

Acetic, Propionic and Butyric Esters of 2-Dimethylaminoethanol, 2-Dimethylaminoethanethiol and 2-Dimethylamino-1-methylethanol

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The nine esters corresponding to 2-dimethylamino-ethanol, 2-dimethylamino-ethanethiol, 2-dimethyl-1-methyl-ethanol and acetic, propionic and butyric acid have been prepared and described as ammonium bromides and free amines. The corresponding acid-base pairs have been used for the determination of pK_a .

Esters of dimethylaminoethanol and related compounds are of interest as precursors of the choline esters in preparative work. In synthesis of the choline esters the corresponding tertiary amines are not necessarily prepared in pure form¹. Some interest has been shown, however, in comparative studies of the tertiary and quaternary compounds in relation to cholinesterase^{2,3}. Moreover, the action on the central nervous system of compounds related to the cholinesters but of the tertiary type has received attention. Some modifications of an earlier method for the preparation of choline esters¹ are therefore presented which enable the tertiary amino esters to be prepared.

It has been shown by Wilson^{2,5} that the ammonium ester is more easily hydrolyzed by cholinesterases than is the amino ester in the case of dimethylaminoethyl acetate. In a system with a given pH and ionic strength, *e. g.* body fluids, the pK_a governs the quotient (amine)/(ammonium). In view of the probable pharmacodynamic disparity of the amino and ammonium forms, due, *e. g.*, to their different affinities for cholinesterase, the degree of protolysis is obviously of interest. It was therefore decided to determine the pK_a of the esters synthesized.

METHODS

The mode of synthesis followed is esterification of the ethanol or thiol by means of acid anhydride, preliminary purification by distillation and precipita-

Table 1. Boiling points of the crude distillates from the esterification.

Alcohol	Acetic ester	Propionic ester	Butyric ester
2-Dimethylaminoethanol	68°/8 mm	70°/8 mm	81°/8 mm
2-Dimethylaminoethanthiol	182°	190°	205°
2-Dimethylamino-1-methyl-ethanol	152°	165°	185°

tion of the amino ester by hydrogen bromide, recrystallisation or liberation of the free amine and redistillation.

Esterification. One mole of the ethanol or thiol (the thiols were prepared *ad modum* Hansen *) derivative is heated on a water bath with 1 mole of acid anhydride overnight. The reaction mixture is distilled. All fractions are collected, up to and including the one at the temperature given in Table 1.

Dimethylammonium ester bromides. The crude distillate from the esterification is diluted six times with anhydrous ether. Hydrogen bromide is bubbled through the solu-

Table 2.

Dimethylamino-ethanol	Amines							Ammonium bromides							
	C _x H _y O _z N	n_D^{25}	d_{25}	R_D		B. p.	M	M	M.p. °C	% Br		% C		% H	
		calc.	found	°C/mm	calc.	found				calc.	found	calc.	found	calc.	found
acetate	C ₈ H ₁₃ O ₂ N	1.4158	0.932	35.2	35.2	44/8	131.2	212.1	84	37.7	37.4	33.9	33.4	6.7	6.6
propionate	C ₇ H ₁₅ O ₂ N	1.4193	0.916	39.8	39.8	59/10	145.2	226.1	112	35.3	35.3	37.2	37.2	7.1	7.0
butyrate	C ₈ H ₁₇ O ₂ N	1.4233	0.909	44.5	44.8	65/8	159.2	240.1	111	33.3	33.4	40.0	39.9	7.6	7.4
Dimethylamino-ethanthiol										% N					
acetate	C ₈ H ₁₃ ONS	1.4763	0.981	41.7	41.6	78/14	147.3	228.2	96	6.14	6.10	31.6	31.3	6.1	6.1
propionate	C ₇ H ₁₅ ONS	1.4762	0.964	46.4	46.6	89/8	161.3	242.2	88	5.79	5.76	34.7	34.2	6.2	6.1
butyrate	C ₈ H ₁₇ ONS	1.4693	0.948	50.8	51.2	101/8	175.3	256.2	80	5.48	5.43	37.5	37.2	6.7	6.9
Dimethylamino-methylethanol										% Br					
acetate	C ₇ H ₁₅ O ₂ N	1.4132	0.907	39.8	39.9	53/13	145.2	226.1	121	35.3	35.3	37.2	37.3	7.1	7.2
propionate	C ₈ H ₁₇ O ₂ N	1.4150	0.893	44.5	44.5	62/8	159.2	240.1	123	33.3	33.2	40.0	39.8	7.6	7.4
butyrate	C ₉ H ₁₉ O ₂ N	1.4191	0.886	49.1	49.2	71/12	173.3	254.2	129	31.4	31.3	42.5	42.3	7.9	7.9

tion until all amine has precipitated. The crude precipitate is recrystallized from dioxan. Thus, a pure preparation is obtained in a yield of about 65 % calculated from the alcohol or thiol. For analytical data see Table 2.

Dimethylamino esters. Sodium hydroxide in water solution is used for liberation of the free amine. Rapid ether extraction, drying of the ether solution with sodium sulfate and distillation under reduced pressure give pure preparations of the amino esters. The yield is about 70 %, calculated from the crude ammonium ester bromide.

Physical data. Densities, refractive indices, boiling points and molar refractions are shown in Table 2. The densities were determined by means of a pycnometer and the refractive index in an Abbe refractometer. Melting points were determined on a "Kofler Heizbank". Molar refractions were calculated from group and atomic refractions given by Vogel ⁶.

Determinations of pK_a

Due to hydrolysis of the esters, time-consuming methods such as titrations had to be avoided in the pK_a determinations. Determinations of pH in solutions of known ionic strength and concentrations of acid and base were considered to be the best method, especially as both amines and corresponding ammonium bromides had been prepared.

For every compound three solutions were prepared, each about 10^{-3} M with regard to the acid and 0.5×10^{-3} M, 10^{-3} M and 2×10^{-3} M with regard to the base. The solutions were prepared by weighing the compounds and dissolution in deionized water of a known volume. The pH determinations were performed immediately after the dissolution.

The pH meter was a PHM3 Radiometer, Copenhagen, and the electrodes (glass/calomel) were checked against a standard buffer solution of potassium hydrogen phthalate (pH 4.01). Temperature was kept at 25° C.

For calculation of pK_a , the following formula was used:

$$pK_a = \text{pH} + \log \frac{(\text{ammonium ion})}{(\text{amine})} + \log f^+$$

$\log f^+$ is defined after Debye-Hückel, and was found to be -0.013 .

RESULTS

The ammonium ester bromides are all colorless, water-soluble crystalline compounds. In the case of dimethylaminoethyl thioacetate as ammonium bromide, a faint red discoloration has frequently been observed, the origin of which is unknown. The bromides are more or less hygroscopic, but since this

Table 3.

Alcohol	pK_a		
	Acetic ester	Propionic ester	Butyric ester
Dimethylaminoethanol	8.35 ± 0.01	8.29 ± 0.01	8.31 ± 0.02
Dimethylaminoethanthiol	8.27 ± 0.02	8.28 ± 0.03	8.32 ± 0.03
Dimethylamino-methyl-ethanol	8.32 ± 0.02	8.26 ± 0.01	8.27 ± 0.01

form is fairly easy to handle, it is recommended as the normal one for laboratory work with these compounds. The amino esters are colorless, hygroscopic, water-soluble oils with very characteristic odors. Dimethylaminoethanthiol butyrate, for instance, develops odors combining the impressions of amines, thiols and butyric acid in a most disagreeable way. A hood is recommended while handling these compounds, not only because of the odors but also in view of their toxic effects.

Water solutions of the amino esters show gradual changes in pH due to hydrolysis. Ether solutions react rapidly with methyl iodide and give choline esters in a yield close to 100 %^{1,4}.

A list of the compounds synthesized, with analytical and physical data, is given in Table 2.

The results of the pK_a determinations are summarized in Table 3. Accuracy is indicated by means of maximum deviations in each group of three determinations.

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