Preparation and properties of dialkylaminoethoxyazachalcones

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Twenty 2-, 3-, and 4-(2-dialkylaminoethoxy)azachalcones have been synthesized by alkylation of hydroxyazachalcone, prepared in advance, or by Claisen—Schmidt condensation of dialkylaminoethoxybenzaldehydes with methyl pyridyl ketone. Ultraviolet, infrared, and ^{1}H-n.m.r. spectra were used to verify the identity of the prepared compounds and establish the geometrical isomerism and conformations. Preliminary tests for antimicrobial activity and acute toxicity have been carried out with some of the azachalcones prepared.

Синтезирована группа из двадцати 2-, 3- и 4-(2-диалкиламиноэтокси)азахалконов. Эти соединения были получены в результате алкилирования ранее приготовленного гидроксиазахалкона или конденсацией по Кляйзену–Шмидту диалкиламиноэтоксибензальдегидов с метилпиридилкетоном. Для идентификации полученных соединений и определения геометрической изомерии и конформации были использованы данные УФ, ИК и ^{1}H-ЯМР спектроскопий. У некоторых полученных азахалконов ориентировочно была оценена антимикробиальная активность и степень острой токсичности.

Chalcones and their heterocyclic analogues have been the object of interest of organic chemists for a long time. These compounds are reactive and can serve as starting substances for series of further more complicated structures. Investigations in recent years have shown that many chalcones and azachalcones are interesting also from the point of view of their biological activity.

In the present work we have focused our attention on preparation of azachalcones with a base salt-forming group in the side chain, as compounds with presumed effect on cardiovascular system. The identity of the prepared azachalcones and their salts was verified, besides elemental analysis, by their u.v., i.r., and ^{1}H-n.m.r. spectra. Interpretation of the spectra helped also to establish the geometrical isomerism and conformations, which can be of essential importance from the view-point of pharmacological activity. Continuing the previous study of

antimicrobial activity of azachalcones (insoluble in water) [1, 2], we made preliminary investigations about the activity of the newly prepared compounds which could be tested as water-soluble salts.

Experimental

The u.v. spectra of the synthesized compounds were measured on a Specord UV VIS (Zeiss, Jena) spectrophotometer in ethanol or methanol solutions at 200—800 nm using 0.1 or 0.2 cm silica cells. When the u.v. spectra were used to find the optimum time for the Claisen—Schmidt condensation, 10 μl of reaction mixture were withdrawn by a constriction micropipette at preset times.

The i.r. spectra were measured by the KBr technique (*ca.* 2 mg compound per 400 or 800 mg KBr) on a Perkin—Elmer 377 or a Specord IR 75 (Zeiss, Jena) spectrophotometer at 4000—400 cm^{-1}.

The ^{1}H-n.m.r. spectra of the solid bases of azachalcones were measured in deuteriochloroform on a Tesla BS 487 A spectrometer at 80 MHz using hexamethyldisiloxane as internal standard; the results were calculated to tetramethylsilane.

Protonization constants were determined potentiometrically on a PHM-26 (Radiometer, Copenhagen) apparatus with a G 202 C glass electrode and a saturated K 100 calomel electrode. The accuracy of measurements was pH ± 0.05.

Acute toxicity was determined on white mice. Subcutaneously were injected 1 % solutions of the compounds tested, the mortality was checked after 24 h. Each dose was applied to two mice and the approximate limits for LD_{50} were estimated.

The antimicrobial activity was tested on standard strains of *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans*. Fire-clay rollers of 5 mm diameter were plunged into 1 % aqueous solutions of the compounds and the inhibition zone was expressed in mm.

Dialkylaminoethoxybenzaldehydes were prepared after the procedure described in [3]. The oily products were purified by distillation under reduced pressure or by crystallization in the form of salts with hydrochloric or citric acid. The prepared compounds are presented in Table 1.

Dialkylaminoethoxyazachalcones

Method A

Into anhydrous ethanol (100 ml) containing metallic sodium (1.15 g) hydroxyazachalcone (0.05 mol) was added and the reaction mixture was shaken mechanically for 2 h at room temperature. Ethanol was distilled off and the solid red residue was washed with ether. To the solid substance toluene (100 ml) and *N*-(2-chloroethyl)dialkylamine (0.05 mol) were added and the reaction mixture was heated under reflux for 4 h. After cooling the solid portion was filtered off and toluene was distilled off under reduced pressure. From the oily or semi-solid products salts were prepared with hydrochloric or citric acid.

Table 1

Dialkylaminoethoxybenzaldehydes

No.	Compound	Formula M_r	Calculated/found % C	 % H	 % N	Yield %	Salt M.p./°C	B.p./°C Pa	n_D °C
I	3-[2-(Dimethylamino)ethoxy]-	$C_{11}H_{15}N_1O_2Cl_1$	57.51	7.02	6.09	64	Chloride	122—125/106	1.5325
	benzaldehyde	229.71	57.38	6.94	6.23		159—161		25
II	4-[2-(Dimethylamino)ethoxy]-					63	Chloride	156/119	1.5588
	-3-methoxybenzaldehyde								21
III	4-[2-(Dimethylamino)ethoxy]-	$C_{13}H_{20}N_1O_3Cl_1$	57.03	7.36	5.11	46	Chloride	144—146/79.9	1.543
	-3-ethoxybenzaldehyde	273.75	56.76	7.11	5.34		131—133		22
IV	4-[2-(Diethylamino)ethoxy]-	$C_{20}H_{29}N_1O_{10}$	54.23	6.60	3.16	58	Citrate		
	-3-methoxybenzaldehyde	443.45	54.58	6.76	3.28		123—126		
V	3-[2-(Diethylamino)ethoxy]-	$C_{14}H_{22}N_1O_3Cl_1$	58.59	7.73	4.88	64	Chloride		
	-4-methoxybenzaldehyde	287.78	58.80	7.69	4.79		178—179		
VI	4-[2-(Diethylamino)ethoxy]-	$C_{15}H_{24}N_1O_3Cl_1$	59.69	8.01	4.64	45	Chloride		
	-3-ethoxybenzaldehyde	301.81	59.31	7.92	4.58		142—143.5		
VII	2-[2-(Diethylamino)ethoxy]-	$C_{15}H_{24}N_1O_3Cl_1$	59.69	8.01	4.64	60	Chloride		
	-3-ethoxybenzaldehyde	301.81	60.07	8.08	4.50		102—103		

Method B1

In anhydrous pyridine (10 ml) dialkylaminoethoxybenzaldehyde (0.1 mol) was dissolved and methyl pyridyl ketone (0.1 mol) and diethylamine (0.1 mol) were added. The mixture was allowed to react at room temperature for several hours. In some cases (Table 2) the mixture was preheated on a water bath and then allowed to react at room temperature. The volatile compounds were removed and from the oily or semi-solid residue salts were prepared. When solid azachalcone was obtained, it was recrystallized from a suitable solvent.

Method B2

Methyl pyridyl ketone (0.1 mol) and dialkylaminoethoxybenzaldehyde (0.1 mol) were dissolved in anhydrous ethanol (10 ml) and piperidine (0.1 mol) was added as catalyst. The reaction mixture was allowed to stay at room temperature or heated under reflux. The optimum reaction time was found by using u.v. spectra. After the reaction was completed the mixture was worked up similarly as in the method *B1*. The prepared azachalcones are presented in Table 2.

Results and discussion

For the preparation of dialkylaminoethoxyazachalcones two methods were applied (Scheme 1). The method *B* was shown to be more advantageous mainly when considering the saving of chemicals. The starting dialkylaminoethoxybenzaldehydes were prepared by alkylation of the appropriate phenolates with *N*-(2-chloroethyl)dialkylamines in toluene for 4 h, which meant, in some cases, a shorter reaction time than reported in the literature. This method has proved to be suitable also for preparation of dialkylaminoethoxybenzaldehydes derived from vanillin and its derivatives which have not been described in the literature.

The Claisen—Schmidt reaction of the appropriate benzaldehyde with methyl pyridyl ketones was at the beginning carried out in pyridine (method *B1*) using diethylamine as catalyst. These conditions were chosen with regard to the works by *Ďurinda et al.* [2] and *Szücs et al.* [4] who prepared a large group of variously substituted pyridine analogues of chalcone by this method. Great difficulties with isolation of the final azachalcones led us to change the reaction medium. The use of ethanol was a success (method *B2*). In comparison with the method *B1*, the yields of the crude product and mainly its purity increased in most cases. The optimum reaction time in this procedure was controlled by the u.v. spectra. Heating the reaction mixture to the boiling point of the solvent (ethanol) and using piperidine as catalyst resulted in significant shortening of the reaction time in comparison with

Table 2

Dialkylaminoethoxyazachalcones

No.	Compound	Formula M_r	Calculated/found % C	% H	% N	Method	Reaction time* *a*	*b*	Yield %	Form of azachalcone	M.p./°C Solvent
VIII	2-[2-(Dimethylamino)ethoxy]-	$C_{24}H_{28}N_2O_4$	59.01	5.78	5.73	*B1*	—	48	68	Citrate	85—88
	-3′-azachalcone	448.50	58.77	5.94	5.65						Ethanol
		$C_{18}H_{20}N_2O_2$	72.96	6.80	9.45	*B2*	—	36	79	Base	84—87
		296.31	73.05	6.79	9.30	*B2*	2	—	82		Cyclohexane
IX	2-[2-(Dimethylamino)ethoxy]-	$C_{18}H_{21}N_2O_2Cl$	64.95	6.36	8.41	*B1*	—	48	64	Chloride	167—168
	-4′-azachalcone	332.83	64.63	6.61	8.50						Ethanol
		$C_{18}H_{20}N_2O_2$	72.96	6.80	9.45	*B2*	—	36	84	Base	58.5—60
		296.31	73.22	6.58	9.32	*B2*	2	—	83		Heptane
X	3-[2-(Dimethylamino)ethoxy]-	$C_{24}H_{28}N_2O_4$	59.01	5.78	5.73	*B1*	—	48	41	Citrate	80—83
	-3′-azachalcone	448.50	58.86	5.51	5.63						Methanol
XI	4-[2-(Dimethylamino)ethoxy]-	$C_{18}H_{20}N_2O_2$	72.96	6.80	9.45	*A*	—	—	17	Base	79—80
	-3′-azachalcone	296.31	73.30	7.14	8.93						Petroleum ether
		$C_{24}H_{28}N_2O_4$	59.01	5.78	5.73	*B1*	—	48	71	Citrate	159—161
		488.50	59.23	5.98	5.68	*B2*	—	36	68		Methanol
XII	4-[2-(Dimethylamino)ethoxy]-	$C_{24}H_{28}N_2O_4$	59.01	5.78	5.73	*A*	—	—	38	Citrate	178—179
	-4′-azachalcone	488.50	59.52	6.10	5.99						Methanol
		$C_{18}H_{21}N_2O_2Cl$	64.95	6.36	8.41	*B1*	—	48	79	Chloride	226—230
		332.83	64.92	6.47	8.15						Ethanol
		$C_{18}H_{20}N_2O_2$	72.95	6.80	9.45	*B2*	—	36	87	Base	70—71
		296.37	72.90	6.87	9.39						Hexane

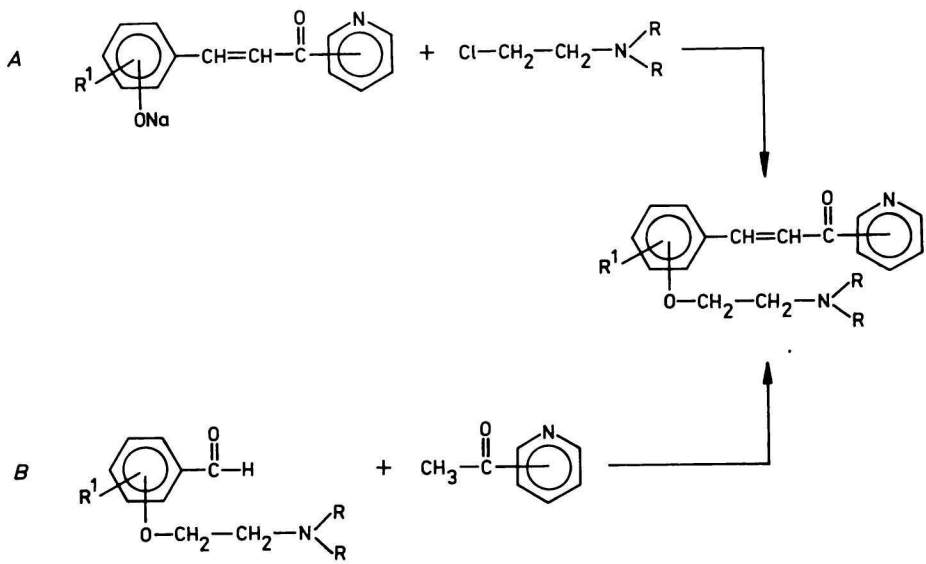
Table 2 (Continued)

No.	Compound	Formula M_r	Calculated/found % C	% H	% N	Method	Reaction time* *a*	*b*	Yield %	Form of azachalcone	M.p./°C Solvent
XIII	2-[2-(Dimethylamino)ethoxy]-3′-azachalcone	$C_{20}H_{30}N_2O_4Cl_2$	55.43	6.97	6.46	*A*	—	—	45	Chloride	158—162
		433.39	55.50	6.76	6.39	*B1*	—	48	52		Ethanol
		$C_{26}H_{32}N_2O_9$	60.46	6.24	5.42	*B2*	—	48	75	Citrate	144—145
		516.55	60.24	6.50	5.31	*B2*	2	—	77		Methanol
XIV	2-[2-(Diethylamino)ethoxy]-4′-azachalcone	$C_{26}H_{32}N_2O_9$	60.46	6.24	5.42	*B2*	—	48	61	Citrate	159—161
		516.55	60.86	6.50	5.61	*B2*	2	—	64		Methanol
XV	3-[2-(Diethylamino)ethoxy]-3′-azachalcone	$C_{26}H_{32}N_2O_9$	60.46	6.24	5.42	*B1*	1	48	48	Citrate	112—115
		516.55	60.68	6.50	5.34	*B2*	—	48	68		Methanol
						B2	2	—			
XVI	3-[2-(Diethylamino)ethoxy]-4′-azachalcone	$C_{26}H_{32}N_2O_9$	60.46	6.24	5.42	*B1*	1	48	56	Citrate	168—170.5
		516.55	60.58	6.48	5.30	*B2*	—	48	69		Methanol
						B2	2	—	71		
XVII	4-[2-(Diethylamino)ethoxy]-3′-azachalcone	$C_{20}H_{25}N_2O_2$	74.05	7.46	8.63	*A*	—	—	17	Base	43—45
		324.43	74.20	7.65	8.51	*B2*	—	48	86		Petroleum ether
		$C_{20}H_{28}N_2O_3Cl_2$	58.48	7.20	6.61	*B2*	2	—	89	Chloride	172—180
		415.37	57.83	6.89	6.74						Ethanol
XVIII	4-[2-(Diethylamino)ethoxy]-4′-azachalcone	$C_{26}H_{34}N_2O_{10}$	58.42	6.41	5.24	*A*	—	—	34	Citrate	116—119
		534.57	58.88	6.53	5.29	*B1*	—	48	42		Methanol
						B2	—	48	91		
						B2	2	—	87		
XIX	4-[2-(Dimethylamino)ethoxy]-3-methoxy-3′-azachalcone	$C_{19}H_{22}N_2O_3$	69.92	6.79	8.58	*B2*	4	—	69	Base	98—101
		326.40	69.76	6.98	8.43	*B2*	—	120	75		Heptane
XX	4-[2-(Dimethylamino)ethoxy]-3-methoxy-4′-azachalcone	$C_{19}H_{22}N_2O_3$	69.92	6.79	8.58	*B2*	3	—	79	Base	108—110
		326.40	69.65	7.10	8.49	*B2*	—	120	81		Heptane

Table 2 (Continued)

No.	Compound	Formula M_r	Calculated/found % C	% H	% N	Method	Reaction time* *a*	*b*	Yield %	Form of azachalcone	M.p./°C Solvent
XXI	4-[2-(Dimethylamino)ethoxy]-3-ethoxy-3′-azachalcone	$C_{20}H_{24}N_2O_3$ 340.43	70.57 70.44	7.11 7.35	8.23 8.14	*B2*	3	—	84	Base	89—90 Heptane
XXII	4-[2-(Diethylamino)ethoxy]-3-methoxy-3′-azachalcone	$C_{27}H_{36}N_2O_{11}$ 564.58	57.44 57.40	6.42 6.69	4.96 4.70	*B2* *B2*	— 2	48 —	91 85	Citrate	86—87 Ethanol
XXIII	4-[2-(Diethylamino)ethoxy]-3-methoxy-4′-azachalcone	$C_{21}H_{26}N_2O_3$ 354.45	71.16 70.93	7.40 7.23	7.90 7.86	*B2* *B2*	— 2	48 —	75 72	Base	101—103 Heptane
XXIV	3-[2-(Diethylamino)ethoxy]-4-methoxy-3′-azachalcone	$C_{21}H_{28}N_2O_3Cl_2$ 426.36	59.16 59.35	6.62 6.90	6.57 6.37	*B2*	4	—	93	Chloride	180—184 Ethanol
XXV	3-[2-(Diethylamino)ethoxy]-4-methoxy-4′-azachalcone	$C_{27}H_{34}N_2O_{10}$ 546.57	59.33 59.69	6.27 6.56	5.12 5.29	*B2*	2	—	91	Citrate	191.5—193 Methanol
XXVI	4-[2-(Diethylamino)ethoxy]-3-ethoxy-3′-azachalcone	$C_{22}H_{28}N_2O_3$ 368.48	71.71 72.03	7.66 7.79	7.60 7.37	*B2*	4	—	84	Base	78—81 Hexane
XXVII	2-[2-(Diethylamino)ethoxy]-3-ethoxy-3′-azachalcone	$C_{22}H_{29}N_2O_3Cl$ 404.93	65.25 64.98	7.22 7.06	6.91 7.09	*B2*	2.5		90	Chloride	158—162 Ethanol

* Reaction time in h; *a*) boiling; *b*) room temperature.



Scheme 1

the reaction proceeding at room temperature (Table 2). The yields and the purity of the compounds prepared at room temperature and at increased temperature were similar.

The prepared dialkylaminoethoxyazachalcones were oily or solid compounds. The solid compounds were purified by crystallization from suitable solvents (Table 2), the oily azachalcones were isolated in the form of salts with hydrochloric or citric acid and purified by crystallization. Attempts to purify these compounds by distillation under reduced pressure led to their decomposition. To optimize the

Table 3

Protonization constants of dialkylaminoethoxyazachalcones

Compound	Protonization constant	
	1st degree	2nd degree
VIII	7.82	3.47
IX	7.65	3.32
XII	7.80	3.38
XXVI	8.45	3.46

Table 4

Spectral characteristics of dialkylaminoethoxyazachalcones

Compound	UV						IR/cm^{-1}				^{1}H-NMR		
	$\lambda_{max\ I}$ nm	$\varepsilon \cdot 10^{-3}$	$\lambda_{max\ II}$ nm	$\varepsilon \cdot 10^{-3}$	$\lambda_{max\ III}$ nm	$\varepsilon \cdot 10^{-3}$	δ(C—H) *trans*	ν(C=O) s-*cis*	ν(C=C)	ν_{as}(COC)	δH_α	δH_β	$I_{\alpha,\beta}$ Hz
VIII	240	11.0	312	10.1	345	12.0	980	1655	1590	1270	7.78	8.09	16.0
IX	238	10.8	303	9.6	356	10.4	992	1653	1595	1248	7.66	8.04	15.7
X	245	7.3	308	9.8									
XI	244	13.7	—		347	25.8	991	1655	1585	1258	7.30	7.80	15.5
XII	240	14.4	—		350	20.9	990	1665	1595	1250	7.31	7.88	16.7
XIII	239	9.2	312	11.0	345	12.0	986	1665	1592	1244			
XIV	235	12.4	307	11.5	352	13.1	982	1661	1584	1240			
XV	sh		310	15.0			994	1658	1595	1250 1265			
XVI	248	10.0	310	15.2			996	1660	1594	1259			
XVII	237	9.0	275	5.0	342	24.0	1001	1661	1604	1254	7.30	7.78	16.0
XVIII	233	7.0	280	5.0	342	17.0	993	1668	1593	1262			
XIX	242	11.6	259	12.2	364	18.9	988	1665	1587	1257	7.31	7.76	15.8
XX	sh		263	9.65	370	17.1	982	1660	1580	1257	7.23	7.74	15.5
XXI							983	1660	1592	1269	7.23	7.72	15.5
XXII	227	15.2	270	11.5	360	8.4	980	1662	1580	1262			
XXIII	sh		262	3.7	374	17.2	983	1661	1590	1265	7.22	7.74	15.8
XXIV	249	13.8	318	7.9	357	20.1	996	1667	1609 1582	1268			
XXV	239	12.5	260	sh	364	18.5	996	1656	1588	1267			
XXVI	247	sh	261	13.5	370	22.0	980	1663	1596	1267	7.30	7.79	15.7
XXVII	sh		303	10.7			990	1669	1604 1591	1274	7.51	8.18	15.5

conditions for the preparation of salts, protonization constants were established with some chosen compounds (Table 3).

The identity of the prepared compounds was verified, besides elemental analysis, by u.v., i.r., and ^{1}H-n.m.r. spectra (Table 4). Evaluation of the spectra helped to determine geometrical isomerism and conformations, too. The u.v. spectral data, the band in the i.r. spectra around 990 cm^{-1}, corresponding to bending vibrations of hydrogens of the vinylene group in *trans* arrangement [5, 6], and the characteristic signals of the AB system of these hydrogens with coupling constant around 16 Hz in the ^{1}H-n.m.r. spectra [7—10] indicated a *trans*-geometrical arrangement.

In the i.r. spectra aborption bands characteristic of carbonyl and vinylene groups can be observed at 1700—1600 cm^{-1}. This fact was utilized in determination of conformation isomers (mutual positions of C=O and C=C double bonds). Mutual relation of intensities of these bands and their distance [11, 12] indicated that in solid state s-*cis* conformers predominated. This assumption was proved also by the results of ^{1}H-n.m.r. spectra utilizing the ASIS effect [8, 9]. The difference in the values obtained, for instance, with the compound *XI* in deuteriochloroform and hexadeuteriobenzene was for H_α +22.4 Hz, for H_β −5.6 Hz indicating s-*cis* conformation after [8, 9]. The ASIS effect was used also for determination of *syn*- or *anti*-periplanar position of nitrogen in pyridyl against oxygen in carbonyl with 3′-azachalcones. The difference in the values obtained in deuteriochloroform and hexadeuteriobenzene was for H-2′ −5.6 Hz and for H-5′ +24.8 Hz pointing to preferred *syn*-periplanar position of these elements. This result is in agreement with the data in [9] for 3′-azachalcone. The results presented above were proved also by detailed conformation analysis of basic azachalcones by quantum chemical PCILO method [13, 14].

Preliminary tests for acute toxicity were carried out with most of the final azachalcones. It was found that the compounds with a side chain in the position 2 were most toxic and the 4-substituted azachalcones were least toxic (Table 5).

In many previous papers [1, 15] dealing with preparation and properties of variously substituted azachalcones also the antimicrobial activity of these compounds was evaluated. All azachalcones tested were little soluble in water and antimicrobially not or little active. We assumed that by introducing a substituent, thus making the salt water-soluble, the antimicrobial activity would increase. Though the activity of the prepared dialkylaminoethoxyazachalcones has not increased significantly, all azachalcones showed, contrary to the previously tested compounds, the inhibition zone against gram-positive bacteria (*Staphylococcus aureus*), some also against gram-negative bacteria (*Escherichia coli*) and yeasts (*Candida albicans*) (Table 5).

With some azachalcones the effect on the heart activity *in vitro* and *in vivo* was evaluated. These results will be published in our next paper.

Table 5

Antimicrobial activity and acute toxicity of some dialkylaminoethoxyazachalcones

Compound	Salt	Acute toxicity Estimate of LD_{50} mg kg^{-1}	Antimicrobial activity								
			Staphylococcus aureus			*Escherichia coli*			*Candida albicans*		
			$\bar{x}$	$s\bar{x}$	$\pm\delta\bar{x}$	$\bar{x}$	$s\bar{x}$	$\pm\delta\bar{x}$	$\bar{x}$	$s\bar{x}$	$\pm\delta\bar{x}$
VIII	Chloride	50—100	9.4	0.245	1.36	0			0		
	Citrate	50—100									
IX	Chloride		16.6	0.245	1.36	8.2	0.200	1.11	6.6	0.245	1.36
XII	Chloride	200—400	12.4	0.245	1.36	8.4	0.245	1.36	6.0	0	0
	Citrate	>600									
XIII	Chloride	<50	12.6	0.400	2.20	8.6	0.245	1.36	0		
	Citrate	<50									
XIV	Chloride	50—100									
	Citrate	100—200	11.0	0.316	1.75	6.8	0.583	3.23	0		
XV	Citrate		8.8	0.374	2.07	7.4	0.245	1.36	0		
XVI	Citrate	100—300	14.2	0.200	1.11	7.4	0.245	1.36	0		
XVIII	Citrate	>600	6.8	0.374	2.07	0			0		
	Chloride	200—400									
XXII	Chloride	500—600	6.0	0	0	0			0		
XXIII	Citrate		6.0	0	0	0			0		
XXIV	Chloride	200—400	7.4	0.245	1.36	0			0		
XXV	Citrate		6.8	0.374	2.07	0			0		
XXVII	Chloride	200—400									

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