Synthesis of some Substituted Pyrido[1,2-*a*]pyrimidin-4-ones and 1,8-Naphthyridines

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The substituted 4*H*-pyrido[1,2-*a*]pyrimidin-4-ones (I) were obtained by the condensation of substituted 2-aminopyridines with β-ketocarboxylic esters in PPA. Some of the derivatives I were transformed into the corresponding 1,8-naphthyridines II and III.

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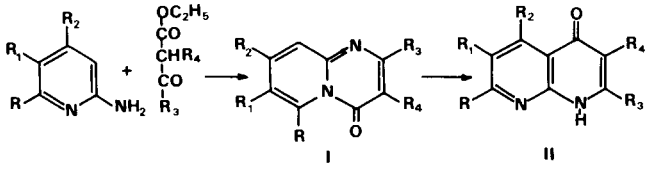
During the past 20 years, many 4*H*-pyrido[1,2-*a*]-pyrimidine derivatives of type I have been synthesized and significant biological properties of a large number of them reported (hypotensive, analgetic, CNS stimulant, bactericide, etc) [1,7].

Moreover, some of these pyridopyrimidinones have been used, as starting materials, for the preparation of 1,8-naphthyridines [1,8,9].

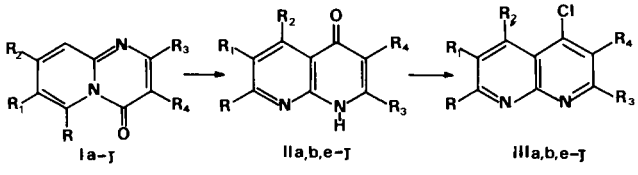
Pursuing our interest in heterocyclic compounds, we describe in this paper, the synthesis and properties of some pyrido[1,2-*a*]pyrimidines and 1,8-naphthyridines.



I II

Compounds I were obtained in good yields by cyclization of 2-aminopyridines with β-ketocarboxylic esters in polyphosphoric acid (PPA) at 110°. Reaction of 2-amino-4-methylpyridine with dimethyl 1,3-acetonedicarboxylate, instead of the expected pyridopyrimidine Is (R = R_1 = R_4 = H, R_2 = CH_3, R_3 = CH_2COOCH_3), gave, as the main product, 2,8-dimethylpyridopyrimidine Iq, which was also obtained by cyclization of 2-amino-4-methylpyridine with ethyl acetoacetate in PPA (Table I).

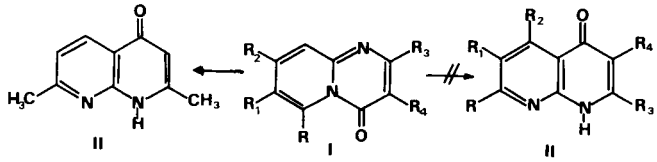
The isomerization of pyridopyrimidines I to 1,8-naphthyridines II was carried out in diphenyl ether under reflux conditions.



Ia-j IIa,b,e-j IIIa,b,e-j

Ring transformation, in agreement with that reported in the literature [1,8-10], occurred depending on the position and the nature of the substituent in the pyridine nucleus. Thus compounds Ia,b,e,-j (R = CH_3), when refluxing in diphenyl ether for 5 hours, were converted in high yields to the corresponding 1,8-naphthyridines IIa,b,e-j.

Some attempts to convert pyridopyrimidine Ic,d (R = CH_3) into the corresponding 1,8-naphthyridines IIc,d were unsuccessful. Both compounds gave instead, in good yields, the same 2,7-dimethyl-1,8-naphthyridin-4-one IIa, which was also obtained by heating 2,6-dimethyl-4*H*-pyrido[1,2-*a*]pyrimidin-4-one Ia in diphenyl ether. In the case of Ig (R = CH_3), under reflux conditions, 65% isomerization was reached after 24 hours.



II I II

c : R=CH_3; R_1=R_2=R_4= H; R_3=CH_2COOCH_3
d : R=CH_3; R_1=R_2=R_4=H; R_3=CH_2Cl

From this last result it appears that ring transformation of pyridopyrimidines I to 1,8-naphthyridines II, by 1-3 N→C acyl migration, is also dependent on the nature of substitution at C-3.

Isomerization of pyridopyrimidineones Ik-r, t-x (R = H) instead failed and the starting materials were recovered.

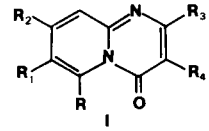
The 1,8-naphthyridines II were then converted in good yields to the corresponding chloro derivatives III by heating with phosphoryl chloride.

Elemental and spectral analyses of all the new compounds described are consistent with the assigned structures. Many of these compounds are, at the moment, under biological screening.

EXPERIMENTAL

Melting points were determined with a Kofler apparatus. The ir spectra were recorded on a Perkin-Elmer Model 197 spectrophotometer in Nujol mulls. The ^{1}H nmr spectra were obtained with a JEOL Model C 60 HL spectrometer with TMS as an internal standard.

Table I

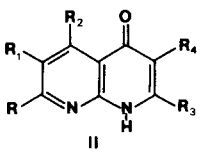


I

Compound No.	R	R_1	R_2	R_3	R_4	Yield %	Mp °C	Empirical Formula	Elemental Analyses Calcd. % C	H	N	Found % C	H	N
Ia	CH_3	H	H	CH_3	H	(11)	—							
Ib	CH_3	H	H	n-C_3H_7	H	62	45-47 (c)	$C_{12}H_{14}N_2O$	71.26	6.97	13.84	71.20	6.85	13.79
Ic	CH_3	H	H	CH_2COOCH_3	H	89	115-120 (c)	$C_{12}H_{12}N_2O_3$	62.06	5.21	12.06	62.36	5.32	12.34
Id	CH_3	H	H	CH_2Cl	H	79	122-123 (d)	$C_{10}H_9ClN_2O$	57.56	4.34	13.42	57.13	4.18	13.11
Ie	CH_3	H	H	CF_3	H	53	120-122 (c)	$C_{10}H_7F_3N_2O$	52.63	3.09	12.27	52.87	3.22	12.19
If	CH_3	H	H	p-$NO_2C_6H_4$		96	256-258 (e)	$C_{15}H_{11}N_3O_3$	64.05	3.94	14.94	64.13	4.06	14.94
Ig	CH_3	H	H	CH_3	Cl	66	195-196 (c)	$C_{10}H_9ClN_2O$	57.56	4.34	13.42	57.83	4.50	13.40
Ih	CH_3	H	CH_3	CH_3	H	71	99-100 (f)	$C_{11}H_{12}N_2O$	70.18	6.43	14.88	70.51	6.27	14.53
Ii (1)	CH_3	H	H	CH_3	CH_3	—	—							
Ij	CH_3	H	CH_3	CH_3	CH_3	77	136-139 (c)	$C_{12}H_{14}N_2O$	71.26	6.97	13.84	71.29	7.08	13.70
Ik	H	CH_3	H	CH_2Cl	H	55	132-135 (c)	$C_{10}H_9ClN_2O$	57.56	4.34	13.42	57.77	4.00	13.22
Il	H	CH_3	H	C_6H_5	H	72	165-166 (c)	$C_{15}H_{12}N_2O$	76.25	5.12	11.86	76.56	5.38	11.82
Im	H	CH_3	H	CH_3	CH_3	80	115-120 (c)	$C_{11}H_{12}N_2O$	70.18	6.43	14.88	70.32	6.29	14.71
In	H	CH_3	H	CH_3	$CH_2COOC_2H_5$	36	135-140 (c)	$C_{14}H_{16}N_2O_3$	64.60	6.20	10.76	64.63	5.97	10.58
Io	H	CH_3	H	CH_3	Cl	56	175-180 (c)	$C_{10}H_9ClN_2O$	57.56	4.34	13.42	57.72	4.07	13.65
Ip	H	Cl	H	CH_3	H	78	170-172 (c)	$C_9H_7ClN_2O$	55.53	3.62	14.39	55.47	3.56	14.10
Iq	H	H	CH_3	CH_3	H	65 (a) 80 (b)	130-132 (c)	$C_{10}H_{10}N_2O$	68.95	5.79	16.08	68.67	5.63	16.12
Ir	H	H	CH_3	$CH(CH_3)_2$	H	41	94-96 (c)	$C_{12}H_{14}N_2O$	71.26	6.97	13.84	71.58	7.23	13.53
It	H	H	CH_3	CH_2Cl	H	41	109-110 (c)	$C_{10}H_9ClN_2O$	57.56	4.34	13.42	57.62	4.33	13.20
Iu	H	H	CH_3	C_6H_5	H	69	138-139 (g)	$C_{15}H_{12}N_2O$	76.25	5.12	11.86	76.51	5.31	12.04
Iv	H	H	CH_3	CH_3	CH_3	48	89-90 (c)	$C_{11}H_{12}N_2O$	70.18	6.43	14.88	70.37	6.51	14.99
Iw	H	H	CH_3	CH_3	$CH_2COOC_2H_5$	38	115-120 (c)	$C_{14}H_{16}N_2O_3$	64.60	6.20	10.76	64.70	6.33	10.51
Ix	H	H	CH_3	CH_3	Cl	33	167-169 (c)	$C_{10}H_9ClN_2O$	57.56	4.34	13.42	57.26	4.12	13.15

(a) From 2-amino-4-methylpyridine and dimethyl-1,3-acetonedicarboxylate (b) From 2-amino-4-methylpyridine and ethyl acetoacetate. Recrystallization solvent: (c) Petroleum ether 60-80°; (d) Water; (e) Chloroform (f) Petroleum ether 100-140°; (g) Carbon tetrachloride.

Table II

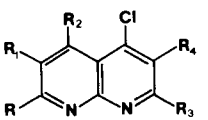


II

Compound No.	R	R_1	R_2	R_3	R_4	Yield %	Mp °C	Recrystallization Solvent	Empirical Formula	Elemental Analyses Calcd. % C	H	N	Found % C	H	N
IIa (9)	CH_3	H	H	CH_3	H	85 (a) 84 (b)	>320	—							
IIb	CH_3	H	H	n-C_3H_7	H	55	220-222	dioxane	$C_{12}H_{14}N_2O$	71.26	6.97	13.84	71.10	6.93	13.60
IIe	CH_3	H	H	CF_3	H	75	231-232	H_2O/EtOH 4:1	$C_{10}H_7F_3N_2O$	52.63	3.09	12.28	52.39	3.20	11.97
IIf	CH_3	H	H	p-$NO_2C_6H_4$	H	95	>320	CH_3COOH	$C_{15}H_{11}N_3O_3$	64.05	3.94	14.94	64.02	4.01	14.92
IIg	CH_3	H	H	CH_3	Cl	65	>320	DMF	$C_{10}H_9ClN_2O$	57.55	4.34	13.42	57.81	3.95	13.65
IIh	CH_3	H	CH_3	CH_3	H	90	285-290 dec	toluene	$C_{11}H_{12}N_2O$	70.18	6.43	14.88	70.01	6.52	14.53
IIi (1)	CH_3	H	H	CH_3	CH_3	—	—	—							
IIj	CH_3	H	CH_3	CH_3	CH_3	60	261-262	benzine 100-140°	$C_{12}H_{14}N_2O$	71.26	6.97	13.84	71.32	7.05	13.72

(a) From Ic. (b) From Id.

Table III



III

Compound No.	R	R_1	R_2	R_3	R_4	Yield %	Mp °C	Recrystallization Solvent	Empirical Formula	Elemental Analyses Calcd. % C	H	N	Found % C	H	N
IIIa	CH_3	H	H	CH_3	H	82	86-87	benzene	$C_{10}H_9ClN_2$	62.34	4.70	14.57	62.27	4.65	14.63
IIIb	CH_3	H	H	n-C_3H_7	H	97	156-158	EtOH anh	$C_{12}H_{13}ClN_2$•picrate	48.06	3.58	15.57	48.18	3.59	15.42
IIIe	CH_3	H	H	CH_3	H	85	124-125	CCl_4	$C_{10}H_6ClF_3N_2$	48.68	2.45	11.35	48.78	2.47	10.95
IIIf	CH_3	H	H	p-$NO_2C_6H_4$	H	95	214-215	AcOEt	$C_{15}H_{10}ClN_3O_2$	60.11	3.36	14.01	60.27	3.22	13.89
IIIg	CH_3	H	H	CH_3	Cl	73	168-170	MeOH/H_2O 2:1	$C_{10}H_8Cl_2N_2$	52.88	3.55	12.33	52.95	3.90	12.01
IIIh	CH_3	H	CH_3	CH_3	H	86	118-119	H_2O	$C_{11}H_{11}ClN_2$	63.92	5.32	13.55	63.91	5.26	13.27
IIIi	CH_3	H	H	CH_3	CH_3	90	177-179	Petroleum ether 100-140°	$C_{11}H_{11}ClN_2$	63.92	5.36	13.55	64.18	5.55	13.45
IIIj	CH_3	H	CH_3	CH_3	CH_3	92	136-137	Petroleum ether 100-140°	$C_{12}H_{13}ClN_2$	65.32	5.93	12.69	64.99	5.87	12.54

General Procedure of the Preparation of Substituted 4*H*-Pyrido[1,2-*a*]-pyrimidin-4-ones (I).

A mixture of 0.05 mole of 2-aminopyridines, 0.06 mole of a suitable β-ketoester and 30 g of poylphosphoric acid was heated at 110° for 4-5 hours with stirring. The cooled mixture was poured into ice and the *p*H of the solution was then adjusted to 6-7 with 10% aqueous sodium hydroxide. The products were separated by one of the following methods and then purified by crystallization (Table I). A) The precipitated pyrido-pyrimidones (Id-l, n-p,r,t-v,x) were collected and washed with water. B) The reaction mixture was extracted with chloroform. The combined extracts were washed with water, dried over magnesium sulfate and evaporated to obtain the pridopyrimidones (Ib,c,m,q,w).

General Procedure for the Preparation of Substituted 1,8-Naphthyridin-4-ones (IIa,b,e-j).

Pyridopyrimidones Ib-j (1.0 g) were added to diphenyl ether (10 ml) and refluxed for 5 hours. Compound Ig was obtained in 65% yield when the mixture was refluxed for 24 hours. After cooling the precipitated naphthyridines were collected and washed with light petroleum (Table II).

General Procedure for the Preparation of Substituted 4-Chloro-1,8-naphthyridines (IIa,b,e-j).

The compounds IIa,b,e-j (5.0 g) were added to ice cooled phosphoryl chloride (30 ml) and the mixture was heated under reflux conditions for one hour. Compound IIb was heated at 80° for 15 hours. The cooled reaction products were poured into ice and then made alkaline (*p*H 9) with cooled concentrated ammonium hydroxide. The precipitated chloro-naphthyridines (IIIe-i) were separated by filtration and washed with water. The 4-chloro-1,8-naphthyridines (IIIa,b,j) were instead extracted with chloroform. The combined extracts were dried over magnesium sulfate and evaporated to dryness *in vacuo* (Table III).

Acknowledgement.

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