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Some Bis-substituted Succinamides as Curare Substitutes. IV

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Earlier some series of dicarboxylic acid bis-aminoamides and their quaternary ammonium salts were described.[1,2] These had been made in conjunction with a family of bis-aminoalkyl esters of dicarboxylic acids and their quaternary ammonium salts[3] in a search for new drugs possessing curare-like activity. While powerful curariform agents were found in the ester series, most outstanding in the case of succinylcholine, the analogously constituted amides were nearly inactive in this sense. However, many of the series of bis-amides proved to act as powerful potentiators, both in duration and intensity of action, of the succinylcholine class of curare-like drugs. Succinylcholine potentiating ability in the various amide series was observed to occur in a wide range of chain lengths, from the malonic through the sebacic acid derivatives, but was frequently found to be maximal in the succinic, glutaric, adipic group. Thus it seemed useful to prepare a cross section of assorted bis-substituted amides from a particular dicarboxylic acid in the optimal region. This paper presents a number of such amides made from succinic acid.

The bis-isoamylsuccinamide, the first compound of Table I, is an isostere of one of the active potentiators of succinylcholine, the bis-dimethylaminoethylsuccinamide.[1] In Table I are summarized the details of structure, melting points and analytical data for a list of alkoxyalkyl- and alkylaminoalkylsuccinamides as well as for some derived bis-quaternary ammonium salts.

The pharmacology of these substances will be reported elsewhere. None of these compounds seemed to be as effective in prolonging the neuromuscular blocking action of succinylcholine as were the compounds described earlier.[1,2]

TABLE I

SUBSTITUTED SUCCINAMIDES $\begin{matrix}CH_2CONHCH_2CH_2R\\ |\\ CH_2CONHCH_2CH_2R\end{matrix}$

R	M.p., °C.	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
$-CH(CH_3)_2$	141–142	$C_{14}H_{28}N_2O_2$	65.6	65.7	11.0	11.0	10.9	10.5
$-CH_2OCH_3$	146–147	$C_{12}H_{24}N_2O_4$	55.3	55.3	9.3	9.1	10.7	10.4
$-CH_2OCH(CH_3)_2$	122–123	$C_{16}H_{32}N_2O_4$	60.7	60.9	10.2	10.1	8.8	8.7
$-CH_2NHCH(CH_3)_2$	104–105	$C_{16}H_{34}N_4O_2$	61.1	61.1	10.9	10.6	17.8	17.8
$-CH_2N(CH_3)_2$	122–123	$C_{14}H_{30}N_4O_2$	58.7	58.5	10.5	10.2	19.6	19.8
$-CH_2N(CH_3)_3I$	211–212	$C_{16}H_{36}I_2N_4O_2$	33.7	33.7	6.4	6.4	9.8	9.7
$-CH_2N(CH_3)_2C_2H_5I$	167–168	$C_{16}H_{40}I_2N_4O_2$	36.1	35.9	6.7	6.4	..	..
$-CH_2N(CH_2CH_2)_2O$	125–126	$C_{18}H_{34}N_4O_4$	58.3	58.4	9.3	9.3	15.1	15.2
$-CH_2N(CH_2CH_2)_2O\cdot CH_3I$	162–163	$C_{20}H_{40}I_2N_4O_4$	36.7	36.7	6.2	6.2	..	..

Experimental

The amides were prepared by the procedure of the previous publications.[1,2] Yields were nearly quantitative. The simple amides were purified by recrystallization from ethyl acetate, while the quaternary salts were recrystallized from methanol–ethyl acetate mixtures.

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5-Acenaphtheneacetic Acid

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The preparation of an acenaphtheneacetic acid, from acenaphthene and α-chloroacetic acid, melting at 174–175° is described in the patent literature by Wolfram, *et al.*[1] In the equivalent British Patent, the acid is described as the 5-isomer,[2] but no melting point is indicated. In another patent[3] the same inventors describe the acid as 5-acenaphtheneacetic acid and give the melting point as 187°. Anderson and Wade[4] prepared 5-acenaphtheneacetic acid by the Willgerodt–Kindler reaction on the known 5-acenaphthenyl methyl ketone. The melting point reported is 179–180°. These authors indicate that they were unable to repeat the preparation of the acenaphthenacetic acid described by Wolfram, *et al.*, in the patent literature.

In this work 5-acenaphtheneacetic acid has been prepared by the condensation of α-chloroacetic acid and acenaphthene with the aid of ferric oxide and potassium bromide as catalysts.[5] The yield, based on the initial reactants, was quite low (28%). However, since a high proportion of the unreacted acenaphthene may be recovered, the preparation offers some advantage. A procedure for the purification of this acid involving fractional precipitation and crystallization of the sodium salt is de-

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(2) British Patent 330,916 (Feb. 19, 1929); *C. A.*, **24**, 6031 (1930).
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(4) A. G. Anderson, Jr., and R. H. Wade, THIS JOURNAL, **74**, 2274 (1952).
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