Cross-Conjugated and Pseudo-Cross-Conjugated Mesomeric Betaines, XVIII[1]:

Bicyclic Mesoionic Pyrimidines with Cardiovascular Activity

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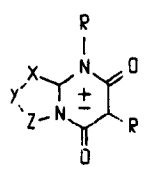
Reaction of α-Anilino-azines **1a-i** with activated malonates (magic malonates) **2a-e** leads to bicyclic mesoionic systems **3-7**. Out of these, pyrido[1,2-*a*]pyrimidines **3b,d** are active as cardiotonics, whereas pyrimido[1,2-*a*]pyrimidines **4a-g** show significant anti-anginal and anti-hypertensive activity.

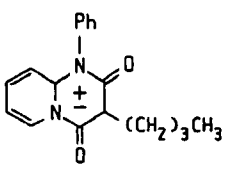
Kreuzkonjugierte und pseudo-kreuzkonjugierte mesomere Betaine, 18. Mitt.: Bicyclische mesoionische Pyrimidinderivate mit Wirkung auf das Cardiovaskuläre System

Die Reaktion von α-Anilino-azinen **1a-i** mit aktiven Malonestern (magic malonates) **2a-e** führt zu bicyclischen mesoionischen Systemen **3-7**. Von diesen sind Pyrido[1,2-*a*]pyrimidine **3b,d** als Cardiotonika wirksam. Pyrimido[1,2-*a*]pyrimidine **4a-g** zeigen antianginöse und antihypertensive Aktivität.

After the discovery of six-membered mesoionic heterocycles in 1971 a rapid development and expansion of the chemistry of these type of compounds took place and a great number of different ring systems have been prepared[2]. From the pharmacological point of view the so-called "mesoionic xanthine analogs" (Structure A) found much attention in recent years[2,3]. Some of these compounds, *e.g.* mesoionic thiazolo[3,2-*a*]pyrimidine-5,7-diones exhibit antibacterial activity against both *Gram*-negative and *Gram*-positive organisms[4]. A number of them show theophylline like activity[5] or act as cyclo-AMP-phosphodiesterase inhibitors[6]. In most of these compounds, however, the mesoionic pyrimidine moiety is connected to a five-membered heterocyclic ring. The biological potential of other bicyclic six-membered mesoionic heterocycles remained unexplored.

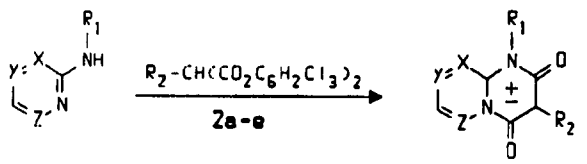


A



3d

Chart 1 X,Y,Z = CH, CR, N, NR, O, S R = Alkyl



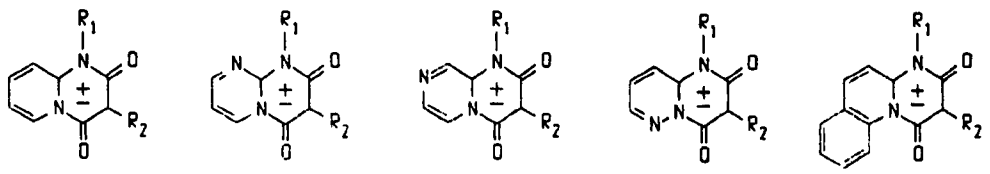
1a-i 3-7

1	X	Y	Z	R_1
a	CH	CH	CH	Ph
b	CH	CH	CH	2-Pyridyl
c	CH	CH	CH	3-CF_3-Ph
d	N	CH	CH	Ph
e	N	CH	CH	3-CF_3-Ph
f	N	CH	CH	2-F-Ph
g	CH	N	CH	Ph
h	CH	CH	N	Ph
i	2-Phenylaminoquinoline			

2	R_2
a	CH_3
b	$(CH_2)_2CH_3$
c	$CH(CH_3)_2$
d	$(CH_2)_3CH_3$
e	Ph

R-Key for 3-7 see Tab. 1

Scheme 1



3 4 5 6 7

Scheme 2

Recently a general pharmacological screening[7] of mesoionic pyrido[1,2-*a*]pyrimidine **3d** revealed that this compound has an interesting cardiotonic profile: Apart from being slightly antihypertensive the main interest focuses on the longlasting positive inotropic effect which is superior to Amrinone (see Pharmacology). These results prompted us to synthesize and to investigate the pharmacological profile of a series of compounds related to **3d** in order to establish a structure-activity relationship.

Chemistry

The synthesis of bicyclic pyrimidine mesoions **3-7** was accomplished by condensation of α-anilino-azines **1a-i**

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Tab. 1: Reaction conditions for the formation of bicyclic mesoions **3-7**

No.	Entry 1	Entry 2	R_1	R_2	Reaction Time (min.)	Reaction Temp.(°C)	Yield (%)	Melt. Point (°C)	solvent[a]
3a	1a	2a	Ph	CH_3	10	180	75	292-298	C
3b	1a	2b	Ph	$(CH_2)_2CH_3$	30	220	70	258-260	B
3c	1a	2c	Ph	$CH(CH_3)_2$	30	220	81	295-298	C
3d	1a	2d	Ph	$(CH_2)_3CH_3$	30	220	66	178-180	B
3e	1b	2b	2-Pyridyl	$(CH_2)_2CH_3$	10	160	75	217-218	B
3f	1b	2d	2-Pyridyl	$(CH_2)_3CH_3$	10	160	88	179-180	B
3g	1c	2c	3-CF_3-Ph	$CH(CH_3)_2$	30	220	81	170-172	D
3h	1c	2d	3-CF_3-Ph	$(CH_2)_3CH_3$	30	220	87	204-207	B
4a	1d	2b	Ph	$(CH_2)_2CH_3$	10	180	81	195-197	A
4b	1d	2c	Ph	$CH(CH_3)_2$	10	180	68	223-227	A
4c	1d	2d	Ph	$(CH_2)_3CH_3$	10	180	80	196-201	A
4d	1e	2c	3-CF_3-Ph	$CH(CH_3)_2$	15	180	66	200-202	A
4e	1e	2d	3-CF_3-Ph	$(CH_2)_3CH_3$	15	180	63	169-171	D
4f	1f	2b	2-F-Ph	$(CH_2)_2CH_3$	5	180	62	187-189	A
4g	1f	2d	2-F-Ph	$(CH_2)_3CH_3$	5	180	60	194-198	A
4h	1d	2e	Ph	Ph	10	180	65	305-320	C
5a	1g	2d	Ph	$(CH_2)_3CH_3$	5	180	68	195-197	D
6a	1h	2d	Ph	$(CH_2)_3CH_3$	10	180	65	258-260	C
7a	1i	2d	Ph	$(CH_2)_3CH_3$	3	160	52	191-193	A

[a] recrystallization solvent: A = Toluene, B = Xylene, C = Bromobenzene, D = Toluene/Petroleum Ether

Tab. 2: Antihypertensive activity and positive inotropic effect of mesoionic pyrido[1,2-α]pyrimidines **3b,d**

No.	Antihypertensive activity ED 50 p.o. (rats) in mg/kg	positiv inotropic effect MIC (in vitro) in ug/ml normal	reserpinized guinea pig atria
3b	50	25	25
3d	25	25	5
Amrinone	-	100	100

Tab. 3: Antianginal- and antihypertensive activity of mesoionic pyrimido[1,2-α]pyrimidines **4a-h**

No.	Antianginal activity ED 100 p.o. (mice) in mg/kg	Antihypertensive activity ED 50 p.o. (rats) in mg/kg
4a	10	2
4b	25	10
4c	25	25
4d	45	10
4e	45	10
4f	100	inactive
4g	12	inactice
4h	inactive	inactive

Tab. 4: Analytical and IR-data of mesoions 3-7

No.	Formula (mol. weight)	Analysis (calcd./found) C	H	N	IR (cm^{-1})
3a	$C_{15}H_{12}N_2O_2$	71.42	4.79	11.10	1700, 1655, 1630
	(252.27)	71.55	4.58	11.10	
3b	$C_{17}H_{16}N_2O_2$	72.84	5.75	9.99	1690, 1650-1630
	(280.33)	72.65	5.80	10.11	
3c	$C_{17}H_{16}N_2O_2$	72.84	5.75	9.99	1690, 1650, 1620
	(280.33)	72.89	5.50	9.94	
3d	$C_{18}H_{18}N_2O_2$	73.45	6.16	9.52	1690, 1650-1630
	(294.35)	73.65	6.06	9.43	
3e	$C_{16}H_{15}N_3O_2$	68.31	5.37	14.94	1715, 1675, 1665-1630
	(281.31)	68.45	5.23	15.06	
3f	$C_{17}H_{17}N_3O_2$	69.14	5.80	14.23	1710, 1670, 1660-1630
	(295.34)	68.97	5.80	14.12	
3g	$C_{18}H_{15}F_3N_2O_2$	62.07	4.34	8.04	1695, 1680, 1650, 1620
	(348.33)	61.95	4.39	7.93	
3h	$C_{19}H_{17}F_3N_2O_2$	62.98	4.73	7.73	1690, 1685, 1645, 1610
	(362.35)	63.14	4.71	7.57	
4a	$C_{16}H_{15}N_3O_2$	68.31	5.37	14.94	1700, 1645-1615
	(281.31)	68.51	5.40	15.11	
4b	$C_{16}H_{15}N_3O_2$	68.31	5.37	14.94	1700, 1650-1615
	(281.31)	68.62	5.47	14.80	
4c	$C_{17}H_{17}N_3O_2$	69.14	5.80	14.23	1700, 1635, 1615
	(295.34)	69.03	5.72	14.43	
4d	$C_{17}H_{14}F_3N_3O_2$	58.45	4.04	12.03	1700, 1680, 1630, 1610
	(349.31)	58.13	4.30	11.79	
4e	$C_{18}H_{16}F_3N_3O_2$	59.50	4.44	11.57	1700, 1685, 1645, 1610
	(363.34)	59.72	4.48	11.47	
4f	$C_{16}H_{14}FN_3O_2$	64.21	4.71	14.04	1690, 1635
	(299.31)	64.38	4.79	13.97	
4g	$C_{17}H_{16}FN_3O_2$	66.12	5.15	13.41	1690, 1635
	(313.33)	66.36	5.06	13.37	
4h	$C_{19}H_{13}N_3O_2$	72.37	4.55	13.33	1680, 1655-1630
		72.11	4.63	12.99	
5a	$C_{17}H_{17}N_3O_2$	69.14	5.80	14.23	1690, 1635
	(295.34)	69.04	5.63	14.12	
6a	$C_{17}H_{17}N_3O_2$	69.14	5.80	14.23	1690, 1635, 1610
	(295.34)	69.24	5.71	14.31	
7a	$C_{22}H_{20}N_2O_2$	76.72	5.85	8.13	1690, 1640, 1610
	(344.33)	76.52	5.92	7.91	

with substituted bis-2,4,6-trichlorophenylmalonates (magic malonates) **2a-e**. This general synthetic approach has been used frequently in the last 20 years for the preparation of mono- and bicyclic six-membered mesoionic heterocycles[2]. In all cases described in Table 1 the reaction was performed without any solvent, by simply heating the two starting compounds in equimolar mixture at the required temp. As seen in Table 1, both, reaction times and reaction temp., vary significantly depending on the heterocyclic system used. Therefore, the rather unreactive 2-phenylamino-pyridine **1a** requires about 220°C (30 min) to react with **2b-d**, whereas the highly reactive 2-phenylamino-quinoline **1i** forms the corresponding tricyclic mesoion **7a** at 160°C (3 min). All mesoions **3-7** were obtained in moderate to good yields as yellow or orange-red colored solids. They are stable in solution at room temp., however, they may hydrolize in protic solvents under acid or basic catalysis.

Pharmacology

According to their pharmacological activity, mesoions **3-7** may be divided into two groups:

a) mesoionic pyrido[1,2-*a*]pyrimidines **3a-h** acting as cardiotonics: In this group the two most active compounds were **3b** and **3d**. Apart from their weak antihypertensive activity the main interest is due to the longlasting positive inotropic effect noted both in normal and reserpinized guinea-pig atria (Table 2). These results were confirmed by studies conducted in anaesthetized dogs at 10 mg/kg i.d. where **3b** proved to be equal in activity to Amrinone[8]; **3d** was even more active. These two compounds seem to be acting through a "xanthine-like" mechanism, by increasing the c-AMP level. Modifications in the alkyl side chain (R_2) to improve the activity proved to be ineffective: **3c** ($R_2 = CH(CH_3)_2$) surprisingly is devoid of any cardiotonic effect, whereas **3a** ($R_2 = CH_3$) is a rather toxic compound (LD_{100} i.p. = 200 mg/kg (mice)). All other compounds (**3e-h**) were inactive.

b) mesoionic pyrimido[1,2-*a*]pyrimidines **4a-h** as anti-anginal drugs: As shown in Table 3, all compounds tested in this series (except **4h**, R_2 = Ph) have anti-anginal activity, in most cases accompanied by a strong antihypertensive effect (e.g.: **4a**). However, slight modifications as in **4g** (R_1 = o-F-Ph instead of Ph) led to compounds with anti-anginal activity only. These mesoions may be acting similar to glyceryl trinitrate[9] or molsidomine[10].

Mesoionic pyrazino[1,2-*a*]pyrimidine (**5**), pyrimido[1,2-*b*]pyridazine (**6**) and pyrimido[1,2-*a*]quinoline (**6**) were devoid of any pharmacological activity.

The authors are very grateful to LIPHA[7] for providing the pharmacological results presented in this article.

Experimental Part

MP.: Gallenkamp melting point apparatus model MFB-595 (open capillary, uncorrected).- IR: Perkin Elmer 298 (KBr disks).- ^{1}H-NMR: Varian EM 360 at 60 MHz (TMS as int. standard).- Elemental analyses: C,H,N-automat Carlo Erba 1106.

Starting materials: 2-Phenylamino-pyridine (**1a**) and 2,2'-dipyridylamine (**1b**) were purchased from ALDRICH and used without further purification. 2-Phenylamino-pyrimidine (**1d**)[11], 2-phenylamino-pyrazine (**1g**)[12], 3-phenylamino-pyridazine (**1h**)[13], and 2-phenylamino-quinoline (**1i**)[14] were prepared from the corresponding chloroheterocycles with aniline following published procedures. 2-(3-Trifluorophenylamino)-pyridine (**1c**), mp. 79-81°C, 2-(3-trifluorophenylamino)-pyrimidine (**1e**), mp. 82-84°C, and 2-(2-fluorophenylamino)-pyrimidine (**1f**), mp. 117-118°C were synthesized in analogy to these procedures[15]. Substituted bis-(2,4,6-trichlorophenyl)-malonates were prepared as described[16].

General procedure for the preparation of bicyclic mesoionic pyrimidines **3-7**

A mixture of 10 mmols of **1a-i** and 10 mmols of the corresponding active malonate **2a-e** was heated to 160-220°C for 3-30 min (Table 1). After cooling to ambient temp. the yellow oil was digested several times with petroleum ether to remove trichlorophenol formed during the reaction. Addition of diethylether yields yellow to orange crystalline products which were recrystallized from the solvents given in Table 1.

Tab. 5: ^{1}H-NMR spectroscopic data of selected mesoions **3-7**

No.	^{1}H-NMR (ppm)[a]
3a	1.96 (s, CH_3), 6.75 (dd, J = 9 Hz, 1.5 Hz, H-9), 7.42 - 8.08 (m, H-7 and H-8), 7.55 (s, 5 ArH), 9.31 (dd, J = 7 Hz, 2 Hz, H-6).
4b	1.19 (d, J = 7 Hz, 2 CH_3), 2.45 (q, J = 7 Hz, CH), 7.21 - 7.65 (m, 6 ArH), 8.92 (dd, J = 5 Hz, 2 Hz, H-8), 9.48 (dd, J = 7 Hz, 1.5 Hz, H-6).
5a	0.93 (t, J = 7 Hz, CH_3), 1.28 - 1.70 (m, CH_2CH_2), 2.52 (t, J = 7 Hz, CH_2), 7.35 - 7.77 (m, 5 ArH), 8.21 (s, H-9), 8.55 (d, J = 4 Hz, H-7), 9.05 (d, J = 4 Hz, H-6).
6a	0.90 (t, J = 7 Hz, CH_3), 1.10 - 1.75 (m, CH_2CH_2), 2.45 (t, J = 7 Hz, CH_2), 7.08 - 7.88 (m, 7 ArH), 8.88 (dd, J = 5 Hz, 1.5 Hz, H-7).
7a	0.92 (t, J = 7 Hz, CH_3), 1.15 - 1.72 (m, CH_2CH_2), 2.44 (t, J = 7 Hz, CH_2), 6.51 (d, J = 9 Hz, H-5), 7.16 - 7.81 (m, 8 ArH), 8.08 (d, J = 9 Hz, H-6), 9.39 (dd, J = 7 Hz, 2 Hz, H-10).

[a] recorded in d_6-DMSO

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