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Original Scientific Paper

Synthesis of 8-Methyl-1,2,3,4-tetrahydropyrido-[3,4-d]pyrimidine-2,4-diones

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A new method is described for the preparation of 8-methyl-1,2,3,4-tetrahydropyrido[3,4-d]pyrimidine-2,4-diones *4*, and 4-imino-8-methyl-1,2,3,4--tetrahydropyrido[3,4-d]pyrimidine-2-ones, *3*, starting from 4-methyl-5-oxazolylureas *1* and substituted olefins.

A plausible mechanism is proposed with a Diels-Alder adduct from the reagents as an intermediate that aromatizes by losing water to yield compounds *3*. The latter give the title compounds *4* after hydrolysis.

Two methods have been published[1,2] for the synthesis of 1,2,3,4-tetrahydropyrido-[3,4-d]pyrimidine-2,4-diones.

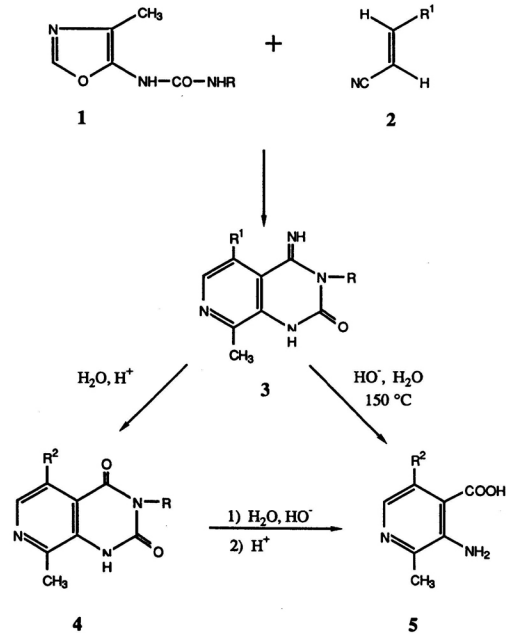
In both methods, substituted pyridine derivatives were used as starting material. In the first method, 3-amino-4-pyridinecarboxylic acid derivatives were fused with urea.[1] In the second one, pyridopyrimidines were prepared by the Hofmann degradation of 3,4-pyridine-dicarboxamide.[2]

Now we report a new and convenient method for the synthesis of 1,2,3,4-tetrahydropyrido[3,4-d]pyrimidine-2,4-diones, with 4-methyl-5-oxazolyurea[3] and its *N*-substituted derivatives (*1*) as starting material reacting with different olefins (*2*).

The parent compounds were prepared from 4-methyl-5-oxazolecarboxamide by the Hofmann degradation and reaction of the isocyanate with amines. Only *N,N'*-di-(4-methyl-5-oxazolyl)-urea was prepared by the Curtius degradation of 4-methyl-5-oxazolecarboxylic acid azide in the presence of water.

When 4-methyl-5-oxazolylureas *1* reacted with acrylonitrile (*2*; R^1 = H). 4-imino-8-methyl-1,2,3,4-tetrahydropyrido[3,4-d]pyrimidine-2-ones *3* (R = H) were obtained. The molecular formula *3* was confirmed by elemental analysis and ^{1}H NMR data. The ^{1}H NMR spectrum revealed the presence of two doublets at 7.2 and 8.2 ppm due to ring protons, and a singlet at 2.5 ppm due to methyl group, with two broad peaks at 9.0–9.8 ppm and 9.8–10.6 ppm due to imino and imido groups. To our knowledge, no reports on the preparation of 4-imino-8-methyl-1,2,3,4-tetrahydropyrido[3,4-d]pyrimidine-2-ones derivatives have yet appeared in the literature.

On hydrolysis in acidic media, compounds *3* were hydrolyzed to yield 8-methyl-1,2,3,4-tetrahydropyrido[3,4-d]-pyrimidine-2,4-diones *4* (R^2 = H).

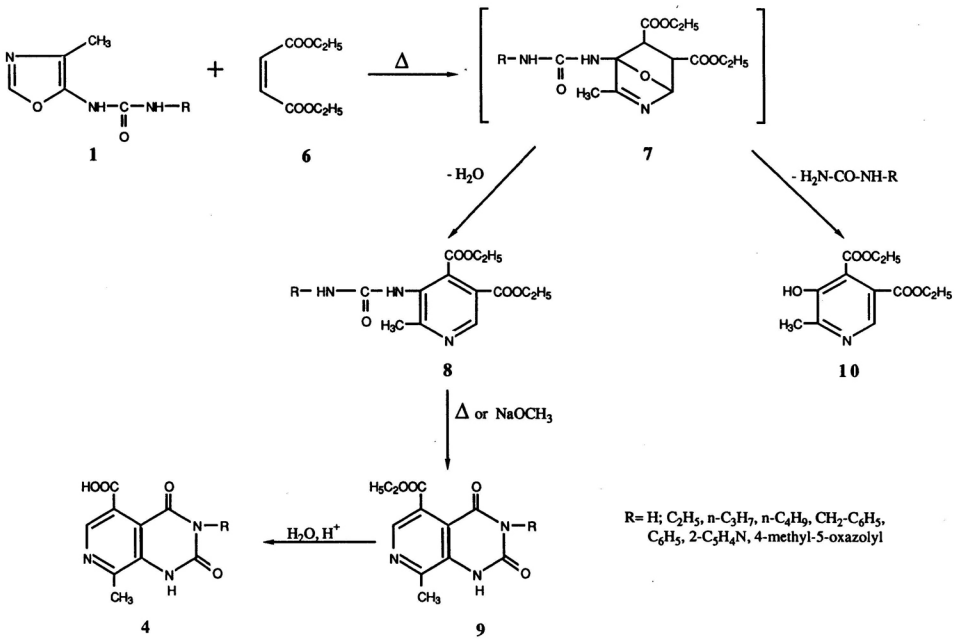


R= H; C_2H_5, n-C_3H_7, n-C_4H_9, CH_2-C_6H_5, C_6H_5, 2-C_5H_4N, 4-methyl-5-oxazolyl
R^1= H, CN
R^2= H, COOH

SCHEME I

Similar reactions of 4-methyl-5-oxazolylurea and its *N'*-substituted derivatives (*1*) were attempted with some other olefins. (*2*). Treatment of *1* with fumaronitrile (*2*; R = CN) afforded 4-imino-5-cyano-8-methyl-1,2,3,4-tetrahydropyrido[3,4,-d]pyrimidine-2-ones (*3*; R^1 = CN) in 30–70 % yield. Compounds *3* (R^1 = CN) were transformed into *4* (R^2 = COOH) by hydrolysis in acidic media. It should be noted that hydrolysis of *3* (R^1 = H, CN) in basic media at 150 °C leads to the opening of pyrimidine ring to give 2-methyl-3-amino-4-pyridinecarboxylic acid derivatives *5* (R^2 = H, COOH).[4]

The most likely mechanism for the generation of the pyridopyrimidine ring is the one involving the formation of substituted pyridine intermediate. Reactions of oxazoles with dienophiles, to generate pyridine ring by Diels-Alder mechanism, are well-known reactions.[5] This intermediate easily cyclized to pyrimidine ring due to the presence of cyano group in the position C–4. This assumption was supported by evidence that the reaction of *1* with diethyl maleate (*6*) gave *N'*-substituted *N*-(3,4-dicarbethoxy-6-methyl-5-pyridyl)-ureas *8*. Their structure was assigned on the basis of spectral and analytical data. The structure *8* was finally confirmed by the intramolecular cyclization of *8* into *9* by the reaction of *8* with sodium methylate.



SCHEME II

The process leading to the formation of pyridine ring obviously involved formation of an adduct *7* by the Diels-Alder reaction, followed by an aromatization to yield the main product *8* (–H_2O) and the byproduct *10*, (–HNCONHR). In the reaction of *1* with acrylonitril only one isomer was formed, since no traces of other isomer, 3-cyano-5-ureido-6-methyl pyridine, was detected in the reaction solution. This is not surprising since interaction of oxazoles with unsymmetrical dienophiles yields, as a rule, only one of the two possible products, in contrast to the usual Diels-Alder reaction where both possible products are generally obtained. In a similar way, the reaction of 5-alkyl or 5-alkoxy substituted oxazoles with acrylic acid leads almost exclusively to substituted isonicotinic acid.[6,7]

By the use of this method, different compounds (*3,4* and *9*) were prepared for the purpose of biological screening, as potential analogues of pteridine class compounds, to be reported elsewhere.

EXPERIMENTAL

Melting points are uncorrected. The IR spectra were recorded with a Model 257 G Perkin-Elmer spectrometer. The ^1H NMR measurements were done on an A-60 Varian apparatus with TMS as the internal standard. TLC was conducted on original plates (Merck-Kieselgel HF_{254}), followed by detection with iodine vapor and UV absorption in the solvent system chloroform-methanol 9 : 1.

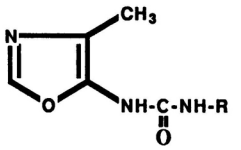
Preparation of N'-substituted Derivatives of 4-Methyl-5-oxazolylurea (1a–1f)

Preparation Procedure

In an aqueous solution containing sodium hypochlorite (80 ml; 7,4 g; 0.1 mol) sodium hydroxide (4.0 g; 0.1 mol) was dissolved. To the obtained solution, 4-methyl-5-oxazolecarboxamide (12.6 g; 0.1 mol) was added in portions at 15 °C, separated crystals were filtered and dissolved in 25 % water solution of amine (1.08 mol). The solution was heated at 80 °C for 1 hour and then cooled to 0 °C. The formed crystals were filtered and recrystallized from water of diluted ethanol. Other data on these compounds are given in Table I.

TABLE I

N'-Substituted 4-methyl-5-oxazolylureas (1a—1g)



Comp.	R	Yield %	*M.p.*/°C	Formula	Calculated/%			Found/%		
					C	H	N	C	H	N
1a	C_2H_5	43	172–174 (H_2O)	$C_7H_{11}N_3O_2$	49.62	6.55	24.84	49.90	6.30	24.91
1b	*n*-C_3H_7	61	136–138 (H_2O)	$C_8H_{13}N_3O_2$	52.44	7.15	22.94	52.44	7.17	23.14
1c	*n*-C_4H_9	28	110–112 (20% EtOH)	$C_9H_{15}N_3O_2$	54.80	7.67	21.31	54.58	7.62	21.58
1d	CH_2-Ph	52	173–176 (96% EtOH)	$C_{12}H_{12}N_3O_2$	62.63	5.67	18.17	62.35	5.91	18.26
1e	Ph	57	185–187 (96% EtOH)	$C_{11}H_{11}N_3O_2$	60.82	5.10	19.35	60.89	4.97	19.40
1f	2-C_5H_4N*	26	197–200 (60% EtOH)	$C_{10}H_{10}N_4O_2$	55.04	4.62	25.68	54.78	4.94	25.69
1g	5-Oxazolyl**	68	222–225 (H_2O)	$C_9H_{10}N_4O_3$	48.65	4.54	25.22	48.37	4.51	25.38

* 2-Pyridyl
** 4-Methyl-5-oxazolyl

N,N'-Di-(4-methyl-5-oxazolyl)-urea (1 g)

A mixture of 4-methyl-5-oxazolecarboxylic acid azide (2.0 g; 0.013 mol), water (0.5 g; 0.028 mol) and dioxane (10 ml), was heated at 90 °C for 3 hours and then cooled to 0 °C. The formed crystals were filtered and recrystallized from 60 % ethanol, yielding *N,N'*-di-(4-methyl-5-oxazolyl)-urea (1.0 g; 68%), *m.p.* 222–225 °C.

Preparation of 4-Imino-8-methyl-1,2,3,4-tetrahydropyrido-[3,4-d]pyrimidine-2-one, the 5-Cyano Derivative and their 3-Substituted Derivatives (3a–3n)

General Procedure

A mixture of 4-methyl-5-oxazolyl urea or its *N'*-substituted derivatives (*1a—1g*; 0.035 mol), dry ethanol 40 ml and acrylonitrile (9 g; 0.17 mol) or fumaronitrile (4.5 g; 0.035 mol) was refluxed for 6 hours and then cooled to 0 °C. Crystals *3a—3n* were filtered and recrystallized from ethanol or DMF. Other data on these compounds are given in Table II.

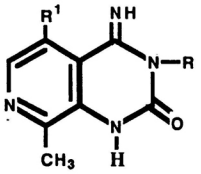
Preparation of 8-Methyl-1,2,3,4-tetrahydropyridol[3,4-d]-pyrimidine-2,4-dione and its 3-Substituted Derivatives (4a–4f)

General Procedure

A suspension of compounds *3a—3f* (0.006 mol) in diluted hydrochloric acid (30 ml, 15%; 0.132 mol) was heated under reflux for 2 hours. The reaction mixture was evaporated to dryness, the residue suspended in ethanol (15 ml) and the crystals formed were filtered and recrystallized from ethanol, DMF or DMSO. Other data on these compounds are given in Table III.

TABLE II

3-Substituted-4-imino-8-methyl-1,2,3,4-tetrahydropyrido[3,4-d]pyrimidine-2-ones (3a—3h) and 4-imino-5-cyano-8-methyl-1,2,3,4-tetrahydropyrido[3,4-d]pyrimidine-2-ones (3i—3n)

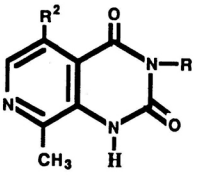


Comp.	R	R^1	Yield %	*M.p.*/°C	Formula	Calculated/% C	H	N	Found/% C	H	N
3a	H	H	58	> 315 (EtOH)	$C_8H_8N_4O$	54.54	4.58	31.80	54.58	4.70	31.66
3b	C_2H_5	H	41	245–247 (EtOH)	$C_{10}H_{12}N_4O$	58.81	5.29	27.47	59.04	6.12	27.54
3c	*n*-C_3H_7	H	48	239–243 (EtOH)	$C_{11}H_{14}N_4O$	60.53	6.47	25.67	60.25	6.60	25.37
3d	*n*-C_4H_9	H	38	191–194 (EtOH)	$C_{12}H_{14}N_4O$	62.05	6.94	24.12	62.01	6.95	24.31
3e	CH_2-Ph	H	50	238–240 (EtOH)	$C_{15}H_{14}N_4O$	67.65	5.30	21.04	67.69	5.57	21.17
3f	Ph	H	63	246–250 (EtOH)	$C_{14}H_{12}N_4O$	66.65	4.79	22.21	66.90	4.78	22.39
3g	2-C_5H_4N*	H	24	> 315 (DMF)	$C_{13}H_{11}N_5O$	61.65	4.38	27.66	61.60	4.40	27.53
3h	5-Oxazolyl**	H	18	308–315 (EtOH)	$C_{12}H_{11}N_5O_2$	56.02	4.31	27.23	55.90	4.48	27.06
3i	H	CN	66	> 315 (EtOH)	$C_9H_7N_5O$	53.73	3.51	34.81	53.99	3.24	35.05
3j	C_2H_5	CN	49	270–273 (DMF)	$C_{11}H_{11}N_5O$	57.63	4.84	30.55	57.51	4.56	30.30
3k	*n*-C_3H_7	CN	30	242–244 (DMF–EtOH)	$C_{12}H_{13}N_5O$	59.25	5.39	28.79	58.99	5.55	28.67
3l	CH_2-Ph	CN	71	275–277 (DMF	$C_{16}H_{13}N_5O$	65.97	4.50	24.04	66.09	4.39	23.82
3m	Ph	CN	62	300–310 (DMF	$C_{15}H_{11}N_5O$	64.97	4.00	25.26	65.20	4.15	25.05
3n	2-C_5H_4N	CN	34	> 315 (DMF)	$C_{14}H_{10}N_6O$	60.42	3.62	30.20	60.14	3.89	30.37

* 2-Pyridyl
** 4-Methyl-5-oxazolyl

TABLE III

3-Substituted-8-methyl-1,2,3,4-tetrahydropyrido[3,4-d]pyrimidine-2,4-diones (4a—4f) and 5-carboxy-8-methyl-1,2,3,4-tetrahydropyrido[3,4-d]pyrimidine-2,4-diones (4g—4i)



Comp.	R	R^2	Yield %	*M.p.*/°C	Formula	Calculated/% C	H	N	Found/% C	H	N
4a	H	H	90	>315 (DMSO)	$C_8H_7N_3O_2$	52.24	3.98	23.72	54.38	3.72	23.43
4b	C_2H_5	H	84	251–253 (EtOH)	$C_{10}H_{11}N_3O_2$	58.53	5.40	20.45	58.77	5.38	20.31
4c	*n*-C_3H_7	H	88	193–194 (H_2O)	$C_{11}H_{13}N_3O_2$	60.26	5.98	19.15	60.55	5.86	19.27
4d	*n*-C_4H_9	H	79	176–178 (H_2O)	$C_{12}H_{15}N_3O_2$	61.78	6.48	18.02	61.81	6.18	18.29
4e	CH_2-Ph	H	89	235–236 (DMF-EtOH)	$C_{15}H_{13}N_3O_2$	67.40	4.90	15.72	67.60	5.14	15.55
4f	Ph	H	85	278–280 (H_2O-EtOH)	$C_{14}H_{11}N_3O_2$	66.37	4.38	16.59	66.65	4.68	16.79
4g	H	COOH	98 (a) 93 (b)	> 315 (DMSO)	$C_9H_7N_3O_4$	48.87	3.19	19.00	48.59	3.45	19.15
4h	C_2H_5	COOH	88 (a) 84 (b)	> 315 (DMF-EtOH)	$C_{11}H_{11}N_3O_4$	53.01	4.45	18.86	52.79	4.70	16.58
4i	CH_2-Ph	COOH	96 (a) 87 (b)	304–307 (DMF-EtOH)	$C_{16}H_{13}N_3O_4$	61.73	4.21	13.50	61.81	4.26	13.78

(a) According to general procedure a.
(b) According to general procedure b.

Preparation of 5-Carboxy-8-methyl-1,2,3,4-tetrahydroxypyrido[3,4-d]pyrimidine-2,4--dione and its 3-Substituted Derivatives (4g–4i)

General Procedures

a. A suspension of compounds *3i, 3j* or *3l* (0.005 mol) in diluted hydrochloric acid (15 ml, 15 %; 0.066 mol) was heated under reflux for 4 hours. The work-up was done as for *4a—4f*) and recrystallization was performed from DMSO or in mixture of ethanol and DMF. Other data on these compounds are given in Table III.

b. A suspension of 5-carbethoxy-8-methyl-1,2,3,4-tetrahydropyrido[3,4-d]pyrimidine-2,4-dione or its 3-substituted derivatives (*9*; 0.002 mol) in diluted hydrochloric acid (10 ml, 15 %; 0.044 mol) was heated under reflux for 2 hours. After the usual work-up, the crystals had an IR spectrum identical with those obtained under a.

Preparation of 2-Methyl-3-amino-4-pyridinecarboxylic Acid (5; R^2 = H)

a. A solution of compound *4a* (R = R^2 = H) (1.0 g; 0.0056 mol) containing sodium hydroxide (20 ml; 9%; 0.054 mol) was heated in autoclave at 155 °C for 3 hours and then cooled to 25 °C. To the solution, hydrochloric acid diluted to pH 9 was added, and the crystals of sodium chloride were filtered. The filtered solution was acidified to pH 6.4 with diluted hydrochloric acid. The crystals formed were filtered, washed with water (10 ml) and recrystallized from water. Yield: 0.45 g (52.4 %) of 5 (R^2 = H); m.p. 324–326 °C (water). IR spectrum (nujol): 1440 (vs), 1365 (vs) cm^{-1}.

Anal. $C_7H_5N_2O_2$ (152,15) calc'd: C 55.25; H 5.30; N 18.41 %
found: C 55.51; H 5.45; N 18.27 %.

b. According to the above procedure (a), 8-methyl-4-imino-1,2,3,4-tetrahydropyrido[3,4-d]pyrimidine-2-one treated with sodium hydroxide gave 0.3 g (35%) of *5* (R^2=H); m.p. 320–325 °C.

Preparation of 2-Methyl-3-amino-4,5-pyridinedicarboxylic Acid (5;R^2 = COOH)

a. The same procedure as for *5* (R^2 = H) was used starting from *4g* (1.0 g; 0.005 mol) and an aqueous solution of sodium hydroxide (20 ml; 2.2 g; 0.054 mol), but sodium chloride was filtered after dilution with HCl to pH 7.8. The filtered solution was acidified to pH 2.2 with diluted hydrochloric acid. The crystals formed were filtered, washed with water (10 ml) and dried. Yield: 0.42 g (39 %) of *5* (R^2 = COOH); m.p. 240–245 °C (decomp.) [Lit.[8] 241–242 °C (decomp.)].

b. According to the above procedure (a), compounds *3i* (1.0 g; 0.05 mol) and *9* (R = H); 1.0 g; 0.04 mol) treated with sodium hydroxide gave 0.38 g (35 %). 0.51 g (59 %), respectively, of *5* (R^2 = COOH); m.p. 240–245 °C (decomp.). IR spectrum was identical with those obtained under a.

Reaction of 4-Methyl-5-oxazolylurea and its N'-Substituted Derivatives with Diethyl Maleinate

General Procedure

A solution of 4-methyl-5-oxazolylurea or its *N'*-substituted derivatives (*1a, 1b, 1d—1f*; 0.02 mol) in diethyl maleinate (10 g; 0.058 mol) was heated at 130 °C for 1.5 hours, and then cooled to 0 °C. The crystals formed were filtered, washed with ethanol (10 ml) and recrystallized from ethanol.

N'-(n-Propyl)-N-(3,4-dicarbethoxy-6-methyl-5-pyridyl)-urea (8:R = n-C_3H_7)

According to the general procedure, *1b* gave 1.3 g (19%) of *8* (R = n-C_3H_7); m.p. 163–164 °C. IR spectrum (KBr): 1720 (vs), 1625 (vs), 1560 (vs) 1300 (vs) cm^{-1}

Anal. $C_{16}H_{23}N_3O_5$(337,37) calc'd: C 56.96; H 6.87; N 12.46 %
found: C 56.78; H 6.90; N 12.67 %

N'-Phenyl-N-(3,4-dicarbethoxy-6-methyl-5-pyridyl)-urea (8; R = Ph)

According to the general procedure, *1e* gave 1.8 g (25%) of *8* (R=Ph); m.p. 210–212 °C. IR spectrum (KBr): 1745 (s), 1720 (vs), 1630 (vs) 1600 (vs) 1500 (vs) cm^{-1}.

^{1}H NMR (DMSO-d_6)δ: 1.3 (t, 2 x CH_2–CH_3), 2.6 (s, C_6–CH_3), 4.3 (q, 2 x CH_2), 6.7–7.6 (m,C_6H_5), 8.1 (s,N'-H), 8.7 (s,C_6-H), 9.0 (s, N-H).

Anal. $C_{19}H_{21}N_3O_5$(371,38) calc'd: C 61.44; H 5.70; N 11.32 %
found: C 61.17; H 5.40; N 11.36 %

N'-Benzyl-N-3,4-dicarbethoxy-6-methyl-5-pyridyl)-urea (8; R = CH_2-Ph)

According to the general procedure, compound *1d* gave 2.3 g (30%) of *8* (R = CH_2-Ph); m.p. 143–145 °C.

IR spectrum (KBr): 1715 (vs), 1640 (vs), 1300 (vs) cm^{-1}.

^{1}H NMR (DMSO-d_6)δ: 1.2 (t, CH_2-CH_3), 1.3 (t, CH_2-CH_3), 2.5 (s, C_6-CH_3), 4.0–4.5 (m, CH_2) 6.9 (t, N'-H), 7.3 (s, C_6H_5), 8.0 (s, N-H),. 8.7 (s, C_2-H).

Anal. $C_{20}H_{23}N_3O_6$(385,21) calc'd: C 62.32; H 6.02; N 10.90 %
found: C 62.28; H 5.84; N 11.02 %

3-Benzyl-5-carbethoxy-8-methyl-1,2,3,4-tetrahydropyrido[3,4-d]-pyrimidine-2,4-dione (9; R = CH_2-Ph)

After recrystallization of the crude product obtained in the general procedure, and separation of crystals of *8* R = CH_2-Ph), the ethanolic filtrate was evaporated and submitted to chromatography on silica gel column using the solvent system chloroform-methanol (9:1). Elution with the same solvent gave 1.8 (27 %) of *9* (R = CH_2-Ph); m.p. 188–189 °C (ethanol).

IR spectrum (KBr): 1715 (vs), 1655 (vs), 1425 (vs) 1215 (vs) cm^{-1}.

^{1}N NMR (DMSO-d_6): 1.3 (t, CH_2-CH_3), 2.6 (s, C_8-CH_3), 4.3 (q, CH_2-CH_3), 5.1 (s, N_3-CH_3), 7.3 (s, C_6H_5), 8.2 (s, C_6-H).

Anal. $C_{18}H_{17}N_3O_4$(339.34) calc'd: C 63.71; H 5.05; N 12.38 %
found: C 63.70; H 5.27; N 12.59 %

Diethyl-5-hydroxy-6-methyl-3,4-pyridinedicarboxylate (10)

After separation of the crude product [mixture of *8* and *9* (R = CH_2-Ph)] obtained in the general procedure, the mother liquor was evaporated and submitted to chromatography on silica gel column using the solvent system chloroform-methanol (9:1). Elution with the same solvent gave a fraction with R_f=0,85, which upon distillation under reduced pressure yielded 0.55 g (11 %) of *10*; b.p. 170–180 °C/0,2 mm Hg. IR spectrum (100%): 1720 (vs), 1680 (vs), 1385 (vs), 1225 (vs) cm^{-1}.

^{1}H NMR ($CDCl_3$)δ: 1.3 (t, CH_2-CH_3), 2.5 (s, C_6-CH_3), 4.2-4.6 (m,. CH_2), 8.2 (s, C_2-H), 10.3 (s, OH).

Anal $C_{12}H_{15}NO_5$(253.25) calc'd: C 56.91; H 5.97; N 5.53 %
found: C 57.07; H 6.23; N 5.76 %.

N'-(2-Pyridyl)-N-(3,4-dicarbethoxy-6-methyl-5-pyridyl)-urea (8; R = 2-C_5H_4N)

According to the general procedure, compound *1f* gave 1,3 g (18%) of *8* (R = 2-C_5H_4N); m.p. 197–200 °C. IR spectrum (KBr): 1740 (vs), 1720 (vs), 1680 (vs), 1300 (vs) cm^{-1}.

^{1}H NMR (DMSO-d_6)δ: 1.2 (t, CH_2-CH_3), 1.3 (t, CH_2-CH_3), 2.5 (s, C_6-CH_3), 6.9–8.3 (m, C_5H_4N), 8.8 (s, C_2-H), 9.7 (s, N-H). 10.6 (s, N-H)

Anal. $C_{18}H_{20}N_4O_5$(372.37) calc'd: C 58.06; H 5.41; N 15.05 %
found: C 58.35; H 5.21; N 15.44 %

3-(2-Pyridyl)-5-carbethoxy-8-methyl-1,2,3,4-tetrahydropyrido-[3,4-d]pyrimidine-2,4-dione (9; R = 2-C_5H_4N)

After recrystallization of the crude product obtained in the general procedure, and separation of crystals *8* (R = 2-C_5H_4N), the ethanolic filtrate was evaporated and submitted to chromatography on silica gel column using the solvent chloroform-methanol (9:1). Elution with the same solvent gave 0.9 g (15%) of *9* (R = 2-C_5H_4N); m.p. 260–262 °C ethanol). IR spectrum (KBr): 1735 (vs), 1665 (vs), 1405 (vs) cm^{-1}.

Anal $C_{16}H_{14}N_4O_4$(326.30) calc'd: C 58.89; H 4.32; N 17.17 %
found: C 58.60; H 4.48; N 17.43 %.

5-Carbethoxy-8-methyl-1,2,3,4-tetrahydropyrido[3,4-d]pyrimidine-2,4-dione (9; R=H)

According to the general procedure, compound *1a* gave 2.0 g (40 %) of *9* (R = H); m.p. 270–271 °C. IR spectrum (KBr); 1740 (s), 1710 (vs), 1670 (vs), 1400 (s) cm^{-1}
^1H NMR (DMSO-d_6)δ: 1.3 (t, CH_2-CH_3), 2.7 (s, CH_3), 4.3 (q, CH_2), 8.2 (s, C_6-H), 10.8 (s, N_1-H), 11.7 (N_3-H).

Anal. $C_{11}H_{11}N_3O_4$(249.22) calc'd: C 53.01; H 4.54; N 16.86 %
found: C 52.96; H 4.58; N 17.07 %

3-Ethyl-5-carbethoxy-8-methyl-1,2,3,4-tetrahydropyrido[3,4-d]-pyrimidine-2,4-dione (9: R = C_2H_5)

According to the above procedure, compound *1b* gave 0.8 g (14 %) of *9* (R = C_2H_5; m.p. 213–214 °C. IR spectrum (KBr): 1730 (vs), 1710 (s), 1650 (s), 1305 (s) cm^{-1}.

Anal. $C_{13}H_{15}N_3O_4$ (277,27) calc'd: C 56.31; H 5.45; N 15.16 %
found: C56.58; H 5.40; N 15.43 %

Preparation of 3-Substituted Derivatives of 5-Carbethoxy-8-methyl-1,2,3,4-tetrahydropyrido[3,4-d]pyrimidine-2,4-dione (9; R = n-C_3H_7,Ph)

General Procedure

A solution of *N'*-substituted derivatives of *N*-(3,4-dicarbethoxy-6-methyl-5-pyridyl)-urea (*8*; R = n-C_3H_7, Ph; 0.01 mol) and sodium methoxide (0.65 g; 0.012 mol) in methanol (10 ml) was refluxed for 1 hour. The crystals formed were filtered and recrystallized from ethanol.

3-(n-Propyl)-5-carbethoxy-8-methyl-1,2,3,4-tetrahydropyrido-[3,4-d]pyrimidine-2,4-dione; (9; R = n-C_3H_7)

Yield: 2.2 g (75 %) of *9* (R = n-C_3H_7;m.p.202–203 °C. IR spectrum (KBr): 1720 (vs), 1650 (vs), 1435 (s), 1410 (s) cm^{-1}.

Anal. $C_{14}H_{17}N_3O_4$(291.3) calc'd: C 57.72; H 5.88; N 14.43 %
found: C 57.62; H 6.07; N 14.40 %

3-Phenyl-5-carbethoxy-8-methyl-1,2,3,4-tetrahydropyrido[3,4-d]pyrimidine-2,4-dione (9; R = Ph)

Yield: 2.9 g (89 %) of *9* (R = Ph); m.p. 279–282 °C. IR spectrum (KBr): 1720 (vs), 1660 (vs), 1410 (s), 1305 (s) cm^{-1}.

Anal.. $C_{17}H_{15}N_3O_4$(325.31) calc'd: C 62.76; H 4.65; N 12.92 %
found: C 63.00; H 4.42; N 13.11 %

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SAŽETAK

Priprava 8-metil-1,2,3,4-tetrahidropirido-[3,4-d]pirimidin-2,4-diona

Nedjeljko Kujundžić i Berislav Gluncić

Opisana je nova metoda za pripravu 1,2,3,4-tetrahidropirido[3,4-d]pirimidin-2,4-diona. Ista metoda iskorištena je i za pripravu 4-imino-1,2,3,4-tetrahidropirido[3,4-d]pirimidin-2-ona. Diskutira se o stvaranju pirido[3,4-d]pirimidinskog prstena reakcijom 4-metil-5-oksazolilurea s olefinima.