Translated from *Usepkhi Khimii* 60 852–880 (1991) U.D.C. 547.298.1:547.554

Synthesis and reactivity of *N*-substituted aminoamides, antiarrhythmic and local anaesthetic activity

G A Tolstikov, E Ya Borisova, M I Cherkashin, V M Komarov, E V Arzamastsev
N N Semenov Institute of Chemical Physics, Academy of Sciences of the USSR, Moscow
M V Lomonosov Moscow Institute of Fine Chemical Technology
Institute of Chemistry, Bashkir Scientific Centre, Urals Division of the Academy of Sciences of the USSR

ABSTRACT. Preparative methods, reactivity and biological action of *N*-substituted aminoamides of the monoacylated diamine type RCONH–CH(–)–(CH$_2$)$_n$N< are considered and systematised. An interconnection has been shown between structure, reactivity and the pharmacological activity of aminoamides.

The bibliography contains 201 references.

Contents

I. Introduction 420
II. Methods of synthesising *N*-substituted aminoamides 420
III. Reactivity of aminoamides 423
IV. Biological action of aminoamides 424

I. Introduction

The interest in aminoamides, organic compounds containing an amino and an amide group, is explained by the wide spectrum of their biological action. Aminoamides display various pharmacological activities and from them several medicinal preparations such as novocainamid, trimecaine, xycaine, flecainide, morphocycline, etc. have been produced in the USSR. A special place is occupied by compounds displaying antiarrhythmic activity, since disturbances of heart rhythm are the most widespread cardiovascular illnesses.

However in contrast to the amides of aminoacids which have been studied in detail, aminoamides of the monoacylated diamine type have received little investigation.

There are no literature reviews on the chemistry and biological action of *N*-substituted aminoamides. However information on individual compounds has been given in reviews.[1–3]

The increase observed in recent years in the number of publications on the development of synthetic methods, on the study of properties and especially on areas for their practical application, has caused a need for correlation and separate consideration of the accumulated information in this new trend in synthetic organic chemistry.

The methods for obtaining, the reactivity and the biological action of *N*-substituted aminoamides of the monoacylated diamine type RCONH–CH(–)–(CH$_2$)$_n$N< are discussed and systematised in the present review. An interconnection has been shown between structure, reactivity and the pharmacological activity of the aminoamides. Literature data published up to and including 1989 are discussed.

II. Methods of synthesis of *N*-substituted aminoamides

All the methods of synthesising aminoamides used at the present time may be provisionally divided into three types and will be considered in turn in this section.

1. Synthesis of aminoamides by introducing an amide group into an amine molecule

The most widespread means of obtaining aminoamides by the first type of method is the acylation of diamines.

$$R_2N(CH_2)_nNH_2 \xrightarrow{R^1COX} R_2N(CH_2)_nNHCOR^1.$$

Acylating agents used include carboxylic acids,[4–8] acid chlorides[9–12] and anhydrides,[13] and esters.[14–18]

Reactions are carried out in benzene, ether, chloroform or without solvent.

A series of aminoamides $RC_6H_4CONH(CH_2)_2NR^1R^2$ (I) has been obtained by acylation of the appropriate diamines with substituted benzoic acids in benzene or toluene in the presence of boron trifluoride and a strong organic base.[19] The yields of aminoamides were from 28 to 100%.

Diethylaminoethylbenzamide was synthesised in 81.8% yield by prolonged stirring of a mixture of the acid and amine in benzene over anhydrous magnesium sulphate.[20]

$$C_6H_5COOH + H_2N(CH_2)_2N(C_2H_5)_2 \xrightarrow[MgSO_4]{BF_3-(C_2H_5)_2O} C_6H_5CONH(CH_2)_2N(C_2H_5)_2.$$

Diamines have been acylated with substituted salicylic acids in dimethylformamide in the presence of ethyl chloroformate and triethylamine at room temperature.[21]

When using carboxylic acids of high molecular weight the reaction is carried out with heating and under pressure.[22]

Carboxylic acid chlorides are most frequently used as acylating agents. Reactions are carried out both in aqueous alkaline medium by the Schotten-Baumann method and in anhydrous organic solvents.

An intermediate aminoamide in the synthesis of novocainamid is obtained by the Schotten-Baumann method,[23] sodium hydroxide is used as the hydrogen chloride acceptor.

A series of arylbenzamides[24] and amides of 2-thiophencarboxylic acid[25] has been obtained in the presence of alkali metal carbonates.

Acylation in organic solvents is frequently carried out in the presence of strong organic bases.[26–29]

However aminoamides contain a strongly basic centre (a tertiary amino group, as a rule) in the molecule and obviously this may serve as an acceptor of hydrogen chloride when obtaining them by the acylation of diamines. In this case the preparation of the hydrochlorides of these compounds in one stage has proved possible.

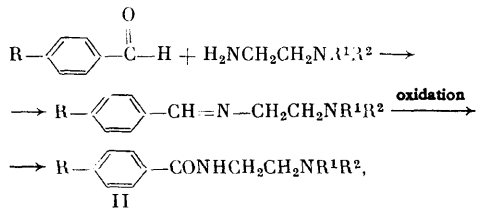
$$H_2N(CH_2)_nNR_2 + ArCOCl \longrightarrow ArCONH{-}(CH_2)_n{-}NR_2 \cdot HCl.$$

The hydrochloride of *N*-(2-diethylaminoethyl)-*p*-nitrobenzamide was obtained from 2-diethylaminoethylamine and *p*-nitrobenzoyl chloride.[24] Aminoamides have also been obtained as hydrochlorides in dry chloroform[30] and dry ether.[31]

The acylation of diamines by the action of acetonitrile and water in the presence of sulphur or a catalyst generating sulphur in the reaction has been described.[32]

$$NH_2{-}(CH_2)_n{-}NR_2 + CH_3CN + H_2O \xrightarrow{S} CH_3CONH(CH_2)_nNR_2.$$

The condensation of a diamine with an aromatic aldehyde has been used for the synthesis of aminoamides (II).[33] The target aminoamide was obtained by the hydrogen peroxide oxidation of the aminoimine formed in the first stage of the reaction.



II

$R = NO_2$, $NR^1R^2 = N$⟨⟩; $R = CH_3O$, $NR^1R^2 = N(C_2H_5)_2$;

$R = NO_2$, $NR^1R^2 = N(C_2H_5)_2$.

The most widespread methods of synthesising diamines are reduction reactions.

The reduction of amino compounds containing a nitro group is carried out with metals in the presence of mineral acid or by catalytic hydrogenation.

$$R_2N(CH_2)_nNO_2 \xrightarrow{M,\ H^{\oplus}} R_2N(CH_2)_nNH_2.$$

The manufacture of paramion, liothyronine, ethmozine, novocainamid, etc. may serve as examples of the industrial application of this method.[34,35]

The reduction of nitriles of aminoacids is carried out with hydrogen in alcoholic-ammonia solution over a rhodium catalyst.[35]

The reductive amination of aminocarbonyl compounds is carried out either catalytically or with formic acid in the presence of ammonia and the amines.

Reductive amination over a platinum catalyst or Raney nickel proceeds usually under mild conditions, but yields differ appreciably.[36] The limitation of this method is the presence in the carbonyl compound or amine molecule of readily reducible groups, such as NO_2 or a double bond. Reductive amination by the Leuchardt reaction proceeds under fairly drastic conditions. Ammonium formate, formamide, and mixtures of them are used as aminating agents.[36] Best results are obtained in this reaction using a mixture of formamide with ammonium formate, occasionally with the addition of 90% formic acid.[37] The reducing action of formamide is enhanced in acidic media, better use is made of the ammonia formed in the reaction and the probability of side reactions occurring is reduced.[38]

$$RCO(CH_2)_nNR_2^1 + 2HCOONH_4 \longrightarrow RC(NHCHO)(CH_2)_nNR_2^1 + 2H_2O$$

$$+ NH_3 + CO_2 \longrightarrow RCH(NH_2)(CH_2)_nNR_2^1.$$

Diamines may be obtained from dibasic alcohols, dihalogen derivatives or halo-amines by a substitution reaction.[35]

Hydrolysis of urethanes or aminoamides is most frequently used.[35]

$$R_2N(CH_2)_nNHCOR^1 \longrightarrow R_2N(CH_2)_nNH_2.$$

In addition diamines are obtained by the interaction of aminoketones with hydroxylamine with subsequent reduction of the resulting amino-oxime.[39]

$$RCO(CH_2)_nNR_2^1 \xrightarrow{HONH_2} HON{=}C(R){-}(CH_2)_nNR_2^1 \xrightarrow{[H]} R{-}CH(NH_2){-}(CH_2)_nNR_2^1.$$

The synthesis of diamines has been described from ketonitriles through oximes by reduction with lithium aluminium hydride in absolute ether.[40]

$$RCO{-}(C)_n{-}CN \longrightarrow R{-}C(HO{-}N){-}(C)_n{-}CN \longrightarrow R{-}CH(NH_2){-}(C)_nNH_2.$$

Aminoamides may also be obtained by the action of primary or secondary amides on an amino-containing compound.[41] The similar reaction with amides proceeds with great difficulty and at increased temperature 170–180 °C, but on the other hand, with urea it proceeds readily and in high yield.[42]

$$RCONH_2 + X(CH_2)_nNR_2^1 \longrightarrow RCONH(CH_2)_nNR_2^1,$$

$X = OH$, Cl.

The addition reaction of acid amides to *N*-vinylamines leading to the formation of aminoamides is known.[43]

$$RCONH_2 + CH_2{=}CH{-}NR_2^1 \longrightarrow RCONHCH_2CH_2NR_2^1.$$

One of the most promising methods of obtaining branched aminoamides is the reaction of aminoalcohols with nitriles in the presence of strong mineral acid (Wieland-Ritter reaction),[44–46] which is widely used in the synthesis of various *N*-substituted amides and nitrogen-containing heterocycles.[47–48]

In addition to 100%[49] and fuming[50–52] sulphuric acid the following may be used as catalysts in the Ritter reaction: 85–96% sulphuric acid,[53–54] phosphoric acid,[55] benzene-sulphonic acid,[56] dichloroacetic acid,[57] toluene-*p*-sulphonic acid,[57] cyclohexane-sulphonic acid,[58] 90% formic acid,[58] 20% solution of sulphuric acid in glacial acetic acid,[59] 10% aqueous solution of hydrogen fluoride,[60] a mixture of concentrated sulphuric and formic acids,[61] and a mixture of sulphuric and phosphoric acids.[62]

The nature of the catalyst proves to have an appreciable influence on the temperature at which reaction occurs. When using sulphuric acid heating of the reaction mixture at 40–80 °C is required,[59,63,64]

but use of formic acid requires a boiling reaction mixture.[58] Depending on the nature of the reacting components the synthesis may be conducted at both low temperature (0 °C) and on heating to 90–175 °C under pressure.[66]

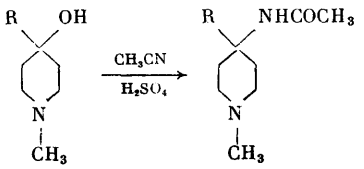
Acetic acid and dibutyl ether are frequently used as solvents in the Wieland-Ritter reaction.[63] The yield of amide is significantly reduced when using formic acid, dioxan, carbon tetrachloride and hexane, and in methyl and ethyl alcohols the reaction does not go at all (Table 1).[67]

Table 1. Influence of solvent on the yield of acrylic acid *N*-t-butylamide.

Solvent	Reaction time, h	Yield of amide, %
Acetic acid	16	98.4
Dibutyl ether	15	86.0
p-Dioxan	24	78.0
Methanol or ethanol	24	0

Ritter and co-workers and also other investigators have described the reaction of olefins and alcohols with various nitriles. Apart from aliphatic[60,66] and aromatic nitriles[45,57] nitriles of dibasic acids such as maleic, adipic, malonic, terephthalic and other acids are widely used in the Ritter reaction.[61] It should be noted that this reaction has been used in a very limited manner until recently for obtaining aminoamides.

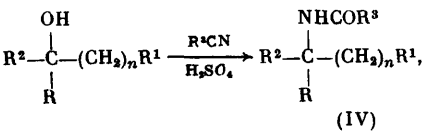
There are definite data in the literature only on the preparation of aminoamides from 1-phenyl-3-piperidino-propanol,[68] diphenyl-(2-piperidylethyl)carbinol[69] and other heterocyclic aminoamides (III).[70]



(III)

R = CH_3, C_2H_5, C_4H_9.

A series of studies has been carried out on the preparation of aminoamides (IV) with various lengths of the methylene chain between the functional groups and with various substituents on nitrogen and in the main chain.[71–77]



(IV)

R = H, CH_3, C_2H_5, C_4H_9, R^1 = $NHCH_3$, NHC_2H_5, NHC_3H_7, NHC_4H_9, NH–⟨⟩, $NHCH_2C_6H_5$, $N(CH_3)_2$, $N(C_2H_5)_2$, N⟨⟩, N⟨⟩O;

R^3 = CH_3, C_2H_5, C_4H_9, C_6H_5; R^3 = H, CH_3, $CH{=}CH_2$, C_6H_5, $CH_2C_6H_5$, $OCH_2C_6H_5$, $C_6H_4R^4$, n = 1–8.

Optimum conditions have been established for carrying out the reaction and it has been shown that in parallel with the main reaction product, viz. the *N*-substituted aminoamide, several side products are formed such as the unsubstituted amide and unsaturated compounds. The structure of the alcohol and especially the character of the susbtituents on the carbonyl carbon atom have a significant influence on the composition of the resulting reaction products. The reaction occurs fairly smoothly with secondary aminoalcohols with 50–70% main product and 15–20% olefin. However replacement of R = H with R = C_2H_5 leads to an increase in the side reaction. Diphenylcarbinols are converted into unsaturated compounds in yields of 70–80%. The influence of the length of the hydrocarbon chain of the aminoalcohol on the yield of the reaction proved to be much weaker (Table 2).[71–73]

The behaviour of nitriles in the Ritter reaction varies depending on their structure. Thus hydrocyanic acid, acetonitrile and benzyl cyanide give amides with both tertiary and secondary alcohols, but benzonitrile and phenoxyacetonitrile react only with secondary aminoalcohols and unsaturated compounds are formed in the remaining cases (Table 3).[74–77]

Table 2. Dependence of yield (as %) of aminoamides (IV) on structure of the initial aminoalcohol (R^2 = C_6H_5, R^3 = CH_3).

R	R^1 $N(CH_3)_2$			$N(C_2H_5)_2$		NC_5H_{10}	NC_4H_8O
	n 1	2	3	1	2	2	2
H	73	67	49	60	63	59	52
C_2H_5	26	25	25	43	29	23	22

Table 3. Dependence of yield (as %) of aminoamides (IV) on the nature of the nitrile [R = $N(CH_3)_2$, R^2 = C_6H_5; n = 2].

R	R^3				
	H	CH_3	C_6H_5	$CH_2C_6H_5$	$CH_2OC_6H_5$
H	52	67	42	42	22
C_2H_5	62	25	0	51	0

The aminoalcohols used in the Wieland-Ritter reaction may be synthesised by various methods.[78–79]

The most widespread means of synthesising aminoalcohols is the interaction of aminoketones and aminoaldehydes with Grignard reagents or by reduction. Variation of these reactants leads to the preparation of primary, secondary and tertiary alcohols. Reduction of aminoketones and aminoaldehydes is effected by catalytic means (platinum and palladium are usually used as catalysts). Reactions are carried out as a rule in alcohol or in aqueous alcohol solution,

mostly at room temperature and atmospheric pressure. The reduction products, viz. primary and secondary aminoalcohols, are formed in good yield. Hydrogenation in the presence of a nickel catalyst is used relatively rarely, since in this case increased pressure and high temperature are necessary.[78]

Lithium aluminium hydride and sodium borohydride are also used as reducing agents.[79] The present method enables reduction of aminoketones without preliminary purification which is accompanied by partial decomposition of the latter.

2. Synthesis of aminoamides by amination of amide-containing compounds

The most widespread example of this approach to the synthesis of aminoamides is the amination of amidoalcohols[80] which is carried out in aqueous solution at 100 °C or in glacial acetic acid at 75 °C.

$$R{-}CONH{-}\underset{|}{\overset{|}{(C)_n}}{-}OH + R_2^1NH \longrightarrow RCONH{-}\underset{|}{\overset{|}{(C)_n}}{-}NR_2^1.$$

It has been established[80] that monoamides are formed by this scheme only when using secondary amides. With primary amines the reaction does not stop at the stage of forming a monoaminoamide but goes further giving bis-aminoamides.

$$RCONHCH_2OH + H_2NCH_3 \longrightarrow (RCONHCH_2)_2NCH_3,$$
$$R = C_6H_5,\ C_6H_5CH_2,\ C_6H_5C_3H_6.$$

Acylketimines[81] and *N*-α-haloalkylamides[82] are also subject to amination.

$$RCON{=}CAr_2 \xrightarrow{R_2^1NH} RCONHC(NR_2^1)Ar_2,$$
$$RCONHCHXR^1 + R_2^2NH \longrightarrow RCONHCH(NR_2^2)R^1.$$

A method has been described for obtaining aminoamides from aminonitriles[83] by acylation of the latter and subsequent reduction over Raney nickel.

$$Ar{-}\underset{|}{\overset{|}{CH}}{-}NH_2 \xrightarrow{RCOCl} Ar{-}\underset{|}{\overset{|}{CH}}{-}NHCOR \xrightarrow[Ni]{[H]} Ar{-}\underset{|}{\overset{|}{CH}}{-}NHCOR.$$
$$\quad\ CN \qquad\qquad\qquad CN \qquad\qquad\qquad\quad CH_2NH_2$$

3. Synthesis of aminoamides by the aminomethylation of acid amides

The most widely used method of synthesising aminomethylamides (V) is by condensation of primary amides with formaldehyde and amines.

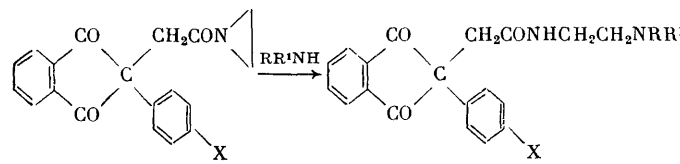
$$RCONH_2 + CH_2O + NHR_2^1 \longrightarrow RCONHCH_2NR_2^1.$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad (V)$$

Condensation is carried out by the usual conditions for the Mannich reaction. It was established that the yield of aminoamide depends to a significant degree on the acidity of the amides and the basicity of the reacting amine.[82] The yield of aminoamide fell from 53% to 0 with an increase in pK_a of the corresponding amide from 1.25 for dichloroacetic acid amide to 4.27 for *m*-toluic acid amide. Such weak bases as aniline (pK_a 4.58), methylaniline (pK_a 4.85) and *o*-toluidine (pK_a 4.39) did not react. The yield of aminoamide reached 50% when using *N*-t-butylamine.

In addition to formaldehyde aromatic aldehydes may be used in the condensation. In this case aliphatic-aromatic aminomethylamines are obtained.

$$Ar{-}CONH_2 + Ar^1CHO + HNC_5H_{10} \longrightarrow ArCONHCH(Ar^1)NC_5H_{10}.$$

A method has been described for the synthesis of aminoamides through acid *N*-ethylenimides.[84] The *N*-ethylenimides having electron-accepting substituents on the nitrogen atom (so-called 'activated' *N*-ethylenimides) readily break the aziridine ring on reaction with amines.[85]



It follows from an analysis of the data mentioned above that the majority of methods of obtaining aminoamides are not universal. This is linked either with limitations peculiar to one or other synthetic method or to the availability of starting materials. Thus aminoamides with branched carbon atoms at the amide group but with a short methylene chain between the functional groups are synthesised by the aminomethylation of acid amides. Branched aminoamides with the most varied methylene chain length are obtined by amination of amide-containing compounds, but here there is a limitation linked with the use of secondary amines only. Aminoamides with a tertiary carbon atom at the amide group are obtained by the acylation of diamines. However in this case the main synthetic complexities are linked with the obtaining of unsymmetrically substituted *N*-t-alkyldiamines.

Of the existing methods the most promising is the Wieland-Ritter reaction for the synthesis of aminoamides with a branched carbon atom on the amide group and any length of methylene chain between the amide and amine groups.

III. Reactivity of aminoamides

The most important feature of the structure of *N*-substituted aminoamides is their bifunctionality which undoubtedly shows up in all the properties of these compounds whether it be salt formation,[10,86] oxidation by peroxides at the amino group[7] or reduction[87] and hydrolysis of the amide group.[88] However there is special interest in those properties of aminoamides in which this influence is clearly shown and may be determined quantitatively. It seemed expedient to consider these in more detail.

It is known that all the properties of amino-containing compounds are determined primarily by their basicity. This depends on the electron density at the nitrogen atom, its steric accessibility and is extremely sensitive even to a small change in structure. Undoubtedly the basicity of aminoamides $RCONH{-}\underset{|}{\overset{|}{C}}{-}(CH_2)_nN\diagup\diagdown$ (VI) depends on the presence of the amide group, the character of the environment of the amino group and on the removability of the polar amide group.

In the general case several factors may influence the basicity of the resulting aminoamide on introducing an amide group into an amine molecule:

a) displacement of electron density to the amide group along the carbon chain (inductive effect, independent of steric obtacles and conformation) and the direct mutual interaction of the amino and amide groups through space (polar effect);

b) formation of an intramolecular hydrogen bond binding the unshared electron pair of the nitrogen atom;

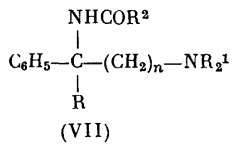
c) increase in the steric obstacles for conversion of the trigonal nitrogen atom into tetrahedral and in the steric difficulties of solvation;

d) formation of a hydrogen bond in the ammonium ion thereby stabilising it;

e) increase in the solvation of molecules due to the appearance of new polar groups.

Factors (a–c) must cause a reduction in the basicity of aminoamides in comparison with simple amines and factors (d–e) an increase. The overall result is determined by their relationship. Data of several studies[89–93] indicate a reduction in the basicity of aminoamides in comparison with the simple amines which indicates the predominant influence of factors (a–c).

Analysis of the data on the basicity of *N*-substituted aminoamides

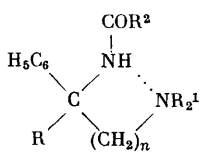


(VII)

in ethanol using correlation equations[92,94] enabled determination of the relationship of effects (a–c).

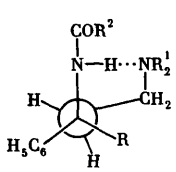
A good correlation was observed[94] between the pK_a values of aminoamides with the inductive constants σ for the influence of substituents.[95] This indicates that in amphoteric strongly solvating solvents aminoamides are in a free, open conformation and all the factors, except the inductive, are of little significance. The influence of the amide group (as for other substituents) is transmitted mainly along the chain of σ-bonds.

In aprotic non-solvating solvents (nitrobenzene, carbon tetrachloride, etc.) aminoamides exist in a folded cyclic conformation with a contiguous disposition of functional groups, stabilised by a hydrogen bond.[96–98]



Quantitative assessment of the stability of such a bond[97] showed that the latter is proportional to the number of CH_2 groups between the amine and amide groups, i.e. on transition from a 5- to a 6- or 7-membered ring the stability of the hydrogen bond was increased. This phenomenon is explained by the change in N–H...N angle, approaching 180° in a 7-membered ring which corresponds to maximum bond strength.

The introduction of a bulky substituent into the α-position to the amide group (R = C_2H_5) leads to strengthening of the hydrogen bond as a result of repulsion between R and $CH_2NR'_2$ and maximum approach of the NH and $CH_2NR'_2$ groups.

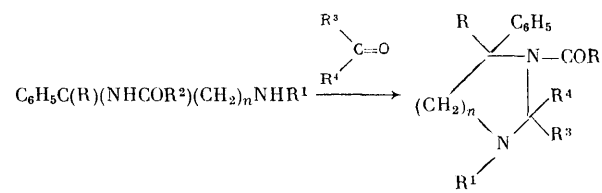


Due to the presence of two polar groups, an amide and an amine, in the aminoamide molecule they are able to form complexes differing in constitution and structure with metals.[99–100]

The complex-forming ability of *N*-lauroylethylenediamine with transition metals has been studied,[101] as has the ability of *N*-picolinoylethylenediamine to form complexes with copper.[102] It was shown with the aid of potentiometric titration and absorption spectra that in similar compounds the metal is bound both with the amide and with the amino group. Most probably the amide group is bound through nitrogen as a result of deprotonation and partially through the carbonyl oxygen.

Investigations have been carried out on the complex-forming ability of several aliphatic-aromatic aminoamides (IV) with Cu, Co and Ni.[103] An analysis of the data obtained was conducted with the aid of correlation equations and enabled an assessment of the contributions of both polar groups to the ability of aminoamides to form complexes with these metals. It was concluded that aminoamides form chelate complexes with transition metals, i.e. both functional groups participate in this process. Furthermore, from the data obtained it proved to be possible to select compounds from the whole series with a high complex-forming ability for use as extractants of non-ferrous metals.[103]

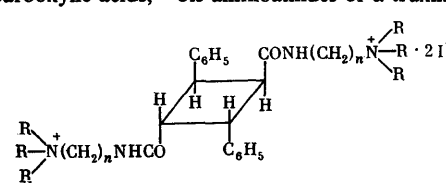
Due to the presence of the amide and amine groups the *N*-substituted aminoamides are capable of cyclisation with aldehydes and ketones with the formation of imidazolidines and hexahydropyrimidines.[104,105]



IV. Biological action of aminoamides

Aminoamides display various physiological activities. Among them substances are known which possess cholinolytic[106] and spasmolytic,[107] hypotensive,[108] antifibrillating[109] and curare-like[110] effects.

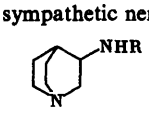
Investigations have shown that on transition from amides of monocarboxylic to dicarboxylic acids the curare-like action of compounds is increased.[110] The nature of the dicarboxylic acid plays an important role. Thus in difference to bis-aminoamides of dibasic alkylcarboxylic acids,[10] bis-aminoamides of α-truxilic acid of the type



possess significantly more marked curare-like activity.[111]

It is possible to name aminoamides which are antibiotics (morphocycline),[112] display insecticidal[112] and bactericidal[113,114] properties and also fungicidal[12] and antiviral[115] effects.

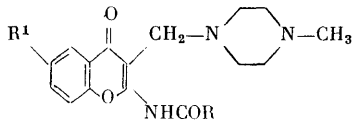
Study of 3-hydroxy- and 3-aminoquinuclidines (VIII)[116] showed that they show a ganglion-blocking action on the parasympathetic and sympathetic nervous systems.



(VIII)

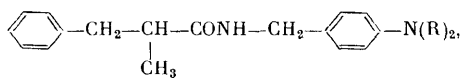
R = COC_6H_5; $COC_6H_4NH_2$.

Derivatives of 2-acylaminochromones[117] show a stimulating action but display high toxicity.



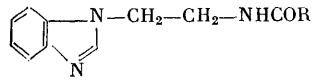
$R = OC_2H_5$, $R^1 = H$; $R = CHCl_2$, $R^1 = H$; $R = CCl_3$, $R^1 = H$; $R = C_6H_5$, $R^1 = H$; $R = OC_2H_5$, $R^1 = Cl$.

Aminoamides of β-phenylisobutyric acid have been synthesised in the search for new neurotropic agents.[118] In physiological action they proved to be antagonists of amphetamine and significantly potentiated the hypnotic effect caused by chloral hydrate and sodium amobarbital. The duration of amobarbital hypnosis was increased along the series $CH_3 \rightarrow C_2H_5 \rightarrow n\text{-}C_3H_7$.

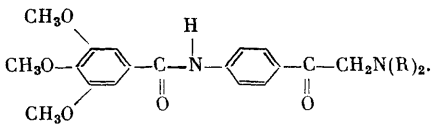


$R = CH_3$; C_2H_5; $n\text{-}C_3H_7$.

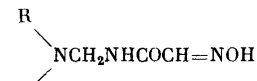
Several acyl derivatives of 1-(2-aminoethyl)benzimidazoles possess weak sedative and antiserotonin activity.[119]



The α-amino derivatives of 4-(3,4,5-trimethoxybenzoylamino)-acetophenone are stimulants and depressants of the central nervous system.[120]

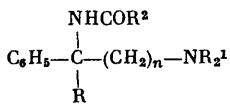


Amides of oximinoacetic acid are active reactivators of cholinesterase.[121] In many cases they are more active than their methiodides.



$R = R^1 = CH_3$; $R = R^1 = H$; $R = H$; $R^1 = CH_3$; $R = R^1 = C_2H_5$; $RR^1N = (CH_2)_4N$; $(CH_2)_5N$.

Introduction of a second quaternary ammonium group strengthens the reactivating properties to cholinesterase. Amides are more stable than esters in aqueous media and show a therapeutic action on contamination of animals by organophosphorus compounds (fosfakol). Compounds with a tertiary amino group are capable of penetrating the blood-brain barrier and show a pharmacological action on the central nervous system. In addition certain aliphatic-aromatic aminoamides display anticholinesterase properties.

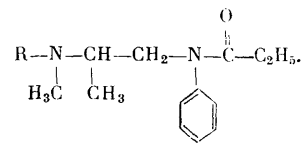


$R = H$, C_2H_5; $R^1 = CH_3$, C_2H_5, C_3H_7, C_4H_9; $R^2 = CH_3$, $CH_2C_6H_5$, C_6H_5; $n = 1$ to 8.

It was shown[122] that these compounds are reversible inhibitors of cholinesterase and their activity depends to a significant extent on the bifunctionality, the character of the amide and amine groups, the branching of the main chain and the distance between the functional groups.

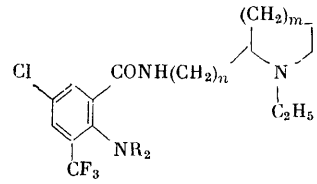
Analgesic activity became apparent when investigating a series of amides of benzilic, diarylglycollic and substituted benzoic acids. It was established that the anaesthetising action depends on the character of the radicals on the tertiary nitrogen atom and on the number of methylene groups between the nitrogen atoms. Enhancement occurs on introducing a methyl group into the amide.[123]

The analgesic activity of compounds (IX) depends on their configuration.[124] It was shown that the (+) (*S*)-isomer was more active than the (–) (*R*)- and (±)-isomers. This indicates that analgesics of the methadone type vary in the form of their bonding with receptors.



(IX)

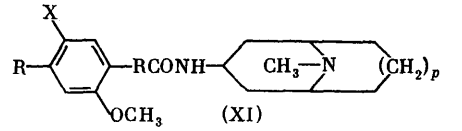
Antitubercular[125] and antibacterial[126] properties have also been described for some aminoamides. Some compounds of this class of chemical susbtances are applied in stomatological practice for the prevention of deposits on teeth.[7] There are several reports on the use of aminoamides as preparations with a wide spectrum of biological action. Thus benzamides (X) are used as antiemetic and antiulcer preparations and also as anticonvulsants and neuroleptics.[127]



(X)

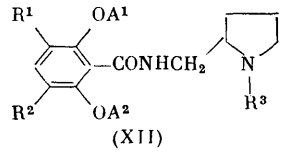
$n = 1.2$; $m = 1.2$.

It has been pointed out that azabicycloalkylbenzamides (XI) may find use in the treatment of arrhythmia, migraine, neuralgia, disturbances of bowel motility, and as antiemetic agents.[128]



$R = NH_2$, acylamino; X = Cl, Br, alkylthio; $p = 0-1$.

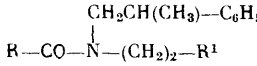
Benzamides (XII) possess psychotropic action and may be considered as potential drugs for psychiatric practice and also as antiemetic agents.[129,130]



(XII)

R^1, $R^- = H$, halogen; $R^3 = A^1 =$ lower alkyl; $A^2 = (C_1-C_6)$ acyl.

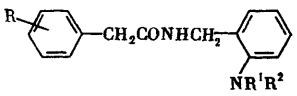
Compounds (XIII) proved to be depressants and analeptics.



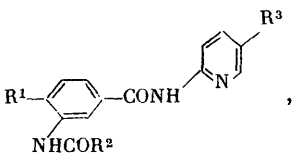
(XIII)

R = CH_3, *p*- and *o*-$CH_3OC_6H_4$; 3,4,5-$(CH_3O)_3C_6H_3$; R^1 = 2- or 4-pyridyl, 2- or 4-alkylated 2-pyridyl.

Diaklylaminoethylanilides[131] synthesised in the search for antihypertensive preparations proved to be active in the treatment of arrhythmia, migraine, hypertonia and glaucoma. Monoalkylated amides of phenylacetic acid[131,132] reduce blood sugar content and may find use in the treatment of diabetes.

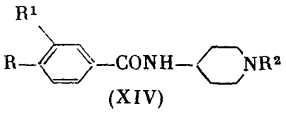


Aminoamides containing a pyridine ring may find use in stomatology.[133]



where R^1 = H, CH_3, OCH_3; R^2 = branched or unbranched C_2-C_8 alkyl, substituted or unsubstituted phenyl; R^3 = H, C_1-C_4 alkyl in various positions.

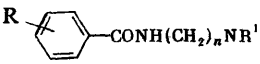
Benzamidopiperidines (XIV) display local anaesthetic and analgesic activity, they are used as antiemetic preparations, tranquilisers, and also in the treatment of diseases of the gastrointestinal tract.[6]



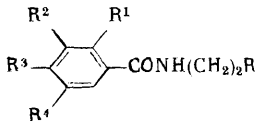
(XIV)

R = H, OCH_3, $NHCOCF_3$, $NHCOCH_2Cl$, R^1 = Cl, H, SO_2NH_2, CH_3SO_2NH, OCH_3; R^2 = H, *p*-$FC_6H_4CO(CH_2)_3$, CH_2CH_3.

Substituted anthranilamides are used as analgesics, antiulcer and antiinflammatory agents.[134]



N-Substituted benzamide derivatives (XV) possess a combination of analgesic, spasmolytic and antiemetic activity.[135]



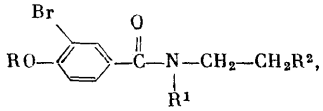
(XV)

R = $N(C_2H_5)_2$, $R^3 = NO_2$, $R^1 = R^2 = R^4 = H$; R = $N(C_2H_5)_2$, R^1 = Cl, $R^2 = R^3 = R^4 = H$; R = $N(C_2H_5)_2$, $R^1 = R^4 = H$, $R^2 = R^3 = CH_3O$; R = NC_5H_{10}, $R^1 = R^2 = R^4 = H$, $R^3 = NO_2$.

The local anaesthetic activity of aminoamides has been studied widely.[136–139] Amides of heterocyclic acids have been studied in most detail,[140,141] to which group the known anaesthetic Sovcaine (dibucaine, cinchocaine) belongs. The activity of these compounds as a rule is increased on introducing a bulky alkyl group into the aminoamide molecule.[141] It is necessary to record that amides of 3-alkoxycinchoninic acid, unlike 2-alkoxy derivatives, do not display anaesthetic activity,[140] which probably indicates the influence of the geometry of the molecule on the physiological properties of the amides.

Alkyl and alkoxy groups aid the development of the pharmacological activity indicated not only in the series of Sovcaine analogues but also among amides of substituted benzoic acids previously considered to have little promise for practical application as drugs.[141] However di- and trimethylbenzamides proved to be effective.[142] The anaesthetic activity of *o*-alkoxy-, especially *o*-butoxy-,[138–143] and also *o*-benzoyloxybenzamides[144] is close to the activity of xylocaine. Compounds containing substituents in the *para*-position are usually less active but some of them are used in medicine because of their low toxicity.[145]

The use of aminoamides with a tertiary nitrogen atom in the amide group (XVI) has been described.[146,147]



(XVI)

R = CH_3, R^1 = H, $R^2 = N(C_2H_5)_2$; R = CH_3, $R^1 = CH_3$, $R^2 = N(C_2H_5)_2$;

R = CH_3, R^1 = H, $R^2 = NC_6H_{10}$, R = CH_3, $R^1 = CH_3$, $R^2 = NC_5H_{10}$;

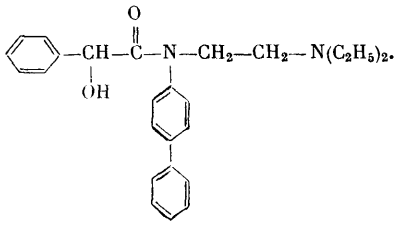
R = C_2H_5, R^1 = H, $R^2 = NC_4H_8O$;

R = C_2H_5, R^1 = iso-C_3H_7, $R^2 = NC_4H_8O$.

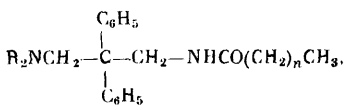
It was established that such compounds display enhanced pharmacological activity compared with compounds with a secondary nitrogen atom. In particular an increase in local anaesthetic and analgesic action was observed for aminoamides with an alkylated nitrogen atom in the amide group (XVI) (R^1 = CH_3, iso-C_3H_7) in comparison with compounds (XVI) (R^1 = H), in which the nitrogen atom is secondary.[146]

This tendency was more marked in aminoamides with *p*-butyloxy- and *p*-amyloxy- than with *p*-methoxy- and *p*-ethoxy-substituents in the phenyl ring. However the toxicity of compounds was not reduced by this.[146]

Arylation of the amide group also increases anaesthetic activity. It is asserted that the following compound is a strong anaesthetic.[147]

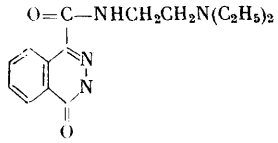


The local anaesthetic activity of γ-dimethylaminodiphenylpropylamides of acetic, propionic and butyric acids has been described.[148]

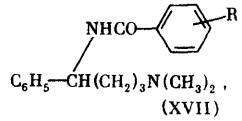


n = 0, 1, 2.

Aminoamides of 4-phthalazone-1-carboxylic acid possess high local anaesthetic activity at low toxicity.[149]



Dimethylaminobutylamides of substituted benzoic acids (XVII) proved to be extremely effective.[150]

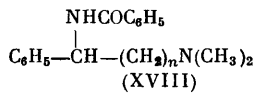


(XVII)

R = H, *p*-CH_3, *m*-NO_2, *p*-Cl, *p*-NH_2.

It was established that the local anaesthetic action of amides depends on the character of the substituent in the benzene ring. Compounds with R = *p*-CH_3 and *m*-NO_2 proved to be most effective and long-acting substances with low toxicity.

An important factor influencing the local anaesthetic activity of aminoamides is the distance between the amide and amino groups. The influence of the number of methylene groups between the nitrogen atoms on conduction, infiltration and terminal anaesthesia of benzamides (XVIII) has been investigated.[151]

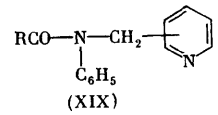


(XVIII)

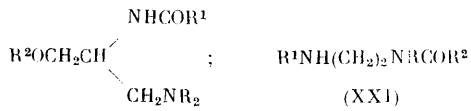
$n = 1$—6.

It was shown that there were maxima of local anaesthetic activity at n = 3, 4 and 6.

Among other active aminoamides it is possible to mention 4-alkoxyphthalimides,[152] 3,3-diphenylacrylamides,[153] amides (XIX),[154] (XX)[155] and *N*,*N*-disubstituted monoacylated ethylenediamines (XXI).[156]

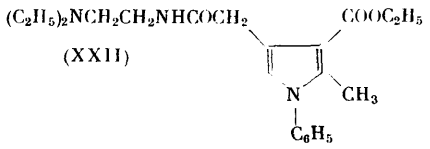


(XIX)



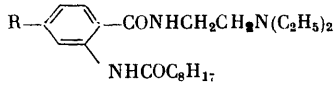
(XX) (XXI)

Preparation (XXII) is of interest, containing in its structure an aminoamide and an aminoacid ester, causing rapid, stable and extended anaesthesia.[157]



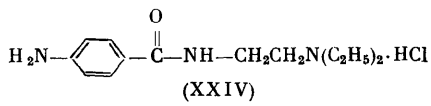
(XXII)

Diamide (XXIII) exceeds novocaine in local anaesthetic activity 200-fold.[158]



(XXIII)

Among other biologically active aminoamides it is possible to mention novocainamid (XXIV) (the β-diethylaminoethylamide of *p*-aminobenzoic acid).[112] It is close to novocaine in chemical structure. Novocainamid also has a similarity to novocaine in pharmacological properties and displays local anaesthetic activity.

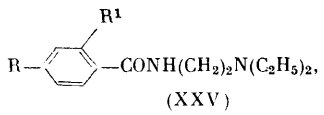


(XXIV)

However the most distinctive feature of (XXIV) is its ability to reduce the excitability of the myocardium and to retard the transmission of a nervous impulse in heart muscle and also to suppress the formation of impulses in ectopic foci of excitation. It is significantly more active than novocaine in this respect. The increased stability of novocainamid *in vivo* is explained by its slow breakdown to novocaine by blood plasma enzymes. It is also less toxic than novocaine. Novocainamid is used in various disorders of cardiac rhythm, viz. the paroxysmal form of ciliary arrhythmia, paroxysmal tachycardia, extrasystolia and other forms of rhythm disturbance. It is used for the prevention and treatment of disorders of cardiac rhythm in operations on the heart, large vessels and lungs.[112]

The (XXIV) molecule has been modified with the aim of increasing activity and reducing toxicity. All parts of the molecule have been changed, viz. the aromatic ring and its substituents, the length and branching of the hydrocarbon chain and the substituents on the nitrogen atom.

Replacement of the amino group in novocainamide (XXIV) by chlorine or an ethoxy group leads to loss of antiarrhythmic activity.



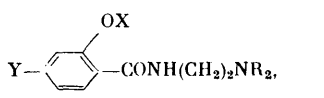
(XXV)

R = NH_2, OC_2H_5, Cl, $NHCOCH_3$; R^1 = Cl, H

Compounds (XXV) (R = NH_2, OC_2H_5, R^1 = Cl) possess an antiemetic action but the *ortho*-chloro derivative (XXV) (R = NH_2, R^1 = Cl) is active,[26,159] and also displays local anaesthetic activity more than 4 times greater than the activity of novocainamid (XXIV).[27] *N*-Acylated novocainamid (XXV) (R = $NHCOCH_3$, R^1 = H) is an active metabolite of novocainamid[160] and interrupts arrhythmia caused by aconitine.

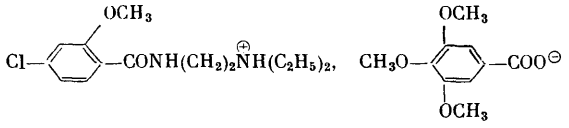
On replacing the NH group in the (XXIV) molecule by a nitro or hydroxy group the antiarrhythmic activity is reduced.[28] The introduction of a methoxy group into the phenyl ring significantly increases the antiarrhythmic effect. 3,4,5-Trimethoxy-*N*-(2-diethylaminoethyl)benzamide is 4 times more active than novocainamid.[29]

Derivatives of salicylamide are active antiarrhythmics.

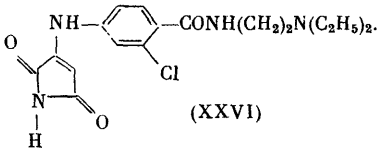


X = H, alkyl; Y = H, Cl, Br; R = alkyl.

The most active of these compounds is the 3,4,5-trimethoxybenzoate salt of 4-chloro-2-methoxy-*N*-(2-diethylaminoethyl)benzamide.[161]

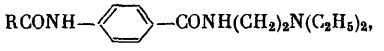


Compound (XXVI), in which nitrogen is alkylated by substitution with a dehydropyrrolidinedione, is also more active than novocainamid.[162]



(XXVI)

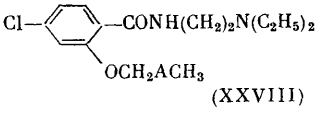
Several derivatives (XXVII) were obtained by acylation at nitrogen. Of this series the acyl derivative with R = CH_2CH_3 shows the greatest activity in calcium chloride arrhythmia.[163]



(XXVII)

R = $ClCH_2$, Cl_2CH, CH_2CH_3, $C(CH_3)_3$, $CH(CH_3)_2$, $CH_2CH_2CH_3$.

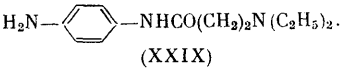
Novocainamid derivatives (XXVIII) are used for stopping vomiting caused by chemotherapeutic preparations.[164]



(XXVIII)

A = CHOH, C = NOH, C = $NOCH_3$.

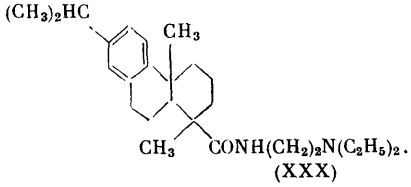
ortho-Methylation significantly increases antiarrhythmic activity.[165] Inversion of the amide group (XXIX) leads to loss of activity.[165]



(XXIX)

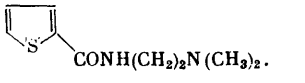
Replacement of the phenyl ring in the novocainamid molecule leads to the preparation of new compounds with various biological activities.

Compound (XXX) displays activity in strophanthin arrhythmia.[166]



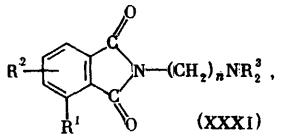
(XXX)

The thiophen analogue of novocainamide shows analgesic and spasmolytic activity.[25]



Analogues of novocainamid are known in which the benzene ring is replaced by another aromatic ring, such as quinoline.[167]

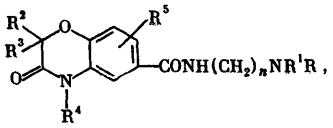
Phthalimides (XXXI) also display antiarrhythmic activity.[168,169] The most active is the compound with $n = 4$, $R^3 = C_2H_5$.



(XXXI)

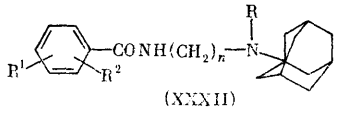
R^1 = H, *o*-alkyl; R^2 = *o*-, *p*-, *m*-NHR^4.

Amides of 1,4-benzoxazinecarboxylic acid, which are novocainamid derivatives, display marked antiarrhythmic properties.[170]



where NRR^1 = piperidino, morpholino, 4-*m*-tolyl-1-piperazine.

N-(Adamantylaminoalkyl)benzamides (XXXII) prevent ventricular fibrillation caused by chloroform.[30] They are less toxic than procainamide.

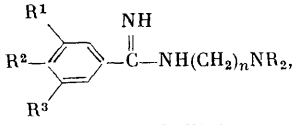


(XXXII)

R = H, C_2H_5; $n = 2, 3$; R^1 = H, Cl, CH_3; R^2 = NH_2, NO_2.

Compound (XXXII) (R = C_2H_5, R^1 = H, R^2 = *p*-NH_2, n = 2) proved to be the most active. The influence of the surroundings of the tertiary nitrogen atom on the antiarrhythmic activity of compounds has also been investigated.[171] Replacement of ethyl groups by another radical (isopropyl) significantly reduces activity, while replacement of one ethyl by an aromatic group significantly increases it.

Compounds (XXXIII) contain a benzimido group.

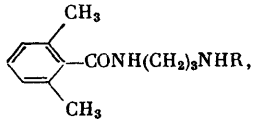


(XXXIII)

n = 2, 4; R = CH_3, C_2H_5 or NR_2 = 2-pyrrolidine; R^1 = H, CF_3, OCH_3; R^2 = H, CH_3, F, NO_2, NH_2, R^3 = H, OCH_3.

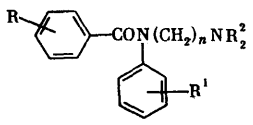
Of 28 *N*-substituted benzimidines synthesised 15 possess antirrhythmic activity, 4 compounds surpass novocainamid in activity and duration of action, display low toxicity and a weak cardiodepressant action.[172–174]

Aminoalkylpropylamides of 2,6-dimethylbenzoic acid interrupt tachycardia in dogs.[175]



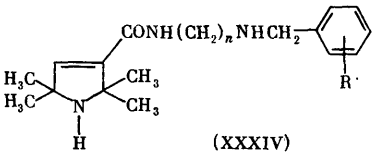
R = C_2H_5, $CH(CH_3)_2$, C_6H_5—CH—$(CH_3)CH_2$.

Benzamides substituted at nitrogen display antiarrhythmic activity.[176]



$n = 2, 3$; R = 3, 4, 5(OCH_3)$_3$, 2, 4,-(OCH_3)$_2$, 2-Cl;
R^1 = H, 2(4)-CH_3, 2(4)-C_2H_5;
NR_2^2 = morpholino, pyrrolidino, piperidino.

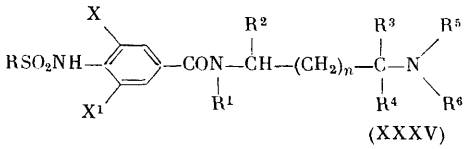
The antiarrhythmic activity of amides of tetramethylpyrrolidinecarboxylic acid (XXXIV) has been described.[177]



(XXXIV)

m = 2, 3; R = H, 4-Cl, 4-CF_3, 2-OCH_3, 2-OH, 4-OC_6H_5, 4-$OCH_2C_6H_5$ etc.

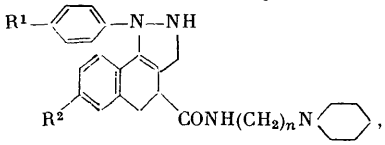
Some of them surpass quinidine in therapeutic index (aconitine arrhythmia model). Aminoamide (XXXIV) (n = 3 and R = $OCH_2CH{=}CH_2$) is 6.3 times more active than quinidine.[177] Substituted sulphonamidobenzamides (XXXV) display antiarrhythmic activity similar to that of novocainamid.[178,179]



(XXXV)

where X and X^1 = H, halogen; R^1, R^2, R^3, R^4 = alkyl, cycloalkyl, alkenyl; R = alkyl, cycloalkyl, benzyl, alkoxyl. Derivatives of (XXXV) containing a methanesulphonylamino group showed antiarrhythmic action of the cordarone type (class III antiarrhythmic preparations).[180] There is an indication of an increase in the duration of action of preparations (XXXV) in comparison with compounds containing an RSO_2 group (prolongation effect).[178]

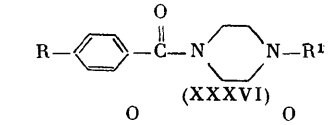
Aminoamides of 4,5-dihydrobenz[d]indazole-3-carboxylic acids are able to retard the ventricular tachycardia induced by aconitine.



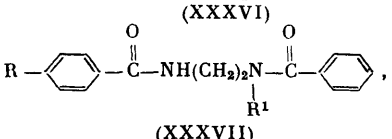
R^1 = H, CH_3O, F, Cl; R^2 = H, Cl, $(CH_3)_2N$, CH_3O; n = 2, 3.

A large group of aminoamides comprises compounds in which the tertiary nitrogen atom is linked with the amide function through a cyclic system.

Cyclic analogues of novocainamid (XXXVI) and diacyl derivatives of ethylenediamine (XXXVII) have been investigated.[181]



(XXXVI)

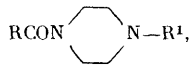


(XXXVII)

R = H, NH_2, NO_2, Cl, OCH_3; R^1 = C_2-C_5 alkyl.

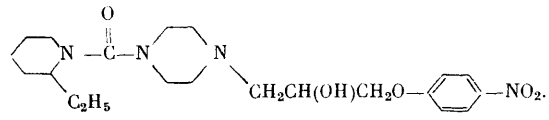
Replacement of the tertiary amino group in the novocainamid molecule by an amido group (XXXVII) leads to loss of antiarrhythmic action as does replacement of the amide and amino nitrogens by piperazine (XXXVI) R = NH_2, R^1 = C_2H_5. Derivatives (XXXVII) with R ≠ NO_2 display depressant activity. The action, like that of novocainamid, is displayed by compounds containing a chlorine atom (XXXVI) R = Cl.

Certain derivatives of piperazine display activity against the arrhythmia induced by adrenaline.[182]

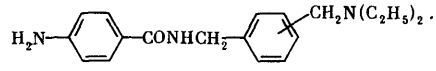


where R = 2-piperidinoethyl, $(C_6H_5)_2N$, 3,4,5-$(CH_3O)_3C_6H_2$. R^1 = phenoxy, piperidino, naphthoxy, 4-CH_3-piperidino, 2-hydroxypropyl, 3,4,5-$(CH_3O)_3C_6H_2CO$.

The most active compound is

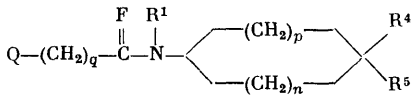


Cyclic analogues of novocainamid (XXXVIII) proved to be weakly active as antiarrhythmics, however *meta*- and *para*-derivatives are 45 and 37 times more active than novocainamid in local anaesthetic action.[183]



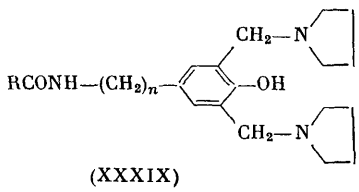
(XXXVIII)

Aminoamides containing saturated rings joining the amide and amino nitrogen atoms in the hydrocarbon chain may be potential antiarrhythmics.[184]



q = 0–4, p = n = (0–9); Q = 1-, 2-naphthyl, C_6H_3XY; R^1 = H, (C_1-C_3) alkyl; R^2 = H, (C_1-C_3) alkyl, branched alkyl; R^3 = alkyl, cycloalkyl; R^4 = H, OH, OCH_3, OC_2H_5, SH; R^5 = H, OH, (C_1-C_3) alkoxy; E = O or S; X = Y = halogen, C≡N, C_6H_5.

Substituted phenols (XXXIX) disclose antiarrhythmic activity and show action on the parasympathetic nervous system.[185]

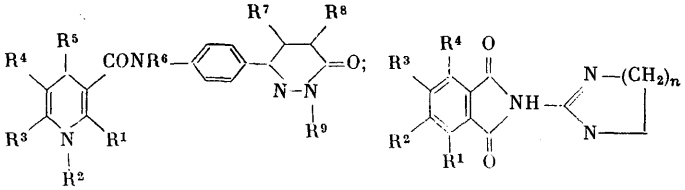


(XXXIX)

R = substituted phenyl or thienyl; n = 0 or 1.

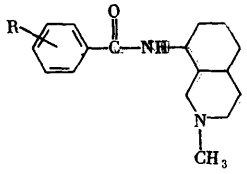
A correlation between antiarrhythmic activity and action on the nervous system was observed for this class of compounds.

Substituted amides of dihydropyridinecarboxylic acids (XL)[186] and phthalimides (XLI)[187] show antiarrhythmic activity in animal experiments.



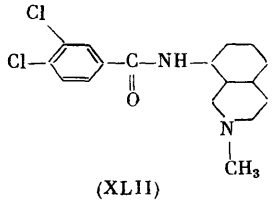
(XL) (XLI)

Certain derivatives of 5-, 6-, and 8-substituted 2-methyldecahydroquinolines surpass quinidine in anti-arrhythmic activity and therapeutic index.[188,189,167]



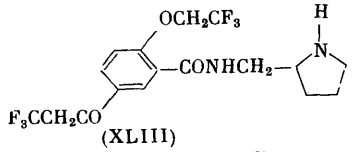
R=H, 4-Cl, 3,4-Cl_2, 4-OCH_3, 3,4-$(OCH_3)_2$, 3,4,6-$(OCH_3)_3$.

The most active compound is *cis*-(XLII), which is more than 2 times as active as quinidine, *trans*-(XLII) surpassed quinidine by almost 4 times in therapeutic index.

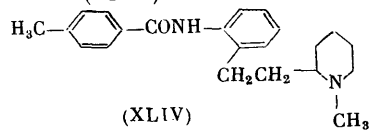


(XLII)

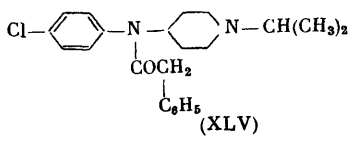
Study of cyclic analogues of novocainamid led to the design of new drugs for the treatment of disturbances of cardiac rhythm, viz. flecainide (XLIII),[190] encainide (XLIV) and lorcainide (XLV).[191]



(XLIII)

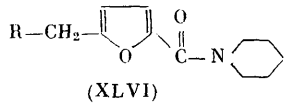


(XLIV)



(XLV)

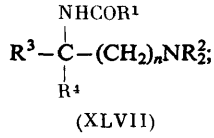
Antiarrhythmic activity is possessed by preparations from the *N*-aryl-8-pyrrolidizinalkanamide[192] and 2-ethoxycarbonylaminophenothiazine[193] series. The synthesis of aminoamides of the furanoic acid series (XLVI) has been reported.[194] Investigations of coronary vasodilator activity showed that the citrates and hydrochlorides of these compounds increase the rate of coronary blood flow by 87–120%.[194]



(XLVI)

R = NC_5H_{10}, HN— etc.

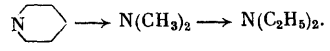
Quite recently a communication[195] appeared on the synthesis and study of the antiarrhythmic and anaesthetic activity of aliphatic-aromatic aminoamide (XLVII) which are analogues of novocainamid with secondary and tertiary carbon atoms on the amide group and various lengths of carbon chain.



(XLVII)

R^1 = H, CH_3, $CH=CH_2$, C_6H_5, $CH_2C_6H_5$, $CH_2OC_6H_5$, RC_6H_4; cycloalkyl, adamantyl; NR^2_2 = $N(CH_3)_2$, $N(C_2H_5)_2$, piperidino, morpholine, $N(C_3H_7)_2$, $N(C_4H_9)_2$, R^3 = alkyl, C_6H_5, $C_6H_4R^5$; R^4 = H, alkyl; n = 1 to 8.

It was shown that removal of the amino or amide group led to loss of activity. Local anaesthetic and antiarrhythmic effects depend on the character of the amino group (NR^2_2) group and fell in the series



Maximum activity was detected for amides of substituted benzoic, adamantanecarboxylic and cyclohexanecarboxylic acids, and minimum for amides of acetic acid. Amides of phenylacetic and phenoxyacetic acids occupy an intermediate position. The introduction of substituents into the benzene ring (R) leads in the general case to a reduction in antiarrhythmic action and toxicity, but local anaesthetic activity depends on the nature of this susbtituent. Donor substituents reduce the activity and acceptor substituents enhance it, halogens increase the local anaesthetic action.

Substitution in the benzene ring of the main chain (R^5) leads to an increase in antiarrhythmic and local anaesthetic action along the series H→CH_3→Br→Cl. The determining influence on the pharmacological action of aminoamides (XLVII) proved to be multiple. All forms of activity have several maxima at various values of *n*.

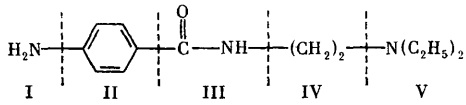
It follows from the data presented that aminoamides differing in chemical structure to a significant degree display antiarrhythmic activity.

Modification of the novocainamid molecule, as the first antiarrhythmic of the monoacylated diamine type of aminoamide, led to the design of a large number of compounds, among which are substances displaying high antiarrhythmic activity.

The multiplicity of chemical structures and the differences in methods of determining antiarrhythmic activity do not permit an unequivocal analysis of the influence of structure on activity. Quantitative data on activity and toxicity are frequently absent.

However it is possible to draw certain conclusions on the dependence of antiarrhythmic activity on the chemical structure of compounds.

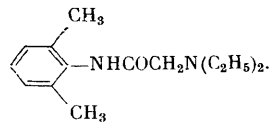
It is possible to divide the novocainamid into five portions which are subject to modification.



I. Acylation of the NH_2 group by fatty acid derivatives leads to an increase in antiarrhythmic activity.[28,160,163] Alkylation also enhances it.[162] Sulphonation of the amino group prolongs the antiarrhythmic action of a preparation.[178] Replacment of the NH_2 group by chlorine or by an ethoxy group leads to loss of antiarrhythmic action.

II. Introduction of various substituents into the *ortho*-position of the benzene ring (Cl, *O*-alkyl, alkyl) increases activity.[27,161,165] The introduction of methoxy groups into the benzene ring increases activity significantly. However in a series of quinoline analogues of novocainamid chlorine substituted derivatives were more active than methoxy compounds.[167,180–189] Replacement of the benzene ring by non-benzenoid systems does not make a significant contribution to antiarrhythmic properties, although *ortho* substitution frequently leads to an increase of activity.[25,166,169,170,177]

III. Inversion of the amide group transforms monoacylated diamines into the aminoacid series. Simple inversion in the novocainamid molecule leads as a rule to a reduction in anti-arrhythmic effect.[165] However the known effective anti-arrhythmic lidocaine (XLVIII) is dimethylaminoacetylxylidine and a large number of its derivatives display antiarrhythmic activity.[3,167]



(XLVIII)

Replacement of the amide group by imido and sulphonamide groups leads to the appearance of new classes of potential anti-arrhythmics.[172–174,184] Arylation of the amide nitrogen in the novocainamid molecule also shows a positive influence on the antiarrhythmic properties of compounds.[176]

IV. An increase in the hydrocarbon chain leads to an increase in the activity of substances,[168,169] although several maxima in activity were observed at various chain lengths.[195] Antiarrhythmic action of compounds increases by several orders of magnitude in comparison with that of novocainamid. The introduction of alkyl[178,179] and aryl radicals[195] into the hydrocarbon chain has a positive influence on activity. Inclusion of nitrogen atoms in one saturated ring leads to loss of antiarrhythmic activity.[181] The inclusion of saturated rings in the hydrocarbon chain between the amino and amide groups may prove to be promising.[184,187–191]

V. The presence of an amino group in the amide molecule is very important for antiarrhythmic activity.[195] It may be secondary in character.[175,177,190] However the majority of the antiarrhythmics of the monoacylated diamine series contain a tertiary amino group in the form of a dialkylamino group, alkylarylamino groups or saturated cyclic amines. In several cases it was shown that cyclic saturated amines increase antiarrhythmic action,[119] replacement of one of the alkyl groups by an aromatic group is also useful.[171]

At the present time there is no conclusive hypothesis on the link between the structure of chemical compounds and their biological activity. It is evident that every change in the conformation of a molecule is accompanied by changes in physiochemical properties and influences its ability to be absorbed, to pass through a membrane to interact with cellular enzymes and receptors.

It has been reported[167,188,189] that among aminoamide derivatives of quinoline which are antiarrhythmically active the *trans*-isomer is as a rule more active.

There are data on the resolution of racemic aminoamides into optical antipodes.[124,184,195,196] Results of pharmacological testing show that the (+) (*S*)-isomer of propionic acid dialkylamino-ethylamide was more active in analgesic activity than the (–) (*R*)- and (±)-isomers.[124]

The preparation flecainide shows approximately the same antiarrhythmic activity for both enantiomers and the racemate.[196] A higher antiarrhythmic and local anaesthetic activity was noted for the (+) (*R*)-isomer than for the (–) (*S*)- and (±)-isomers in a series of dialkylaminopentylamides.[195] The enantiomers also differed in toxicity.

Conclusions have been drawn on the influence of basicity[190] and lipophilicity[197] on the antiarrhythmic properties of aminoamides. The more basic and the better soluble in lipids a substance is then the higher the antiarrhythmic activity it displays.

- - - o0o - - -

Several publications on the synthesis,[199,200] biological action[200] and study of the interconnection of structure and biological activity[201] of aminoamides have appeared since the manuscript was prepared for printing.

In spite of the large number of publications devoted to the search for promising antiarrhythmics and of the significant quantity of antiarrhythmic preparations used in therapy, the search for new active compounds is as pressing as ever.[3] There is a need for long-acting drugs with low toxicity. There is a requirement for preparations to treat post-infarct disturbances. One of the most rational approaches in the search for promising new compounds is the investigation of the dependence of activity on structure in chemical series among representatives of which active anti-arrhythmics have been detected.[198]

The available data on practically useful properties of *N*-substituted aminoamides and the interesting chemical and physicochemical properties discovered separate them into a discrete class of organic compounds which is of interest not only for chemistry but also for other regions of science and technology.

References

1. E N Zil'berman *Usp. Khim.*, 1960, **29**(6) 716 [English translation in *Russ. Chem. Rev.*, 1960(6)]
2. M A Dumnis, N I Kudryashova *Khim. Farm. Zh.*, 1983, **17** 1159
3. L N Yakhontov, S S Liberman *Khim. Farm. Zh.*, 1985, **19** 1306
4. BRD P. 2 523 633; *Chem. Abs.*, 1977, **86** 90998j
5. British P. 1 438 418; *Chem. Abs.*, 1976, **85** 193573a
6. BRD P. 251 136; *Chem. Abs.*, 1976, **84** 30908d
7. US P. 4 093 711; *Chem. Abs.*, 1978, **89** 157616r

8. US P. 4 168 278; *Chem. Abs.*, 1979, **90** 926783
9. P A Petyunin, G P Petyunin *Khim. Farm. Zh.*, 1968, **2** 16
10. I A Shaps, N A Mukhina, T V Mikhailova, et al. *Khim. Farm. Zh.*, 1968, **2** 21
11. US P. 3 374 244; *Chem. Abs.*, 1968, **69** 35575t
12. British P. 1 382 773; *Chem. Abs.*, 1975, **83** 58829g
13. Belgian P. 615 478; *Chem. Abs.*, 1963, **59** 7496h
14. V S Shklyaev, V I Pantsurkin *Zh. Org. Khim.*, 1967, **3** 1828
15. I N Somin, S G Kuznetsov *Khim. Farm. Zh.*, 1968, **2** 39
16. H J Chang, O Vogl *J. Polym. Sci.*, 1977, **15** 311
17. Czechoslovakian P. 186 612; *Chem. Abs.*, 1981, **95** 133907j
18. H E Zaugg, B W Horromb *J. Am. Chem. Soc.*, 1953, **75** 292
19. J Tani, T. Oine, I Inoue *Synthesis*, 1975, **2** 714
20. Japanese P. 7 584 510; *Chem. Abs.*, 1975, **83** 178603a
21. T Kurihara, K Sagawa, H Takeda *Tonoku Jakka. Daigaku Kenkyu Petro.*, 1968, (15) 49
22. US P. 4 039 565; *Chem. Abs.*, 1977, **87** 153366v
23. L Ledochowski, M Bogucka, A Lodochowski *Przem. Chem.*, 1959, **38** 91
24. Authors Certificate 1 160 932 USSR; *Byull. Izobret.*, 1985, (21); *Chem. Abs.*, 1982, **97** 72372v
25. T Kametani, T Katagi, T Fujiwara *Japan. J. Pharm.*, 1954, **26** 544
26. F Besanson *J. Physiol.*, 1958, **50** 979
27. D B Reisher, M G Cordasco *J. Org. Chem.*, 1958, **23** 1403
28. D E Drayer, B H Slaver, M M Reidenberg *J. Med. Chem.*, 1977, **20** 270
29. Y-Sun Liu, Zhou-Shan, Gu Ke-Jia *Yao H. Suchbao.*, 1981, **16** 158
30. V L Narayanan, F J Sweeny *J. Med. Chem.*, 1972, **15** 443
31. Kh G Radushkevich *Materialy po Obmenu Perevodym Opytom, Khim. Farm. Prom.*, 1958, (1) 22
32. Japanese P. 15 925; *Chem. Abs.*, 1968, **68** 39331
33. South African P. 6 7 01 820; *Chem. Abs.*, 1969, **70** 77623h
34. L N Yakhontov, R G Glushkov *Sinteticheskie Lekarstvennye Sredstva* (Synthetic Drugs), Meditsina, Moscow, 1983
35. M V Rubtsov, A G Baichikov *Sinteticheskie Khimiko-farmatsevticheskie Preparaty* (Synthetic Pharmaceuticals), Meditsina, Moscow, 1971
36. S B Bogoslovskii *Reaktsii i Metody Issledovaniya Organicheskikh Soedinenii Sb. Z.* (Reactions and Methods of Investigating Organic Compounds. Collective Vol.), Goskhimizdat, 1954
37. F S Crossley, M L Moore *J. Org. Chem.*, 1944, **9** 529
38. Europ. P. 155 888; *Chem. Abs.*, 1985, **104** 68759a
39. US P. 2 793 212; *Chem. Abs.*, 1957, **51** 16563e
40. G Vita, G Bucher *Chem. Ber.*, 1966, **99** 3387
41. US P 3 055 906; *Chem. Abs.*, 1963, **58** 6808a
42. W I Weaver, J K Simons, W E Baldwin *J. Am. Chem. Soc.*, 1944, **66** 222
43. P G Krist'yanson, A O Suurnere, K Yu Siimer *Tr. Tallin. Politekhn. In-ta*, 1975, (390) 89
44. M Wieland, E Dorner *Ber., 1930*, **63** 404
45. J J Ritter, P P Mineri *J. Am. Chem. Soc.*, 1948, **70** 4045
46. J J Ritter, J Kalish *J. Am. Chem. Soc.*, 1948, **70** 4048
47. Authors Certificate 466 231 USSR; *Byull. Izobret.*, 1975, (13)
48. K Shishido, C Ishida *Juki Gosei, Kagaku Kyokai Shi.*, 1967, **25** 298
49. J J Ritter *J. Am. Chem. Soc.*, 1948, **70** 4253
50. T Clarke, J Devine, D K Dicher *J. Am. Oil. Chem. Soc.*, 1964, **41** 78
51. J Well, R G Goekel, E R Talp *Am. Chem. Soc. Div. Petrol. Chem. Preprints*, 1963, **8** 95
52. US P. 3 161 679; *Chem. Abs.*, 1965, **62** 9020
53. S Tanimoto, M Kimura, M Okano *J. Synth. Org. Chem. Japan.*, 1970, **28** 1035
54. E T Roe, D Swern *J. Am. Chem. Soc.*, 1955, **77** 5408
55. J Somers *Br. Rayon. Silk J.*, 1953, **30** 52
56. US P. 2 573 673; *Chem. Abs.*, 1952, **46** 9548i
57. M Anaor, A Zilkha *Eur. Polym. J.*, 1969, **5** 21
58. US P. 2 628 217; *Chem. Abs.*, 1953, **47** 5129g
59. P M Greaves, P D Landor, S R Landor, O Odyek *Tetrahedron Lett.*, 1973, **3** 209
60. J R Norell *J. Org. Chem.*, 1970, **35** 1611
61. T C Lee Lester, E M Pearce *J. Polym. Sci.*, 1971, **9** 557
62. E Ya Borisova, S Ya Skachilova, N I Zheltukhin, et al. *Tez. V Mosk. Konf. po Organ. Khimii i Technologii* (Abstracts of the Vth Moscow Conference on Organic Chemistry and Technology), Moscow, 1989, 242
63. J C Richer, R Bisson *Can. J. Chem.*, 1969, **47** 2488
64. J Anatol, A Medete *C. R. Seances Acad. Sci., C*, 1971, **272** 1157
65. J N Gardner *Can. J. Chem.*, 1973, **51** 1416
66. US P. 2 457 660; *Chem. Abs.*, 1949, **43** 3028g
67. G Glikmans, B Torch, M Mellin *Bull. Soc. Chim. Fr.*, 1966, 31
68. US P. 2 778 835; *Chem. Abs.*, 1958, **52** 129306
69. B Prasnar *Chem. Anal. (Warsaw)*, 1963, **8** 255
70. V A Zagorevskii, K I Lopatina *Zh. Obshch. Khim.*, 1963, **33** 2525
71. E M Cherkasova, E Ya Borisova *Dokl. Akad. Nauk SSSR*, 1967, **172** 1350
72. E Ya Borisova, M G Zaitseva, I A Rubtsov, et al. *Zh. Org. Khim.*, 1969, **5** 1056
73. E Ya Borisova, V T Lobodina, M G Zaitseva, et al. *Zh. Org. Khim.*, 1969, **5** 284
74. E Ya Borisova, L A Lukashova, R V Kolenkova, et al. *Zh. Vses. Khim. D I Mendeleeva*, 1974, (4) 225
75. E Ya Borisova, I A Rubtsov, L A Botova, et al. *Izv. Vuzov Ser. Khim. Khim. Tekhnol.*, 1977, **20** 366
76. E Ya Borisova, E M Cherkasova, E I Bulgakova *Zh. Org. Khim.*, 1972, **8** 1157
77. E Ya Borisova, T T Vasil'eva, L A Lukashova, et al. *Zh. Org. Khim.*, 1975, **11** 943
78. D L Farmuni *J. Am. Chem. Soc.*, 1970, **89** 8970
79. E M Cherkasova, E Ya Borisova, G P Petrova, et al. *Zh. Org. Khim.*, 1972, **8** 701
80. R D Haworth, D H Peacock, W R Smith *J. Chem. Soc.*, 1952, 2972
81. F M Hoover, H B Stevenson, H S Rothrock *J. Org. Chem.*, 1963, **28**(7) 1825
82. J R Willard, C S Hamilton *J. Am. Chem. Soc.*, 1953, **75** 2370
83. E Malovski, C Bachmeyer *Ber.*, 1944, **77** 495
84. D E Val'ter, S P Val'ter, A E Kittya *Zh. Org. Khim.*, 1968, **4** 445
85. P A Gembitskii, D S Zhuk, V A Kargin *Khimiya Etilenimina* (Chemistry of Ethyleneimine), Moscow, 1966, 111
86. Authors Certificate 503 853; *Byull. Izobret.*, 1976, (7) 6
87. V Evdokimoff, B Tucci-Bucci, A Calo *Aun. Jst. Super. Sanita*, 1965, **1** 746
88. G London, J James *J. Chem. Soc., Chem. Commun.*, 1980, (9) 377

89. D D Perrin *Dissociation Constants of Organic Bases in Aqueous Solution*, London, 1965
90. S T Kuznetsov, E V Roginskaya *Zh. Obshch. Khim.*, 1963, **33** 1570
91. B Luming *Acta Chem. Scand.*, 1960, **14** 321
92. E Ya Borisova, S V Bogatkov, B V Unkovskii, et al. *Reakts. Sposobnost. Org. Soedin., Tartu Gos. Univ.*, 1968, **5** 148
93. V S Shklyaev, V I Pantsurkin *Reakts. Sposobnost Org. Soedin., Tartu Gos. Univ.*, 1976, **13** 148
94. L A Kundryutskova, I E Sukhova, E Ya Borisova, et al. *Reakts. Sposobnost Org. Soedin., Tartu Gos. Univ.*, 1969, **6** 642
95. V A Pal'm *Osnovy Kolichestvennoi Teorii Organicheskikh Rekatsii* (Fundamentals of the Quantitative Theory of Organic Reactions), Khimiya, Leningrad, 1967
96. J R Merrill, R G Bennet *J. Chem. Phys.*, 1965, **43** 1410
97. E Ya Borisova, M G Zaitseva, E M Cherkasova *Reakts. Sposobnost. Org. Soedin., Tartu Gos. Univ.*, 1969, **6** 135
98. L A Lukashova, E Ya Borisova, R V Kozlenklova, et al. *Tr. MITKhT M V Lomonosova Moscow*, 1973, **3** 52
99. N V Dierk *Report from Gov. Rep. Announce Index*, 1981, **81** 2796
100. R Barbucci, V Barone, P Furruti *J. Chem. Soc., Dalton Trans.*, 1980, (2) 253
101. T Takeshita, S Meada *J. Am. Oil Chem. Soc.*, 1969, **49** 344
102. T Kaden, A Zuberbuchler *Helv. Chem. Acta*, 1971, **54** 1361
103. E Ya Borisova, E P Buchikhin, L A Lukashova, et al. *Zh. Obshch. Khim.*, 1977, **47** 2099
104. Authors Certificate 505 637 USSR; *Chem. Abs.*, 1977, **86** 16668k
105. Authors Certificate 451 698 USSR; *Byull. Izobret.*, 1974, (44) 53
106. R Dahlbom, B Karlen, A Lindquist, et al. *Acta Pharm. Succica*, 1967, **22** 1057
107. W Chiti, C Superbi *Farmaco. Ed. Sci.*, 1967, **22** 1057
108. French M. 5819; *Chem. Abs.*, 1969, **71** 81413c
109. French P. 1 558 926; *Chem. Abs.*, 1970, **72** 54893v
110. D A Kharkevich, A P Arendaruk, A P Skoldikov *Khim. Farm. Zh.*, 1968, (3) 7
111. A L Mnzhdoyan, S T Agbalyan *Dokl. Akad. Nauk Arm. SSR*, 1955, **21** 215
112. M D Mashkovskii *Lekarstvennye Sredstva (Drugs)*, Meditsina, Moscow, 1985, Pt. 1
113. US P. 2 438 200; *Chem. Abs.*, 1948, **42** 7337
114. B Chechelska, T Urbanski *Roczniki Chem.*, 1953, **27** 396
115. A S Lebedeva, I S Tolmacheva, N A Yushchenko, et al. *Khim. Farm. Zh.*, 1968, (4) 22
116. E E Mikhlina, K A Zaitseva, V Ya Vorob'eva, et al. *Khim. Farm. Zh.*, 1973, (8) 20
117. Sh M Glozman, N S Tomacheva, L A Zhmurenko, et al. *Khim. Farm. Zh.*, 1973, (2) 9
118. N I Kudryashova, N A Novikova, Yu G Bobkova *Tez. Konf. po Problemam Napravlennogo Sinteza Fiziologicheski Aktivnikh Veshchestv* (Abstracts of the Conference on Problems of the Directed Synthesis of Physiologically Active Susbtances), Erevan, 1968, 20
119. I A Shaps, N A Mukhina, T V Mikhailova, et al. *Khim. Farm. Zh.*, 1968, (9) 21
120. V V Klyushin, V A Portnyagina, V A Pochinok *Ukr. Khim. Zh. (Russ. Ed.)*, 1984, **50** 129
121. I M Somin, S T Kuznetsov *Khim. Farm. Zh.*, 1968, (6–8) 39
122. E M Cherkasova, L A Lukasheva, E Ya Borisova *Dokl. Akad. Nauk Beloruss. SSR*, 1973, **17** 168
123. Yu S Grossman, A S Zaks, L T Zil'bermints, et al. *Materialy Konf. 18.06.69* (Proceedings of the Conference of 18.06.69), Leningrad, 1969, 14
124. H F Casy, M M Masson *J. Pharm. Pharmacol.*, 1967, **19** 17
125. G R Wendt, B V Shetty, W F Bruce *J. Am. Chem. Soc.*, 1959, **81** 4233
126. G N Huntanen, T J Micich *J. Am. Oil Chem. Soc.*, 1978, **55** 854
127. BRD P. 2 639 645; *Chem. Abs.*, 1978, **89** 6231k
128. Europ. P. 220 011; *Chem. Abs.*, 1987, **107** 58874g
129. Authors Certificate 1 261 561 USSR; *Byull. Izobret.*, 1986, (36)
130. Authors Certificate 1 355 122 USSR; *Byull. Izobret.*, 1987, (43)
131. Europ. P. 180 994; *Chem. Abs.*, 1986, **105** 78680c
132. Authors Certificate 1 170 969; *Byull. Izobret.*, 1985, (28)
133. Europ. P. 0 077 534; *Chem. Abs.*, 1983, **99** 122308w
134. Brit. P. 1 057 667; *Chem. Abs.*, 1968, **68** 21717h
135. Japanese P. 7 032 421; *Chem. Abs.*, 1970, **75** 19979w
136. South African P. 6 8 02 031; *Chem. Abs.*, 1968, **71** 38606f
137. Finnish P. 371 109; *Chem. Abs.*, 1970, **72** 111102r
138. H Schoenberger, L Bindl, A Petter *Arch. Pharm.*, 1970, **303** 798
139. M Haring, G Stille *Helv. Chim. Acta*, 1961, **44** 642
140. T Eckert, E Kilb, H Hoffman *Arch. Pharm.*, 1964, **297** 31
141. E M Cherkasova, S V Bogatkov *Usp. Khim.*, 1962, **31** 963
142. B Hach, Z Horakova, J Reichelt *Chem. Listy*, 1957, **57** 547
143. Brit. P. 877 846; *Chem. Abs.*, 1962, **56** 8649e
144. French M. 6 209; *Chem. Abs.*, 1971, **74** 125201a
145. J Thuiller, H Nakajima *Anesth. Analg. Reamin.*, 1962, **19** 827
146. T Kurihara, K Sagana, H Takeda *Tonoku Yakka Daigaku Kentyu Netpo*, 1968, (15) 49
147. BRD P. 1 247 315; *Chem. Abs.*, 1968, **68** 955566
148. H E Zaungg, B W Horrom *J. Am. Chem. Soc.*, 1953, **75** 292
149. K V Grablyauskas, V Yu Reklyavichius, M I Grablyauskane, et al. *Khim. Farm. Zh.*, 1968, (9) 35
150. E Ya Borisova, L A Lukashova, A M Kuyantseva, et al. *Khim. Farm. Zh.*, 1981, (10) 43
151. H I Borisova, L A Lukashova, H M Cherkasova, et al. *Drag. Exp. Clin. Res.*, 1986, **12** 735
152. S I Kanevskaya, V B Brasyuk *Zh. Obshch. Khim.*, 1959, **29** 1930
153. F Mori *Japan. J. Anesthesiol.*, 1959, **8** 677
154. V Carelli, M Cardellini, F Siberatore *Farmacol. Ed. Sci.*, 1961, **16** 375
155. BRD P. 1 636 476; *Chem. Abs.*, 1970, **72** 90482
156. J Legheaud, G Cuisinaud, M Sabbagh, et al. *Ann. Pharm. Fr.*, 1977, **35** 45
157. G Morelli, M L Stein *J. Med. Pharm. Chem.*, 1960, **2** 45
158. R Harard, P Chabrier, J Bourdals *Therapie, 1965*, **20** 1043
159. K Staniszewski *Arch. Int. Pharmacodynamic*, 1960, **124** 263
160. D E Drayer, M M Redenberg, R W Sevy *Proc. Soc. Exp. Biol. Med.*, 1974, **146** 358
161. Roumanian P. 69 027; *Chem. Abs.*, 1981, **95** 24589
162. C Luu-Dac, A Marsura, C Charlou, et al. *Farmaco, Ed. Sci.*, 1985, **40** 253
163. J Kusovska, J Sienkiekiez *Acta Pol. Pharm.*, 1985, **42**(4) 367
164. Authors Certificate 1 398 771 USSR; *Byull. Izobret.*, 1988, (3)
165. D K Yung, M M Vorba, J Chu *J. Pharm. Sci.*, 1970, **59** 1405
166. L Vrbavsky *Bratislav. Lec. Listy*, 1972, **56**(2) 161
167. P H Morgan, J W Mathison *J. Pharm. Sci.*, 1976, **65**(5) 635
168. BRD P. 2 705 639; *Chem. Abs.*, 1977, **87** 167765 m
169. Japanese P. 8 242 669; *Chem. Abs.*, 1982, **97** 6144z
170. BRD P. 2 509 155; *Chem. Abs.*, 1977, **86** 55458m

171. P T Thyrum, J Conn, P J Luchi *Arch. Int. Pharmacodyn. Therm.*, 1964, **151** 494
172. P Reynaud, J D Brion, G Menard, et al. *Eur. J. Med. Chem. Ther.*, 1976, **11**(6) 513
173. French P. 2 323 378; *Chem. Abs.*, 1978, **88** 104945v
174. M L Guerin, H Morin *Therapie*, 1977, **32**(4) 501
175. L Szekeres, G I Papp *Experimental Cardiac Antiarrhythimias and Antiarrhythmic Drugs*, Budapest, 1971, p. 354
176. X Zhou, Y Lin, J Zhu *Shanghai Diyi Yihueynau Huebao*, 1984, **11**(6) 413
177. O H Hankovsky, K Hideg, J Bodi, et al. *J. Med. Chem.*, 1986, **29**(7) 1138
178. US P. 4 544 654; *Chem. Abs.*, 1986, **104** 168176b
179. US P. 4 629 739; *Chem. Abs.*, 1987, **106** 175958c
180. W Zumma, A Wohle, D Davey, et al. *J. Med. Chem.*, 1987, **30**(5) 755
181. L Kavzycka, W Bialasiewier, A Szadowska *Pol. J. Pharmacol. Pharm.*, 1986, **38** 545
182. D K Yung, L G Chatten, D P MacLeod *J. Pharm. Sci.*, 1968, **57**(12) 2073
183. *Cyclovinylogs of Procainamides Arch. Pharm. (Weinheim, Germany)*, 1982, **315** 1003
184. US P. 8 607 257; *Chem. Abs.*, 1987, **107** 33193w
185. D M Stout, W L Matier, Y C Bareelon, et al. *J. Med. Chem.*, 1984, **27**(10) 1347
186. BRD P. 3 445 852; *Chem. Abs.*, 1986, **105** 152945m
187. S Grosrkowski, J Bieniazz, J Krezel *Pharmazie*, 1984, **39**(4) 497
188. J W Mathison, R C Guelder *J. Org. Chem.*, 1968, **33** 2510
189. J W Mathison, P H Morgan *J. Org. Chem.*, 1977, **39** 3210
190. *Somani Pitambar Clin. Pharmacol. Ther.*, 1980, **27**(4) 464
191. A J Camm *Europ. Hert. J.*, 1984, **5**(Suppl. B), 75
192. M Seiji, S Kunihiro, S Fumio, et al. *J. Med. Chem.*, 1985, **28** 714
193. A M Grishchenko, A P Skoldinov *Khim. Farm. Zh.*, 1986, (6) 485
194. E G Paronikyan, T R Akopyan, S A Vartanyan *Arm. Khim. Zh.*, 1985, **38** 715
195. E Ya Borisova, V M Komarov, M I Cherkashin, et al. *Dokl. Akad. Nauk SSSR*, 1990, **313**(3) 616
196. E H Banitt, J R Schmid, R A Newmark *J. Med. Chem.*, 1986, **29** 299
197. G R Ehring, L M Hondeghem *Proc. West Pharmacol. Soc.*, 1981, **24** 221
198. S Yu Berdyaev *Farmakol. Toksikol.*, 1987, (4) 5
199. Z A Talaikite, V I Vidutrene, G A Tavenas, et al. *Zh. Org. Khim.*, 1989, **25**(7) 1497
200. V A Zagorevskii, A V Val'dman, M M Kozlovskaya, et al. *Khim. Farm. Zh.*, 1989, (11) 1304
201. M I Cherkashin, E Ya Borisova, V M Komarov, et al. *Dokl. Akad. Nauk SSSR*, 1990, **313**(3) 623