Nitrogen Bridgehead Compounds. Part 42.[1] Cyclization of Diethyl 2-(2-Pyridylaminomethylene)-succinates and -glutarates in Ethanolic Sodium Ethoxide†

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2-(Pyridylaminomethylene)-succinates (**1**) and -glutarates (**2**) were treated with ethanolic sodium ethoxide solution. The succinates (**1**) gave, in reversible reactions, pyridopyrimidines (**3**) and pyridylpyrrolinones (**5**), and also underwent *Z–E* geometric isomerization. The cyclizations (*Z*)-(**1**) to (**3**) and (*E*)-(**1**) to (**5**) were more rapid than the isomerization of (**1**). Thus, short (1-min) reactions starting from (*Z*)-(**1**) produced the pyridopyrimidine (**3**) and those from (*E*)-(**1**) the pyridylpyrrolinone (**5**) in good yield. Longer (15-min) reactions yielded equilibrium mixtures, consisting mainly of pyridylpyrrolinones (**5**). Substituents at position 6 of the pyridine ring inhibited the formation of the pyridopyrimidines, whereas those at position 3 hindered or inhibited the formation of the pyridylpyrrolinones.

The unsubstituted glutarate (**2a**) formed the pyridopyrimidine (**4a**) whereas the 6-substituted ones did not yield any cyclic product.

Results of the sodium ethoxide ring closure were compared with those of the previously studied $POCl_3$–PPA and thermal cyclizations.

In previous publications[2,3] we discussed the $POCl_3$–PPA (polyphosphoric acid) and thermal ring closures of diethyl 2-(2-pyridylaminomethylene)-succinates (**1**) and -glutarates (**2**). Having two reactive nitrogen atoms and two different carboxylic ester groups, these compounds gave rise to various cyclic products (Scheme). Both in $POCl_3$–PPA at 110 °C and in Dowtherm A at 250 °C, the succinates formed pyrido[1,2-*a*]-pyrimidines (**3**) and pyridylpyrrolinones (**5**) as primary products. The ratio of these products was independent of whether we started from the *E* or *Z* geometric isomers, but did depend upon the reaction conditions and upon the pyridine ring substituents. Substituents at position 3 hindered ring closure onto the nearby amino-nitrogen, whereas those at position 6 hindered ring closure onto the neighbouring pyridine nitrogen. The glutarates (**2**) formed only pyrido[1,2-*a*]pyrimidines (**4**).

As a continuation of our previous studies, we now give an account of the ring closure of the title compounds in ethanolic sodium ethoxide. Finally, we compare the results obtained in the three different (acidic, thermal, and alkaline) ring closures.

Cyclization of *N*-substituted 2-(aminomethylene)succinates (**7**) on the action of alkali metal, alkali metal oxide, alkali metal hydroxide, or alkali metal alkoxide catalysts leads to 5-oxo-4,5-dihydropyrrole-3-carboxylic esters (**8**)[4–7] (Figure 1). Alkali-catalysed ring closure of the 2-(2-pyridylaminomethylene)succinates (**1**), where alternative routes for the ring closure are possible, has not been investigated previously.

Results and Discussion

We added the succinates (**1**) to freshly made ethanolic sodium ethoxide solution; the mixture was stirred, and worked up by the addition of ethanolic hydrogen chloride solution until the mixture became acidic (pH = 6). To avoid hydrolysis we used 'super-dry' ethanol (see Experimental section).

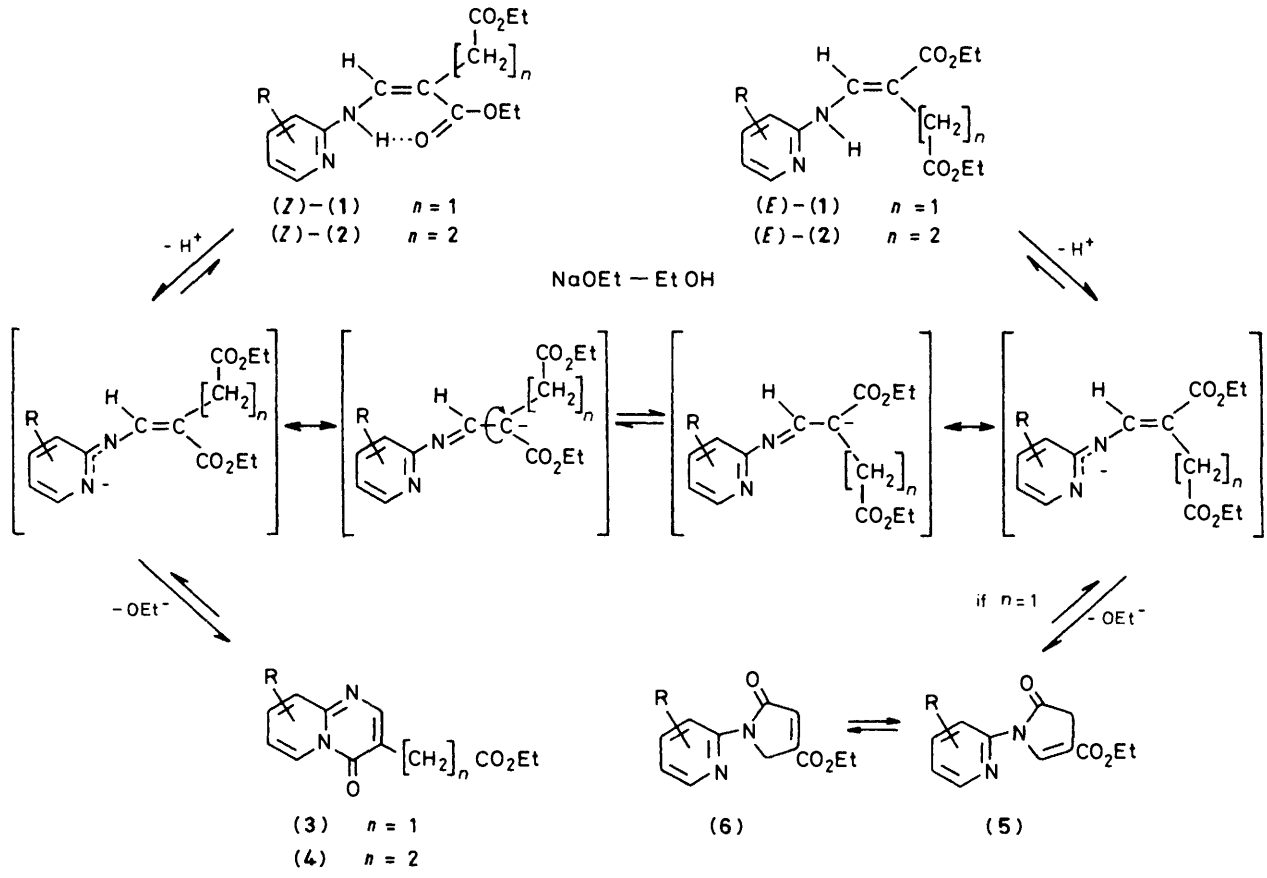
Cyclization of the E *and* Z *Isomers of the Succinate* (**1a**; R = H).—In our first experiments we investigated the reactions of the *E* and *Z* isomers of (**1a**; R = H). In the reaction mixtures both of the expected cyclic products (**3a**) and (**5a**) appeared. One main point in which the sodium ethoxide ring closure differed from the previously investigated $POCl_3$–PPA and thermal ring closures was that in ethanolic sodium ethoxide the cyclic products (**3a**) and (**5a**) were obtained in reversible reactions. Excess of sodium ethoxide shifted the equilibrium towards the cyclic products. When 3 mol equiv. of sodium ethoxide was used, t.l.c. showed the cyclic products, (**3a**) and (**5a**), to be the main components of the reaction mixtures. Nevertheless, when the reaction mixture was neutralized with ethanolic hydrogen chloride at room temperature, the cyclic products gradually reverted to the starting material. Starting from pure (*E*)-(**1a**) or (*Z*)-(**1a**) we obtained *E–Z* isomeric mixtures. If commerical absolute ethanol was used instead of 'super-dry' ethanol, a hydrolysis product (**9**), the mono ester of (**1**), was also isolated. In the next experiments we cooled the reaction mixture to −17 °C before the neutralization and kept the temperature below −10 °C during the addition of the ethanolic hydrogen chloride solution. In this way we succeeded in obtaining the cyclic products in good yields. Reaction for 15 min resulted in 15% pyridopyrimidine (**3a**) and 54% pyridylpyrrolinone (**5a**), independently of whether we started from (*E*)-(**1a**) or (*Z*)-(**1a**).

T.l.c. observations, however, suggested the investigation of shorter reactions, too. We therefore carried out 1-min reactions on (*E*)-(**1a**) and (*Z*)-(**1a**). (The reaction mixtures were cooled to −17 °C immediately after the dissolution of the starting material.) In this way, from (*E*)-(**1a**) we obtained almost exclusively the pyridylpyrrolinone (**5a**), and from (*Z*)-(**1a**) the pyridopyrimidine (**3a**). Results of the 1-min and 15-min reactions of (*E*)-(**1a**) and (*Z*)-(**1a**) are shown in Table 1. (The somewhat lower overall yields in the 15-min reactions are probably a consequence of tarring and hydrolysis.)

We have previously shown[2] that the pyridylpyrrolinone (**5**) arises only from the *E* geometric isomer of (**1**), and the pyridopyrimidine (**3**) only from the *Z* isomer. In the previously investigated $POCl_3$–PPA and thermal ring closures the isomerization of (**1**) was always faster than the cyclization reactions.[2,3] The results in Table 1, however, indicate that in ethanolic sodium ethoxide the rates of the cyclizations (*Z*)-(**1a**) ⟶ (**3a**) and (*E*)-(**1a**) ⟶ (**5a**) are higher than the rate of the interconversion between the geometric isomers of (**1**). Thus, the products of the 1-min reactions reflect the geometry of the starting materials.

Not only the cyclization, but also (somewhat more slowly)

† This paper is also deemed to be Part 10 of the series, 'Ring Transformation,' Part 9 is ref. 1.



Scheme.

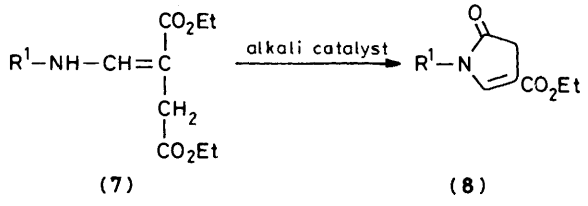
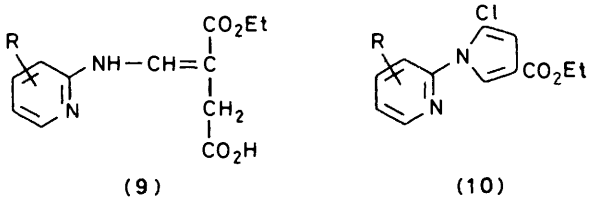


Figure 1.



the isomerization takes place in ethanolic sodium ethoxide. Thus, in time a dynamic equilibrium is reached between the isomers of (**1a**) and the cyclic products (**3a**) and (**5a**). At room temperature this equilibrium is achieved from (*E*)-(**1a**) or (*Z*)-(**1a**) within 15 min, and the equilibrium composition of the products is 15% (**3a**) and 54% (**5a**).

The Scheme outlines the equilibrium processes in the ethanolic sodium ethoxide solution of (**1a**). Sodium ethoxide catalyses both the cyclization and the isomerization reactions, by abstraction of a proton from the amino group of (**1**). The resulting mesomeric anion (shown in the Scheme in two of its resonance structures, which explain the reactivity) is the intermediate for both the cyclic and the isomerized products.

Table 1. Cyclization products of (*E*)-(**1a**) and (*Z*)-(**1a**) in 3 mol equiv. of ethanolic sodium ethoxide

	Yield of products (%) in the			
	1-min reaction		15-min reaction	
Starting material	(**3a**)	(**5a**)	(**3a**)	(**5a**)
(*Z*)-(**1a**)	68	5	54	15
(*E*)-(**1a**)	6	63	54	15

Ring Closures of the Substituted Succinates (**1**).—Having discovered the behaviour of the unsubstituted succinate (**1a**), we carried out cyclizations of the substituted derivatives (**1b**—**p**). The results are shown in Table 2.

The succinates (**1k** and **l**; R = 3-NO_2, 5-NO_2) precipitated from the reaction mixtures as sodium salts and did not react. (**1n**; R = 5-$CONH_2$) was recovered mainly unchanged, although the cyclic products (**3n**) and (**5n**) were detected in t.l.c. in the reaction mixture. No cyclic product was formed from (**1j**; R = 3,5-Cl_2).

The remaining succinates gave rise to cyclic products in good overall yields.

Similarly to (**1a**; R = H), most of the substituted succinates formed the pyridylpyrrolinones (**5**) as major products. Exceptions to this were the 3-substituted succinates (**1b** and **g**). The 3-methyl-substituted succinate (**1b**) did not form a

Table 2. Cyclization products of substituted succinates (**1**) and glutarates (**2**) (15-min reactions in 3 mol equiv. of ethanolic sodium ethoxide)

Starting material[a]	R	Yields of products (%) Pyridopyrimidine (**3**)	Pyridylpyrrolinone (**5**)[b]
(**1a**)	H	15	54
(**1b**)	3-Me	69	
(**1c**)	4-Me	13	55
(**1d**)	5-Me	11	55
(**1e**)	6-Me		68
(**1f**)	4,6-Me_2		68
(**1g**)	3-OH	30	10
(**1h**)	6-OH		63
(**1i**)	5-Cl	3	61
(**1j**)	3,5-Cl_2		
(**1k**)	3-NO_2		
(**1l**)	5-NO_2		
(**1m**)	6-NHAc		57
(**1n**)	5-$CONH_2$		
(**1p**)	5,6-(CH=CH)$_2$		61
		(**4**)	
(**2a**)	H	72	
(**2e**)	6-Me		
(**2h**)	6-OH		
(**2m**)	6-NHAc		

[a] The letter suffixes correspond to those in refs. 2 and 3. Hence (**1o**) was not studied in the present work. [b] (**5**) contains various amount of (**6**) (see text).

pyridylpyrrolinone at all, but gave the pyridopyrimidine (**3b**) in high yield. This indicates that under the conditions of the sodium ethoxide ring closure a methyl group at position 3 of the pyridine ring totally inhibited the ring closure onto the nearby amino-nitrogen, and proceeded exclusively in the alternative route, onto the pyridine nitrogen. The 3-hydroxy-substituted succinate (**1g**) formed the corresponding pyridylpyrrolinone (**5g**), but only in low (10%) yield.

The 6-substituted succinates (**1e**, **f**, **h**, **m**, and **p**) did not form pyridopyrimidines but gave the pyridylpyrrolinones in high yield. This means that substituents at position 6 of the pyridine ring fully inhibited the ring closure onto the neighbouring pyridine nitrogen. 6-Substituted pyridopyrimidines were not detected even after long reaction times at 78 °C.

Tautomerism of the Pyridylpyrrolinones.—We have reported in previous work[3] that pyridylpyrrolinones have two stable tautomeric forms, i.e. in this case the 1-(2-pyridyl)-5-oxo-4,5-dihydropyrrole-3-carboxylic ester (**5**) and the 1-(2-pyridyl)-5-oxo-2,5-dihydropyrrole-3-carboxylic ester (**6**). Of the two tautomers (**5**) is the primary product of the cyclization of (**1**) and, on the basis of literature data[8–11] on related compounds, (**5**) is the more stable isomer. Tautomerization of pyrrolinones was shown to take place with heat, bases, and acids.[9] The pyridylpyrrolinones obtained in the thermal ring closures were mixtures of the two tautomers (**5**) and (**6**). The desmotropes were separated in only one case, (**5e**) and (**6e**), and differed in their m.p.s and u.v., i.r., and particularly ^{1}H n.m.r. spectral characteristics.[3]

The pyridylpyrrolinones obtained in the sodium ethoxide ring closures also contained a small amount of (**6**) besides (**5**). The isomeric composition also depended on the work-up, separation, and purification conditions. For instance the product obtained from (**1e**) contained 5—8% (**6e**) besides (**5e**) if the reaction mixture was carefully acidified to pH = 6, and was not treated with acids during the separation process. If the pH of the reaction mixture was adjusted to pH = 2, the product contained 30% (**6e**) besides (**5e**), indicating that the isomerization is very sensitive to acids.

Ring-transformation Reactions.—The equilibrium state outlined in the Scheme, and the equilibrium ratios given in Table 2, were achieved not only from (*E*)-(**1**) and (*Z*)-(**1**), but also from the cyclic products (**3**) and (**5**). For example, when the pyridopyrimidine (**3a**) was stirred in 3 mol equiv. of ethanolic sodium ethoxide, a mixture of 28% pyridopyrimidine (**3a**) and 32% pyridylpyrrolinone (**5a**) was obtained within 10 min, whereas in 20 min an equilibrium mixture of 14% (**3a**) and 54% (**5a**) resulted. From the pyridylpyrrolinone (**5a**) the same equilibrium was also achieved within 20 min. Under the above conditions, the 6-substituted pyridopyrimidines (**3e**, **f**, **h**, and **m**) were fully transformed into the corresponding pyridylpyrrolinones (**5e**, **f**, **h**, and **m**). For example, (**3e**) gave (**5e**) in 68% yield within 5 min. As the equilibria between compounds (**5**) $\rightleftharpoons$ (**1***E*) $\rightleftharpoons$ (**1***Z*) $\rightleftharpoons$ (**3**) always lie on the side of the pyridylpyrrolinones, except for the 3-substituted compounds, this ring-transformation reaction can mainly be used for the preparation of pyridylpyrrolinones, and especially to obtain 6-substituted pyridylpyrrolinones.

Cyclization of the 2-(2-*Pyridylaminomethylene*)*glutarates* (**2**).—The glutarate (**2a**; R = H), treated with 3 mol equiv. of sodium ethoxide, gave rise to only one product, the pyridopyrimidine (**4a**), as in the $POCl_3$–PPA and thermal ring closures.[2,3] The 6-substituted glutarates, in contrast, did not form any cyclic product, even after prolonged heating in ethanolic sodium ethoxide solution, and the starting glutarates, as *E*–*Z* isomeric mixtures, were recovered (see Table 2).

Comparison of the Thermal, $POCl_3$–PPA, *and Sodium Ethoxide Ring Closures of the Succinates* (**1**).—As we have shown in the present and previous[2,3] studies, under the most varied conditions the succinates (**1**) formed pyridopyrimidines (**3**) and pyridylpyrrolinones (**5**), in competitive reactions. Although compounds (**3**) may only arise from the (*Z*), and compounds (**5**) from the (*E*) geometric isomers of (**1**), the ratio of the products did not depend on the geometry of the starting material, because in Dowtherm A at 250 °C and $POCl_3$–PPA at 110 °C the isomerization of (**1**) is much faster than the cyclizations, and in ethanolic sodium ethoxide at 25 °C the reactions are reversible, and in 15 min the equilibrium compositions are obtained.

The ratio of the cyclic products (**3**) and (**5**) depended strongly upon the reaction conditions. Compared with the thermal ring closures, the $POCl_3$–PPA reaction conditions favoured formation of the pyridopyrimidines (**3**), while reactions in sodium ethoxide favoured formation of the pyridylpyrrolinones (**5**).

In a given system the ratio of the products depended upon the pyridine ring substituents. These may determine the product ratio by influencing the relative reactivities of the two nitrogen atoms, through their electronic effects. In addition, substituents at positions 3 and 6 of the pyridine ring may also influence the product ratio through their steric effects. Substituents at position 6 may hinder ring closure onto the pyridine nitrogen. Such an irregular behaviour of 6-substituted 2-aminopyridine derivatives in cyclization reactions to give pyridopyrimidines has also been observed by other authors.[12] Substituents at position 3 may hinder ring closure onto the nearby amino-nitrogen. This effect is understandable if we consider the structure of the pyridylpyrrolinones. ^{1}H N.m.r. studies and quantum chemical calculations have revealed that the two rings of the pyridylpyrrolinones are nearly coplanar, and in the stable conformation the oxo group and the pyridine nitrogen are

Table 3. Substituent effects in the ring closure of succinates (**1**)

Starting material	R	Yields of products (%) in: Dowtherm A, 250 °C, 30 min (3)	(5)[a]	$POCl_3$–PPA 110 °C, 1.5 h (3)	[(5) + (10)][b]	NaOEt–EtOH 25 °C, 15 min (3)	(5)[c]
(**1a**)	H	54	28	82	4	15	54
(**1c**)	4-Me	21	62	85	4	13	55
(**1d**)	5-Me	50	32	83	4	11	55
(**1e**)	6-Me	44	36	42	40		68
(**1f**)	4,6-Me_2	12	70	40	38		68
(**1b**)	3-Me	65		92		65	
(**1h**)	6-OH	57	22	Decomp.			63
(**1g**)	3-OH	74	8	80		30	10
(**1r**)	3-CO_2Et	62		50			
(**1s**)	4-CO_2Et	66	17	90	*d*	6	46
(**1t**)	5-CO_2Et	33	50	65	*d*		
(**1u**)	6-CO_2Et	30	54	19	*d*		51

[a] The pyridylpyrrolinones (**5**) contain various amounts of the desmotrope (**6**) (see ref. 3). [b] The pyridylpyrrolinones (**5**) are partially or fully transformed into 5-chloro-1-(2-pyridyl-3-ethoxycarbonylpyrroles (**10**) (see ref. 2). The yields given here are overall yields of [(**5**) + (**10**)]. [c] The pyridylpyrrolinones (**5**) contain various amounts of the desmotrope (**6**) (see text). [d] The ethoxycarbonyl-substituted pyridylpyrrolinones (**5s**, **t**, and **u**) decompose in $POCl_3$–PPA at 110 °C. This may be the reason why (**5**) and/or (**10**) were not obtained (see Experimental section).

positioned as far as possible from each other.[13] The oxo group lies near the substituent at position 3, and thus steric interaction may be expected.

In Table 3 we have collected from our present and previous[2,3] works the yields of the methyl- and hydroxy-substituted derivatives. To make the comparison more complete, we carried out additional ring closures, starting from ethoxycarbonyl-substituted succinates[14] (**1r**, **s**, **t**, and **u**), not investigated previously.

As concerns the effects of the 6-substituents, on the basis of the fairly similar ratios obtained in the thermal ring closures from the 5-methyl- (**1d**) and 6-methyl-substituted (**1e**) succinates (50:32 and 44:36) and also from the 5-ethoxycarbonyl- (**1t**) and 6-ethoxycarbonyl-substituted (**1u**) succinates (33:50 and 30:54) it may be concluded that in Dowtherm A at 250 °C a 6-methyl or 6-ethoxycarbonyl group does not cause serious hindrance for the ring closure onto the pyridine nitrogen.

In $POCl_3$–PPA at 110 °C the drastic decrease in the yields of the 6-methyl- and 6-ethoxycarbonyl-substituted pyridopyrimidines, as compared with the yields of the respective 4- and 5-substituted pyridopyrimidines, points to a significant steric effect of the 6-substituents, under the applied conditions.

Finally, in ethanolic sodium ethoxide a methyl or a hydroxy substituent at position 6 totally inhibited the ring closure onto the pyridine nitrogen. The corresponding pyridopyrimidine was not formed from the remaining 6-substituted succinates (**1m**, **p**, and **u**) or from the 6-substituted glutarates (**2e**, **h**, and **m**) either.

As for the effect of the 3-substituents, the 3-methyl- and the 3-ethoxycarbonyl-substituted succinates (**1b**) and (**1r**) never formed even a trace of the respective 3-substituted pyridylpyrrolinones. From the 3-hydroxy-substituted succinate (**1g**), however, (**5g**) was obtained both in the thermal and the sodium ethoxide ring closures, but only in poor yields. The difference between the steric effects caused by a 3-methyl and a 3-hydroxy group may be a consequence of the smaller bulk of the hydroxy group as compared with that of the methyl group.

Table 4. Results of the CNDO/2 calculations and ^{15}N n.m.r. spectroscopic analysis of compounds (**1a**) and (**1c**)

	Net charge: Amino N	Pyridine N		Chemical shift (δ_N p.p.m.): Amino N	Pyridine N
(**1c**)	−0.181	−0.213	(*E*)-(**1c**)	−268.8	−120.4
(**1a**)	−0.180	−0.202	(*E*)-(**1a**)	−268.7	−113.5

Resonance Effect of Substituents at Position 4 *of the Pyridine Ring.*— Of the results in Table 3, the effects of the 4-substituents on the thermal ring closure were found to be surprising. One would expect a methyl group at position 4 (*para* to the pyridine nitrogen) to promote ring closure onto the pyridine nitrogen, *i.e.* to help the formation of the pyridopyrimidine (**3**), as compared with the *meta*-substituted 5-methyl derivative. The 4-methyl group, however, caused a significant *decrease* in the yield of the pyridopyrimidine (**3**) in favour of the pyridylpyrrolinone (**5**) [the 4-methyl-substituted pyridopyrimidines (**3c**) and (**3f**) were formed in 21 and 12% yield, and the 5-methyl-substituted (**3d**) *in* 50% yield].

Similarly, the electron-withdrawing ethoxycarbonyl group at position 4, instead of decreasing the ratio of the pyridopyrimidine, increased it as compared with the yield of the 5-ethoxycarbonyl-substituted derivative [*cf.* the 66% yield of the 4-ethoxycarbonyl-substituted (**3s**) with the 33% yield of the 5-ethoxycarbonyl-substituted (**3t**)].

To explain the above results we considered that in 2-aminopyridines the charge-separated resonance species also makes a contribution to the structures[15] (Figure 2). In the charge-

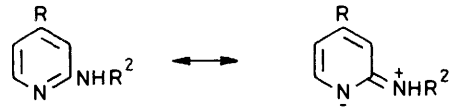


Figure 2.

separated species the substituent at position 4 of the pyridine ring can exert its electronic effect on the amino-nitrogen, too. The results in Table 3 suggest that in the thermal ring closure the amino-nitrogen was more sensitive than the pyridine nitrogen to the electronic effects of the substituents at position 4. These electronic effects, however, are not present in the ground state of (**1c**), since chemical shift and charge density values for the amino-nitrogen are practically the same in (**1c**) and in (**1a**), while those for the pyridine nitrogen have somewhat higher negative values in (**1c**) than in (**1a**) (see Table 4).

Experimental

M.p.s are uncorrected. I.r. spectra were recorded in KBr pellets with a Zeiss US-20 spectrophotometer, u.v. spectra in ethanolic solutions with a Unicam SP-800 spectrophotometer, and ^1H and ^{13}C n.m.r. spectra were recorded with a Bruker WP80 spectrometer in $CDCl_3$ solutions with $SiMe_4$ as internal standard. The ^{15}N n.m.r. spectra of (**1a**) and (**1c**) were recorded with a Jeol FX-100 spectrometer in $CDCl_3$ at 10.04 MHz with proton broad-band decoupling. Chemical shifts were determined relative to the signal of external aqueous $K^{15}NO_3$ ($\delta_{K^{15}NO_3}$ −3.55 p.p.m.) and then converted to the external nitromethane standard. Analytical results on the new

compounds agreed with calculated data. Details are given in Supplementary Publication No. SUP 23936 (6 pp.).*

Starting Materials.—The succinates (**1a**—**n**, and **p**) and the glutarates (**2a**, **e**, **h**, and **m**) were prepared and the *E* and *Z* geometric isomers were separated as reported previously.[2] The succinates (**1r**, **s**, **t**, and **u**) were obtained as reported.[14]

Cyclizations in Ethanolic Sodium Ethoxide Solution.—General procedure. Depending on the experiment, the *E*- or *Z*-isomer, or an *E*–*Z* isomeric mixture, of the succinate (**1**) or glutarate (**2**) (20 mmol) was added to stirred ethanolic sodium ethoxide solution, made from 3 mol equiv. of sodium (1.38 g, 60 mg-atom) and 'super-dry' ethanol[16] (30 ml). The clear solution was stirred at 25 °C for the required period (1 min or 15 min) and quickly cooled to −17 °C with a freezing mixture of ice and salt.

Work-up procedures. The cold reaction mixture was neutralized and made acidic (pH = 6) with saturated ethanolic hydrogen chloride solution, made from 'super-dry' ethanol and hydrogen chloride gas dried by passage through conc. H_2SO_4. During the neutralization the temperature was kept below −10 °C. The ethanol was then distilled off under reduced pressure. The products were separated by one of the procedures (A–D) below. The pyridylpyrrolinones obtained in this way contained a small amount of (**6**) (see text). Yields are given in Tables 1 and 2.

A. The residue obtained from the reaction of (**1a**, **c**, **d**, and **i**) was stirred in a mixture of benzene (50 ml) and 2.5% hydrochloric acid (50 ml). The phases were separated. The aqueous acidic layer was washed with benzene (2 × 10 ml). The combined benzene phases were dried (Na_2SO_4) and evaporated, and the residue crystallized from ethanol, to obtain the pyridylpyrrolinones (**5a**, **c**, **d**, and **i**). For m.p.s see ref. 3. The aqueous acidic layer was neutralized with $NaHCO_3$ and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated, and the residue was crystallized from ethanol to obtain compounds (**3a**, **c**, **d**, and **i**). By evaporation of the filtrate and treatment of the residue with ethanolic hydrogen chloride a second crop of (**3**) was obtained in the form of the hydrochloride salt. For m.p.s see ref. 2.

B. The residue obtained from the reaction mixture of (**1b**) or (**2a**) was treated with water (50 ml), neutralized with $NaHCO_3$, and extracted with chloroform. The extract was dried (Na_2SO_4) and evaporated, and the residue was crystallized from ethanol to obtain the pyridopyrimidines (**3b**) and (**4a**), respectively. For m.p.s see ref. 2.

C. The residue obtained from the reaction mixtures of (**1e**, **f**, **h**, **m**, and **p**) was dissolved in a mixture of water (50 ml) and benzene (50 ml). The phases were separated and the aqueous layer was shaken with benzene (3 × 10 ml). The combined organic layers were dried (Na_2SO_4) and evaporated, and the residue was crystallized from ethanol to obtain the pyridylpyrrolinones (**5e**, **f**, **h**, and **m**). For m.p.s see ref. 3.

D. The residue obtained from the reaction mixture of (**1g**) was stirred in a mixture of water (50 ml) and benzene (50 ml). The insoluble crystals of (**3g**)·HCl were filtered off. For m.p. see ref. 2. The phases of the filtrate were separated and the aqueous layer was extracted with benzene. The combined benzene layers were dried (Na_2SO_4) and evaporated. The residue was purified by column chromatography [silica gel (0.063—0.125 mm mesh); eluant benzene] to obtain (**5g**). For m.p. see ref. 3.

Succinates (**1j**, **k**, and **l**) and glutarates (**2e**, **h**, and **m**) did not cyclize, and (**1n**) cyclized only in very poor yield; they were recovered as *E*–*Z* isomeric mixtures.

* For details of the Supplementary publications scheme, see Instructions for Authors (1984), *J. Chem. Soc., Perkin Trans 1*, 1984, Issue 1.

Separation of the Monoester (**9e**).—When cyclization of (**1e**) was carried out in ethanolic sodium ethoxide solution, made from commercial absolute ethanol, the following work-up procedure was applied. From the reaction mixture ethanol was distilled off under reduced pressure, the residue was dissolved in benzene–water, and the phases were separated. The benzene layer contained the *E*–*Z* isomers of (**1e**). The aqueous acidic layer (pH = 6) was extracted with chloroform, the phases were separated, the chloroform layer was dried (Na_2SO_4) and evaporated, and the residue was crystallized from ethanol to obtain a *ca.* 1:1 *E*–*Z* isomeric mixture of (**9a**), m.p. 134—137 °C. By fractional crystallization the pure (*E*)-(**9e**), m.p. 141—143 °C, was also obtained. Assignment of the CO_2H group in (*E*)-(**9e**) was made with the help of ^{13}C n.m.r. spectra: of the two carboxylic carbon atoms, the one adjacent to the sp^3 carbon is expected to appear at lower field. This carbon atom (at δ_C 175.7 p.p.m.) gives rise to a triplet, with $^2J_{CO,CH_2}$ 7.9 Hz, and showed no further splitting. The carbon atom of the ester carbonyl group (at δ_C 168.2 p.p.m.) appears as a multiplet due to ^3J couplings with the protons of the O–CH_2, =C–CH_2, and –C=CH– groups. Characteristic ^1H n.m.r. data: (*E*)-(**9e**) δ 3.52 (2 H, s, CH_2), 8.05 (1 H, br s, =CH), and 9.25 (1 H, br, NH); (*Z*)-(**9e**) 3.27 (2 H, s, CH_2), 8.02 (1 H, d, =CH), and 10.17 (1 H, d, NH); $^3J_{NH,CH}$ 11.8 Hz.

Ring Transformation of the Pyridopyrimidines (**3**).—*General procedure.* Ethyl 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine-3-acetates (**3**) (10 mmol), obtained by the literature methods,[2,3] were added to freshly prepared sodium ethoxide solution, made from sodium (0.69 g) and 'super-dry' ethanol (15 ml). The solution was stirred for the required period (10—20 min) and worked up. Products were separated by the respective procedures above.

Thus a 10-min reaction, starting from (**3e**), and worked up according to procedure *A*, resulted in a 32% yield of the pyridylpyrrolinone (**5a**) and 28% unchanged pyridopyrimidine. A 20-min reaction of (**3a**) gave 54% of the pyridylpyrrolinone (**5a**) and 14% unchanged pyridopyrimidine.

Reactions starting from 6-substituted pyridopyrimidines (**3e**, **f**, **h**, and **m**), and worked up according to procedure *C*, gave the pyridylpyrrolinones (**5e**, **f**, **h**, and **m**) in 68, 68, 63, and 57% yield, respectively. The starting pyridopyrimidines could not be detected in the reaction mixtures after 10 min.

Ring Transformation of the Pyridylpyrrolinone (**5a**).—Ethyl 5-oxo-1-(2-pyridyl)-4,5-dihydropyrrole-3-carboxylate (**5a**) (10 mmol), obtained according to the literature method,[3] was added to freshly prepared sodium ethoxide solution, made from sodium (0.69 g) 'super-dry' ethanol (15 ml). The reaction mixture was stirred for 20 min at room temperature and worked up by procedure *A*. In this way a 14% yield of the pyridopyrimidine (**3a**) and 54% unchanged pyridylpyrrolinone (**5a**) were obtained.

Separation of the Geometric Isomers of the Succinates (**1r**, **s**, **t**, *and* **u**).— The ethoxycarbonyl-substituted succinates (**1r**, **s**, **t**, and **u**), obtained according to the literature method,[14] were *E*–*Z* isomeric mixtures. In some cases the geometric isomers were separated. The *E* isomers were obtained by repeated crystallizations, the *Z* isomers by column chromatography [silica gel (0.063—0.25 mm mesh); eluant benzene], and by crystallization. The products with their m.p.s (°C) are as follows. (*E*)-(**1r**), 62—64 (EtOH); (*E*)-(**1s**), 128—130 (EtOH); (*Z*)-(**1s**), 104—106 (MeOH); (*E*)-(**1t**), 146—148 (EtOH); (*Z*)-(**1t**), 108—111 (EtOH); (*E*)-(**1u**), 144—146 (EtOH); (*Z*)-(**1u**), 63—66 (EtOH).

Cyclization of the Succinates (**1r**, **s**, **t**, *and* **u**).—(1) *In Dowtherm A.* Diethyl 2-[(ethoxycarbonyl-2-pyridyl)amino-methylene]succinates (**1r**, **s**, **t**, and **u**) (3.5 g, 10 mmol) were

added to stirred hot Dowtherm A (50 ml) and the mixture was stirred at 250 °C for 30 min. Compound (**1r**) was treated for 1.5 h. [In (**1r**) very strong double hydrogen-bonding exists.[14] This may cause the lower reactivity, and poorer yields.]

Work-up. The reaction mixtures were diluted with light petroleum (*100—120* °C) (100 ml) and shaken with 2.5% hydrochloric acid (3 × 20 ml). The aqueous acidic phase was neutralized, extracted with benzene, and the extract was dried (Na_2SO_4) and evaporated to obtain the pyridopyrimidines (**3r**, **s**, **t**, and **u**). The Dowtherm A—light petroleum phase was extracted with 20%, and then with conc. hydrochloric acid, the combined acidic phases were neutralized with $NaHCO_3$ and extracted with benzene, and the extract was dried (Na_2SO_4) and evaporated to obtain the pyridylpyrrolinones (**5s**, **t**, and **u**). The pyridylpyrrolinones obtained in this way contained 40—45% of the isomeric (**6s**, **t**, and **u**). Yields are given in Table 3. Products and m.p.s (°C) are as follows, from (**1r**): (**3r**), 130—133 (CCl_4); from (**1s**): (**3s**), 105—108 (EtOH) and (**5s**), 143—145 (EtOH); from (**1t**): (**3t**), 98—101 (EtOH) and (**5t**), 123—133 (EtOH); from (**1u**): (**3u**), 45—51 [purified through the hydrochloride salt, m.p. 214—216 °C (EtOH)] and (**5u**), 122—132 (EtOH).

(2) *In* $POCl_3$–PPA. The succinates (**1r**, **s**, **t**, and **u**) (7.0 g 20 mmol) were cyclized in phosphoryl trichloride (60 mmol) and polyphosphoric acid (0.6 ml) and then treated with absolute ethanol (20 ml) in the usual manner.[2]

Work-up procedures. The reaction mixture of (**1r**) was diluted with water (100 ml) and extracted with benzene (3 × 30 ml). The combined extract was washed with 5% hydrochloric acid, the washings were added to the aqueous layer, the combined aqueous acidic layer was neutralized with $NaHCO_3$ and extracted with benzene, and the benzene extract was dried (Na_2SO_4) and evaporated. From the residue (5.0 g), consisting of (**3r**) and 2-amino-3-ethoxycarbonylpyridine, compound (**3r**) (1.82 g, 30%) was obtained by fractional crystallization from ethanol.

Compound (**3s**) crystallized from the corresponding reaction mixture as the hydrochloride salt (0.6 g, 9%), m.p. 202—206 °C (EtOH).

Compound (**3t**) crystallized from the corresponding reaction mixture as the hydrochloride salt (3.74 g, 55%), m.p. 182—186 °C (EtOH). The filtrate was diluted with water (100 ml) and extracted with light petroleum (b.p. 100—120 °C) to obtain unchanged (**1t**). The aqueous layer was neutralized and extracted with chloroform. From the chloroform extract 2-amino-5-ethoxycarbonylpyridine was extracted with 5% hydrochloric acid. The chloroform layer was then evaporated to obtain an additional crop of (**3t**) (0.6 g, 10%).

Compound (**3u**) crystallized from the reaction mixture as the hydrochloride salt (1.3 g, 19%), m.p. 214—216 °C (EtOH). The filtrate was diluted with water (100 ml) and extracted with benzene. The extract, as shown by t.l.c. investigation, contained a series of compounds, but the pyridylpyrrolinone (**5u**) was not detected. Authentic (**5u**), on being heated in a $POCl_3$–PPA mixture, gave a series of decomposition products which, by their R_F values, seemed to be identical with the unidentified components of the benzene extract, indicating that (**5u**) was probably formed but immediately decomposed under the conditions of the ring closure.

(3) *In ethanolic sodium ethoxide.* Each of the compounds (**1r**, **s**, **t**, and **u**) was cyclized in the usual manner (see General Procedure, above).

The succinates (**1r**) and (**1t**) precipitated from the reaction mixture in the form of their sodium salts and produced the cyclic materials only in low yields: (**1r**) gave (**3r**) in 9% yield, (**1t**) gave (**3t**) and (**5t**) in 2 and 11% yield, respectively.

Compound (**1s**) and (**1u**) dissolved in ethanolic sodium ethoxide, and cyclized in good yields. The reaction mixture of (**1s**) was worked up by procedure *A* but, instead of 2.5% hydrochloric acid, 5% hydrochloric acid was used. In this way (**3s**) (2.8 g, 46%) and (**5s**) (0.39 g, 6.4%) were obtained.

The reaction mixture of (**1u**) was worked up by procedure *C* to obtain (**5u**) (3.1 g, 51%).

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