Saturated Heterocycles, Part 172†. Synthesis of 2,6-Disubstituted-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidine Derivatives

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The title compounds were synthesized *via* the addition of methyl acrylate to benzylamine or to α-aminopyridine, which gave the corresponding diesters, *e.g.* **12**, followed by Dieckmann condensation of the latter to yield the keto-esters **13**, which were condensed with amidines and guanidines, **3**, **14**. Removal of the benzyl group by hydrogenolysis and subsequent alkylation of the nitrogen atom at position 6 in the resulting compound **5**, with variation of the substituents on C-2, gave a number of products with potential biological action; some of them gave analgesic and anti-inflammatory effects.

J. Heterocyclic Chem., **27**, 1885 (1990).

Introduction.

As a continuation of our research on pyrimidin-4(3*H*)-one derivatives [1,2], a number of variously substituted tetrahydropyrido[4,3-*d*]pyrimidine derivatives **1** with promising pharmacological actions were synthesized [3] (Figure 1).

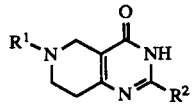

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Figure 1

Syntheses of tetrahydropyrido[4,3-*d*]pyrimidine derivatives have so far been described mainly in patents [4-15]; anti-inflammatory, diuretic and coronary dilator effects of these compounds have been reported.

The carbon atom at position 2 and the nitrogen atom at position 6 in the tetrahydropyrido[4,3-*d*]pyrimidine ring system offer further possibilities of substitution, and analogues containing nitrogen in the carbocycle have promising biological properties; therefore, as a continuation of our earlier researches [1,2], it appeared worthwhile to synthesize new pyrimidines fused with piperidine. The preparation of the title compounds was prompted not only by the aspects of drug research, but also by our wish to study some reactions, such as aromatization [16], of this family of compounds.

Synthesis.

The starting compound *N*-benzyl-3-methoxycarbonyl-4-piperidone (**2**) was synthesized by a modification of Morosawa's method [17]; the diester resulting from the addition of benzylamine and methyl acrylate was subjected to Dieckmann condensation and the product was reacted with amidines and guanidines **3**. From the resulting 1-benzylpyrido[4,3-*d*]pyrimidone derivative **4**, the benzyl group was removed by hydrogenolysis, and the fused-skeleton piperidine-pyrimidone obtained **5** was used for the preparation of a large number of derivatives. Removal of the benzyl group by hydrogenolysis could be effected in 90% acetic acid with a modification of the previous procedure [15]; in this way, compound **2** gave 3-methoxycarbonyl-4-piperidone (**6**), a useful starting material in our synthesis (Figure 2).

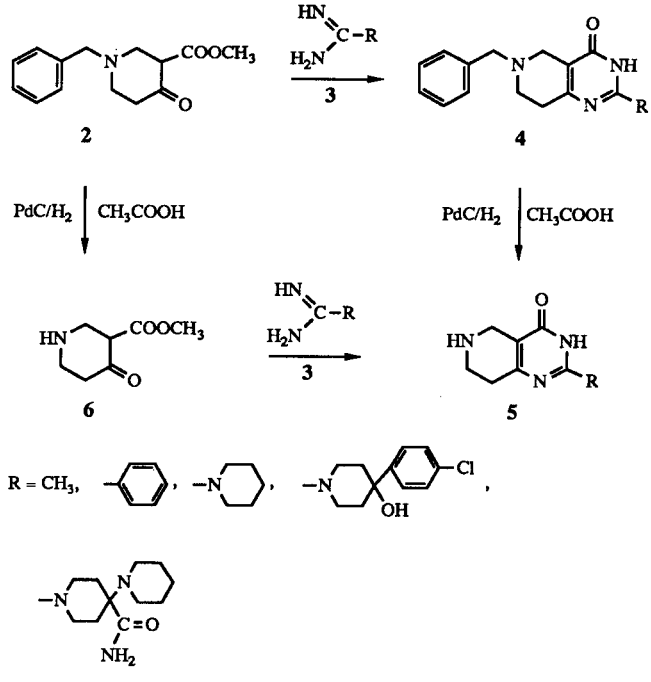


Figure 2

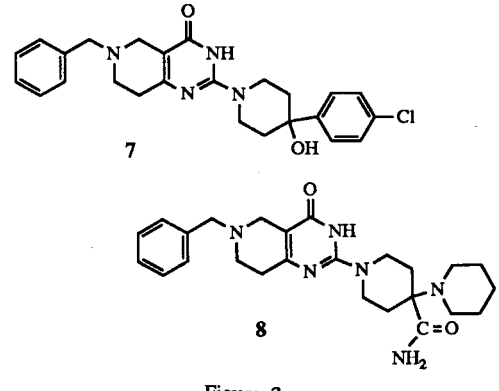


Figure 3

Compounds containing various pharmacophore groups on C-2 in **4** and **5** were prepared, such as the 4-hydroxy-4-(*p*-chlorophenyl)-1-piperidino (**7**) [18] and 4-(1-piperidino)-4-carboxamidopiperidine derivatives **8** [19] (Figure 3).

The guanidine derivatives **3** [20] used in these syntheses were prepared with *S*-methylisothiourea sulfate [21].

The reaction of **5** with cyclohexene oxide (Figure 4) gave the 6-(*trans*-2-hydroxycyclohexyl)-substituted compound **9**; the methyl, phenyl, 1-piperidino and 4-hydroxy 4-(*p*-chlorophenyl)-1-piperidino derivatives were also prepared.

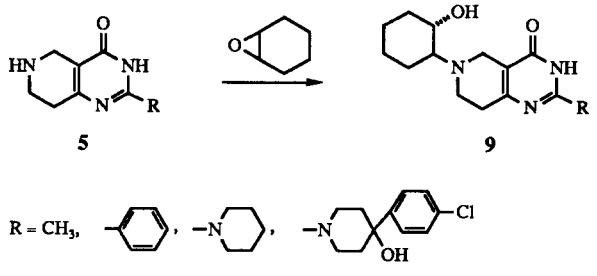


Figure 4

Other compounds synthesized were those alkylated on the nitrogen atom at position 6, **10**. This nitrogen atom was substituted with the CNS-active group 4-(4'-fluorobutyrophenone) [18], or groups occurring in anaesthetic or antiarrhythmic drugs (2,6-dimethylphenyl)carbamoyl methyl, (2,6-dichlorophenyl)carbamoylmethyl and *p*-methoxypropionylanilide groups (Figure 5).

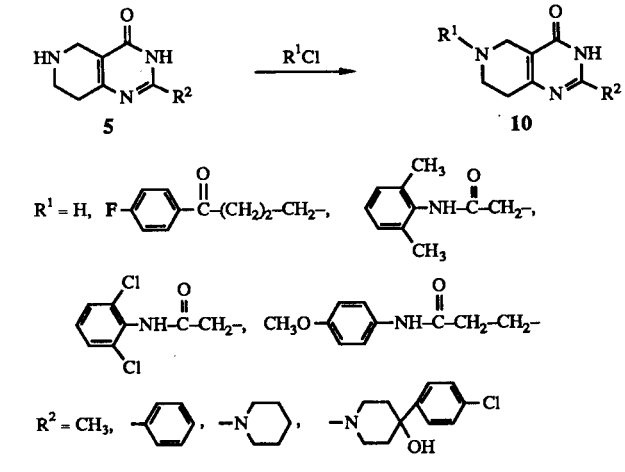


Figure 5

The 6-(2-pyridyl)-substituted derivatives **11** were synthesized by the addition of methyl acrylate to 2-aminopyridine; the resulting diester **12** was converted to the β-keto-ester **13** and this was condensed with variously substituted *N*-methylpiperazinoguanidines **14** (Figure 6).

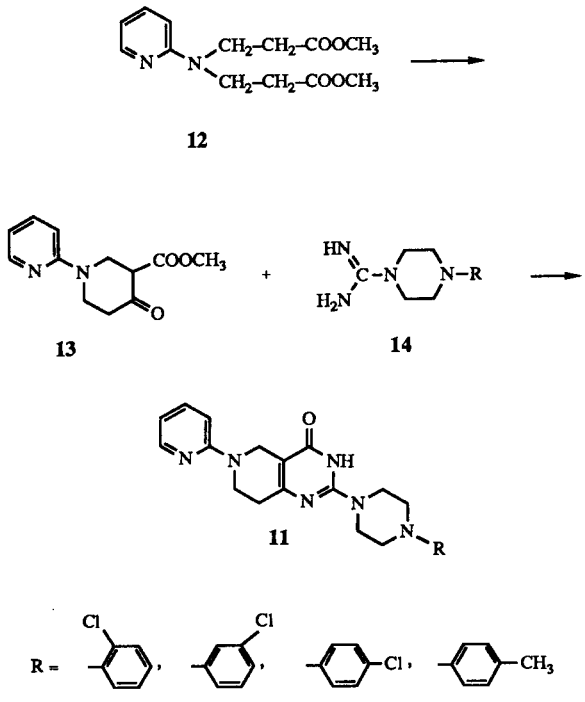


Figure 6

On the analogy of the secondary acid amide structure of Trimetozin® [23], derivatives acylated at position 6, **15** (Figure 7) were also prepared by treatment with different acid chlorides of the guanidine derivatives substituted with secondary amines at C-2.

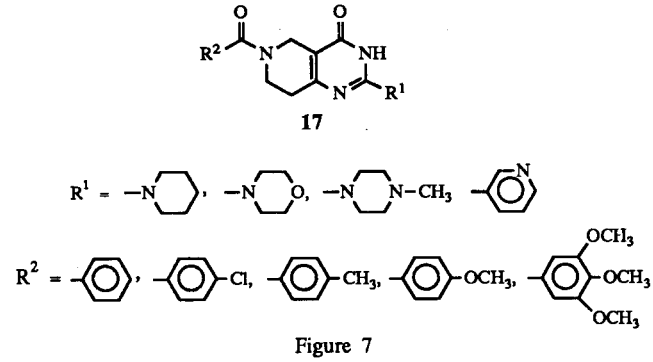
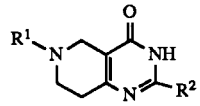


Figure 7

On the basis of a consideration of the relevant data reported in the literature, the potential drugs synthesized in this work were tested for biological action in the CHINOIN Chemical and Pharmaceutical Works Ltd., Budapest. Some of the compounds were found to exhibit minor analgesic and anti-inflammatory actions.

Table 1

Characteristics of Compounds **5**, **7** and **8**



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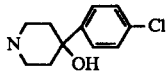
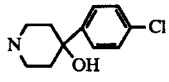
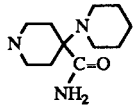
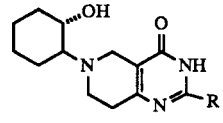
Compound	R^1	R^2	Empirical Formula (Molecular weight)	Mp °C [a]	Mp °C [b]	Analysis Calcd. %/Found % C	H	N	Cl
5	H		$C_{18}H_{23}N_4O_2Cl_3$ (433.77)	167-170 [e]	275-277 [d, g, h]	49.84 50.18	5.34 5.60	12.91 12.72	24.51 24.14
7			$C_{25}H_{29}N_4O_2Cl_3$ (523.89)	241-242 [c]	239-240 [d, g, h]	57.31 57.05	5.57 5.62	10.69 10.95	20.30 19.98
8			$C_{25}H_{37}N_6O_2Cl_3$ (599.97)	242-243 [c]	225-226 [g]	53.62 53.20	6.66 6.91	15.00 14.61	

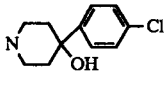
[a] Mp of the base. [b] Mp of the hydrochloride. [c] From dimethylformamide. [d] Dec. [e] From ethanol. [f] From toluene [g] From ethanol-ether. [h] Dihydrochloride. [i] Trihydrochloride.

Table 2

Characteristics of Compounds **9a-d**



9a-d

Compound	R	Empirical Formula (Molecular weight)	Mp °C [a]	Mp °C [b]	Analysis Calcd. %/Found % C	H	N	Cl
9a	CH_3	$C_{14}H_{24}N_3O_2Cl_2$ (337.27)	249-250 [d, e]	242-243 [d, g]	49.85 49.42	7.17 7.83	12.45 11.95	21.03 20.72
9b	C_6H_5	$C_{19}H_{22}N_3O_2Cl$ (359.86)	266-268 [c,d]	268-270 [d, g]	63.41 63.71	6.16 6.36	11.67 11.85	
9c		$C_{18}H_{30}N_4O_2Cl_2$ (405.37)	235-236 [e]	210-212 [d, g, h]	53.33 53.10	7.45 7.80	13.82 13.56	17.49 17.24
9d		$C_{24}H_{33}N_4O_3Cl_2$ (567.36)	254-255 [d,e]	210-212 [g, i]	50.80 50.38	5.86 6.21	9.87 9.78	24.99 24.85

[a] Mp of the base. [b] Mp of the hydrochloride. [c] From dimethylformamide. [d] Dec. [e] From ethanol.[f] From toluene. [g] From ethanol-ether. [h] Dihydrochloride. [i] Trihydrochloride

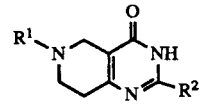
EXPERIMENTAL

Melting points were determined on a Boetius melting point apparatus (Franz Küstner, Dresden) and are uncorrected. Thin-layer chromatography (silica gel G, benzene-ethanol 4:1, detection in iodine vapour) showed the compounds to be homogeneous. The results of microanalysis (C, H, N, Cl) were consistent with the formulae given.

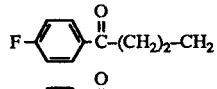
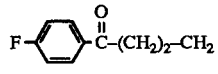
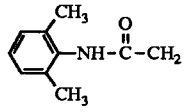
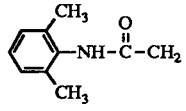
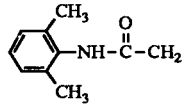
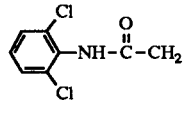
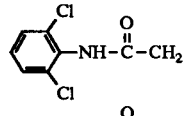
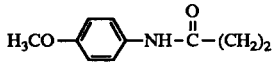
N-Benzyl-3-methoxycarbonyl-4-piperidone Hydrochloride (**2**).

Benzylamine (1 mole) was dissolved in methanol (300 ml), and methyl acrylate (2.2 moles) was quickly added dropwise, during

Table 3
Characteristics of Compounds **10a-b**



10a-h

Compound	R^1	R^2	Empirical Formula (Molecular weight)	Mp °C [a]	Mp °C [b]	Analysis Calcd. %/Found % C	H	N	Cl
10a		CH_3	$C_{18}H_{22}N_3O_2FCl_3$ (402.30)	214-216 [f]	193-195 [g, h]			10.48 10.17	
10b		C_6H_5	$C_{23}H_{23}O_2N_3FCl$ (427.90)	266-268 [d, f]	252-254 [g]	64.55 64.25	5.41 5.83	9.81 9.98	
10c		CH_3	$C_{18}H_{24}N_4O_2Cl_2$ (399.32)	244-245 [d, e]	271-273 [d, g, h]	54.14 53.85	6.05 6.32	14.03 13.71	17.75 17.36
10d		C_6H_5	$C_{23}H_{26}N_4O_2Cl$ (425.94)	272-273 [c, d]	270-271 [d, g]	64.85 65.00	6.15 6.50	13.15 13.36	8.32 8.50
10e			$C_{22}H_{31}N_5O_2Cl$ (468.42)	248-250 [d, e]	248-250 [g, h]	56.41 56.13	6.67 7.05	14.95 15.30	15.13 14.82
10f		C_6H_5	$C_{21}H_{18}N_4O_2Cl_2$ (429.30)	289-292 [c, d]		58.75 59.12	4.22 4.68	13.05 13.44	
10g			$C_{20}H_{23}N_5O_2Cl_2$ (436.34)	274-276 [c, d]		55.05 54.76	5.31 5.70	16.04 15.38	
10h		C_6H_5	$C_{29}H_{24}N_4O_3$ (404.47)	244-245 [c, d]		68.30 67.96	5.98 6.08	13.85 13.77	

[a] Mp of the base. [b] Mp of the hydrochloride. [c] From dimethylformamide. [d] Dec. [e] From ethanol. [f] From toluene. [g] From ethanol-ether [h] Dihydrochloride. [i] Trihydrochloride.

constant reflux of the reaction mixture. The solution was further refluxed until tlc showed that a homogeneous product had been formed; the solvent and the excess of methyl acrylate were then removed by distillation. The residue was dissolved in xylene or toluene (300 ml), and this solution was poured onto freshly-prepared sodium methoxide (1.4 moles). The mixture was stirred until complete dissolution, and it was then concentrated on a rotary evaporated until crystallization had started. A solvent was added to the residue, and the mixture was heated in an oil bath at 100° for 3 hours. The distillation and heating were repeated; the mixture was then cooled and with cooling and shaking, concentrated hydrochloric acid (250 ml) was added in small portions. It was left to stand overnight in a refrigerator. The precipitated product, was filtered off, washed with acetone and dried, to give compound **2** (245 g, 86%), mp 182°.

3-Methoxycarbonyl-4-piperidone Hydrochloride (**6**).

The *N*-benzyl compound **2** (50 g) was dissolved in 90% acetic acid (about 300 ml). The mixture was hydrogenated in the presence of palladium-on-carbon (10%, 5 g). The catalyst was removed by filtration. The filtrate was evaporated to dryness and the residue was recrystallized from methanol, yield 92%, mp 178-180° dec.

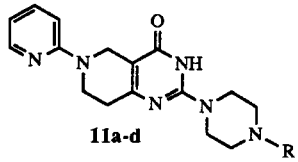
Anal. Calcd. for $C_7H_{12}O_3NCl$ (193.63): C, 43.22; H, 6.76; N, 7.23; Cl, 18.30. Found: C, 43.18; H, 6.66; N, 7.55; Cl, 18.30.

5,6,7,8-Tetrahydroypridо[4,3-*d*]pyrimidines **4**, **5**. Method A. Preparation of 2-Alkyl and 2-Aryl Derivatives. General Procedure.

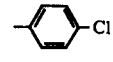
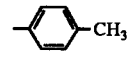
3-Methoxycarbonyl-4-piperidone hydrochloride (**6**) or its *N*-substituted derivative **2** (0.1 mole) was dissolved in absolute ethanol (100 ml). A solution of the appropriate amidine **3** (0.11 mole) in absolute ethanol (50 ml) and then a solution of metallic sodium (0.21 g-atom) in absolute ethyl alcohol (50 ml) were added. The mixture was maintained, with stirring, at 100° in an oil-bath for 12 hours. It was then evaporated to dryness, and the

Table 4

Characteristics of Compounds **11a-d**



11a-d

Compound	R	Empirical Formula (Molecular weight)	Mp °C [a]	Mp °C [b]	Analysis Calcd. %/Found % C	H	N	Cl
11a		$C_{22}H_{25}N_6OCl_3$ (495.74)	208-210	174-176 [c]	53.30	5.08	16.95	21.45
					53.18	5.52	17.30	21.94
11b		$C_{22}H_{26}N_6OCl_4$ (532.30)	136-138	180-182 [c]	49.64	4.92	15.78	–
					49.76	5.44	15.36	–
11c		$C_{22}H_{26}N_6OCl_4$ (532.30)	261-262 [c]	184-185 [c]	49.64	4.92	15.78	26.64
					49.28	5.37	15.42	26.30
11d		$C_{23}H_{29}N_6OCl_3$ (511.88)	199-201	178-182 [c]	53.96	5.71	16.41	–
					53.45	6.17	16.26	–

[a] Mp of the base. [b] Mp of the di- or trihydrochloride. [c] Dec.

residue was suspended in water, filtered off and washed with water and acetone. The product was purified by recrystallization from ethanol, or benzene, or dimethylformamide. In the case of the 2-alkyl derivatives, crystalline products could not be obtained on the addition of water; therefore, the mixture was extracted with chloroform and the solvent was evaporated off; the addition of acetone resulted in the deposition of crystals, which were filtered off and recrystallized, to give the product in 50-60% yield.

Method B.

Preparation of Saturated Hetero-substituted Derivatives **4** and **5**. General Procedure.

3-Methoxycarbonyl-4-piperidone hydrochloride (**6**) (0.1 mole) or its *N*-substituted derivative **2** and the appropriate guanidine sulfate (0.05 moles) were suspended in absolute ethanol (100 ml) and a solution of metallic sodium (0.2 g-atom) in absolute ethanol (50 ml) was added. The mixture was stirred and heated for 12 hours in an oil-bath at 100° and it was then evaporated to dryness. The residue was suspended in water. The precipitated solid was filtered off and washed with water and then with acetone. If the product was not crystalline, it was extracted with chloroform and the extract was dried over sodium sulfate. After evaporation of the solvent, the residue was triturated with acetone, filtered off and crystallized from ethanol or dimethylformamide, yield 50-60%.

Data on the prepared compounds are listed in Table 1, **5**, **7** and **8**.

Hydrogenolysis of *N*-Benzyl-2-substituted-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4(3*H*)-ones **4**. General Procedure.

The *N*-benzyl derivative **4** (0.1 mole) or its hydrochloride was hydrogenated in 90% acetic acid (400 ml) at 50°, in the presence of palladium-on-carbon (10%) catalyst (3 g); the reaction was monitored by tlc. When the reduction was complete, the catalyst was removed by filtration and the acetic acid was evaporated off. The residue was dissolved in a small amount of water and the solution was made alkaline by the addition of ammonium hydroxide. It was allowed to stand overnight, and the precipitated crystalline base was filtered off and recrystallized from ethanol. The product **5** was obtained in nearly quantitative yield.

Synthesis of *trans*-2-Hydroxycyclohexyl-5,6,7,8-tetrahydropyrido-[4,3-*d*]pyrimidine Derivatives **9**.

Compound **5** (0.05 mole) was dissolved in absolute ethanol (200 ml), and cyclohexene oxide (0.06 mole) was added to the solution. The mixture was refluxed for 24 hours. After cooling, the crystalline reaction product was filtered off, washed with ethanol and recrystallized from the same solvent, yield 80%.

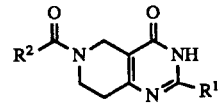
Characteristics of the compounds thus prepared are shown in Table 2, **9a-d**.

Synthesis of *p*-Fluorobutyrophenone Derivatives **10a**, **10b**.

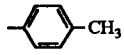
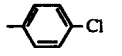
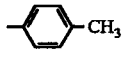
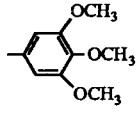
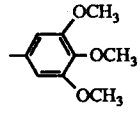
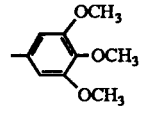
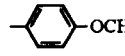
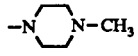
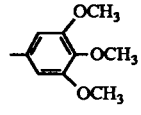
Compound **5** (0.05 moles) was dissolved in methyl isobutyl ketone (100 ml); 4-chloro-4'-fluorobutyrophenone (0.06 mole) [19], finely powdered anhydrous sodium carbonate (8 g) and sodium iodide (0.10 g) were added, and the mixture was stirred and heated in an oil-bath at 120°. The reaction was monitored by tlc. After evaporation to dryness, the residue was suspended in water, and the solid was filtered off and washed with acetone. If the product failed to crystallize on the addition of water, the mixture was extracted with chloroform. The extract was concentrated, and the residue was triturated with acetone and stored in a refrigerator to achieve crystallization. The product was filtered off and recrystallized from toluene or ethanol, yield 30-40%.

Characteristics of the compounds thus prepared are listed in Table 3, **10a**, **10b**.

Table 5
Characteristics of Compounds **15a-i**



15a-i

Compound	R^1	R^2	Empirical Formula (Molecular weight)	Mp °C	Analysis Calcd. %/Found % C	H	N
15a			$C_{20}H_{24}N_4O_2$ (352.44)	239-240	68.16 67.86	6.86 6.67	13.89 14.12
15b			$C_{19}H_{21}N_4O_2Cl$ (372.85)	262-263	61.20 60.88	5.67 6.05	15.02 14.83
15c			$C_{19}H_{22}N_4O_3$ (351.41)	318-319	64.39 64.68	6.25 6.45	15.80 15.48
15d			$C_{22}H_{28}N_4O_6$ (428.49)	238-239	61.66 61.84	6.58 7.21	13.07 13.56
15e			$C_{19}H_{22}N_4O_2Cl$ [a] (373.86)	258-259	61.04 61.17	5.93 6.28	14.98 14.63
15f			$C_{21}H_{26}N_4O_6$ (430.46)	213-215	58.59 59.00	6.08 6.20	13.00 12.78
15g			$C_{22}H_{22}N_4O_5$ (422.44)	252-253	62.55 61.28	5.24 5.47	13.26 13.52
15h			$C_{20}H_{18}N_4O_3$ (362.39)	232-233	66.28 66.53	5.00 5.36	15.46 15.73
15i			$C_{22}H_{29}N_5O_5$ (443.50)	210-213	59.58 59.92	6.59 6.22	

[a] Hydrochloride. *Anal.* Calcd.: Cl, 9.48. Found: Cl, 9.12.

Synthesis of *N*-(2,6-Dimethyl-, 2,6-Dichlorophenylcarbamoylmethyl- or 4-Methoxyphenylcarbamoylmethyl)-2-substituted-5,6,-7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4(3*H*)-one derivatives **10c-10h**.

Compound **5** (0.05 mole) was dissolved in methyl isobutyl ketone (100 ml), and 2,6-dimethyl- or 2,6-dichloroacetanilide (0.05 mole) or 4-methoxyphenyl-3-chloropropionylanilide (0.05 mole), finely powdered sodium carbonate (8 g) and sodium iodide (0.10 g) were added to the solution. The mixture was stirred and heated in an oil-bath at 120° for 12 hours. It was then evaporated to dryness, and the residue was suspended in water and filtered off. The solid product was washed with water and then with acetone, and recrystallized from ethanol, yield 65-70%.

Data on the compounds thus prepared are summarized in Table 3, **10c-10h**.

Preparation of substituted quanidine sulfates **3**, **14** [20].

S-Methylisothiourea sulfate (0.01 mole) [21] was refluxed, with stirring, in 50% ethanol (100-150 ml) with the appropriate cyclic secondary amine (piperidone, morpholine, *etc.*) (0.2 mole) for 10-12 hours, until the evolution of methyl mercaptan had ceased. The reaction mixture was evaporated to dryness, and the residue was collected by filtration with the aid of ethanol, washed with ethanol and dried, yield 60-70%.

2,6-Dimethylchloroacetanilide [24].

2,6-Dimethylanilide (121.2 g, 1 mole) was dissolved in chloroform (600 ml), and magnesium oxide (60 g) was suspended in the solution. Over a period of 1 hour, chloroacetyl chloride (123 g, 1.1 moles) dissolved in chloroform (400 ml) was added dropwise, with stirring. The mixture was then stirred and refluxed in a water-bath for 2 hours. After cooling, with continuous stirring, water (200 ml) and then dilute hydrochloric acid (1:1) (200 ml) were slowly added. The mixture was stirred until dissolution of the magnesium oxide was complete. The chloroform layer was separated while the mixture was still warm, and the solvent was

evaporated off. Crystallization of the residue from ethanol gave the pure product (169 g, 86%), mp 148-150°.

2,6-Dichloro-α-chloroacetanilide [25].

Magnesium oxide (30 g) was suspended in a solution of 2,6-dichloroanilide (81.0 g, 0.5 mole) in chloroform (600 ml). Chloroacetyl chloride (61.5 g, 0.55 mole), dissolved in chloroform (400 ml), was added to the solution dropwise during 1 hour, with stirring. The mixture was subsequently stirred and refluxed for 2 hours on a water-bath. After cooling, water (100 ml) and then dilute hydrochloric acid (1:1) (100 ml) were added and stirring was continued until complete dissolution of the magnesium oxide. The chloroform layer was separated while the mixture was still warm, and the solvent was evaporated off. The residue was crystallized from ethanol, to give 106 g (89%) of the product; mp 188-189° (lit [25] mp 171-173°).

4-Methoxy-β-chloropropionanilide [26].

Magnesium oxide (60 g) was suspended in a solution of *p*-anisidine (123.2 g, 1 mole) in chloroform (600 ml) and a solution of β-chloropropionyl chloride (139.6 g, 1.1 moles) in chloroform (400 ml) was added dropwise, with stirring, over a period of 1 hour. The mixture was next stirred and refluxed for 2 hours. After cooling, water (100 ml) and dilute (1:1) hydrochloric acid (100 ml) were added dropwise; stirring was continued until complete dissolution of the magnesium oxide. The chloroform layer was separated and the solvent was evaporated off. Crystallization of the residue from ethanol furnished the pure product (177 g, 83%), mp 126-127° (lit [26] mp 124°).

Dimethyl 2-Aminopyridine-*N*,*N*'-dipropionate (**12**).

Methyl acrylate (248 g, 3 mmoles) was added to a solution of 2-aminopyridine (94.1 g, 1 mole) in methanol (100 ml). The solution was refluxed for 92 hours; the progress of the reaction was monitored by tlc. The solvent and the excess of methyl acrylate were removed by distillation. The residue was mixed with ethyl ether and allowed to crystallize. The product was filtered off and washed with ether, to obtain the pure compound (175 g, 66%), mp 59-60°. A sample was recrystallized from ether for analysis.

Anal. Calcd. for $C_{13}H_{18}N_2O_4$ (266.29): C, 58.63; H, 6.81; N, 10.51. Found: C, 59.06; H, 7.12; N, 10.92.

6-(2-Pyridyl)-2-(*N*-substituted-phenylpiperazino)-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4(3*H*)-one Derivatives **11a-11d**.

N-(2-Pyridyl)-3-methoxycarbonyl-4-piperidone (**13**) was prepared in the same way as described for *N*-benzyl-3-methoxycarbonyl-4-piperidone (**2**). The product, obtained in low yield (about 25-30%), was used without purification. Reactions with *N*-(substituted-phenylpiperazinoguanidines) **14** led to the isolation of the scarcely soluble final products **11**.

Characteristics of the compounds thus prepared are shown in Table 4, **11a-11d**.

N-Acyl-2-substituted-5,6,7,8-tetrahydropyrido[4,3-*d*]pyrimidin-4(3*H*)-ones **15a-15i**. General Procedure.

The variously 2-substituted-5,6,7,8-tetrahydropyrido[4,3-*d*]-pyrimidin-4(3*H*)-ones (**5**) (0.02 mole) was suspended in chloroform (50 ml). The appropriate acid chloride (0.022 mole) dissolved in chloroform (20 ml) was added at room temperature, with stirring. The mixture was stirred for 1 hour more, sodium carbonate (5 g) in water (25 ml) was then added to the heterogeneous mixture and stirring was continued for a further 3 hours at room temperature. The chloroform layer was separated, washed with water and the solvent was evaporated. The residue, which crystallized on the addition of acetone or a mixture of acetone and ether, was recrystallized from ethanol to give the product in 55-75% yield.

Characteristics of the compounds thus prepared are listed in Table 5, **15a-15i**.

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