# 142. Regioselective Synthesis of 2-oxo-2,8-dihydro-[1,2,4]-oxadiazolo[2,3-*a*]pyrimidine-7-carbamates: A New Class of Antihypertensive Peripheral Vasodilators

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*Summary*

The synthesis of new 2-oxo-2,8-dihydro-[1,2,4]-oxadiazolo-[2,3-*a*] pyrimidinecarbamates **3** described in this paper is based upon a regioselective heterocyclization of the pyrimidine-2,6-bis(alkoxycarbonylamino) *N*-oxides **4**. Structural and mechanistic aspects of that cyclization are discussed.

**Introduction.** – The discovery of the antihypertensive activity of the vasodilator hydralazine (**1**) by *Gross, Druey & Meier* [1] more than 30 years ago has provided a new therapeutic alternative for the treatment of essential hypertension by correcting one of the basic abnormalities shown in hypertension, namely the increase in total peripheral vascular resistance. Subsequently minoxidil (**2**) was developed as a potent long lasting antihypertensive vasodilator [2–4]. There is nevertheless still a need [5] for an antihypertensive agent with minimal side effects. Like most antihypertensive vasodilators, minoxidil (**2**) induces reflex tachycardia, sodium and water retention [6]. Minoxidil and some of its metabolites also tend to accumulate in vascular tissues [7]. We envisaged modifying the triaminopyrimidine *N*-oxide structure. With the hypothesis that changes both in the hydrophilic lypophilic balance and in the acidic character of our new compounds would assist removal of side effects, while conserving the potent antihypertensive activity of the parent drug.

We describe here the synthesis of new 2-oxo-2*H*-[1,2,4]-oxadiazolo-[2,3-*a*]-pyrimidinecarbamates **3** *via* a regioselective heterocyclization of the *N*-oxides **4**. This work led to the discovery of **3a** (Ro 12-4713) and its development for the treatment of hypertension.

**Results and discussion.** – Treatment of 2,4-diamino-6-chloropyrimidine **5** with excess 40% solution of peracetic acid in ethanol at 0° *(Scheme 1)* afforded the known *N*-oxide **6** [8] (80%). Nucleophilic displacement of the Cl-atom of **6** by 1,2,3,6-tetrahydropyridine used as a solvent led to the pyrimidine *N*-oxide **7** [9] (85%). When **7** was treated at 0° with a large excess of various alkylchloroformates in the presence of a base, the corresponding dicarbamates **4** were easily obtained (56–94% *Table 1*). They are stable at r. t., but undergo thermally a facile regioselec-

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tive heterocyclization accompanied by the elimination of the corresponding alcohol leading to the new 2-oxo-2*H*-[1,2,4]-oxadiazolo-[2,3-*a*] pyrimidinecarbamates **3** (61–95%, *Table 2*). The structures of **3a–f** investigated by IR., NMR., and microanalysis data were confirmed byX-ray crystallographic analysis of **3a** (see following article).

*Scheme 1*

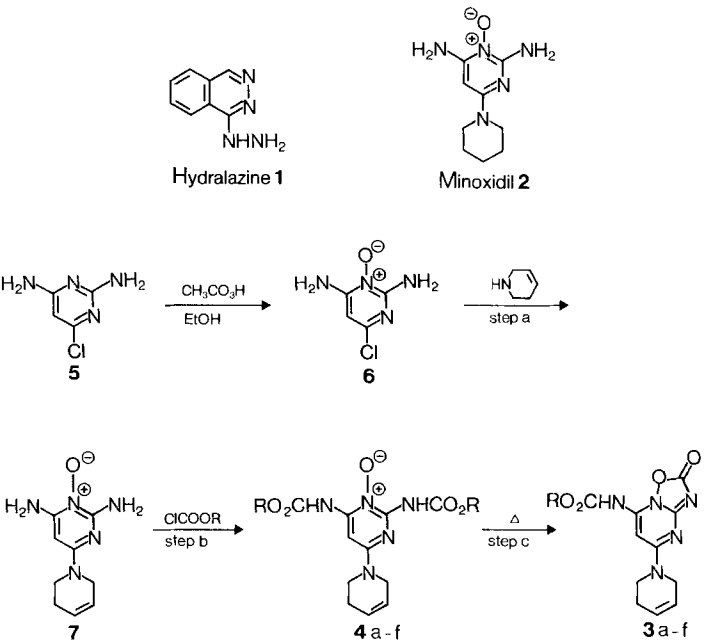



Table 1. *Data of compounds* **4a–f**

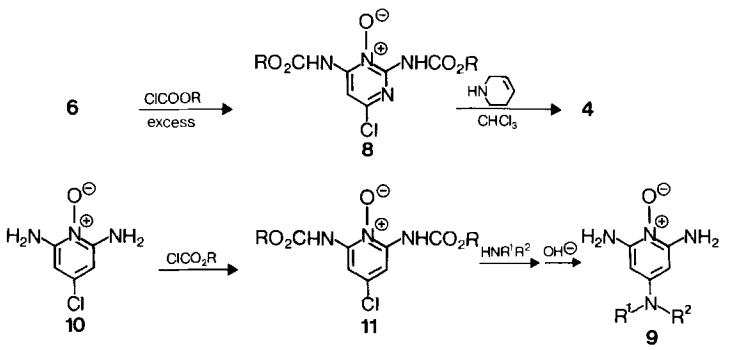
| 4 | R | Mp. [°C] | Yield [%] | Molecular formula | Analyses Calc./Found [%] C | H | N | IR. [cm$^{-1}$] KBr | $^1$H-NMR. for H–C(5) |
|---|---|---|---|---|---|---|---|---|---|
| **a** | methyl | 202–206 | 94 | $C_{13}H_{17}N_5O_5$ 323.309 | 48.30 48.33 | 5.30 5.41 | 21.66 21.75 | 1770 1745 | 7.28 ($CF_3COOH$) |
| **b** | ethyl | 154–155 | 85 | $C_{15}H_{21}N_5O_5$ 351.363 | 57.28 50.93 | 6.02 6.04 | 19.93 19.85 | 1767 1746 | 6.99 ($CDCl_3$) |
| **c** | butyl | 131–132 | 56 | $C_{19}H_{29}N_5O_5$ 407.471 | 56.01 56.16 | 7.17 7.50 | 17.19 17.18 | 1763 1736 | 7.01 ($CDCl_3$) |
| **d** | *i*-butyl | 137–139 | 73 | $C_{19}H_{29}N_5O_5$ 407.471 | 56.01 55.73 | 7.17 7.30 | 17.19 16.90 | 1762 1745 | 6.98 ($CDCl_3$) |
| **e** | benzyl | 172 | 87 | $C_{25}H_{25}N_5O_5$ 475.505 | 63.15 63.10 | 5.30 5.44 | 14.73 14.47 | 1754 1741 | 6.93 ($CDCl_3$) |
| **f** | 2-methoxy-ethyl | 126–128 | 73 | $C_{17}H_{25}N_5O_7$ 411.415 | 49.63 49.52 | 6.13 6.30 | 17.02 17.37 | 1764 1740 | 7.00 ($CDCl_3$) |

Table 2. *Data of the compounds* **3a–f**

| 3 | R | Mp. [°C] | Yield [%] | Molecular formula | Analyses Calc./Found [%] C | H | N | IR. [cm$^{-1}$] KBr | $^1$H-NMR. for H–C(6) |
|---|---|---|---|---|---|---|---|---|---|
| **a** | methyl | 215 (dec.) | 95 | $C_{12}H_{13}N_5O_4$ 291.267 | 49.48 49.49 | 4.50 4.56 | 24.04 24.05 | 1782 1748 | 6.77 ($D_6$-DMSO) |
| **b** | ethyl | 205 (dec.) | 83 | $C_{13}H_{15}N_5O_4$ 305.294 | 51.15 51.10 | 4.95 5.11 | 22.94 22.48 | 1787 1742 | 6.75 ($D_6$-DMSO) |
| **c** | butyl | 189 (dec.) | 63 | $C_{15}H_{19}N_5O_4$ 333.348 | 54.05 53.91 | 5.75 5.70 | 21.01 21.11 | 1786 1746 | 6.80 ($CDCl_3$) |
| **d** | *i*-butyl | 203 (dec.) | 64 | $C_{15}H_{19}N_5O_4$ 333.348 | 54.05 54.15 | 5.75 5.69 | 21.01 21.37 | 1791 1750 | 6.80 ($CDCl_3$) |
| **e** | benzyl | 218 (dec.) | 61 | $C_{18}H_{17}N_5O_4$ 367.365 | 58.85 58.59 | 4.66 4.68 | 19.06 19.18 | 1781 1744 | 6.75 ($CDCl_3$ + $D_6$-DMSO) |
| **f** | 2-methoxy-ethyl | 196 (dec.) | 81 | $C_{14}H_{17}N_5O_5$ 335.320 | 50.15 49.85 | 5.11 5.17 | 20.89 20.88 | 1782 1744 | 6.70 ($D_6$-DMSO) |

*Step a.* An alternative way to prepare **4** is shown in *Scheme 2*. Treatment of **6** with excess of an alkyl chloroformate in $CH_2Cl_2$ or dimethylformamide (DMF) provides a dicarbamate **8**, easily transformed into the corresponding **4** by heating in $CHCl_3$ with excess 1,2,3,6-tetrahydropyridine. In the case of **8a**, the reaction occurs at r. t., the presence of two strong electron-withdrawing methoxycarbonyl groups facilitating the nucleophilic attack of the amine on C(6). The fact is in complete accordance with the finding of *Lawson & Dennis* [10] who prepared trisubstituted pyridine-*N*-oxides **9** from 2,4-diamino-6-chloropyridines **10** *via* the dicarbamates **11**.

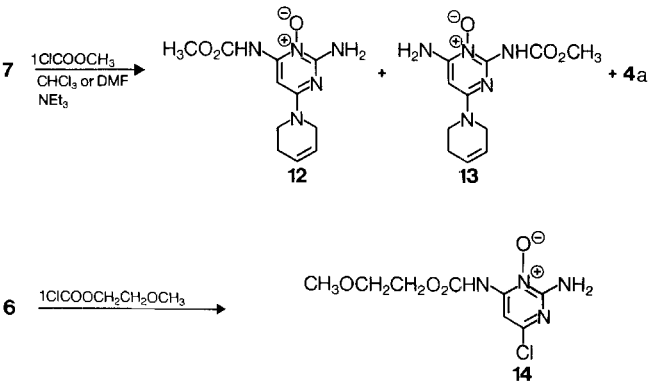
*Scheme 2*




*Step b.* Reaction of 2,4-diaminopyrimidine *N*-oxides **6** or **7** with alkyl chloroformates appears to be unusually fast and reveals an important difference of nucleophilic character between the amino groups at C(2) and C(4). When **7** reacted overnight at r. t. with an equimolar quantity of methyl chloroformate in DMF in the presence of triethylamine, starting material (34%), monocarbamates **12** and **13** (25%,

22:3)[1]) and dicarbamate **4a** (27%) were isolated. A similar observation was made for the reaction between 2,4-diamino-6-chloropyrimidine **6** and 2-methoxyethyl chloroformate leading to **14**. Both reactions occur preferentially on the amino group at C(4). Therefore we examined whether the *N*-oxide group could participate in a O→ N alkoxycarbonyl transfer reaction. The reaction of **7** with a large excess methyl chloroformate at 0° for 10 min provides **4a** in quantitative yield *(Scheme 3)*. Under the same conditions, no reaction occurs with the trisubstituted pyrimidine **15** (prepared according to [11]). Nevertheless **15** can be transformed into **16** at r. t. within 1 h. A similar study on the reactivity of aminopyrimidines *N*-oxides with different acid anhydrides is reported [12]. Whereas the pyrimidine *N*-oxide **7** was transformed into the diacetamide **17** at 0° within 30 min in presence of 2.5 equiv. of acetic anhydride, obtaining **18** from **15** required 5 equiv. of acetic anhydride at reflux temperature during 12 h *(Scheme 4)*. Since most of the compounds display very poor solubility in organic solvents, kinetic studies could not be undertaken. The reaction mechanism has not been clarified; *O*-acylation might occur in the first step *(Scheme 5)*.

*Scheme 3*

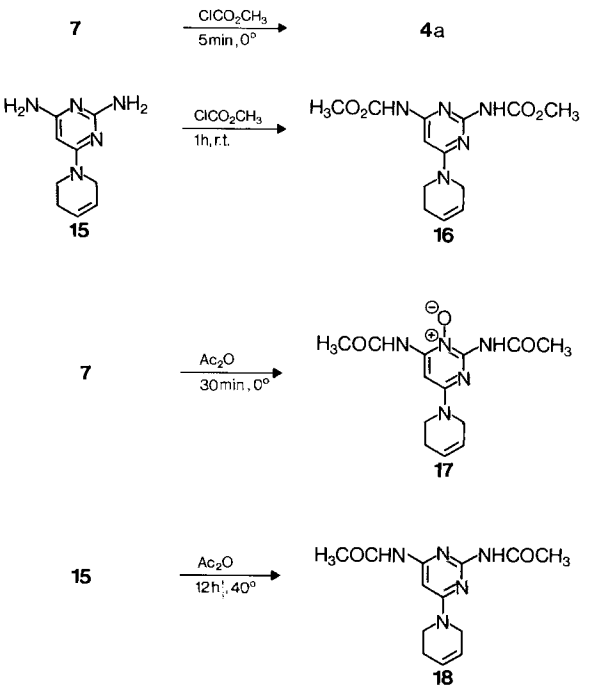



*Step c.* The formation of 2-oxo-2,8-dihydro-[1,2,4]oxadiazolo[2,3-*a*]pyridine **20** from the corresponding carbamate **19** by thermal elimination of ethanol at 150° was first reported by *Katritzky* in 1956, who later discussed its properties [13]. We felt that a careful analysis of the spectral data of the two carbamate moieties of **4** would help understanding of the remarkable regioselectivity of the cyclization **4**→ **3**, but with the exception of the IR. absorptions of the 2 CO groups, no significant differences were noticed[2]). X-ray crystallographic analysis clearly showed that the crystals possess structure **4a** *(Figure)*[2]).

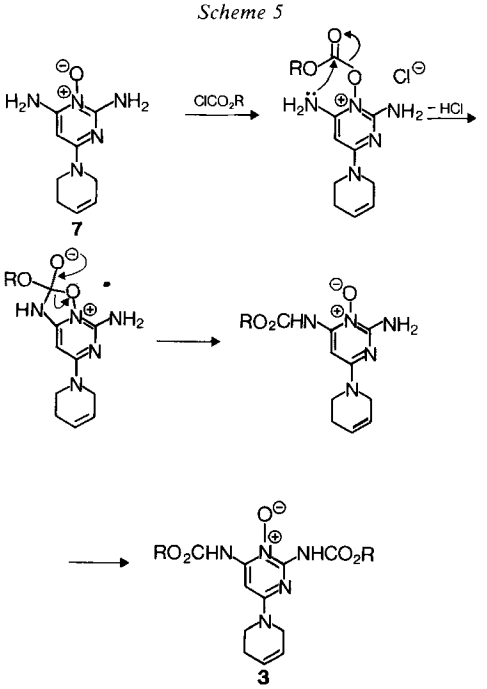
[1]) Structures **12** and **13** were ascertained by analogy (IR., NMR.) with similar compounds (see following article).

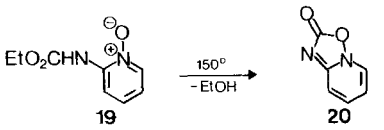
[2]) Following article.

*Scheme 4*




*Scheme 5*






19 20

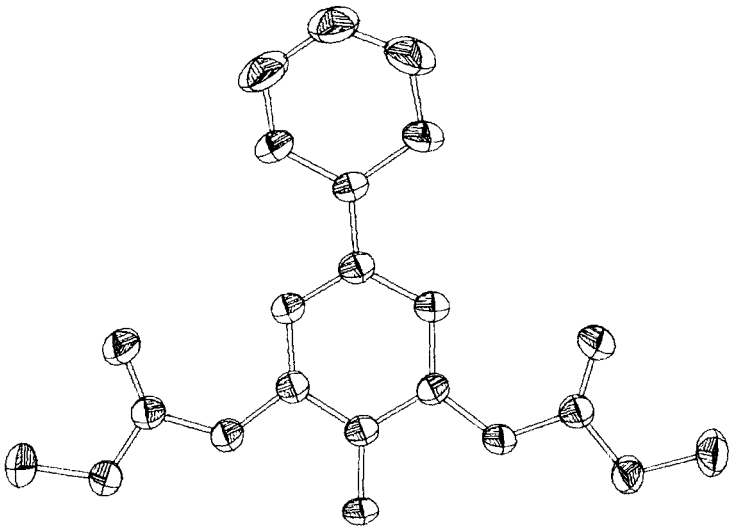


Figure. *Computer-generated drawing of* **4a**

Derivatives **3** are rather stable towards nucleophilic agents and can be recrystallized from alcohols, while **20** undergoes ring opening under similar conditions [13]. When treated with an equimolar amount of a strong base, **3** form stable salts. The p*Ka* of **3a** (from UV.) was 7.02.

The 2-oxo-2,8-dihydro-[1,2,4]-oxadiazolo-[2,3-*a*]pyrimidine-7-carbamates **3** display a potent and long lasting antihypertensive activity in various animals and **3a** did not induce reflex tachycardia or water and sodium retention [14]. Because of this unique pharmacological profile, **3a** was chosen to undergo clinical trials. Numerous results confirmed the data obtained from animal studies [15].

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## Experimental Part

All reactions were performed under argon. For TLC. precoated silica gel plates (F 254, *Merck*, Darmstadt) were used. Melting points (m.p.) were determined on a *Tottoli* apparatus and are uncorrected. IR. spectra ($\gamma$[cm$^{-1}$]) were taken on a *Beckmann IR 9* instrument. Mass spectra (MS.) were recorded on an *AEI MS 9, CEC 21-103* or a *Varian CH-5* spectrometer. NMR.-data were obtained on a *Varian A-60, HA-100* or *XL-100* instrument and the chemical shifts are given in ppm relative to tetramethylsilane as an internal standard, and coupling constants (*J*) in Hz.

*Preparation of 2,4-diamino-6-chloropyrimidine 3-oxide* (**6**). To a stirred suspension of 144.5 g of **5** (1.0 mol) in 2 l of ethanol warmed to 35° for 15 min and then cooled to 7° were added in 40 min 175 ml of 40% peracetic (1.08 mol) in acetic acid. After 30 min, the mixture was left to warm to r.t., stirred for 3 h and 2 l of petroleum ether were added. After standing overnight, the mixture was filtered, the precipitate washed with petroleum ether and dried under reduced pressure (146 g, 91%). An analytical sample of **6**, m.p. 193°, can he obtained on recrystallization from ethanol [8].

*Preparation of 2,6-diamino-4-(1,2,3,6-tetrahydro-1-pyridyl)pyrimidine 1-oxide* (**7**). A stirred mixture of 155 g (0.965 mol) of **6** 640 ml of *o*-xylene and 260 ml (2.84 mol) of 1,2,3,6-tetrahydropyridine was heated to reflux for 30 min at 120°, then cooled to 5°, treated with 400 ml of 10% NaOH-solution and stirred at 5° for 1 h. The precipitate was filtered off, washed with $H_2O$, recrystallized from 3 l of $H_2O$ and dried under reduced pressure, giving 125 g (62%) of **7** were obtained, m.p. 263–265° (dec.). – IR. (KBr): 3440, 3360, 1652, 1625, 1570, 1476, 1236. – $^1$H-NMR. (80 MHz, ($D_6$DMSO): 2.12 (*m*, 2 H); 3.56 (*t*, *J*=6, 2 H); 375 (*m*, 2 H); 5.37 (*s*, 1 H); 5.90 (*m*, 2 H); 6.93 ( 2 br. *s*, 2×2 H). – MS.: 207 ($M^+$).

$C_9H_{13}N_5O_1$ (207.238) Calc. C 52.16 H 6.32 N 33.80% Found C 52.08 H 6.51 N 33.64%

*Preparation of 2,6-diamino-4-(1,2,3,6-tetrahydro-1-pyridyl)pyrimidine 1-oxide* (**7**). A solution of 83 g (1 mol) of 1,2,3,6-tetrahydropyridine and 113 g (1 mol) of ethyl cyanoacetate was heated to 110°, the ethanol formed being distilled off continuously. After 18 h, the mixture was distilled under reduced pressure, to afford *N*-cyanoacetyl-1,2,3,6-tetrahydropyridine, m.p. 58–59°.

A solution of 25 g (0.2 mol) of *N*-cyanoacetyl-1,2,3,6-tetrahydropyridine and 32.2 g (0.218 mol) of trimethyloxonium-tetrafluoroborate in 230 ml of dry $CH_2Cl_2$ was stirred for 20 h. The mixture was then poured into a cold solution of 31.8 g (0.30 mol) of $K_2CO_3$ in 34.5 ml of $H_2O$ and stirred at 0° for 30 min. The organic phase was separated, washed with a $K_2CO_3$-solution, dried ($K_2CO_3$) and evaporated under reduced presure. The residue was dissolved in 150 ml of ethanol, the solution treated with 6 g (0.142 mol) of cyanamide, stirred overnight and then treated with 5 g (0.072 mol) of hydroxylamine hydrochloride and 15 g (0.108 mol) of $K_2CO_3$. The mixture was stirred at r.t. for 35 h. The precipitated salts were filtered off and washed with ethanol. The filtrate was evaporated and the residue crystallized from $H_2O$ to afford 11 g (32%) of **7**, m.p. 262–266° (dec.), identical with the compound **7** described above.

*Preparation of 4-(1,2,3,6-tetrahydro-1-pyridyl)-2,6-bis(methoxycarbonylamino)-pyrimidine 1-oxide* (**4a**). *Methode A.* A solution of 45 g (0.217 mol) of **7** in 600 ml of $CH_2Cl_2$ and 90 ml of triethylamine was cooled to 5°, 90 ml (1.64 mol) methyl chloroformate was added dropwise. The mixture was stirred at 5° for 30 min and at r.t. for 18 h, then treated with 100 ml of $CH_3OH$ and subsequently extracted with 400 ml of $CH_2Cl_2$, washed with $H_2O$, dried ($K_2CO_3$) and evaporated under reduced pressure. Recrystallization of the residue from $CH_3OH$ yielded 61 g (86.5%) of **4a**, m.p. 202–203°.

*Methode B.* To a stirred suspension of 20 g (0.0965 mol) of **7** in 100 ml of $CH_2Cl_2$ and 200 ml of $H_2O$ were added dropwise 25 ml (0.323 mol) of methyl chloroformate in 50 ml of $CH_2Cl_2$ and 30 ml (0.21 mol) of 28% aqueous NaOH-solution, such that the pH was maintained between 7.5 and 8.5. After completion of the addition, the suspension was stirred for a further hour and the precipitate formed was filtered off. The filtrate was washed with $CH_2Cl_2$ and the organic phase combined with the precipitate. Methanol was added to dissolve the solid residue, the organic phase dried ($MgSO_4$) and partially evaporated *in vacuo*. The residue was recrystallized from $CH_2Cl_2$ and $CH_3OH$ to afford **4a**, m.p. 202–206° (dec.).

*Preparation of methyl 2-oxo-5-(1,2,3,6-tetrahydro-1-pyridyl)-2,8-dihydro[1,2,4]oxadiazolo[2,3-a]pyrimidine-7-carbamate* (**3a**). A solution of 50.0 g (0.155 mol) of **4a** in 300 ml DMF was heated at 140° for 30 min. After distillation of the solvent under reduced pressure, the residue was crystallized from $CH_3OH$ and $CH_2Cl_2$ affording 39 g (79%) of **3a**, m.p. 213–215°.

*Preparation of methyl 2-oxo-5-(1,2,3,6-tetrahydro-1-pyridyl)-2,8-dihydro[1,2,4]oxadiazolo[2,3-a]pyrimidine-7-carbamate* (**3a**). A solution of 35.1 g (0.01 mol) of **4a** in 300 ml $CH_2Cl_2$ was treated at r.t. with 300 ml of 3% aqueous NaOH-solution for 3 h. The aqueous phase was separated, acidified with 3N $H_2SO_4$, the precipitate filtered off, washed with $H_2O$ and dried under reduced pressure affording 28.04 g of **3a** (86%), m.p. 210–212°.

*Preparation of dimethyl 4-chloro-2,6-bis(methoxycarbonylamino)pyrimidine 1-oxide* (**8a**). To a solution of 56 g (0.349 mol) of **6** in 500 ml of DMF and 100 ml of triethylamine cooled to 0°, 80 ml (0.692 mol) of methyl chloroformate was added dropwise within 1 h. After the addition, the mixture was stirred for 48 h. The precipitate was filtered off, suspended in a mixture of 2500 ml of $CH_2Cl_2$ and 500 ml of

$CH_3OH$ and stirred for 80 min. The insoluble residue was filtered off and dried, giving 46.3 g of pure **8a** (55%), m.p. 204° (dec.).

$C_8H_9ClN_4O_5$ (276.636) Calc. C 34.73 H 3.28 N 20.25% Found C 34.92 H 3.19 N 20.02%

*Preparation of 2,6-bis(methoxycarbonylamino)-4-(1,2,3,6-tetrahydro-1-pyridyl)pyrimidine 1 oxide* (**4a**). A suspension of 10 g (0.041 mol) of **8a** in 40 ml $CH_2Cl_2$ was treated with 20 ml (0.157 mol) of 1,2,3,6-tetrahydropyridine and stirred at r.t. for 16 h. The resulting precipitate was filtered off and recrystallized from $CH_2Cl_2$/MeOH affording 10 g of **4a** (75% yield), m.p. 203°.

*Preparation of 4-chloro-2,6-bis[(2-methoxy)ethoxycarbonylamino]pyrimidine 1-oxide* (**8f**). A stirred suspension of 6 g (0.037 mol) of **6** in 50 ml of $CH_2Cl_2$ and 6 ml of triethylamine was treated dropwise at 0° with 9.5 ml (0.082 mol) of 2-methoxyethyl chloroformate in 15 ml of $CH_2Cl_2$. The mixture was stirred at 0° for 4 h and then at r.t. overnight. The solid residue was filtered off and washed with $CH_2Cl_2$, the filtrate washed with cooled 1% HCl-solution and dried ($MgSO_4$). The organic phase was evaporated under reduced presure and the residue crystallized from $CH_2Cl_2$ and ether affording 8.4 g (62%) of pure **8f**, m.p. 109–111°.

| | | | | | |
|---|---|---|---|---|---|
| $C_{12}H_{17}ClN_4O_7$ | Calc. | C 39.52 | H 4.70 | Cl 9.72 | N 15.36% |
| (364.74) | Found | „ 39.18 | „ 4.77 | „ 9.60 | „ 15.25% |

*Preparation of 2,6-bis[(2-methoxy)ethoxycarbonylamino]-4-(1,2,3,6-tetrahydro-1-pyridyl) 1-oxide* (**4f**). A solution of 1.30 g (0.0356 mol) of **8f**, 10 ml $CHCl_3$ and 2.0 ml (0.016 mol) of 1,2,3,6-tetrahydropyridine was heated at 50° for 10 h. After filtration of an insoluble residue, the organic phase was washed with $H_2O$, dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The solid residue was recrystallized from $CH_2Cl_2$/ether to afford 1.1 g (75%) of **4f**, m.p. 126–128°.

*Preparation of 2-amino-6-(methoxycarbonylamino)-4-(1,2,3,4-tetrahydro-1-pyridyl)pyrimidine 1-oxide* (**12**) and *6-amino-2-(methoxycarbonylamino)-4-(1,2,3,6-tetrahydro-1-pyridyl)pyrimidine 1 oxide* (**13**). A suspension of 4.14 g (0.02 mol) of **7** in 100 ml of DMF and 4 ml (0.04 mol) of triethylamine was treated dropwise with 1.55 ml (0.02 mol) of methyl chloroformate and stirred at r.t. for an additional 18 h. The precipitate was filtered off and washed successively with $CH_2Cl_2$, $CH_3OH$ and $H_2O$. The filtrate was evaporated under reduced pressure and the residue dissolved in $CH_2Cl_2$/MeOH and washed with $H_2O$. The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure. The residue was chromatographed over silica gel leading to 1.42 g (34%) of unreacted **7**, 1.72 g of dicarbamate **4a** (27%), 1.15 g of **12**[2]) (22%), m.p. 174–175°, and 0.16 g of **13**[2]) (3%), m.p. 110–112°.

*Preparation of 2-amino-4-chloro-6-[(2-methoxy)ethoxycarbonylamino]pyrimidine 1-oxide* (**14**). A stirred suspension of 5.0 g (0.031 mol) of **6** in 50 ml DMF and 5 ml of triethylamine at 0° was treated dropwise with 4.3 g (0.031 mol) of 2-methoxyethyl chloroformate within 15 min. The mixture was stirred at 0° for 2 h and at r.t. overnight. The solvent was evaporated at 25° under reduced pressure (1 Torr) and the residue treated with $CH_2Cl_2$. The solid was filtered off, washed with $CH_2Cl_2$, MeOH and $H_2O$. The filtrate was washed with more water and the organic phase dried ($MgSO_4$) and concentrated under reduced pressure. The residue was recrystallized from $CH_2Cl_2$/ether to afford 2.8 g (34.3%) of **14**, m.p. 176–178°.

| | | | | | |
|---|---|---|---|---|---|
| $C_8H_{11}ClN_4O_4$ | Calc. | C 36.58 | H 4.22 | Cl 13.50 | N 21.33% |
| (262.65) | Found | „ 36.54 | „ 4.21 | „ 13.79 | „ 21.33% |

*Preparation of 2,6-diamino-4-[1,2,3,6-tetrahydro-1-pyridyl]pyrimidine* (**15**). A stirred mixture of 15 g (0.072 mol) of **7** in 600 ml of $CH_3OH$ at 0° was treated dropwise with a 15% $TiCl_3$-solution so as to maintain the blue color. The mixture was stirred for an additional hour and concentrated *in vacuo*. The residue was dissolved in water, treated with $Na_2CO_3$ to pH 10, and filtered through *Celite*. The filtrate was extracted with $CH_2Cl_2$ and dried ($Na_2SO_4$). The solvent was evaporated *in vacuo*, and the crystalline residue was recrystallized from $CH_2Cl_2$ to afford 11.6 g (83%) of **15**, m.p. 151–152°. – $^1$H-NMR.: 5.01 (*s*, 1 H). – MS.: 191 ($-M^+$).

$C_9H_{13}N_5$ (191.24) Calc. C 56.53 H 6.85 N 36.62% Found C 56.34 H 6.83 N 36.46%

*Preparation of dimethyl-4-[1,2,3,6-tetrahydro-1-pyridyl]-2,6-pyrimidinedicarbamate* (**16**). A well stirred suspension of 0.95 g (4.9 mmol) of **15** in 30 ml of $CH_2Cl_2$ and 2.3 ml of triethylamine was treated at r.t. with 0.945 g (10 mmol) of $ClCOOCH_3$ for 1 h, then diluted with $CH_2Cl_2$, washed with 1N HCl, the organic phase dried and concentrated *in vacuo*. The residue was filtered through silica gel and crystal-

lized from $CH_2Cl_2$ and ether to afford 450 mg of **16** (30%), m.p. 150–155° (dec.). – IR. (KBr): 1763 (shoulder), 1743, 1699. – $^1$H-NMR. ($CDCl_3$): 3.80 (*s*, 6 H); 6.90 (*s*, 1 H). – MS.: 307 ($M^+$).

$C_{13}H_{17}N_5O_4$ (307.31) Calc. C 50.81 H 5.58 N 22.79% Found C 50.72 H 5.60 N 22.36%

*Preparation of 2,6-bis(acetylamino)-4-(1,2,3,4-tetrahydro-1-pyridyl)pyrimidine 1-oxide* (**17**). A stirred suspension of 2.5 g (0.012 mol) of **7** in 100 ml of $CH_2Cl_2$ and 2.5 ml of pyridine at 0° was treated with 3 ml of acetic anhydride. The mixture was stirred for 30 min, washed with 1N HCl and the organic phase evaporated *in vacuo*. The residue was filtered through silica gel to afford 3 g of crude material which was recrystallized from $CH_2Cl_2/CH_3OH$, m.p. 235–245°. IR. (KBr): 1741, 1691. – $^1$H-NMR. ($CF_3COOH$): 2.50 (*s*, 3 H); 2.61 (*s*, 3 H); 7.65 (*s*, 1 H). – MS. 291 ($M^+$).

$C_{13}H_{17}N_5O_3$ (291.31) Calc. C 53.60 H 5.88 N 24.04% Found C 53.25 H 5.86 N 23.82%

*Preparation of 4-(1,2,3,6-tetrahydro-1-pyridyl)pyrimidine-2,6-bis(acetamide)* (**18**). A stirred suspension of 2.8 g (0.0146 mol) of **15** in 120 ml of $CH_2Cl_2$ and 3.5 ml of pyridine was treated with 15 ml (0.147 mol) of acetic anhydride and heated at reflux for 12 h. The mixture was acidified with 1N HCl to pH 3 and the organic phase dried and concentrated *in vacuo*. The residue was filtered through silica gel, then crystallized from $CH_2Cl_2/CH_3OH$ to afford 2.75 g (68.5%) of pure **18**, m.p.: 280–290°. – IR. (KBr): 1714, 1684. – $^1$H-NMR. ($CF_3COOH$): 2.45 (*s*, 3 H); 2.51 (*s*, 3 H); 6.35 (*s*, 1 H). – MS.: 275 ($M^+$).

$C_{13}H_{17}N_5O_2$ (275.31) Calc. C 56.71 H 6.22 N 25.44% Found C 56.45 H 6.13 N 25.17%

## REFERENCES


[1] *F. Gross, J. Druey & R. Meier*, Experientia *6*, 11 (1950).

[2] U.S. Patent 3,461,461 (1965).

[3] *a) J. M. McCall, R. E. Tenbrink & J. J. Ursprung*, J. Org. Chem. *40*, 3304 (1975); b) *J. M. McCall & R. E. Tenbrink*, Synthesis *1978*, 673; c) US. Patent 4,098,791 (1978).

[4] a) *E. Gilmore, J. Weil & C. Chidsey III*, New Engl. J. Med. *282*, 521 (1970).

[5] *J. Koch-Weser*, Arch. Int. Med. *133*, 1017 (1974).

[6] *G. R. Zins:* 'Recent Advances in Renal Physiology'. L. G. Weson & G. M. Fanelli (eds.) Baltimore Univ. Park Press 1974, 165–186.

[7] *R. G. Pluss, J. Orcutt & C. A. Chidsey*, J. Lab. Clin. Med. *79*, 639 (1972).

[8] a) *W. C. Anthony*, U.S. Patent 3, 644, 364 (1970); b) *T. J. Delia & D. L. Venton*, J. Heterocycl. Chem. *9*, 73 (1972).
Our patent application was already filed in different countries when

[9] *T. J. Ward*, Brit. Patent 1,486,682 (1975) was diselosed.

[10] *J. E. Lawson, & R. D. Dennis*, U.S. Patent 4,021,562 (1977).

[11] *J. M. McCall & R. E. Tenbrink*, Synthesis *1975*, 335.

[12] *J. M. McCall, R. E. Tenbrink, M. E. Royer & H. Ko*, J. Heterocycl. Chem. *15*, 1529 (1978).

[13] a) *A. R. Katritzky*, J. Chem. Soc. *1965*, 2063, ibid *1957*, 4385; b) *A. R. Katritzky & J. M. Lagowski:* 'Chemistry of the Heterocyclic N-Oxides'. Academic Press London & New York 1971.

[14] *M. Gerold, R. Eigenmann, F. Hefti, A. Daum & G. Haeusler*, J. Pharmacol. & Exp. Therapeutics *216*, 624 (1981).

[15] a) *D. Chu, G. Cocco, C. Strozzi, R. Vallini, M. Nomato & R. Amrein*, Eur. J. Clin. Pharmacol. *19*, 233 (1981); b) *M. Grimm, P. Weidmann, A. Meier, H. Schiffl & W. H. Ziegler*, Eur. J. Clin. Pharmacol. *20*, 79 (1981).