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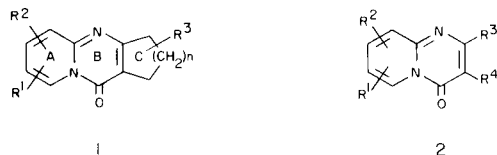
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A series of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones was prepared by the cyclization of substituted 2-aminopyridines with β ketocarboxylic esters in polyphosphoric acid or in mixtures of the latter with phosphoryl chloride. Catalytic hydrogenation (over palladium on charcoal or Raney nickel) of the products afforded the corresponding 6,7,8,9-tetrahydropyridopyrimidinones. Thermal treatment of the 6-substituted derivatives gave 1,8-naphthyridin-4-ones in high yields. Oxo to thio exchange was successful only with substrates unsubstituted at C-6.

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Earlier we reported on the synthesis (1a,2), some characteristic reactions (2,3) and favorable biological properties (4) of a large number of 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones. In the preceding paper of this series (1a) we described the synthesis and some reactions of 2,3-tri-, tetra-, penta- and hexamethylenepyridopyrimidinones substituted in rings A and C (1). The favorable analgetic properties of these tricyclic compounds prompted us to investigate whether ring C was necessary for the desired activity. In this paper the synthesis and selected reactions of 2,3-dialkylpyrido[1,2-*a*]pyrimidin-4-ones (2), analogues of 1 with an "open" C ring is reported. Only few such compounds have been described (5), and their chemical and pharmacological properties have not been studied in detail.

Scheme 1



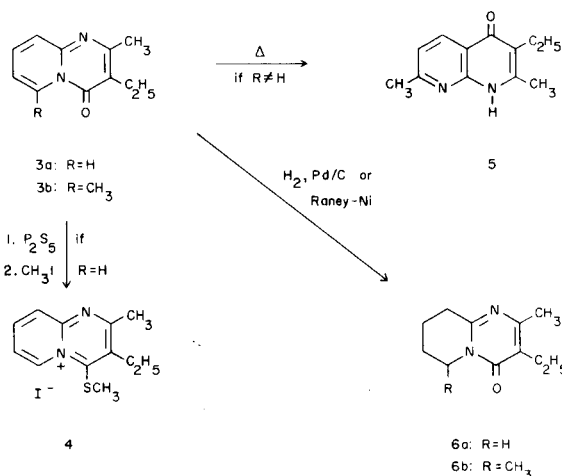
The syntheses of compounds 2 have been achieved by cyclization of 2-aminopyridines with β -ketocarboxylic esters in polyphosphoric acid (PPA) or in its mixture with phosphoryl chloride. Cyclizations in PPA gave the required pyrido[1,2-*a*]pyrimidines in high purity and in yields higher than 70%. Condensation in phosphoryl chloride-polyphosphoric acid followed by work-up with ethanol afforded, in general, similarly high yields. In some instances yields were reduced owing to poor crystallization of the product.

As we have observed earlier that pyridopyrimidine-3-carboxylic acids substituted and unsubstituted in position 6 had markedly different reactivities (2b,3); we compared the reactivity of 3a with that of its 6-methyl analogue 3b. Whereas catalytic hydrogenation of 6-unsubstituted pyridopyrimidine-3-carboxylic acids over palladium on

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charcoal gave 1,6,7,8,9,9a-hexahydro- and that of the 6-substituted acids, 6,7,8,9-tetrahydro derivatives (2b), no such difference was observed between 3a and 3b. Both compounds gave quantitatively the corresponding 6,7,8,9-tetrahydro derivatives (6a and 6b) when hydrogenated at room temperature and atmospheric pressure in the presence of palladium on charcoal or Raney nickel. The analogous tricyclic derivatives behave similarly (1a).

Scheme 2

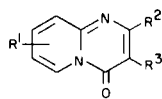


Oxo to thio exchange, described by Potts, *et al.*, for 2-methyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (6) was only successful with the 6-unsubstituted derivatives 3a. The product was converted without isolation to 4 by reaction with methyl iodide at room temperature. Oxo to thio exchange failed with 3b even under forcible conditions, presumably due to steric hindrance caused by the substituent at C-6.

Thermal isomerization to 1,8-naphthyridine, a characteristic transformation of 6-substituted pyrido-pyrimidines described by us earlier (3), proceeded smoothly with the present systems as well. Isomerization of 3b in paraffin oil at 300° gave, independently of the

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Table I
Substituted 4*HP*Pyrido[1,2-*a*]pyrimidin-4-ones

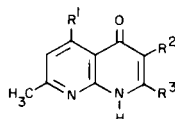


R ¹	R ²	R ³	M.p., °C (a)	Solvent of Recrystallization (b)	Yield % (c)	Molecular Formula	Analysis (a)					
							C	H	Cl	Found C H Cl		
6-CH ₃	CH ₃	CH ₃	155-156 215 subl.	Petroleum ether	86	C ₁₁ H ₁₂ N ₂ O	70.18	6.43		70.16	6.40	
H	CH ₃	C ₂ H ₅	92-93 (d) 185-190	Ether	78 64	C ₁₁ H ₁₂ N ₂ O	70.18 58.81	6.43 5.83	15.78	70.20 58.74	6.60 5.62	15.77 15.64
6-CH ₃	CH ₃	C ₂ H ₅	127-128 233	Ethanol	79 92	C ₁₂ H ₁₄ N ₂ O	71.26 60.38	6.98 6.33	14.85	71.50 60.44	7.22 6.40	14.61
7-CH ₃	CH ₃	C ₂ H ₅	151-152 210-220	Ethanol	87	C ₁₂ H ₁₄ N ₂ O	71.26 60.38	6.98 6.33	14.85	71.30 60.41	6.71 6.47	14.61
8-CH ₃	CH ₃	C ₂ H ₅	127-129 195-200	Petroleum ether	69 64	C ₁₂ H ₁₄ N ₂ O	71.26 60.38	6.98 6.33	14.85	71.34 60.41	6.87 6.38	14.67
9-CH ₃	CH ₃	C ₂ H ₅	94-95 125-130	Petroleum ether	77	C ₁₂ H ₁₄ N ₂ O	71.26 60.38	6.98 6.33	14.85	71.41 60.32	7.18 6.40	14.54
H	H	<i>n</i> -C ₃ H ₇	oil 146-150		58 44	C ₁₁ H ₁₂ N ₂ O						
6-CH ₃	H	<i>n</i> -C ₃ H ₇	42-43 175-186	Petroleum ether	67 42	C ₁₂ H ₁₄ N ₂ O	71.26 60.38	6.98 6.33	14.85	71.31 60.70	6.88 6.48	14.71
H	CH ₃	<i>n</i> -C ₃ H ₇	58-59 210-215	<i>n</i> -Hexane	85 62	C ₁₂ H ₁₄ N ₂ O	71.26 60.38	6.98 6.33	14.85	71.32 59.93	6.86 6.30	14.65
6-CH ₃	CH ₃	<i>n</i> -C ₃ H ₇	46-47 180-185	Petroleum ether	69 58	C ₁₃ H ₁₆ N ₂ O	72.19 61.78	7.46 6.78	14.03	72.22 61.52	7.51 6.92	13.95
H	CH ₃	<i>n</i> -C ₄ H ₉	58-60 240-242	Petroleum ether	59 66	C ₁₃ H ₁₆ N ₂ O	72.19 61.78	7.46 6.78	13.03	72.28 61.65	7.36 6.84	13.24
6-CH ₃	CH ₃	<i>n</i> -C ₄ H ₉	44-46 218-219	Petroleum ether	78 35	C ₁₄ H ₁₈ N ₂ O	73.01 63.03	7.88 7.18	13.29	73.12 62.62	7.91 6.96	13.46
6-CH ₃	CH ₃	<i>i</i> -C ₄ H ₉	oil 178-185	Petroleum ether	76 57	C ₁₄ H ₁₈ N ₂ O						
H	CH ₃	<i>n</i> -C ₁₀ H ₂₁	67-68 200-202	Petroleum ether	52 40	C ₁₉ H ₂₈ N ₂ O	75.95 67.74	9.39 8.68	10.52	75.94 67.50	9.42 8.84	10.70
6-CH ₃	CH ₃	<i>n</i> -C ₁₀ H ₂₁	55-57 194-195	Petroleum ether	48 30	C ₂₀ H ₃₀ N ₂ O	76.39 68.45	9.62 8.90	76.21 10.10	9.62 68.35	8.72	10.15
6,8-di-CH ₃	CH ₃	C ₂ H ₅	128-129 195-205	Ethanol	77 71	C ₁₃ H ₁₆ N ₂ O	72.19 61.78	7.46 6.78	14.03	72.24 62.08	7.54 6.81	13.82
7-Cl	CH ₃	C ₂ H ₅	114-116 176-180	Isopropyl ether	90 92	C ₁₁ H ₁₁ ClN ₂ O	59.30 50.98	4.98 4.67	13.68	59.41 50.82	5.03 4.74	13.44
7,9-di-Cl	CH ₃	C ₂ H ₅	178-180 (e)	Ethanol	61	C ₁₁ H ₁₀ Cl ₂ N ₂ O	51.39	3.92		51.42	3.86	
9-OH	CH ₃	C ₂ H ₅	128 175-178	Ethanol/Water (3:1)	73 59	C ₁₁ H ₁₂ N ₂ O ₂	64.69 55.12	5.92 5.47	14.79	64.90 55.22	6.15 5.51	14.67
6-CH ₃	C ₂ H ₅	CH ₃	87-88 195-202	Petroleum ether	75 76	C ₁₂ H ₁₄ N ₂ O	71.26 60.38	6.98 6.33	14.85	71.14 60.11	6.76 6.70	14.56
6-CH ₃	<i>n</i> -C ₃ H ₇	C ₂ H ₅	74-76 160-165	Petroleum ether	76 75	C ₁₄ H ₁₈ N ₂ O	73.01 63.02	7.88 7.18	13.29	73.04 63.28	7.98 7.32	13.15
H	CH ₃	C ₆ H ₅ CH ₂	111-112 185-192	Ethanol	85	C ₁₆ H ₁₄ N ₂ O	76.78 67.02	5.64 5.27	12.36	76.72 67.14	5.61 5.35	11.98
6-CH ₃	CH ₃	C ₆ H ₅ CH ₂	142-143 186-191	Ethanol	65	C ₁₇ H ₁₆ N ₂ O	77.25 67.49	6.10 5.70	11.79	77.31 67.28	6.16 5.97	12.05
H	CH ₃	CH ₂ C ₆ H ₄ Cl(p)	136-137 176-182	Ethanol	60	C ₁₆ H ₁₃ ClN ₂ O	67.49 59.83	4.60 4.39	11.04	67.18 59.88	4.56 4.46	10.89
H	CH ₃	C ₆ H ₁₁ CH ₂	112-114 155-162	Ether	62	C ₁₆ H ₂₀ N ₂ O	74.96 65.63	7.86 7.23	12.11	74.88 65.48	7.90 7.31	11.96

6-CH ₃	CH ₃	C ₆ H ₁₁ CH ₂	124-126 165-170	Petroleum ether	68	C ₁₇ H ₂₂ N ₂ O	75.52 66.55	8.20 7.56	11.55	75.67 66.65	8.22 7.48	11.28
6-CH ₃	1-Adamantyl	H	oil 175-182		38	C ₁₉ H ₂₂ N ₂ O	68.95	7.00	10.71	68.82	7.07	10.50

(a) In the first line the data for the bases, in the second those for the hydrochlorides are shown. (b) Hydrochlorides were all crystallized from ethanol-ether. (c) Yields in the first line refer to ring closure with PPA, those in the second to that with phosphoryl chloride-PPA followed by decomposition with ethanol. (d) Literature (5) m.p. 92-95°, yield 76%. (e) Recrystallization of the hydrochloride from ethanol gave back the base.

Table II
Substituted 1,4-Dihydro-1,8-naphthyridin-4-ones



R ¹	R ²	R ³	M.p., °C	Solvent of Recrystallization	Yield %	Molecular Formula	Analysis			
							Calcd. C	Calcd. H	Found C	Found H
H	CH ₃	CH ₃	300	DMF	81	C ₁₁ H ₁₂ N ₂ O	70.18	6.43	70.12	6.56
H	C ₂ H ₅	CH ₃	268-270	Ethanol	89	C ₁₂ H ₁₄ N ₂ O	71.26	6.98	71.45	7.12
CH ₃	C ₂ H ₅	CH ₃	236-239	Ethanol	85	C ₁₃ H ₁₆ N ₂ O	72.19	7.46	72.36	7.45
H	H	<i>n</i> -C ₃ H ₇	215-217	Ethanol	68	C ₁₂ H ₁₄ N ₂ O	71.26	6.98	71.17	6.91
H	<i>n</i> -C ₃ H ₇	CH ₃	255-257	Ethanol	92	C ₁₃ H ₁₆ N ₂ O	72.19	7.46	72.22	7.51
H	<i>n</i> -C ₄ H ₉	CH ₃	227-228	Ethanol	76	C ₁₄ H ₁₈ N ₂ O	73.01	7.88	73.16	7.91
H	CH ₂ C ₆ H ₁₁	CH ₃	292-293	Ethanol	72	C ₁₇ H ₂₂ N ₂ O	75.52	8.20	75.48	8.26
H	H	1-Adamantyl	259-262	Ethanol	51	C ₁₉ H ₂₂ N ₂ O	77.52	7.53	77.66	7.51

nature of substitution at C-2 and C-3, the 1,8-naphthyridines **5** in high yields (7).

It is characteristic of the pmr spectrum of **6a** that, as a consequence of the flexibility of the piperidine ring, axial and equatorial protons associated with the methylene groups attached to the pyrimidinone ring (CH₂-6, CH₂-9) are isochronous. In **6b** however, the methyl group at C-6 eliminates this mobility and, like in similar systems (1a), the predominant conformer is the one in which this methyl group is axial relative to the plane of the pyrimidinone ring.

Pharmacological testing of the compounds described was carried out by Professor J. Knoll and his co-workers at the Semmelweis Medical University, Budapest. As it had been found earlier for compounds of type **1**, many of them exhibited favorable analgetic and excellent morphine potentiating effects (8).

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and are uncorrected. Ir spectra were taken in potassium bromide pellets with a Unicam SP 200 spectrometer. The pmr spectra were obtained on a JEOL 60 spectrometer with tetramethylsilane as internal standard.

2,6-Dimethyl-3-ethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one (**3b**).

Method A.

2-Amino-6-methylpyridine (2.16 g., 0.02 mole) and ethyl 2-ethylacetoacetate (20.0 g., 0.02 mole) were stirred with polyphosphoric acid (20 g.) in an oil bath of 120° for 90 minutes. The hot mixture was cautiously diluted with some water and then neutralized with 10% aqueous sodium

hydroxide. The beige precipitate was separated and washed with water to give almost pure **3** (3.2 g., m.p. 125-127°), recrystallized from ethanol, m.p. 127-128°; ir ν max: 1665, 1640, 1485 cm⁻¹; pmr (deuteriochloroform): δ 1.15 (t, 3H, CH₂-CH₃), 2.41 (s, 3H, CH₃-2), 2.63 (q, 2H, CH₂CH₃), 3.04 (s, 3H, CH₃-6), 6.60 (m, 1H, H-7), 7.30 (m, 2H, H-8, H-9).

Method B.

To a mixture of 2-amino-6-methylpyridine (21.6 g., 0.20 mole) and ethyl 2-ethylacetoacetate (31.6 g., 0.20 mole) a mixture of phosphoryl chloride (46 ml., 0.50 mole) and polyphosphoric acid (14.0 g.) was added dropwise followed by stirring for 3 hours in an oil bath of 110°. The reaction mixture was then decomposed at 70-80° with dry ethanol (200 ml.) and, after having allowed the mixture to stand overnight, the hydrochloride of **3b** was filtered off. The m.p. and spectra of the base prepared from this material were identical with those of **3b** prepared by Method A. For physical and analytical data of **3b** and other pyrido[1,2-*a*]pyrimidin-4-ones synthesized by Methods A and B are listed in Table I.

2-Methyl-3-ethyl-4-methylthiopyrido[1,2-*a*]pyrimidin-5-ium Iodide (**4**).

Compound **3a** (1.88 g., 0.01 mole) (prepared analogously to **3b**) and phosphorus pentasulfide (2.2 g) were refluxed in pyridine (50 ml.) for 16 hours. The reaction mixture was cooled and poured onto ice. The product was extracted with ether, the ethereal solution dried over magnesium sulfate and the solvent evaporated. The residue was dissolved in dry benzene (10 ml.), methyl iodide (5.0 ml.) was added and the mixture allowed to stand overnight. The yellow crystalline product (2.3 g., 66%, m.p. 124-127°) had, after recrystallization, m.p. 126-128° (ethanol); ir ν max: 3000, 1625, 1580 cm⁻¹; pmr (deuteriochloroform): δ 1.41 (t, 3H, CH₂CH₃), 2.85 (s, 3H, CH₃-2), 3.02 (s, 3H, SCH₃), 3.40 (q, 2H, CH₂CH₃), 8.60 (m, 3H, H-7, H-8, H-9), 10.12 (m, 1H, H-6).

Anal. Calcd. for C₁₂H₁₅IN₂S: C, 41.53; H, 4.37. Found: C, 41.46; H, 4.38.

2,7-Dimethyl-3-ethyl-1,4-dihydro-1,8-naphthyridin-4-one (**5**).

Compound **3b** (1.01 g., 5 mmole) was added to paraffin oil (50 ml.) preheated to 300° and kept at this temperature for 30 minutes. After

cooling, dilution of the mixture with an equal volume of petroleum ether gave a precipitate which was separated on a glass filter and rinsed with petroleum ether to obtain **5** (0.89 g., 89%); ν max: 1615, 1525, 1460 cm^{-1} ; pmr (deuteriotrifluoroacetic acid): δ 1.30 (t, 3H, CH_2CH_3), 2.92 (q, 2H, CH_2CH_3), 2.94 (s, 3H, CH_3 -2), 2.95 (s, 3H, CH_3 -7), 7.67 (d, 1H, H-6), 9.92 (d, 1H, H-5).

Physical and analytical data of **5** and other 1,8-naphthyridines synthesized by the same method are listed in Table II.

2-Methyl-3-ethyl-6,7,8,9-tetrahydro-4H-pyrido[1,2-a]pyrimidin-4-one (**6a**). Method A.

Hydrogenation of **3a** (1.88 g., 0.01 mole) in ethanol (25 ml.) over Raney nickel (2 g.) at room temperature and atmospheric pressure gave, after the usual work-up, a colorless oil which was distilled from a Hickman collar flask to give **6a** (1.8 g., 94%) as an oil (b.p. 146-148°/6 mm), which shortly crystallized; ν max: 2960, 1655, 1540 cm^{-1} ; pmr (deuteriochloroform): δ 1.10 (t, 3H, CH_2CH_3), 1.95 (m, 4H, CH_2 -7, CH_2 -8), 2.28 (s, 3H, CH_3), 2.57 (q, 2H, CH_2CH_3), 2.88 (t, 2H, CH_2 -9), 3.95 (t, 2H, CH_2 -6).

Anal. Calcd. for $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}$: C, 68.72; H, 8.39. Found: C, 68.67; H, 8.40.

Method B.

Hydrogenation of **3a** (0.01 mole) over 10% palladium on charcoal in ethanol (25 ml.) was accomplished quantitatively in 5 hours and gave a product which was identified by its spectra with the one obtained by Method A.

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

Reduction of **3b** with either of Methods A and B gave **6b** in quantitative yield, b.p. 127-128°/6 mm (crystallizing); ν max: 2960, 1650,

1535 cm^{-1} ; pmr (deuteriochloroform): δ 1.10 (t, 3H, CH_2CH_3), 1.35 (d, 3H, CH_3 -6), 1.90 (m, 4H, CH_2 -7, CH_2 -8), 2.17 (s, 3H, CH_3 -2), 2.55 (q, 2H, CH_2CH_3), 2.90 (m, 2H, CH_2 -9), 4.95 (m, 1H, H-6).

Anal. Calcd. for $\text{C}_{12}\text{H}_{18}\text{N}_2\text{O}$: C, 69.87; H, 8.80. Found: C, 69.82; H, 8.40.

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