NITROGEN BRIDGEHEAD COMPOUNDS PART 39[1]. SYNTHESIS AND REACTIONS OF 3-PHENOXY-2-METHYL-4H-PYRIDO[1,2-a]PYRIMIDIN-4-ONES

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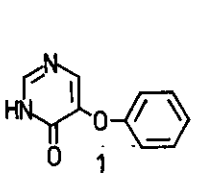
Abstract —— 3-Phenoxy- and 3-chloro-2-methyl-4H-pyrido[1,2-a]-pyrimidin-4-ones (2) and (5) were prepared by the reactions of 2-aminopyridines and 2-phenoxy- or 2-chloroacetoacetate (4) and (7) in a mixture of phosphoryl chloride — polyphosphoric acid. The ring-transformation reactions of the pyridopyrimidines (2b) and (5b), and hydrogenation and nitration of the phenoxy derivatives (2) were also studied.

5-Phenoxy-4(3H)-pyrimidinones (1) were recently reported to possess a significant bronchodilatory activity[2]. The present work deals with the synthesis and some chemical transformations of the structurally related 3-phenoxy-4H-pyrido-[1,2-a]pyrimidinones (2). Since many of the pyrido[1,2-a]pyrimidines display a favourable biological effect on the pulmonary system (they show antiasthmatic-antiallergic activity), we expected the new compounds (2) and (9) to have favourable pharmacological properties. The 9-hydroxypyridopyrimidines are known[4] as antibacterial agents.



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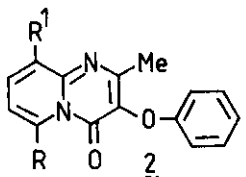

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Synthesis and Reactions: 3-Aryloxypyridopyrimidines have not been synthesized previously. The 2-phenoxypyridopyrimidin-4-one was prepared[5] from the 2-chloropyridopyrimidin-4-one.

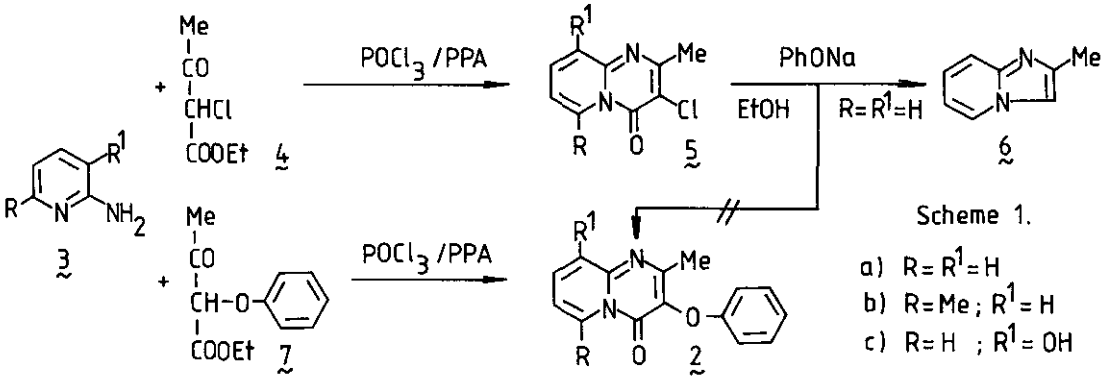
We planned to obtain the 3-phenoxypyridopyrimidinones (2) by two routes:

Route A: a two-step synthesis involving preparation of the 3-chloropyridopyrimidinone, followed by exchange of the chloro atom for a phenoxy group.

Route B: the direct synthesis of the 3-phenoxypyridopyrimidinones from 2-aminopyridines (Scheme 1).

Route A: 2-Aminopyrimidines (3) were reacted with 2-chloroacetoacetate (4) in a mixture of phosphoryl chloride — polyphosphoric acid. The 3-chloropyridopyrimi-

dinones (5) were obtained in 19.5-40.2% yields. Earlier the chloropyridopyrimidinone (5a) was synthesized by Böhme and Weisel[6] by cyclization in PPA, in a yield of 59%. The chloro→phenoxy exchange was attempted by treating the chloropyridopyrimidinones (5a) with sodium phenolate in ethanol at reflux temperature. Instead of the chloro→phenoxy exchange, however, a ring-transformation reaction took place, leading to 2-methylimidazo[1,2-a]pyridine (6). The product proved identical with the authentic sample[7].



Scheme 1.

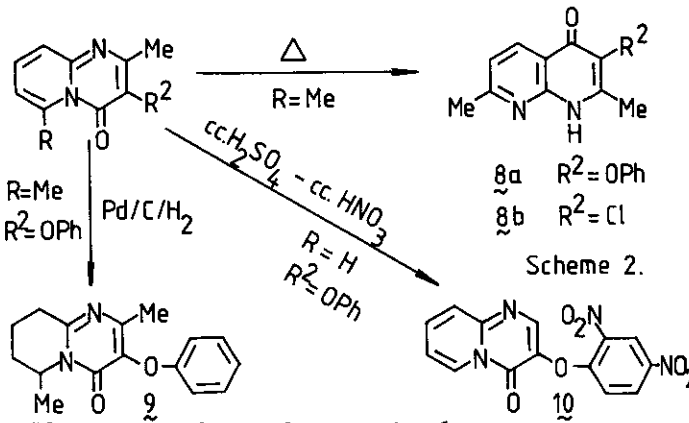
a) R = R¹ = H
b) R = Me ; R¹ = H
c) R = H ; R¹ = OH

Table 1. Analytical and Physical Data on Pyridopyrimidines (2), (5) and (8)

Compd	R	R^1	R^2	Yield %	mp °C	Recrystn solvent	Formula M.w.	Analysis % Calcd/Found C	H	N	Cl
2a	H	H	PhO	56.5	192-193	EtOAc	$C_{15}H_{12}N_2O_2$ 252.274	71.42 71.78	4.79 4.83	11.10 11.20	
2b	Me	H	PhO	33.4	204-205	EtOH	$C_{16}H_{14}N_2O_2$ 266.300	72.16 72.36	5.30 5.29	10.52 10.57	
2c	H	OH	PhO	29.5	169	EtOH	$C_{15}H_{12}N_2O_3$ 268.274	67.16 67.17	4.51 4.34	10.44 10.54	
5a	H	H	Cl	40.2	187	EtOH	$C_9H_7ClN_2O$ 194.621	55.54 55.54	3.63 3.50	14.39 14.23	18.22 18.15
5b	Me	H	Cl	19.5	192	MeOH	$C_{10}H_9ClN_2O$ 208.648	57.57 57.74	4.35 4.40	13.42 13.66	16.99 16.86
5c	H	OH	Cl	24.5	188-189	AcOH	$C_9H_7ClN_2O_2$ 210.620	51.32 51.20	3.35 3.21	13.30 13.81	16.83 16.94
8a			PhO	65	>300		$C_{16}H_{14}N_2O_2$ 266.300	72.16 71.90	5.30 5.06	10.52 10.41	
8b			Cl	55	>300		$C_{10}H_9ClN_2O$ 208.648	57.57 57.83	4.35 4.38	13.42 13.16	16.99 17.04

Route B: Reactions of the 2-aminopyridines (3) with ethyl 2-phenoxyacetoacetate (7), the latter prepared[8] from sodium phenolate and ethyl 2-chloroacetoacetate (4), were carried out successfully in a mixture of phosphoryl chloride — polyphosphoric acid and the expected phenoxypyridopyrimidinones (2) were obtained in 29.5-56.5% yields. In polyphosphoric acid (2a) was formed in only 5.5% yield.

Next we studied some reactions of the pyridopyrimidinones (Scheme 2). The 6-substituted 4H-pyrido[1,2-a]pyrimidinones are known to transform[9] into 1,8-naphthyridines under the effect of heat. The ring-transformations of the 6-methyl derivatives (2b) and (5b) were effected in paraffin oil at 300° and 350 °C and yielded the 1,8-naphthyridines (8a) and (8b) in 65% and 55% yields, respectively. Catalytic hydrogenation of (2b) on palladium on charcoal gave the 6,7,8,9-tetrahydropyridopyrimidinone (9) in 87% yield. The nitration of (2a) at ambient temperature in a 1:2 mixture of nitric acid and sulphuric acid resulted in the 2,4-dinitrophenoxy derivative (10) in 90.2% yield.



Scheme 2.

Spectroscopic characterization: Uv and ir and ^{1}H-nmr data on the pyridopyrimidinones (2) and (5) and the 1,8-naphthyridines (8) are compiled in Table 2. Table 3 contains the ^{13}C-nmr data on the 6-methylpyridopyrimidinones (2b), (5b), (9) and 1,8-naphthyridine (8b).

The characteristic uv maxima above 340 nm indicate[9a] the presence of the pyridopyrimidinone skeleton. In the isomeric 1,8-naphthyridines (8) the longest wavelength absorption is found below 340 nm. In the ir spectra of the pyridopyrimidines the stretching band of the 4-carbonyl group appears between 1670 and 1700, whereas in the 1,8-naphthyridines it occurs between 1600 and 1620 cm^{-1}.

Due to the $A^{1,3}$ type allylic strain[10] between the 6-methyl and 4-carbonyl groups in the tetrahydropyridopyrimidine (9), the 6-methyl group occupies the axial position. This is supported by the ^{1}H and ^{13}C-nmr spectra. In the ^{1}H-nmr spectrum the chemical shift of the equatorial 6-H appears at relatively low field (4.75-5.15 ppm) as a consequence of the diamagnetic anisotropy of the adjacent carbonyl group. In the ^{13}C-nmr spectrum, the C-8 signal appears at 15.1 ppm, owing to the γ steric effect of the axial methyl group in position 6.[10a] The ^{1}H-nmr spectrum of the dinitro compound (10) confirms that the electrophilic substitution took place on the phenyl ring and not on the pyridopyrimidinone skeleton. In the ^{1}H-nmr spectrum only three phenyl protons can be found: at 7.43, 8.36 and 8.90 ppm. The coupling constants between H-3' and H-5' (3 Hz) and between H-5' and

Table 2. Spectral Data of Pyridopyrimidines (2) and (5) and 1,8-Naphthyridines (8).

2a: uv 342 (lgε 4.10) 245nm (4.18); ir 1690, 1270cm^{-1}; nmr 2.50s 2-Me; 6.85-7.45m 3-OPh+9-H; 7.60-7.80m 8-H+7-H; 9.00dt 6-H (J=7, J=1 Hz).

2b: uv 360 (lgε 4.04) 255nm (4.13); ir 1680, 1260cm^{-1}; nmr 2.40s 2-Me; 3.05d 6-Me (J=1Hz); 6.62t 9-H (J=4.5Hz); 6.85-7.45m 3-OPh+8-H+7-H.

2c: uv 362 (lgε 4.22) 346 (4.14) 265nm (4.06); ir 1670, 1280cm^{-1}.

5a: uv 345 (lgε 4.06) 256 (4.05) 248nm (4.08); ir 1700cm^{-1}; nmr 2.65s 2-Me; 7.05--7.35m 9-H; 7.50-7.95m 8-H+7-H; 9.03ddd 6-H (J=7Hz).

5b: uv 363 (lgε 4.02) 261 (4.06) 255nm (4.07); ir 1700cm^{-1}; nmr 2.55s 2-Me; 3.10d 6-Me (J=1Hz); 6.60-6.80m 9-H; 7.25-7.50m 8-H+7-H.

5c: uv 367 (lgε 4.23) 350 (4.10) 320 (3.84) 270 (3.98) 260 (3.98) 245nm (3.97); ir 1678cm^{-1}; nmr DMSO-d_6 2.55s 2-Me; 7.25dd 8-H+7-H (J=4, J=1Hz); 8.45dd 6-H.

8a: uv 332 (lgε 4.09) 288 (3.67) 276 (3.74) 248nm (4.51); ir 1600, 1285, 1260, 3210cm^{-1}; nmr DMSO-d_6 2.31s 7-Me; 2.62s 2-Me; 6.60-7.50m 3-OPh; 7.27d 6-H (J=8Hz); 8.37d 5-H (J=8Hz); 12.15broad NH.

8b: uv 330 (lgε 3.97) 292 (3.43) 282 (3.36) 252nm (4.38); ir 1610, 3215cm^{-1}; nmr 2.91s 7-Me; 2.97s 2-Me; 7.80d 6-H (J=8Hz); 9.11d 5-H (J=8Hz).

H-6' (9 Hz) indicate the meta and ortho positions of these protons.

None of the pyridopyrimidinones (2) and (8) exhibited pharmacological (bronchodilatory or antiasthmatic-antiallergic) effects on the pulmonary system.

The 9-hydroxypyridopyrimidinone displayed weak antibacterial activity.

EXPERIMENTAL All melting points are uncorrected. Ultraviolet (uv) spectra were obtained in ethanol on a UNICAM SP 800 spectrophotometer. Infrared (ir) spectra were determined with KBr disks on a ZEISS UR 20 spectrophotometer. The ^{1}H and ^{13}C-nmr spectra were recorded with a Brucker WP-80 DS spectrometer. The ^{1}H and ^{13}C chemical shifts were determined on the δ scale by using tetramethylsilane (δ=0) as internal standard.

General method for the ring-closure reaction: A mixture of 2-aminopyridine (3) (0.04 mol) and ethyl 2-substituted acetoacetate (4) or (7) (0.04 mol) was stirred in phosphoryl chloride — PPA (12 ml and 2.8 g, respectively) at 120 °C for 3 h. After the evolution of hydrogen chloride had ceased, ethanol (40 ml) was added dropwise to the reaction mixture under stirring and external ice-cooling. The precipitated hydrochloride of the pyridopyrimidinone (2) or (5) was filtered off and converted into the base. In the case of (5c) the hydrochloride salt did not

Table 3. ^{13}C-nmr Data on Compounds (2b), (5b), (9), and (8a)

	2b	5b	9		8a
2-Me	19.0q	22.7q	19.0q	2-Me	16.3q
6-Me	24.6q	24.6q	18.1q	7-Me	22.1q
C-2	150.1s	150.6s	152.4s	C-2	154.5s
C-3	132.6s	113.3s	135.4s	C-3	137.4s
C-4	157.7s	159.9s	157.7s	C-4	168.3s
C-6	144.1s	143.9s	48.1d	C-4a	118.4s
C-7	117.8d	118.5d	27.8t	C-5	142.6d
C-8	134.2d	135.0d	15.1t	C-6	125.0d[a]
C-9	125.2d	125.0d	30.9t	C-7	144.9s
C-9a	155.5s	158.0s	154.6s	C-8a	165.0s
C-1'	157.7s		157.3s	C-1'	157.7s
C-2', C-6'	115.1d		115.0d	C-2', C-6'	115.8d
C-3', C-5'	129.8d		129.5d	C-3', C-5'	131.5d
C-4'	122.4d		122.1d	C-4'	124.3d[a]

a The assignments may be reversed.

precipitate. The reaction mixture was diluted with water and neutralized and the precipitated base was filtered off. The products (2) and (5) were crystallized from the solvents given in Table 1. For the mp, yield and analytical data, see Table 1, and for the spectral data see Table 2.

Cyclization in polyphosphoric acid: A mixture of ethyl 2-phenoxyacetoacetate (7) (8.89 g, 0.04 mol) and 2-aminopyridine (3a) (3.76 g, 0.04 mol) was heated in PPA (40 g, Fluka) on a steam bath for 3 h. The reaction mixture was diluted with water (35 ml) and neutralized with 10% sodium hydroxide solution. The precipitated 3-phenoxypyridopyrimidinone (2a) was filtered off (0.55 g, 5.5%) and crystallized from ethyl acetate. The product did not give a mp depression with the sample prepared by ring-closure in a mixture of phosphoryl chloride-PPA.

Ring-transformation reaction: The 6-methylpyridopyrimidinone (2b) or (5b) was added to liquid paraffin at 300° and 350 °C, respectively. The mixture was heated for 30 min., then cooled to ambient temperature and diluted with ligroin (100 ml). The precipitated 1,8-naphthyridine (8) was filtered off and washed with ligroin. For mp, yield and analytical data, see Table 1.

2,6-Dimethyl-3-phenoxy-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (9)

2,6-Dimethyl-3-phenoxy-4H-pyrido[1,2-a]pyrimidin-4-one (3c) (2.66 g, 10 mmol) was hydrogenated in ethanol (200 ml) over a 10% palladium on charcoal catalyst at ambient temperature. The catalyst was filtered off and the filtrate was evaporated. The resulting pale-green oil was treated with cyclohexane (25 ml) to give the tetrahydropyridopyrimidine (9) (2.35 g, 87%) as white crystals, mp 94 °C (from acetone). Anal. Calcd. for $C_{16}H_{18}N_2O_2$ (270.332): C, 71.09; H, 6.71: N, 10.36. Found: C, 70.89; H, 6.79; N, 10.27%. uv 277(3.88); 235nm(3.76); ir 1680, 1240,

1080cm^{-1}; ^{1}H-nmr ($CDCl_3$) 1.36d 6-Me (J=6Hz); 1.70-2.25m 7-H_2+8-H_2; 2.25s 2-Me; 2.75-3.10m 9-H_2; 4.75-5.15m 6-H; 6.80-7.45m 3-OPh.

2-Methyl-3-(2,4-dinitrophenoxy)-4H-pyrido[1,2-a]pyrimidin-4-one (10) Fuming nitric acid (4.5 ml, d=1.52) was added dropwise to 3-phenoxy-2-methyl-4H-pyrido-[1,2-a]pyrimidin-4-one (5.04 g, 20 mmol) in conc. sulphuric acid (9 ml) at 0-5 °C within a period of 1 h. The orange-coloured solution was stirred at ambient temperature for an additional 1 h and was then poured into ice, and the pH was adjusted to 3-4 with sodium carbonate. The precipitated yellow dinitro compound (10) (6.2 g, 90.2%) was filtered off and washed with water, mp 252 °C (from acetic acid). Anal. Calcd. for $C_{15}H_{10}N_4O_6$ (342.270): C, 52.64; H, 2.94; N, 16.37. Found: C, 52.97; H, 3.10; N, 16.55%. uv 346(4.19); 280(4.07); 244nm(4.29); ir 1690, 1280cm^{-1}. ^{1}H-nmr (DMSO-d_6) 2.40s 2-Me; 7.43d 6'-H (J=9Hz); 7.30-7.55m 9-H; 7.65-8.15 7-H+8-H; 8.36dd 5'-H ($J_{3',5'}$=3Hz, $J_{5',6'}$=9Hz); 8.75-9.05m 6-H; 8.90d 3-H.

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