3 g. (56%), m.p. 122°; ir: 1725 (s), 1650 (s) cm^{-1}; ^1H nmr: δ 2.41 (3 H, s), 4.42 (2 H, q).

Table I

Selected Spectral Data of Representative Cyclization Products

^{1}H Nmr (Deuteriochloroform) δ (Protons and Substituents)

Product	At: C-1	C-2	C-3	H-5 (a)	C-6	C-7	H-8 (b)	Ir (Potassium Bromide) ν (C=O), cm^{-1}
3a	2.31 (3 H, s)	2.38 (3 H, s)	2.59 (3 H, s)	7.51	6.25-6.65	(2 H, m)	7.02	1765 ester 1660 ketone
3c	8.3-8.5 (2 H, m) 7.85-7.5 (3 H, m)	2.38 (3 H, s)	2.63 (3 H, s)	7.65	6.40-6.80	(2H, m)	7.21	1735 ester 1655 ketone
4a	6.59 (1 H, s)	2.48 (3 H, s)	2.70 (3 H, s)	7.61	6.30-6.85	(2 H, m)	7.23	1650 ketone
4b	6.96 (1 H, s)	2.68 (3 H, s)	10.41 (1 H, s)	9.84	6.80-7.50	(2 H, m)	7.64	1670 ketone 1625 aldehyde
5a	6.45 (1 H, s)	2.38 (3 H, s)	2.56 (3 H, s)	6.70 (c)	5.29 (c)	5.82 (c)	6.61 (c)	1740 ester 1730 1655 ketone
6	16.85 (1 H, s) 1.89 (6 H, s)	2.22 (3 H, s)	8.72 (d) 7.79 (1 H, m) 7.7-7.0 (2 H)	8.60	6.40-7.00	(2 H, m)	*ca.* 7.3	1660 ketone 1580 diketone
7a	6.64 (1 H, s)	2.47 (3 H, s)	2.71 (3 H, s)	7.72	6.36 (e)	1.98 (6 H, s) 16.55 (1 H, s)	7.08	1660 ketone 1590 diketone
10b	6.65 (1 H, s)	1.15 (3 H, t) 4.08 (2 H, q)	0.99 (3 H, t) 3.88 (2 H, q) 4.10 (2 H, s)	7.52	6.10-6.50	(2 H, m)	7.07	1730 1715 aliphatic ester 1690 aromatic ester
10c	6.86 (1 H, s)	1.13 (3 H, t) 4.08 (2 H, q)	7.35 (5 H, s)	7.64	6.10-6.70	(2 H, m)	7.22	1700 ester
14a	1.42 (3 H, t) 4.48 (2 H, q) 2.44 (3 H, s)		8.67 (d) 8.0-7.1 (3 H, m)	9.01	6.60-7.10	(2 H, m)	7.76	1735 ester 1715 lactone

(a) Broad d, $J_{5,6}$ = *ca.* 7 Hz. (b) Broad d, $J_{7,8}$ = *ca.* 9 Hz. (c) $J_{5,6}$ = 1.6 Hz, $J_{6,7}$ = 5.5 Hz, $J_{7,8}$ = 10 Hz, δ 2.06 and 2.07 (3 H, s). (d) Broad d, $J_{5',6'}$ = *ca.* 5 Hz. (e) dd, J = 7 and 2 Hz.

Table II

Cyclizations of the 2-(2-Pyridyl)methylene-1,3-dicarbonyl Compounds **2a-d**

Product	Medium	Temperature (°C)	Time (h)	Yield (%)	M.p. (°C)	Formula	Calcd. % C	Calcd. % H	Calcd. % N	Found % C	Found % H	Found % N
For the Diketone **2a**												
3a	Ac_2O	60	1	86	93	$C_{13}H_{13}NO_3$	67.50	5.65	6.05	67.60	5.40	6.10
3b	$(EtCO)_2O$	40	6	54	77	$C_{14}H_{15}NO_3$	68.55	6.15	5.70	68.70	6.00	5.35
3c	Bz_2O (a)	40	20	46	131	$C_{18}H_{15}NO_3$	73.70	5.15	4.80	73.65	5.35	4.65
4a	Ac_2O	130	15 min	40 (b)	73	(8)						
5a	Ac_2O	100	0.5	5 (b)	163	$C_{15}H_{17}NO_5$	61.85	5.90	4.80	61.45	5.85	5.00
6	DMSO	170	2	64	174 (c)	$C_{20}H_{18}N_2O_3$	71.85	5.45	8.40	71.85	5.55	8.10
7a	Ac_2CH_2/Ac_2O	80	1	76	83	$C_{16}H_{17}NO_3$	70.85	6.30	5.15	70.85	6.70	5.40
7b	Ac_2CH_2/Ac_2O	140	1	90 (b)	liquid	$C_{18}H_{19}NO_4$	69.00	6.10	4.45	69.05	6.00	4.50
7c	Ac_3CH/Ac_2O (d)	80	1 (d)	81	177 (c)	$C_{18}H_{19}NO_4$	69.00	6.10	4.45	69.40	6.00	4.25
7d	$AcCH_2CO_2Et/Ac_2O$	80	1	80 (b)	liquid	$C_{17}H_{19}NO_4$	67.75	6.35	4.65	67.70	6.40	4.80
8	$AcCH_2CO_2Et/Ac_2O$ (e)	80	1	82	183 (c)	$C_{28}H_{28}N_2O_5$	71.15	5.95	5.95	71.05	6.20	5.60
For the Keto esters **2b** and **2c**												
5b	Ac_2O	100	1	6 (b)	132	$C_{16}H_{19}NO_6$	59.80	5.95	4.35	59.70	6.00	4.00
9a	Ac_2O	40	5	79 (f)	120	$C_{14}H_{15}NO_4$	64.35	5.80	5.35	64.15	5.80	5.15
9b	$(EtCO)_2O$	40	10	68 (f)	118	$C_{15}H_{17}NO_4$	65.45	6.20	5.10	65.70	6.05	5.05
9c	Bz_2O (a)	40	15	41 (f)	103	$C_{19}H_{17}NO_4$	70.55	5.30	4.35	70.45	5.20	4.75
10a	Ac_2O	130	15 min	40 (b)	48	(8)						
11a	$AcCH_2CO_2Et/Ac_2O$	80	1	83	135	$C_{18}H_{21}NO_5$	65.25	6.40	4.25	65.20	6.40	3.95
11b	Ac_2CHCO_2Et/Ac_2O (d)	80	1 (d)	69	77	$C_{20}H_{23}NO_6$	64.35	6.20	3.75	64.70	6.15	3.85
12	DMSO	170	2	64 (b)	liquid	$C_{22}H_{22}N_2O_5$	70.00	5.60	7.10	70.20	5.60	6.85
13a	Ac_2O	130	15 min	22 (b)	112	$C_{14}H_{13}NO_4$	64.85	5.05	5.40	64.70	5.05	5.20
14a	Bz_2O	120	3	21 (b)	181 (c)	$C_{20}H_{16}N_2O_4$	68.95	4.65	8.05	68.85	4.85	8.30
For the Keto ester **2d**												
10c	Ac_2O	110	2	17 (b)	61	$C_{17}H_{15}NO_2$	76.95	5.70	5.30	77.05	5.55	5.25
13b	Ac_2O	110	2	13 (b)	155	$C_{19}H_{15}NO_4$	71.00	4.70	4.35	70.80	4.80	4.10
14b	Bz_2O	140	6	8 (b)	170 (c)	$C_{25}H_{18}N_2O_4$	73.15	4.40	6.85	73.00	4.45	6.75
15a	Ac_2O	110	2	22 (b)	73	$C_{19}H_{17}NO_4$	70.55	5.30	4.35	70.60	5.20	4.75
15b	Bz_2O	140	6	15 (b)	127	$C_{24}H_{19}NO_4$	74.80	4.95	3.65	75.00	5.00	3.70

(a) Chloroform added to dissolve benzoic anhydride. (b) Chromatography necessary. (c) Crystallized from ethanol. (d) The tricarbonyl species was prepared from the corresponding 1,3-dicarbonyl compound by acetylation with excess of acetic anhydride/potassium acetate. (e) 0.20 mole of ethyl acetoacetate. (f) From **2b**.

The Keto Ester **2b**.

The *Z*-isomer (**2c**) was converted into the *E*-isomer by irradiation with a Hg-lamp (Hanau-7F118) in chloroform at 60°. After 3 hours, the conversion was 90% (nmr). Evaporation and recrystallization gave **2b**, m.p. (ether) 91°; ir: 1700 (s), 1680 (s) cm^{-1}; ^1H nmr: δ 2.50 (3 H, s), 4.28 (2 H, q); MS: m/e: 219 (M).

The Keto Ester **2d**.

From ethyl 3-oxo-3-phenylpropanoate and **1** by an analogous process as described above for **2c**, to give **2d** (7), yield 62%, m.p. 102°; ir: 1690 (s), 1655 (s) cm^{-1}.

General Procedures for the Cyclizations.

The pyridyldicarbonyl compound (**2a-d**) (0.10 mole), and a dicarbonyl compound (0.10 mole) if present, were heated in an excess of acid anhydride (50 g.) (Table II, temperature and time given). After the reaction all volatile materials (acetic anhydride or propionic anhydride) were removed *in vacuo*. The excess of benzoic anhydride was decomposed by boiling with a saturated sodium hydrogencarbonate solution. In the case of DMSO an aqueous work-up was performed. The residue was fractionated, when necessary, by column chromatography (Woelm silica, benzene containing increasing amounts of dichloromethane as eluent), and the components purified by recrystallization from light petroleum (b.p. 40-60°) if not otherwise stated.

Oxidation of **4a** with Benzoyl Peroxide.

To **4a** (2.60 g.) in 50 ml. of dichloromethane, 4.8 g. of dibenzoyl peroxide was added at 10° and the mixture stirred for 1.5 hours. After evaporation and chromatography there were obtained: **2a** (3%); **3c** (4%); and the aldehyde **4b** in 9% yield, m.p. 142°.

Anal. Calcd. for $C_{11}H_9NO_2$: C, 70.60; H, 4.85; N, 7.50. Found: C, 70.35; H, 4.85; N, 7.25.

Cyclization of Ethyl 3-Oxo-3-(2-pyridyl)propanoate.

Treatment of ethyl 3-oxo-3-(2-pyridyl)propanoate (9) with acetic anhydride/potassium acetate (1/20/10, mole/mole/mole) at 130° for 1 hour afforded **9a** (12%).

The Perkin Reaction of **1** in the Presence of Diethyl Acetonedicarboxylate.

Treatment of **1** with diethyl acetonedicarboxylate, acetic anhydride and potassium acetate (1/1/20/10) at 120° for 0.5 hours gave: **10a** (9%) and the indolizineacetate **10b**, yield 17%, m.p. 80°.

Anal. Calcd. for $C_{15}H_{17}NO_4$: C, 65.45; H, 6.20; N, 5.10. Found: C, 65.55; H, 6.10; N, 5.10.

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REFERENCES AND NOTES

(1) E. Pohjala, *Heterocycles*, 2, 585 (1974).
(2) E. Pohjala, *Acta Chem. Scand. B*, 30, 198 (1976).
(3) E. Pohjala, *ibid.*, 30, 512 (1976).
(4) R. M. Acheson and J. N. Bridson, *J. Chem. Soc. C*, 1143 (1969).
(5) R. Kuhn and M. R. Hensel, *Chem. Ber.*, 86, 1333 (1953).
(6) C. S. Marvel and J. K. Stille, *J. Org. Chem.*, 22, 1451 (1957).
(7) E. Profft, F. Schneider and H. Beyer, *J. Prakt. Chem. [4]*, 2, 148 (1955).
(8) J. Hurst, T. Melton and D. G. Wibberley, *J. Chem. Soc.*, 2948 (1965).
(9) W. Wunderlich, *J. Prakt. Chem. [4]*, 2, 302 (1955).