PROGRESS IN THE CHEMISTRY OF LOCAL ANAESTHETICS IN THE LAST DECADE

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CONTENTS

Introduction 452

I. Some theoretical principles 452

II. Procaine-type compounds 453

1. The acid component 453
2. The alkyl component 454
3. The amine component 455
4. Brief summary 456

III. Compounds not containing the anaesthesiophore grouping 456

1. Amino-acid derivatives 456
2. Amino-ketones 458
3. Amino-alcohols 458
4. Amines 458
5. Simple amides and amidines 459
6. Compounds not containing nitrogen 460

INTRODUCTION

It is now more than 80 years since the Russian doctor Vasili Konstantinovich Anrep† administered cocaine subcutaneously as an anaesthetic and thus initiated the use of local anaesthetics in surgery. Since that time, local anaesthesia has, of course, undergone a great evolution. In the search for new anaesthetics, less toxic than cocaine, many organic compounds of the most diverse kind have been synthesised and tested, and a large amount of valuable factual knowledge has accumulated on the relation between molecular structure and anaesthetic activity; many attempts have been made to elucidate the mechanism of anaesthetic action, and the methods of anaesthesia themselves have been perfected. Nevertheless, the problem of local anaesthetics remains important, because no single available preparation meets all modern clinical requirements.

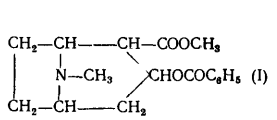
Progress in synthetic chemistry is so great and increasing so rapidly from day to day that it might be thought the time is not far off when the problem of synthesising the "ideal" local anaesthetic will be solved by the combined efforts of chemists and pharmacologists.

† Strange as it may seem, some authors outside the Soviet Union[1,2] still give priority for this discovery to Koller on the basis of a telegram he sent to the Congress of Ophthalmologists in Vienna in 1884. Not only was this report five years late, but Koller recommended a surface paint for the mucous membrane of the eye, whereas as early as 1879 Anrep first used a subcutaneous injection[3,4]; this was of fundamental importance in the practice of local anaesthesia[5].

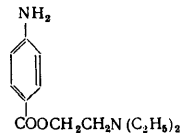
In planning future developments, it is useful from time to time to review the past and to evaluate the present state of a problem under investigation. This review is devoted to the progress in the chemistry of anaesthetics over the past decade.

I. SOME THEORETICAL PRINCIPLES

The disadvantages of cocaine stimulated the search for new local anaesthetics, and at first the work was directed towards simplifying the cocaine molecule (I) to give norcocaine, eucaine A, eucaine B, and procaine (novocaine) (II)[6]:

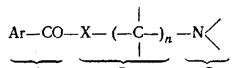


(I)



(II)

Several active anaesthetics were synthesised. The presence of a common structure in all these compounds gave rise to the idea of a special "anaesthesiophore grouping" (III) responsible for the anaesthetic function, and made up of three component parts, acid *A*, alkyl *B*, and amine *C*.



(III)

where X = O, NH, S.

Cocaine, the eucaines, procaine, and also cinchocaine and amethocaine, which were discovered later, do in fact contain this grouping. However, there are many compounds with local anaesthetic activity in which it is not present. Amino-alcohols, amino-ketones, simple amines, and even compounds containing no nitrogen have been found to be more active than the well-known preparation; this shows that the principle of an essential anaesthesiophore grouping is clearly unsatisfactory. We estimate that in the past ten years more than 60% of the papers on the synthesis of new local anaesthetics have been concerned with compounds that do not contain this grouping. The compounds synthesised show great variations in physicochemical and physiological properties, such as the rate of penetration through the tissues, the duration of action because of differences in tissue fixation, the distribution coefficient between aqueous and non-polar phases, and side reactions of the tissues[2].

A large amount of experimental material has now accumulated on anaesthetics and this has resulted in efforts being made to set up a theory to explain the mechanism of their action and to provide a guide for chemists to useful synthetic approaches.

It is still not clear on what links of the reflex arc of the body local anaesthetics act. Many workers[7-9] consider that anaesthetics destroy the conduction of nerve fibre, either by prolonged depolarisation of the membrane, or by the opposite process of steady polarisation. In both cases, the transmission of the nerve impulse, which according to modern concepts[10] is related to temporary reversible polarisation of the cell membrane with corresponding changes in permeability, becomes impossible. It has been shown experimentally by several workers[11-14] that local anaesthetics do affect the permeability of the membrane to Na^+ and K^+ ions.

Other workers[15-16] consider that anaesthetics destroy nerve conductivity not in the fibre itself but in the cell synapses. It is now accepted that the synaptic transmission of an impulse is effected by special compounds called mediators (these include acetylcholine, adrenaline, and noradrenaline) that act directly on the receptors[17-20], or through certain enzyme cycles[21,22]. The anaesthetics may interfere with the production or the adsorption of the mediator[23,24], but their effect is more probably due to intervention in the enzyme cycle, which is thus interrupted[25]. This is confirmed by the action of local anaesthetics on many enzyme reactions[26-28] and also by the relation between anaesthetic and anticholinesterase effects[29,30]. The most likely hypothesis is that different local anaesthetics react by different mechanisms, depending on their structures and physicochemical properties. This is supported, on the one hand, by the great diversity of anaesthetics, and on the other hand, by the fact that the regularities in structure, physicochemical properties (dissociation constant[32,33], rate of hydrolysis[34,35], penetrating power[36-38], and others[39,40]), and activity established for some homologous series do not hold when applied to other classes of anaesthetics[31,41,42]. This appears to be related to a change in the mechanism of action of the anaesthetic, that is, a change in the way the nerve impulse is interrupted or inhibited, or in the site at which this occurs.

II. PROCAINE-TYPE COMPOUNDS‡

Although procaine is one of the most popular preparations, it has several great disadvantages, the main ones being its low surface anaesthetic activity, its depressor properties, and the short duration of its action; it must therefore be used in combination with adrenaline, which produces several side effects, especially complications in wound healing. For this reason, more and more work is done every year on the synthesis of procaine analogues with improved properties.

As already mentioned, the procaine molecule may be considered to consist of three component parts:

$$\underbrace{p\text{-}NH_2C_6H_4CO}_{A}\text{—}\underbrace{OCH_2CH_2}_{B}\text{—}\underbrace{N(C_2H_5)_2}_{C}$$

acid *A*, alkyl *B*, and amine *C*. Research on the effect of modifying different parts of the molecule on the activity of the compound has accordingly taken three main directions.

1. The Acid Component

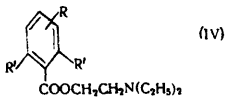
The problem that arose in the first instance concerning the part played by the aromatic radical may be considered to be largely solved. Notwithstanding isolated cases in which anaesthetic properties are shown by esters of cycloalkylcarboxylic acids[43-48], these properties are in the main characteristic of the aromatic series. Esters of aliphatic acids are virtually inactive§.

‡ Although, as will be clear from the foregoing, the division of anaesthetics into those having an anaesthesiophore grouping and those that have not is purely arbitrary, this division is used here for convenience of arrangement.

§ This applies to esters of monocarboxylic acids. Bisdialkylaminoalkyl esters of the aliphatic dicarboxylic acids, and even such derivatives as diethylaminoethyl ethyl malonate show considerable activity, although in these only one carboxyl is esterified by an amino-alcohol residue[52,53].

The nature and positions of the substituents in the phenyl radical of the acid greatly influence the activity. The introduction of alkyl groups such as isopropyl, or t-butyl into the *p*-position to increase the lyophylic properties of the molecule retards hydrolysis and enhances the infiltration activity[49,50], but at the cost of increased irritancy. The activity of the alkylamino-esters of the 2,3,5,6-tetraalkylbenzoic acids, which is much superior to that of procaine in duration[51], can be explained in the same way.

Recently the (trimethylsilyl)benzoates of some amino-alcohols[54] have been found to show pharmacological activity, the first to be observed in the organosilicon compounds. Several of the alkoxybenzoates having the general formula (IV):



(IV)

where R = *p*-AlkO—[55, 56, 59], *m*-CH_3O—[59], 3, 4-(CH_2O_2)[57, 58], *p*-$C_6H_5OCH_2CH_2O$—[59], 3, 4-$(CH_3O)_2$,[61] C_2H_5S,[62, 63] R′ = CH_2,[56] H,[57—63] CH_3O.[60].

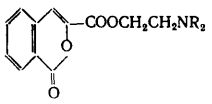
have been found to have therapeutic value.

The anaesthetic action of these compounds depends on the alkoxy-radical, reaching a maximum in the *p*-hexyloxybenzoates (see Table 1)[55]. The introduction of the *p*-phenoxyethoxy-groups into the benzoic acid nucleus prolongs the activity up to six weeks or more; in the words of the authors[59], after this time "muscular control is lost over the injection area and the animal is completely insensitive to stimulation in this area". The *p*-alkylthio-derivatives[62,63] are of great interest in this class of compounds; the diethylaminoethyl ester of *p*-ethylthiocinnamic acid is five times as effective as procaine intravenously and 20 times as effective as cocaine topically[63]; also of interest are the dialkoxybenzoates, in which the increase in activity is related to an increase in the distribution coefficient between a non-polar and an aqueous phase[61].

Recently, most work has been devoted to the aminobenzoic acid esters, as the most closely related to procaine. A survey of the work done shows that alkylation of the amino-group and introduction of hydroxy- and alkoxy-residues or halogens into the aminobenzoic acid nucleus leads to compounds some of which are superior to procaine and cocaine. Japanese workers[64] have made the important observation that electron-donor groups are more effective in the *o*-position of *p*-aminobenzoic acid, and electron-acceptor groups in the *m*-position. This has been confirmed in many ways: it has been shown, for example, that the 4-amino-2-chlorobenzoates have valuable pharmacological properties; in particular, the diethylaminoethyl ester is 10 times as active as procaine with two-thirds its toxicity[65,66]. Of the hydroxyamino-derivatives[67-72] the 2-alkoxy-4-aminobenzoates are also the most active; as with the compounds described above, the anaesthetic activity and toxicity increase with the size of the alkyl group, but here the maximum therapeutic effect is observed with the C_2H_5O- and C_3H_7O-groups[68,72]. In the 3-alkoxy-4-aminobenzoates, the C_4H_9O-group confers the greatest activity[69,70]. All these facts show that electronic structure has an important influence on anaesthetic activity.

Other substituted benzoic acids have also been found active, including mono- and di-halogen-substituted[73-76], *m*- and *o*-aminobenzoic acids[77-81], etc. Of recent work on the replacement of the amino-group, that of French workers[82] on the carbalkoxylation of procaine is of greatest interest. It has been shown that when the hydrogen of the amino-group is replaced by ROOC, the activity increases to a maximum with the compound having R = C_7H_{15}; this compound is 10–12 times as active as cocaine and 4–7 times as toxic. The simultaneous introduction of a hydroxy-group into position 2 reduces the toxicity without affecting the high activity.

If, as has already been mentioned, the question of the necessity of an aromatic radical can be regarded as settled, the second question on the role of conjugation of the carbonyl group with the double bond of the benzene nucleus still remains undecided. Up to now there has been no agreement as to whether such conjugation is necessary or whether unsaturation of the carbon adjacent to the carbonyl group (on the principle of "vinylogy") is sufficient. It is also not clear whether anaesthetic activity in general is related to the conjugated system. On the one hand, reduction of the duration of anaesthesia by a factor of 2–4 when the esters of ββ-diarylacrylic acid[83] are hydrogenated, and the absence of anaesthetic activity in the alkylaminoesters of isocoumarinic--3-acid (V) (in which the nature of the double bond is changed because of the adjacent oxygen[84]), tend to confirm the role of the system of conjugated bonds in anaesthetic



(V)

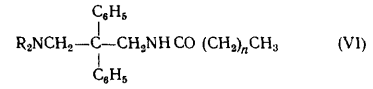
activity and justify the conclusion of Shilov and Kanevskaya[84] that "destruction of conjugation leads to loss of anaesthetic activity". However, on the other hand, many workers have found significant local anaesthetic activity in the esters of such acids as diarylacetic[85,86], benzilic[87,90], mono-, di- and tri-arylpropionic[91-93] and others, in which the chain of conjugated bonds is interrupted by one or even several methylene groups. Many of these compounds are superior to the corresponding unsaturated derivatives. Nazarov and Cherkasova[94-96], Shapiro *et al.*[73], and others have shown that the phenoxyacetates of various amino-alcohols are not inferior to the benzoates in activity, and some of them are superior. These facts cast doubt on the necessity for a conjugated system of double bonds in local anaesthetics. Obviously the question may be answered in different ways, according to the mechanisms by which different groups of compounds act.

In addition to the esters of benzoic acids, the alkylaminoesters of heterocyclic- and naphthalene-carboxylic acids have also been examined for activity; Sergievskaya[97,98] found that some naphthalene compounds were superior to the corresponding benzene derivatives. The activity of most esters of acids with heterocyclic nuclei[99-114] is comparatively low; according to Burger[115], it decreases in the order: phenyl > 2-furyl > 2-thienyl > 4-piperidyl.

Highly active derivatives, for example, phenothiazine- and coumarin-carboxylates are very toxic: they irritate the mucous membrane and depress the central nervous system. The best acid analogues of procaine are therefore the alkamino-esters of acids containing the benzene or naphthalene nucleus, either linked directly to the carboxyl group or separated from it by ethylene or methylene groups.

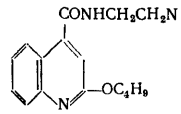
2. The Alkyl Component

In studies on the alkyl component, most attention has been paid to the bond between the carbonyl group and the methylene chain. Replacement of the ester by an amide group in several benzoic acids leads to a reduction in anaesthetic activity: the diethylaminoethylbenzamides are less active than the corresponding esters[116-121]. The highly active *N*-(dialkylaminoethyl)-*p*-dialkylaminobenzamides with radicals of high molecular weight at the nitrogen atom[122], and also the cyanamides[123] alkylated at the amide nitrogen, are the only exceptions to this rule. In contrast, several amides in the aliphatic series are far superior to the esters. Thus, the γ-dialkylamino-ββ-diphenylpropylamides of acetic, propionic, and butyric acids (VI)[124] (with n = 0, 1, 2), and also the dialkylaminosuccinimides[125] are powerful local anaesthetics, but the esters of these acids are inactive.



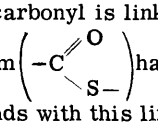
(VI)

However, the amides with the most pronounced physiological properties are those of heterocyclic acids, particularly of the quinolinecarboxylic acids; these include cinchocaine (sovcaine, dibucaine, nupercaine) (VII), now one of the most widely used anaesthetics,

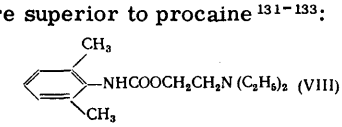


(VII)

which is about 25 times as powerful as procaine. Some of the analogues are also equally active; as usual, the effectiveness of the preparation increases with the size of the radical in the alkoxy-group[126,127]. However, all these compounds, including cinchocaine, are very toxic.

A variant in which the carbonyl is linked to the methylene chain by a sulphur atom  has also been examined. Some compounds with this link are highly active therapeutically[128,129]; for example, the 4-amino-2--hexyloxythiolbenzoate of diethylaminoethanol is 500 times as active as cocaine and only 60 times as toxic, with relatively little irritancy[60].

Carbamylation of procaine and procaine amide, that is, introduction of an NH-group between the carbonyl carbon and the acid nucleus, greatly increases the activity. These derivatives combine high anaesthetic activity with insignificant side effects[130]. *o*-Substitution in the nucleus of phenylcarbamic acid also increases the activity; compounds of type VII are superior to procaine[131-133]:



(VIII)

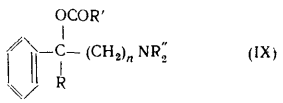
This may be related to stabilisation of the carbamate bond on *o*-substitution. The activity of several substituted phenylcarbamates, especially alkoxy-derivatives, changes in parallel with their capacity for coagulating colloids[134].

The relations between the structure of the carbamates and their properties are similar to those in the ester series. For example, the presence of an aromatic or heterocyclic radical is essential for activity in both series: aliphatic and alicyclic derivatives are inactive[135], and in both series

the diethylamino- and dibutylamino-groups confer optimum activity [136-138]. Of the carbamates, the *NN*-diarylcarbamates are the most powerful: diethylaminoethyl *N*-*p*-butoxyphenyl-*N*-phenylcarbamate is 76 times as active as cocaine in surface anaesthesia and 40 times as active as procaine in infiltration anaesthesia [139].

Elucidation of the part played by the length of the hydrocarbon chain between the carbonyl group and the nitrogen atom and the effect of branching of this chain have also been the subject of studies on the alkyl component. The many experimental results that have now accumulated suggest that the trimethylene chain, characteristic of cocaine (see Table 1), usually confers optimum activity. However, it is still impossible to make generalisations of any kind; for example, some of the diethylaminopropyl 2-alkoxy-4--aminobenzoates are more active and more toxic than the corresponding diethylaminoethyl esters [140], and the esters of chlorocinnamic and chlorobenzoic acids become less effective therapeutically because of increased toxicity as the chain is lengthened [141].

With regard to branching of the main chain, the work of Nazarov, Cherkasova, Erkolmaishvili, and others [94-96,142] on the local anaesthetic properties of the esters of tertiary aliphatic-aromatic amino-alcohols (IX):

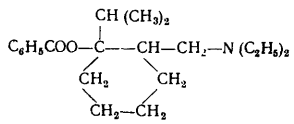


(IX)

(where R = H, CH_3, or C_2H_5, and n = 1, 2, or 3) may be mentioned. In this series, the esters of the 1-alkyl-3--dialkylamino-1-phenylpropanols (IX, n = 2) have been investigated in greatest detail; these may be regarded as acyl derivatives of the 4-phenyl-4-piperidols cleaved through the piperidine ring. Some of the uncleaved derivatives had previously been found to be powerful analgesics (for example, promedol), and cleavage of the ring was found to change the compounds from analgesics to local anaesthetics, the most potent anaesthetics being the esters of tertiary alcohols, which had hardly been investigated up to then. The esters of secondary alcohols have almost no anaesthetic activity. The nature of the acyl radical is very important: the esters of aliphatic acids are inactive, and the highest activity is shown by the phenoxyacetates and cinnamates of certain alcohols; for example, 3-dimethylamino-1-ethyl-2,2-dimethyl-1-phenylpropyl phenoxyacetate is as powerful as amethocaine but much less toxic. Several further conclusions on the relation between structure and physiological activity can be drawn from these investigations. The significance of the phenyl residue in the alcohol part of the molecule has also been confirmed by several workers outside the Soviet Union [73,87,143], but they find that some secondary alcohols are active [73], which is not in agreement with the results of the Soviet workers.

The introduction of ester-linked oxygen, sulphur, or an NH-group into the alkyl chain does not improve the pharmacological properties [144-147].

In recent years, there has been an increase in the number of papers on compounds in which the alkyl chain between the nitrogen and the oxygen is replaced by a cyclic grouping [148-150]; 2-diethylaminomethyl-1-isopropylcyclohexyl benzoate (X) is highly active; the *cis*- and *trans*--isomers differ in activity.



(X)

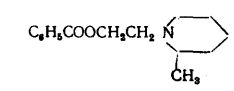
The first papers on compounds in which the alkyl chain is replaced by a heterocyclic residue showed that the 4-piperidyl benzoates [151,152] were highly toxic. Soviet workers later found that the introduction of substituents into the piperidine ring increased the therapeutic effect; this enabled highly active compounds of low toxicity to be prepared, especially by replacing the hydrogen on the ring--nitrogen atom by unsaturated residues [153-158]. Similar derivatives with the pyrrolidine residue, some of them as active as cinchocaine, were described [159-161] in 1960.

TABLE 1.

R	n	p-ROC$_6$H$_4$COO(CH$_2$)$_n$NR$'_2$			
		NR$'_2$	activity		LD_{50}, mm/kg
			surface	infiltration	
CH_3	2	$N(C_2H_5)_2$	0	0	575
C_2H_5	2	$N(C_2H_5)_2$	1.3	2.2	300
C_3H_7	2	$N(C_2H_5)_2$	1.7	1.6	254
C_3H_7	2	$N(CH_3)_2$	2.3	1.6	242
C_3H_7	2	NC_4H_8	2.4	1.8	208
C_3H_7	3	$N(C_2H_5)_2$	3.3	2.4	142
C_3H_7	3	NC_4H_8	3.6	2.8	73
C_4H_9	2	$N(C_2H_5)_2$	2.7	1.9	192
C_4H_9	2	$N(CH_3)_2$	2.6	1.5	258
C_4H_9	2	NC_4H_8	2.0	1.8	242
C_4H_9	3	$N(C_2H_5)_2$	3.6	2.6	192
iso-C_3H_9	2	$N(C_2H_5)_2$	3.9	2.8	158
s-C_4H_9	2	$N(C_2H_5)_2$	4.0	2.1	442
C_5H_{11}	2	$N(C_2H_5)_2$	3.6	2.5	291
C_6H_{13}	2	$N(C_2H_5)_2$	6.3	3.7	258
C_8H_{17}	2	$N(C_2H_5)_2$	0	0.6	175
$C_{16}H_{33}$	2	$N(C_2H_5)_2$	0	0	—
Procaine			—	1	202
Cocaine			1	1.8	62

3. The Amine Component

The amine component of the procaine molecule has been varied in three main ways: (*a*) the diethylamino-group is replaced by another dialkylamino-group or by a heterocyclic residue; (*b*) the tertiary amino-group is replaced by a secondary or primary group; (*c*) the tertiary amino--group is converted into a quaternary salt by coupling with an alkyl halide. Tests on the first modification showed that an increase in the molecular weight of the radicals at the nitrogen atom increases the activity and, to a lesser degree, the toxicity, the net results being an increase in the overall therapeutic effect of the compound. However, work done during the past ten years [69,73,97,162,163] suggests that the diethylamino-group gives the optimum effect (see Table 1); this may be related to the physiological specificity of the ethyl group, which was already emphasised by Ehrlich [164]. Of the other dialkylamino-groups, the dibutylamino- and the diallylamino-groups [165] may be of interest. Of the heterocyclic derivatives [166,167], the only compounds with high activity are some benzoates of piperidinoethanols, for example metycaine (XI); most of the



(XI)

compounds containing heterocyclic residues are either much more toxic than the diethylamino-analogues, or less effective. The monoalkylaminoalkyl esters are of interest here.

Because of their relatively low molecular weight (an increase in which usually increases the toxicity), these compounds would be expected to have a good therapeutic effect. In fact, many of the esters of the monoalkylamino-alcohols are not inferior in activity to the analogues with a tertiary amino-group, and they are therapeutically more effective than procaine or cocaine; examples include hexylcaine [168], monocaine, amylcaine, amylaminoethyl 3-amino-5-heptyloxybenzoate, which is more than 200 times as active as cocaine [79], and many others [169-172]. It is important to note that in the monoalkylamino-derivatives the effect of the structure of the alkyl chain on pharmacological properties was found to be opposite to that in the dialkylaminoalkyl ester series. Thus, compounds with the dimethylene chain are the most active, while esters of the monoalkylaminopropanols are very toxic [173]; α-branching of the chain enhances the activity, but β-branching diminishes it. Some compounds containing an alicyclic [174,175] or a heterocyclic [176,177] radical instead of the usual aliphatic alkyl (aliphatic alkyls with 5-7 carbon atoms confer optimum activity) are irritant, and they are inferior to procaine.

On the whole, investigation of the monoalkylaminoalkyl esters appears to be one of the most promising directions for research, especially as some compounds in this series have been found to have vasopressor action; this opens the possibility of preparing compounds that combine anaesthetic with vasoconstricting action.

The work of Ullyot [178] on the *p*-aminobenzoates of the aminoethanols describes one of the few attempts to discover local anaesthetics among the esters of amino-alkanols unsubstituted at the nitrogen atom. There are practically no pharmacological data in this field. The quaternary salts have been examined in detail, but the results obtained are fairly contradictory. French workers [179,180] have shown that in a series of well-known anaesthetics the methiodides are more toxic than the hydrochlorides, and they have a greater hypotensive effect and curare-like action, but lower anaesthetic activity; the anaesthetic properties are lost entirely when the amino-oxides are formed [31]. Barlow [1] states, "The quaternary salts cannot be local anaesthetics because they are always ionised". However, it was soon found that the benzyl bromides have high local anaesthetic activity and they are more long-acting because of slower absorption [181]. The quaternary salts of some anaesthetics with esters of the α-bromocarboxylic acids show a still greater increase in activity [73,182].

4. Brief Summary

The experimental material analysed here shows that general rules about the effect on pharmacological properties of structural changes in the acid, alkyl, and amine components of the procaine molecule can only be applied to a narrow range of its most closely related analogues. Outside this range the rules are modified and sometimes they are even contradictory. No definite generalisations on the relation between structure and local anaesthetic activity can therefore be made from the properties of procaine analogues.

III. COMPOUNDS NOT CONTAINING THE ANAESTHESIOPHORE GROUPING

These include many esters and amides, amino-ketones, amino-alcohols, amines, compounds containing no nitrogen, and some others grouped here according to some common structural feature.

1. Amino-Acid Derivatives

Benzocaine (anaesthesin, ethyl *p*-aminobenzoate) (XII) is one of the oldest anaesthetics, having been introduced into medical practice in 1902:

$$p\text{-}NH_2C_6H_4COOC_2H_5 \qquad \text{(XII)}$$

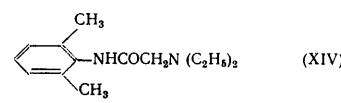
Benzocaine does not contain the anaesthesiophore grouping. Investigation of the alkyl esters of amino-acids has shown that the action of the 2-alkoxy-4-alkylaminobenzoates and the 4-amino-2,6-dimethylbenzoates of butyl and pentyl alcohols is much more prolonged than that of benzocaine [183-185]. Esters of alicyclic [186], heterocyclic [187,188], aliphatic-aromatic [189,190], and even aliphatic acids have also been found to be active. It has been shown [191,192] that the alkyl esters of dialkylamino-acids (XIII) are about as active as the alkyl esters of acids, but they are less toxic.

$$R'_2NCH_2COOCH_2R \qquad \text{(XIII)}$$

This work confirms that local anaesthetic action is associated with the structure and properties of the molecule as a whole and is not the sum of the activities of the component parts (for example, *p*-aminobenzoic acid and diethylaminoethanol), as some workers have asserted [193].

The alkyl esters of *p*-alkoxy- and *p*-aminoalkoxy--phenylcarbamic acids have also been found to be highly active, the most active being the heptyl and cycloheptyl esters [194-196]; for example, heptyl *p*-(2-morpholinoethoxy)-phenylcarbamate is 40 times as active as cocaine and twice as active as cinchocaine, with a lower toxicity [197].

In recent years much work has been devoted to investigation of amino-acids amides, primarily the diethylaminoacetanilides. One of these, lignocaine (xylocaine, maricaine, lidocaine) (XIV) proved to be a highly potent anaesthetic:



(XIV)

Its action is more rapid and more prolonged than that of procaine, and it is widely used in clinical practice. This led to the development of a number of analogues and homologues differing in the substituents on the nucleus and at the amino-acid nitrogen; as with the procaine analogues, it was found that an increase in lyophilic properties by the introduction of additional alkyl or alkoxy-groups into the nucleus prolongs the anaesthesia [198-208]. In contrast, reduction in the lyophilic properties and increased polarity due to the introduction of NO_2 and NH_2 substituents reduces the activity and increases the irritancy [199,209-212]. Thus a change in the electron-affinity greatly affects the properties of the compounds (see Table 2). However, the analogues of lignocaine do not show the direct relation between activity and basicity [199] that is found in the diethylaminoacetates of various alcohols and the dialkylaminoalkyl esters of some acids. Examination of other substituted anilides [213-223] has confirmed the relationships mentioned above.

With regard to substituents at the amino-acid nitrogen, it was found that the same relationships are observed here

TABLE 2.

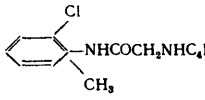
R	NR'_2	Change in pharmacological properties in comparison with lignocaine(xylocaine)	References
2,4,6-$(CH_3)_3$	$N(C_2H_5)_2$	increase in duration of action, decrease in toxicity and irritancy	198—200
2-CH_3-6-t-C_4H_9	$N(C_2H_5)_2$		204
2,6-$(CH_3)_2$-4-C_6H_5O	$N(C_2H_5)_2$		203
2,6-Cl_2-4-R″O*	$N(C_2H_5)_2$		205—206
2,6-Cl_2-4-R″S*	$N(C_2H_5)_2$		205—206
2-CH_3-	$N(C_2H_5)_2$	decrease in activity and increase in irritancy	210
2,4-$(CH_3)_2$-	$N(C_2H_5)_2$		211
2-CH_3-6-CH_3O	$N(C_2H_5)_2$	ditto	199,209
2,6-$(CH_3)_2$-4-NO_2	$N(C_2H_5)_2$	»	199 209
2,6-$(CH_3)_2$-4-NH_2	$N(C_2H_5)_2$	increase in activity and toxicity	210,224,279
2,6-$(CH_3)_2$	$N(C_4H_9)_2$	increase in irritancy with retention of anaesthetic activity	198
2,6-$(CH_3)_2$	NC_5H_{10}	increase in activity and therapeutic index	226—227
2,4,6-$(CH_3)_3$	NC_4H_8	increase in therapeutic index (23 times as large as that of cocaine)	225
2,4,6-$(CH_3)_3$	2,4,6-$(CH_3)_3$—C_5H_7N	increase in activity and therapeutic index	229—232
2,4,6-$(CH_3)_3$	NHC_6H_{13}	ditto	230
2-Cl-6-CH_3	NHC_4H_9		

* R″=CH_3, C_2H_4, C_6H_7, C_6H_9.

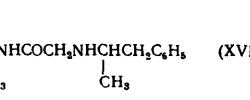
TABLE 3.

$2,4,6\text{-}(CH_3)_3C_6H_2NHCOCH_2NR'R''$			$2,4,6\text{-}(CH_3)_3C_6H_2NHCOCH_2NR'R''$		
NR′R″	relative therapeutic effect		NR′R″	relative therapeutic effect	
	surface	infiltration		surface	infiltration
$N(C_2H_5)_2$	2.2	1.3	β-Pipecolyl	11.1	8.8
NHC_4H_9	1.1	1.2	γ-Pipecolyl	4.8	3.2
NHC_6H_{13}	10.0	10.6	2,6-Copelidyl	12.00	3.0
NHC_6H_{11}	2.9	2.2	2,4,6-Lupetidyl	23.0	8.7
NHC_6H_5	—	—	Morpholyl	1.0	3.6
Pyrrolidyl	1.6	1.9	N-carbethoxypiperazyl	0.4	1.5
Piperidyl	1.0	0.8	Cocaine	1.0	—
α-Pipecolyl	1.0	1.9	Procaine	—	1.0

as in the procaine-analogue series; thus, the $(C_2H_5)_2N$- -group[210,224] gives the optimum effect, with the $(C_4H_9)_2N$- -group[225] forming an exception. Pyrrolidine derivatives[226,227], and also compounds containing the piperidine ring with several substituent methyl groups[225], were found to be the best of the compounds containing a heterocyclic residue. "Quaternisation" of the amine nitrogen usually leads to shallower and more limited anaesthesia with increased toxicity[198,228]. In the amide series, the derivatives of monoalkylaminoacetic acids are very promising[228-232] (Table 3); these include hostacaine (XV), which is four times as active as procaine on the sciatic nerve of the frog[230].



(XV)



(XVI)

Of the amides, compounds of the type of N-(α-methylphenethyl)-α-methylphenethylacetamide (XVI) are of particular interest, as they have a pressor in addition to significant local anaesthetic activity[233,234].

Koelzer and Wehr[224,235,236] compared the homologues and analogues of lignocaine with well-known anaesthetics (procaine, amethocaine, cinchocaine) and they proposed a formula to represent the "overall suitability of a preparation":

$$Z = \frac{(a \ln d_m + b)(a \ln p_m + b)}{2a}$$

where d_m is the mean stimulating dose, p_m is the mean lethal dose, and a and b are constants. According to Koelzer and Wehr, this formula may be used to evaluate the quality of a preparation. In fact, application of the formula to the anilides of diethylaminoacetic acid (Table 4) gave results close to those obtained by application of the usual criteria, but it does not follow that this empirical formula, introduced for a narrow range of analogues, can be extended to other compounds.

The more remote analogues of lignocaine include compounds in which the benzene nucleus at the amide nitrogen is replaced by a naphthalene[237-239], anthracene, or fluorene[240-242] nucleus, by a β-aryloxyethyl residue[224,235], or even by an aliphatic radical with 7–9 carbon atoms, for example, N-(2-methyl-2-octyl)-piperidinoacetamide [probably N-(1,1-dimethylnonyl)piperidinoacetamide Ed. of Translation], which is 20 to 30 times as active as lignocaine[243]. Amides of longer-chain acids are also of interest. Koelzer and Wehr[244] found that, in contrast to the α-amino-acid anilides, in which chain lengthening reduces the pharmacological properties, the anilides of the ω-amino-acids become more active when the chain is lengthened. Good pharmacological qualities have been noted in the anilides of β-dialkylaminopropionic acid[245,246], the anilides of type (XVII)[235,247]:

$$ArNHCO(CH_2)_nX(CH_2)_mNR_2 \qquad (XVII)$$

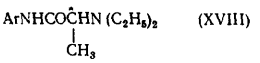
(where X = O or S), and especially in the aminobutyranilides[248-251]. The introduction of 2,6-dimethyl-, p-methyl-, or p-chloro-substituents into the aromatic nucleus of the aminobutyranilides greatly increases the toxicity without changing the activity; this contrasts with the behaviour of the acetanilides. On the other hand, carbalkoxylation of the nucleus produces an increase in activity and a decrease in toxicity.

Recent papers[252,253] by Soviet workers on the relation between local anaesthetic activity and optical isomerism are of great interest. Having confirmed the general principle mentioned above that α-branching of the acetamides greatly increases irritancy with a slight increase in activity, they turned their attention to the relation between

TABLE 4.

$R'R''C_6H_2NHCOCH_2NR_2$				$R'R''C_6H_2NHCOCH_2NR_2$			
R′	R″	NR₂	Z	R′	R″	NR₂	Z
H	H	$N(C_2H_5)_2$	83	2-CH_3	4-Cl	$N(C_2H_5)_2$	0
2-CH_3	H	$N(C_2H_5)_2$	103	2-CH_3	6-Cl	$N(C_2H_5)_2$	125.8
2-C_6H_5O	H	$N(C_2H_5)_2$	0	2-Cl	6-Cl	$N(C_2H_5)_2$	78.2
2-C_4H_9O	H	$N(C_2H_5)_2$	0	2-CH_3	H	NC_5H_{10}	110
4-C_2H_5O	H	$N(C_2H_5)_2$	40.5	2-Cl	H	NC_5H_{10}	92
2-CH_3COO	H	$N(C_2H_5)_2$	0	4-C_2H_5O	H	NC_4H_8	0
2-CH_3	6-CH_3	$N(C_2H_5)_2$	114	2-CH_3	6-CH_3	NC_4H_8	154
3-CH_3	4-CH_3	$N(C_2H_5)_2$	9.7	4-Cl	H	NC_4H_9	8.36
2-Cl	H	$N(C_2H_5)_2$	0	2-CH_3	6-Cl	NC_4H_8	269
4-Cl	H	$N(C_2H_5)_2$	0	2-Cl	6-Cl	NC_4H_9	138
2-CH_3	3-Cl	$N(C_2H_5)_2$	0	4-Cl	5-CF_3	NC_4H_8	0

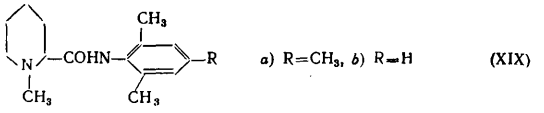
optical activity and stereoisomerism. They found that (-)-isomers of the α-diethylamino-α-methylacetanilides (XVIII):



(XVIII)

are generally more potent than the racemates, and the (+)-isomers are less potent; a definite correlation was observed between the magnitude of the specific rotation and the difference in activity between the (+)- and the (-)-isomers. Although these are preliminary results, in our view they are of fundamental importance for establishing the mechanism by which local anaesthetics act.

To conclude this section, we should mention the high activity of the amides of *N*-alkylpipecolinic, *N*-alkylnipecotinic and *N*-alkylisonipecotinic acids[254-256]; in this series the activity decreases in the ratio 7 : 2 : 1 and the toxicity in the ratio 2.7 : 1 : 1, that is, the *N*-alkylpipecolylanilides have the best therapeutic effect; these include such useful anaesthetics as carbocaine (XIX*a*)[255] and mepivacaine (XIX*b*)[256]:

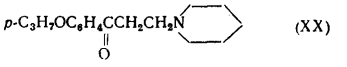


a) R=CH$_3$, *b*) R=H (XIX)

The amino-acid amides therefore include many compounds having very high local anaesthetic activity, although they do not contain the anaesthesiophore grouping.

2. Amino-Ketones

Because the –O–, –S–, –NH–, and –CH$_2$-groups are isosteric, the hetero-atom X between the carbonyl group and the alkyl chain may be replaced by a methylene group without loss of local anaesthetic properties. The well-known amino-ketone anaesthetic falicaine (XX) is 10 times as active as cocaine or procaine[257]:



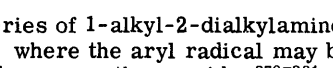
(XX)

Between 1950 and 1960, a large number of falicaine homologues and analogues were prepared[258-271]. It was found that, in contrast to other types of compounds (see above), piperidine was the most active nitrogen residue in this series of compounds, and alkylation of the piperidine in position 4 (with an ethyl or particularly with a butyl radical) increased the strength and duration of the anaesthetic activity[258,259]; moreover, the activity decreased in the order: pyrrolidine > morpholine > diethylamine > dimethylamine[260]. However, some morpholine, dipropyl and dibutylamino-analogues deserve attention, because they are less toxic and therefore therapeutically more effective than falicaine[261-264]; for example, *p*-butoxy-β-dibutylaminopropiophenone with a toxicity one-seventh that of falicaine is 10 times as active as cocaine and 17 times as active as procaine[264]. As a nuclear substituent, the C$_5$H$_{11}$O-group[260,265] gives the optimum effect in the β-piperidinopropiophenones, and the heptyloxy-group[261] in the morpholine analogues.

Further lengthening of the chain in both these groups reduces the activity. It is surprising that the butyl and isopentyl homologues of falicaine are not only more active, but also less toxic[266], although the toxicity usually increases with the size of R. When a normal alkyl is replaced by a branched or cyclic alkyl, the therapeutic effect is enhanced because of a decrease in toxicity; in contrast, the presence of unsaturated residues in the alkoxy-group impairs the pharmacological properties. Other modifications of falicaine have been examined, but, notwithstanding extensive research, falicaine is still superior[266,270,271] in its combined physiological properties (activity, toxicity, and lack of irritancy) to all closely related analogues.

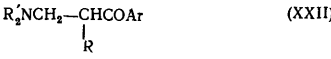
The amino-ketones containing a diphenyl, diphenylmethane or benzidine residue instead of the phenyl nucleus, which were described by Profft[272] in 1960, form a characteristic group of falicaine analogues. These compounds have a high surface anaesthetic activity, the diphenylmethane derivative being equal to falicaine. Surprisingly, it was found that the introduction of an alkoxy-group reduces the activity. The phenyl nucleus linked to the carbonyl group may be replaced by a heterocyclic residue such as that of piperidine[273], phenothiazine[274], or hexamethylamine[275]; some of these compounds have a prolonged and powerful action.

Of other active amino-ketones, some analogues of amidone (XXI)[276-279] deserve mention:



(XXI)

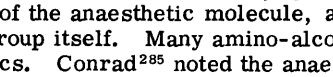
and also the series of 1-alkyl-2-dialkylaminoethyls aryl ketones (XXII), where the aryl radical may be anthracene, fluorene, thiophene, or other residue[279-284]:



(XXII)

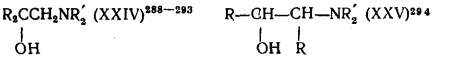
3. Amino-Alcohols

A hetero-atom linked to the carbonyl group is not an essential part of the anaesthetic molecule, and neither is the carbonyl group itself. Many amino-alcohols are effective anaesthetics. Conrad[285] noted the anaesthetic properties of ephedrine and Kupchik[286] showed that a 1% solution of ephedrine produces anaesthesia only slightly inferior to that produced by procaine. The local anaesthetic properties of quinine and its derivatives are well known. The synthetic amino-alcohols prepared by Epstein[287] (XXIII):



(XXIII)

are highly effective anaesthetics when R contains 4 to 6 atoms of carbon on the *o*- or *m*-positions. Compounds containing two phenyl, naphthyl, cyclohexyl, phenothiazine, or thiophene residues R (XXIV – XXV) have anaesthetic properties:

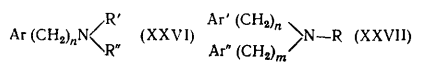


But on the whole the amino-alcohols as anaesthetics have been comparatively little studied; until recently attention has been mainly devoted to their action on peripheral nerve endings, in particular to their spasmolytic, vasodilating, and antihistaminic properties.

4. Amines

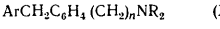
Compounds that have no ester, amide, or carbonyl group may have local anaesthetic properties. Some simple amines, in fact, are highly active. Unfortunately, in most

reports on these, quantitative pharmacological characteristics are not given, which makes comparisons difficult. However, it has been firmly established that *NN*-dialkylaralkylamines (XXVI) and *NN*-diaralkylalkylamines (XXVII):



(XXVI) (XXVII)

have anaesthetic properties. Compounds of type (XXVI) combine analeptic, spasmolytic, and antinarcotic properties[295-298] with anaesthetic activity. Some of these — for example, compounds with a diphenylmethane structure (XXVIII) — are much superior to procaine[299,300] in the rapidity and duration of their action:



(XXVIII)

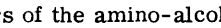
Heinzelmann[301,302] found that compounds of type (XXVII) containing alkoxy-groups in the nucleus with branched alkyl chains — for example, *N*-benzyl-*N*-(2-*o*-methoxyphenylisopropyl)alkylamines — had good pharmacological properties. The presence of a double bond in the chain between the aromatic residue and the nitrogen, or replacement of the aromatic by a heterocyclic residue, confers analgesic activity on the molecule, and in some compounds the local anaesthetic activity is completely suppressed[303-307].

Of the secondary amines, the *NN*-diaralkylamines have attracted most attention. Even *NN*-di-(2-phenylethyl)amine has some activity, and introduction of alkoxy-groups or the *p*-$(C_2H_5)_2N$-group into the aromatic nucleus leads to such effective preparations as *NN*-di-(2-*o*-methoxyphenylisopropyl)amine, which is 200 times as active as cocaine in surface anaesthesia, and 2 to 4 times as active as amethocaine in infiltration anaesthesia, with lower toxicity[308].

Although esters of the amino-alcohols with a primary amino-group are generally inactive (see above), some primary amines are active anaesthetics. As Niinobe[309,310] has shown, the physiological action of the primary amines depends more on molecular weight than on structure. Thus the alkyl and phenylalkylamines first show anaesthetic activity when the total number of carbon atoms in the molecule reaches 11, and the activity increases with the molecular weight; but the diphenylalkylamines (which have more than 11 carbon atoms) are all pharmacologically active. The molecular weight of the aromatic amines is also significant; the anaesthetic activity of the 2-alkoxy-4-nitroanilines increases markedly with the size of the alkyl group[311-313]. Unfortunately, most of the primary amines are strong irritants, which diminishes their value as anaesthetics. The *m*- and *p*-benzhydrylamines are the only exceptions here; these are sufficiently active but non-irritant to tissue.

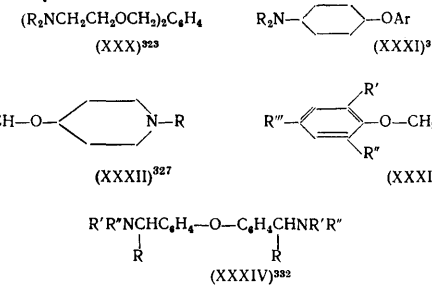
In contrast to procaine derivatives, in which quaternisation of the nitrogen generally eliminates the activity, the aralkyltrimethyl- and aralkyltriethylammonium bromides are powerful and long-acting anaesthetics[314].

Many papers have been published on amino-ethers; as in the esters of amino-alcohols, the introduction of an aromatic residue R' into the molecule (XXIX) confers local anaesthetic properties[315], whereas an aliphatic or an



(XXIX)

alicyclic residue does not[316]. A special feature of compounds of this type is the enhancement of anaesthetic activity on the introduction of halogen, CN-, COOR-, or other groups[317-321,329] into the phenyl nucleus. A great variety of amino-ethers [(XXX) – (XXXIV) and others] have been prepared by different workers; some of these are superior to cocaine and procaine in activity and they have few side-effects[322-336]:



(XXX)[323] (XXXI)[324] (XXXII)[327] (XXXIII)[326-331]

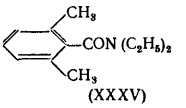
(XXXIV)[332]

The best anaesthetics of this type are the ethers of substituted isoquinoline[337,338]. Thus, some 3-alkyl-1-(2-diethylaminoethoxy)isoquinolines are active at concentrations lower than 0.001%, while the 3-butyl homologue (cuotan) is 1000 times as active as cocaine and 10 times as active as cinchocaine, with only half the toxicity of cinchocaine[338]. Compounds containing other heterocyclic rings, for example, phthalazine[339] or 4,5-diphenylthiazole[340], are active, but some of them are toxic. Replacement of oxygen by sulphur does not improve the properties of the compounds: the thio-derivatives are not superior to procaine, but they have antihistaminic properties[322,341].

To conclude this section, we shall mention the anaesthetic activity of heterocyclic compounds in which nitrogen enters into the ring, usually six-membered[342-365]. Derivatives of dihydroisoquinoline are the most valuable of these, especially 6-benzyloxy-7-methoxy-1-methyldihydroisoquinoline, a 0.15% solution of which produces more prolonged anaesthesia than a 1% solution of procaine[342,343]. Thus, a great variety of amines have local anaesthetic activity.

5. Simple Amides and Amidines

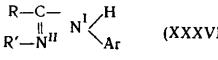
As mentioned above, some amides containing another NH_2-group are highly active pharmacologically, for example, cinchocaine and lignocaine. However, simple substituted amides, such as lidocaine (XXXV)¶:



(XXXV)

have powerful anaesthetic properties; 4-hydroxylidocaine is less active but also less toxic than lidocaine[366], and many other amides of aromatic and aliphatic–aromatic acids[367-371] are also active.

Many of the amidines (XXXVI) (compounds in which the >CO-group of the amides is replaced by the >C=N–R'-group) are more, rather than less, effective than the amides[372].



(XXXVI)

Like the amides, the amidines in which R is an aromatic or heterocyclic radical[372-378] are generally active. The only known exceptions are some acetamidines that have aromatic radicals attached to the N^I or N^{II} atoms[379] and act as

¶ The term "lidocaine" is used in some papers as a synonym for lignocaine (xylocaine).

local anaesthetics. Only fragmentary work has been done on the effect of other structural details on the activity of the amidines. For example, it has been found that the activity and toxicity increase[375-378,380] with the size of the alkyl radicals at N^I and N^{II}. The most active compounds have N^I and N^{II} dibutyl or diisobutyl, or N^I-monoaryl (especially with Ar-*p*-$CH_3C_6H_4$)[377] substituents. It has also been established that the introduction of a *p*-alkylthio-group into the benzamidine nucleus enhances the infiltration activity[375], but *p*-carboxylation diminishes it[381].

Finally, local anaesthetic activity, sometimes fairly high, has been found in a number of derivatives of guanidine, urea, hydantoin, carbonic acid[382-385], and also in some barbiturates and thiobarbiturates[386-389].

6. Compounds Not Containing Nitrogen

The work reviewed above is concerned with nitrogen-containing compounds. This is the only element common to these compounds that can be considered essential for anaesthetic activity. It is true that the anaesthetic properties of several alcohols, for example, octanol, salicyl alcohol, benzoylmethanol, etc. have been known for over 50 years, but as they have only surface anaesthetic activity and this is weak, they were regarded as forming an exception that did not violate the essential nitrogen concept. However, in 1950–1955, the preparation was described[390-392] of polyethyleneoxyethers (XXXVII) having considerable surface and infiltration activity, which reaches a maximum when R = $C_{12}H_{25}$ and n = 9.

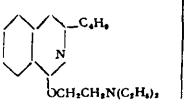
$$RO(CH_2CH_2O)_nCH_2CH_2OH \qquad \text{(XXXVII)}$$

During the same period, Kuhn and Dury[393] discovered the very powerful anaesthetic effect of diethyl-α,δ-dihydroxyadipate monobenzoate (XXXVIII):

$$C_2H_5OOCCH(OCOC_6H_5)-CH_2CH_2CH(OH)COOC_2H_5 \qquad \text{(XXXVIII)}$$

and of the bisalicyl esters of furandicarboxylic acid, which approach cocaine in physiological activity[394]. Recently, local anaesthetic activity was reported in polyglycol esters of benzoic and cinnamic acids[395-397], and in the alkyl esters of 3,5-dipropyl-4-allylhydroxybenzoic acid, which also have analgesic and narcotic properties[398]. Although these facts are still comparatively few, they show conclusively that organic compounds of the most diverse kind can act as local anaesthetics†.

TABLE 5. The most effective local anaesthetics.

Name	Formula	Pharmacological properties	References
Diethylaminoethyl *p*-ethylthiocinnamate	*p*-$C_2H_5SC_6H_4CH$= =$CHCOOCH_2CH_2N(C_2H_5)_2$	5 times as powerful as procaine by intravenous injection, and 20 times the surface action	63
Diethylaminoethyl 4-amino-2-hexyloxy-thiolbenzoate	4-NH_2-2-$C_6H_{13}OC_6H_3$— —$COSCH_2CH_2N(C_2H_5)_2$	500 times as active as cocaine and 60 times as toxic with slight irritancy	60
Diethylaminoethyl *N*-*p*-butoxyphenyl-*N*-phenylcarbamate	*p*-$H_9C_4OC_6H_4N$(C$_6$H$_5$)—$COOCH_2CH_2N(C_2H_5)_2$	76 times as powerful as cocaine in surface anaesthesia and 40 times as powerful as procaine in infiltration anaesthesia	139
1-Ethyl-2,2-dimethyl-3-dimethylamino-1-phenylpropan-1-ol-phenoxyacetate	C_2H_5, $OCOCH_2OC_6H_5$, C_6H_5—C—C—CH_2—$N(CH_3)_2$, CH_3, CH_3	equal to amethocaine with much lower toxicity	94
Amylaminoethyl 3-amino-5-heptyloxybenzoate	3-NH_2-5-$C_7H_{15}OC_6H_3$— —$COOCH_2CH_2$—N(H)—C_5H_{11}	200 times as active as cocaine	70
Heptyl *p*-(2-morpholinoethoxy)-phenylcarbamate	*p*-$OH_2C_4NCH_2CH_2OC_6H_4$— —$NHCOOC_7H_{15}$	40 times as active as cocaine and twice as active as cinchocaine with lower toxicity	197
N-(2-methyl-2-octyl) piperidinoacetamide	$C_5H_{10}NCH_2CON$—C(CH$_3$)$_2$—$(CH_2)_5$—CH_3	20 to 30 times as active as lignocaine(xylocaine)	243
p-Butoxy-β-dibutylaminopropiophenone	*p*-$C_4H_9OC_6H_4COCH_2CH_2N(C_4H_9)_2$	10 times as active as cocaine and 17 times as active as procaine with toxicity one-seventh that of falicaine	244
NN-di-(2-*o*-methoxyphenylisopropyl)-amine	[*m*-$CH_3OC_6H_4C(CH_3)_2$]$_2$NH	200 times as active as cocaine in surface anaesthesia; 2 to 4 times as active as amethocaine in infiltration anaesthesia	399
3-Butyl-1-(2-diethylaminoethoxy)-isoquinoline		1000 times as active as cocaine and 10 times as active as cinchocaine, with half the toxicity of cinchocaine	399

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† To assist the reader, we have selected the most effective (based on the evidence of the authors of the papers in which they are described) local anaesthetics and tabulated them in Table 5.

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