One Step Synthesis of Pyrimido[1,2-*a*][1,8]naphthyridinones, Pyrido[1,2-*a*]pyrimidinones and 1,8-Naphthyridinones. Antihypertensive Agents. V

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The condensation of 2,6-diaminopyridine and 2-acetamido-6-aminopyridine with β-keto esters in polyphosphoric acid was studied. In this reaction some 1,8-naphthyridinones, pyrido[1,2-*a*]pyrimidinones and pyrimido[1,2-*a*][1,8]naphthyridinones variously substituted were obtained.

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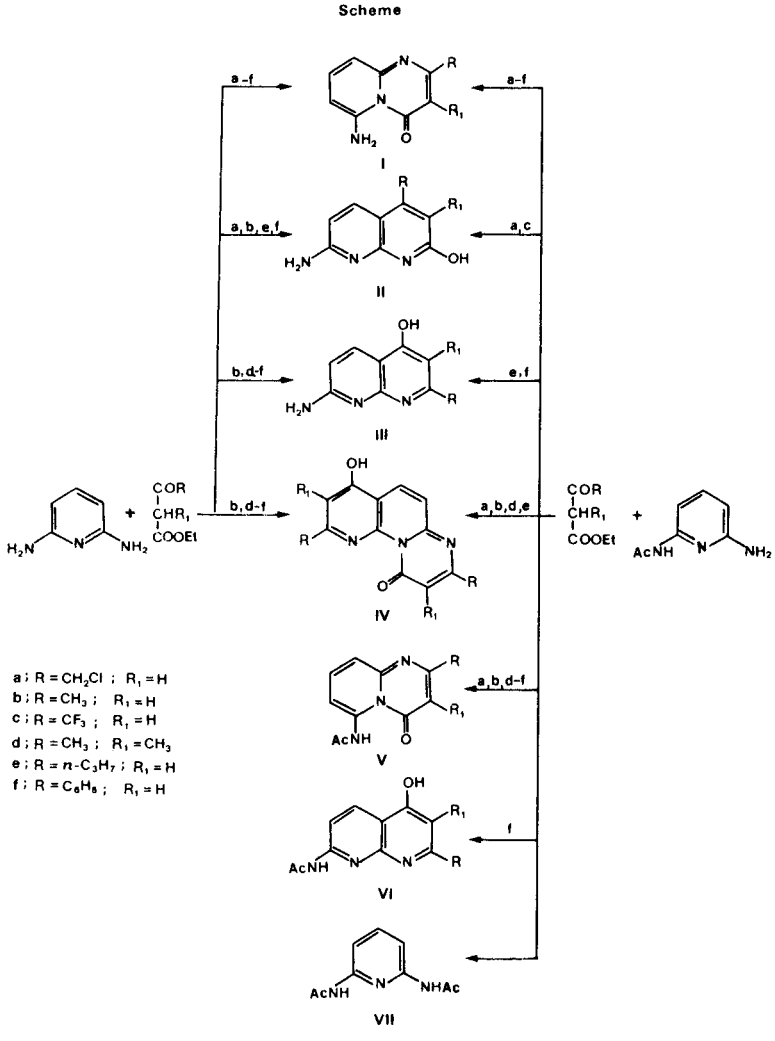
Several substituted 2-hydroxy- and 4-hydroxy-1,8-naphthyridines have been prepared by condensation of substituted aminopyridines with β-ketocarboxylic esters or EMME in concentrated sulfuric acid or Dowtherm A [1-8].

More recently, we described the synthesis of several substituted 2-hydroxy- and 4-hydroxy-10*H*-pyrimido[1,2-*a*]-[1,8]naphthyridin-10-ones. The general synthetic procedure used in the preparation of these compounds involved the condensation of the substituted 2-amino-7-hydroxy-1,8-naphthyridines or 2,6-diaminopyridine with a suitable β-ketocarboxylic ester and the subsequent cyclization of the anil derivatives in Dowtherm A [4,7,9-12].

The pyrido[1,2-*a*]pyrimidin-4-ones, as known, are easily accessible by condensation of substituted aminopyridines with β-ketocarboxylic esters in poliphosphoric acid (PPA) [8,13,14].

Scheme



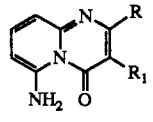
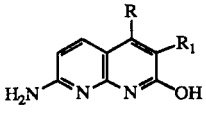
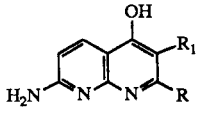
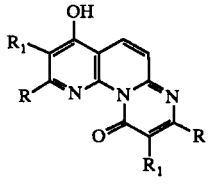
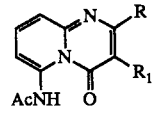
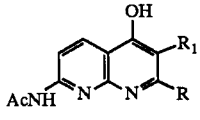
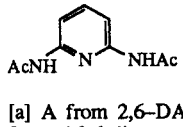
In a previous paper we described the condensation of methylaminopyridines with ethyl 4-chloroacetoacetate in PPA to give the corresponding 6-, 7-, and 8-methyl-2-chloromethylpyrido[1,2-*a*]pyrimidin-4-ones for the preparation of potential antihypertensive molecules [13]. In the course of this research program we required the preparation of 6-amino-2-chloromethylpyrido[1,2-*a*]pyrimidin-4-one **Ia**. Attempts to prepare **Ia** by condensation of 2,6-diaminopyridine with ethyl 4-chloroacetoacetate in PPA failed, but this reaction appeared of interest. Consequently our interest in the chemistry of heterocyclic compounds prompted us to examine the condensation of 2,6-diaminopyridine and 2-acetamido-6-aminopyridine [15] with various β-ketocarboxylic esters in PPA (Scheme).

This reaction was carried out essentially under the same conditions reported in a previous paper for the synthesis of pyrido[1,2-*a*]pyrimidinones [8].

Under these conditions, when 2,6-diaminopyridine was allowed to react with β-ketoesters at 80° for 4 hours, a mixture of compounds **I, II, III** and **IV** was generally obtained, whose ratio depending on the substituents of β-ketocarboxylic esters (Tables I-IV). Under the same condi-

Table I

Condensation of 2,6-Diamipyridine or 2-Acetamido-6-aminopyridine: Yields %

Compound		a		b		c		d		e		f	
	R	CH_2Cl		CH_3		CF_3		CH_3		n-C_3H_7		C_6H_5	
	R_1	H		H		H		CH_3		H		H	
	[a]	A	B	A	B	A	B	A	B	A	B	A	B
	I	9	6	12	4	78	39	7	8	10	9	4	5
	II	50	2	3 [1]	–	–	4	–	–	5	–	16 [2]	–
	III	–	–	51 [4]	–	–	–	41	–	41	5	15	15
	IV [b]	–	42	27	50	–	–	16	68	22	45	4	–
	V	–	6	–	5	–	–	–	2	–	12	–	2
	VI	–	–	–	–	–	–	–	–	–	–	–	22
	VII [c]	–	47	–	68	–	37	–	73	–	50	–	41

[a] A from 2,6-DAP; B from 2-diacetamido-6-aminopyridine. [b] Yields calculated on the β-ketoester. [c] Yields calculated on the theoretically formed 2,6-diacetamidopyridine.

Table II

Substituted 2- Hydroxy- and 4-hydroxy-1,8-naphthyridines II, III and VI

Compound No.	Mp°C	Recrystallization Solvent	Empirical Formula	Elemental Analyses Calcd./Found C	H	N
IIa	>320	DMSO	$C_9H_8N_3OCl$	51.56 51.72	3.84 4.18	20.04 20.41
IIc	>320	CH_3COOH	$C_9H_6N_3OF_3$	47.16 47.00	2.64 2.81	18.33 18.56
IIe	>320	DMF	$C_{11}H_{13}N_3O$	65.00 65.17	6.45 6.50	20.68 20.76
IIId	>320	EtOH	$C_{10}H_{11}N_3O$	63.47 63.48	5.86 5.95	22.21 21.93
IIIe	270-271	Water	$C_{11}H_{13}N_3O \cdot H_2O$	59.71 60.03	6.83 7.12	18.99 19.15
IIIf	160-162	Water	$C_{14}H_{11}N_3O \cdot 2H_2O$	61.52 61.37	5.53 5.28	15.37 15.27
VIf	267-269	DMF/Water	$C_{16}H_{13}N_3O_2$	68.80 69.12	4.69 4.57	15.05 15.32

Table III

Substituted Pyrido[1,2-*a*]pyrimidin-4-ones I and V

Compound No.	Mp°C	Recrystallization Solvent	Empirical Formula	Elemental Analyses Calcd./Found C	H	N
Ia	170-173	Petroleum Ether 100-140°	$C_9H_8N_3OCl$	51.56 51.60	3.84 4.01	20.04 19.82
Ib	184-186	Water	$C_9H_9N_3O$	61.70 62.05	5.18 5.42	23.99 23.99
Ic	181-184	Petroleum Ether 100-140°	$C_9H_6N_3OF_3$	47.16 47.42	2.64 2.88	18.33 18.31
Id	164-166	Petroleum Ether 100-140°	$C_{10}H_{11}N_3O$	63.47 63.68	5.86 5.91	22.21 22.08
Ie	132-133	Petroleum Ether 100-140°	$C_{11}H_{13}N_3O$	65.00 65.14	6.45 6.62	20.68 21.01
If	137 dec.	Petroleum Ether 100-140°	$C_{14}H_{11}N_3O$	70.87 70.90	4.67 4.74	17.71 17.61
Va	158-160	Petroleum Ether 100-140°	$C_{11}H_{10}N_3O_2Cl$	52.48 52.74	4.00 4.02	16.69 17.03
Vb	169-170	Petroleum Ether 100-140°	$C_{11}H_{11}N_3O_2$	60.82 60.55	5.10 4.93	19.35 19.03
Vd	138-140	Petroleum Ether 100-140°	$C_{12}H_{13}N_3O_2$	62.32 62.05	5.67 5.43	18.17 17.88
Ve	90-92	Petroleum Ether 100-140°	$C_{13}H_{15}N_3O_2$	63.66 63.34	6.16 6.12	17.13 17.14
Vf	152-155	Petroleum Ether 100-140°	$C_{16}H_{13}N_3O_2$	68.80 68.98	4.69 4.49	15.05 14.88

Table IV

Substituted Pyrimido[1,2-*a*][1,8]naphthyridin-10-ones IV

Compound No.	Mp°C	Recrystallization Solvent	Empirical Formula	Elemental Analyses Calcd./Found C	H	N
IVa	165-168	DMSO	$C_{13}H_9Cl_2N_3O_2$	49.70 49.89	2.88 3.00	13.38 13.10
IVb	222-225	Water	$C_{13}H_{11}N_3O_2$	64.72 64.91	4.60 4.57	17.42 17.32
IVd	214-216	AcOEt	$C_{15}H_{15}N_3O_2$	66.90 67.17	5.61 5.85	15.61 15.81
IVe	153-154	*i*-PrOH	$C_{17}H_{19}N_3O_2$	68.66 68.95	6.44 6.60	14.31 14.36
IVf	269-272	*n*-BuOH	$C_{23}H_{15}N_3O_2$	75.60 75.38	4.14 4.15	11.50 11.21

tions 2-acetamido-6-aminopyridine gave generally a mixture of **I, II, III, IV, V** and **VI** together with 2,6-diacetamidopyridine **VII** (Tables I-IV). This last compound was also obtained in good yield, by transamidation, heating 2-acetamido-6-aminopyridine at 80° in PPA.

The structure of **IVa** was established by single X-ray determination (the ORTEP diagram is shown in Figure 1) and by mass spectroscopy [m/e: 309 (M^+)]. Moreover the structure of compounds **IVa** was confirmed by catalytic reduction to the known **IVb** [4].

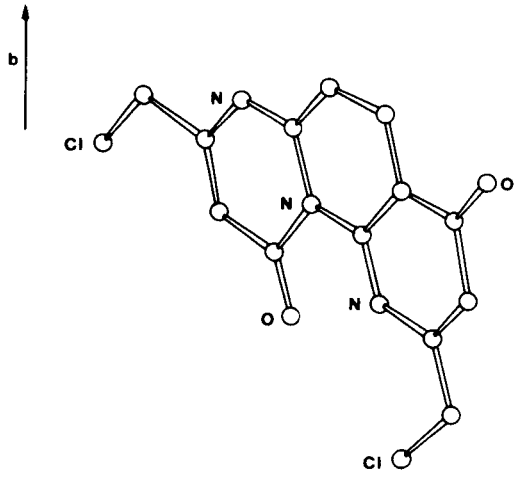


Figure 1

The uv spectra of **IVd-f** show absorption patterns in good agreement with those found for **IVa,b** and were different to that of 2-hydroxy-4,10-dimethyl-10*H*-pyrimido-[1,2-*a*][1,8]naphthyridin-10-one **VIII** [9]. In this way the structure of **IVd-f** were unequivocally proved (Table V).

Table V

UV Data of Substituted Pyrimido[1,2-*a*]naphthyridin-10-ones IV and VIII

Compound No.	UV nm (ε)
IVa	234.5 (20, 120), 337.9 (7,952), 397.8 (14,475), 400.8 (13,227)
IVb	239.9 (18,817), 333.7 (6,520), 357.9 (8,749), 375.1 (13,128)
IVd	239.9 (25,170), 340.9 (8,912), 362.1 (12,066), 380.2 (16,607), 401.1 (13,304)
IVe	253.3 (25,788), 319.2 (6,039), 334.5 (8,349), 357.6 (11,160), 375.3 (16,892), 395.8 (15,009)
IVf	294.8 (38,577), 349.6 (7,319), 369.9 (10,269), 389.9 (17,760), 412.4 (18,683)
VIII	283.4 (20,443), 369.5 (9,093), 388.0 (15,961), 409.5 (18,110)

The structures of **IIa** was established by catalytic reduction to **IIb** [1] and consequently those of **IIc-f**. The isomeric compounds **III** showed different absorption patterns to that of the corresponding compounds **II** as seen in Table VI.

The structures of the all compounds were supported by analytical, ir and ^1H nmr data.

The ^1H nmr spectra of **IV** show two doublets in the range of δ 8.56-8.33 and δ 7.33-7.23 due to H_5 and H_6 respectively and two singlets in the range of δ 7.23-6.36 due to H_3 and H_9.

The ^1H nmr spectra of 2-hydroxynaphthyridines **II** show two doublets in the range of δ 7.76-7.63 and 6.33-5.60 assigned to H_5 and H_6 respectively and one singlet in the range of δ 6.33-4.83 due to H_3.

Table VI

UV Data of Substituted 2-Hydroxy- and 4-hydroxy-1,8-naphthyridines II, III and VI

Compound No.	UV nm (ε)
IIa	228.4 (1,190), 357.6 (1,755)
IIb [1]	338.0 (3,441), 355.2 (3,155)
IIc	228.4 (2,465), 355.2 (6,849), 373.2 (7,488)
IIe	341.2 (8,253), 356.2 (9,005)
IIf [2]	246.6 (10,560), 345.4 (10,840), 359.5 (11,800)
IIIb [4]	243.4 (16,660), 306.8 (7,465), 319.3 (8,932), 332.0 (8,071)
IIId	244.7 (25,677), 307.2 (9,739), 320.5 (13,020), 334.8 (9,427)
IIIe	243.4 (27,736), 305.5 (13,227), 319.8 (5,227), 330.3 (13,990)
IIIf	248.3 (23,963), 328.5 (13,865)
VIf	256.6 (17,500), 291.5 (11,062)

The ^{1}H nmr spectra of the 4-hydroxynaphthyridines **III** exhibit three characteristic signals, which appeared as two doublets in the range of δ 8.13-7.96 and δ 6.56-6.00 due to H_5 and H_6 respectively and one singlet in the range of δ 7.35-5.76.

The ^{1}H nmr spectra of **I** show a signal in the range of δ 7.50-7.36 assigned to H_8, one singlet in the range of δ 6.49-5.83 due to H_3 and two doublets in the range of δ 7.30-5.83 assigned to H_7 and H_9.

The ^{1}H nmr spectra of the acetamido derivatives **V** exhibit a broad multiplet in the range of δ 8.40-7.26 due to H_7, H_8 and H_9 and one singlet in the range of δ 6.73-6.23.

Crystals of **IVa** $C_{13}H_9N_3O_2Cl_2$ were studied by the Weissenberg technique and were found to be monoclinic space group $P2_{1/c}$ with a = 14.07(9) b = 19.130(8) c = 4.981(2) Å, β = 90.0(4)°, V = 1340 Å^3, z = 4. The quality of diffraction patterns was not very good, showing spots relatively weak and broad. However the best crystal was chosen for the subsequent data collection. Intensity measurement was carried out on a single crystal diffractometer Ital Structure collecting 1376 reflections in the range of $3 < \theta < 20°$ with $0 < h < 13$ $0 < k < 18$ and $-4 < l < 4$.

Intensity data was corrected for Lorenz, polarization and absorption and the structure was solved by direct methods and refined by standard full matrix least-square technique.

Unfortunately, probably because the poor quality of the crystal, the final reliability factor was very high, R = 0.21. We are now trying to obtain crystals of better quality to improve the refinement and obtain more reliable data. However we believed useful to show in this paper a representation of "connectivity" in the molecule although the standard deviations on the distances and angles are at this stage very high.

Studies on the biological activities of these compounds and related derivatives are in progress.

EXPERIMENTAL

All compounds were routinely checked for their structure by ir and ^{1}H nmr spectroscopy. Melting points were determined in a Köfler hot-stage and are uncorrected. The ir spectra were measured with a Perkin-Elmer Infracord Model 1310. The ^{1}H nmr spectra were determined in DMSO-d_6 or deuteriochloroform with TMS as the internal standard, on a Varian EM 360A spectrometer or a Fourier transform spectrometer Varian Mod. CFT 20. Analytical tlc was carried out on Merck 0.2 mm precoated silica gel glass plates (60 F-254) and location of spots was detected by illumination with an uv lamp. Flash chromatography was carried out on silica gel (60 size 0.04-0.063 mm) at low pressure. The mixtures of compounds were dissolved in methanol and then mixed to five times their amount with silica gel, previously treated with 10% of water. The solvent was evaporated to dryness *in vacuo* and the residue was put on the column previously prepared. Mass spectrum was obtained by V.G. 70-70E spectrometer, 70 eV. The uv spectra were determined on a Perkin-Elmer Lambda 15 spectrophotometer in ethanol. Elemental analyses of all synthesized compounds for C, H and N were within ±0.4 of the theoretical values and were performed by our Analytical Laboratory.

General Procedure for the Condensation of 2,6-Diaminopyridine or 2-Acetamido-6-aminopyridine with β-Ketocarboxylic Esters.

A stirred mixture of 10.0 mmoles of 2,6-diaminopyridine or 2-acetamido-6-aminopyridine, 10.0 mmoles of suitable β-ketocarboxylic ester and 20 g of PPA was heated at 80° for 4 hours. The solution obtained, after cooling, was poured into crushed ice and the *p*H of the solution was then adjusted to 9 with concentrated ammonium hydroxide.

The pure products were then obtained by the following methods.

A) Only for:

2,6-Diaminopyridine with Acetoacetate.

By treatment of the basic mixture with chloroform compound **IIb** was separated and collected by filtration. The chloroform mother liquors were evaporated to dryness *in vacuo* to give a mixture of compounds, that were separated by flash chromatography with ethyl acetate as eluent to obtain **Ib** and **IVb** (Rf: **Ib** > **IVb**). After standing overnight at room temperature from the aqueous solution compound **IIIb** crystallized.

B) For the Other Reactions:

The solid was collected and the aqueous solution extracted with chloroform. The combined extracts were washed with water, dried over magnesium sulfate and the solvent evaporated to dryness *in vacuo* to give a residue, which was mixed with the solid obtained by filtration. The reaction products were then generally

separated from this mixture by flash chromatography.

2,6-Diaminopyridine with 4-Chloroacetoacetate.

The mixture, by elution with ethyl acetate and then with ethyl acetate and methanol (5:1), gave **Ia** and **IIa** respectively.

2,6-Diaminopyridine with Trifluoroacetoacetate.

In this reaction only compound **Ic** was obtained.

2,6-Diaminopyridine with 2-Methylacetoacetate.

The mixture was eluted with ethyl acetate and methanol (15:1) to give **Id**, **IVd** and **IIId** (Rf: **Id** > **IVd** > **IIId**).

2,6-Diaminopyridine with Butyrylacetate.

The mixture was extracted with hot water and the solid residue **IIe**, practically pure was collected and after cooling from the aqueous solution **IIIe** crystallized. The mothers liquors was then evaporated to dryness *in vacuo* and the mixture separated with ethyl acetate and methanol (9:1) as eluent to obtain **Ie** and **IVe** (Rf: **Ie** > **IVe**).

2,6-Diaminopyridine with Benzoylacetate.

The mixture was treated with hot methanol and the solid residue **IIf**, practically pure was collected. The compounds soluble in methanol were then separated using ethyl acetate and then ethyl acetate and methanol (10:1) as eluents to give **If** and **IVf** (Rf: **If** > **IVf**) and **IIIf** respectively.

2-Acetamido-6-aminopyridine with Acetoacetate.

The mixture was crystallized from ethyl acetate to give **IVb**. The solution was concentrated *in vacuo* and the mixture was eluted with ethylacetate to give **VII** and a mixture of two products, that by elution with ethyl acetate, petroleum ether and diethylamine (DEA) (6:12:1) gave **Vb** and **Ib** (Rf: **Vb** > **Ib**).

2-Acetamido-6-aminopyridine with 4-Chloroacetoacetate.

By elution with ethyl acetate compounds **Va**, **Ia**, **VII** and **IVa** (Rf: **Va** > **Ia** > **VII** > **IVa**) were separated. Derivative **IIa** was then obtained using ethyl acetate and methanol (3:1) as eluent.

2-Acetamido-6-aminopyridine with Trifluoroacetoacetate.

Compound **Ic** was isolated from the mixture by fractional crystallization with petroleum ether, 100-140°. After removal of the solvent *in vacuo* the products were separated with ethyl acetate, petroleum ether and DEA (6:3:2) to obtain **VII** and **IIc** (Rf: **VII** > **IIc**).

2-Acetamido-6-aminopyridine with 2-Methylacetoacetate.

The elution of the mixture with ethyl acetate, petroleum ether and DEA (6:3:1) gave **Vd**, **Id**, **IVd** and **VII** (Rf: **Vd** > **Id** > **IVd** > **VII**).

2-Acetamido-6-aminopyridine with Butyrylacetate.

The elution of the mixture with ethyl acetate, petroleum ether and DEA (6:3:1) gave **Ve**, **Ie** (Rf: **Ve** > **Ie**) and a mixture of **IVe**, **VII** and **IIIe**, which were separated using ethyl acetate, petroleum ether and methanol (4:10:1) as eluent (Rf: **IVe** > **VII** > **IIIe**).

2-Acetamido-6-aminopyridine with Benzoylacetate.

Compounds **Vf**, **If**, **VIf**, **VII** and **IIIf** (Rf: **Vf** > **If** > **VIf** > **VII** > **IIIf**) were separated with ethyl acetate and petroleum ether (1:2).

7-Amino-2-hydroxy-4-methyl-1,8-naphthyridine **IIb**.

A solution of 0.28 g of **IIa** in 20 ml of DMF was hydrogenated (Pd/C 10%) at room temperature and pressure. The mixture was filtered and the solvent evaporated to dryness *in vacuo* to give 0.19 g (80%) of **IIb** [1].

2-Hydroxy-4,10-dimethyl-8*H*-pyrimido[1,2-*a*][1,8]naphthyridin-8-one **IVb**.

This compound was obtained in 94% from **IVa** by hydrogenation under the same conditions for the compound **IIb**.

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