61. Synthesis of 2-Oxo-2*H*-[1,2,4]oxadiazolo-[2,3-*c*]pyrimidine-5-carbamates

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

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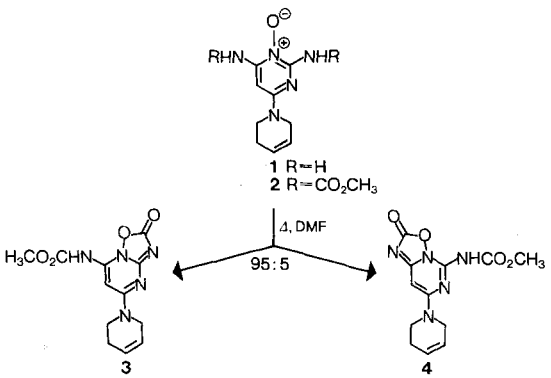
Summary

Thermal cyclization of the pyrimidine-*N*-oxide dicarbamate **2** gives a 95:5 mixture of the 2-oxo-2*H*-[1,2,4]oxadiazolo[2,3-*a*]- and [2,3-*c*]pyrimidinecarbamates **3** and **4**. An efficient procedure for the conversion of **3** to **4**, and *vice versa,* is described.

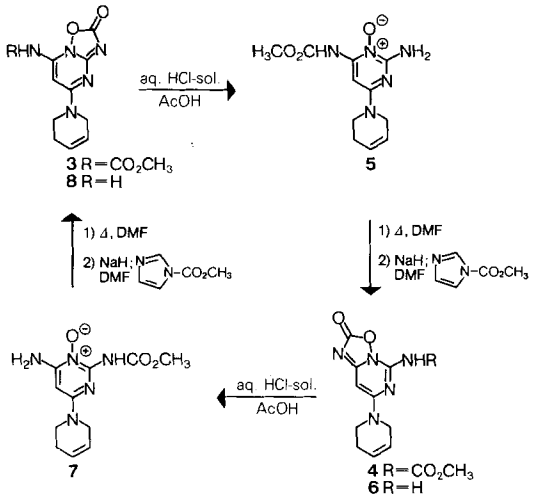
The 2-oxo-2*H*-[1,2,4]oxadiazolo[2,3-*a*]pyrimidine-7-carbamate **3** belongs to a new class of potent peripheral vasodilators. This compound was shown to exert a strong and long-lasting antihypertensive effect in experimental animals as well as in humans [1]. Its synthesis was previously reported [2], the last step being a highly regioselective cyclization of the pyrimidine-*N*-oxide dicarbamate **2** (*Scheme 1*). Subsequently, we examined this reaction in more detail and found that thermal ring closure of **2** led to a 95:5 mixture of the regioisomers **3** and **4**. The structure of the major isomer **3** has been unequivocally established before by an X-ray crystallographic analysis [2b]. The minor component, isolated from the mother liquor by high pressure liquid chromatography, was identified as **4** on the basis of its spectroscopic properties.

Scheme 1



In the following, an efficient and practical synthesis of the new 2-oxo-2*H*-[1,2,4]oxadiazolo[2,3-*c*]pyrimidine-5-carbamate **4** is presented *(Scheme 2)*. For the preparation of the intermediate **5** neither direct acylation of **1** with 1 equivalent methyl chloroformate [2a] nor partial hydrolysis of **2** with aqueous base was selective enough to be preparatively useful. On the other hand, treatment of **3** with aqueous HCl-solution in acetic acid opened smoothly the oxadiazole ring with concomitant decarboxylation to afford **5** in 78% yield. This compound cyclized readily at 135° in DMF to the oxadiazolo[2,3-*c*]pyrimidin-2-one **6**. The remaining acylation of **6** to **4** was first attempted with methyl chloroformate in various solvents, but this reaction gave only low yields of product owing to the poor nucleophilicity of the amino function. *Dyer & Richmond* [3] have demonstrated that aminopyrimidines unreactive towards chloroformates can be converted into the corresponding ethyl carbamates with diethyl pyrocarbonate. We solved the problem in a different manner by forming the anion of **6** with sodium hydride, this ion then reacting with 1-methoxycarbonylimidazole [4], a reagent compatible with the solvent. After workup and recrystallization pure **4** was obtained in 82% yield (58% overall yield from **3**).

Scheme 2



Employing this acylating procedure, analogous carbamates *(Table)* became accessible from the newly available **6** and the corresponding 1-alkoxycarbonylimidazoles prepared by the method of *Loozen et al.* [5].

Finally, compound **4** was subjected to the three-step reaction sequence depicted in *Scheme 2* and was converted back, *via* the intermediates **7** and **8**, to the 2-oxo-2*H*-[1,2,4]oxadiazolo[2,3-*a*]pyrimidine-7-carbamate **3**. This reaction cycle corroborates the correct assignment of structure **4** to the minor isomer formed in the cyclisation of **2**.

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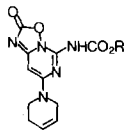
Table. *Data of new 2-oxo-2H-[1,2,4]oxadiazolo[2,3-c]pyrimidine-5-carbamates*

	R	M.p. (dec.) [°C]	Yield [%]	Molecular formula	Analyses Calc./Found [%]		
					C	H	N
	Methyl	215	82	$C_{12}H_{13}N_5O_4$	49.48	4.50	24.04
				291.27	49.59	4.52	24.09
	Ethyl	202–204	59	$C_{13}H_{15}N_5O_4$	51.15	4.95	22.94
				305.30	51.03	4.89	22.97
	Butyl	197–198	56	$C_{15}H_{19}N_5O_4$	54.05	5.75	21.01
				333.35	53.92	5.68	21.01
	i-Butyl	197–198	65	$C_{15}H_{19}N_5O_4$	54.05	5.75	21.01
				333.35	53.71	5.75	21.03
	2-Methoxyethyl	203–204	69	$C_{14}H_{17}N_5O_5$	50.15	5.11	20.89
				335.32	49.83	5.13	21.13
	Allyl	207–209	70	$C_{14}H_{15}N_5O_4$	52.99	4.77	22.07
				317.31	53.16	4.80	22.40

Experimental Part

General remarks. Melting points (m.p.) were taken on a melting point apparatus *Büchi 510* and are not corrected. IR. spectra (cm^{-1}) were obtained on a *Beckman IR 9* instrument. ^{1}H-NMR. spectra were recorded on a 80-MHz *Bruker*-instrument and are reported in ppm downfield from internal tetramethylsilane. Mass spectra were recorded on a *MS 9 (AEI)* spectrometer.

Methyl 2-amino-6-[3,6-dihydro-1(2H)-pyridyl]pyrimidine-4-carbamate 3-oxide (**5**). A stirred mixture of 41.4 g (0.142 mol) methyl 5-[3,6-dihydro-1(2*H*)-pyridyl]-2-oxo-2*H*[1,2,4]oxadiazolo[2,3-*a*]pyrimidine-7-carbamate (**3**), 260 ml of glacial acetic acid and 130 ml of 4N aq. HCl was heated at 57° for 10 h. The brown-orange solution was partitioned between 1.25N aq. NaOAc (800 ml) and $CHCl_3$ (500 ml), and the org. layer was washed with water and aq. $NaHCO_3$-sol. The aq. phases were reextracted with $CHCl_3$ (2× 500 ml), and the combined org. phases were dried ($MgSO_4$) and concentrated *in vacuo* to afford 29.2 g (77.5%) of **5**, m.p. 222° (dec.; melted and solidified between 170 and 180°). The analytical sample was prepared by recrystallization from $CHCl_3$/EtOAc: white crystals, m.p. 223° (dec.). – IR. (KBr): 3380, 3260, 1751, 1655, 1611, 1561. – ^{1}H-NMR. ($CDCl_3$): 2.2 (*m*, 2 H); 3.66 (*t*, *J* = 5.5, 2 H); 3.80 (*s*, 3 H); 3.93 (*m*, 2 H); 5.5–6.0 (*m*, 2 H); 6.09 (br. *s*, 2 H); 6.73 (*s*, 1 H). – MS.: 265 (M^+).

$C_{11}H_{15}N_5O_3$ (265.27) Calc. C 49.81 H 5.70 N 26.40% Found C 49.52 H 5.74 N 26.10%

5-Amino-7-[3,6-dihydro-1(2H)-pyridyl]-2H-[1,2,4]oxadiazolo[2,3-c]pyrimidin-2-one (**6**). A solution of compound **5** (28.8 g, 0.109 mol) in 350 ml DMF was stirred in an oil bath of 135° for 30 min. The brown solution was concentrated *in vacuo*, and the residue was slurried with ether (350 ml). The crystalline product was filtered, washed with ether and dried to give 23.4 g (92.5%) of **6**, m.p. 228° (dec.). The analytical sample was prepared by recrystallization from CH_3OH: white crystals, m.p. 231° (dec.). – IR. (KBr): 3480, 1780, 1670, 1588, 1531. – ^{1}H-NMR. ((D_6)DMSO): 2.2 (*m*, 2 H); 3.70 (*t*, *J* = 5.5, 2 H); 3.97 (*m*, 2 H); 5.68 (*s*, 1 H); 5.6–6.0 (*m*, 2 H); 7.82 (br. *s*, 2 H). – MS.: 233 (M^+).

$C_{10}H_{11}N_5O_2$ (233.23) Calc. C 51.50 H 4.75 N 30.03% Found C 51.58 H 4.79 N 29.81%

Methyl 7-[3,6-dihydro-1(2H)-pyridyl)-2-oxo-2H-[1,2,4]oxadiazolo[2,3-c]pyrimidine-5-carbamate (**4**). Sodium hydride dispersion (55–60% in oil, 4.30 g, *ca.* 100 mmol) was washed with hexane and suspended under Ar in 150 ml dry DMF. Compound **6** (20.54 g, 88 mmol) was added portionwise over 10 min while the temperature was kept at 14° with an ice bath. After the mixture has been stirred at r.t. for 30 min, 1-methoxycarbonylimidazole [6] (15.8 g, 125 mmol) in 50 ml DMF was added and the solution stirred at 20–25° for 1 h. The mixture was poured into 1.2 l of water and the slightly turbid solution was filtered. Acetic acid (40 ml) was added to the stirred solution. The crystalline precipitate was collected, washed with water and MeOH, and dried to afford 23.37 g (91%) of **4**, m.p. 213° (dec.). Crude **4** (10.00 g) was dissolved in 500 ml of MeOH and 25 ml of triethylamine at reflux. Acetic acid (20 ml) in MeOH (50 ml) was added dropwise to the hot solution, and the resulting

suspension was stirred at r.t. for 30 min. The precipitate was collected, washed with several portions of MeOH, and dried to yield 8.99 g (82%) of **4** as white crystals, m.p. 215° (dec.). – IR. (KBr): 3234, 1775, 1652, 1601, 1540, 1267, 1248, 1219. – ^{1}H-NMR. ((D$_6$)DMSO): 2.2 (*m*, 2 H); 3.71 (*s*, 3 H); 3.75 (*t*, *J* = 5.5, 2 H); 4.01 (*m*, 2 H); 5.6–6.0 (*m*, 2 H); 6.04 (*s*, 1 H); 11.1 (br. *s*, 1 H). – MS.: 291 (M^+).

*Methyl 4-amino-6-[3,6-dihydro-1(2*H*)-pyridyl]pyrimidine-2-carbamate 3-oxide* (**7**). A mixture of 5.82 g (20 mmol) of **4**, 36 ml of glacial acetic acid and 18 ml of 4N aqueous HCl was heated at 57° for 12 h. Workup, as described for compound **5**, afforded 3.33 g (63%) of **7**, m.p. 244° (dec.; melted and solidified between 100 and 110°). The analytical sample was prepared by recrystallization from CH_2Cl_2/EtOAc: off-white crystals, m.p. 246° (dec.). – IR. (KBr): 3434, 1765, 1653, 1576, 1504. – ^{1}H-NMR. ($CDCl_3$): 2.2 (*m*, 2 H); 3.68 (*t*, *J* = 5.5, 2 H); 3.76 (*s*, 3 H); 3.85 (*m*, 2 H); 5.42 (*s*, 1 H); 5.5–6.0 (*m*, 2 H); 6.30 (br. *s*, 2 H). – MS.: 265 (M^+).

$C_{11}H_{15}N_5O_3$ (265.27) Calc. C 49.81 H 5.70 N 26.40% Found C 49.56 H 5.77 N 26.47%

*7-Amino-5-[3,6-dihydro-1(2*H*)-pyridyl]-2*H*-[1,2,4]oxadiazolo[2,3-a]pyrimidin-2-one* (**8**). A solution of crude **6** (2.91 g, 11 mmol) in 50 ml DMF was stirred in an oil bath of 135° for 30 min. The brown solution was concentrated to half its volume, MeOH (80 ml) was slowly added to the hot solution and the mixture stirred at r.t. for 1 h. The precipitate was filtered off, washed with MeOH and dried to afford 1.47 g (57%) of **8** as beige crystals, m.p. 262° (dec.). – IR. (KBr): 3364, 3184, 1765, 1748, 1684, 1628, 1585. – ^{1}H-NMR. ((D$_6$)DMSO): 2.2 (*m*, 2 H); 3.66 (*t*, *J* = 5.5, 2 H); 3.90 (*m*, 2 H); 5.28 (*s*, 1 H); 5.5–6.0 (*m*, 2 H); 7.72 (br. *s*, 2 H). – MS.: 233 (M^+).

$C_{10}H_{11}N_5O_2$ (233.23) Calc. C 51.50 H 4.75 N 30.03% Found C 51.26 H 4.78 N 29.88%

*Methyl 5-[3,6-dihydro-1(2*H*)-pyridyl]-2-oxo-2*H*-[1,2,4]-oxadiazolo[2,3-a]pyrimidine-7-carbamate* (**3**). Compound **8** (1.055 g, 4.5 mmol) was added portionwise to an ice bath-cooled suspension of 240 mg (*ca.* 6 mmol) of sodium hydride (55–60% in mineral oil) in 12 ml DMF. The resulting turbid solution was stirred at r.t. for 15 min. 1-Methoxycarbonylimidazole (0.855 g, 6.8 mmol) was added, and the mixture was stirred for 30 min. The solution was poured into water (180 ml), and the aq. phase, after extraction with ether, treated with 2.0 ml of acetic acid. The precipitate was collected, washed with water and dried to give 1.094 g (83%) of **3**, m.p. 210° (dec.). This material was recrystallized in the manner described for compound **4** to afford 0.875 g (67%) of **3** as white crystals, m.p. 212° (dec.), identical (LC., UV., IR., ^{1}H-NMR.) with the previously described compound [2a].

$C_{12}H_{13}N_5O_4$ (291.27) Calc. C 49.48 H 4.50 N 24.04% Found C 49.54 H 4.56 N 24.04%

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