Nitrogen Bridgehead Compounds. Part 5. Cyclization of 2-(2-Pyridylaminomethylene)-succinates and -glutarates

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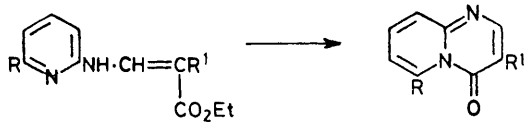
A study has been made of the cyclization reactions of some 2-(2-pyridylaminomethylene)-succinates (7) and -glutarates (8) in phosphoryl chloride–polyphosphoric acid. In the cyclization of the succinates (7) we have found that of the possible cyclic products pyrido[1,2-*a*]pyrimidines (9) and pyridylpyrrolinones (13) are formed, and the latter, subsequently, may form pyridylpyrroles (15) although the reaction conditions favour the formation of pyridopyrimidines (9). The ratio of pyridopyrimidines (9) and pyridylpyrroles [(13) : (15)] was independent of the geometry of the starting succinates (7), but was dependent upon the substituent of the pyridine ring, and on its position. Substituents in position 6 hindered the formation of pyridopyrimidines (9) while those in position 3 inhibited the formation of pyridylpyrrolinones (13). From the homologous glutarates (8) only pyrido[1,2-*a*]pyrimidines (10) are formed.

In our earlier publications [1-3] we have discussed the cyclization of acrylates (1)—(3) in phosphoryl chloride–polyphosphoric acid, which lead to the pyrido[1,2-*a*]-pyrimidines (4)—(6) in good yield (Scheme 1).



(1) R^1 = Me
(2) R^1 = Ph
(3) R^1 = CO_2Et

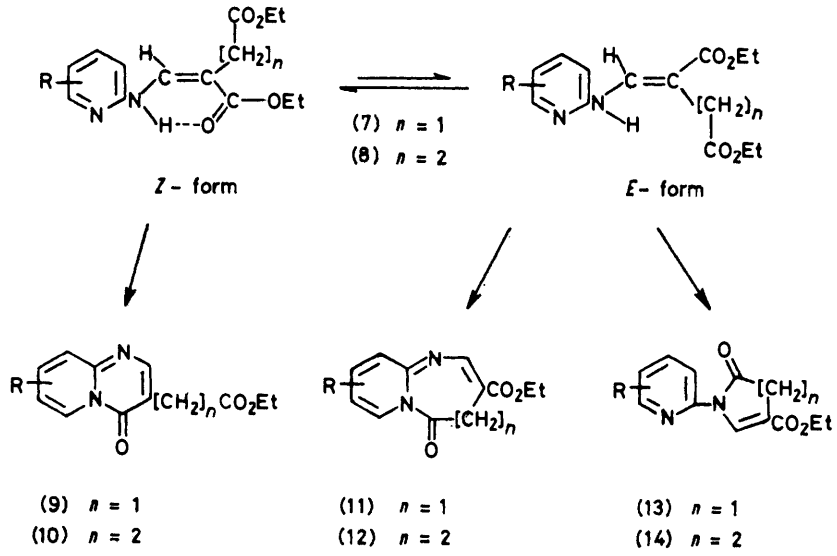
(4) R^1 = Me
(5) R^1 = Ph
(6) R^1 = CO_2Et

SCHEME 1

glutarates (8) were expected to give rise to additional cyclic products (see Scheme 2).

We have investigated which of the possible cyclic products are formed and the effect on ring closure of different substituents in different positions of the starting materials (7) and (8).

Preparation and Investigation of the Starting Succinates (7) *and Glutarates* (8).—Diethyl 2-formylsuccinate [4] and diethyl 2-formylglutarate [5] reacted readily with the variously substituted 2-aminopyridines. The condensation was carried out in organic solvents (CH_2Cl_2 or MeOH) under reflux conditions, or without solvent at a temperature of 110—130 °C. Using the above method 15 differently substituted succinates (7a—p) and 3 glutarates (8a, e, m) have been prepared (see Experimental section). In a reaction analogous to the prepar-



(7) *n* = 1
(8) *n* = 2

Z- form

E- form

(9) *n* = 1
(10) *n* = 2

(11) *n* = 1
(12) *n* = 2

(13) *n* = 1
(14) *n* = 2

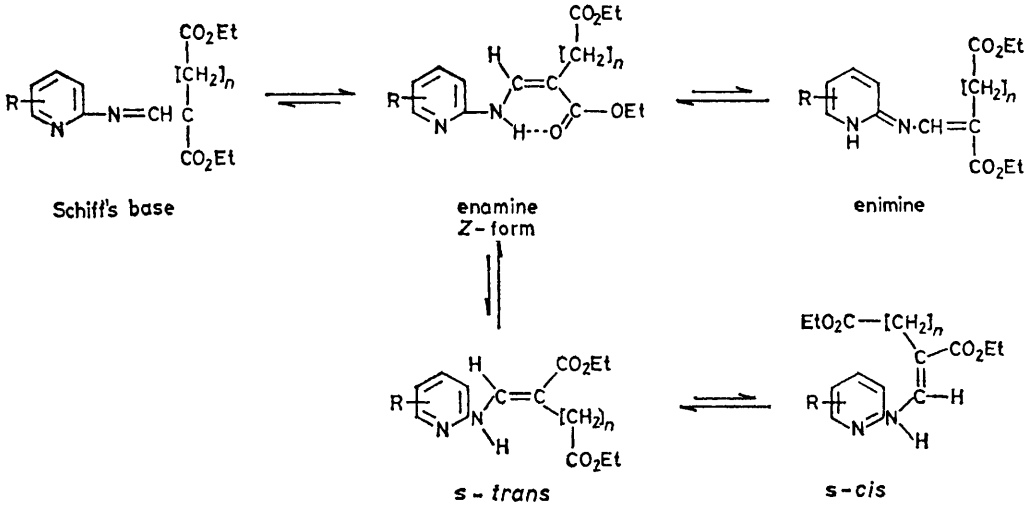
SCHEME 2

This paper deals with the cyclization of the succinates (7) and glutarates (8) [homologues of the malonates (3)] under similar conditions. The succinates (7) and

[1] Z. Mészáros, J. Knoll, P. Szentmiklósi, Á. Dávid, G. Horváth, and I. Hermecz, *Arzeim.-Forsch.*, 1972, **22**, 815.
[2] G. Náray-Szabó, I. Hermecz, and Z. Mészáros, *J.C.S. Perkin I*, 1974, 1753.
[3] I. Hermecz, Z. Mészáros, L. Vasvari-Debreczy, A. Horváth, G. Horváth, and M. Pongor-Csákvári, *J.C.S. Perkin I*, 1977, 789.
[4] W. Wislicenius, E. Böklen, and F. Reuthe, *Annalen*, 1908, **363**, 340.
[5] J. Biggs and P. Sykes, *J. Chem. Soc.*, 1959, 1849.

ation of the malonate (3),[6] reaction of diethyl 2-ethoxymethylenesuccinate [7] with 2-aminopyridines failed to give the succinates (7)].

The condensation products (7) and (8) may exist in three different tautomeric forms (*i.e.* Schiff's base, enamine, or enimine) each of which exists as different geometric isomers (see Scheme 3). ^{1}H N.m.r. spectra of the condensation products provided information on their tautomeric form, and showed clearly that it is the enamine form [(7) and (8)] which predominates. [Methylene protons of the $=C-CH_2-CO_2$ moiety in the succinate (7) appear as a singlet, while those belonging to the $-NH-CH=$ moiety give rise to two doublets. After addition of deuterium oxide the NH signal disappears, and the $-CH=$ proton appears as a singlet. A similar phenomenon was observed with the glutarate (8).]



R	R
(a) H	(i) 5-Cl
(b) 3-Me	(j) 3,5-Cl_2
(c) 4-Me	(k) 3-NO_2
(d) 5-Me	(l) 5-NO_2
(e) 6-Me	(m) 6-NHAc
(f) 4,6-$(Me)_2$	(n) 5-$CONH_2$
(g) 3-OH	(p) 5,6-$(CH{=}CH)_2$
(h) 6-OH	

SCHEME 3

In the condensation reaction, mixtures of the *E* and *Z* geometric isomers of the succinates (7) and the glutarates (8) are formed, the *E* isomers generally predominating. The geometric isomers can be separated from their isomeric mixtures by fractional crystallization or by column chromatography. Geometric isomers of the succinates (7) and the glutarates (8) can readily be distinguished and identified on the basis of their ^{1}H n.m.r. spectra. The NH proton of the *E* isomers resonates in the range $\delta = 7$—9 while that of the *Z* isomers resonates over $\delta = 10$, which indicates a chelate ring structure. The coupling constant $J_{NH-CH=}$ = 10—13 Hz suggests the presence of the s-*trans* conformer in the *E* isomers. The geometric isomers of the succinates (7) can also be distinguished on the basis of their $=C-CH_2-CO-$ methylene singlet, which appear in the *Z* isomer in the range $\delta = 3.2$—3.4, and in the *E* isomer in the range $\delta = 3.4$—3.6. By measuring the intensity of these singlets it was also possible to determine the approximate ratio of isomers in the isomeric mixtures.

For some succinates (7) we investigated the influence of solvent on the ratio of the isomers. Pyridine as solvent favours formation of the *E* isomer while nitromethane as solvent favours the *Z* isomer (see Table 1).

TABLE 1

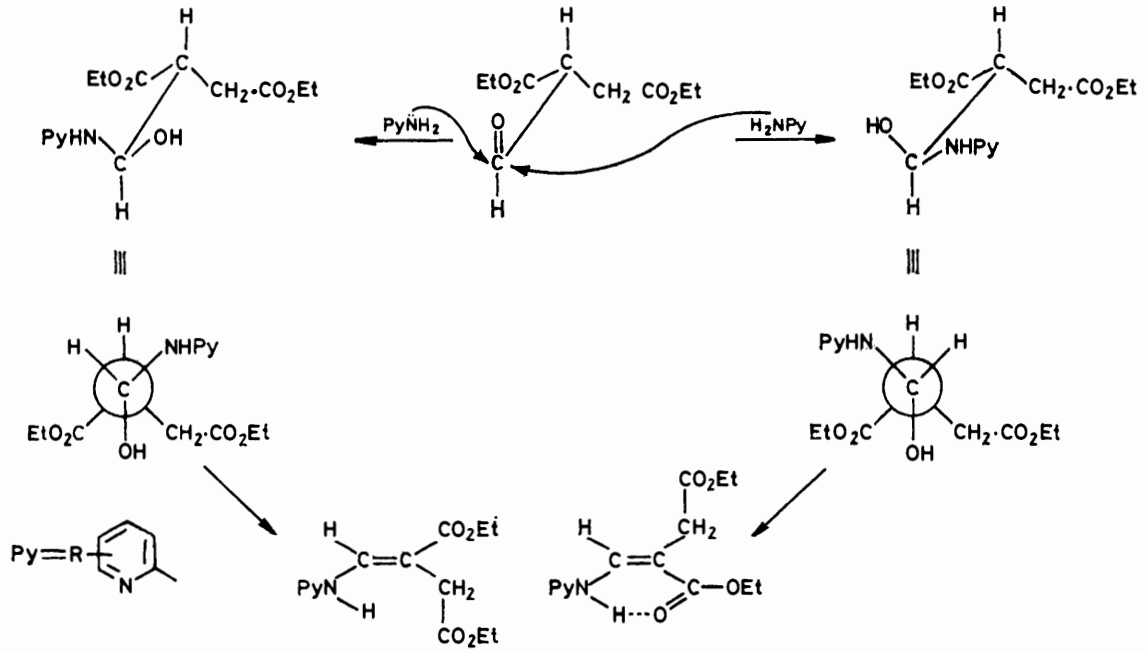
The ratio of *E* and *Z* isomer of the succinates (7) in the reaction of 2-aminopyridines and diethyl 2-formylsuccinate at 80 °C

	Solvent					
	CCl_4 *		Pyridine		$MeNO_2$	
Pyridines	*E*%	*Z*%	*E*%	*Z*%	*E*%	*Z*%
2-Amino	70	30	92	8	68	32
2-Amino-6-methyl	78	22	100	0	61	39
2-Amino-5-methyl	71	29	90	10	48	52
2-Amino-4-methyl	73	27	91	9	56	44
2-Amino-3-methyl	81	19	100	0	36	64
2-Amino-5-chloro	78	22	100	0	76	24
2-Amino-5-nitro		†	100	0	47	53

* At the boiling-point. † 2-Amino-5-nitropyridine does not dissolve.

[6] G. R. Lappin, *J. Amer. Chem. Soc.*, 1948, **70**, 3348.
[7] P. H. Payot, *Helv. Chim. Acta*, 1959, **42**, 1356.

Although no isomerization occurred under the conditions employed, it does in the presence of acid or alkali or through the effect of heat. In equilibrium mixtures the *Z* isomer predominates.



SCHEME 4

The predominance of the thermodynamically less stable *E* isomer in the reaction mixtures indicates that generally steric approach control is present in the first step of the addition–elimination reaction (see Scheme 4).

It may be noted in connection with the different tautomeric forms of the succinate (7) and glutarate (8) that the Schiff's base character of these compounds must be more pronounced than that of the malonate (3) because whilst the latter easily forms salts, *e.g.* with hydrochloric acid, the former decompose under similar reaction conditions. At the same time the pyrido-[1,2-*a*]pyrimidine derivatives (9) and (10) can be derived [8] from only the 'enimine' tautomeric form of the succinate (7) and glutarate (8).

Ring Closure in Phosphoryl Chloride–Polyphosphoric Acid.—As mentioned earlier the succinates (7) and glutarates (8) were expected to give rise to several types of cyclic products [(9)—(14), Scheme 2]. Of these cyclic products formally pyrido[1,2-*a*]pyrimidine (9) and (10) can only be derived from the *Z* isomer of the starting materials while pyrido[1,2-*a*][1,3]diazepine (11), pyrido-[1,2-*a*][1,3]diazocine (12), pyridylpyrrolinone (13), and pyridylpyridone (14) only from the *E* isomer. The substituent of the pyridine ring may also effect the route of the ring closure.

Ring closure of the 15 differently substituted succinates (7a—p) and three glutarates (8a, e, m) were carried out by heating them in $POCl_3$–PPA (PPA = polyphosphoric acid) solution for 2.5 h. The ring closures were in most cases carried out starting from both the *E* and *Z* geometric isomers of the succinates (7) and glutarates (8).

T.l.c. investigations of the reaction mixtures of the succinates (7) showed that they produced one, two, or three different products depending on the substituent R. These could be separated on the basis of their different basicities and solubilities, and were identified by analytical and spectroscopic methods. The main product proved to be the pyrido[1,2-*a*]pyrimidine (9). In addition to pyridopyrimidine (9) some succinates (7) gave rise also to pyridyl-pyrrolinones (13) and/or pyridylpyrrole (15). There is some evidence to indicate that the pyridylpyrrole (15) formed from the pyridylpyrrolinone (13) by way of OH ⟶ Cl exchange. The succinate (7a), which during a 2.4 h reaction period gave only the pyridylpyrrole (15a), for a shorter time (1.5 h) also gave the pyridylpyrrolinone (13a). The pyridylpyrrolinones (13a, f) treated with $POCl_3$ were gradually converted into the pyridyl-pyrroles (15a, f). Table 2 presents the results of this ring closure.

Since the *E*- and *Z*-isomers, and mixtures of the two, gave similar yields and ratios of the various cyclic products isomerization of the starting material is more rapid than the cyclization reactions.

Table 2 clearly shows that substituents on the pyridine ring have a considerable effect on the route of the ring closure.

The cyclization in $POCl_3$–PPA favours the formation of the pyridopyrimidine (9). The pyridylpyrrolinone (13) and the pyridylpyrrole (15) are usually obtained in low percentage yield. However, from the succinates

[8] M. Shur and S. S. Israelstam, *J. Org. Chem.*, 1968, **33**, 3015.

(7e, f, p) which contain a 6-substituent, the pyridopyrimidines (9e, f, p) and the pyridylpyrroles (13)

TABLE 2

Cyclization of the succinates (7) and the glutarates (8)

(7) $n = 1$ / (8) $n = 2$ → (9) $n = 1$ / (10) $n = 2$ → (13) + (15)

Starting material	% Yield of (9) or (10)	% Yield of (13)	% Yield of (15)
(7a; H)	82		4
(7b; 3-Me)	92		
(7c; 4-Me)	85	4	
(7d; 5-Me)	83		4
(7e; 6-Me)	42		40
(7f; 4,6-Me_2)	40	19	19
(7g; 3-OH)	80		
(7h; 6-OH)		Decomp.	
(7i; 5-Cl)	65		3
(7j; 3,5-Cl_2)	65		
(7k; 3-NO_2)	42		
(7l; 5-NO_2)	40		
(7m; 6-NHAc)		Decomp.	
(7n; 5-$CONH_2$)			
(7o; 5-CN) [from (3n)]	71		
[7p; 5,6-(CH=CH)$_2$]	42		16
(8a; H)	81		
(8e; 6-Me)	75		
(8m; 6-NHAc)		Decomp.	

(9a) m.p. 115—116, HCl m.p. 239—240; (15a) m.p. 43—46, b.p. 160—170/0.8 mmHg; (9b) m.p. 88—90, HCl m.p. 171—172; (9c) m.p. 119—120, HCl m.p. 206—208; (13c) m.p. 157—158; (9d) m.p. 129—130, HCl m.p. 224—225; (15d) m.p. 54—56, b.p. 165—170/0.7 mmHg; (9e) m.p. 86—88, HCl m.p. 223—224; (15e) m.p. 35, b.p. 165—170/0.8 mmHg, $HClO_4$ m.p. 193—195; (9f) m.p. 96—98, HCl m.p. 171—173; (15f) m.p. 56—59, b.p. 170—180/1.0 mmHg; (13f) m.p. 122—123; (9g) m.p. 175—177, HCl m.p. 284—286; (9i) m.p. 141—142, HCl m.p. 218—219; (15i) m.p. 87—89, b.p. 180/0.8 mmHg; (9j) m.p. 127—129; (9k) m.p. 114—116; (9l) m.p. 132—136, HCl m.p. 212—214; (9o) m.p. 184—185; (9p) m.p. 121—122, HCl m.p. 213; (15p) m.p. 78—79; (10a) m.p. 103—105, HCl m.p. 187—189; (10e) m.p. 91—93, HCl m.p. 168—170°.

and (15e, f, p) are formed in nearly equal proportions. This can be explained by the steric effect of the 6-substituent which, hindering ring closure onto the adjacent nitrogen atom, makes ring closure on the two nitrogen atoms (pyridine-nitrogen and amino-nitrogen) roughly equivalent.

From the succinates (7b, g, j) which are substituted in the 3-position no pyridylpyrroles [(13) or (15)] are formed since the substituent inhibits the ring closure onto the neighbouring amino-nitrogen.

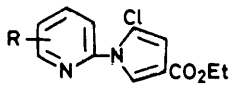
The pyridylpyrroles (13) or (15) are not formed from the succinates (7k, l) which contain a strong electron-withdrawing group (NO_2). From these starting materials the pyridopyridines (9k, l) are also formed in poor yield.

The pyridine ring substituent also has an effect on the OH ⟶ Cl exchange of the initially formed pyridylpyrrolinone (13). The OH ⟶ Cl exchange of pyridylpyrrolinone (13c) and (13f) which contain a 4-methyl substituent proceeds only after a long reaction time (13f) or does not occur even after repeated heating in $POCl_3$–PPA (13c).

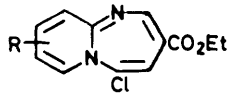
* See Notices to Authors No. 7, Index issue, 1977 for details of the Supplementary Publications scheme.

The cyclization of the glutarates (8) was performed under similar conditions. The glutarate (8m) decomposed in a similar fashion to the homologous succinate (7m). The glutarate (8a, e) gave only one product, the pyrido[1,2-*a*]pyrimidine (10a, e).

Spectroscopic Evidence for Ring-closured Products.— U.v. spectra for the pyrido[1,2-*a*]pyrimidines (9) and (10) are practically identical with that [2] of the 3-methylpyrido[1,2-*a*]pyrimidine (4). In the ^1H n.m.r. spectra of pyrido[1,2-*a*]pyrimidines (9) and (10) the 6-proton is deshielded (δ 8.90—9.30) compared to the other pyridine ring protons (δ 6.11—7.93). In the pyrido[1,2-*a*]-pyrimidines (9) and (10), the 2-H gives rise to a singlet in the range δ = 8.10—8.50.



(15)



(16)

When deciding between structures (11) and (13) and (15) and (16) the following evidence was taken into consideration. In structure (11) the chromophoric system is similar to that of pyridopyrimidine (9). The u.v. spectra of the product and pyridopyrimidine (9), however, differ considerably.

In structure (11) too, the effect of the ring carbonyl group should result in deshielding of the 6-H of the pyridine ring. However in the ^1H n.m.r. spectrum of the product deshielding of the 3-H of the pyridine ring was observed; [9] this is in agreement with structure (13).

Structure (15) for the chloro-derivatives is supported by their u.v. spectra. Comparing structures (16), (15), and (9), pyrido[1,2-*a*][1,3]diazepine (16) has the most extended conjugated π electron system. However, while pyrido[1,2-*a*]pyrimidines (9) have $\pi \rightarrow \pi^*$ $\lambda_{max.}$ = 349—395 nm the chloro-derivatives have $\lambda_{max.}$ = 268—285 nm, which although inconsistent with structure (16), is in agreement with that of (15).

EXPERIMENTAL

I.r. spectra were measured for KBr pellets with a Zeiss UR-20 spectrometer, u.v. spectra for ethanolic solutions with a Unicam SP 800 spectrometer, and n.m.r. data with a Perkin-Elmer R 12 spectrometer ($SiMe_4$ was used as a standard in $CDCl_3$). Analyses for the products agreed with calculated figures; details of these together with i.r., u.v., and n.m.r. spectral results are given in Supplementary Publication No. 22212 (7 pp.).*

Preparation of the Succinates (7) *and the Glutarates* (8).— *Method A.* The *aminopyridine* (0.1 mol) and diethyl 2-formylsuccinate or diethyl 2-formylglutarate (0.1 mol) were boiled in dichloromethane (50 ml) for 3 h with removal of water. The solution was evaporated and the residue was crystallized from ethanol [except the succinate (7b) which was crystallized from light petroleum]; yield 82—89%. [For the preparation of the succinate (7m) 500 ml of dichloromethane was used.]

Method B. The *aminopyridine* (0.1 mol) and diethyl

[9] P. Dvortsák, G. Náray-Szabó, and L. Vasvári-Debreczy, *Z. Naturforsch.*, 1975, **30b**, 784.

2-formylsuccinate (0.1 mol) were boiled in methanol (200 ml) for 6 h. The solution was evaporated *in vacuo*. The residue was dissolved in $CHCl_3$, washed with 5% $NaHCO_3$ solution and water, dried, evaporated, and crystallized (yield 68—70%) [succinate (7g) from benzene; succinate (7h) from carbon tetrachloride].

were crystallized from ethanol, the parent bases liberated in the usual manner, and crystallized from ethanol [(9a—e), (9i—p), (10a, e, m)], carbon tetrachloride (9f), or benzene (9g).

The filtrate was diluted to three times its volume with water and extracted with benzene (3 × 200 ml). The

TABLE 3

Diethyl 2-(2-pyridylaminomethylene)-succinates (7) and -glutarates (8)

Compound	Method (isomer)	Isomer	M.p. (°C)	N.m.r. data		
				–CO–CH_2–C=	NH	J_{NH-CH}/Hz
(7a)	A (*E*)	(*E*)	117—118	3.48	8.10	13
	D (*Z*)	(*Z*)	Oil	3.26	10.35	12
(7b)	A (*E*)	(*E*)	61—62	3.52	8.30	12
	D (*Z*)	(*Z*)	Oil	3.27	10.40	11
(7c)	A (*E*)	(*E*)	125—126	3.46	8.10	12
	D (*Z*)	(*Z*)	Oil	3.24	10.28	13
(7d)	A (*E*)	(*E*)	122—123	3.46	8.00	12
	D (*Z*)	(*Z*)	Oil	3.24	10.37	12
(7e)	A (*E*)	(*E*)	99—100	3.44	8.00	13
	D (*Z*)	(*Z*)	Oil	3.28	10.25	12
(7f)	A (*E*)	(*E*)	138—140	3.44	7.95	12
	D (*Z*)	(*Z*)	Oil	3.21	10.32	12
(7g)	B (*Z* + *E* 65 : 35)	(*E*)		3.49	7.90	?
		(*Z*)	151—153	3.28	10.45	13
(7h)	B (*Z* + *E*)	(*E*)				
		(*Z*)	124—127	3.23	10.15	12
(7i)	A (*E*)	(*E*)	138—140	3.46	8.30	12
	D (*Z*)	(*Z*)	Oil	3.24	10.58	11
(7j)	A (*Z*)	(*Z*)	120—122	3.28	10.75	11
(7k)	C (*Z*)	(*Z*)	87—89	3.34	12.45	11
(7l)	C (*Z* + *E* 66 : 34)	(*E*)	163—166	3.50	8.85	11
		(*Z*)	109—111	3.29	10.75	11
(7m)	C (*Z* + *E* 65 : 35)	(*E*)	170—172	3.47	8.10	12
		(*Z*)	126—129	3.24	10.25	12
(7n)	C (*Z* + *E*)	(*E*)	207	3.49	9.85	12
		(*Z*)	164—166	3.28	10.50	11
(7p)	C (*Z* + *E*)	(*E*)		3.54	?	?
		(*Z*)	93—95	3.33	10.52	12
(8a)	A (*E*)	(*E*)	112—114	2.64	8.45	10
	D (*Z*)	(*Z*)	Oil	2.56	10.24	12
(8e)	A (*E*)	(*E*)	62—64	2.63	8.15	13
	D (*Z*)	(*Z*)	Oil	2.54	10.32	12
(8m)	A (*E* + *Z*)		Oil			

Method C. The *aminopyridine* (0.1 mol) and diethyl 2-formylsuccinate (0.1 mol) were stirred between 100 and 110 °C for 3 h and the product was crystallized from ethanol.

Method D. The *E*-isomer of the succinate (7) or the glutarate (8) was heated to above its melting point and was held for 7 h at 130 °C. The *Z*-isomer of the succinate (7) or glutarate (8) was separated from the mixture (containing 20—28% of the *E*-isomer and 80—72% of the *Z*-isomer) by means of column chromatography [on silica gel (0.063—0.125 mm diam); eluant benzene]. Separation of the *E* and *Z* isomers of (7l—n) was carried out by fractional crystallization from ethanol [(7l, m)] or methanol [(7n)]. Table 3 lists the succinates (7) and glutarates (8) which were prepared.

Cyclization of the Succinates (7) *and the Glutarates* (8).—The succinate (7) or glutarate (8) (0.5 mol) was dissolved in phosphoryl chloride (1.5 mol) at 110—120 °C and polyphosphoric acid (15 ml) was added to the solution dropwise during 10—15 min. After termination of the gas evolution (after about 2.5 h) the mixture was treated at 80—100 °C with ethanol (500 ml). On cooling the mixture, the pyrido-[1,2-*a*]pyrimidines (9) or (10) precipitated as hydrochloride salts, or sometimes as the parent bases [(9j, o)]. The salts

benzene solution was dried (Na_2SO_4) and evaporated to give the pyridylpyrroles [(13) and/or (15)] which were purified by vacuum distillation [(15a, d—f, i)], crystallization from ethanol [(13c, f), (15p)], or column chromatography.

From the benzene-extracted aqueous phase, after neutralization with Na_2CO_3 and extraction with chloroform, a second crop of pyrido[1,2-*a*]pyrimidines (9) or (10) was obtained. Compounds [(9k, l) which did not precipitate from the original reaction mixture were obtained only in this extraction.] Table 2 shows yields and m.p.s.

Cyclization of Diethyl 2-(2-*Pyridylaminomethylene*)*succinate* (7a).—The method was the same as that described above with a reaction time of 1.5 h; 60% of the pyrido[1,2-*a*]-pyrimidine (9a) and 2% of the pyridylpyrrolinone (13a) m.p. 148 °C (from ethanol), were obtained.

Ethyl 5-*Chloro*-1-(4,6-*dimethyl*-2-*pyridyl*)*pyrrole*-3-*carboxylate* (15f).—The pyridylpyrrole (13f) (2.32 g, 10 mmol) was boiled in phosphoryl chloride–polyphosphoric acid (23 and 0.5 g respectively) for 1 h. The reaction mixture was worked up as described above. After evaporation of the benzene solution the oil obtained was distilled *in vacuo*; an 80% yield of the *chloropyridylpyrrole* (15f) was obtained (see Table 2).

[7/471 *Received*, 17*th March*, 1977]