782. *Pyrido*[3,2-d]*pyrimidin*-4(3H)-*ones*

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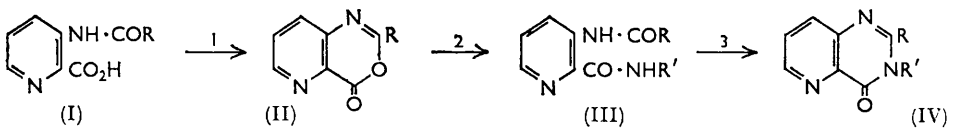
2-Methyl- and 2-phenyl-pyrido[3,2-*d*]-[1,3]-oxazin-4-ones have been prepared from 3-aminopicolinic acid. Treatment of these with primary amines yielded derivatives of 3-acetamido- and 3-benzamido-picolinamide which were cyclised under various conditions, to give two series of 2,3-disubstituted pyrido[3,2-*d*]pyrimidin-4(3*H*)-ones.

Most known pyrido[3,2-*d*]pyrimidines (1,3,5-triazanaphthalenes) have been synthesised from 3-aminopicolinic acid either directly, by heating with an amide,[1] urea,[2] or related compound, or indirectly from the products derived from such reactions. The method is an extension of the Niementowski synthesis of 4-hydroxyquinazolines which has been shown to proceed *via* the intermediate formation of an acyl anthranilamide.[3] Such intermediates are also formed in the synthesis of 2,3-disubstituted quinazolin-4-ones by the action of amines on benzo[*d*]-[1,3]-oxazin-4-ones.

We have now demonstrated that similar fused 1,3-oxazin-4-ones in the pyridine series can be converted into the analogous pyrido[3,2-*d*]pyrimidin-4(3*H*)-ones. For example, the action of acetic anhydride on 3-aminopicolinic acid yielded 2-methylpyrido[3,2-*d*]-[1,3]-oxazin-4-one (II; R = Me), and a similar cyclisation of 3-benzamidopicolinic acid (I; R = Ph) with acetic anhydride yielded 2-phenylpyrido[3,2-*d*]-[1,3]-oxazin-4-one (II; R = Ph). The stability to atmospheric moisture of the pyrido[3,2-*d*]-[1,3]-oxazin-4-ones was closely similar to that of their benzo-analogues.[3] Their infrared spectra showed the high carbonyl absorption (1770 cm.$^{-1}$) expected of δ-lactones of such structure, in addition to the weaker absorption of the C=N stretching vibration in the 1630—1650 cm.$^{-1}$ region.



(I) (II) (III) (IV)

Reagents: 1, Ac_2O; 2, $R'NH_2$; 3, $R'NH_2$ or heat or $POCl_3$

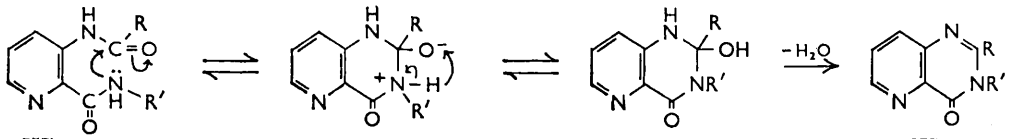
A series of amines, both aliphatic and aromatic, ammonia, hydroxylamine, and hydrazine all underwent an immediate reaction with both 2-methyl- and 2-phenyl-pyrido-[3,2-*d*[-[1,3]-oxazin-4-one. In the 2-phenyl series the product was invariably a 3-benzamidopicolinamide (III; R = Ph), and cyclisation to the pyridopyrimidine was effected by dissolution in phosphoryl chloride. In the 2-methyl series, considerable variations were observed in the ease of cyclisation (III ⟶ IV) of the 3-acetamidopicolinamides. Their

[1] C. C. Price and D. Y. Curtin, *J. Amer. Chem. Soc.*, 1946, **68**, 914.
[2] V. Oakes, R. Pascoe, and H. N. Rydon, *J.*, 1956, 1045; R. K. Robins and G. H. Hitchings, *J. Amer. Chem. Soc.*, 1956, **78**, 973.
[3] D. T. Zentmeyer and E. C. Wagner, *J. Org. Chem.*, 1949, **14**, 967.

infrared spectra had a characteristic broad intense band in the 1460—1540 cm.$^{-1}$ region, mainly due to the two amide II combination bands.

Treatment of the pyrido-oxazine (II; R = Me) at room temperature with an excess of hydroxylamine, hydrazine, or ammonia, respectively, yielded the corresponding pyrido-pyrimidine (IV; R = Me, R′ = OH, NH_2, or H) without the need for prior isolation of the intermediate amide. The pyrido-oxazine (II; R = Me) and the amine, heated together at 150—200°, yielded directly the pyridopyrimidine with the amines phenylhydrazine, aniline, *p*-dimethylaminoaniline, *p*-toluidine, *p*-anisidine, 1-naphthylamine, and 3-aminopyridine. Under similar conditions the pyrido-oxazine (II; R = Me) and t-butylamine, benzylamine, and *p*-nitroaniline all yielded the corresponding amides. The amides derived from the latter two amines were cyclised to the pyridopyrimidines with phosphoryl chloride, but that from t-butylamine was unchanged under such conditions.

A plausible mechanism for the cyclisation of the amides in the absence of catalysts is as follows:



(III) (IV)

The initial step is the nucleophilic attack of the nitrogen of the picolinamido-group on the carbonyl carbon of the acetamido-group. If this is the rate-determining step, any factors which increase the nucleophilicity of the picolinamido nitrogen atom should increase the rate of reaction. Within the aromatic and heterocyclic series, where such a comparison could be made readily, this was certainly true. Thus, the amide (III; R = Me, R′ = 3-Pyr) derived from 3-aminopyridine could not be cyclised at 150°, and the *p*-nitroanilide (III; R = Me, R′ = *p*-NO_2·C_6H_4) could be cyclised only by the use of phosphoryl chloride. In these cases the interaction of the nitrogen lone-pair of electrons with the aromatic π-orbital is enhanced, but for the *p*-dimethylaminoanilide (III; R = Me, R′ = *p*-Me_2N·C_6H_4), where the tendency for such a delocalisation is considerably reduced, cyclisation occurred at room temperature.

In the case of the aliphatic amines, where increasing basic strength of the original amine gave a lower overall rate of reaction, the first step of the above reaction cannot be rate-determining. In the presence of an excess either of base or of phosphoryl chloride the mechanism must be different.

The reluctance of 3-benzamidopicolinamides, even those derived from the more basic aromatic amines, to yield pyridopyrimidines in the absence of catalysts is not surprising in view of the known reduction in the electrophilic properties of a carbonyl group when attached to an aromatic nucleus.[4] Difficulty was experienced in the cyclisation of the amide derived from *p*-dimethylaminoaniline (III; R = Ph, R′ = *p*-Me_2N·C_6H_4), and that from 3-aminopyridine (III; R = Ph, R′ = 3-Pyr) could not be cyclised under any conditions, whereas the *m*-nitroanilide (III; R = Ph, R′ = *m*-NO_2·C_6H_4) gave a good yield of the pyridopyrimidine (IV; R = Ph, R′ = *m*-NO_2·C_6H_4). This suggests that, in these instances, quaternary-salt or complex formation (in the R′ group) lowers the rate of reaction by causing the enhanced delocalisation of the picolinamido nitrogen lone-pair of electrons.

In an attempt to convert 4-hydroxy-2-methylpyrido[3,2-*d*]pyrimidine into the 3-amino-2-methyl analogue by refluxing in hydrazine hydrate, a type of synthesis employed successfully in the quinazoline series,[5] 3-aminopicolinhydrazide was produced. The

[4] Jack Hine, " Physical Organic Chemistry," McGraw-Hill, New York, 1962, p. 257.
[5] N. J. Leonard and W. V. Ruyle, *J. Org. Chem.*, 1948, **13**, 903; N. J. Leonard and D. Y. Curtin, *ibid.*, 1946, **11**, 341.

same hydrazide was obtained by the action of hydrazine hydrate on both 4-hydroxypyrido-[3,2-*d*]pyrimidine and 3-acetamidopicolinhydrazide.

The *N*-aminopyridopyrimidine (IV; R = Me, R′ = NH_2) had the properties expected [6] in that it readily formed an acetyl derivative and yielded 4-hydroxy-2-methylpyrido-[3,2-*d*]pyrimidine when treated with nitrous acid.

The ability of the methyl group in 4-hydroxy-2-methylpyrido[3,2-*d*]pyrimidine (IV; R = Me, R′ = H) and 2-methyl-3-phenylpyrido[3,2-*d*]pyrimidin-4(3*H*)-one to react with benzaldehyde to form styryl compounds indicates the activation by the adjacent C=N bond. The methyl group in 4-hydroxy-2-methylpyrido[3,2-*d*]pyrimidine is also readily oxidised by fuming nitric acid. However, the product is 4-hydroxypyrido[3,2-*d*]pyrimidine, the intermediate 2-carboxylic acid being decarboxylated under the reaction conditions.

Experimental

Infrared spectra were determined, unless otherwise stated, in chloroform solution on a Unicam S.P. 200 spectrophotometer; major peaks only are recorded except where assignment of a minor peak was obvious. Sublimation and reaction temperatures are those of the external bath.

2-*Methylpyrido*[3,2-d]-[1,3]-*oxazin*-4-*one* (II; R = Me).—3-Aminopicolinic acid (1·0 g.) and acetic anhydride (10 ml.) were refluxed together for 90 min. The excess anhydride was removed under reduced pressure, and the residue yielded the *pyrido-oxazine* (0·95 g., 87%), needles, m. p. 115—116° (from benzene–light petroleum) (Found: C, 59·2; H, 3·9; N, 17·5. $C_8H_6N_2O_2$ requires C, 59·3; H, 3·7; N, 17·3%), $\nu_{max.}$ 1770 (" vinyl ester type " C=O), 1650 (C=N), 1590, 1465, and 1375 (C–H bend), 1430, 1260 (C–O), 1050 $cm.^{-1}$. A suspension of the pyrido-oxazine (0·1 g.) in water (2·0 ml.) was stirred for 3 hr., to yield 3-*acetamidopicolinic acid* (0·09 g.), m. p. 222—223° (sublimation at 160°/0·3 mm.) (Found: C, 53·2; H, 4·5; N, 15·4. $C_8H_8N_2O_3$ requires C, 53·3; H, 4·4; N, 15·55%), $\nu_{max.}$ (Nujol) 3100sh (N–H), 2700—2500 (bonded O–H), 2150, 1695, and 1675 (C=O), 1600, 1530 (amide II), 1295 (C–O), 1230, 825 $cm.^{-1}$. The same amido-acid was formed when the pyrido-oxazine was left in the air for one day, and when 3-aminopicolinic acid was warmed with acetic anhydride on a water-bath for a few min. Treatment of the amido-acid with acetic anhydride (90 min. reflux) re-formed the pyrido-oxazine (II; R = Me).

2-*Phenylpyrido*[3,2-d]-[1,3]-*oxazin*-4-*one* (II; R = Ph).—Benzoylation of 3-aminopicolinic acid (1·0 g.) in sodium hydroxide solution yielded 3-*benzamidopicolinic acid* (1·25 g., 71%), isolated as its sparingly soluble sodium salt. The amido-acid was sublimed at 150°/0·1 mm. and gave needles, m. p. 207—208° (from acetic acid) (Found: C, 64·4; H, 4·2; N, 11·4. $C_{13}H_{10}N_2O_3$ requires C, 64·5; H, 4·1; N, 11·6%), $\nu_{max.}$ (Nujol) 3100 (N–H), 2050, 1680, and 1665 (C=O),

[6] J. A. Moore, *J. Amer. Chem. Soc.*, 1955, **77**, 3417.

TABLE 1

3-Amidopicolinamides (III)

Compound		Reaction temp.	Yield (%)	M. p.	Found (%)			Formula	Required (%)		
R	R′				C	H	N		C	H	N
Me	NH_2	20°	85	171—172°	49·55	4·95	29·2	$C_8H_{10}N_4O_2$	49·5	5·2	28·9
Ph	H	20	93	196—197	64·8	4·5	17·2	$C_{13}H_{11}N_3O_2$	64·7	4·6	17·4
Ph	NH_2	20	80	201—202	60·9	4·5	22·6	$C_{13}H_{12}N_4O_2$	60·9	4·7	21·9
Me	Bu^t	200 *	55	114—115	61·4	7·3	17·9	$C_{12}H_{17}N_3O_2$	61·3	7·2	17·9
Me	3-Pyr	150	74	156—160	61·1	4·7	22·1	$C_{13}H_{12}N_4O_2$	60·9	4·7	21·9
Me	*p*-NO_2·C_6H_4	150	48	192—193	56·0	4·3	18·45	$C_{14}H_{12}N_4O_4$	56·0	4·0	18·7
Ph	$PhCH_2$	150	88	108—109	72·6	5·1	12·9	$C_{20}H_{17}N_3O_2$	72·5	5·1	12·7
Ph	PhNH	150	72	182—183	68·9	4·8	16·7	$C_{19}H_{16}N_4O_2$	68·7	4·8	16·6
Ph	3-Pyr	150	63	188—190	67·8	4·5	17·8	$C_{18}H_{14}N_4O_2$	67·9	4·4	17·6
Ph	Ph	150	95	146—148	71·8	4·8	13·3	$C_{19}H_{15}N_3O_2$	71·9	4·7	13·3
Ph	*m*-NO_2·C_6H_4	150	86	204—205	62·8	3·8	15·2	$C_{19}H_{14}N_4O_4$	63·0	3·9	15·5
Ph	*p*-MeO·C_6H_4	200 *	81	153—154	69·0	5·1	11·9	$C_{20}H_{17}N_3O_3$	69·2	4·9	12·1
Ph	*p*-Me_2N·C_6H_4	200 *	69	211	70·0	5·7	15·6	$C_{21}H_{20}N_4O_2$	70·0	5·6	15·6

* The higher temperatures were used in an attempt to cyclise by heat alone.

TABLE 2

Main absorption bands ($cm.^{-1}$) in infrared spectra of 3-amidopicolinamides (III)

Compound R	Compound R′	NH	Amide I	Amide II	Other bands
Me	H *	3450, 3200	1690, 1670	1530	1600, 1500, 1290 (Amide III)
Me	NH_2 *	3350, 3150	1690, 1660	1520—1460	1600, 1290, 960, 940
Me	$PhCH_2$	3400, 3200	1695, 1660	1530—1480	1600, 1400 (C–H), 1285, 1260
Me	Bu^t	3350, 3200	1690, 1660	1540—1500	1590, 1400, 1370, 1295, 1265
Me	3-Pyr	3300	1705, 1670sh	1540—1480	1590, 1400, 1290
Me	*p*-NO_2·C_6H_4	3300	1705, 1670sh	1510	1540 and 1350 (NO_2), 1610, 1590, 1400
Ph	H *	3450, 3300	1695, 1670	1520	1600, 1500, 1290
Ph	NH_2 *	3300, 3190	1690, 1650	1520—1490	1600, 950
Ph	$PhCH_2$	3350, 3200	1675, 1670	1520—1490	1590, 1400, 1290, 1260
Ph	PhNH	3350, 3200	1670	1520—1490	1595, 1400, 1285, 1260
Ph	3-Pyr	3350, 3250	1690	1540—1480	1600, 1400, 1290, 1260
Ph	Ph	3350, 3250	1690	1540—1480	1600, 1400, 1290
Ph	*m*-NO_2·C_6H_4	3300, 3200	1670	1520—1495	1540 and 1360 (NO_2), 1600, 1400, 1295
Ph	*p*-MeO·C_6H_4	3300, 3200	1670	1540—1490	2840 (O–CH_3), 1600, 1400, 1250 (C–O)
Ph	*p*-Me_2N·C_6H_4	3350, 3200	1670	1540—1490	2800 (N–CH_3), 1600, 1405

* Nujol mulls.

1600, 1590, 1285, 1260 (C–O), 1140 $cm.^{-1}$. The amido-acid (1·25 g.) and acetic anhydride (12 ml.) were refluxed together for 90 min., to yield the *pyrido-oxazine* (0·98 g., 85%), needles, m. p. 171—172° (from benzene) (Found: C, 68·5; H, 3·5; N, 12·3. $C_{13}H_8N_2O_2$ requires C, 69·65; H, 3·6; N, 12·5%), $\nu_{max.}$ 1770 (" vinyl ester type " C=O), 1630 (C=N), 1590, 1250 (C–O). The pyrido-oxazine was unchanged by exposure to the air for several weeks.

3-*Acetamidopicolinamide* (III; R = Me, R′ = H).—There was an immediate exothermic reaction when 2-methylpyrido[3,2-*d*]-[1,3]-oxazin-4-one was treated with ammonia (5·0 ml.; *d* 0·88). The mixture was stirred for 30 min. and the precipitated *amide* (0·27 g., 81%) collected, plates, m. p. 174—175° (from benzene) (Found: C, 53·9; H, 5·1; N, 22·8. $C_8H_9N_3O_2$ requires C, 53·6; H, 5·0; N, 23·5%). The first three amides in Table 1 were prepared similarly. The infrared absorption peaks are in Table 2.

3-*Acetamido*-N-*benzylpicolinamide* (III; R = Me, R′ = Ph·CH_2).—2-Methylpyrido[3,2-*d*]-[1,3]-oxazin-4-one (0·86 g.) and benzylamine (0·5 ml.) were heated together at 200° for 30 min. The cooled melt was triturated with light petroleum (or ethanol) to yield the *amide* (1·03 g., 78%), plates, m. p. 80—81° (from benzene–light petroleum) (Found: C, 66·8; H, 5·4; N, 15·75. $C_{15}H_{15}N_3O_2$ requires C, 67·1; H, 5·6; N, 15·6%).

3-*Acetamido*- and 3-*benzamido-picolinamides*, prepared analogously from the appropriate amine and pyrido-oxazine, are described in Table 1; infrared spectra are in Table 2.

3-*Hydroxy*-2-*methylpyrido*[3,2-d]*pyrimidin*-4(3H)-*one* (IV; R = Me, R′ = OH).—Hydroxylamine hydrochloride (0·28 g.) was added to a solution of sodium (0·07 g.) in ethanol (10 ml.). The precipitated sodium chloride was removed and 2-methylpyrido[3,2-*d*]-[1,3]-oxazin-4-one (0·32 g.) added to the filtrate. The mixture was stirred for 24 hr. and the precipitated pyrido-pyrimidine (0·19 g., 54%), needles, m. p. 255—256° (from ethanol) alone and on admixture with a sample prepared by the action of hydroxylamine on ethyl 3-acetamidopicolinate [7] (Found: C, 54·4; H, 4·0; N, 23·5. Calc. for $C_8H_7N_3O_2$: C, 54·2; H, 4·0; N, 23·7%). The product was a cyclic hydroxamic acid and gave a wine-red colour with ferric chloride.

3-*Amino*-2-*methylpyrido*[3,2-d]*pyrimidin*-4(3H)-*one* (IV); R = Me, R′ = NH_2).—When a solution of the 2-methylpyrido-oxazine (1·0 g.) in ethanol (10 ml.) was stirred with hydrazine hydrate (3·0 ml.), 3-acetamidopicolinhydrazide precipitated almost immediately, and after being stirred for 7 days at room temperature the solution was clear again. Concentration to low bulk yielded the *pyridopyrimidine* (0·35 g., 32%), pale buff needles, m. p. 235—236° (from ethanol) (Found: C, 54·4; H, 4·7; N, 31·75. $C_8H_8N_4O$ requires C, 54·55; H, 4·5; N, 31·8%). The same product was isolated in higher yield (72%) by heating the intermediate hydrazide for 30 min. at 180°. The *acetyl derivative* formed prisms, m. p. 295° (decomp.) (from ethanol) (Found: C, 54·9; H, 4·5; N, 25·5. $C_{10}H_{10}N_4O_2$ requires C, 55·0; H, 4·6; N, 25·7%).

[7] D. Harrison and A. C. B. Smith, *J.*, 1960, 2157.

4-*Hydroxy*-2-*methylpyrido*[3,2-d]*pyrimidine* {2-*Methylpyrido*[3,2-d]*pyrimidin*-4(3H)-*one*} (IV; R = Me, R′ = H).—(*a*) The 2-methylpyrido-oxazine (1·0 g.) was added to ammonia (10 ml.; *d* 0·88) and the suspension of the precipitated amide was stirred until solution was complete (2—3 days). The solvent was evaporated, to yield the *pyridopyrimidine* (0·83 g., 84%), m. p. 271—273° (from 2-ethoxyethanol) (after sublimation at 200°/0·5 mm.) (Found: C, 59·8; H, 4·5; N, 26·3. $C_8H_7N_3O$ requires C, 59·6; H, 4·3; N, 26·1%). The same compound could not be prepared by heating 3-acetamidopicolinamide at 150° for 30 min.

(*b*) A solution of 3-amino-2-methylpyrido[3,2-*d*]pyrimidin-4(3*H*)-one (0·1 g.) in 2N-hydrochloric acid (3 ml.) and ethanol (5 ml.) was treated with sodium nitrite (0·3 g.) in water (1 ml.). The mixture was stirred at room temperature for 30 min., neutralised with sodium hydroxide, evaporated to dryness and extracted with ethanol. Concentration of the extract yielded the *pyridopyrimidine* (0·055 g., 60%), m. p. 271—273° alone and on admixture with a sample from (*a*).

4-*Hydroxypyrido*[3,2-d]*pyrimidine* {*Pyrido*[3,2-d]*pyrimidin*-4(3H)-*one*} (IV; R = R′ = H).—A solution of 4-hydroxy-2-methylpyrido[3,2-*d*]pyrimidine (1·0 g.) in fuming nitric acid (*d* 1·5; 10 ml.) was heated on a water-bath under reflux for 4 hr. The solution was evaporated to dryness and the residual semi-solid yellow mass crystallised from water to give 4-hydroxypyrido[3,2-*d*]pyrimidine (0·37 g., 40·5%), plates, m. p. 354° (decomp.) (from ethanol) (Found: C, 57·2; H, 3·5; N, 28·2. Calc. for $C_7H_5N_3O$: C, 57·15; H, 3·4; N, 28·6%). A sample of identical infrared spectrum and undepressed mixed m. p. was prepared from 3-aminopicolinic acid and formamide by the method of Oakes, Pascoe, and Rydon.[2]

3-*Aminopicolinhydrazide*.—4-Hydroxy-2-methylpyrido[3,2-*d*]pyrimidine (0·2 g.) and hydrazine hydrate (2 ml.) were refluxed together for 2 hr. The solution was evaporated to dryness,

TABLE 3

2-Methylpyrido[3,2-*d*]pyrimidin-4(3*H*)-ones (IV; R = Me)

Compound R′	Reaction temp.	Yield (%)	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N
p-Me·C_6H_4 ...	200°	44	155—156°	71·9	4·9	16·7	$C_{15}H_{13}N_3O$	71·7	5·2	16·7
1-Naphthyl *	200	21	254—255	75·2	4·6	14·4	$C_{18}H_{13}N_3O$	75·3	4·5	14·6
PhNH	150	67	200—201	66·9	5·0	22·2	$C_{14}H_{12}N_4O$	66·7	4·8	22·2
3-Pyr	200	57	231—232	65·2	4·5	23·7	$C_{13}H_{10}N_4O$	65·5	4·2	23·5
p-MeO·C_6H_4	150	54	217—218	67·1	5·1	16·3	$C_{15}H_{13}N_3O_2$	67·4	4·9	15·7
p-Me_2N·C_6H_4 †	150	71	249—250	68·7	6·0	20·4	$C_{16}H_{16}N_4O$	68·6	5·7	20·0

* Chromatographed on alumina and then sublimed at 200°/1·0 mm. † Also cyclises at room temperature in ethanol (36%).

TABLE 4

2,3-Disubstituted pyrido[3,2-*d*]pyrimidin-4(3*H*)-ones (IV)

Compound R	R′	Yield (%)	M. p.	Found (%) C	H	N	Formula	Required (%) C	H	N
Ph	H *	69	260°	69·8	4·2	19·05	$C_{13}H_9N_3O$	69·95	4·0	18·8
Ph	NH_2	56	256—258	65·4	4·25	23·8	$C_{13}H_{10}N_4O$	65·5	4·2	23·5
Ph	PhNH	90	232—234	72·2	4·7	17·7	$C_{19}H_{14}N_4O$	72·6	4·5	17·8
Ph	Ph	76	227	76·2	4·3	13·7	$C_{19}H_{13}N_3O$	76·25	4·3	14·05
Ph	*p*-MeO·C_6H_4 †	76	227—228	73·0	4·8	12·8	$C_{20}H_{15}N_3O_2$	73·0	4·6	12·8
Ph	*m*-NO_2·C_6H_4 †‡	80	207—208	65·8	3·7	16·4	$C_{19}H_{12}N_4O_3$	66·3	3·5	16·3
Me	*p*-NO_2·C_6H_4 †	71	281—284	59·3	3·8	20·4	$C_{14}H_{10}N_4O_3$	59·6	3·5	19·9
Ph	*p*-Me_2N·C_6H_4 †§	44	282—283	73·6	5·1	16·5	$C_{21}H_{18}N_4O$	73·7	5·3	16·4

* Required 5 days in phosphoryl chloride to cyclise. † Extraction with chloroform in place of benzene. ‡ Requires heating for several days on a water-bath to dissolve. § Recovered starting material, 28%.

the residue extracted with hot benzene, and the extract cooled, to yield the hydrazide (0·035 g., 29%), m. p. 115—116° (Found: C, 47·5; H, 5·3; N, 37·1. Calc. for $C_6H_8N_4O$: C, 47·4; H, 5·3; N, 36·8%), $\nu_{max.}$ (Nujol) 3400 and 3300—3200 (N–H), 1640 (C=O), 1620, 1545, 1500, 1240, 1145, 950 $cm.^{-1}$. The same hydrazide was formed (44·5%) in a similar reaction from 4-hydroxypyrido[3,2-*d*]pyrimidine, and in addition from 3-acetamidopicolinhydrazide and hydrazine hydrate under reflux (34%). All these products were shown, by mixed m. p.s, to be identical with a sample prepared by the action [2] of hydrazine on ethyl 3-aminopicolinate.

TABLE 5

Main absorption bands ($cm.^{-1}$) in infrared spectra of pyrido[3,2-*d*]pyrimidines (IV)

Compound R	R′	
Me	Ph	1705 (C:O), 1610 (C:N), 1590, 1470, and 1380 (C–H), 1435, 1110
Me	*p*-Me·C_6H_4	1705 (C:O), 1605 (C:N), 1590, 1475, and 1385 (C–H), 1265, 1110
Me	1-Naphthyl *	1695 (C:O), 1605 (C:N), 1590, 1470, and 1380 (C–H), 1300, 1270
Me	PhNH	3360 (N–H), 1705 (C:O), 1610 (C:N), 1600, 1480 and 1375 (C–H), 1430, 1240, 1110
Me	3-Pyr	1705 (C:O), 1610 (C:N), 1580, 1480 and 1380 (C–H), 1430
Me	$PhCH_2$	1690 (C:O), 1600sh (C:N), 1590, 1460 and 1380 (C–H), 1340, 1320
Me	*p*-NO_2·C_6H_4	1700 (C:O), 1615 (C:N), 1590, 1540 and 1350 (NO_2), 1475 and 1385 (C–H), 1440, 1230
Me	OH *	2700—2350 (bonded O–H), 1695 (C:O), 1600, 1580, 1200, 940
Me	NH_2 *	3350 and 3200 (N–H), 1700 (C:O), 1615sh (C:N), 1610, 1440, 1230, 830
Me	MeCO·NH *	3150 (N–H), 1720 and 1700 (C:O), 1615 (C:N), 1600sh, 1270, 830
Me	H *	3200 (N–H), 1695 (C:O), 1625 (C:N), 1600, 1500, 1280, 830
H	H *	3150—2500 (N–H and O–H), 1710 and 1670 (C:O), 1605, 1580, 1405, 1240, 825
Ph	H *	3100 (N–H), 1680 (C:O), 1620 (C:N), 1600, 1590, 1500, 1410, 1300
Ph	NH_2	3350 (N–H), 1695 (C:O), 1620 (C:N), 1600, 1580
Ph	PhNH	3350 (N–H), 1710 (C:O), 1605, 1585, 1495, 1310, 1240
Ph	Ph	1705 (C:O), 1610 (C:H), 1590, 1340, 1310
Ph	*p*-MeO·C_6H_4	2840 (OMe), 1705 (C:O), 1615 (C:N), 1580, 1515, 1470, 1350, 1255 (C–O)
Ph	*m*-NO_2·C_6H_4	1705 (C:O), 1610 (C:N), 1585, 1540 and 1355 (NO_2), 1435, 1250
Ph	*p*-Me_2N·C_6H_4	2800 (N–Me), 1695 (C:O), 1615 (C:N), 1580, 1530, 1470 and 1370sh (C–H), 1350, 1260
PhCH:CH	H *	1690 (C:O), 1645, 1580, 970 (*trans*-CH:CH)
PhCH:CH	Ph	1700 (C:O), 1620, 1610sh, 1570, 1550, 1440, 1350, 1255, 980 (*trans*-CH:CH)

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4-Hydroxy-2-styrylpyrido[3,2-d]*pyrimidine* {*2-Styrylpyrido*[3,2-d]*pyrimidin-4*(3*H*)-*one*} (IV; R = Ph·CH:CH, R′ = H).—4-Hydroxy-2-methylpyrido[3,2-*d*]pyrimidine (0·1 g.), benzaldehyde (1·0 ml.), and piperidine (1 drop) were refluxed for 1 hr. The solution was evaporated to dryness, to yield the *styrylpyridopyrimidine* (0·05 g., 32%), plates, m. p. 252—253° (from ethanol) (Found: C, 72·2; H, 4·5; N, 17·1. $C_{15}H_{11}N_3O$ requires C, 72·3; H, 4·4; N, 16·9%).

2-Methyl-3-phenylpyrido[3,2-d]*pyrimidin-4*(3H)-*one* (IV; R = Me, R′ = Ph).—The 2-methylpyrido-oxazine (0·16 g.) and aniline (0·1 ml.) were heated together in an open tube at 150° for 30 min. The cooled melt was extracted with benzene and the extract concentrated to yield the *pyridopyrimidine* (0·2 g., 88%), plates, m. p. 234—235° (from benzene) (Found: C, 71·05; H, 4·7; N, 17·6. $C_{14}H_{11}N_3O$ requires C, 70·8; H, 4·6; N, 17·7%). The intermediate 3-acetamidopicolinanilide (III; R = Me, R′ = Ph) (m. p. 185—190° when heated rapidly) was prepared by stirring the 2-methylpyrido-oxazine with aniline in ethanol (30 min.). Sufficient of the amide cyclised to give an incorrect analysis, and cyclisation was complete after attempted purification by sublimation at 150°/0·1 mm.

The *pyridopyrimidines* recorded in Table 3 were prepared in a similar manner from the appropriate amine and pyrido-oxazine heated together for 30 min. at the stated temperature.

3-Benzyl-2-methylpyrido[3,2-d]*pyrimidin-4*(3H)-*one* (IV; R = Me, R′ = $PhCH_2$).—3-Acetamido-*N*-benzylpicolinamide (1·0 g.) was dissolved in phosphoryl chloride by gentle warming. The solution was left for 2 days and poured into ice–water (50 ml.). The mixture was basified with ammonia and extracted with hot benzene. Concentration of the extract yielded the *pyridopyrimidine* (0·76 g., 82%), plates, m. p. 177—178° (from ethyl acetate) (Found: C, 71·45; H, 5·1; N, 16·7. $C_{15}H_{13}N_3O$ requires C, 71·7; H, 5·2; N, 16·7%).

The *pyridopyrimidines* in Table 4 were prepared similarly from the appropriate picolinamide and phosphoryl chloride. The infrared spectra are in Table 5.

3-Phenyl-2-styrylpyrido[3,2-d]*pyrimidin-4*(3H)-*one* (IV; R = PhCH:CH, R′ = Ph).—A mixture of 2-methyl-3-phenylpyrido[3,2-*d*]pyrimidin-4(3*H*)-one (0·1 g.), benzaldehyde (1·0 ml.), and piperidine (1 drop) was refluxed for 1 hr. The solution was evaporated to dryness and triturated with ethyl acetate, to yield the *styrylpyridopyrimidine* (0·08 g., 58·3%), prisms, m. p. 216—217° (from 2-ethoxyethanol) (Found: C, 78·0; H, 4·8; N, 12·6. $C_{21}H_{15}N_3O$ requires C, 77·5; H, 4·6; N, 12·9%).

Attempted Cyclisation of 3-(3′-*Benzamidopicolinamido*)*pyridine*.—The amide (II; R = Ph,

R′ = 3-Pyr) was recovered unchanged after heating to 300°, stirring in ammonia (7 days) or in phosphoryl chloride (7 days), or by heating under reflux in a mixture of phosphoryl chloride and phosphorus pentachloride.

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