Nitrogen Bridgehead Compounds. Part 4.[1] 1 → 3 *N* → *C*-Acyl Migration. Part 2 [1]

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Ring closure of 2-substituted 3-(2-pyridylamino)acrylates (1) in phosphoryl chloride–polyphosphoric acid gives pyrido[1,2-*a*]pyrimidines (2), whereas (6-substituted 2-pyridyl) derivatives in Dowtherm A afford pyrido[1,2-*a*]-pyrimidines (2) and 1,8-naphthyridines (3). The 6-substituted pyrido[1,2-*a*]pyrimidines (2) can be converted thermally into 1,8-naphthyridines (3) by 1 → 3 *N* → *C*-acyl migration. Similar acyl migrations can be observed in other such systems.

We have reported [1] that, in contrast to literature data,[2] ethyl 1,4-dihydro-7-methyl-4-oxo-1,8-naphthyridine-3-carboxylate (3b) is not formed directly from diethyl (6-methyl-2-pyridylaminomethylene)malonate (1b) but by way of pyrido[1,2-*a*]pyrimidine (2b), and that compound (2b) is converted into (3b) by 1 → 3 *N* → *C*-acyl migration. We have also shown that, in addition to the pyrido[1,2-*a*]pyrimidines (2h and j),[3] the 1,8-naphthyridines (3h and j) can be prepared from the esters (1h and j).

We now report further experiments conducted in order to establish (i) whether the behaviour of the acrylic acid derivatives (1b, h, and j) also applies to other acrylic acid derivatives (1), (ii) whether ring transformation also occurs with other pyrido[1,2-*a*]pyrimidines (2), and (iii) whether the acyl migration also occurs in other similar ring systems.

Ring closure was carried out in Dowtherm A at 250 °C or in phosphoryl chloride–polyphosphoric acid at 130 °C. The results are summarized in Table 1. Pyrido[1,2-*a*]-pyrimidines and 1,8-naphthyridines were separated on the basis of the differences in solubilities and basicities. In both reactions the same results were obtained from either the *Z*- or the *E*-isomer [if $R^1 \neq CO_2Et$ in (1)] indicating a fast isomerization under the given conditions.

Ring transformations occurred in Dowtherm A at 250 °C and in liquid paraffin at 300—350 °C. The results are presented in Table 2. Isomerization failed with the pyridopyrimidines (2; $R^2 = H$). At temperatures between 250 and 350 °C the starting substances were unaffected and at higher temperatures (350—400 °C) charring occurred. Isomerization was however successful for the compounds (2; $R^2 \neq H$).

The nitrile (2h) was prepared from the carboxamide [4] (2; $R^1 = CO{\cdot}NH_2$, $R^2 = Me$, $R^3 = H$) with phosphoryl chloride. The pyridopyrimidines (2w, x, and y) [5a] were prepared from the corresponding isopropylidene (2-pyridylaminomethylene)malonates.[5a] The pyridopyrimidine (2aa) was prepared from 2-amino-6-methylpyridine and ethyl 3-oxovalerate in phosphoryl chloride–polyphosphoric acid, similarly to (2z),[6] and (2cc) was obtained from (2bb) [6] with piperidine.

Characterization of Pyrido[1,2-a]*pyrimidines and* 1,8-*Naphthyridines.*—Tschitschibabin [7] observed that on boiling pyrido[1,2-*a*]pyrimidines with acids or bases they decompose to the initial aminopyridines, whereas the 1,8-naphthyridine ring system remains stable under similar conditions. The pyrido[1,2-*a*]pyrimidines have lower m.p.s (see Table 2) and dissolve in organic solvents more readily than the corresponding 1,8-naphthyridines.

U.v. spectra. The longest wavelength absorption maximum appears above 350 nm in the case of the pyrido[1,2-*a*]pyrimidines and is below 340 nm in that of the 1,8-naphthyridines (see Table 3).† These bands can be attributed to π–π^* transitions of charge-transfer character. In ethanolic solution a bathochromic shift of about 25 nm can be observed [8] with the pyridopyrimidines when a donor substituent is present in position 6 or an acceptor substituent in position 3. In other positions substituents have smaller effect. The 1,8-naphthyridines exist predominantly in the 4-oxo rather than the 4-hydroxy forms; for example the u.v. spectrum of the 3,7-dimethyl derivative (3m) is very similar to that of the 1-ethyl derivative (4) (see Figure 1). We have obtained similar results with the other 1,8-naphthyridines (3).

I.r. spectra. The stretching band of the carbonyl group in position 4 of the 1,8-naphthyridines appears between 1 615 and 1 680 cm^{-1}, whereas in the pyrido[1,2-a]-pyrimidines it occurs between 1 670 and 1 705 cm^{-1} (see Table 4).

Discussion.—In the ring closure of the acrylic acid derivatives (1), initial cyclization always occurred on the nitrogen atom of the pyridine ring, and was occasionally followed by ring transformation (1 → 3 *N* → *C*-acyl migration). In the ring closures performed in Dowtherm A, the presence of a pyrido[1,2-*a*]pyrimidine could be detected by t.l.c. even when only a 1,8-naphthyridine was isolated. If, however, the pyrido[1,2-*a*]pyrimidine

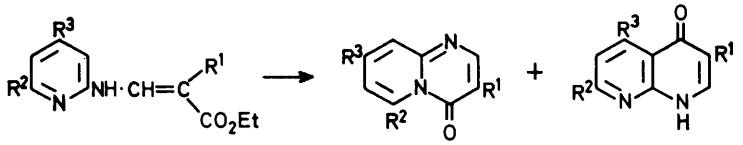
† Tables 3 and 4 and Figures 1 and 2 are available as Supplementary Publication No. SUP 21970 (5 pp.) (see Notice to Authors No. 7, *J.C.S. Perkin I*, 1976, Index issue).

[1] Previous part, Z. Meszaros and I. Hermecz, *Tetrahedron Letters*, 1975, 1019.
[2] G. R. Lappin, *J. Amer. Chem. Soc.*, 1948, **70**, 3348.
[3] H. Antaki, *J. Amer. Chem. Soc.*, 1958, **80**, 3066.
[4] G. Náray-Szabó, I. Hermecz, and Z. Mészáros, *J.C.S. Perkin I*, 1974, 1753.
[5] (*a*) B.P. 1,147,760 (*Chem. Abs.*, 1969, **71**, 49,967a); (*b*) B.P. 1,147,759 (*Chem. Abs.*, 1969, **71**, 70125j).
[6] Z. Mészáros, J. Knoll, P. Szentmiklósi, Á. Dávid, G. Horvath, and I. Hermecz, *Arzeim.-Forsch.*, 1972, **22**, 815.
[7] A. E. Tschitschibabin, *Ber.*, 1924, **57**, 1168.
[8] G. Horváth, Á. I. Kiss, Z. Mészáros, and I. Hermecz, *Acta Chim. Acad. Sci. Hung.*, 1974, **83**, 15.

contained in position 3 a more weakly electron-withdrawing group than the ester group, in Dowtherm A the primary pyrido[1,2-*a*]pyrimidine product could be isolated even in the case of the 6-substituted pyridine leading to a larger quantity of 1,8-naphthyridine. For example compound (1s) in 60 min gave 69.4% (2s) and 18.6% (3s), in 90 min 54.4% (2s) and 41.5% (3s), in 120 min 42.4% (2s) and 51.8% (3s), in 180 min 29.2%

TABLE 1

Ring closure of acrylic esters (1)



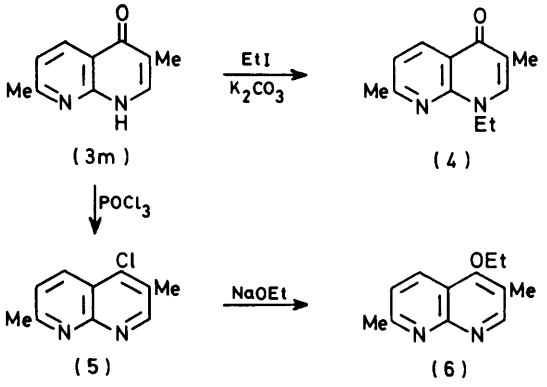
(1) (2) (3)

			Dowtherm A (250 °C)			$POCl_3$–PPA (130 °C)	
R^2	R^3	R^1	2%	3%	Ref.	2%	Ref.
a; H	H	CO_2Et	94	0	*a*	95	*f*
b; Me	H	CO_2Et	0	90	*b*	95	*f*
c; Et	H	CO_2Et	0	43	*c*	80	*f*
d; Me	Me	CO_2Et	0	?	*c*	80	
e; NHAc	H	CO_2Et	0	52	*c*	Decomp.	
f; Br	H	CO_2Et	Decomp.		*b*	No reaction	*f*
g; H	H	CN	?	0	*d*	No reaction	
h; Me	H	CN	?	0	*d*	No reaction	*e*
			0	60 *	*e*		
i; H	H	COMe	82	0	*d*	Decomp.	
j; Me	H	COMe	?	0	*d*	Decomp.	*e*
			13	35			
			0	80 *	*e*		
k; Me	H	$COCF_3$	0	70		40	
l; H	H	Me	94	0		96	*g*
m; Me	H	Me	85	4		85	*g*
n; OH	H	Me	91	0		Decomp.	
o; NHAc	H	Me	60	23		Decomp.	
p; H	H	Et				90	
q; Me	H	Et	62	11		95	
r; H	H	Ph	97	0		85	*g*
s; Me	H	Ph	82	10		98	*g*
t; OH	H	Ph	61	0		Decomp.	
u; NHAc	H	Ph	0	85		Decomp.	

* At 300 °C in paraffin oil.

[a] R. Adams and I. J. Pachter, *J. Amer. Chem. Soc.*, 1952, **74**, 5491. [b] Ref. 2. [c] G. Y. Lesher and M. D. Gruett, Belg. P., 612,258, (*Chem. Abs.*, 1963, **58**, 7953). [d] Ref. 3. [e] Ref. 1. [f] Ref. 6. [g] Ref. 4.

derivatives [see *e.g.* (1m, q, and s) in Table 1]. When the reaction period was longer or the temperature higher



(3m) (4) (5) (6)

SCHEME 1

in the case of the acrylic acid derivatives (1m, n, o, q, s, and t), thermodynamic product control prevailed, (2s) and 61.0% (3s), in 240 min 11.0% (2s) and 85.5% (3s), and in 300 min 8.5% (2s) and 87.2% (3s).

Ring closure of the cyanoacetic acid derivative (1h) took place only above 280 °C, whereas the ring transformation of (2h) occurred even at 250 °C.

The ring transformation of the 6-substituted pyrido-[1,2-*a*]pyrimidines is due to the fact that the 6-substituent and the 4-oxo-group are nearly in the same plane; thus the C(4)–N(5) bond is stretched, and upon transfer of adequate energy 1 ⟶ 3 *N* ⟶ *C*-acyl migration occurs. For example the length of this bond in (2b) is 1.472 Å.[9]

Cyclization is inhibited by the presence of a bulky group such as a bromine atom, in position 6 of the acrylic acid derivative (1)

Ring transformation is affected primarily by R^2 and also by R^1. With respect to R^2, transformation is influenced in the following order: OH < Me < NHAc,

[9] K. Sasvári, J. Csonka-Horvai, and K. Simon, *Acta Cryst.*, 1972, **28B**, 2405.

whereas for R^1 the order is: $CO_2Et \sim CN \sim COCF_3 \sim COCH_3 > Ph > H >$ alkyl.

It is of interest to compare the rate of ring closure (k_1) with that of ring transformation (k_2) in the case of the 6-methylpyridylaminoacrylic acid derivatives (1). The compounds investigated can be classified as follows: (a) $k_1 > k_2$ if R^1 = Me, Et, H, or Ph (in Dowtherm A after a short reaction period, when kinetic control prevails, mainly pyrido[1,2-*a*]pyrimidine is formed); (b) $k_1 \sim k_2$ if $R^1 = CO_2Et$, COMe, or $COCF_3$ (in Dowtherm A essentially only 1,8-naphthyridine can be isolated, even after short reaction periods); and (c) $k_1 < k_2$ if R^1 = CN [cyclization of (1h) can only be carried out above 280 °C, even though ring transformation occurs at 250 °C].

The discrepancies in the literature concerning the chemistry of pyrido[1,2-*a*]pyrimidines and 1,8-naphthyridines may probably be ascribed to a lack of knowledge of this ring transformation.

Richardson and McCarty [10] presumed that the 1,8-naphthyridine (8) was formed in the cyclization of the malonic ester (7) in Dowtherm A. However, the product appears in fact to have been the pyrido[1,2-*a*]pyrimidine (9), as indicated by the similarity of its u.v. spectrum (Figure 2) to those of other pyrido[1,2-*a*]pyrimidines (see Scheme 2).

The observed ring transformation of 6-substituted acrylates (1) may well take place in case of other similar α-amino-heterocycles too (Scheme 3).

TABLE 2

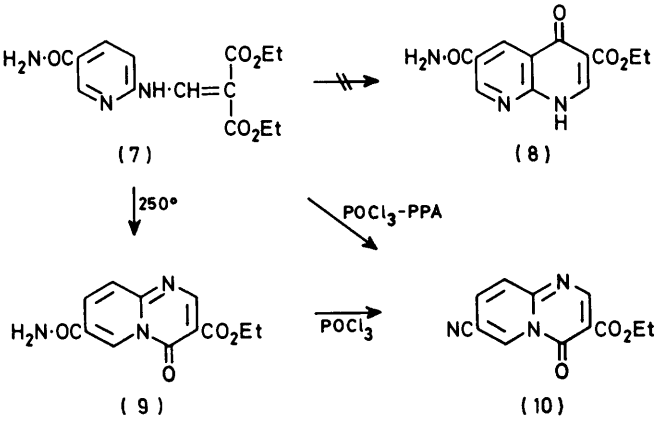
Ring transformations of the pyridopyrimidines (2)

(2) (3)

R^2	R^3	R^1	R^4	Temp. (°C)	Time (min)	(2) m.p. (C°)	(3) m.p. (C°)	Yield (%)
b; Me	H	CO_2Et	H	250	30	98—100	274—277	80
c; Et	H	CO_2Et	H	250	30	88—89	249—250	75
d; Me	Me	CO_2Et	H	250	30	146—147	232—234	80
h; Me	H	CN	H	250	150	206	>300	60
j; Me	H	COMe	H	250	60	129—130	>300	60
k; Me	H	$COCF_3$	H	250	30	172—173	>300	70
m; Me	H	Me	H	340	30	73—74	280	80
n; OH	H	Me	H	350	15	335—338	350—355	60
o; NHAc	H	Me	H	250	200	102—104	322—325	80
q; Me	H	Et	H	325	30	68—70	215—216	70
s; Me	H	Ph	H	345	15	124—125	315—317	100
t; OH	H	Ph	H	345	15	325—326	>360	40
v; Me	H	H	H	350	30	178—179	Decomp.	
w; OH	H	H	H	350	20	290	>360	40
x; NHAc	H	H	H	250	20	166—167	310—315	90
y; Me	H	H	Me	350	25	108—109	320—323	80
z; Et	H	H	Me	350	20	72—73	242—243	80
aa; Me	H	H	Et	350	20	92—94	214—215	70
bb; Me	H	H	Cl	320	20	123—124	Decomp.	
cc; Me	H	H	Pi *	350	10	83—85	210—212	80

* Pi = piperidino.

Conversion of Pyrimido[1,2-a][1,8]*naphthyridines* (12) *into Anthyridines* (13).—Carboni *et al.*[11] have studied the ring closure of the acrylates (11) in polyphosphoric acid



(7) (8) (9) (10)

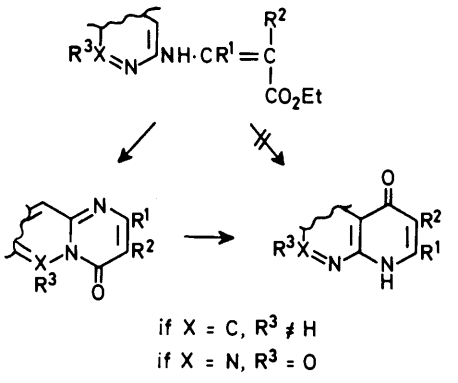
SCHEME 2

at 200 °C, in Dowtherm A at 250 °C, and in liquid paraffin at 300—340 °C. Pyrimido[1,2-*a*][1,8]naphthyridines (12) were obtained under milder conditions than

[10] A. Richardson, jun. and F. J. McCarty, *J. Medicin. Chem.*, 1972, **15**, 1203.

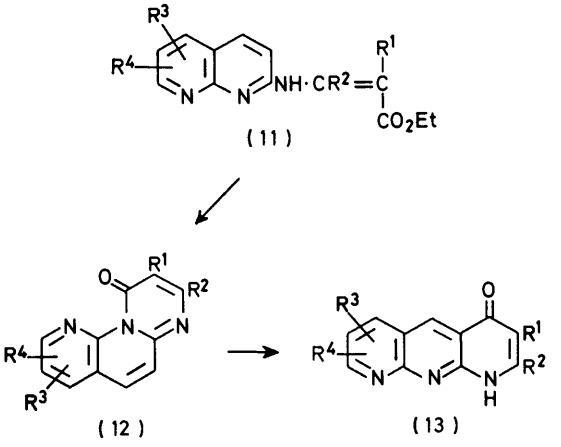
[11] (*a*) S. Carboni, A. Da Settimo, G. Pirisino, and D. Segnini, *Gazzetta*, 1966, **96**, 103; (*b*) S. Carboni, A. Da Settimo, D. Segnini, and I. Tonetti, *ibid.*, 1966, **96**, 1443; (*c*) S. Carboni and A. Da Settimo, *ibid.*, 1967, **97**, 1262; (*d*) S. Carboni, A. Da Settimo, P. L. Ferrarini, I. Tonetti, and D. Bertini, *ibid.*, 1967, **97**, 1274; (*e*) S. Carboni, A. Da Settimo, D. Bertini, and G. Biagi, *ibid.*, 1969, **99**, 677; (*f*) S. Carboni, A. Da Settimo, and I. Tonetti, *J. Heterocyclic Chem.*, 1970, **7**, 875; (*g*) S. Carboni, A. Da Settimo, P. L. Ferrarini, and I. Tonetti, *Gazzetta*, 1971, **101**, 129.

anthyridines (13). Some anthyridines (13) were formed from the corresponding pyrimidonaphthyridines (12) by thermal isomerization in the melt or in solution.



SCHEME 3

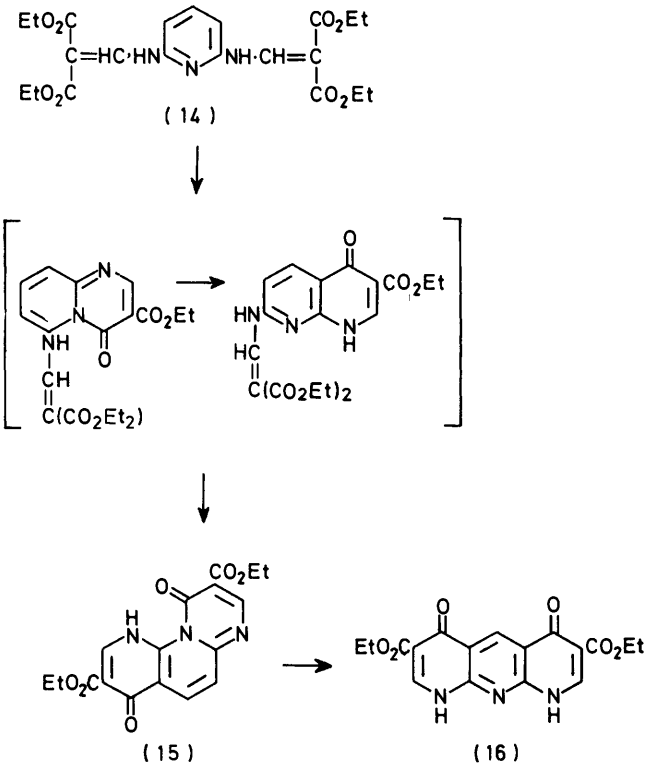
Cyclizations of the malonic esters (11; $R^1 = CO_2Et$), the cyanoacetic esters (11; $R^1 = CN$), and the acetoacetic esters (11; $R^1 = COMe$) were studied in detail by Harper and Wibberley.[12] They obtained either pyrimido[1,2-*a*][1,8]naphthyridines [12a] or anthyridines,[12b] depending on the nature of the starting material. Ring closure was usually carried out in Dowtherm A. However, cyanoacetic acid derivatives could be cyclized only at 330—340 °C in liquid paraffin, to give anthyridines. In the formation of the anthyridines, Harper and Wibberley assumed that cyclization occurred directly on C-3 of the naphthyridine. In our opinion, in the case of the acrylic acid derivatives (11), initial cyclization occurs



on the ring nitrogen atom; this hypothesis is supported by the observation of Carboni *et al.*[11b,c]

Ring closure of the bismalonate (14) (Scheme 4) gave both an anthyridine (16) [11f] (after 6 h) and a pyrimido-[1,2-*a*][1,8]naphthyridine (15) [11g,12a] (after 10—15 min) in Dowtherm A at 250 °C. When we heated compound (15) in Dowtherm A for 6 h, the anthyridine (16) was formed.

If the initial acrylic acid derivative (11) carried a -CH= group instead of N in position 8, or if the N atom was in another position, the initially formed nitrogen bridgehead compounds could not be isomerized to linear products. Thus, we obtained from the quinoline derivative (17a) [10,13] and from the quinoxaline derivative (17c) the corresponding nitrogen bridgehead compounds,



SCHEME 4

but our attempt to isomerize the products (18a and c) in liquid paraffin at temperatures up to 370 °C failed. From the 1,6-naphthyridine derivative (17b) similarly a nitrogen-bridgehead compound (18b) was obtained [14] in Dowtherm A.

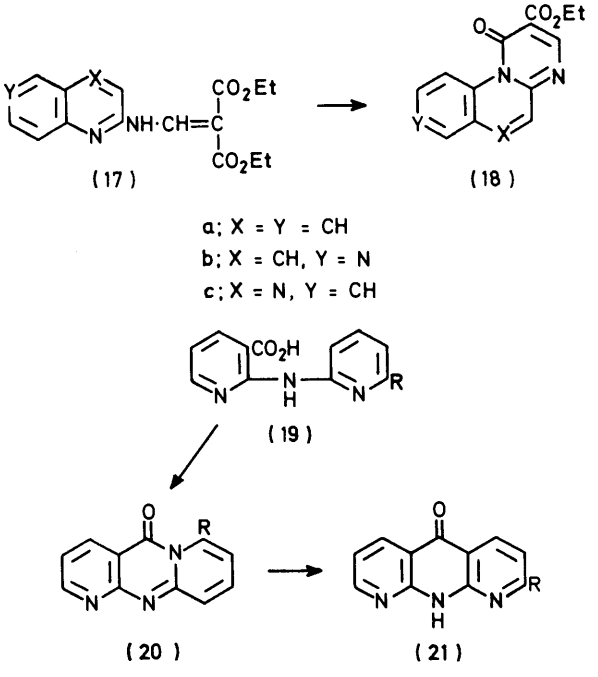
Conversion of Dipyrido[1,2-a:2′,3′-d]*pyrimidines* (20) *into Anthyridines* (21).—From the 2-(2-pyridylamino)-nicotinic acid (19; R = H), Carboni *et al.*[15a] obtained the dipyrido[1,2-*a*:2′,3′-*d*]pyrimidine (20; R = H), which could not be isomerized to the anthyridine (21).[15b] Cyclizations of the amino-derivative [15b] (19; $R = NH_2$) and of the methyl derivative [15c] (19; R = Me) in polyphosphoric acid at 170 °C also afforded the corresponding

[12] J. F. Harper and D. G. Wibberley, *J. Chem. Soc.* (*C*), 1971, (*a*) p. 2985; (*b*) p. 2991.
[13] I. Hermecz, Z. Mészáros, J. Knoll, Á. Horváth, L. Debreczy, P. Dvortsák, and M. Csákvári, Hung.P. 166,577 (Hung. Teljes 9049).
[14] E. M. Hawes and D. K. J. Gorecki, *J. Heterocyclic Chem.*, 1974, **11**, 151.
[15] (*a*) S. Carboni and M. Pardi, *Ann. Chim.* (*Italy*), 1959, **49**, 1228; (*b*) S. Carboni, A. Da Settimo, and D. Segnini, *J. Heterocyclic Chem.*, 1969, **6**, 369; (*c*) S. Carboni, A. Da Settimo, D. Bertini, C. Mori, and I. Tonetti, *ibid.*, 1971, **8**, 637.

dipyridopyrimidines (20). The amino-derivative (20; R = NH_2) could be isomerized to the anthyridine (21) under milder conditions (200 °C in sulphuric acid) than the methyl derivative (21; R = Me) (270 °C in sulphuric acid). The anthyridines (21) were also prepared directly from the appropriate nicotinic acids (19; R ≠ H) under the above conditions.

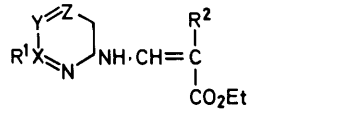
Conversion of Pyrimido[1,2-a]*pyrazines* (23) *into pyrido*-[2,3-b]*pyrazines* (24).—In Dowtherm, the pyrazine derivative (22; R^1 = H) gave [16] the pyrimido[1,2-*a*]-pyrazine (23; R^1 = H). 6-Methoxypyrimido[1,2-*a*]-pyrazine-4-one was formed [5a] from isopropylidene (6-methoxypyrazin-2-ylamino)methylenemalonate, whereas the methoxy-derivative of (22) afforded the pyrido-[2,3-*b*]pyrazine (24).[17] Pyrido[2,3-*b*]pyrazines (24) were also formed [18,19] from other 6-substituted pyrazines (22; R^1 ≠ H), but the 6-methyl derivative (22; R^1 = Me) gave both the pyrimido[1,2-*a*]pyrazine (23; R^1 = Me) and the pyrido[2,3-*b*]pyrazine (24; R^1 = Me).

Conversion of Pyrimido[1,6-a]*pyrimidines* (26) *into Pyrido*[2,3-d]*pyrimidines* (27).—Derivatives of pyrimido-[1,6-*a*]pyrimidine (26) were obtained [20] from the pyrimidine derivatives (25) unsubstituted in position 2, whereas

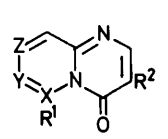


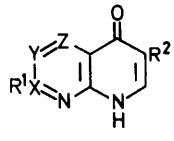
the 2-substituted compounds yielded [21,22a,b] pyrido-[2,3-*d*]pyrimidines (27).

Conversion of Pyrimido[1,2-b]*pyridazines* (29) *into Pyrido*[2,3-c]*pyridazines* (30).—From the pyridazine derivatives (28; XR^1 = N), pyrimido[1,2-*b*]pyridazines (29) were obtained [23a-c,24] in polyphosphoric acid at 100—120 °C or Dowtherm A at 250 °C, whereas the *N*-oxides (28; XR^1 = N ⟶ O) in Dowtherm A gave [23d]



(22) X = C, Y = CH, Z = N
(25) X = C, Z = CH, Y = N
(28) Y = Z = CH, XR^1 = N or N→O





(23) X = C, Y = CH, Z = N, R^1 = H
(26) X = C, Y = N, Z = CH, R^1 = H
(29) Y = Z = CH, XR^1 = N

(24) X = C, Y = CH, Z = N, R^1 ≠ H
(27) X = C, Z = CH, Y = N, R^1 ≠ H
(30) Y = Z = CH, XR^1 = N→O

pyrido[2,3-*c*]pyridazines (30). (In the latter case direct cyclization onto the carbon atom cannot be exluded.)

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 R12 spectrometer (tetramethylsilane standard in $CDCl_3$).

Cyclizations in Phosphoryl Chloride–Polyphosphoric Acid.—The acrylate (1) (0.1 mol) was stirred at 130—135 °C in phosphoryl chloride–polyphosphoric acid (45.6 and 7 g, respectively). After evolution of hydrogen chloride had ceased, the mixture was broken up at 80—100 °C with ethanol (100 ml). The hydrochloride of (2) which precipitated on cooling was filtered off, washed with ethanol, and converted into the base.

If no hydrochloride was precipitated, the mixture was poured into water (300 ml), neutralized with aqueous 20% sodium carbonate, and extracted with chloroform. The extract was then clarified with activated carbon, dried (Na_2SO_4), and evaporated, and the product crystallized (yields in Table 1).

Cyclizations in Dowtherm A.—The *acrylate* (1) (5 g) was added to Dowtherm A (100 ml) at 250—255 °C, then the mixture was stirred for 30 min and cooled quickly to room temperature. The precipitate (3) was filtered off and the filtrate diluted with light petroleum (200 ml). If compound

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(2) was not precipitated, the system was extracted with 5% hydrochloric acid; the extract was neutralized (with aqueous 10% Na_2CO_3) then extracted with chloroform. The dried (Na_2SO_4) solution was evaporated. Yields are in Table 1, m.p.s in Table 2.

Cyclizations in Liquid Paraffin.—The *acrylate* (1) (1 g) was added to liquid paraffin (100 ml) at 300 °C. The mixture was heated for 30 min, then cooled to room temperature, and the product (3) was filtered off and washed with benzene. Yields are in Table 1.

Ring Transformations in Dowtherm A.—After heating Dowtherm A (100 ml) to 250—255 °C, the 6-substituted pyridopyrimidine (2) (5 g) was added and the mixture was heated for the period given in Table 2. After cooling, the precipitated product (3) was filtered off and washed with benzene. M.p.s and yields are in Table 2.

Ring Transformations in Liquid Paraffin.—Liquid paraffin (100 ml) was heated to the temperature given in Table 2, the 6-substituted pyridopyrimidine (2) (1 g) was added, and the mixture was heated for the given period. After cooling and dilution with light petroleum (100 ml) the precipitated (3) was filtered off and washed with benzene. M.p.s and yields are in Table 2.

6-Methyl-4-oxopyrido[1,2-a]*pyrimidine-3-carbonitrile* (2h). — 6-methyl-4-oxopyrido[1,2-*a*]pyrimidine-3-carboxamide [4] (2.03 g) was suspended in dimethylformamide (7.3 g) and phosphoryl chloride (3.1 g) was added dropwise at 15—20 °C. The mixture was stirred for 1 h at 60 °C and for 1 h at 100 °C, cooled, and poured into ice (50 g). The pH of the solution was adjusted to 7 with aqueous 20% sodium carbonate. The precipitated nitrile (2h) (0.9 g) was filtered off; m.p. 206° (from ethanol) (lit.,[3] 207°).

2-Ethyl-6-methylpyrido[1,2-a]*pyrimidin-4-one* (2aa).—2-Amino-6-methylpyridine (10.8 g) and ethyl 3-oxovalerate (14.4 g) were stirred for 3.5 h at 130 °C in phosphoryl chloride (36 ml) and polyphosphoric acid (7 g), then the mixture was broken up (100 ml) between 80—100 °C with ethanol. After cooling the precipitated hydrochloride of (2aa) (15.9 g; m.p. 271°) was filtered off and converted into the *base*, m.p. 92—95° (from ethanol), δ 1.30 (3 H, t, Me), 2.65 (2 H, q, CH_2), 3.06 (3 H, s, 6-Me), 6.23 (1 H, s, 3-H), 6.56—6.80 (1 H, m, 7-H), and 7.30—7.57 (2 H, m, 8- and 9-H) (Found: C, 70.0; H, 6.3; N, 14.8. $C_{11}H_{12}N_2O$ requires C, 70.2; H, 6.4; N, 14.9%).

6-Methyl-2-piperidinopyrido[1,2-a]*pyrimidin-4-one* (2cc). —A solution of piperidine (5.1 g) in dioxan (5 ml) was added dropwise to a solution of the chloro-pyridopyrimidine (2bb) (3.88 g) in dioxan (20 ml) kept at 60 °C, then the mixture was stirred for 1.5 h at 60 °C. After cooling, the precipitated piperidine hydrochloride was filtered off, the filtrate was evaporated, and the residue recrystallized from ethyl acetate–ether, giving the *product* (2cc) (3.5 g); m.p. 83—85°, δ 1.5—1.9 (6 H, m, 3, 4, and 5-H_2 of piperidino), 2.98 (3 H, s, 6-Me), 3.45—3.80 (4 H, m, 2- and 6-H_2 of piperidino), 5.50 (1 H, s, 3 H), 6.30—6.55 (1 H, m, 7-H), 6.92—7.51 (2 H, m, 8- and 9-H) (Found: C, 68.3; H, 7.2; N, 17.3. $C_{14}H_{17}N_3O$ requires C, 69.1; H, 7.1; N, 17.2%).

4-Chloro-3,7-dimethyl-1,8-naphthyridine (5).—The naphthyridone (3m) (1.74 g) was heated in phosphoryl chloride (15 ml) in an oil-bath, the temperature of which was gradually raised from 95 to 130 °C in 35 min. The cooled mixture was poured into ice (50 g), neutralized with aqueous 20% sodium carbonate, and extracted with chloroform (3 × 50 ml). The *chloronaphthyridine* (5) (1.75 g), obtained after evaporation was recrystallized from acetone; m.p. 134—135°, $\lambda_{max.}$ 320 (log ε 3.87), 307 (3.81), and 269 nm (3.70), δ 3.54 (3 H, s, Me), 2.80 (3 H, s, Me), 7.45 (1 H, d), 8.46 (1 H, d), and 8.96 (1 H, s, 2-H) (Found: C, 62.6; H, 4.7; Cl, 18.5; N, 14.5. $C_{10}H_6ClN_2$ requires C, 62.4; H, 4.7; Cl, 18.4; N, 14.5%).

4-Ethoxy-3,7-dimethyl-1,8-naphthyridine (6).—Sodium ethoxide [from sodium (0.23 g) in ethanol (6 ml)] was added to a solution of the chloro-naphthyridine (5) (1.92 g) in ethanol (8 ml). The mixture was stirred for 1 h at room temperature and then evaporated. A solution of the residue in chloroform (30 ml) was washed with water (2 × 30 ml), dried (Na_2SO_4), and evaporated. The resulting *ethoxynaphthyridine* (6) (1.7 g) was recrystallized from light petroleum; m.p. 75—77°, $\lambda_{max.}$ 316.5 (log ε 3.77), 304 (3.77), and 277 nm (3.65), δ 1.50 (3 H, t, Me), 2.44 (3 H, s, Me), 2.79 (3 H, s, Me), 4.21 (2 H, q, O·CH_3), 7.38 (1 H, d), 8.40 (1 H, d), and 8.96 (1 H, s, 2-H) (Found: C, 71.4; H, 7.0; N, 13.9. $C_{12}H_{14}N_2O$ requires C, 71.3; H, 7.0; N, 13.9%).

1-Ethyl-3,7-dimethyl-1,8-naphthyridin-4(1H)-one (4).—After stirring the naphthyridone (3m) (8.7 g) in dimethylformamide (500 ml) in the presence of ethyl iodide (46.5 g) and potassium carbonate (14 g) for 6 h at 100 °C, the mixture was evaporated *in vacuo*. The residue was dissolved in water (1 l) with heating, and the solution was clarified, filtered, and extracted with chloroform (4 × 100 ml). The dried (Na_2SO_4) extract was evaporated. The resulting ethylnaphthyridone (4) (8.3 g) was recrystallized from water and dried (P_2O_5); m.p. 112—113°, $\nu_{max.}$ 1 640 cm^{-1}, $\lambda_{max.}$ 342 (log ε 3.98), 289 infl (3.01), 278 (3.23), and 249 nm (4.35), δ 1.44 (3 H, t, Me), 2.15 (3 H, s, Me), 2.65 (3 H, s, Me), 4.43 2 H, q, N·CH_2), 7.19 (1 H, d), 7.67 (1 H, s, 2-H), and 8.67 (1 H, d) (Found: C, 71.2; H, 6.8; N, 13.9. $C_{12}H_{14}N_2O$ requires C, 71.3; H, 7.0; N, 13.9%).

6-Acetamidopyrido[1,2-a]*pyrimidin-4-one* (2x).—Isopropylidene (6-acetamido-2-pyridylamino)methylenemalonate [5b] (19 g) was added to Dowtherm A (200 ml) at 250 °C, and after 4 min the mixture was quickly cooled to room temperature. The precipitated naphthyridone (3x) was filtered off (0.7 g, 5.5%), m.p. 315° (lit.,[5a] 319—320°), then the filtrate was diluted with light petroleum (800 ml). The precipitated pyridopyrimidone (2x) (10 g, 79%) was filtered off and recrystallized from ethanol; m.p. 166—167 (lit.,[5a] 162.6—164.0°).

Ethyl 7-Carbamoyl-4-oxopyrido[1,2-a]*pyrimidine-3-carboxylate* (9).—The malonate (7) (6.14 g) was heated for 25 min in Dowtherm A (200 ml) at 250 °C. After cooling, the amide (9) (5.4 g) was filtered off; m.p. 275° (from dimethylformamide) (lit.,[10] 260—262°), $\lambda_{max.}$ 368 (log ε 4.16) and 255 nm (3.72), $\nu_{max.}$ 1 755, 1 700, and 1 670 cm^{-1}.

Ethyl 7-Cyano-4-oxopyrido[1,2-a]*pyrimidine-3-carboxylate* (10).—(*a*) The malonate (7) (6.14 g) was heated for 4 h at 140 °C in phosphoryl chloride (9 ml) and polyphosphoric acid, (1.4 g) then the mixture was broken up with ethanol (30 ml). After cooling, the precipitated crystals were filtered off, suspended in chloroform (10 ml) and filtered off again. The pyridopyrimidine hydrochloride [(10),HCl] (5.8 g), m.p. 196—199°, was heated for 30 min in benzene (300 ml) and triethylamine (30 ml), then triethylamine hydrochloride was filtered off and benzene was removed by evaporation, leaving the pyridopyrimidine (10) (3.2 g), m.p. 203—204° (from ethanol).

(*b*) The amide (9) (2.61 g) was heated in phosphoryl chloride (11 ml) for 4 h at 110—120 °C, then the phosphoryl chloride (9.5 ml) was removed by distillation and the residue was broken up with ethanol (10 ml). After cooling, the

precipitated hydrochloride of (10) was filtered off, suspended in chloroform (10 ml) and filtered off again. The base was liberated; m.p. 202—203°.

Diethyl 1,4,6,9-*Tetrahydro*-4,6-*dioxoanthyridine*-3,7-*dicarboxylate* (16).—The pyrimidonaphthyridine (15) [11g] (1 g) was stirred for 6 h in Dowtherm A (20 ml) at 250—255 °C. After cooling, the precipitated anthyridine (16) (0.8 g) was filtered off and washed with benzene; m.p. 300° (lit.,[11f] >320°).

Ethyl 1-*Oxopyrimido*[1,2-a]*quinoxaline*-2-*carboxylate* (18c).—The acrylate (17c) (15.8 g) was added to Dowtherm A (200 ml) at 250—255 °C and the mixture was stirred for 1 h. After cooling, the mixture was diluted with light petroleum (800 ml). The precipitated *pyrimidoquinoxaline* (18c) (11 g) was filtered off and washed with light petroleum; m.p. 128° (from ethanol), $\lambda_{max.}$ 413 (log ε 3.92), 392 (4.08), 284 (3.94), and 264 nm (4.04), δ 1.44 (3 H, t, Me), 4.49 (2 H, q, O·CH_2), 7.69—8.00 (2 H, m), 8.06—8.25 (1 H, m), 8.99 (2 H, s, 3- and 5-H), and 9.75—10.20 (1 H, m, 10-H) (Found: C, 62.6; H, 4.2; N, 15.8. $C_{14}H_{11}N_3O_3$ requires C, 62.5; H, 4.1; N, 15.6%).

[6/1351 *Received*, 12*th July*, 1976]