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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-

(1) A. P. Phillips, THIS JOURNAL, **73**, 5822 (1951).
(2) A. P. Phillips, *ibid.*, **74**, 4320 (1952).
(3) A. P. Phillips, *ibid.*, **71**, 3264 (1949).

(1) A. Wolfram, L. Schornig and E. Hausdorfer, German Patent 562,391 (Feb. 2, 1929); *C. A.*, **27**, 734 (1933).
(2) British Patent 330,916 (Feb. 19, 1929); *C. A.*, **24**, 6031 (1930).
(3) U. S. Patent 1,951,686 (March 20, 1934); *C. A.*, **28**, 3423 (1934).
(4) A. G. Anderson, Jr., and R. H. Wade, THIS JOURNAL, **74**, 2274 (1952).
(5) Y. Ogata and J. Ishiguro, *ibid.*, **72**, 4302 (1950).

scribed. The purified acid melted at 179.5–181°.[6] The position of the acetic acid residue in the acenaphthene nucleus was established by conversion to 5-acenaphthylmethylamine by the Curtius reaction[7] and treatment of the amine with nitrous acid to give 5-hydroxymethylacenaphthene.[8] A mixed melting point of this carbinol with that prepared by the lithium aluminum hydride reduction of the known 5-acenaphthoic acid showed no depression.

Experimental[9]

5-Acenaphtheneacetic Acid.—A mixture comprising 92 g. (0.6 mole) of acenaphthene, 28 g. (0.3 mole) of α-chloroacetic acid, 0.5 g. of potassium bromide and 0.2 g. of ferric oxide was heated on a sand-bath under gentle reflux for 24 hours. During this period of heating, the temperature of the melt reached 220°. The resulting dark mass was cooled and extracted exhaustively with warm 10% sodium hydroxide solution. Acidification of the dark alkaline extract precipitated 30 g. of dark and impure acid melting at 135–150°. There was also obtained 68 g. of dark, alkali-insoluble residue. The crude acid was dissolved in 250 ml. of warm alcohol, filtered, and the dark filtrate slowly diluted with water which precipitated a dark oil. The addition of water was continued until crystallization of the acid from the yellow liquor commenced, after which the solution was decanted from the precipitated oil. Further addition of water to the mother liquor yielded a pale yellow crystalline product, m.p. 150–160°. The precipitated oil was redissolved in alcohol and the separation repeated. There was thus obtained 18 g. of acid (28%, based on α-chloroacetic acid), which was further purified by solution in 300 ml. of hot 5% sodium hydroxide solution from which the sodium salt of the acid crystallized on cooling. It was filtered and washed with ice-water. Solution of the salt in warm water and acidification gave 13.5 g. of acid melting at 176–179°. Recrystallization of the sodium salt and final crystallization from dilute alcohol with the addition of decolorizing charcoal gave colorless needles, m.p. 179.5–181°.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.21; H, 5.70. Found: C, 79.24; H, 5.80.

Attempts to purify the crude alkaline extract of the reaction mixture by repeated crystallization and treatment with decolorizing charcoal were less satisfactory.

The amide was obtained as white needles from *n*-propanol, m.p. 236–237°.

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.58; H, 6.20. Found: C, 79.80; H, 6.53.

The phenacyl ester was obtained as fine white needles from alcohol, m.p. 89–90°.

Anal. Calcd. for $C_{22}H_{18}O_3$: C, 79.96; H, 5.48. Found: C, 80.00; H, 5.60.

The unreacted acenaphthene contained in the alkali insoluble residue was recovered by distillation, collecting the fraction boiling at 265–274°. There was obtained 39 g. (42% of the initial acenaphthene) which crystallized from alcohol as white needles, m.p. 95–96°, and formed a picrate, m.p. 161°.

Degradation of 5-Acenaphtheneacetic Acid.—The crude acid (7.2 g., 0.034 mole), m.p. 176–179°, was mixed with 40 ml. of dry benzene and 6 ml. of thionyl chloride and refluxed for 2 hours, after which the 5-acenaphtheneacetyl chloride was distilled collecting the fraction b.p. 185–195° at 11 mm. The yellow oil soon solidified; yield 4.6 g. (59%).

A mixture comprising 4.5 g. of the acid chloride, 2.2 g. of sodium azide, and 50 ml. of dry benzene was refluxed for 6 hours and then filtered. Concentrated hydrochloric acid, 40 ml., was added to the filtrate and the mixture refluxed for 4 hours, cooled, and the separated amine hydrochloride removed by filtration. There was obtained 2.8 g.—65%—of product which was recrystallized from dilute hydrochloric acid.[7]

Anal. Calcd. for $C_{13}H_{14}ClN$: N, 6.37; Cl, 16.16. Found: N, 6.30; Cl, 16.30.

The benzamide of the amine crystallized from dilute alcohol as fine white needles, m.p. 182–184°.

Anal. Calcd. for $C_{20}H_{17}NO$: C, 83.58; H, 5.97. Found: C, 83.33; H, 6.05.

The benzenesulfonamide crystallized as fine white needles from alcohol, m.p. 148–149°.

Anal. Calcd. for $C_{19}H_{17}NO_2S$: C, 70.56; H, 5.28. Found: C, 70.86; H, 5.33.

5-Hydroxymethylacenaphthene.—A solution of 0.2 g. of 5-acenaphthenemethylamine hydrochloride in 75 ml. of water was treated with 8 drops of 3 *N* hydrochloric acid followed by an excess of sodium nitrite solution. This mixture, on standing overnight at room temperature, deposited a white solid which was removed by filtration, dried and crystallized from benzene. The white needles melted at 156–157° (lit. 153.8–154°).[8] A mixed melting point of the 5-hydroxymethylacenaphthene obtained by the degradation of 5-acenaphtheneacetic acid and a sample prepared as described below by the reduction of the known 5-acenaphthoic acid showed no depression.

5-Acenaphthoic Acid.—This acid was prepared in 57% yield by treating 46 g. (0.2 mole) of 5-bromoacenaphthene in 125 ml. of absolute ether with *n*-butyllithium prepared from 30 g. (0.32 mole) of *n*-butyl chloride and 4.5 g. of lithium wire[10] in 200 ml. of ether. The resulting solution was poured on powdered solid carbon dioxide, allowed to stand one hour, acidified, and the precipitated acid filtered. This product was purified by washing a solution in 5% sodium hydroxide with ether followed by precipitation. There was thus obtained 22.5 g. of acid, m.p. 214–218°. Crystallization from dilute alcohol gave a product, m.p. 220–221°.[11]

5-Hydroxymethylacenaphthene by Reduction of 5-Acenaphthoic Acid.—Finely divided solid 5-acenaphthoic acid (19.8 g., 0.1 mole) was slowly added to a solution of 7.6 g. of lithium aluminum hydride in 600 ml. of dry ether[12] contained in a 2-l. three-neck flask fitted with a stirrer and reflux condenser. After stirring for 1 hour, the mixture was decomposed by the slow addition of 250 ml. of 10% sulfuric acid. The precipitated solid was filtered and extracted with warm 5% sodium hydroxide. There was thus obtained 13.8 g. of the carbinol. An additional 2.6 g. was obtained by evaporating the initial ether filtrate to give 16.4 g. (82%) of carbinol which crystallized from alcohol as fine white needles, m.p. 155–156°.

The acetate, obtained by reaction with acetic anhydride in pyridine, crystallized from hexane, m.p. 60.5–61.5°.

Anal. Calcd. for $C_{15}H_{14}O_2$: C, 79.64; H, 6.22. Found: C, 79.9; H, 6.31.

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(6) Anderson and Wade[4] were unable to cyclize this acid to 1-pyracenone. Our attempts to effect this ring closure likewise were unsuccessful.

(7) P. A. S. Smith, "Organic Reactions," Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 337.

(8) L. F. Fieser and J. E. Jones, THIS JOURNAL, **64**, 1667 (1942).

(9) All melting points are corrected.

(10) Metalloy Corp., Rand Tower, Minneapolis, Minn.

(11) H. Gilman, W. Langham and F. W. Moore, THIS JOURNAL, **62**, 2332 (1940).

(12) R. F. Nystrom and W. G. Brown, *ibid.*, **69**, 2548 (1947).

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Hydrogen Bonding Ability and Structure of Ethylene Oxides

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The very low electron donor ability of substituted ethylene oxides, compared with other cyclic ethers, in hydrogen bonding was reported recently.[1] The

(1) S. Searles and M. Tamres, THIS JOURNAL, **73**, 3704 (1951).