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Okamoto et al.

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[45] **Oct. 21, 1975**

[54] **POLYMERIC LOCAL ANESTHETIC AND ANTI-ARRHYTHMIC AGENTS**

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[52] **U.S. Cl.** ..... **260/472;** 260/295 PA; 260/326.25; 260/562 R; 424/267; 424/274; 424/310; 424/320

[51] **Int. Cl.²** **C07C 101/56**

[58] **Field of Search** ..... 260/295 PA, 501.11, 518 R, 260/519, 562 R, 472, 326.25

[56] **References Cited**

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Roberts, J. P., *Basic Principles of Organic Chemistry*, (1965), pub. by W. A. Benjamin, Inc.-N.Y. pp. 1107-1109 relied on.

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[57] **ABSTRACT**

Polymers comprising repeating units of local anesthetic moieties covalently bonded by means of an amide linkage to a group derived from a carboxyl of a polymeric acid backbone exhibit local anesthetic and anti-arrhythmic activity similar to the parent moiety but of significantly longer duration.

23 Claims, No Drawings

POLYMERIC LOCAL ANESTHETIC AND ANTI-ARRHYTHMIC AGENTS

BACKGROUND OF THE INVENTION

Local anesthetics are universally used in medicine and dentistry for the blockage of conduction through nerve cells, thereby reducing or eliminating the sensation of pain associated with dental and medical procedures and from disease. Two of the most frequently employed local anesthetic agents are procaine and lidocaine.

While these local anesthetic agents have had extensive use, this use is limited to therapeutic circumstances commensurate with the extents of their durations of action, that is, they produce their anesthetic effect only for relatively short periods of time ranging from a few minutes up to, depending upon dosage, 2 or 3 hours.

In view of the many ailments and conditions which are accompanied by intermittent, constant and presently intractable pain, such as arthritis, neuritis, cancer, and so forth, it would be highly desirable to develop local anesthetic agents having durations of action that would persist for long periods of time, for example, as long as one day or more. Such long-acting local anesthetics would relieve the need for repeated administration of the presently available local anesthetics.

In addition, local anesthetics, particularly lidocaine, have been administered systemically to counteract cardiac arrhythmia. Lidocaine presently is the drug of choice in the management of various vertricular arrhythmias; it is therefore a principal drug for those arrhythmias that occur commonly after myocardial infarctions. However, the extremely short duration of action (minutes) systemically makes therapy difficult and constant intravenous administration by infusion is necessary. Therefore, it would be desirable to have for systemic administration a lidocaine-type local anesthetic drug haveing a longer duration of action, such that single or reasonably spaced single administrations would provide effective and safe anti-arrhythmic effects.

The attachment of biologically active molecules to large, relatively inert, substrates is known in the art. In particular, prior workers have linked biologically-active molecules such as proteins and polypeptides to polymeric backbones. See, for example, U.S. Pat. No. 3,679,653 to Schuck, et al. Catecholamines have also been covalently bound to glass beads to produce biologically active, although insoluble, substances. Venter, et al., *Proc. Nat'l Acad. Sci.*, Vol. 69, p. 1141 (1972).

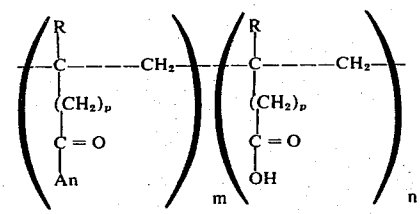
Recently, polymeric drugs containing covalently bound phenothiazine moieties (Japanese Pat. No. 4,734,585) and covalently bound quinine moieties (Russian Pat. No. 364,632) have been prepared by polymerization of the drugcontaining monomers.

In unrelated work, local anesthetic molecules have been combined with polymers to form ionic salts which are disclosed to have local anesthetic properties and be of greater activity and longer duration than the parent drug. See, for example, French Pat. No. 2,116,453, wherein β-diethylaminoethyl-p-aminobenzoate (procaine) was reacted with polyvinyl alcohol carboxymethyl ether to form such an active salt. However, in such compound there is no covalent bond between the polymeric backbone and the drug moiety, i.e., the bond is merely ionic. Furthermore, the salt formation involves the diethylamino group of the drug moiety,

which group is the molecular moiety responsible for the procaine-type action of the drug.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to novel polymeric drugs exhibiting surprisingly long-acting local anesthetic and anti-arrhythmic activities. More specifically, the present invention relates to polymeric long-acting local anesthetics and anti-arrhythmics of the formula



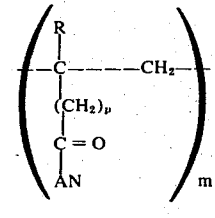
I

wherein An is a radical formed by removal of a hydrogen atom from a free primary or secondary aromatic amino group of a known local anesthetic molecule or an aromatic amino derivative of a known local anesthetic molecule:



An is a covalent amide linkage involving said aromatic amino group of the An moiety; *m* is an integer of from 1 to 1,000; *n* is an integer of from 0 to 1,000 with the proviso that the sum of *m* and *n* is 2 or greater; *R* is hydrogen or lower alkyl; *p* is an integer of from 0 to 5; with the understanding that the repeating units designated within the separate parentheses are arranged in random fashion; and the salts thereof with pharmaceutically acceptable acids and bases.

The polymers represented by formula I may be further subdivided into two main classes: those where *n* is 0 and those wherein *n* is 1 or greater. It will be appreciated that those polymers wherein *n* is 0 represent derivatives of a polymeric acid in which each carboxyl group of the polymeric acid chain is substituted by a local anesthetic moiety. These polymers may be represented by formula II



II

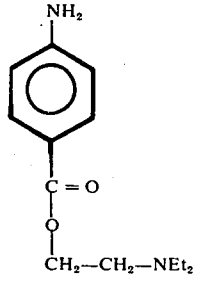
wherein *R*, *p* and *m* are as above, and are preferred embodiments of the class of polymers represented by formula I.

In the second class of polymers, i.e., wherein *n* is 1 or greater, the polymeric acid chain is not completely substituted, and consists of a mixture of units having local anesthetic moieties bonded to the carbonyl group thereof and units having a free carboxyl group. It should be understood that in the latter class of polymers, the units which are substituted and those which have a free carboxyl group are randomly distributed on

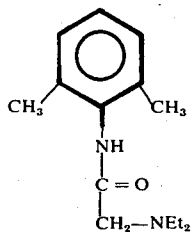
the chain. The method of preparation of both clases of polymers will be described hereinafter.

As mentioned above, the moiety An is derived from either a known local anesthetic which has a free primary or secondary aromatic amino group, or from a primary or secondary aromatic amino derivative of a local anesthetic which does not have a free primary or secondary aromatic amino group. The parent local anesthetic or amino derivative molecule is represented by the designation AnH. The two classes of radicals represented by An may be more fully described by reference to some known local anesthetic drugs.

Known commonly used local anesthetics themselves fall into two main chemical classes of compounds: esters, basic esters and basic amides of benzoic acid and their derivatives; and basic amides of aniline and their derivatives. For example, to illustrate both classes of local anesthetic agents, the formulas for procaine the lidocaine are presented below. Procaine is an example of the former class (benzoic acid ester) and lidocaine is an example of the latter (aniline amide)



procaine



lidocaine

Procaine is an ester of para-aminobenzoic acid with β-diethylamino ethanol. Lidocaine is an amide of 2,6-dimethyl aniline was β-diethylaminoacetic acid.

Procaine is an example of a local anesthetic moiety which contains a free primary aromatic amino group, and lidocaine is an example of such a moiety for which it is necessary, in order to link to the polymeric backbone, to first introduct a free amino group into the aromatic ring.

Further examples of known local anesthetic agents which contain free primary or secondary amino groups in the aromatic ring are as follows: benzocaine, procaine amide (amide of P-aminobenzoic acid with N,N-diethylethylenediamine), butacaine, benoxinate, nesacaine, proparacaine, tetracaine and propoxycaine.

Further examples of local anesthetic agents which do not contain a free primary or secondary aromatic amino group are as follows: cyclomethycaine, mepivacaine, hexylcaine, diperodon, and dibucaine.

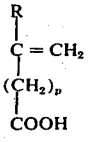
The above mentioned known local anesthetics may contain a variety of substituents of the aromatic ring as well as on the basic side chain. Substituents on the aromatic ring include lower alkoxy groups (e.g., propoxy, butoxy), cycloalkoxy groups (e.g., cyclohexyloxy, cyclopentyloxy), halogen groups (e.g., chloro or bromo) and so forth. The basic nitrogen in the side chain may be substituted by two lower alkyl groups (e.g., dimethyl, diethyl, dibutyl), one lower alkyl group and one cycloalkyl group, or may form a part of a ring such as a piperidine or pyrrolidine ring.

Amino derivatives of local anesthetic agents which do not have a free primary or secondary amino group in the aromatic ring may be prepared by standard techniques well known in the art. For example, an amino group may be introduced by nitration of the aromatic ring using standard nitrating techniques (such as the use of nitric acid and sulfuric acid) followed by reduction of the nitro group to an amino group, again using standard techniques (for example, reaction with phenylhydrazine or reduction with hydrogen and Raney nickel catalyst). To prepare a amino derivative of a local anesthetic agent, it is in many cases simpler to start with a simple benzoic acid or aniline derivative, and complete the basic side chain after partial or complete construction of the desired amino group.

Thus, for example, for the preparation of an amino-substituted lidocaine, a typical sequence might involve: conversion of 2,6-dimethylaniline to its N-chloroacetyl derivative by use of, for example, chloroacetyl chloride; nitration of this compound to afford a mixture of nitro-derivatives, primarily the derivative having the nitro group meta to the substituted amine; completion of the amide side chain, to that of lidocaine, utilizing diethylamine, and then reduction of the nitro group to an amino group using phenylhydrazine or hydrogen in the presence of Raney nickel catalyst.

Other techniques for introducing an amino group into the aromatic ring of a local anesthetic, or precursor thereof, will be readily apparent to one skilled in the art.

The acids which may be utilized either as free acids, or in an activated form to form the polymer backbone of the present compounds are alkenoic acids of formula III



III

wherein R and *p* are as above.

Among the acids which may be mentioned are:

R = H	p = 0	acrylic acid (propenoic acid)
R = CH_3	p = 0	methacrylic acid (2-methylpropenoic acid)
R = C_2H_5	p = 0	2-ethylpropenoic acid
R = C_3H_7	p = 0	2-propylpropenoic acid
R = C_4H_9	p = 0	2-butylpropenoic acid
R = H	p = 1	3-butenoic acid
R = CH_3	p = 1	3-methyl-3-butenoic acid
R = C_2H_5	p = 1	3-ethyl-3-butenoic acid
R = H	p = 2	4-pentenoic acid
R = CH_3	p = 2	4-methyl-4-pentenoic acid
R = C_2H_5	p = 2	4-ethyl-4-pentenoic acid
R = H	p = 3	5-hexenoic acid
R = CH_3	p = 3	5-methyl-5-hexenoic acid
R = C_2H_5	p = 3	5-ethyl-5-hexenoic acid
R = H	p = 4	6-heptenoic acid
R = CH_3	p = 4	6-methyl-6-heptenoic acid
R = C_2H_5	p = 4	6-ethyl-6-heptenoic acid
R = H	p = 5	7-octenoic acid
R = CH_3	p = 5	7-methyl-7-octenoic acid
R = C_2H_5	p = 5	7-ethyl-7-octenoic acid

Preferred acids (or derivatives thereof) which may be incorporated into the polymer backbone are acrylic acid and methacrylic acid. Acrylic acid is particularly preferred.

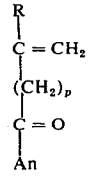
The formation of a covalent amide bond between the An moiety and the carbonyl of the monomeric or polymeric acid, or derivative thereof, as hereinafter described, is accomplished by standard techniques for forming such bonds.

In general, one may form such a bond by reaction of an activated derivative of the carboxyl group of a monomeric or polymeric acid with the amino group of the molecule AnH. Examples of activated derivatives of the aforementioned carboxyl group are, acyl halides (e.g., acryloyl chloride or polyacryloyl chloride); activated esters (e.g., acryloyl or polyacryloyl p-nitrobenzoates); carbonyl imidazoles; and so forth.

Other methods for formation of the amide bond involve direct coupling of the carboxyl group of the monomeric or polymeric acid moiety with the amino group of the AnH moiety. Reagents which are commonly employed for this purpose are dehydrating agents well known in peptide chemistry such as the carbodiimides, for example, dicyclohexylcarbodiimide (DCC).

The polymeric drugs themseleves are formed in different fashion depending upon the nature of the final polymer, i.e., whether n is 0, or whether n is 1 or greater.

To prepare a polymer with n as 0, i.e., a polymeric acid derivative having all carboxyl groups substituted by an An moiety, it is necessary to polymerize a monomer having a polymerizable alkenoyl group covalently bonded to the An moiety, that is, a monomer of the formula



IV

wherein An, R and p are as above.

In such a case, the monomer is first prepared by reacting an appropriate polymerizable alkenoic acid or an acitvated carboxyl derivative thereof, as hereinbefore described, with the local anesthetic molecule, or amino derivative thereof, represented by AnH. The method of preparation of a polymer drug by polymerization of a monomer containing the drug moiety is yet another aspect of the present invention and provides polymer drugs having a very high density of drug moieties.

If it is desired to prepare a polymeric drug where n is 1 or greater, this is done by coupling a polymeric acid, or an activated carboxyl derivative thereof, with the local anesthetic agent, or amino derivative thereof, AnH. In such a procedure, only some of the available carboxyl groups are converted to amides. The nature of extent of substitution will depend upon the reaction conditions, the nature of the polymer utilized, and the drug being coupled.

As aforementioned, the preparation of polymeric drugs wherein n is 0 involves polymerization of a monomer containing the An moiety. Particularly preferred An moieties for this purpose are those derived from procaine, procaine amide and amino derivatives and lidocaine, and particularly preferred monomers of polymerization are acrylyl amides, i.e., where p is 0 and R is hydrogen.

The size of polymer obtained from polymerization of a monomer containing the An moiety will depend greatly upon the reaction conditions, and the nature of the alkenoyl and An moieties. The particular polymerization parameters chosen, for example, solvents, concentrations, temperature, initiator, and so forth, are common variables of all polymerizations and are best left to the discretion of one skilled in the polymerization art. However, a brief mention of solvents that may be employed in the polymerization reaction include, for example, water, lower alkanols such as methanol and ethanol, ethers such as tetrahydrofuran and dioxane, and mixtures of the above.

Suitable polymerization initiators that may be utilized include the common free radical polymerization initiators such as peroxides, e.g., benzoyl peroxide, acetyl peroxide, butyryl peroxide, ditertiary butyl peroxide, lauroyl peroxide, and so forth; azo compounds, e.g, azobisisobutyronitirile; and ultraviolet irradiation. The exact size (molecular weight) of the polymer resulting from any particular set of polymerization conditions will vary depending upon the choice of solvents, initiator, temperature, pressure, concentration, pH, nature of the An moiety and so forth.

To illustrate this, it might be mentioned that polymerization of acrylylprocaine under neutral conditions in organic solvents has afforded polyacrylyl procaines having average molecular weights in the 3,000–6,000 dalton range, i.e., where m ranges from 10 to 20. On the other hand, polymerization of acrylylprocaine in acidic aqueous or methanolic solution at about pH 2 affords polymers of much higher average molecular weight, averaging approximately 100,000 daltons (m is approximately 300 to 400). Similar results may be obtained by polymerization of acrylylprocaine amide.

Polymerization of the monomer derived from meta- or para- amino lidocaine in organic solvents under neutral conditions affords polymers having an average molecular weight of from about 3,000 to 6,000 daltons (m is 10 to 20), generally in the range of about 5,000 daltons ($m = 17$).

The preparation of polymers wherein n is 1 or greater will, of course depend upon the specific polymeric acid, or derivative thereof, which is chosen to form the polymeric drug.

One can choose a polymeric acid or derivative having a wide range of molecular weight or, alternatively, one may begin with a polymeric acid or derivative thereof of relatively narrow molecular weight range. If it is desired to separate the product into discreet molecular weight ranges this can be done by standard techniques such as a gel filtration.

For example, reaction procaine with polyacryloyl chloride (average m.w. 8,000–10,000) affords a polymer with a wide molecular weight range. This can be separated into discreet fractions, for example, a fraction of low molecular weight, in the 3,000 to 6,000 dalton range, averaging about 5,000 daltons, ($m + n$ is 10 to 20) and a fraction of high molecular weight, approximately 90,000 to 120,000 daltons, averaging about 100,000 daltons ($m + n$ is 300 to 400).

The polymeric drugs which are formed may be converted to pharmaceutically acceptable salts. Since all of the compounds possess an amine function in the side chain of the ester or amide portion of the molecule, they can be converted to acid addition salts of said amine. Suitable pharmaceutically acceptable acid addition salts include salts with mineral acids such as hydrochloric acid and sulfuric acid; and salts with organic acids such as acetic acid, maleic acid, tartaric acid, and so forth. In those compounds wherein n is 1 or greater,

there are free carboxyl groups present so that the polymers may be converted to salts with pharmaceutically acceptable bases. Examples of pharamceutically acceptable bases are alkali metal salts, such as sodium or potassium, alkaline earth metal salts, such as calcium or magnesium, and salts with amines such as ammonia, diethylamine, pyridine, and so forth.

The physical characteristics of the polymers vary greatly depending upon the molecular weight and the number of An moieties substituted thereon. In general, the polymers, either in free form or as acid or basic addition salts, exhibit solubility in aqueous media, said solubility decreasing with increasing molecular weight of the polymer. The high degree of aqueous solubility of the polymers is due to a large extent to the substantial absence of cross-linking. In soluble form, the polymeric products have the advantages of suitability for administration in solution or suspension, as well as their inherent greater stability and prolonged activity as compared with the parent known local anesthetics.

As mentioned earlier, the gross pharmacology of the polymeric drugs represented by Formula I is very similar to that of the parent local anesthetic agents. In those cases where the parent local anesthetic agent does not contain an aromatic amino group (for example, lidocaine), comparison should be made with the amino derivative (for example, meta- or para- aminolidocaine) as well as the unsubstituted parent (e.g., lidocaine).

Systemic toxicity testing of these compounds furnishes precise data for potency comparisons and also provides general evidence of pharmacological actions characteristic of local anesthetic-type drugs. For example, in toxicity studies on mice involving intravenous administration of the drug, the polymeric derivatives exhibit exactly the same systemic effects as the parent drug: respiratory paralysis, clonic convulsions, and CNS hyperexcitability. Death, when it occured, characteristically resulted from both centrally and peripherally induced failure of respiration. The LD_{50} for the polymers as compared with the parent drugs is generally of the same order of magnitude.

The great difference between the polymeric drugs and their parent drugs in in the onset and duration of action. In general, the onset of action of the polymeric drugs is slower than that of the parent drugs, as is the average time to death, when death occurs. For example, using lidocaine hydrochloride, those animals that do not die recover completely within two to three minutes, whereas with polyacrylyl-meta-aminolidocaine, full recovery occurs, but requires two to three hours. Similar results are obtained with polyprocaine and with other polylidocaine derivatives, regardless of the exact nature of the polymer, i.e., the value of *m* and *n*.

In in vitro tests utilizing excised frog sciatic nerves, dramatic differences in onset and duration of activity can also be demonstrated by measuring conduction in nerve. In vivo nerve blockage, as demonstrated in the tail flick test, gave similar results.

The polymeric drugs of the present invention exhibit the identical gross anti-arrhythmic effects as do the parent local anesthetics, as demonstrated in the anesthetized cat in which ventricular arrhythmias are induced by epinephrine. Again, the striking difference between the parent local anesthetics and certain polymers is in the duration of action, which is prolonged like that observed in the toxicity and nerve conduction studies mentioned above. Preferred polymers having extended durations of anti-arrhythmic action are those derived from procaine and procaine amide.

The preparation of a variety of polymeric local anesthetic and antiarrhythmic agents, as well as experiments demonstrating their biological properties, are presented in the following specific examples. The examples are for illustrative purposes only and are not to be construed as limiting the present invention in any fashion.

EXAMPLE 1

Polyacryloyl chloride was prepared as follows. Acryloyl chloride, 60 ml (freshly distilled) and 1.0 g of azobisisobutyronitrile were dissolved in 60 ml of freshly distilled dioxane. The dioxane solution was placed in a 500 ml round bottom flask and the stopper was tightened by wires. The solution was kept 48 hours at 50°C. of an oil bath. To the resulting homogeneous dioxane solution, was added 200 ml of benzene, whereupon the gummy polymer was precipitated out. The solvent was decanted. The polymer was dried by water aspirator. It was reprecipitated by first dissolving in tetrahydrofuran (heating) and then by adding benzene. The resulting polyacryloyl chloride was dried under high vacuum, and had an average molecular weight of 8,000–10,000.

EXAMPLE 2

Polyacryloyl chloride (average molecular weight 8,000–10,000) 10 g, 0.11 mole, was dissolved in 50 ml of dry tetrahydrofuran by stirring for 2.5 hrs. at 65°C. Procaine hydrochloride (29.9 g, 0.11 mole, Abbott Labs) was added to the tetrahydrofuran solution, and magnetically stirred overnight between 40°–60°C. The solvent was removed under vacuum. The polymeric residue was dissolved in 200 ml of dry dimethyl sulfoxide by stirring overnight at 40°C. The polyacrylylprocaine was precipitated out by the addition of benzene and was washed several times with benzene and with hot benzene. The polymer was dried under high vacuum overnight. The polymeric product was treated with hot ethanol in order to remove a trace amount of monomeric or low molecular weight procaine compounds and was again dried under the high vacuum to give the solid polymeric product. This material was separated on a Sephadex G-100 or G-200 column in aqueous solution to afford high molecular weight (>100,000 daltons, average — *m:n* ratio 1:1.7) and low molecular weight (approximately 5,000 daltons, average — *m:n* ratio 1:0.5) fractions.

EXAMPLE 3

A solution of procaine hydrochloride (54.4 g, 0.2 mole) in 1 l. water was neutralized with 10 g sodium bicarbonate to pH 7–8. Anhydrous sodium acetate (65.6 g) was added in aqueous solution, and stirred vigorously at 0°–5° with the aid of external ice-cooling.

Acryloyl chloride (54 g, 0.6 mole), freshly distilled and dissolved in 100 ml acetone, was dropwise added to the aqueous solution over a period of 20 mins. After 30 mins. of striing at 0°–5°, the mixture was made alkaline to pH 8–9 with 200 g sodium bicarbonate. The aqueous solution was salted with 100 g sodium chloride, and the undissolved sodium chloride was filtered off. The aqueous filtrate was extracted with 5 × 100 ml ether. The ether layer was dried over anhydrous potassium carbonate and concentrated. The crude product was recrystallized by dissolving in benzene and adding

petroleum ether to yield 25 g of acrylylprocaine was a white powder; m.p. 73°–5°. $\mu_{max.}^{CHCl_3}$ 1715 cm^{-1}. $\lambda_{max.}^{EtOH}$ 290 nm.

Anal. Calcd. for $C_{16}H_{22}N_2O_3$: C, 66.2; H, 7.58; N, 9.65. Found: C, 66.0; H, 7.68; N, 9.85.

EXAMPLE 4

Polymerization of Acrylylprocaine

Monomeric acrylylprocaine from Example 3 (5g) was dissolved in 30 ml of freshly distilled dioxane. Azobisisobutyronitrile (0.25 g, 5 weight %) was added. The resulting dioxane solution was degassed twice by freezing and melting under high vacuum. The sealed polymerization tube was heated 3.5 days at 50°–70° in an oil bath. Benzene (400 ml) was added with stirring to the dioxane solution. The polymer precipitate was filtered and dried at high vacuum to yield 3.1 g polyacrylylprocaine, $\nu_{max.}^{CHCl_3}$ 1700 cm^{-1}, $\lambda_{max.}^{H_2O}$ 292 nm.

The polymerization conditions for the preparation of a number of polyacrylylprocaines are presented in the following table:

Polymerization conditions				
weight monomer	solvent	catalyst (azobisiso-butyronitrile)	average mol. wt. product	sample no.
2 g	30 ml (dioxane)	0.2 g	3,900	1
5 g	30 ml (dioxane)	0.25 g	5,030	2
5 g (HCl salt)	50 ml (water)	0.1 g	100,000	3
5 g (HCl salt)	50 ml (water)	0.2 g	100,000	4

The latter two polymers of average m.w. ~100,000 are not appreciably soluble in water, dioxane or methanol. The first two polymers are soluble in water and organic solvents.

EXAMPLE 5

α-Diethylamino-3-amino-2,6-dimethylacetanilide (meta-amino lidocaine) was obtained via a typical sequence involved conversion of 2,6-dimethylaniline to its 1-chloroacetyl derivative with chloroacetyl chloride and nitration (HNO_3—H_2SO_4) to afford meta-nitro lidocaine; for a typical reaction, chloroacetyl chloride (12 ml) was added with vigorous stirring to a solution of 2,6-dimethyl aniline (22 g) and dry pyridine (11.6 ml) in 750 ml benzene.

The 1-chloroacetylamino-2,6-dimethylbenzene precipitated was collected. washed with water and dried. Recrystallization from benzene gave white crystals. To a solution of 11.0 g of the 1-chloroacetylamino-2,6-dimethylbenzene in 30 ml of concentrated sulfuric acid was added with stirring at 5°C, a mixture of 45 ml of nitric acid ($d = 1.4$) and 9 ml of concentrated sulfuric acid. After 24 hours standing at room temperature, the solution was poured into 600 ml of water, made alkaline with concentrated ammonia and the 1-chloroacetylamino-2,6-dimethyl-3-nitrobenzene obtained was filtered. The compound was recrystallized from ethyl alcohol. The chloroacetyl derivative (8.2 g) was refluxed for 10 hrs with diethylamine (10 ml) in 60 ml dry benzene. After cooling the reaction mixture was filtered and then extracted thoroughly with 2 N hydrochloric acid. The extract was made alkaline with 4 N sodium hydroxide. The α-diethylamino-nitro-2,6-dimethylacetanilide obtained was recrystallized from ethyl alcohol. The nitro compound (8.2 g) dissolved in ethyl alcohol (70 ml) was hydrogenated at room temperature under 50 psi hydrogen pressure over Raney nickel (0.7 g) for 10 hrs. The catalyst was filtered off and the solvent was evaporated in vacuo. The residue was recrystallized from ethyl alcohol, to afford α-diethylamino-3-amino-2,6-dimethyl-acetanilide (meta-aminolidocaine), m.p. 145°–147°C. Para-aminolidocaine was synthesized according to the method of Dahlbom, et al, *Acta. Chem. Scand.*, 13, **1145** (1959).

EXAMPLE 6

12 g (0.13 mole) of acryloyl chloride in 30 mol of tetrahydrofuran was added with vigorous stirring to a solution of 25 g (0.1 mole) m-aminolidocaine and 10 ml (0.13 mole) dry pyridine in 50 ml tetrahydrofuran at 0° to 5°C. The α-diethylamino-3-acrylylamido-2,6-dimethylacetanilide (acrylyl-m-aminolidocaine) obtained was collected and washed with water and then dried. The compound was purified by repeated precipitation from benzene solution by adding petroleum ether.

Anal. Calcd for $C_{17}H_{25}N_3O_2$: C, 67.33; H, 8.25; N, 13,86. Found: C, 67.75; H, 7.69; N, 13,94.

EXAMPLE 7

Acrylyl-m-aminolidocaine (5 g) was dissolved in 40 ml of freshly distilled dioxane. Azobisisobutyronitrile (0.25 g) was added. The dioxane solution was degassed twice by freezing and melting under reduced pressure. The polymerization was carried out in sealed tubes at 50°–60°C for 4 days. The polyacrylyl-m-aminolidocaine obtained was precipitated by adding petroleum ether into the dioxane solution and the solid was repeatedly washed with benzene. The average molecular weight of the polymer was found to be 4800.

EXAMPLE 8

Using similar procedures to those in Examples 6 and 7, there were also prepared acrylyl-p-amino-lidocaine;

Anal. Calcd. for $C_{17}H_{25}N_3O_2$: C, 67,37; H, 8.25; N, 13.86. Found: C, 66.55; H, 8.21; N, 13.58.

and polyacrylyl-p-aminolidocaine, average m.w., approximately 4800.

EXAMPLE 9

A solution of procaine amide hydrochloride (85 g, 0.31 mole) in 1.5 1. water was neutralized with 20 g sodium bicarbonate to pH 7–8. Anhydrous sodium acetate (110 g) was added in aqueous solution, and stirred vigorously at 0°–5° with the aid of external ice-cooling.

Acryloyl chloride (82 g, 0.90 mole), freshly distilled was dropwise added to the above aqueous solution over a period of 30 min. After additional 30 min. of stirring at 5°, the mixture was made alkaline to pH 9 with 5% sodium hydroxide and extracted with 3 × 500 ml chloroform. The chloroform layer was dried over anhydrous sodium carbonate. The crude acrylylpropcaine amide was purified by repeatedly dissolving in chloro-

form and adding petroleum ether, to yield 65 g of acrylylprocaine amide; m.p. 127°–128°.

Anal. Calcd. for $C_{16}H_{23}N_3O_2$: C, 66.4; H, 7.95; N, 14.5. Found: C, 66.2; H, 7.62; N, 15.0.

EXAMPLE 10

Acrylylprocaine amide (10g) was dissolved in 100 ml of freshly distilled dioxane. Azobisisobutyronitrile (0.5 g) was added. The resulting mixture was placed in a polymerization tube and degassed twice by freezing and melting under reduced pressure. The solution was heated 3 days at 50°–60° in an oil bath. As the polymerization proceeded, the solution became semi-transparent and some of the polymer was precipitated. After 3 days reaction, 200 ml of dioxane was added to the reaction solution. The polymer produced was precipitated from the dioxane solution by adding petroleum ether to afford 8 g of polyacrylylprocaine amide, average m.w. approximately 4500.

EXAMPLE 11

Toxic Effects in Mice and LD_{50}'s

Test Methodology

The drugs tested were dissolved as hydrochlorides in mammalian physiological saline; in one instance a polyacrylyl procaine (Example 2, high m.w.) was dissolved in dilute NaOH, pH 10.8. The solutions were adjusted so that all doses were administered in a volume of 0.1 ml/10 gm in a tail vein.

Albino mice (Swiss/Webster) of either sex and weighing between 20–25 gm were used. In each test of a compound, the mice were divided into dose groups and in addition to the determination of lethality, the gross signs of poisoning were recorded, as well as the time to onset, duration and recovery from these effects. From plots of percent lethality as a function of the log of dose, LD_{50} values were determined for each compound.

Results

All of the polyacrylyl procaines, polyacrylyl lidocaines and their monomers caused toxic manifestations in mice identical to those caused by the reference compounds: procaine, lidocaine, p-aminolidocaine and m-aminolidocaine. These typical effects included a hyperexcitability of the CNS increasing progressively with dose and block of neuromuscular transmission. Hyperexcitability was evidenced by an increased startle response, tremors, and most severly bh clonic convulsions. Block of neuromuscular transmission was evidenced by a general muscular weakness, ataxia, labored respiration and respiratory failure. Death was due to respiratory failure secondary to both central and peripheral drug actions.

The differences among the compounds tested were quantitative and not qualitative. Potency differences were reflected by LD_{50}'s determined from log dose-response plots in which parallelism of the regression slopes reinforced the common mode of action of all of the tested drugs. The LD_{50}'s are shown in Table I.

TABLE I

Compound	Mol. Wt. or Average Mol. Wt.	Ratio An/Monomeric Unit	LD_{50} Mouse i.v. mg/kg
Procaine.HCl	272	—	69
Polyacrylyl-procaine (Example 2, high m.w.)	~100,000	1/2.7	8.4
Polyacrylyl-procaine (Example 2, low m.w.)	~5,000	1/1.5	144
Acrylylprocaine monomer (Example 3)	290	1	72
Polyacrylyl-procaine (Example 4, sample 1)	3900	1	27
Polyacrylyl-procaine (Example 4, sample 2)	5030	1	41.5
Lidocaine .HCl	270	—	39
m-aminolidocaine (Example 5)	249	—	118
Acrylyl-m-amino-lidocaine monomer (Example 6)	303	1	142
Polyacrylyl-m-aminolidocaine (Example 7)	4800	1	82
p-aminolidocaine	249	—	83
Acrylyl-p-amino-lidocaine monomer (Example 8)	303	—	approx. 110
Polyacrylyl-p-aminolidocaine (Example 8)	4800	1	100

The principal and important differences were in the time course of action. In general, the polymeric local anesthetic drugs exhibited a slower onset and development of the toxic effects and a longer duration of these effects than were shown by the prototype reference drugs, procaine and lidocaine. The time course of action of the monomers resembled that of procaine and lidocaine.

The time course of these drug actions are shown in Table II.

TABLE II

Time Course of the Development of Toxic Signs in Mice Following i.v. Injection

Compound	Dose* mg/kg	Average Time to Onset	Time to Recovery**
Procaine	70	Immed.	3–5′
Polyacrylyl-procaine (Example 2, high m.w.)	10	30″	5–15′
Polyacrylyl-procaine (Example 2, low m.w.)	150	5″	5–10′
Acrylylprocaine monomer (Example 3)	75	Immed.	3–5′
Polyacrylyl-procaine (Example 4, sample 1)	25	1′	15–30′
Polyacrylyl-procaine (Example 4, sample 2)	40	1″	15–30′
Lidocaine	37.5	Immed.	2–3′
Acrylyl-m-amino-lidocaine			

TABLE II-Continued

Time Course of the Development of Toxic Signs in Mice Following i.v. Injection

Compound	Dose* mg/kg	Average Time to Onset	Time to Recovery**
monomer (Example 6)	150	Immed.	2-3'
Polyacrylyl-m-amino-lidocaine (Example 3)	75	5-10'	120-180'

*All doses were approximately equipotent LD_{50}.
**Measured as recovery from respiratory paralysis for all animals which did not die.

In all instances in which death did not occur, recovery was complete, although as shown in Table II, the times for recovery differed.

EXAMPLE 12

Conduction Block in Frog Nerve in Vitro

Test Methodology

To test whether conduction in frog nerve is vulnerable to the polymeric local anesthetic drugs, their monomers and the local anesthetic substituent molecules, the excised sciatic nerves from R. pipiens were used. Frogs were pithed and the sciatic nerves excised in a length of 7 cm. The nerves were mounted in a chamber on pairs of platinum stimulating and recording electrodes separated by 5 cm. and between which was placed a ground electrode. The preparation in the chamber was immerse in frog Ringer's solution at pH 7.

Compound action potentials were recorded in each case in air, by elevating the electrodes and the overlying nerve from the solution. During a test period, supramaximal single stimuli were delivered from a Grass S4 stimulator at intervals of 1 sec. Recorded potentials were fed into a Tektronix high gain differential amplifier (E unit), the output of which was connected to differential amplifier of a Tektronix oscilloscope. Recorded potentials were photographed by a Polaroid camera.

Following control recordings of compound action potential, the nerves were soaked for varying periods in the drug test solutions. These solutions contained either the reference local anesthetic or a polymeric local anesthetic or its monomer; in all instances, the drug (as its hydrochloride, except the polyacrylylprocaine, Example 2, high m.w.; which was first dissolved in dilute NaOH, pH 10.8) was dissolved in frog Ringer's solution. If a significant depression of the compound action potential amplitude occurred (usually 50%), the reversibility of this drug action was tested by returning the nerve to normal Ringer's solution and repeatedly washing.

Results

all of the polymeric local anesthetics and their monomers produced a reversible conduction block of the compound action potential in frog sciatic nerve in vitro. In this respect, these compounds were indistinguishable from the prototype local anesthetics: procaine and lidocaine. The concentrations of drug necessary to cause approximately equivalent conduction blocks differed. However, a striking difference between the polymeric local anesthetics and their reference prototype drugs emerged when the time courses of their blocking actions were compared. These differences are shown in Table III.

TABLE III

Compound	Conc. mM	%Block	Time to Peak	Time to Recovery
Procaine	25	95	30'	60'
Polyacrylyl-procaine (Example 2, high m.w.)	100	95	50'	15 hrs.
Lidocaine	2	95	30'	15'
Acrylyl-m-aminolidocaine monomer (Example 6)	10	60	30'	60'
Polyacrylyl-m-aminolidocaine (Example 7)	100	60	30'	120'

From the data in Table III, it can be seen that the local anesthetic action of the polymeric drugs is slower in onset and considerably longer in duration (i.e., much more slowly reversible) than is the case for the reference prototypes or their monomeric acrylyl derivatives.

EXAMPLE 13

Anti-arrhythmic Effect

Test Methodology

Reversible ventricular arrhythmias, chiefly of the nodal type, were produced by epinephrine injection in intact cats anesthetized with chloralose 80 mg/kg i.v. Following anesthesia, the ECG, usually lead II, was recorded with a Brush Mark 220 Recorder. After control tracings established the identity of the normal waves, epinephine HCl was injected rapidly i.v. in varying doses and the number and duration of etopic ventricular beats occurring were related to log dose. All epinephrine doses were administered randomly in a volume of 0.1 ml/kg; epinephrine doses were separated by 30 min. intervals. End blood pressure was recorded from a carotid artery. In control studies, it was shown that epinephrine doses of 5, 10, 20 and 40 μ-gm/kg i.v., produced increasing numbers of ectopic beats which related linearly to log dose. Therefore, a dose of 20 ugm/kg was chosen as a standard challenge dose.

After reproducible control arrhythmias were evoked by the epinephrine challenge dose, the anitarrhythmic effects of the polymers were compared with the antiarrhythmic effects of procaine and procaime amide. Doses of either the test or reference drugs (as hydrochlorides) were given i.v. and epinephrine challenges made at varying times thereafter.

Results

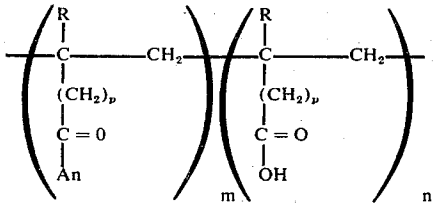
All of the polymeric drugs administered intravenously to the cat, variably suppressed the development of epinephrine-induced ectopic ventricular beats. In this respect, the action of the polymeric drugs was similar to the parent moieties from which they were derived. On the average, the most striking difference between the polymers and the parent drugs was in the greater duration of antiarrhythmic activity of the polymers. This is summarized by the data of Table IV.

TABLE IV

Drug	i.v. Dose mg/kg	No. Cats	SUPPRESSION OF EPINEPHRINE ARRHYTHMIA IN THE CAT Percent Suppression range	average	Time to Peak range	Recovery Time t ½	Remarks
Procaine	15	13	0–100	80	1–5′	<30′ av.	—
	30	5	24–100	85	1–5′	<30′ av.	lethal range
Polyacrylyl-procaine (Example 4, sample 2)	10	9	61–100	88	1–5′	3½–4½ hrs.	—
	20	7	56–100	85	1–5′	3½–4½ hrs.	—
Procaine amide	15	5	18–100	67	1–5′	1½–3½ hrs.	—
	30	7	0–100	55	1–5′	ca. 30′	1 assisted resp.
Polyacrylyl-procaine amide (Example 10)	5	5	0–74	47	30′	see Remarks	78% of control 3½–5½ hrs.
	15	4	100	100	1–5′	3½–7½ hrs	2/4 dead

We claim:

1. A compound of the formula



wherein An is a radical formed by removal of a hydrogen atom from a free primary or secondary aromatic amino group of a known local anesthetic molecule or an aromatic amino derivative of a known local anesthetic molecule;



An is a covalent amide linkage involving said aromatic amino group of the An moiety; *m* is an integer of from 1 to 1,000; *n* is an integer of from 0 to 1,000 with the proviso that the sum of *m* and *n* is 2 or greater; R is hydrogen or lower alkyl; *p* is an integer of from 0 to 5; with the understanding that the repeating units designated within the separate parentheses are arranged in random fashion; and the salts thereof with pharmaceutically acceptable acids and bases.

2. The compound of claim **1** wherein *p* is 0 and R is hydrogen.

3. The compound of claim **2** wherein An is selected from the group consisting of radicals derived from procaine, procaine amide or an aromatic amino-substituted lidocaine.

4. The compound of claim **1** wherein *n* is 0.

5. The compound of claim **4** wherein *m* is between about 10 and 20.

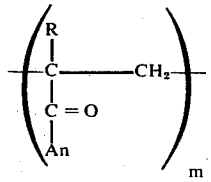
6. The compound of claim **4** wherein *m* is between about 300 and 400.

7. The compound of claim **1** wherein *n* is 1 or greater.

8. The compound of claim **7** wherein $m + n$ is between about 10 and 20.

9. The compound of claim **7** wherein $m + n$ is between about 300 and 400.

10. A compound of the formula



wherein An is a radical formed by removal of a hydrogen atom from a free primary or secondary aromatic amino group of procaine, procaine amide or an aromatic amino-substituted lidocaine;



An is a covalent linkage involving said aromatic amino group of the An moiety; *m* is an integer of from 1 to 1,000; R is hydrogen; and the salts thereof with pharmaceutically acceptable acids and bases.

11. The compound of claim **10** wherein *m* is between about 10 and 20.

12. The compound of claim **10** wherein *m* is between about 300 and 400.

13. The compound of claim **11** wherein An is derived from procaine.

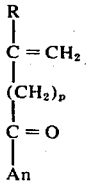
14. The compound of claim **11** wherein An is derived from procaine amide.

15. The compound of claim **11** wherein An is derived from m-aminolidocaine.

16. The compound of claim **11** wherein An is derived from p-aminolidocaine.

17. The compound of claim **12** wherein An is derived from procaine.

18. A compound of the formula



wherein An is a radical formed by removal of a hydrogen atom from a free primary or secondary aromatic amino group of a known local anesthetic molecule or an aromatic amino derivative of a known local anesthetic molecule;



An is a covalent amide linkage involving said aromatic amino group of the An moiety; R is hydrogen or lower alkyl; and *p* is an integer of from 0 to 5.

19. The compound of claim **18** wherein R is hydrogen and *p* is 0.

20. The compound of claim **19** which is acrylylprocaine.

21. The compound of claim **19** which is acrylylprocaine amide.

22. The compound of claim **19** which is acrylyl-m-aminolidocaine.

23. The compound of claim **19** which is acrylyl-p-aminolidocaine.

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