

## The Preparation of Thiocholine Esters

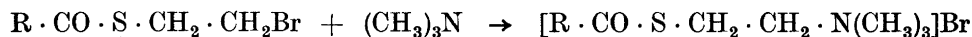
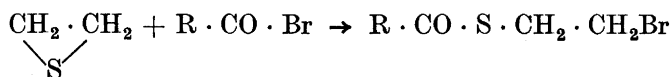
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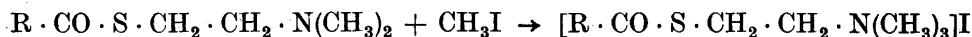
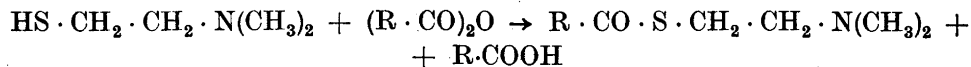
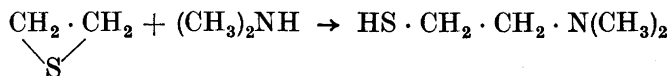
Ethylene sulphide has been prepared. From this the thiocholine esters of acetic, propionic, *n*-butyric, *n*-valeric, and benzoic acids have been synthesized in two ways. According to the first method, ethylene sulphide was treated with acyl bromides, and the 1-bromoethanethiol-(2) esters formed were transformed to thiocholine esters by trimethylamine. By the second method, dimethylamine and ethylene sulphide gave 1-dimethylaminoethanethiol-(2), which was esterified with acid anhydrides and then quaternized with methyl iodide. The methods are discussed, and the second one recommended for use.

Esters of thiocholine have, during the last years, attracted much interest within biochemistry because of their relationship to choline esters<sup>1</sup>, and in histochemistry as a means for localizing choline esterases in tissues<sup>2</sup>. It thus seemed reasonable to study the preparation of thiocholine esters.

Several methods for the synthesis of acetyl thiocholine have been described in the literature<sup>3-5</sup>. Of these methods, the one according to Ivin<sup>5</sup> (Method A) seemed to be the most convenient and thus was used with some modifications.



Moreover, a new method (Method B) using acylation of 1-dimethylaminoethanethiol-(2) with acid anhydride and subsequent quaternization with methyl iodide was tested.



The reaction between alkene sulphide and amines other than dimethylamine has been discussed in two earlier papers <sup>6,7</sup>. The last two steps are analogous to those used by Tammelin <sup>8</sup> for the preparation of choline esters.

The ethylene sulphide required for the two methods was synthesized by modifying a method used by Bordwell and Andersen <sup>9</sup> for the preparation of propylene sulphide.

### EXPERIMENTAL

*Ethylene sulphide.* To a mixture of 80 g (1.05 mole) of thiourea, 250 ml of water and 30 ml (0.55 mole) of concentrated sulphuric acid, a solution of 49 ml (1.00 mole) of ethylene oxide in 125 ml of xylene was added. The mixture was continuously stirred and the temperature was kept below +10°. A solution of 106 g (1.00 mole) of anhydrous sodium carbonate in 500 ml of water was added during 3 h without external cooling. After a further half-hour's stirring, the organic phase was separated, dried with calcium chloride and filtered. Distillation through a 25 cm glass spiral column gave 29 g (0.48 mole) of ethylene sulphide at 55–56°. Yield 48 %.

The experiments had to be performed in a well ventilated fume-hood because of the odours evolved.

### Method A

*Esters of 1-bromoethanethiol-(2).* 59 ml (1.00 mole) of ethylene sulphide was dissolved in 300 ml of dry carbontetrachloride, and 1.00 mole of acid bromide was added. The temperature of the reaction mixture increased to about 40°. The small precipitate formed was removed. The carbontetrachloride was distilled off at ordinary pressure. The residue gave a colourless product when distilled at reduced pressure. The results are given in Table 1.

Table 1. Esters of 1-bromoethanethiol-(2).

Acid	Formula	Mol.wt.	B. p./mm Hg	Yield in g from 1 mole of ethylene sulphide
Acetic	C <sub>4</sub> H <sub>7</sub> BrOS	183.1	66–8°/6	123
Propionic	C <sub>5</sub> H <sub>9</sub> BrOS	197.1	78–80°/6	138
<i>n</i> -Butyric	C <sub>6</sub> H <sub>11</sub> BrOS	211.1	96–7°/8	114
<i>n</i> -Valeric	C <sub>7</sub> H <sub>13</sub> BrOS	225.1	75.5°/0.9	157
Benzoic	C <sub>9</sub> H <sub>9</sub> BrOS	245.1	113–8°/0.4–0.5	220

*Esters of thiocholine bromide.* 90 ml (1.20 mole) of anhydrous trimethylamine were added to a mixture of 1.00 mole of ester of 1-bromoethanethiol-(2) and 1 l of dry acetone, cooled to –10°. White crystals were as a rule formed within a quarter of an hour. After a week at room temperature, 1 l of dry ether was added to precipitate the ester of thiocholine bromide still in solution. The precipitate was filtered off and recrystallized for analyses as follows: the acetic, propionic and benzoic derivatives from ligroin/absolute ethanol (1:1), the butyric derivative from dry acetone and the valeric derivative from dry acetone/ligroin (2:1). After drying in a vacuum desiccator the melting-points and analyses, given in Table 2, were obtained.

### Method B

*1-Dimethylaminoethanethiol-(2).* 59 ml (1 mole) of ethylene sulphide, dissolved in 100 ml of dry ether, were cooled to –10° and 88 ml (1.33 mole) of anhydrous dimethylamine were added. The mixture was allowed to stand at room temperature for 4 days.

Table 2. Esters of thiocholine bromide.

Acid	Formula	Mol. wt.	M.p. *	C		H		Br		Yield in %
				calc.	found	calc.	found	calc.	found	
Acetic	C <sub>7</sub> H <sub>16</sub> BrNOS	242.2	227°	34.7	35.0	6.7	6.7	33.0	32.9	65
Propionic	C <sub>8</sub> H <sub>18</sub> BrNOS	256.2	196°	37.5	37.6	7.1	7.0	31.2	31.2	96
<i>n</i> -Butyric	C <sub>9</sub> H <sub>20</sub> BrNOS	270.2	150°	40.0	40.2	7.5	7.4	29.6	29.6	94
<i>n</i> -Valeric	C <sub>10</sub> H <sub>22</sub> BrNOS	284.3	114°	42.3	42.3	7.8	7.8	28.1	28.4	94
Benzoic	C <sub>12</sub> H <sub>18</sub> BrNOS	304.3	239°	47.4	47.2	6.0	6.0	26.3	26.3	94

\* Determined with a "Kofler Heizbank".

The small precipitate formed was removed. The dimethylamine and the ether were distilled off at ordinary pressure. The residue was fractionated through a 25 cm glass spiral column under reduced pressure. The fraction collected at 58–59°/63 mm contained 73 g (0.70 mole) 1-dimethylaminoethanethiol-(2). In the distillation flask a few ml of a high boiling liquid remained.  $n_D^{25} = 1.4630$ ;  $d_4^{25} = 0.8943$  g/cm<sup>3</sup>. (Found: C 46.0; H 10.6. Calc. for C<sub>6</sub>H<sub>11</sub>NS (105.2): C 45.7; H 10.5).

*Esterification of 1-dimethylaminoethanethiol-(2)*. 117 ml (1.00 mole) of 1-dimethylaminoethanethiol-(2) and 1.05 mole of acid anhydride were mixed. The temperature at once rose to 70–100°, except in the reaction with benzoic anhydride when it rose to only about 40°. The mixture was distilled under reduced pressure until the temperature exceeded the values given in Table 3. Almost no residue remained in the distillation flask. The distillates were colourless and evil-smelling. The viscosity of the benzoic derivative was very high.

Table 3. Esters of 1-dimethylaminoethanethiol-(2).

Acid	Acetic	Propionic	<i>n</i> -Butyric	<i>n</i> -Valeric	Benzoic
Final b.p./mm Hg	70°/8	80°/8	93°/8	109°/9	104°/0.01

*Esters of thiocholine iodide*. The distillate from the esterification of 1.00 mole of 1-dimethylaminoethanethiol-(2) was dissolved in 750 ml of dry ether and 100 ml (1.60 mole) of methyl iodide were added. A white precipitate was formed at once. After three days at room temperature it was filtered off and dried in a vacuum desiccator. Recrystallization did not change the melting-points or analyses given in Table 4.

Table 4. Esters of thiocholine iodide.

Acid	Formula	Mol. wt.	M. p. *	C		H		I	
				calc.	found	calc.	found	calc.	found
Acetic	C <sub>7</sub> H <sub>16</sub> INOS	289.2	204°**	29.1	29.2	5.6	5.7	43.9	44.0
Propionic	C <sub>8</sub> H <sub>18</sub> INOS	303.2	208°	31.7	31.8	6.0	6.3	41.9	41.8
<i>n</i> -Butyric	C <sub>9</sub> H <sub>20</sub> INOS	317.2	173°	34.1	34.0	6.4	6.5	40.0	40.1
<i>n</i> -Valeric	C <sub>10</sub> H <sub>22</sub> INOS	331.3	146°	36.3	36.3	6.7	6.5	38.3	37.9
Benzoic	C <sub>12</sub> H <sub>18</sub> INOS	351.3	>250°***	41.0	41.2	5.2	5.1	36.1	—

\* Determined with a "Kofler Heizbank".

\*\* Renshaw *et al.* observed 203–4°.

\*\*\* " " " " " 257°.

## DISCUSSION

In method A no analyses have been made of the esters of 1-bromoethanethiol-(2), because of their partial decomposition during the distillation. If they were allowed to stand for a few weeks, a red-violet colour appeared, probably caused by the oxygen in the air. The addition of trimethylamine to the bromo esters was found to proceed much faster in acetone than in ether.

The 1-dimethylaminoethanethiol-(2) prepared in method B can also be obtained from 1-dimethylamino-2-chloroethane hydrochloride <sup>4, 10, 11</sup>, but in that case a great part of the thiol is oxidized to the corresponding disulphide. The reactions between acid anhydrides and the thiol start at room temperature and are very exothermic because of the heat of neutralization evolved during the formation of the ammonium salt instead of the free acid and aminoester. This shows that it is impossible to separate the esters of the 1-dimethylaminoethanethiol-(2) from the acids by directly applied distillation. However, the acid impurities do not seem to have a bad effect on the subsequent quaternization. The tertiary esters can be prepared from their hydrobromides <sup>12</sup>.

Of the two methods used for the preparation of thiocholine esters, method B is to be preferred. It gives iodides which are less hygroscopic than the bromides obtained according to method A and the products formed give correct analyses without recrystallization. The only disadvantage is that method B is restricted to mono esters.

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

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Received January 8, 1957.