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Structure and Properties of Cyclic Polymethylene Ureas, III[1,2]

Synthesis and Biological Activity of Some Mannich Bases of Tetrahydro-2-(1*H*)-Pyrimidinone

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Some *N*-mono-**2a–e** and *N,N'*-bis(aminomethyl) derivatives **3a–b** of tetrahydro-2-(1*H*)-pyrimidinone **1a** and tetrahydro-2(1*H*)-pyrimidinethione **1e** are obtained by the *Mannich* reaction of **1a** or **1e** with formaldehyde and secondary amines. The compounds show a marked antiviral activity.

Struktur und Eigenschaften cyclischer Polymethylen-Harnstoffe, 3. Mitt.: Synthese und biologische Aktivität von einigen Tetrahydro-2(1*H*)-Pyrimidinon-Mannich-Basen

Es wurden N-mono- **2a–e** und N,N'-bis-aminomethyl-Derivate **3a–b** von Tetrahydro-2-(1*H*)-pyrimidinon **1a** und Tetrahydro-2(1*H*)-pyrimidinthion **1e** durch *Mannich* Reaktion von **1a** oder **1e** mit

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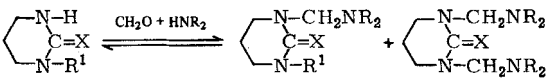
Formaldehyd und sekundären Aminen synthetisiert. Die Verbindungen üben markante virostatische Wirkungen aus.

It is well known that some N-mono- and N,N′-disubstituted derivatives of cyclic urea tetrahydro-2(1*H*)-pyrimidinone **1a** have shown to be biologically active agents. Its N,N′-dialkyl derivatives are respiratory stimulators[3,4] and 1-benzyl-tetrahydro-2(1*H*)-pyrimidinones stimulate the CNS[5]; some N-monoacyl derivatives are sedatives and myorelaxants[6]; Schiff bases of 1-amino-tetrahydro-2(1*H*)-pyrimidinone and aromatic and heterocyclic aldehydes show antibacterial activity[2,7].

The N-aminomethylation presents a possibility to obtain biologically active compounds. However there are no data for the N-aminomethyl derivatives of **1a.** Among the cyclic ureas are known only N-*Mannich* bases of 2-imidazolidinone[8] and 2-imidazolidinethione. The latter show antimicrobial activity[9].

The present paper reports the synthesis and biological studies of some N-Mannich bases of tetrahydro-2(1*H*)-pyrimidinone **1a**, 1-benzoyl-tetrahydro-2(1*H*)-pyrimidinone **1d** and tetrahydro-2(1*H*)-pyrimidinethione **1e**. They are obtained according to the following scheme:



1a, d, e **2a-e** **3a, b**

1	X	R^1	2	X	R^1	NR_2	% Yield	3	X	NR_2	% Yield
a	O	H	a	O	H	Morpholino	35,6	a	O	Morpholino	77,1
d	O	COPh	b	O	H	Piperidino	12,6	b	O	Piperidino	28,6
e	S	H	c	O	H	Pyrrolidino	20,6				
			d	O	COPh	Morpholino	41,8				
			e	S	H	Morpholino	59,5				

Mannich condensation occurs in water, methanol or ethanol at pH > 7. In an aqueous solution the results obtained are unsatisfactory because of the reversibility of the process and difficulties in isolation of the products.

The ratio between the N-mono- **2a–c** and N,N′-bis-aminomethyl derivatives **3a,b** depends mainly on the molar ratio of the initial reagents. In a larger dilution and an excess of **1a** the process runs with a higher yield of the N-monoaminomethyl compound.

The total yield of the *Mannich* base depends on the nature of the initial urea **1** and on the amine basicity. The nitrogen atoms of **1a** show a decreased nucleophilicity because of a more expressed conjugation with the carbonyl group[1,10]. Therefore the yields of the corresponding aminomethyl derivatives are lower in comparison to those obtained with an urea[11]. The presence of a N-acyl substituent in the molecule of **1d** decrease further the nucleophilicity of the second nitrogen and the yield of corresponding *Mannich* base. The substitution of the oxygen atom in **1a** with sulfur –**1e**– results also in a lower yield. The ratio **1e**: CH_2O: morpholine = 1 : 2 : 2 was optimal for obtaining the N-monoaminomethyl compound **2e**, which exists in the thion-form, according to its IR and ^{1}H-NMR spectra. It

was not possible to obtain the N,N'-bis-aminomethyl derivative of **1e.** This fact can be explained also with a decreased nucleophilicity of the N-atoms connected with the C=S group[4]. In the ^{1}H-NMR spectrum of **2e** in comparison to that of **2a** the proton of the N-H group appears in a weaker field.

The yields of the *Mannich* bases depend on pK_a of the secondary amines and are highest with morpholine (pK_a = 8.3). With the more basic amines piperidine (pK_a = 11.12) and pyrrolidine (pK_a = 11.27) the yields are very low, because the equilibrium is drawn back to the initial reagents. This fact is in accordance with studies on the degradation kinetics of some N-*Mannich* bases[12]. The yields of the *Mannich* bases of the more basic amines increase when absolute ethanol was used as solvent. The reaction of **1a** and N-methylene-piperidinium chloride in dry acetonitrile after the method of *Kinast* et al[13] gave also satisfactory results (**3b**·2HCl – method B).

The new compounds and the parent compounds **1a** and **1e** were tested for antiviral activity against picorna (poliovirus 1, PV–1), orthomyxo (fowl plague virus, FPV), paramyxo (Newcastle disease virus, NDV), herpes (herpes simplex virus type 1, HSV–1) and pox (vaccinia virus, VV) through a two-stage test system for screening in vitro, combination of the agar-diffusion plaque-inhibition test according to *Rada* and *Závada*[16] and the one-step virus growth cycle set-up[17]. The results are presented in Tables 1 and 2.

A marked antiviral effect of some of the obtained compounds against the orthomyxo-virus FPV – **2a, 2d, 2e** and **3a** – was established by both stages of testing. In the agar-diffusion plaque-inhibition test an effect of **3b**·2HCl against paramyxovirus NDV and an effect of **2c** against poxvirus VV were found.

Table 1: Antiviral activity by the agar-diffusion plaque-inhibition method

Comp. No.	Virus														
	PV-1			FPV			NDV			HSV-1			VV		
	D_1	D_2	E	D_1	D_2	E	D_1	D_2	E	D_1	D_2	E	D_1	D_2	E
1a	0	0	–	0	9,0	–	0	19,5	–	0	17,0	–	0	65,0	–
2a	0	9,5	–	48,5	23,2	++	0	27,5	–	0	23,5	–	0	43,2	–
2c	0	19,5	–	0	47,5	–	0	17,0	–	n.d.*			54,2	33,2	++
2d	0	22,2	–	62,0	18,5	++	0	21,5	–	0	24,0	–	0	9,2	–
3a	0	41,5	–	50,9	26,5	++	0	24,7	–	0	30,0	–	42,3	38,4	–
3b·2HCl	0	24,7	–	n.d.*			40,2	23,5	+	0	25,5	–	9,5	6,0	–
1e	0	0	–	0	16,0	–	0	18,5	–	0	26,0	–	0	43,0	–
2e	0	34,0	–	54,0	26,9	++	0	13,5	–	0	27,5	–	0	45,8	

D_1 = Diameter of inhibition zone, mm
D_2 = Diameter of toxicity zone, mm; $D_1 - D_2 = \Delta D$
E = Antiviral effect: (–) : $\Delta D \leq 5$ mm; (±) : $\Delta D = 6-10$ mm; (+) : $\Delta D = 11-20$ mm; (++) : $\Delta D > 20$ mm
*) not done

Table 2: Antiviral activity by the one-step growth cycle set-up

Compd.	Conc. μg/ml	Inhibition %	
		Infectious virus yield	Hemagglutinating virus yield
2a*	60	91,50	> 75,0
	50	75,50	> 75,0
	40	51,50	⩾ 75,0
	20	50,00	50,0
2e*	40	87,50	> 75,0
	30	56,00	> 75,0
	20	45,00	75,0
2d*	80	90,00	
	60	82,00	75,0
3a*	80	99,61	
	60	99,28	87,5
	40	87,00	
	20	77,00	
3b · 2HCl**	100	80,00	

* against FPV; ** against NDV

Experimental

Melting points: Boëtius microscop (uncorr.). *IR-spectra:* UR-20 Spectrophotometer Carl Zeiss – Jena. *^{1}H-NMR spectra:* 80 MHz BS-487 Tesla – Brno, TMS as inn. stand. *TLC:* Silica gel G (Merck), n-BuOH/AcOH/H_2O = 4:1:1 v/v, detect. J_2. *Column chromatography:* Kieselgel 60 (Merck), chloroform/methanol 1 : 1 v/v. *Elem. anal.:* N-Kjeldahl

1-Morpholinomethyl-tetrahydro-2(1H)-pyrimidinone **(2a)**

A solution of 1,7 ml 33 % (0,02 mol) formalin and 1,74 g (0,02 mol) morpholine in 20 ml methanol was added dropwise for 2,5 h. to a heated (60°C) suspension of 2 g (0,02 mol) **1a**[7] (m.p. 263–266°) in 30 ml methanol. The mixture was stirred at the same temp. for 2 h. The solvent was evaporated under reduced pressure, the residue washed with dry ether and boiled with ethylacetate. The undissolved **1a** (0,6 g, 30 %) was filtered, **2a** (1,6 g, 40 %) was crystalized from ethylacetate and **3a** (1,2 g, 20 %) was obtained after concentration of mother liquid. **2a** was recrystallized from absol. ethanol; yield 1,42 g (35,6 %), m.p. 142–145°. IR (nujol): 3300, 3225 (NH), 1660 (C=O), 1120 cm^{-1} (C-O-C); IR ($CHCl_3$): 3452 (NH), 1650 (C=O), 1120 cm^{-1} (C-O-C). ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1,92 (m, 2H, J = 5,8 Hz, CH_2-$\underline{CH_2}$-CH_2), 2,52 (m, 4H, J = 4,5 Hz, N-CH_2 morpholine), 3,32 (m, 4H, CO-N-CH_2, J = 5,8 Hz), 3,68 (m, 4H, J = 4,5 Hz, O-CH_2 morph.), 4,02 (s, 2H, N-CH_2-N), 5,83 (s, 1H, NH). $C_9H_{17}N_3O_2$ (199,25) Calcd.: C 54,3 H 8,60 N 21,1 Found: C 54,1 H 8,67 N 21,1. **2a** · HCl, m.p. 176–178° (absol. ethanol).

1-Piperidinomethyl-tetrahydro-2(1H)-pyrimidinone **(2b)**

Analog **2a** from 2 g (0,02 mol) **1a**, 1,7 ml (0,02 mol) 33 % formalin and 1,7 g (0,02 mol) piperidine in 50 ml methanol. The remaining oil after evaporation of methanol showed 3 spots – **1a, 2b, 3b** – in TLC. The oil was dissolved in absol. ethanol, ether/HCl was added and the precipitate was recrystallized repeatedly from absol. ethanol. The salt with m.p. 205,5–208° was dissolved in water, the solution was saturated with K_2CO_3 and extracted with ether to yield 0,5 g **2b** (12,6 %), m.p. 137–139°. IR ($CHCl_3$): 3455 (N-H), 1655 cm^{-1} (C=O). $C_{10}H_{19}N_3O$ (197,28) Calcd.: N 21,3 Found: N 21,1. **2b**. HCl – IR (nujol): 3455, 3395 (NH), 2630–2540 (NH), 1665 cm^{-1} (C=O).

1-Pyrrolidinomethyl-tetrahydro-2(1H)-pyrimidinone **(2c)**

Analog. **2a** from 3 g (0,03 mol) **1a**, 2,55 ml (0,03 mol) 33 % formalin and 2,13 g (0,03 mol) pyrrolidine in 75 ml absol. ethanol. The solvent was removed . i. vac. and the water was eliminated azeotropic through 2 x 15 ml dry benzene. The residue was washed with 3 x 10 ml dry ether and recrystallized to yield 1,1 g (20,6 %) of **2c**, m.p. 106,5–109° (n-hexane). IR ($CHCl_3$): 3450 (NH), 1645 cm^{-1} (C=O). $C_9H_{17}N_3O$ (183,25). Calcd.: N 22,9 Found: N 23,3.

1-Benzoyl-3-morpholinomethyl-tetrahydro-2(1H)-pyrimidinone **(2d)**

2 g (0,01 mol) **1d**[6] (m.p. 144-146°) was added to a solution of 1,1 ml (0,02 mol) 33 % formalin and 1 g (0,012 mol) morpholine in 30 ml methanol and the mixture was boiled for 4 h. The methanol was evaporated under reduced pressure and the remaining oil crystallized in a refrigerator after addition of 1 ml ethanol; yield 1,25 g (41,2 %) of **2d**, m.p. 136–137° (ethanol). IR ($CHCl_3$): 1680 (C=O), 1120 cm^{-1} (C-O-C). $C_{16}H_{21}N_3O_3$ (303,35) Calcd.: N 13,9 Found N 13,8.

1-Morpholinomethyl-tetrahydro-2(1H)-pyrimidinethione **(2e)**

Analog. **2d** from 5,8 g (0,05 mol) **1e**[14] (m.p. 212–214°) 9,2 ml (0,109 mol) 36 % formalin and 9 g (0,104 mol) morpholine in 60 ml methanol after boiling for 2 h. Removal of the solvent and crystallization from ethanol gave 6,4 g (59,5 %) of **2e**, m.p. 156–158°. IR ($CHCl_3$): 3435 (ν_{NH}), 1520 (δ_{NH}), 1110 cm^{-1} (C-O-C). ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1,97 (m, 2H, J = 5,8 Hz, CH_2-$\underline{CH_2}$-CH_2), 2,62 (m, 4H, J = 4,5 Hz, N-CH_2 morpholine), 3,33* (t, 2H, J = 5,8 Hz, $\underline{CH_2}$NH-CO), 3,47* (t, 2H, J = 5,8 Hz, CH_2-$\underline{CH_2}$-N-CO), 3,68 (m, 4H, J = 4,5 Hz, O-CH_2 morph.), 4,60 (s, 2H, N-CH_2-N), 7,2 (s, 1H, NH; H/D exchangeable), *after exchange with D_2O. $C_9H_{17}N_3OS$ (215,31) Calcd.: N 19,5 S 14,9 Found: N 19,3 S 14,5. **2e** · HCl, m.p. 170–172,5° (absol. ethanol).

1,3-Bis-(morpholinomethyl)-tetrahydro-2(1H)-pyrimidinone **(3a)**

Analog. **2d** from 1 g (0,01 mol) **1a**, 1,9 ml (0,022 mol) 33 % formalin and 1,9 g (0,022 mol) morpholine in 15 ml methanol after boiling for 4 h. The methanol was removed i. vac., the residue was washed with dry ether and recrystallized to yield 2,3 g (77,1 %) of **3a**, m.p. 121-123° (ethylacetate). IR ($CHCl_3$): 1635 (C=O), 1120 cm^{-1} (C-O-C). ^{1}H-NMR ($CDCl_3$): δ (ppm) = 1,95 (m, 2H, J = 5,8 Hz, CH_2-$\underline{CH_2}$-CH_2), 2,52 (m, 4H, J = 4,5 Hz, N-CH_2 morpholine), 3,40 (t, 4H, J = 5,8 Hz, CH_2-CO-N), 3,68 (m, 4H, J = 4,5 Hz, O-CH_2 morph.), 4,05 (s, 4H, N-CH_2-N). $C_{14}H_{26}N_4O_3$ (298,38) Calcd.: N 18,8 Found N 18,8. **3a** · 2HCl, m.p. 172,5–176,5° (absol. ethanol). $C_{14}H_{28}Cl_2N_4O_3$ (371,30) Calcd.: N 15,1 Cl 19,1 Found: N 14,9 Cl 18,7.

1,3-Bis-(piperidinomethyl)-tetrahydro-2(1H)-pyrimidinone **(3b)**

Method A – Anal. **2d** from 1 g (0,01 mol) **1a**, 2 ml (0,022 mol) 33 % formalin and 1,9 g (0,022 mol) piperidine in 20 ml methanol after boiling for 10 h. The solvent was evaporated; the oil residue, 3 g,

contained 3 compounds: **1a, 2b** and **3b** (TLC). 1 g of the oil was dissolved in absol. ethanol and chromatographed on Kieselgel 60 column. Eluation with chloroform/methanol gave 0,2 g (30,4 %) of **2b** and 0,3 g (30,6 %) of **3b**, which was crystallized after long storage in an ice-box; m.p. 95–101°. Attempts for purification decomposed **3b**. IR ($CHCl_3$): 1630 cm^{-1} (C=O). 2 g of the oil was converted in the HCl-salt (ethanol/ether/HCl), m.p. 184–206°. After repeated recrystallisation from absol. ethanol 0,7 g (28,6 %) of **3b** · 2HCl was obtained, m.p. 186–191°. IR (nujol): 2550–2490 ($\overset{\oplus}{N}H$), 1685 cm^{-1} (C=O). $C_{16}H_{32}Cl_2N_4O$ (367,36) Calcd. N 15,3 Cl 19,3 Found N 14,9 Cl 19,0.

Method B – A mixture of 1 g (0,01 mol) **1a** and 2,67 g (0,02 mol) N-methylenepiperidinium chloride[15] (m.p. 248–252°) was heated at 80° in dry acetonitrile for 0,5 h. After cooling 1,8 g (49,0 %) of **3b**: · 2 HCl was crystallized, m.p. 186–191° (absol. ethanol/ether).

Antiviral testing

The antiviral activities in agar-diffusion plaque-inhibition method were tested using 2% solutions of **1a**, **2a**, **2c**, **2e**, **3a** and **3b** · 2HCl in water and of **1e** and **2d** in ethanol. The viruses were grown in cell cultures of chick embryo fibroblasts (FPV, Weibridge strain; NDV, Hertfordshire strain; VV), rabbit kidney cells (HSV type 1) and human diploid embryo fibroblasts (poliovirus 1, Mahoney strain). Maximal tolerated doses of the compounds for the cell cultures were determined by cytomorphological methods after 72 h treatment of monolayer cultures in stationary phase.

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