

The Preparation of Thiocholine Esters

II. Esters of α - and β -Methyl-thiocholine

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The paper describes the preparation of α -methyl- and β -methyl-thiocholine halide esters of the lower fatty acids and of benzoic acid. The α -methyl compounds were prepared from propylene sulphide either by addition of acid bromide and then trimethylamine or preferably by addition of dimethylamine, acid anhydride and finally methyl halide. The last two steps were also used for the synthesis of the β -methyl compounds from 1-dimethylamino-propanethiol-(2).

The preparation of thiocholine esters in two ways from ethylene sulphide has been described earlier¹. This paper gives methods for the syntheses of α - and β -methyl-thiocholine esters, which were of interest for biochemical, physicochemical^{2,3} and pharmacological comparisons with the thiocholine esters.

The 1-dimethylamino-propanethiol-(2) required for the preparation of the β -methyl-thiocholine derivatives was synthesized as described by Renshaw *et al.*⁴ from 1-dimethylamino-2-chloropropane hydrochloride and thiourea. The melting-point of the intermediate isothiuronium compound could not, even after several recrystallizations, be raised above 154°, and the value 201—2° found by Renshaw *et al.*⁴ seems doubtful.

An attempt to prepare 2-dimethylamino-propanethiol-(1) in the same way from 2-dimethylamino-1-chloropropane hydrochloride and thiourea failed and resulted in 1-dimethylamino-propanethiol-(2)⁵. However, the 2-dimethylamino-propanethiol-(1) was easily obtained as the only product from the addition of dimethylamine to propylene sulphide in ether solution⁵.

The esters of the α - and β -methyl-thiocholine halides were prepared in good yields from the thiols by esterification with acid anhydride and quaternization with methyl halide. Another method for the α -methyl-thiocholine esters was based on the addition of an acid bromide to propylene sulphide, which gave a 2-bromo-*n*-propyl-thiolo ester⁶. This was quaternized with trimethylamine.

All the α -methyl-thiocholine compounds, independent of the method of preparation, at once formed crystals, whereas some of the β -methyl-thiocholine

iodides could not be obtained in crystalline form. Thus the esters of the *iso*-butyric, *n*-butyric and *n*-valeric acids were obtained as oils of which the last-mentioned partially crystallized after one or two days. The melting-points of the aliphatic esters of the α -methyl-thiocholine were higher than those of the corresponding β -methyl-thiocholine derivatives. The compounds were found to be hygroscopic, and even a few minutes exposure to moist air produced, in some cases, enough hydrolysis to give, some time later, a smell of the acid component. Owing to the formation of iodine the iodides assumed a yellow discolouration when stored in light. The solubility of the salts decreased in water and increased in ethanol with increasing molecular weight.

The acetyl and benzoyl β -methyl-thiocholine iodides have been described by Renshaw *et al.*⁴ The melting-points given by them were found to be a few degrees below those now reported.

Ivin⁷ has prepared a compound which, according to him, is acetyl α -methyl-thiocholine iodide. The compound was obtained by treating propylene sulphide with acetyl iodide and then adding trimethylamine. It gave acceptable nitrogen and sulphide analyses, but its iodine content was in accordance with a wrongly calculated value (found 35.5, calc. 35.3; correctly calc. 41.9). Furthermore the melting-point 238° is much higher than that for the compound prepared in this institute, 164°. It thus seems clear that Ivin's compound cannot have been acetyl α -methyl-thiocholine iodide or that he by mistake has reported some erroneous values.

EXPERIMENTAL

Propylene sulphide. Propylene oxide and thiourea gave propylene sulphide (b.p. 74–76°; yield 58 %) when treated as described for the preparation of ethylene sulphide¹.

Esters of 2-bromo-propanethiol-(1). The esters were obtained from propylene sulphide and acid bromides in the same way as the esters of 2-bromo-ethanethiol-(1)¹. The boiling points and yields are given in Table 1. The products were not analysed.

Table 1. Esters of 2-bromo-propanethiol-(1).

Acid	Formula	Mol.wt	B.p./mm Hg	Yield in %
Acetic	C ₂ H ₅ BrOS	197.1	72–73°/6 *	73
Propionic	C ₃ H ₇ BrOS	211.1	93–96°/9	66
<i>n</i> -Butyric	C ₄ H ₉ BrOS	225.1	99.5–100.5°/8	53
<i>n</i> -Valeric	C ₅ H ₁₁ BrOS	239.2	125–126.5°/10	53

* Davies and Savige⁶ found 45°/0.2.

Esters of α -methyl-thiocholine bromide. The esters of 2-bromo-propanethiol-(1) were allowed to react in dry acetone (the valeric derivative in dry acetone/ligroin 1:1) with excess of trimethylamine. The precipitates were recrystallized, the acetic ester from dry ethanol/ligroin and the other ones from dry acetone/ligroin. Analyses and melting-points are given in Table 2.

Table 2. Esters of α -methyl-thiocholine bromide.

Acid	Formula	Mol. wt.	M. p.	C		H		Br		Yield in %
				calc.	found	calc.	found	calc.	found	
Acetic	C ₈ H ₁₆ BrNOS	256.2	187°	37.5	37.2	7.1	7.0	31.2	31.3	63
Propionic	C ₉ H ₂₀ BrNOS	270.2	154°	40.0	39.9	7.5	7.5	29.6	29.3	63
<i>n</i> -Butyric	C ₁₀ H ₂₂ BrNOS	284.3	170°	42.3	42.2	7.8	7.6	28.1	28.3	54
<i>n</i> -Valeric	C ₁₁ H ₂₄ BrNOS	298.3	179°	44.3	44.0	8.1	8.1	26.8	26.9	67

2-Dimethylamino-propanethiol-(1). A solution of 46 g (0.63 mole) of propylene sulphide dissolved in 65 ml of dry ether was cooled to 0° and 75 ml (1.05 mole) of anhydrous dimethylamine were added. The mixture was stored at room temperature for two days and then distilled through a 25 cm Widmer column, the excess of dimethylamine and the ether being removed at ordinary pressure and the 2-dimethylamino-propanethiol-(1) being distilled under reduced pressure. Yield 51.5 g (69 %) at 71°/88 mm; $n_D^{25} = 1.4538$; $d^{25} = 0.8693$ g/cm³. (Found: C 50.4; H 10.8. Calc. for C₅H₁₃NS (119.2): C 50.4; H 11.0.)

1-Dimethylamino-2-chloropropane hydrochloride was prepared from thionyl chloride and 1-dimethylamino-propanol-(2), obtained by adding dimethylamine to propylene oxide. M. p. 185°. Schultz and Sprague⁸ observed 185–186°.

S-(1-Dimethylaminopropyl-(2))-isothiuronium chloride hydrochloride. One mole of 1-dimethylamino-2-chloropropane hydrochloride and 1.02 mole of thiourea in 600 ml of absolute ethanol were refluxed for 65 h. The solution was cooled to room temperature and ethyl acetate then added in small portions until the first permanent opalescence was obtained. The vessel was scratched with a glass rod and two days later crystals had formed. They were removed by suction, washed with absolute ethanol/ethyl acetate (1:1) and dried in air. Yield 122 g (52 %). After being recrystallized from *n*-propanol and dried at 75° the compound melted at 154°. (Found: C 30.4; H 7.3. Calc. for C₆H₁₇Cl₂N₂S (234.2): C 30.8; H 7.3.)

By performing the reaction in *n*-propanol Renshaw *et al.*⁴ obtained the *isothiuronium* compound in 92 % yield. Their method was tried without success, nor could their melting-point, 201–202°, be reproduced.

1-Dimethylamino-propanethiol-(2). One mole of the *isothiuronium* compound was dissolved in 280 ml of water. The solution was covered with ether in an extraction apparatus. With cooling, a solution of 2.0 moles of sodium hydroxide in 80 ml of water was added in portions. The reaction mixture was continuously extracted with ether until there was no further change in the volume of the water phase. The ether solution was dried with calcium chloride and distilled through a 25 cm Vidmer column, the ether at ordinary and the thiol under reduced pressure. Yield 64 %; b. p. 78.5°/70 mm; $n_D^{25} = 1.4684$; $d^{20} = 0.9046$ g/cm³.

Esterification of the dimethylamino-propanethiols. The reactions between the thiols and the acid anhydrides were carried out as described for 2-dimethylamino-ethanethiol¹. The boiling ranges are given in Table 3.

Table 3. B.p./mm Hg of esters of α -dimethylamino-propanethiol-(y).

Acid Thiol	Acetic	Propionic	<i>n</i> -Butyric	<i>Isobutyric</i>	<i>n</i> -Valeric	Benzoic
$x = 1, y = 2$	76–82°/11	78–88°/10	74–85°/1.8	86–92°/12	67–82°/0.3	120–125°/0.63
$x = 2, y = 1$	64.5–66°/11	67–81°/12	80–88°/9	85–94°/10	53–60°/0.07	88–96°/0.01

Table 4. Esters of α -methyl-thiocholine halides.

x	Acid	Formula	Mol. wt.	M. p.	C		H		Halogen		Yield* in %
					calc.	found	calc.	found	calc.	found	
α	Acetic	C ₈ H ₁₈ BrNOS	256.2	188°	37.5	37.6	7.1	7.1	31.2	31.1	—
β	»	C ₈ H ₁₈ BrNOS	256.2	168°	37.5	37.5	7.1	7.2	31.2	—	—
α	»	C ₉ H ₁₈ INOS	303.2	164°	31.7	31.8	6.0	5.9	41.9	41.8	50
β	»	C ₉ H ₁₈ INOS	303.2	150°**	31.7	31.7	6.0	6.0	41.9	41.8	70
α	Propionic	C ₉ H ₂₀ INOS	317.2	155°	34.1	34.3	6.4	6.2	40.0	39.6	61
β	»	C ₉ H ₂₀ INOS	317.2	132°	34.1	34.0	6.4	6.3	40.0	39.9	65
α	n-Butyric	C ₁₀ H ₂₂ INOS	331.3	130°	36.3	36.3	6.7	6.7	38.3	38.8	62
β	»	C ₁₀ H ₂₂ BrNOS	284.3	164°	42.3	41.8	7.8	7.8	28.1	28.3	67
α	Isobutyric	C ₁₀ H ₂₂ INOS	331.3	158°	36.3	35.9	6.7	6.5	38.3	38.3	82
β	»	C ₁₀ H ₂₂ BrNOS	284.3	140°	42.3	42.4	7.8	7.8	28.1	—	32
α	n-Valeric	C ₁₁ H ₂₄ INOS	345.3	152°	38.3	38.4	7.0	6.8	36.8	—	62
β	»	C ₁₁ H ₂₄ INOS	345.3	74°	38.3	38.1	7.0	7.0	36.8	36.5	31
α	Benzoic	C ₁₃ H ₂₀ INOS	365.3	136°	42.7	42.4	5.5	5.4	34.8	—	54
β	»	C ₁₃ H ₂₀ INOS	365.3	194°***	42.7	42.5	5.5	5.6	34.8	—	76

* Calculated on the thiol. ** Renshaw *et al.*⁴ reported 144—145°. *** Renshaw *et al.*⁴ found 185—186°.

Esters of methyl-thiocholine iodides and bromides. The esters of the dimethylamino-propanethiols were quaternized with methyl bromide or iodide according to the method used earlier¹. Of the α -methyl esters the acetic, butyric and benzoic compounds were recrystallized from dry acetone/ligroin (2:1). The acetyl β -methyl-thiocholine bromide was recrystallized from dry acetone/absolute ethanol (3:1) and the benzoic ester from water. Table 4 contains the melting-points, analyses and yields of the compounds.

All melting-points have been determined with a »Kofler Hot Bench».

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