SOME NEW ANALOGUES OF VERAPAMIL AND MEPAMIL. SYNTHESIS AND BASIC PHARMACOLOGICAL PROPERTIES

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Some new analogues of verapamil (*Ia*) and mepamil (*Ib*), calcium antagonists of arylalkylamine type, were synthesized and screened for cardiovascular activities. The basic structure was modified *a*) on the phenyl ring, attached to the quaternary carbon, *b*) on the alkyl group, attached to the quaternary carbon and *c*) on the alkylamino group, attached in position 3 to the n-propyl fragment. Except of 2-(2-chlorophenyl)-2-isopropyl-5-(N-methylhomoveratrylamino)valeronitrile (*VIa*), all the synthesized compounds exhibited lower hypotensive activity, than the mother compound, verapamil.

The studies, dealing with the structure–activity relationships of the arylalkylamine type of calcium antagonists are quite limited[1,2]. The presence of the nitrile group, attached to the quaternary carbon seems to be essential for the maintenance of the calcium antagonistic properties. The presence of both aromatic rings and the amino group is important. The substituents present on the aromatic ring of the benzyl cyanide moiety influences the calcium antagonistic activity dramatically, while the substituents on the right ring and/or the isopropyl group are less important. According to Mannhold[3], meta substitution of the left phenyl ring is optimum for potency while ortho substitution diminishes potency, probably by steric effects. Hoeltje[4] could demonstrate from EHT-MO calculations, that the phenyl and the cyanide group are coplanar in most stable conformation. Thus, ortho substitution disables the molecule to occupy the coplanar conformation due to steric reasons, correspondingly, the typical negative inotropic activity is drastically diminished. It is important to point out, that the pronounced negative inotropic efficacy of a drug is not necessarily required and in many cases limits the clinical use.

Mepamil[5] (*Ib*), although containing an ortho substituent was found in clinical tests to be a useful drug, exhibiting lower inotropic activity, compared with the mother compound. It lowers blood pressure and possess coronary dilating properties.

Now we wish to report about the synthesis and basic pharmacologic activities of a series of compounds, potentially belonging to the arylalkylamine class of calcium antagonists. The basic structure was modified *a*) on the phenyl ring, attached to the quaternary carbon, *b*) on the alkyl group, attached to the quaternary carbon and *c*) on the alkylamino group, attached in position 3 to the n-propyl fragment.

Compounds Modified on the Phenyl Ring Attached to the Quaternary Carbon (VIa – VIe)

The starting benzyl cyanides of a general formula *II* were prepared using the procedures published in the literature (*IIa* (ref.[6]), *IIb* (ref.[7]), *IIc* (ref.[8]), *IId* (ref.[9])), or by the reaction of the appropriate benzyl halogenide with sodium cyanide in aqueous ethanolic solution (*IIf*, *IIg*). 2-Bromobenzyl cyanide (*IIe*) was prepared by dehydration of 2-bromophenyl acetamide with phosphorus pentoxide at elevated temperature.

The α-alkyl derivatives *IIIb*, *IIId* – *IIIg* were prepared by the reaction of the appropriate benzyl cyanide and 2-bromopropane using sodium amide in 1,2-dimethoxyethane. A phase transfer catalyzed reaction of the benzyl cyanide (*IIa*, *IIc*) and 2-bromopropane afforded the α-alkyl benzyl cyanides *IIIa* and *IIIc*. The best results were obtained using tetrabutylammonium hydrogen sulfate as a phase transfer catalyst. The yields were ranging from 67.2% to 91.0%. The procedure used and boiling point data are collected in Table I.

An attempt to introduce the n-propyl moiety into molecules of general formula *III* using 1-chloro-3,3-diethoxypropane as alkylating agent under the conditions of a phase transfer catalysis was not successful probably because of the destruction of the alkylating agent. We isolated the appropriate carboxamides as products of hydrolysis taking place during a prolonged reaction. The only system, in which we were able to obtain the desired acetals *IVa* – *IVg* was using sodium amide as a base in refluxing toluene arranged, as described in the experimental section. When we added the solution of both reaction components to a suspension of the amide in toluene, the reaction yields decreased considerably. The results are collected in Table II.

The hydrolysis of the acetals *IVa* – *IVg* proceeds smoothly using oxalic acid in aqueous acetone. The aldehydes of a general formula *V* were not stable enough and were used without purification in a further reaction step. The yields were almost quantitative.

The final amines *VIa* – *VIe* were prepared by reductive amination of aldehydes *Va* – *Ve* with commercially available N-methylhomoveratryl amine (*XIa*). Except for *VIc* and *VIe*, the reduction was carried out with hydrogen on Adams catalyst. In the case of *VIc* and *VIe*, formic acid was used as a reducing agent. The yields and melting points of the appropriate salts and procedure used are collected in Table III.

Compounds Modified on the Alkyl Group Attached to the Quaternary Carbon (VIf – VIi)

The substituted benzyl cyanides *IIIh* – *IIIj* were synthesized by phase transfer catalyzed alkylation of *IIc* with methyl iodide, n-propyl and n-octyl bromide. Reacting them with

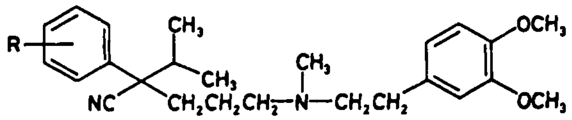
1-chloro-3,3-diethoxypropane in refluxing toluene/sodium amide system, acetals *IVh* – *IVj* were obtained. The reaction of the unsubstituted 2-methylbenzyl cyanide with the same alkylating agent afforded the acetal *IVk*.

The aldehydes *Vh* – *Vk*, obtained by an acid catalyzed hydrolysis of acetals *IVh* – *IVk*, were subjected to reductive amination with N-methylhomoveratryl amine (*XIa*) using formic acid as a reducing agent. The final amines *VIf* – *VIi* were obtained in good yields. The results are collected in Table III.

TABLE I
Yields, boiling points and analytical data of compounds *IIIa* – *IIIj*

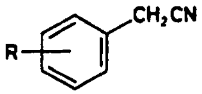
Compound	Procedure Yield, %	B. p., °C Pa	Formula (M. w.)	Calculated/Found		
				% C	% H	% N
IIIa[a]	*B*	148 – 151	$C_{13}H_{17}NO_2$	71.21	7.81	6.39
	81	34	(219.3)	71.12	7.76	6.10
IIIb[b]	*A*	124 – 126	$C_{11}H_{12}ClN$	68.21	6.25	7.23
	91	1 065	(193.7)	68.86	6.51	6.91
IIIc[c]	*B*	112 – 112.5				
	88	670				
IIId	*A*	129 – 131	$C_{12}H_{15}NO$	76.15	7.99	7.40
	90	1 065	(189.3)	76.18	8.16	7.61
IIIe[d]	*A*	135	$C_{11}H_{12}BrN$	55.48	5.08	5.88
	89	1 300	(238.1)	56.29	5.12	6.03
IIIf	*A*	115	$C_{15}H_{21}NO$	77.88	9.15	6.05
	75	120	(231.3)	78.14	9.24	5.83
IIIg[e]	*A*	98	$C_{12}H_{15}NS$	70.19	7.36	6.82
	67	30	(205.3)	70.19	7.75	6.70
IIIh	*B*	106	$C_{10}H_{11}N$	82.72	7.64	9.65
	83	800	(145.2)	82.84	7.75	9.78
IIIi	*B*	119	$C_{12}H_{15}N$	83.19	8.73	8.09
	86	800	(173.3)	83.27	8.92	8.07
IIIj	*B*	135	$C_{17}H_{25}N$	83.89	10.35	5.76
	74	53	(243.4)	84.04	10.72	5.68

[a] ^{1}H NMR spectrum was consistent with that shown in ref.[17]; [b] calculated: 18.31% Cl, found: 17.89% Cl; [c] see ref.[5]; [d] calculated: 33.56% Br, found: 33.00% Br; [e] calculated: 15.62% S, found: 15.21% S.

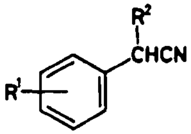


Ia, R = 3,4-$(MeO)_2$

Ib, R = 2-Me



II



III

IIa, R = 3,4-$(MeO)_2$

IIb, R = 2-Cl

IIc, R = 2-Me

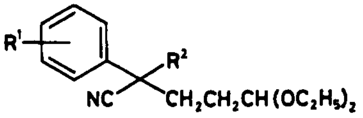
IId, R = 2-MeO

IIe, R = 2-Br

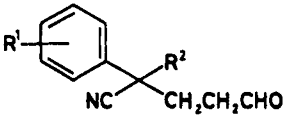
IIf, R = 2-BuO

IIg, R = 2-MeS

	R^1	R^2
IIIa	3,4-$(MeO)_2$	i-Pr
IIIb	2-Cl	i-Pr
IIIc	2-Me	i-Pr
IIId	2-MeO	i-Pr
IIIe	2-Br	i-Pr
IIIf	2-BuO	i-Pr
IIIg	2-MeS	i-Pr
IIIh	2-Me	Me
IIIi	2-Me	Pr
IIIj	2-Me	$(CH_2)_7CH_3$



IV



V

In formulae *IV* and *V* :

	R^1	R^2
a	3,4-$(MeO)_2$	i-Pr
b	2-Cl	i-Pr
c	2-Me	i-Pr
d	2-MeO	i-Pr
e	2-Br	i-Pr
f	2-BuO	i-Pr
g	2-MeS	i-Pr
h	2-Me	Me
i	2-Me	Pr
j	2-Me	$(CH_2)_7CH_3$
k	2-Me	H

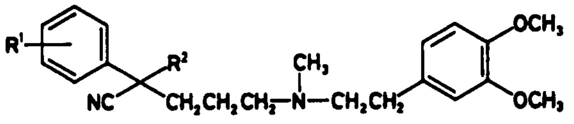
Compounds Modified on the Alkylamino Group Attached in Position 3 to the n-Propyl Fragment (VIIa – VIIt, VIIIa – VIIIc, IXa, IXb and X)

Piperazino derivatives *VIIa* – *VIIq*, acylethylenediamino derivatives *VIIIa*, *VIIIb* hydroxyethyl derivatives *IXa*, *IXb* and isoquinoline derivative *X* were prepared by reductive amination of aldehydes *Va* or *Vc* either with commercially available 1-methyl- (*XIIf*), 1-(2-hydroxyethyl)- (*XIIg*), 1-phenyl- (*XIIh*), 1-benzyl- (*XIIi*), 1-etho-

TABLE II
Yields, boiling points and analytical data of compounds *IVa* – *IVk*

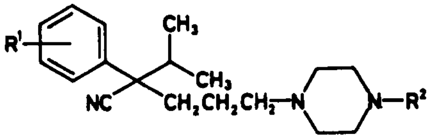
Compound	Yield, %	B. p., °C Pa	Formula (M. w.)	Calculated/Found		
				% C	% H	% N
IVa[a]	70	140 – 148				
		3				
IVb[b]	65	100 – 101	$C_{18}H_{26}ClNO_2$	66.75	8.09	4.33
		3	(323.9)	67.13	8.14	4.42
IVc	80	115 – 116	$C_{19}H_{29}NO_3$	75.20	9.63	4.62
		13	(303.4)	75.85	9.83	4.61
IVd	59	122 – 125	$C_{19}H_{29}NO_4$	71.44	9.15	4.39
		13	(319.4)	71.21	9.12	4.74
IVe[c]	34	130 – 131	$C_{18}H_{26}BrNO_2$	58.69	7.11	3.80
		30	(368.3)	59.85	7.23	3.89
IVf	59	129 – 132	$C_{22}H_{35}NO_3$	73.09	9.76	3.87
		7	(361.5)	73.68	9.86	3.86
IVg[d]	72	122	$C_{19}H_{29}NO_2S$	68.02	8.71	4.18
		4	(335.5)	67.75	9.02	4.08
IVh	71	93 – 95	$C_{17}H_{25}NO_2$	74.14	9.15	5.09
		3	(275.4)	74.57	9.30	5.19
IVi	85	107 – 108	$C_{19}H_{29}NO_2$	75.20	9.63	4.62
		1.5	(303.4)	75.72	9.89	4.68
IVj	96[e]	142 – 144	$C_{24}H_{39}NO_2$	77.16	10.52	3.75
		3	(373.6)	77.82	10.53	3.86
IVk	80[f]	103	$C_{16}H_{23}NO_2$	73.55	8.87	5.36
		1.5	(261.4)	73.55	8.69	4.88

[a] Ref.[18] gives b. p. 160 – 163 °C/5 Pa; [b] calculated: 10.95% Cl, found: 10.98% Cl; [c] calculated: 21.70% Br, found: 21.25% Br; [d] calculated: 9.56% S, found: 9.76% S; [e] yield of crude product; [f] for the preparation of *IVk* we started from *IIc* and used the procedure described for the preparation of butyronitriles *III/B*.



VI

	VIa	*VIb*	*VIc*	*VId*	*VIe*	*VIf*	*VIg*	*VIh*	*VIi*
R^1	2-Cl	2-MeO	2-Br	2-BuO	2-MeS	2-Me	2-Me	2-Me	2-Me
R^2	i-Pr	i-Pr	i-Pr	i-Pr	i-Pr	Me	Pr	$(CH_2)_7CH_3$	H



VII

	R^1	R^2
VIIa	$3,4-(MeO)_2$	$CH_3CH(OCH_3)CO$
VIIb	$3,4-(MeO)_2$	2-furoyl
VIIc	$3,4-(MeO)_2$	C_6H_5CO
VIId	2-Me	$CH_3CH(OCH_3)CO$
VIIe	2-Me	2-furoyl
VIIf	2-Me	C_6H_5CO
VIIg	2-Me	$3,4-(MeO)_2-C_6H_3CO$
VIIh	2-Me	C_2H_5OCO
VIIi	$3,4-(MeO)_2$	Me
VIIj	2-Me	Me
VIIk	$3,4-(MeO)_2$	$HOCH_2CH_2$
VIIl	2-Me	$HOCH_2CH_2$
VIIm	$3,4-(MeO)_2$	C_6H_5
VIIn	2-Me	C_6H_5
VIIo	$3,4-(MeO)_2$	$C_6H_5CH_2$
VIIp	2-Me	$C_6H_5CH_2$
VIIq	$3,4-(MeO)_2$	(1,4-benzodioxan-2-yl)methyl
VIIr	2-Me	H
VIIs	2-Me	$(C_6H_5)_2CH$
VIIt	2-Me	$4-Cl-3-SO_2NH_2-C_6H_3CO$

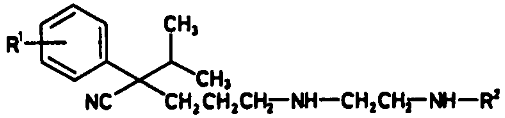
xycarbonylpiperazine (*XIIe*), ethanolamine, or with 1-(2-methoxypropionyl)-[10] (*XIIa*), 1-(2-furoyl)-[11] (*XIIb*), 1-benzoyl-[12] (*XIIc*), 1-(3,4-dimethoxybenzoyl)-[13] (*XIId*), 1-(1,4-benzodioxan-2-yl-methyl)piperazine[14] (*XIIj*), 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline[15] (*XIb*), N-(2-furoyl)ethylenediamine[16] (*XIIIa*) prepared by procedures described in the literature. N-(4-Chloro-3-sulfamoylbenzoyl)ethylenediamine (*XIIIb*) a precusor for the preparation of *VIIIc*, was synthesized by acylation of ethylenediamine by methyl ester of 4-chloro-3-sulfamoylbenzoic acid[19] as described in the experimental section. Preparation of the piperazino derivative *VIIb* was also described by alkylation of 1-furoyl piperazine[20]. The yields, procedures used and melting points are collected in Tables IV and V.

2-Isopropyl-5-(1-piperazinyl)-2-(2-methylphenyl)valeronitrile (*VIIr*), prepared by catalytic debenzylation of *VIIp*, was alkylated with benzhydryl bromide to afford 5-(4-benzhydryl-1-piperazinyl)-2-(2-methylphenyl)valeronitrile *VIIs*.

TABLE III
Yields, melting points and analytical data of compounds *VIa* – *VIi*

Compound[a]	Procedure Yield[b], %	M. p., °C Solvent	Formula (M. w.)	Calculated/Found			
				% C	% H	% N	% Cl
VIa . HCl	*A*	162 – 164	$C_{25}H_{34}Cl_2N_2O_2$	64.51	7.36	6.02	15.24
	77	i-PrOH	(465.5)	64.61	7.52	5.92	15.24
VIb . HCl	*A*	147 – 149	$C_{26}H_{37}ClN_2O_3$	67.73	8.09	6.08	7.69
	85	i-PrOH	(461.0)	67.50	8.08	6.54	7.72
VIc[c] . HCl	*B*	154 – 155	$C_{25}H_{34}BrClN_2O_2$	58.88	6.90	5.49	6.95
	92	i-PrOH	(509.9)	58.70	6.90	5.60	7.03
VId . HFUM	*A*	133 – 134	$C_{33}H_{46}N_2O_7$	68.29	7.97	4.85	–
	80	i-PrOH–Et_2O	(582.7)	68.01	7.96	4.81	–
VIe[d, e]	*B*		$C_{26}H_{36}N_2O_2S$	70.87	8.24	6.36	–
	85		(440.6)	70.58	8.44	6.19	–
VIf . HCl	*B*	132 – 134	$C_{24}H_{33}ClN_2O_2$	69.13	7.98	6.72	8.50
	86	i-PrOH	(417.0)	69.23	7.99	6.65	8.56
VIg . HOX	*B*	125 – 127	$C_{28}H_{38}N_2O_6$	67.44	7.68	5.62	–
	85	i-PrOH	(498.6)	67.29	7.61	5.58	–
VIh[d, f]	*B*		$C_{31}H_{46}N_2O_2$	77.78	9.69	5.85	–
	93		(478.7)	78.24	9.28	5.95	–
VIi . HOX	*B*	163 – 164	$C_{25}H_{32}N_2O_6$	65.77	7.07	6.14	–
	71	EtOH	(456.5)	65.77	7.31	6.18	–

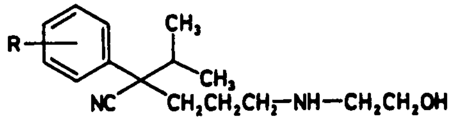
[a] HFUM hydrogen fumarate, HOX hydrogen oxalate; [b] yield of crude base; [c] calculated: 15.67% Br, found: 15.47% Br; [d] free base; [e] b. p. 201 – 203 °C/2.5 Pa; [f] b. p. 210 – 212 °C/2.5 Pa.



VIIIa, R^1 = 3,4-$(MeO)_2$; R^2 = 2-furoyl

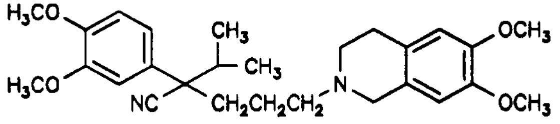
VIIIb, R^1 = 2-Me ; R^2 = 2-furoyl

VIIIc, R^1 = 3,4-$(MeO)_2$; R^2 = 4-Cl-3-SO_2NH_2–C_6H_3CO

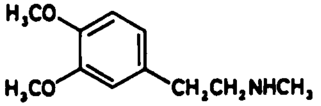


IXa, R = 3,4-$(MeO)_2$

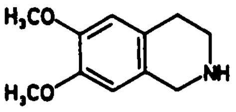
IXb, R = 2-Me



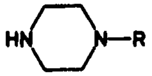
X



XIa



XIb



$H_2NCH_2CH_2NHR$

XIIa, R = $CH_3CH(OCH_3)CO$

XIIb, R = 2–furoyl

XIIc, R = C_6H_5CO

XIId, R = 3,4-$(MeO)_2$–C_6H_3CO

XIIe, R = C_2H_5OCO

XIIf, R = Me

XIIg, R = $HOCH_2CH_2$

XIIh, R = C_6H_5

XIIi, R = $C_6H_5CH_2$

XIIj, R = (1,4-benzodioxan–2–yl)methyl

XIIIa, R = 2–furoyl

XIIIb, R = 4–Cl–3–SO_2NH_2–C_6H_3CO

The infrared, ^{1}H NMR and ^{13}C NMR spectra of the final amines *VIa* – *VIi*, *VIIa* – *VIIt*, *VIIIa* – *VIIIc*, *IXa*, *IXb*, and *X* were consistent with the assigned structures.

Acute oral and intravenous toxicities of the final amines (in form of salts, as indicated in Tables IV and V) were determined in mice. The ED_{50} values were ranging from 200 – 2 000 mg/kg for oral and 5 – 1 125 mg/kg for intravenous administration.

Three tests were used for the evaluation of the antiarrhytmic activities of the synthesized compounds. Model arrhythmias were induced either by intravenous administration of aconitine, acetylcholine, or calcium chloride (Wistar–Hannover male rats). Following compounds, administered in a dose of 10^{-5} mol/kg, at least in one model, caused 50% or larger decrease of mortality, compared to control group (95% mortality): *VIa* (VÚFB 16222), *VIb* (VÚFB 16240), *VIc* (VÚFB 16250), *VId* (VÚFB 16244), *VIe* (VÚFB 16260), *VIf* (VÚFB 17970), *VIg* (VÚFB 17971), *VIi* (VÚFB 17969), *VIIe* (VÚFB 17992), and *X* (VÚFB 17948).

The basic hemodynamic parameters (heart rate, systolic and diastolic blood pressure, d*P*/d*t* in the left ventricle and blood flow in arteria carotis) of pentobarbital anesthetized dogs were altered significantly by the following compounds (intravenous administration, 10^{-5} mol/kg): *VIa* (VÚFB 16222), *VIb* (VÚFB 16240), *VIIb* (VÚFB 17954), *VIIe* (VÚFB 17943), and *VIIj* (VÚFB 17942).

In conclusion, except of *VIa* (VÚFB 16222), all of the synthesized compounds exhibited weaker hypotensive activity, than the mother compound, verapamil (*Ia*).

The negative inotropic activities of the ortho substituted compounds *VIa* (VÚFB 16222), *VIb* (VÚFB 16240), *VIc* (VÚFB 16250), and *VId* (VÚFB 16244) were found to be in the same range as the mother compound (verapamil). These results indicated, that the free rotation of the phenyl ring in the benzyl cyanide of the molecule is of lower importance.

TABLE IV

Yields, melting points and analytical data of compounds *VIIa* – *VIIt*

Compound[a]	Procedure Yield[b], %	M. p., °C Solvent	Formula (M. w.)	Calculated/Found			
				% C	% H	% N	% Cl
VIIa . HFUM	*B*	116 – 130	$C_{28}H_{41}N_3O_8 . 0.5\ H_2O$	60.41	7.61	7.55	–
	43	EtOH–Et$_2$O	(556.6)	60.54	7.37	7.46	–
VIIb . HCl	*B*	125 – 133	$C_{25}H_{34}ClN_3O_4$	63.08	7.20	8.83	7.54
	78	Me$_2$CO–i-PrOH	(473.0)	65.09	7.37	8.80	7.54
VIIc . HCl	*B*	144 – 148	$C_{27}H_{36}ClN_3O_3$	66.72	7.47	8.65	7.29
	75	Me$_2$CO–i-PrOH	(486.1)	65.85	7.48	8.40	7.30
VIId . HCl	*B*	165 – 179	$C_{23}H_{36}ClN_3O_2$	65.46	8.60	9.96	8.40
	49	Me$_2$CO	(422.0)	65.60	8.85	10.26	8.10

TABLE IV
(*Continued*)

Compound[a]	Procedure Yield[b], %	M. p., °C Solvent	Formula (M. w.)	Calculated/Found			
				% C	% H	% N	% Cl
VIIe . HCl	*B*	199 – 201	$C_{24}H_{32}ClN_3O_2 \cdot 0.5\ H_2O$	65.66	7.58	9.57	8.08
	84	Me_2CO-H_2O	(438.1)	65.76	7.88	9.82	8.16
VIIf . HCl	*B*	79 – 90	$C_{26}H_{34}ClN_3O$	70.97	7.79	9.55	8.06
	50	i-PrOH–Et_2O	(440.0)	69.64	7.71	9.40	7.99
VIIg . HFUM	*B*	149 – 153	$C_{32}H_{41}N_3O_7$	66.30	7.13	7.25	–
	56	i-PrOH–Et_2O	(579.7)	66.14	7.18	7.15	–
VIIh . HCl	*B*	157 – 161	$C_{22}H_{34}ClN_3O_2$	64.77	8.40	10.30	8.69
	29	Me_2CO-Et_2O	(408.0)	65.17	8.49	10.47	8.79
VIIi . 2 HCl	*B*	198 – 204	$C_{21}H_{35}Cl_2N_3O_2$	58.33	8.16	9.72	16.40
	43	Me_2CO-Et_2O	(432.3)	58.44	8.32	9.16	16.29
VIIj . 2 HCl	*B*	201 – 206	$C_{20}H_{33}Cl_2N_3$	62.17	8.61	10.87	18.35
	74	MeOH–Me_2CO	(386.4)	62.34	8.77	11.03	17.95
VIIk . 2 HCl	*B*	164 – 169	$C_{22}H_{37}Cl_2N_3O_3$	57.14	8.06	9.09	15.33
	26.6	Me_2CO	(462.5)	57.24	8.20	9.00	15.34
VIIl . 2 HCl	*B*	177 – 186	$C_{21}H_{35}Cl_2N_3O$	60.59	8.47	10.09	17.03
	45.2	MeOH–Me_2CO	(416.4)	61.09	8.65	10.11	16.92
VIIm . 2 HCl	*B*	112 – 117	$C_{26}H_{37}Cl_2N_3O_2 \cdot H_2O$	60.93	7.67	8.20	13.84
	74.5	EtOH–i-Pr_2O	(512.5)	60.84	7.44	8.34	14.13
VIIn . HCl	*B*	184 – 193	$C_{25}H_{34}ClN_3$	72.87	8.32	10.72	8.61
	64.3	H_2O	(412.0)	72.96	8.27	10.72	8.69
VIIo . 2 HFUM	*B*	175 – 180	$C_{31}H_{41}N_3O_6$	61.30	6.91	6.13	–
	61.6	MeOH–Me_2CO	(551.7)	61.46	6.62	6.29	–
VIIp . 2 HCl	*B*	181 – 185	$C_{26}H_{37}Cl_2N_3$	67.52	8.06	9.09	15.33
	88.9	i-PrOH	(462.5)	67.50	7.96	9.03	15.41
VIIq . 2 HFUM	*B*	124 – 131	$C_{37}H_{47}N_3O_{12} \cdot H_2O$	59.75	6.64	6.65	–
	46.7	EtOH–Et_2O	(743.8)	60.04	6.37	5.62	–
VIIr . 2 HCl	*c*	102 – 110	$C_{19}H_{31}N_3 \cdot H_2O$	58.46	8.52	10.76	18.16
		Me_2CO	(390.4)	57.75	8.24	10.80	18.78
VIIs . 2 HCl	*c*	184 – 188	$C_{32}H_{41}Cl_2N_3 \cdot 0.5\ H_2O$	70.18	7.73	7.67	12.95
		i-PrOH–Et_2O	(547.6)	70.15	7.61	7.54	12.93
VIIt[d] . HCl	*c*	114 – 119	$C_{26}H_{34}Cl_2N_4O_3S \cdot H_2O$	54.64	6.35	9.80	12.41
		i-PrOH–i-Pr_2O	(571.6)	54.65	6.20	9.69	12.33

[a] HFUM hydrogen fumarate; [b] yield of crude base; [c] see Experimental; [d] calculated: 5.61% S, found: 6.03% S.

EXPERIMENTAL

The melting points of analytical preparations were determined in Kofler's block and are not corrected. The IR spectra (in KBr or $CHCl_3$) were recorded with 435-Shimadzu spectrophotometer, ^1H NMR and ^{13}C NMR spectra (in hexadeuteriodimethyl sulfoxide or deuteriochloroform, tetramethylsilane as internal standard) with Tesla BS-487 (80 MHz) or Tesla BS-567 A (100 MHz) spectrometer. Chemical shifts are given in ppm (δ-scale), coupling constants (*J*) in Hz. The homogenity of the products and the reactions were monitored using thin layer chromatography on silica gel (Fertigplatte Kieselgel 60 F_{254}, Merck) or GLC (Chrom 5, Laboratorní přístroje Praha).

Benzyl cyanides *IIa* (ref.[6]), *IIb* (ref.[7]), *IIc* (ref.[8]), and *IId* (ref.[9]) were prepared using the procedures described in the literature.

2-Bromobenzyl Cyanide (*IIe*)

Mixture of 2-bromophenyl acetamide (56.7 g, 0.265 mol) and P_4O_{10} (75.2 g, 0.530 mol) was heated in vacuo (1.3 kPa). The crude product distilled from the reaction mixture (45.7 g). By distillation 42.5 g (82%) of pure 2-bromobenzyl cyanide (*IIe*) was obtained. B.p. 132 – 133 °C/1.33 kPa. For C_8H_6BrN (196.1) calculated: 49.0% C, 3.08% H, 40.76% Br, 7.15% N; found: 49.72% C, 3.15% H, 39.23% Br, 7.29% N.

2-Butoxybenzyl Cyanide (*IIf*)

Solution of 2-butoxybenzyl chloride (16.8 g, 85 mmol) in ethanol (13.6 ml) was added in small portions into a stirred mixture of sodium cyanide (5.3 g, 100 mmol) and water (4.8 ml) and heated on a steam bath for 45 min. After heating to reflux temperature for another 4 h, the reaction mixture was poured into 80 ml of water. The oily product was extracted with ether (3 × 50 ml). The combined organic layers were washed with water (3 × 50 ml), dried (anhydrous magnesium sulfate) and the solvent was removed on a rotatory evaporator. By distillation of the residue, 7.4 g (46%) of pure product *IIf* was obtained. For $C_{12}H_{15}NO$ (189.3) calculated: 76.15% C, 7.99% H, 7.40% N; found: 77.35% C, 8.25% H, 7.42% N.

TABLE V
Yields, melting points and analytical data of compounds *VIIIa* – *VIIIc*

Compound	Procedure Yield, %	M. p., °C Solvent	Formula (M. w.)	Calculated/Found % C	% H	% N
VIIIa . HFUM	*C*	168 – 173	$C_{27}H_{35}N_3O_8$	61.23	6.66	7.94
	98	[a]	(529.6)	61.17	6.70	7.91
VIIIb . HMAL	*C*	86 – 94	$C_{26}H_{33}N_3O_6$	64.58	6.88	8.69
	72	i-PrOH–i-Pr_2O	(483.6)	64.39	6.87	8.48
VIIIc[b] . HCl	*C*	204 – 210	$C_{25}H_{34}Cl_2N_4O_5S \cdot 0.33\,H_2O$	51.81	6.03	9.67
	59	H_2O	(579.5)	51.94	5.91	9.61

[a] i-PrOH–Me_2CO–Et_2O; [b] calculated: 1.04% H_2O, 12.33% Cl, 5.53% S, found: 1.04% H_2O, 12.33% Cl, 5.72% S.

2-Methylthiobenzyl Cyanide (*IIg*)

Starting from 2-methylthiobenzyl chloride (38.1 g, 0.22 mol) and sodium cyanide (13.5 g, 0.275 mol), using the above described procedure title compound *IIg* (22.7 g, 65%) was obtained. B.p. 88 – 89 °C/27 Pa. For C_9H_9NS (163.2) calculated: 66.22% C, 5.56% H, 8.58% N, 19.64% S; found: 65.98% C, 5.96% H, 7.42% N, 19.67% S.

General Procedure for the Preparation of Nitriles *IIIa* – *IIIj*

A) The solution of the appropriate nitrile *II* (0.19 mol) in 1,2-dimethoxyethane (40 ml) was dropwise added to a stirred, cold (0 – 5 °C) suspension of sodium amide (8.95 g, 0.30 ml) in toluene (10 ml) and 1,2-dimethoxyethane (33 ml). After stirring at room temperature for 3 h, the solution of 2-bromopropane (30.6 g, 0.248 mol) in 1,2-dimethoxyethane (24 ml) was dropwise added at 10 °C. After the addition was complete (15 min), the reaction mixture was stirred at 15 °C for 30 min, then 5 h at room temperature. The reaction mixture was diluted with water (530 ml) and the product was extracted into benzene (5 × 75 ml). The combined organic extracts were washed with water (1 × 100 ml), 1M solution of sodium hydroxide (1 × 150 ml), water (2 × 80 ml), sulfuric acid (10%, 2 × 75 ml) and finely with water, until neutral pH. After drying (anhydrous magnesium sulfate) the solvent was evaporated under diminished pressure. The remaining crude product was purified by distillation under reduced pressure.

B) The appropriate alkyl halogenide (0.4 mol) was added dropwise during 2.5 h to a vigorously stirred mixture of the appropriate benzyl cyanide *II* (0.2 mol), tetrabutylammonium hydrogen sulfate (1.0 g, 2.9 mmol) and 50% solution of sodium hydroxide (77 ml). The temperature of the reaction mixture was kept during the addition and for next two hours below 45 °C, finally at 60 °C for 3 h. After cooling to room temperature, the reaction mixture was diluted with water (70 ml), and extracted with ether (3 × 50 ml). The combined organic extracts were washed with water, sulfuric acid (10%) and water until neutral pH. After drying (anhydrous magnesium sulfate) and evaporation of the solvent under reduced pressure, the remaining oil was purified by distillation under reduced pressure. The results are collected in Table I.

General Procedure for the Preparation of Acetals *IVa* – *IVk*

The suspension of sodium amide (9.0 g, 0.23 mol) in 10 ml of toluene was added dropwise to a boiling solution of the appropriate nitrile *III* (0.2 mol) and 1-chloro-3,3-diethoxypropane (36.55 g, 0.219 mol) in toluene (210 ml) under vigorous stirring. After 5 h stirring at reflux temperature, the reaction mixture was cooled and poured into a mixture of water (360 ml) and ether (180 ml). The layers were separated and the aqueous phase was extracted with ether (100 ml). The combined organic extracts were washed with water until neutral pH, and dried (anhydrous magnesium sulfate). The crude product was obtained by evaporation of the solvent in vacuo and purified by distillation under reduced pressure. The results are collected in Table II.

General Procedure for the Preparation of Aldehydes *Va* – *Vk*

Solution of the appropriate acetal (0.030 mol) and oxalic acid dihydrate (4.2 g, 0.033 mol) in the mixture of acetone (70 ml) and water (25 ml) was stirred for 3 h at 40 °C. After cooling to 5 °C, the pH was adjusted with 50% solution of potassium carbonate to 6.0 – 6.5. The precipitate was filtered off and washed with cold acetone. The filtrate was evaporated to dryness under reduced pressure. The residue was taken up into water (25 ml) and extracted with ether (3 × 50 ml). The combined organic extracts were washed with a solution of sodium bicarbonate and water until neutral pH. After drying (annhydrous magnesium sulfate) the solvent was evaporated under diminished pressure (the bath temperature was kept below 30 °C).

General Procedure for Reductive Amination of Aldehydes *Va* – *Vk*

A) The solution of aldehyde *V* (prepared from 0.03 mol of acetal *IV* using the procedure described above) and the appropriate amine (0.03 mol) in methanol (50 ml) was hydrogenated at atmospheric pressure using Adams's catalyst (0.1 g). After absorption of theoretical amount of hydrogen, the catalyst was filtered off and the filtrate was evaporated to dryness under reduced pressure. The residue was taken up into water (120 ml) and acidifed with 0.1M-HCl (40 ml). The non-basic products were extracted into ether (90 ml, 2 × 30 ml). The water layer was alkalized with a solution of 1M-NaOH (70 ml) and the free base was extracted with ether (4 × 70 ml). The combined organic extracts were washed with water (3 × 30 ml), dried (anhydrous magnesium sulfate) and the solvent was evaporated under diminished pressure. The residual free base was transformed to the appropriate salt and purified by crystallization.

B) The mixture of the appropriate aldehyde *V* (prepared from 0.03 mol of acetal *IV* by the procedure described above), appropriate amine (0.028 mol) and formic acid (90%, 1.27 ml, 0.03 mol) in toluene (50 ml) was stirred at reflux temperature for 1 h. After cooling to room temperature the reaction mixture was acidified with 0.1M-HCl to pH 4. After shaking, the organic layer containing the non-basic products was separated. The aqueous layer was made alkaline with 1M solution of sodium hydroxide (60 ml) and the bases were extracted into ether (100 ml, 2 × 50 ml). The combined extracts were washed with water (5 × 50 ml) and after drying (anhydrous sodium sulfate) the solvent was evaporated to dryness. The residual free base was transformed into the appropriate salt and purified by crystallization.

C) The solution of the appropriate aldehyde *V* (prepared from 0.03 mol of acetal *IV* by the procedure described above) and the appropriate amine (0.028 mol) in methanol (60 ml) was heated to reflux temperature for 1 h. After cooling to 5 °C, sodium borohydride (5.0 g, 0.126 mol) was added in small portions. The reaction mixture was stirred at room temperature 8 h. The solvent was evaporated under reduced pressure, and the residue was taken up into water (200 ml). After acidifying with concentrated hydrochloric acid (30 ml), the non-basic products were extracted into ether (2 × 100 ml). The aqueous phase was made alkaline with 1M-NaOH and the free base was extracted with chloroform (3 × 100 ml). The crude base was transformed to a appropriate salt and purified by crystallization.

The results are collected in Tables III, IV and V.

2-Isopropyl-2-(2-methylphenyl)-5-(1-piperazinyl)valeronitrile (*VIIr*)

A solution of *VIIp* dihydrochloride (15.6 g, 0.034 mol) was hydrogenated on 15% Pd/charcoal (2.3 g) in a mixture of 15 ml water and 150 ml methanol at atmospheric pressure until the calculated amount of hydrogen (820 ml) was consumed. The catalyst was filtered off and the solvent was evaporated under reduced pressure. 13.0 g (100%) of crude *VIIr* dihydrochloride was obtained, which was purified by crystallization from acetone, m.p. 102 – 110 °C. The yield of the pure product was 12.4 g (99%). ^{1}H NMR spectrum (($^2H_3C)_2SO$): 0.78 d, 1.05 d, 6 H (CH_3, isopropyl); 2.49 s, 3 H ($Ar-CH_3$); 8.25 m, 4 H (Ar–H).

5-(4-Benzhydryl-1-piperazinyl)-2-isopropyl-2-(2-methylphenyl)valeronitrile (*VIIs*)

Dihydrochloride of *VIIr* (3.75 g, 0.010 mol) was added to a solution of sodium methoxide (0.46 g Na in 50 ml methanol). The solvent was evaporated under diminished pressure and the residue taken up into acetone (65 ml). After addition of benzhydryl bromide (3.47 g, 0.014 mol) and potassium carbonate (5.5 g) the stirred reaction mixture was heated to reflux temperature for 7 h. After cooling to room temperature, the solid was filtered off and the solvent was evaporated to dryness under reduced pressure. The residue was diluted with hydrochloric acid (3%, 100 ml) and the non-basic products were extracted into ether (2 × 100 ml). The aqueous phase was made alkaline (1M-NaOH) and extracted with chloroform (4 × 100 ml). The combined organic extracts were dried (anhydrous sodium sulfate) and the solvent was evaporated under reduced pressure. The raw base (5.8 g) was transformed into dihydrochloride and purified by crystallization from 2-propanol–ether, m.p. 184 – 188 °C. The yield of the pure product was 3.8 g (71%). ^{1}H

NMR spectrum (($(^2H_3C)_2SO$): 0.8 d, 1.08 d, 6 H (CH_3, isopropyl); 2.50 s, 3 H (CH_3–Ar); 3.20 bm, 4 H (H-3, H-5, piperazine); 3.50 bm, 4 H (H-2, H-6, piperazine); 5.12 bs, 1 H (CH, benzhydryl); 7.20 – 8.00 m, 14 H (Ar–H). ^{13}C NMR spectrum ($(^2H_3C)_2SO$): 19.57 t (C-4, valeronitrile), 21.06 q (CH_3–Ar), 31.67 t (C-3, valeronitrile), 33.99 d (CH, isopropyl), 47.06 t (C-3, C-5, piperazine), 47.80 t (C-2, C-6, piperazine), 52.73 s (C-2, valeronitrile), 54.45 t (C-5, valeronitrile), 73.28 d (CH, benzhydryl), 121.23 s (C-1, valeronitrile), 134.08 bm (C-2, arom.), 134.90 s (C-1, arom.), 137.22 s (C-1, arom., benzhydryl). IR spectrum (KBr, cm^{-1}): 2 462 (N^+–H); 2 263 (CN); 752, 722 (mono- and disubstituted arom.).

5-[4-(4-Chloro-3-sulfamoylbenzoyl)-1-piperazinyl]-2-isopropyl-2-(2-methylphenyl)valeronitrile (*VIIt*)

Dihydrochloride of *VIIr* (3.75 g, 0.010 mol) was added to a solution of sodium methoxide (0.46 g Na in 50 ml of methanol). After evaporation of the solvent under reduced pressure, the residue was taken up into ethyl acetate (17 ml). Solution of sodium bicarbonate (1.4 g) in water (12 ml) was added. After addition of the solution of 4-chloro-3-sulfamoylbenzoyl chloride (2.54 g, 0.010 mol) in ethyl acetate (10 ml) the reaction mixture was stirred at room temperature for 2 h. The solvent was evaporated under diminished pressure. The residue was diluted with water (50 ml) and the product was extracted with chloroform (4 x 100 ml). The combined organic extracts were dried (anhydrous sodium sulfate) and the solvent was evaporated under reduced pressure. The crude base was transformed into hydrochloride and crystallized from the mixture of isopropyl alcohol and diisopropyl ether, m.p. 114 – 119 °C. 1.6 g (27%) of pure hydrochloride was obtained. ^1H NMR spectrum ($(^2H_3C)_2SO$): 0.74 d and 1.02 d, 2 x 3 H ($(CH_3)_2CH$, J = 7.0); 6.90 – 7.90 m (SO_2NH_2, Ar–H); 7.96 s, 1 H (H-2'); 11.22 bs, 1 H (N^+–H).

2-(3,4-Dimethoxyphenyl)-5-(2-hydroxyethylamino)-2-isopropylvaleronitrile (*IXa*)

Title compound was prepared from aldehyde *Va* (16.2 g, 46.2 mmol) and ethanolamine (2.3 g, 46.2 mmol) using the procedure described for the preparation of amines *VIII* (general procedure for the reductive amination of aldehydes *V/C*) in 88% yield. Melting point of the hydrochloride of *IXa* was 117 – 120 °C (acetone/ether). For $C_{18}H_{29}ClN_2O_3$ (356.9) calculated: 60.47% C, 8.19% H, 9.93% Cl, 7.85% N; found: 60.44% C, 8.22% H, 10.04% Cl, 7.81% N.

5-(2-Hydroxyethylamino)-2-isopropyl-2-(2-methylphenyl)valeronitrile (*IXb*)

Title compound was prepared from aldehyde *Vc* (14.8 g, 53.0 mmol) and ethanolamine (3.3 g, 53.0 mmol) in 76% yield using the procedure described for *IXa*. Melting point of the hydrochloride of *IXb* was 130 – 134 °C (tetrahydrofuran–diisopropyl ether). ^1H NMR spectrum (C^2HCl_3): 0.78 d, 1.10 d, 6 H (CH_3, isopropyl); 1.08 – 1.20 m, 1 H (CH, isopropyl); 2.40 s, 3 H (CH_3–Ar); 1.92 – 2.70 m, 6 H (CH_2CH_2–N–CH_2); 3.52 bt, 2 H (O–CH_3); 7.04 – 7.22 m, 3 H (H-3, H-4, H-5); 7.32 – 7.55 bm, 1 H (H-6). IR (KBr, cm^{-1}): 3 400 (NH, OH, intramolecular bond); 2 200 (CN); 1 975, 1 915, 1 880, 1 840, 1 770 (1,2-disubst. arom.); 1 600, 1 490, 1 480 (arom.); 1 385, 1 330, 1 170 (isopropyl); 1 050 (OH). For $C_{17}H_{28}ClN_2O$ (310.9) calculated: 65.68% C, 8.75% H, 11.28% Cl, 9.01% N; found: 65.59% C, 8.69% H, 11.28% Cl, 8.92% N.

2-(3,4-Dimethoxyphenyl)-5-(6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl)-2-isopropylvaleronitrile (*X*)

Title compound was prepared from the aldehyde *Va* (11.5 g, 30.1 mmol) and 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (*XIb*, 5.8 g, 30.1 mmol) in 61% yield using the procedure described for preparation of amines *VII* (general procedure for reductive amination of aldehydes *V/B*). Melting point of hydrochloride of *X* was 180 – 186 °C (tetrahydrofuran–ethanol–diisopropyl ether/water). ^1H NMR spectrum ($(C^2H_3C)_2SO$): 0.72 d and 1.15 d, 2 x 3 H ($(CH_3)_2CH$, J = 6.5); 1.65 bm, 1 H (CH of isopropyl); 2.22 bt, 4 H (H-1, H-2, propyl, J = 7.0); 3.80 s and 3.75 s, 12 H (CH_3O–Ar); 4.16 bs, 2 H (Ar–CH_2–N); 6.80 bs, 2 H (Ar'–H); 7.02 bs, 3 H (Ar–H); 11.10 bs 1 H (N^+–H). IR spectrum (KBr, cm^{-1}): 2 963, 2 938, (CH_3, CH_2, CH); 2 837 (OCH_3); 2 578 (NH); 2 231 (CN), 1 611, 1 591, 1 518 (arom.); 1 465 (CH_3); 1 440 (CH_2); 1 415, 1 391 (isopropyl); 1 260, 1 146 (C-O-C); 855 (tetrasubst. arom.); 805, 767 (trisubst. arom.). For $C_{27}H_{37}ClN_2O_4$. 0.5 H_2O (498.1) calculated: 65.11% C, 7.69% H, 7.12% Cl, 5.62% N; found: 65.25% C, 7.75% H, 7.07% Cl, 5.35% N.

N-(4-Chloro-3-sulfamoylbenzoyl)ethylenediamine (*XIIIb*)

A mixture of the ethyl ester of 4-chloro-3-sulfamoyl benzoic acid[19] (10.0 g, 0.040 mol) and ethylenediamine (7.2 g, 0.120 mol) was stirred for 24 h at room temperature. The separated solid was filtered of and washed with ethanol. The product was purified by crystallization from a mixture of methanol and hexane. The yield of the pure product was 3.6 g (32%). Melting point of the pure base was 182 – 184 °C dec. (methanol), hydrochloride 257 – 260 °C dec., (ethanol). For $C_9H_{13}Cl_2N_3O_3S$ (314.2) calculated: 34.40% C, 4.17% H, 22.57% Cl, 13.37% N, 10.21% S; found: 34.21% C, 4.37% H, 22.36% Cl, 13.27% N, 10.30% S.

REFERENCES

1. Mannhold R., Ziernig P., Bayer E., Rodenkirchen R., Steiner R.: Arzneim.-Forsch. *31*, 773 (1981).
2. Mannhold R., Steiner R., Haas W., Kaufman R.: Naunyn-Schmiedebergs Arch. Pharmacol. *302*, 217, (1978).
3. Mannhold R.: Drugs Today *20*, 69 (1984).
4. Hoeltje H. D.: Arch. Pharm. *315*, 317 (1982).
5. Bláha L., Rajšner M., Helfert I., Trčka V.: Czech. 258537 (1986).
6. Kindler K., Gehlhaar E.: Arch. Pharm. *274*, 377 (1936).
7. Kampbell N., McKail E.: J. Chem. Soc. *1948*, 1251.
8. Newman M. S.: J. Am. Chem. Soc. *62*, 2295 (1940).
9. Niederl J. B., Roth R. T.: J. Am. Chem. Soc. *60*, 2140 (1938).
10. König J., Rajšner M., Mácová S., Trčka V.: Czech. 236097 (1984); Chem. Abstr. *101*, 151886y (1984).
11. Nenzer M., Kazmirowski H. G., Carstens E., Lehmann D.: Ger. (G.D.R.) 130658 (1978); Chem. Abstr. *90*, 104015 (1979).
12. Moore S. T., Boyle M., Thorn V. M.: J. Am. Chem. Soc. *51*, 39 (1929).
13. Sugihara H., Itoh K., Nishikawa K. (Takeda): Eur. 284359 (1988); Chem. Abstr. *110*, 95274u (1989).
14. Lafon L. (Laboratoire L. Lafon): Ger. Offen. 2353059 (1974); Chem. Abstr. *81*, 63682s (1974).
15. Buck S. J.: J. Am. Chem. Soc. *56*, 1769 (1934).
16. Large M. S., Smith L. H.: J. Med. Chem. *25*, 1417 (1982).
17. Liang C. D. (Searle): Eur. 219813 (1987); Chem. Abstr. *107*, 134044d (1987).
18. Dengel F. (Knoll A. G.): Ger. Offen. 2631222 (1978); Chem. Abstr. *88*, 169796s (1978).
19. Parke, Davis & Co.: Brit. 915259 (1963); Chem. Abstr. *61*, 6962 (1964).
20. Laguerre M., Boyer C., Carpy A., Panconi E., Cognic F., Vaugien B.: Eur. J. Med. Chem. *25*, 351 (1990).

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