Nitrogen Bridgehead Compounds. Part 74.[1] Cyclization of 2-(2-Pyridylaminomethylene)succinates in Ethanolic Sodium Ethoxide. Part 2.[2] Michael Addition of Pyridyldihydropyrrolones

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2-(2-Pyridylaminomethylene)succinates, which in ethanolic sodium ethoxide solution yielded equilibrium mixtures of the pyridopyrimidines (**3**) and the pyridyldihydropyrrolones (**5**) and (**6**), within 15 min, furnished a dihydropyrrolone dimer as the main product on longer ($\geq$2 h) reaction. The dimer had the unusual 4,4′-connection between the five-membered rings, and was shown to be the pure *trans*-diastereoisomer (**7**); it is considered to be formed by a Michael addition reaction of the pyrrolones (**5**) and (**6**). These longer reactions are accompanied by hydrolytic processes.

We have reported[2] the cyclization of the *E*- and *Z*-isomers of diethyl 2-(2-pyridylaminomethylene)succinates (**1**) and the corresponding glutarates (**2**)† in ethanolic sodium ethoxide. The glutarates (**2**) only formed pyridopyrimidines (**4**), whereas the succinates (**1**) gave equilibrium mixtures of the pyridopyrimidines (**3**) and the pyridyldihydropyrrolone desmotropes (**5**) and (**6**) (see Scheme 1). Equilibrium between (**3**) and (**5**) + (**6**) was reached in about 15 min. Substituents at position 3 hindered formation of the pyridyldihydropyrrolones (**5**) and (**6**), while those at position 6 inhibitied formation of the pyridopyrimidines (**3**) and (**4**).

To confirm the inhibitory effect of substituents at position 6, we carried out reactions at elevated temperature (78 °C) and for longer times (1—2 h). The present paper reports the unexpected results of these longer reactions.

Results and Discussion

Extended Reaction of the Succinates (**1**) *in Ethanolic Sodium Ethoxide.*—The reaction was carried out as reported earlier,[2] *i.e.* the succinate was added to freshly made ethanolic sodium ethoxide, and the mixture was stirred at room temperature. In the reaction mixture from the succinate (**1e**) (R = 6-Me), which yielded only pyridyldihydropyrrolones (**5e**) and (**6e**) in the 15 min reaction, a new product was detected by t.l.c. after about 20 min. The amount of this new product increased with time, at the expense of the pyridyldihydropyrrolones (**5e**) and (**6e**). After 2 h, the new product was the main component. The pyridopyrimidine (**3e**) was not detected. Work-up and separation processes gave the new product in 39% yield (m.p. 130—132 °C). Elemental and high resolution mass spectral analysis indicated the presence of a dimer (*M*, 492.2010; $C_{26}H_{28}N_4O_6$).

A similar reaction with the succinate (**1a**) (R = H) resulted in a 10% yield of the new product (m.p. 195—198 °C; *M*, 464.1696; $C_{24}H_{24}N_4O_6$) together with 14% of the pyridopyrimidine (**3a**) and a few percent of the pyridyl dihydropyrrolones (**5a**) and (**6a**).

The succinate (**1b**) (R = 3-Me), which yielded only the pyridopyrimidine (**4b**) in the 15 min reaction,[2] did not give a similar new product.

These results suggested that the dimer is formed from the pyridyldihydropyrrolones (**5**) and (**6**).

Structure of the dimer. To elucidate the structures of the new products, we carried out detailed ^1H and ^{13}C n.m.r. studies together with high and low resolution mass spectrometric investigations. Signals were assigned with the aid of known spectra of the pyridyldihydropyrrolone desmotropes (**5**) and (**6**). On the basis of these results, structure (**7**) was ascribed to the dimers.

Evidence supporting structure (**7**). (*a*) The dihydropyrrolone structure of ring *A* is shown by the CH_2 proton chemical shifts and that of the sp^3 carbon atom (see Tables 1 and 2). For example, the methylene protons of ring *A* give rise to a signal at δ 4.89 for (**7e**) (R = 6-Me), at δ 4.84 for (**6e**) (R = Me), and at δ 3.57 for (**5e**) (R = 6-Me). The signal of the sp^3 carbon atom of ring *A* appears at δ 50.7 for (**7e**) (R = 6-Me), at δ 51.2 for (**6e**), and at δ 38.4 for (**5e**).

(*b*) The 4,4′-connection of rings *A* and *B* is proved by the multiplicities of the signals. For ring *A* in (**7e**) the ^1H n.m.r. spectrum exhibits a $C(2)H_2$ methylene singlet, and the ^{13}C off-resonance spectrum a singlet for C(4). For ring *B*, the ^{13}C off-resonance spectrum exhibits a triplet for (C2′).

(*c*) The high values of the coupling constants of the protons of ring *B* (^3J > 9 Hz) indicate that the pyrrolidinone ring assumes an envelope conformation, in which H(4′) and H(2′) are in a *trans*-diaxial relationship with respect to H(3′).

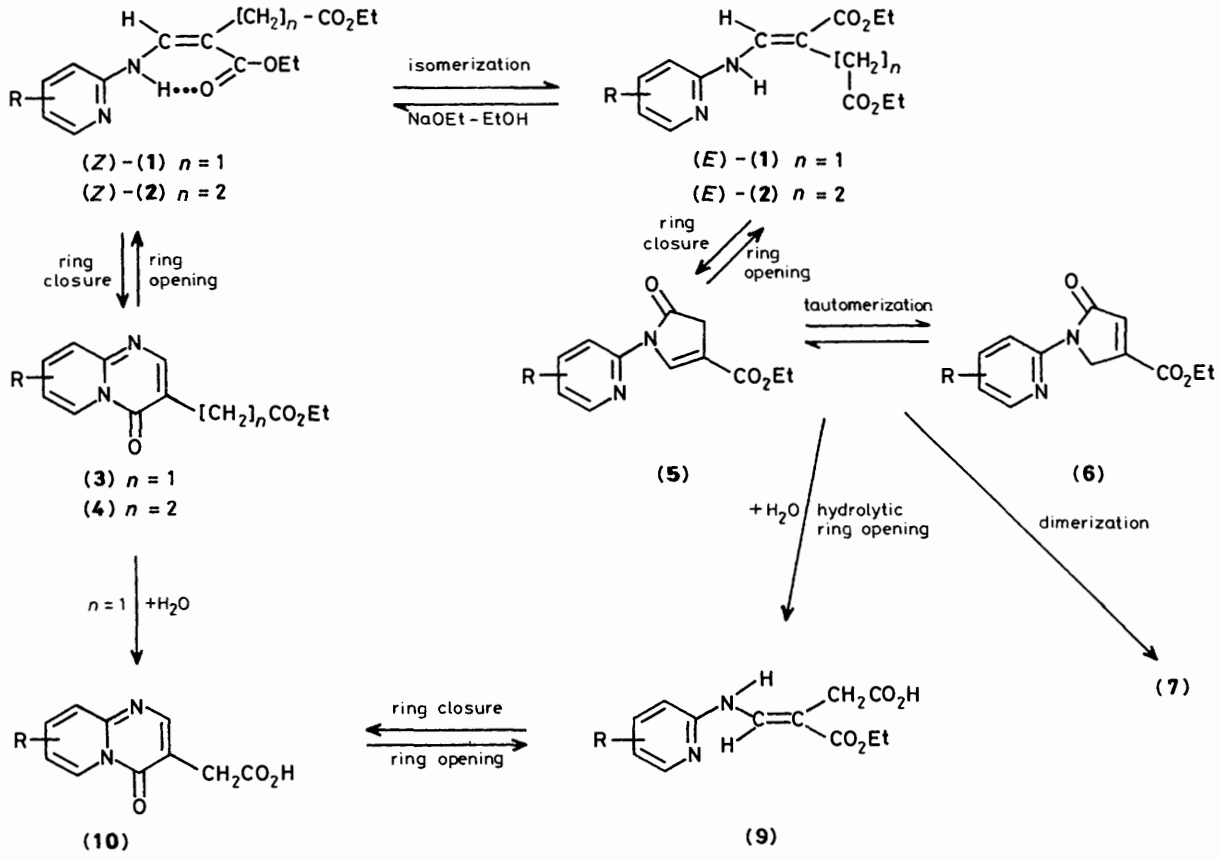
(*d*) The base peak in the 70 eV electron impact mass spectra of (**7**) results from rupture of the bond connecting rings *A* and *B*. Thus cleavage of the monomer position containing ring *A* is the most favoured fragmentation step, giving rise to the most stable fragment ion; *i.e.* the complementary part of the molecule containing ring *B*. This main fragmentation route (Figure) proves the given structure (**7**).

(*e*) Elemental compositions supporting structure (**7**) were calculated from the high resolution (*R* = 10.000) mass measurement of the molecular ions ($M^{+\bullet}$) and of the ions giving the most abundant (*I* = 100%) peaks in the spectra of the dimers.

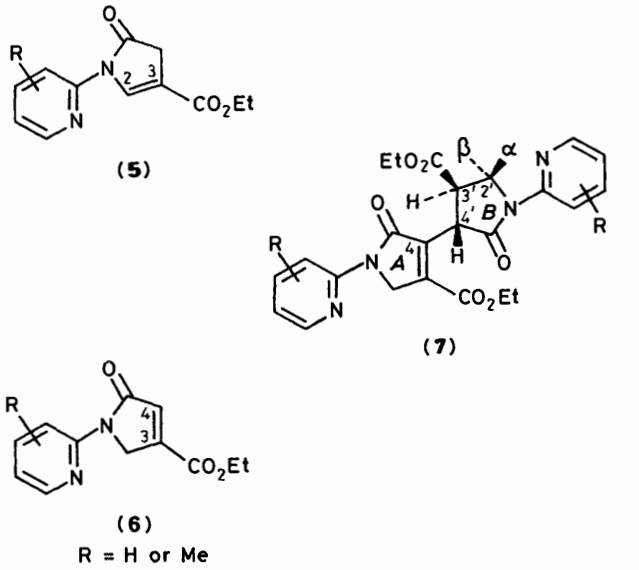
(*f*) In the course of the addition reaction, two asymmetric centres are formed (in ring *B*). The n.m.r. spectra indicate the presence of only one diastereoisomer, *i.e.* that which contains the substituents on C(3′) and C(4′) in the *trans*-position [structure (**7**)].

Mechanism of dimerization. The dimer (**7**) may be formed from the pyridyldihydropyrrolones (**5**) and (**6**) by a Michael-type intermolecular nucleophilic addition reaction, as outlined in the Scheme 2. Under the basic reaction conditions applied, the anion (**8**) is formed from (**5**) and/or (**6**). This anion attacks C(4) of (**6**), which (as a β-carbon atom of an α,β-unsaturated ester) is positively polarized. Compound (**6**) contains an α,β-unsaturated carboxamide moiety too. Thus, nucleophilic attack might be expected at C(3) as well. The result of such an attack, a 4,3′-dimer, was not obtained, however, indicating that it is the polarizing effect of the ethoxycarbonyl and not the carboxamide

† The numbers assigned to compounds (**1**)—(**6**) and the suffix letters defining substituents R correspond to those in ref. 2.



Scheme 1.



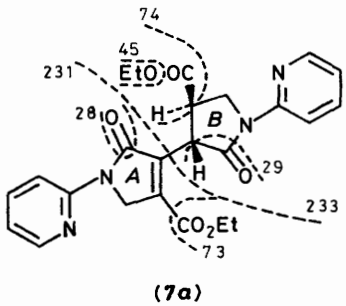
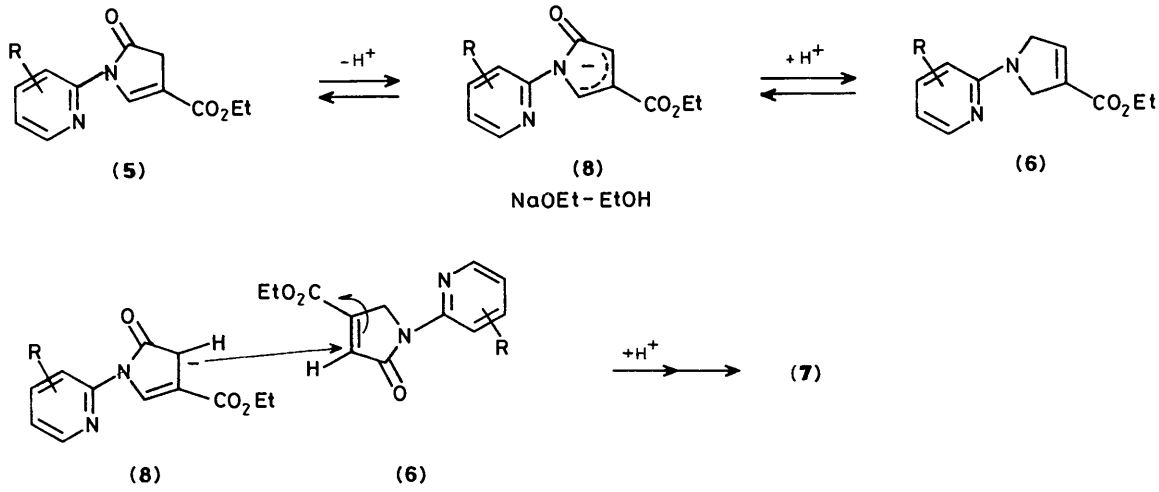


Figure. Characteristic mass spectral fragments of the dimer (**7a**)

group which is exerted on the double bond of the dihydropyrrolone ring of (**6**). This is in accord with the fact that the electronegativity of an ester group is greater than that of a carboxamide.[3] As C(3) in (**6**) carries a substituent, whereas C(4) does not, formation of the 4,4′-dimer is probably favoured sterically, too.

Dihydropyrrolones have been reported to dimerize on treatment with base,[4] acid,[5–7] heat,[4] or acyl chloride.[4] The resulting connection of the rings was found to be dependent on the structure, the substituents, and the reaction conditions, but in the reactions described previously the dimerization always took place on the carbon atom next to the dihydropyrrolone nitrogen; thus 2,3′- or 2,2′-dimers were formed. The dihydropyrrolone dimer obtained in the Michael addition[4] had a 2,3′-connection. In these previous reactions, however, the starting dihydropyrrolones did not have an ethoxycarbonyl substituent at position 3.

Hydrolytic Processes.—In the long cyclization reactions of the succinates (**1**) in ethanolic sodium ethoxide, some by-products appeared, as a result of hydrolytic processes. These products were only minor components when 'super-dry' ethanol was used (see Experimental section), but they were obtained in higher ratios when commercial absolute ethanol was used. These products have structures (**9**)[2] [formed from (**5**) or (**6**) by hydrolytic ring opening], and (**10**) [formed from (**4**) by ester hydrolysis]. The carboxylic acid (**10**) may also arise from (**9**) by ring closure under the given reaction conditions. The reversible



Scheme 2.

Table 1. ^{1}H N.m.r. data for the five-membered rings of compounds (**5**)—(**7**)

Compound	R		δ 2-H	δ 4-H_2			$^4J_{2,4}$/Hz			
(**5a**)	H		8.55t	3.55d			1.9			
(**5e**)	6-Me		8.62t	3.57d			1.9			
			2-H_2	4-H						
(**6a**)	H		4.88d	6.87t			1.9			
(**6e**)	6-Me		4.84d	6.88t			1.9			
			2-H_α	2-H_β	3-H	4-H	$^2J_{2\alpha,2\beta}$	$^3J_{2\alpha,3}$	$^3J_{2\beta,3}$	$^3J_{3,4}$
(**7a**)	H	Ring *A*	4.91s							
		Ring *B*	4.26dd	4.62dd	3.85ddd	5.06d	−11.4	9.4	9.2	10.9
(**7e**)	6-Me	Ring *A*	4.89s							
		Ring *B*	4.25dd	4.62dd	3.82ddd	5.02d	−11.3	9.5	9.2	10.9

Table 2. ^{13}C N.m.r. data for the five-membered rings of compounds (**5**)—(**7**)

Compound	R		δ C(2)	C(3)	C(4)	C(5)	C(O)O–
(**5a**)	H		140.1	110.4	38.3	174.2	163.2
(**5e**)	6-Me		140.3	110.1	38.4	174.2	163.4
(**6a**)	H		51.2	147.0	133.8	168.6	162.1
(**6e**)	6-Me		51.2	146.8	133.9	168.4	162.3
(**7a**)	H	Ring *A*	50.7	142.2	141.9	167.9	162.3
		Ring *B*	47.5	41.1	44.6	171.4	170.5
(**7e**)	6-Me	Ring *A*	50.7	142.3	141.8	167.8	162.5
		Ring *B*	47.5	41.1	44.9	171.7	170.4

and irreversible processes taking place in ethanolic sodium ethoxide solutions of compounds (**1**) are shown in the Scheme 1.

As a result of the irreversible secondary processes (dimerization and hydrolysis), the cyclization products (**3**), (**5**), and (**6**) formed first from the succinates (**1**) slowly disappear from the reaction mixture. In the absence of moisture they are transformed into the dimer (**7**), and in the presence of water or moisture into (**7**), (**9**), and (**10**).

Experimental

I.r. spectra were recorded for KBr pellets with a Zeiss UR-20 spectrophotometer; u.v. spectra for ethanolic solutions with a Unicam SP-800 spectrophotometer; ^{1}H and ^{13}C n.m.r. spectra for solutions in $CDCl_3$ with a Bruker WP 80 spectrometer, with $SiMe_4$ as internal standard; and mass spectra with a JEOL JMS-D300 spectrometer (ionization potential 70 eV) with a direct sample inlet. Analytical results for the new compounds agreed with calculated data (Table 4).

Preparation and Isolation of Dimers (**7**).—The succinate (**1e**) (20 mmol, 5.88 g), or the pyridyldihydropyrrolone (**5e**), or the pyridopyrimidine (**3e**) (20 mmol, 4.92 g) was added to ethanolic sodium ethoxide freshly prepared from sodium (60 mmol. 1.38 g) and 'super-dry' (99.95%) ethanol (30 ml).[8] The mixture was stirred at room temperature for 2 h, and then adjusted to pH 6

Table 3. Characteristic ions and relative intensities (%) in the 70 eV mass spectra of compounds (**5**)—(**7**) [elemental composition of $M^{+\cdot}$ calculated on the basis of high resolution (R = 10.000) mass measurement of the molecular ions]

Ion	(**5a**) R = H	(**5e**) R = 6-Me	(**6a**) R = H	(**6e**) R = 6-Me	(**7a**) R = H	(**7e**) R = 6-Me
$M^{+\cdot}$	232.0839 (100) ($C_{12}H_{12}N_2O_3$)	246.1004 (100) ($C_{13}H_{14}N_2O_3$)	232.0841 (90) ($C_{12}H_{12}N_2O_3$)	246.1010 (90) ($C_{13}H_{14}N_2O_3$)	464.1696 (81) ($C_{24}H_{24}N_4O_6$)	492.2010 (100) ($C_{26}H_{28}N_4O_6$)
$M - 28$	204 (11)	218 (13)	204 (9)	218 (10)		
$M - 29$	203 (15)	217 (28)	203 (18)	217 (30)	435 (3)	463 (7)
$M - 45$	187 (23)	201 (15)	187 (15)	201 (12)	419 (13)	(447 (18)
$M - 28 - 29$	175 (30)	189 (45)	175 (51)	189 (51)		
$M - 72$	160 (23)	174 (7)	160 (16)	174 (8)		
$M - 73$	159 (38)	173 (17)	159 (31)	173 (15)	391 (32)	419 (58)
$M - 72 - 28$	132 (26)	146 (28)	132 (30)	146 (29)		
$M - 73 - 28$	131 (75)	145 (98)	131 (100)	145 (100)		
$M - 73 - 46$					345 (60)	373 (64)
$M - 73 - 74$					317 (13)	345 (12)
$M/2 + 1$					233.0926 (100) ($C_{12}H_{13}N_2O_3$)	247.1083 (100) ($C_{13}H_{15}N_2O_3$)
$M/2$					232 (7)	246 (30)

Table 4. Elemental analysis data of new compounds

Compd.	R			C (%)	H (%)	N (%)
(**7a**)	H	$C_{24}H_{24}N_4O_6$	Reqd.	62.1	5.2	12.1
			Found	61.9	5.3	12.0
(**7e**)	6-Me	$C_{26}H_{28}N_4O_6$	Reqd.	63.4	5.7	11.4
			Found	63.35	5.8	11.2
(**10a**)	H	$C_{10}H_8N_2O_3$	Reqd.	58.8	3.95	13.7
			Found	58.9	4.0	13.8

with ethanolic hydrogen chloride. The ethanol was distilled off under reduced pressure. The residue was dissolved in a mixture of water (50 ml) and benzene (50 ml), the phases were separated, and the benzene layer was washed with water, dried (Na_2SO_4), and evaporated. To the dark residue, ethanol (1 ml) was added and the mixture was allowed to crystallize for a few days. The crystals were filtered off and recrystallized from ethanol to yield the dimer (**7e**) (1.92 g, 39%) as white crystals, m.p. 130—132 °C (EtOH); for n.m.r. data, see Tables 1 and 2.

The succinate (**2a**) (20 mmol, 5.56 g), or the pyridyldihydropyrrolone (**5a**), or the pyridopyrimidine (**3a**) (20 mmol, 4.64 g) was treated similarly with sodium ethoxide. After work-up, the residue was dissolved in aqueous 5% hydrochloric acid (50 ml) and benzene (50 ml). The benzene layer was separated, dried (Na_2SO_4), and evaporated, and the residue was allowed to crystallize from ethanol (1 ml). The crystals were filtered off [the mother liquor contained the pyrrolone (**5a**)], and recrystallized from ethanol to give the *dimer* (**7a**), m.p. 195—198 °C (from EtOH); for n.m.r. and mass spectral data, see Tables 1—3; $\lambda_{max.}$ 300infl (log ε 3.87), 284infl (4.09), 277 (4.13), 238infl (4.32), and 230 nm (4.37); ν_{CO} 1 740—1 670 cm^{-1}.

From the 5% hydrochloric acid layer after neutralization, extraction with chloroform, and evaporation, the pyridopyrimidine (**3a**) (0.65 g, 14%) was obtained; for physical characteristics, see ref. 2.

Ring Closure of the Monoester (**9a**).—The monoester (**9a**)[2] (20 mmol, 5.0 g) was treated similarly with ethanolic sodium ethoxide. The sodium salt of the pyridopyrimidine-3-carboxylic acid (**10a**) precipitated from the reaction mixture; m.p. 275 °C (decomp.) (from EtOH); yield 1.26 g (35.4%); δ_H[$(CD_3)_2SO$] 3.20 (s, 2 H, CH_2), 7.75 [dd, 1 H, C(8)H], 7.58 [d, 1 H, C(9)H], 7.81 [dd, 1 H, C(7)H], 8.22 [s, 1 H, C(2)H], and 8.91 [d, 1 H, C(6)H].

To liberate the *carboxylic acid* (**10a**) the sodium salt was dissolved in water and the pH was adjusted to 2 with aqueous 10% hydrochloric acid. The resulting crystals were filtered off, washed with water, and dried; m.p. 244 °C (decomp.).

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