ACTA CHEMICA SCANDINAVICA 10 (1956) 1068—1070

Syntheses of Dimethylhydrazoniumethyl Esters of Aliphatic Dicarboxylic Acids

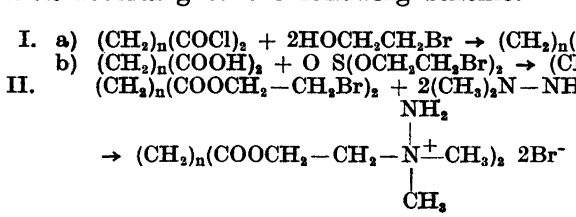
L.-E. TAMMELIN

Research Institute of National Defence, Dept. 1, Sundbyberg 4, Sweden

The choline analogue N′,N′-dimethyl-N′-hydroxyethylhydrazonium bromide has been prepared.

The bis-(ω-bromoethyl)-esters of oxalic, malonic, succinic, glutaric and adipic acids have been prepared. It is shown that these esters, except the oxalic ester, react with unsym. dimethylhydrazine in ether at 25° C yielding a product which is a bis quaternary ammonium compound of the N′,N′-dialkyl-N′-amino-ammonium type. The compounds are analogous to choline esters and have neuro-muscular blocking effects.

It has been shown by Renouf[1] that unsym. dimethylhydrazine reacts with alkyl halogenides to form N′,N′-dimethyl-N′-alkyl-N′-amino-ammonium halogenides, compounds having most of the properties of ordinary tetra alkyl ammonium compounds. An analogue of the acetylcholine has been synthesized by Schuler *et al.*[2] which contains the N′,N′-dimethyl-N′-amino-ammonium group. The purpose of this paper is to report methods of syntheses of similar analogues of succinylcholine and its homologues. The synthesis was performed according to the following scheme:



I. a) $(CH_2)_n(COCl)_2 + 2HOCH_2CH_2Br \rightarrow (CH_2)_n(COOCH_2CH_2Br)_2 + 2HCl$

b) $(CH_2)_n(COOH)_2 + O\,S(OCH_2CH_2Br)_2 \rightarrow (CH_2)_n(COOCH_2CH_2Br)_2 + H_2SO_3$

II. $(CH_2)_n(COOCH_2-CH_2Br)_2 + 2(CH_3)_2N-NH_2 \rightarrow$

$\rightarrow (CH_2)_n(COOCH_2-CH_2-\overset{\overset{NH_2}{|}}{\overset{+}{N}}(CH_3)_2\ 2Br^-$

$\underset{CH_3}{|}$

According to II the resulting product is analogous to a choline ester, except that choline is substituted for N′,N′-dimethyl-N′-hydroxyethyl-hydrazonium bromide. This compound was also synthesized.

EXPERIMENTAL

Bis-(ω-bromoethyl) esters of the aliphatic dicarboxylic acids

Unsym. dimethylhydrazine was prepared according to H. H. Hatt [3].

a) The bis-(ω-bromoethyl)esters of oxalic, malonic, succinic, glutaric and adipic acids were prepared as follows. 1 Mole of acid dichloride in 500 ml of benzene was added to 3 moles of ethylenebromhydrine and 1 mole of potassium carbonate in 500 ml of benzene. Nitrogen was bubbled through the reaction mixture and the reaction vessel was fitted with a reflux condenser and sealed with calcium chloride to eliminate moisture. The reaction was complete in 2 hours after which the potassium chloride was filtered off, the solution treated with calcium chloride, filtered again and finally fractioned by distillation. The esters were distilled *in vacuo*. For data see Table 1.

b) *A method according to Voss and Blanke* [4] was also tested for the preparation of bromoethyl esters of aliphatic dicarboxylic acids. The esters of oxalic and glutaric acids were prepared. For data see Table 1.

Table 1.

ω-Bromo-ethyl-ester of	Formula	M	Method of preparation	b. p. °C/mm Hg	m. p. °C	n_D^{20}	d_4^{20}	MR		% Br		Yield calc. on acid in %
								calc.	found	calc.	found	
Oxalic acid	$C_6H_8O_4Br_2$	304.0	a, b	122—124/0.25	54—55	—	—	—	—	52.8	52.7	(a) 45 (b) 60
Malonic acid	$C_7H_{10}O_4Br_2$	318.0	a	152/1	<20	1.5000	1.7393	53.1	53.7	—	—	(a) 57
Succinic acid	$C_8H_{12}O_4Br_2$	332.0	a	161/1	<20	1.5012	1.6990	57.7	57.7	—	—	(a) 63
Glutaric acid	$C_9H_{14}O_4Br_2$	346.0	a, b	148/0.3	<20	1.4962	1.6293	62.4	62.1	—	—	(a) 30 (b) 63
Adipic acid	$C_{10}H_{16}O_4Br_2$	360.1	a	156—161/0.3	<20	1.4928	1.5612	67.1	67.0	—	—	(a) 64

Bis-(ω-bromoethyl) ester of oxalic acid. 3.3 Moles of bis-(ω-bromoethyl)sulfite and 1 mole of oxalic acid [$(COOH)_2$, $2H_2O$] were mixed and heated on a steam bath for two hours. The reaction mixture was extracted with ether and the ether solution washed twice with water and finally with a sodium bicarbonate solution. The solution was dried with sodium sulfate and fractionated by distillation. The ester was distilled *in vacuo*. For data see Table 1.

Bis-(ω-bromoethyl) ester of glutaric acid. 1.1 Moles of bis-(ω-bromoethyl)sulfite, 1 mole of glutaric acid and one drop of conc. sulfuric acid were mixed and heated for two hours on a steam bath. The reaction mixture was extracted with ether and the ether solution was washed twice with water and finally with a sodium bicarbonate solution. The solution was dried with sodium sulfate and fractionated by distillation. The ester was distilled *in vacuo*. For data see Table 1.

Dimethyl-hydrazoniumethyl esters of the aliphatic dicarboxylic acids

1 Mole of the bis-(ω-bromoethyl)ester and 2.2 moles of unsym. dimethylhydrazine were mixed with about eight volume parts of dry ether in a glass stoppered round bottomed flask. After three weeks at 25° C a crystalline or viscous precipitate was filtered off from the ether. When viscous products occurred the preparation was stored for a few

Table 2.

Acid esterified by N′,N′-dimethyl-N′,-hydroxyethyl hydrazonium bromide	Formula	M	m. p. °C	% Br		% C		% H		Yield in % of theoretical
				calc.	found	calc.	found	calc.	found	
Malonic acid	$C_{11}H_{26}O_4N_4Br_2$	438.2	80—100	36.5	35.9	30.2	30.2	6.0	6.0	55
Succinic »	$C_{12}H_{28}O_4N_4Br_2$	452.2	158—164	35.4	34.6	31.8	31.6	6.2	6.1	62
Glutaric »	$C_{13}H_{30}O_4N_4Br_2$	466.2	104	34.3	34.4	33.6	33.7	6.5	6.6	50
Adipic »	$C_{14}H_{32}O_4N_4Br_2$	480.3	108	33.3	33.8	35.0	35.0	6.7	6.5	57

days in a desiccator for crystallization. The compounds were recrystallized from ethanol. For data see Table 2.

N′,N′,-dimethyl-N′-hydroxyethylhydrazonium bromide

1 Mole of ethylenebromhydrine and 1.1 moles of unsym. dimethylhydrazine were mixed with about eight volume parts of dry ether in a glass stoppered round bottomed flask. After three days the colourless precipitate was filtered off. (Yield 76 %; m. p. < 50°, hygroscopic). (Found: C 25.8; H 7.0; Br 43.6. Calc. for $C_4H_{13}N_2OBr$ (185.1) C 25.9; H 7.1; Br 43.2).

The ω-bromo-ethyl esters of the aliphatic dicarboxylic acids have been shown to react with unsym. dimethylhydrazine with the formation of N′,N′-dimethyl-N′-amino-ammonium-ethyl ester bromides, although the reaction does not seem to be possible with the oxalic ester, yielding precipitates which differ in composition from the end product of reaction II. The esters of malonic, succinic, glutaric and adipic acids are all colourless crystalline compounds of salt character. They are easily soluble in water and the bromine content has been determined by means of directly applied argentometric titration. Since this was possible the compounds are completely dissociated in bromine ions and the organic cations. By means of pH-measurements and potentiometric titrations the amino groups have been shown to fail in protolytic properties in ordinary water solutions and seem even in this respect to correspond to the third methyl group in choline. A report on the pharmacological properties of these compounds will be given elsewhere.[5] It might be worth mentioning, however, that they possess neuromuscular blocking activity, but are less potent than the corresponding choline esters.

My sincere thanks are due to the Director of this Institute, Professor G. Ljunggren, for his kind interest in this work.

REFERENCES

1. Renouf, E. *Ber.* **13** (1880) 2172.
2. Schuler, F. W. and Calvin, H. *Arch. intern. pharmacodynamie* **88** (1951) 351.
3. Hatt, H. H. *Org. Syntheses Coll. Volume* **II** (1946) 211.
4. Voss, V. and Blanke, E. *Ann.* **485** (1931) 258.
5. Fredriksson, T. *Acta Pharmacol. Toxicol.* (1957), *in press.*

Received April 13, 1956.