80. A New Route to the Synthesis of 2-Amino-6-(methoxycarbonyl)amino-4-(tetrahydropyridyl)pyrimidine 1-Oxide

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Dedicated to Prof. *A. Hürlimann* on the occasion of his 60th birthday

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Summary

A new approach to 2-amino-6-(methoxycarbonyl)amino-4-(1,2,3,6-tetrahydro-1-pyridyl)pyrimidine 1-oxide (**3**) is described. Methyl [1-ethoxy-2-(ethoxycarbonyl)-ethylidene]carbamate (**5**) reacted with guanidine to the pyrimidinecarbamate **6**, which was successively transformed into methyl 2-amino-6-(*p*-tolylsulfonyl)oxy-4-pyrimidinecarbamate (**8**). Oxidation of **8** led to the corresponding pyrimidine *N*-oxide **9**, a useful starting material to **3**.

In a series of reports, we recently described the synthesis of new 2-oxo-2*H*-[1,2,4]oxadiazolo[2,3-*a*]pyrimidine-7-carbamates **1** [1] [2] and the synthesis of the regioisomers 2-oxo-2*H*-[1,2,4]oxadiazolo[2,3-*c*]pyrimidine-5-carbamates **2** [3], which both possess interesting cardiovascular properties. As a result of these investigations, **1a** *(Ro 12-4713)*, a potent antihypertensive agent was chosen to undergo clinical trials. One of the main metabolites of *Ro 12-4713* in animals as well as in man was found to be the 2-amino-6-(methoxycarbonyl)amino-4-(1,2,3,6-tetrahydro-1-pyridyl)pyrimidine 1-oxide (**3**) [4].

To secure **3** in quantities sufficient for its biological evaluation and for its further transformation into **2**, it was necessary to develop an alternative to the previously reported routes [1] [3].

We describe here a new synthesis of 2,4,6-trisubstituted pyrimidine nucleus which allows introduction of the carbamate moiety in position 4 at an early stage, whereas the substitution with tetrahydropyridyl in position 6 is performed at the last step.

Treatment of ethyl cyanoacetate with HCl in EtOH gave the 3-amino-3-ethoxyacrylate hydrochloride **4**. Transformation of **4** into the methyl carbamate **5** (mixture

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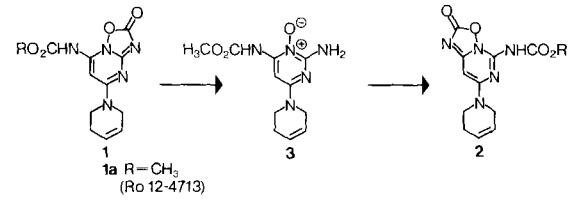

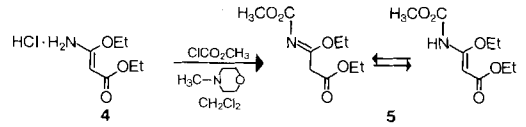

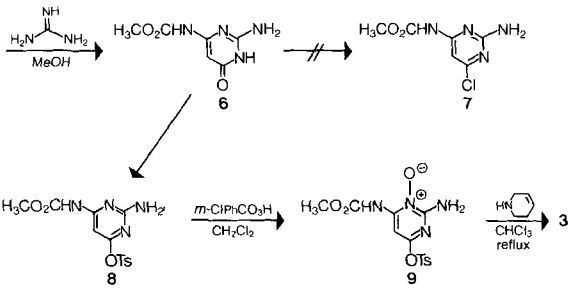

of tautomers) was best performed with methyl chloroformate in CH_2Cl_2 containing an excess of *N*-methylmorpholine. The rather unstable carbamate **5** was immediately treated with a slight excess of guanidine in MeOH at room temperature affording the methyl 2-amino-1,6-dihydro-6-oxo-4-pyrimidinecarbamate (**6**). Even under forcing conditions, **6** could not be transformed into the corresponding chloride **7**. The surprising ease of the *O*-tosylation, with *p*-toluenesulfonyl chloride in presence of *N*-methylmorpholine to the methyl 2-amino-6-(*p*-tolylsulfonyl)oxy-

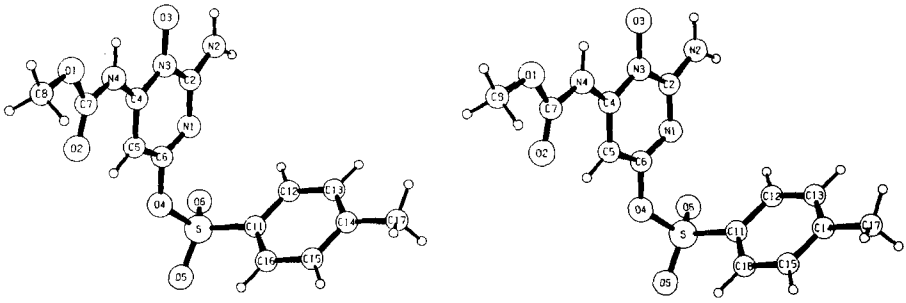

Figure. *A perspective drawing of a molecule of* **9**

4-pyrimidinecarbamate (**8**) was therefore astonishing and has not been presently rationalized.

N-Oxidation of **8** was carried out with 3-chloroperbenzoic acid in CH_2Cl_2 and gave the 2-amino-6-(methoxycarbonyl)amino-4-(*p*-tolylsulfonyl)oxypyrimidine 1-oxide (**9**) in 73% yield. The unequivocal proof of the positional assignment for the *N*-oxide was obtained by an X-ray crystallographic analysis of **9** (s. the *Fig.* and *Exper. Part*). Nucleophilic displacement of the *p*-tolylsulfonyloxy group by 1,2,3,6-tetrahydropyridine was conducted in refluxing $CHCl_3$ and afforded crystalline **3**.

The reported synthesis, although not fully optimized, allowed the preparation of **3** in 25–30% overall yield starting from ethyl cyanoacetate.

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Experimental Part

General remarks. S. [1], but reactions were not performed under Ar.

Preparation of ethyl 3-amino-3-ethoxyacrylate hydrochloride (**4**). A stirred mixture of 226 g (2 mol) of ethyl cyanoacetate in 200 ml of EtOH was saturated with HCl-gas at 0°, and subsequently stirred at 0° overnight. The cooled mixture was treated with 1500 ml of *t*-butyl methyl ether. The formed precipitate was filtered off and dried *in vacuo* at 35° to afford 351 g (90%) of **4**, m.p. 103–104° [5].

$C_7H_{13}NO_3 \cdot HCl$	Calc.	C 42.97	H 7.21	N 7.16	Cl 18.12%
(195.748)	Found	„ 42.87	„ 7.33	„ 7.14	„ 18.36%

Preparation of methyl [1-ethoxy-2-(ethoxycarbonyl)ethylidene]carbamate (**5**). A stirred solution of 96 g (0.49 mol) of **4** in 800 ml of CH_2Cl_2 and 120 ml (1.1 mol) of *N*-methylmorpholine was refluxed while a solution of 65 ml (0.84 mol) of methyl chloroformate in 350 ml of CH_2Cl_2 was added portionwise during 2 h. Refluxing and stirring were continued for 2 h, and the formed precipitate was filtered off. The filtrate was concentrated *in vacuo* to afford 107 g of a pale yellow oil which was sufficiently pure to be used in the next reaction. – IR. (Film): 1744 (C=O), 1711 (C=O), 1688, 1627 (C=N). – ^{1}H-NMR. ($CDCl_3$): 1.27 (*t*, *J* = 7, 3 H); 1.31 (*t*, *J* = 7, 3 H); 3.58 (*s*, 2 H); 3.80 (*s*, 3 H, CH_3O); 4.18 (*qa*, *J* = 7, 2 H); 4.23 (*qa*, *J* = 7, 2 H). – MS.: 217 (5, M^+), 115 (100, $M^+ - 102$), 114 (100, $M^+ - 103$).

$C_9H_{15}NO_5$ (217.22) Calc. C 49,76 H 6.96 N 6.45% Found C 49.59 H 7.26 N 6.85%

Preparation of methyl 2-amino-1,6-dihydro-6-oxo-4-pyrimidinecarbamate (**6**). To a stirred mixture of 30 g (0.31 mol) of guanidine · HCl in 200 ml of a 2N NaOMe, a solution of 50 g (0.23 mol) of **5** in 150 ml of MeOH was added at r.t. The resulting suspension was stirred overnight and concentrated at 40° *in vacuo*. The obtained residue was treated with 600 ml of H_2O, and the pH was adjusted to 5 by addition of AcOH. The precipitate was filtered off, washed with water and dried *in vacuo* at 50° to afford 36 g (85%) of a white powder, m.p. > 310° (dec.). – IR. (KBr): 3200 (NH_2), 1751 (C=O, carbamate), 1650, 1629 (C=O amide). – ^{1}H-NMR. (D_6-DMSO): 3.70 (*s*, 3 H, CH_3O); 6.1 (*s*, 1 arom. H); 6.43 (*s*, 2 H, H_2N); 9.50 (*s*, 1 H, HN); 10.5 (br. *s*, 1 H, HN). – MS.: 184 (M^+), 152 (100, $M^+ - 32$).

$C_6H_8N_4O_3$ (184.16) Calc. C 39.13 H 4.38 N 30.42% Found. C 39.35 H 4.49 N 30.55%

Preparation of methyl 2-amino-6-(p-tolylsulfonyl)oxy-4-pyrimidinecarbamate (**8**). A stirred suspension of 500 g (2.7 mol) of **6** in 1450 ml of *N*-methylmorpholine and 9000 ml of CH_2Cl_2 was refluxed and treated with 815 g (4.3 mol) of *p*-toluenesulfonyl chloride. The mixture was stirred at reflux overnight and concentrated *in vacuo*. The residue was treated with 9000 ml of H_2O and the insoluble material washed successively with H_2O and Et_2O. Drying at 40° afforded 751 g (82%) of a slight brown solid, m.p. 188–190°. An anal. sample was recrystallized from CH_2Cl_2/MeOH. – IR. (KBr): 3450 (NH_2),

1753 (C=O), 1373, 1176 (SO_2). – ^{1}H-NMR. ($CDCl_3/CD_3OD$): 2.49 (*s*, 3 H, CH_3); 3.80 (*s*, 3 H, CH_3O); 6.89 (*s*, 1 arom. H); 7.43 (*d*, $J=9$, 2 arom. H); 7.95 (*d*, $J=9$, 2 arom. H). – MS.: 307 (M^+), 242 (100, M^+-65), 214 (90, M^+-93).

$C_{13}H_{14}N_4O_5S$	Calc.	C 46.15	H 4.17	N 16.56	S 9.48%
(338.34)	Found.	„ 45.88	„ 4.12	„ 16.74	„ 9.29%

*Preparation of 2-amino-6-(methoxycarbonyl)amino-4-(*p*-tolylsulfonyl)oxypyrimidine 1-oxide* (**9**). A suspension of 350 g (1.03 mol) of **8** in 6300 ml of CH_2Cl_2 and 1000 ml of MeOH was treated with 370 g (2.1 mol) of *m*-chloroperbenzoic acid at r.t. and stirred overnight. The yellow solution was washed

Table 1. *Bond lengths [Å] with standard deviations in parentheses*

S–O(4)	1.627 (2)	N(3)–C(4)	1.360 (3)
S–O(5)	1.421 (2)	N(4)–C(4)	1.354 (4)
S–O(6)	1.420 (2)	N(4)–C(7)	1.385 (4)
S–C(11)	1.736 (3)	C(4)–C(5)	1.384 (4)
O(1)–C(7)	1.332 (4)	C(5)–C(6)	1.372 (4)
O(1)–C(8)	1.447 (4)	C(11)–C(12)	1.381 (4)
O(2)–C(7)	1.186 (4)	C(11)–C(16)	1.389 (5)
O(3)–N(3)	1.344 (3)	C(12)–C(13)	1.370 (5)
O(4)–C(6)	1.382 (4)	C(13)–C(14)	1.367 (6)
N(1)–C(2)	1.337 (4)	C(14)–C(15)	1.386 (5)
N(1)–C(6)	1.321 (4)	C(14)–C(17)	1.500 (5)
N(2)–C(2)	1.316 (4)	C(15)–C(16)	1.374 (5)
N(3)–C(2)	1.365 (4)		

Table 2. *Bond Angles [°] with standard deviations in parentheses*

O(4)–S–O(5)	100.4 (1)	N(4)–C(4)–C(5)	128.0 (2)
O(4)–S–O(6)	110.1 (1)	C(4)–C(5)–C(6)	115.6 (2)
O(4)–S–C(11)	103.9 (1)	O(4)–C(6)–N(1)	118.4 (2)
O(5)–S–O(6)	119.6 (1)	O(4)–C(6)–C(5)	114.8 (2)
O(5)–S–C(11)	110.9 (2)	N(1)–C(6)–C(5)	126.8 (3)
O(6)–S–C(11)	110.5 (1)	O(1)–C(7)–O(2)	126.8 (3)
C(7)–O(1)–C(8)	114.3 (3)	O(1)–C(7)–N(4)	108.1 (3)
S–O(4)–C(6)	124.8 (2)	O(2)–C(7)–N(4)	125.1 (3)
C(2)–N(1)–C(6)	116.1 (2)	S–C(11)–C(12)	121.7 (3)
O(3)–N(3)–C(2)	119.4 (2)	S–C(11)–C(16)	118.8 (2)
O(3)–N(3)–C(4)	119.7 (2)	C(12)–C(11)–C(16)	119.5 (3)
C(2)–N(3)–C(4)	120.9 (2)	C(11)–C(12)–C(13)	119.7 (3)
C(4)–N(4)–C(7)	125.7 (3)	C(12)–C(13)–C(14)	122.1 (3)
N(1)–C(2)–N(2)	121.1 (3)	C(13)–C(14)–C(15)	117.7 (3)
N(1)–C(2)–N(3)	121.7 (2)	C(13)–C(14)–C(17)	121.9 (3)
N(2)–C(2)–N(3)	117.1 (3)	C(15)–C(14)–C(17)	120.4 (4)
N(3)–C(4)–N(4)	113.1 (2)	C(14)–C(15)–C(16)	121.7 (4)
N(3)–C(4)–C(5)	118.9 (2)	C(11)–C(16)–C(15)	119.2 (3)

Table 3. *Crystal Data*

Space group	$P2_1/n$	Space group	$P2_1/n$
a	13.967 (2) Å	*Z*	4
b	8.633 (2) Å	^{d}calc.	1.502 g cm^{-3}
c	13.720 (3) Å	μ(Cu*Kα*)	21.6 cm^{-1}
β	108.66 (1)°		

with 3000 ml of 2N $NaHCO_3$. The aq. phase was extracted with 1000 ml of CH_2Cl_2, and the combined org. phases washed with sat. NaCl-solution. The solvents were evaporated *in vacuo* and the residue recrystallized from CH_2Cl_2, MeOH and hexane to afford 270 g (73%) of white crystals of **9**, m.p. 145–147°. – IR. (KBr): 3432 (NH_2), 1756 (C=O), 1393, 1178 (SO_2). – ^{1}H-NMR. ($CDCl_3/CD_3OD$): 2.51 (*s*, 3 H, CH_3); 3.87 (*s*, 3 H, CH_3O); 7.12 (*s*, 1 arom. H); 7.35 (*d*, $J=9$, 2 arom. H); 7.93 (*d*, $J=9$, 2 arom. H).

$C_{13}H_{14}N_4O_6S$	Calc.	C 44.07	H 3.98	N 15.81	S 9.05%
(354.34)	Found.	„ 43.91	„ 3.97	„ 15.85	„ 8.94%

Preparation of 2-amino-6-(methoxycarbonyl)amino-4-(1,2,3,6-tetrahydro-1-pyridyl)pyrimidine 1-oxide (**3**). A suspension of 24.89 (0.07 mol) of **9** in 400 ml of $CHCl_3$ containing 14.5 g (0.175 mol) of 1,2,3,6-tetrahydropyridine was refluxed for 90 min. The cooled mixture was filtered and the org. phase washed with HCl at pH 5, H_2O and dried over Na_2SO_4. The solvent was removed *in vacuo* and the obtained residue recrystallized from CH_2Cl_2, MeOH and Et_2O to afford 10.5 g (56%) of **3**, m.p. 221–223° (dec.).

$C_{11}H_{15}N_5O_3$ (265.27) Calc. C 49.81 H 5.70 N 26.40% Found C 49.69 H 5.82 N 26.12%

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