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INVERSE AMIDES AND METHOD OF MAKING

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7 Claims. (Cl. 260—294)

This invention relates to novel derivatives having unexpected activity in prolonging the action of curariform drugs. The compounds of the invention are useful both in human and veterinary medicine.

Compounds having the structure

$$R_3{}^+NCH_2CH_2OCOCH_2CH_2COOCH_2CH_2{}^+NR_32X^-$$

and especially succinylcholine (R=methyl in the above formula) are potent curarizing agents although their period of action is rather short. This brevity of action is at times advantageous but it is sometimes desirable to prolong it. Compounds of the succinylcholine type may be prolonged in activity by the concurrent administration, either simultaneously or shortly beforehand, of certain derivatives found to have a prolonging effect on the curariform compound. These agents apparently function by preventing the elimination of the curariform compound by body enzymes or other systematic chemicals. These substances have the formula

$$R_2NCH_2CH_2NHCO(CH_2)_n—CONHCH_2CH_2NR_2$$

and their diquaternary salts are the subject of U. S. Patent 2,653,898 and our copending application No. 333,334.

We have now discovered that similar unexpected activity of a still more desirable nature appears in the series of compounds which we term "inverse amides." These compounds may be represented by the formula

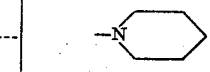
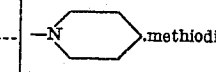
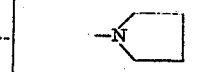
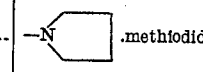
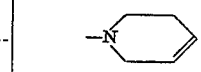
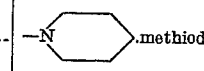
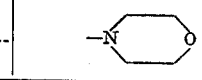
$$R_2NCH_2CONH(CH_2)_nNHCOCH_2NR_2$$

wherein n has the values 2–6 inclusive, and R_2N is an amino radical selected from the class consisting of the piperidino and pyrrolidino radicals. Typical data establishing these limits are shown in Table I. It is apparent that within the chosen limits the compounds of the present series are much more active than their own quaternary salts and also more active than compounds with closely similar values for NR_2.

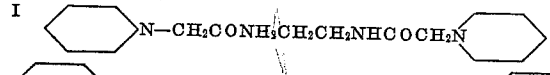
TABLE I

Potency of compounds

$R_2NCH_2CONH(CH_2)_nNHCOCH_2NR_2$

n	NR_2	Dose, mg./kg. cat. required to double the period of action of succinylcholine
2	—NMe_2.methiodide	1.0
2	—NEt_2	2.0
2		0.1
2	 .methiodide	2.0
2		0.2
2	 .methiodide	1.0
6		0.1
6	 .methiodide	2.0
6		No effect

Within the chosen limits the compounds of the present invention are as active as the most potent compounds of our copending application No. 333,334. Their superiority over those substances rests in their lower toxicity. Since the chain length between terminal nitrogen atoms in the two series is not identical, a comparison of the two groups is not easily made. However, the four compounds I to IV are approximately equipotent. (The figures appropriate for the right-hand column in Table I being: 0.1; 0.3; 0.1 and 0.1 respectively.) The corresponding toxicities (intravenous LD–50 for mice in mg./kg.) are 170; 8.4; 19.2 and 3.5. Thus, the compounds of the present invention are ten to twenty times less toxic than those of the previous patent applications referred to.

I 

II $n=2$

III $n=3$

IV $n=4$

The free bases of our new series are somewhat soluble in water and, since the required dose is small, they may be administered directly in aqueous solution or dissolved in physiological saline. Alternatively, they may be dissolved in dilute acids before administration or converted

to solid salts which may be desirable for better preservation. However, the acid used and present as its anion, contributes nothing to the physiological activity. Furthermore, its quantity is small and is insignificant in comparison to the large amounts of anions present in the body (such as chloride, phosphate, bicarbonate, etc.) Therefore, all salts with acids not themselves markedly toxic are considered to be equivalent to each other and the free bases and to be comprehended in the scope of this invention. Of the many possible salts the hydrochlorides are perhaps the most obvious, most easily made and devoid of complications. Hydrobromides, phosphates, sulfates, lactates, acetates, succinates, fumarates, malates and many others could be considered but offer no special advantages.

The compounds of the present invention are conveniently made by reacting chloroacetylchloride with an alkylene diamine to form a bis chloroacetyl alkylenediamine. This derivative is then warmed with an excess of piperidine or pyrrolidine and affords the di-tertiary amine. These bases are nicely crystalline solids having melting points that are not inconveniently low. When dissolved in ether and neutralized with alcoholic hydrogen chloride the hydrochlorides crystallize. When the bases are dissolved in acetone and reacted with excess methyl iodide they are converted to bis methiodides. These latter can serve as compounds of characterization but are not otherwise of interest at present.

Example 1

PREPARATION OF THE N,N'-BIS CHLOROACETYL-AMIDES

A mixture containing 0.2 mole of the diamine, 0.50 mole of sodium bicarbonate (or sodium hydroxide), and 50 to 100 cc. of water was chilled in an ice bath. To this was added dropwise, with stirring and chilling, 0.44 mole of chloroacetyl chloride during a period of about an hour. The product usually was very little soluble in water and was collected by filtration, and washed with water. After removing inorganic salts in this way the bis chloracetyl amide was further purified by recrystallization from methanol or ethylacetate.

In this way the bis chloroacetylamides were prepared from ethylene diamine (M. P. 174–175°; described earlier by W. A. Jacobs and M. Heidelberger. J. Biol. Chem., 21, 151 (1915)) from trimethylene diamine (M. P. 127–128°; described earlier by J. von Braun, F. Dengel, and A. Jacob, Ber. 70B, 994 (1937)), from tetramethylene diamine (M. P. 130°), from hexamethylene diamine (M. P. 131–132°), from p-phenylene diamine (M. P. >310°; described earlier by A. P. Phillips, J. Am. Chem. Soc., 74, 6125 (1952)), and from piperazine (M. P. 136–137°; described earlier by E. Abderhalden and E. Rossner, Z. Physiol. Chem., 144, 219 (1925)).

Example 2

PREPARATION OF N,N'-BISPIPERIDINOACETYL-ETHYLENE DIAMINE

A mixture of 2.1 g. (0.01 mole) of N,N'-bis chloroacetyl ethylene diamine and 8.5 g. (0.1 mole) of piperidine was heated for 18 hours on a steam bath. Addition of 30 cc. of cold water dissolved the excess unused piperidine, the piperidine hydrochloride formed during the reaction and precipitated the product which was not very soluble in cold water. The product was collected by filtration, was washed with cold water and after purification by recrystallization from ethyl acetate melted at 138–139°. The yield was essentially quantitative.

In similar fashion were prepared bis pyrrolidinoacetyl ethylene diamine (M. P. 115–116°) whose bis methiodide melts at 227–228°, bis piperidinoacetyl trimethylene diamine (M. P. 83–84°) and its bis methiodide melting at 203–204°, bis pyrrolidino acetyl hexamethylene diamine (M. P. 82–83°), its bis methiodide melting at 137–138°, the bis piperidinoacetyl hexamethylene diamine (M. P. 108–109°) its bis methiodide, M. P. 175–176°, bis pyrrolidino acetyl piperazine and bis piperidino acetylpiperazine (M. P. about 205°).

We claim:

1. A compound selected from the class consisting of the free base and its acid addition salts, said free base having the formula:

$$R_2N.CH_2CONH(CH_2)_nNHCOCH_2NR_2$$

wherein R_2N is an amino radical selected from the class consisting of the piperidino and pyrrolidino radicals and n is an integer of from 2 to 6.

2. N,N'-bis (piperidinoacetyl) ethylene diamine.

3. N,N'-bis (piperidinoacetyl) trimethylene diamine.

4. N,N'-bis (piperidinoacetyl) hexamethylene diamine.

5. N,N'-bis (pyrrolidino acetyl) ethylene diamine.

6. N,N'-bis (pyrrolidinoacetyl) hexamethylene diamine.

7. The method of forming compounds selected from the class consisting of those having the free base formula:

$$R_2N.CH_2CONH(CH_2)_nNHCOCH_2NR_2$$

and its acid addition salts, wherein R_2N is an amino radical selected from the class consisting of the piperidino and pyrrolidino radicals and n is an integer of from 2 to 6 which comprises reacting chloroacetylchloride with an alkylenediamine to form a bis chloroacetyl alkylenediamine and reacting the latter derivative with an excess of a compound selected from the class consisting of piperidine and pyrrolidine and recovering the di-tertiary amine.

No references cited.