been obtained. The isolation and properties of this alkaloid have been studied. On hydrolysis, it yields a base, kopsidine, $C_{20}H_{24}N_2O_3$, m. p. 142°; and on hydrogenation, a dihydro derivative, m. p. 218° (dec.).

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

# A New Series of Testosterone Esters

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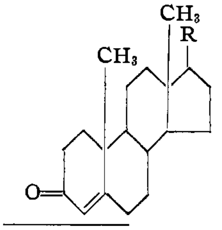
The literature is replete with attempts by workers in the field to prepare esters of testosterone which would show both more intensive and more prolonged androgenic action than testosterone itself. It was shown in early studies[2] that the lower aliphatic acid esters are most effective; as one increases the length of the carbon chain in the fatty acid residue, the effect becomes more prolonged but the intensity decreases rapidly. Ruzicka,[3] by his preparation and testing of the acetate and benzoate esters, initiated work which resulted in the general adoption of testosterone propionate as an activated form of testosterone. These workers[4] prepared a long series of aliphatic acid esters. Miescher's group[5] made a study of halogenated, aminated, and unsaturated aliphatic esters as well as carbonate esters. This latter group of workers[6] also studied the enol diesters of testosterone. Rabold and Dietrich[7] have made a study of the glucoside and tetraacetyl glucoside. The patent literature[8] describes a sulfonic acid and a phosphoric acid ester.

However, since it was felt that the field had not been combed thoroughly enough in view of the importance of the problem, there has been prepared a new series of esters several of which show activities surpassing testosterone propionate in rat tests where the weight increase of the seminal vesicles and the prostate was studied. A preliminary summary of the results obtained is shown in Table III. More complete biological results will be published[9] at a later date.

Esters of the general types



I, R = —OCOR′
II, R = —OCOR″—Y—R‴
III, R = —OCOR″OCOR‴

have been prepared (Table III) where R′ is of the carbocyclic or heterocyclic type, R″ and R‴ are various aliphatic or aromatic radicals and Y is oxygen or sulfur. Types I and III have been prepared from the acid chlorides and type II from the acid chlorides and anhydrides.

The acids shown in Table I were prepared by three methods. Method A involves the reaction of the appropriate sodium alkoxide or mercaptide with a halogenated acid. The second method, B, was used only to make ethyl or methylmercapto acids by the alkylation of the appropriate mercapto acid with ethyl or methyl sulfates. Method C involves hydrolysis of the corresponding nitrile.

In preparing the acid chlorides shown in Table II, both thionyl chloride (D) and phosphorus trichloride (E) were used. Phosphorus trichloride possesses the advantage that a colorless product almost always results. This is of decided advantage in the preparation of a color-free ester. Furthermore, in some instances in which thionyl chloride results in tar formation, phosphorus trichloride gives a fair yield of product. From the viewpoint of yield, however, thionyl chloride is usually to be preferred.

Some of the acids and acid chlorides described are old compounds but are included where the characterization is somewhat more complete than that described in the literature. Those acids which were obviously used but not described may be found elsewhere in the literature.

## Experimental

**$n$-Butylmercaptoacetic Acid (Method A).**—To 21.6 g. of $n$-butylmercaptan (0.24 mole) dissolved in 200 cc. of 18% sodium hydroxide solution was added 20.8 g. of chloroacetic acid (0.22 mole) dissolved in 100 cc. of 18% sodium hydroxide. The mixed solutions were heated for two hours on a steam-bath. The solution was then cooled and acidified and the product extracted with ether and distilled. Distillation gave 29 g. of product, b. p., 136-137° at 10 mm.

**2-Ethylmercaptopropanoic Acid (Method B).**—A solution of 43.5 g. (0.41 mole) of 2-mercaptopropanoic acid was prepared by dissolving it in a solution containing 36 g. (0.9 mole) of sodium hydroxide in 45 cc. of water. While this solution was being stirred and heated on a steam-bath 63.2 g. (0.41 mole) of diethyl sulfate was added dropwise. Heating was continued until a single phase resulted. The solution was cooled, acidified with dilute sulfuric acid, and extracted with ether three times. The ether was evaporated and the residue distilled, yielding 24.5 g. of product, b. p. 111-113° at 8 mm.

**4-Methylmercaptobutanoic Acid (Method C).**—Eighteen grams of methyl mercaptan (0.37 mole) was dissolved

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(2) Miescher, Wettstein and Tschopp, *Biochem. J.*, **30**, 1970 (1936).

(3) Ruzicka and Kägi, *Helv. Chim. Acta*, **19**, 842 (1936).

(4) Ruzicka and Wettstein, *Helv. Chim. Acta*, **19**, 1141 (1936).

(5) Miescher, *et al.*, *Biochem. Z.*, **294**, 39 (1937).

(6) Miescher, Fischer and Tschopp, *Biochem. Z.*, **300**, 14 (1938).

(7) Rabold and Dietrich, *Z. physiol. Chem.*, **259**, 251 (1939).

(8) Hartmann, Wettstein, U. S. Patent 2,182,920.

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TABLE I

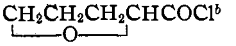
ACIDS

| | B. p. °C. | Mm. | $n^{25}$D | Yield, % | Method | Molecular formula | Analyses, % sulfur Calcd. | Found |
|---|---|---|---|---|---|---|---|---|
| $n$-$C_3H_7SCH_2COOH$ | 126–128 | 11 | 1.4805 | 83 | A | $C_5H_{10}O_2S$ | 23.89 | 23.78 |
| $i$-$C_3H_7SCH_2COOH$ | 118–119 | 10 | 1.4788 | 65 | A | $C_5H_{10}O_2S$ | 23.89 | 24.19 |
| | | | | 39 | B | | | |
| $n$-$C_4H_9SCH_2COOH$ | 136–137 | 10 | 1.4780 | 89 | A | $C_6H_{12}O_2S$ | 21.63 | 21.13, 21.18 |
| $CH_3SCH_2CH_2COOH$ | 119–123 | 12 | 1.4884 | 88 | B | $C_4H_8O_2S$ | 26.68 | 26.86 |
| $CH_3CH(SCH_3)COOH$ | 105–106 | 8 | 1.4815 | 27 | B | $C_4H_8O_2S$ | 26.68 | 26.94 |
| $CH_3CH(SC_2H_5)COOH$ | 111–113 | 8 | 1.4764 | 45 | B | $C_5H_{10}O_2S$ | 23.89 | 24.25 |
| $CH_3SCH_2CH_2CH_2COOH$ | 130 | 9 | 1.4823 | 65[a] | C | $C_5H_{10}O_2S$ | 23.89 | 23.44 |
| $CH_3CH_2CH(SCH_3)COOH$ | 115–116 | 8 | 1.4788 | 71 | A | $C_5H_{10}O_2S$ | 23.89 | 23.60 |
| $n$-$C_3H_7SCH_2CH_2CH_2COOH$ | 168–170 | 23 | 1.4778 | 78[a] | C | $C_7H_{14}O_2S$ | 19.76 | 19.38 |
| $i$-$C_3H_7OCH_2COOH$ | 96–98 | 9 | 1.4190 | 80 | A | $C_5H_{10}O_3$ | C, 50.83 | 50.99 |
| | | | | | | | H, 8.53 | 8.60 |

[a] This yield is an over-all yield for condensation of a sodium mercaptide with a halogenated nitrile and hydrolysis of the resulting product.

TABLE II

ACID CHLORIDES

| | B. p. °C. | Mm. | $n^{25}$D | Chlorination agent | Yield, % | Molecular formula | Analyses, % chlorine Calcd. | Found |
|---|---|---|---|---|---|---|---|---|
| $CH_3SCH_2COCl$ | 49–50 | 14 | 1.4967 | E | 45 | $C_3H_5ClOS$ | 28.46 | 28.28 |
| $C_2H_5SCH_2COCl$ | 61–64 | 14 | 1.4888 | D | 75 | $C_4H_7ClOS$ | 25.58 | 25.57 |
| $n$-$C_3H_7SCH_2COCl$ | 63–64 | 8 | 1.4846 | D | 92 | $C_5H_9ClOS$ | 23.23 | 23.10 |
| $i$-$C_3H_7SCH_2COCl$ | 57–58 | 8 | 1.4820 | D | 99 | $C_5H_9ClOS$ | 23.23 | 23.55 |
| $n$-$C_4H_9SCH_2COCl$ | 83–84 | 8 | 1.4828 | D | 90 | $C_6H_{11}ClOS$ | 21.31 | 21.58 |
| $C_6H_5SCH_2COCl$ | 117–119 | 6 | 1.5806 | D | 93 | $C_8H_7ClOS$ | 18.99 | 18.80 |
| $C_6H_5CH_2SCH_2COCl$ | 130 | 5.5 | 1.5682 | D | 67 | $C_9H_9ClOS$ | 17.67 | 17.51 |
| $CH_3SCH_2CH_2COCl$ | 96–97 | 45 | 1.4941 | E | 37 | $C_4H_7ClOS$ | 25.58 | 25.60 |
| $CH_3CH(SCH_3)COCl$ | 77–78 | 45 | 1.4873 | E | 52 | $C_4H_7ClOS$ | 25.58 | 25.20 |
| $CH_3CH(SC_2H_5)COCl$ | 56–57 | 8 | 1.4805 | E | 64 | $C_5H_9ClOS$ | 23.23 | 23.35 |
| $CH_3SCH_2CH_2CH_2COCl$ | 98–100 | 20 | 1.4898 | E[a] | 80 | $C_5H_9ClOS$ | 23.23 | 22.98 |
| $CH_3CH_2CH(SCH_3)COCl$ | 58–59 | 8 | 1.4835 | E | 83 | $C_5H_9ClOS$ | 23.23 | 23.06 |
| $n$-$C_3H_7SCH_2CH_2CH_2COCl$ | 106–108 | 9 | 1.4835 | E | 79 | $C_7H_{13}ClOS$ | 19.62 | 19.45 |
| $i$-$C_3H_7OCH_2COCl$ | 139–141 | 760 | 1.4188 | E | 92 | $C_5H_9ClO_2$ | 26.00 | 25.70 |
| $CH_3OCH_2CH_2COCl$ | 137–138 | 760 | 1.4260 | E | 70 | $C_4H_7ClO_2$ | 28.93 | 29.40 |
| $C_2H_5OCH_2CH_2COCl$ | 150–151 | 760 | .... | E | 72 | $C_5H_9ClO_2$ | 26.00 | 26.17 |
|  $\underbrace{CH_2CH_2CH_2CH}_{O}COCl$[b] | 80–81 | 30 | 1.4592 | E | 70 | $C_5H_7ClO_2$ | 26.33 | 26.35 |
| $C_2H_5COOCH_2COCl$ | 58 | 10 | 1.4265 | .. | .. | $C_5H_7ClO_3$ | 22.64 | 22.54 |
| $(CH_3SCH_2CO)_2O$ | 111–112 | 0.25 | 1.5162 | .. | 62 | $C_6H_{10}O_3S_2$ | C, 37.09 | 37.12 |
| | | | | | | | H, 5.18 | 5.32 |
| $(C_2H_5SCH_2CO)_2O$ | 94 | 0.07 | 1.5030 | .. | 60 | $C_8H_{14}O_3S_2$ | S, 28.77 | 28.98 |
| | | | | | | | C, 43.36 | 43.52 |
| | | | | | | | H, 6.33 | 6.61 |

[a] Using thionyl chloride, only tar results. [b] Decomposes violently on standing at room temperature for some time.

in 125 cc. of 35% sodium hydroxide solution and 125 g. of crushed ice. To this was added 25.8 g. (0.25 mole) of 4-chlorobutanenitrile in 100 cc. of 95% ethanol. The solution was refluxed for two and one-half hours. After diluting the reaction mixture with water, it was extracted with ether to remove unhydrolyzed nitrile. The alkaline solution was then acidified with hydrochloric acid and again extracted with ether. There resulted 18.6 g. of product, b. p. 129-130° at 9 mm.

***n*-Butylmercaptoacetyl Chloride (Method D).**—A mixture of 23.8 g. (0.16 mole) of *n*-butylmercaptoacetic acid and 29 cc. of thionyl chloride was heated gently on a steam-bath until evolution of hydrogen chloride ceased. The residue was distilled to give 24.2 g. of product, b. p., 83-84° at 8 mm.

**2-Ethylmercaptopropanol Chloride (Method E).**—A mixture of 21.3 g. (0.16 mole) of 2-ethylmercaptopropanoic acid and 8.8 g. (0.064 mole) of phosphorus trichloride was allowed to stand overnight and then heated on a steam-bath for one hour. The product was decanted from the sirupy phosphoric acids. Distillation gave 15.4 g. of product, b. p. 56-57°, at 8 mm.

**Ethylmercaptoacetic Anhydride.**—A solution of 370 g. (3.1 mole) of ethylmercaptoacetic acid in 1100 g. of acetic anhydride was refluxed for six hours and then fractionally distilled. The product was collected at 100-103° at 0.1 mm., yield 166 g.

**Testosterone *n*-Butoxyacetate.**—Six-tenths gram of testosterone was dissolved in 25 cc. of dry ether with 4 cc. of dry pyridine. To this was added 1 g. of *n*-butoxyacetyl chloride in 10 cc. of dry ether. A solid immediately precipitated. The suspension was refluxed for one-half hour and poured into water. The ether extract was washed with dilute sodium carbonate solution, dilute sulfuric acid and water. The ether was evaporated and the residue taken up in Skellysolve A containing about 20% of ether.

TABLE III

TESTOSTERONE ESTERS[d]

| R | M. p., °C. | Activity[a] | Molar extinction coef. × 10³ | Position of max.[b] λ in mμ | [α]D[b] at | X, °C. | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Sulfur Calcd. | Sulfur Found | Molecular formula |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| $CH_3CH_2COO$– | 120–121 | 100 | 16.9 | 241 | 88.3 | 25 | 76.67 | 76.88 | 9.37 | 9.15 | | | $C_{22}H_{32}O_3$ |
| $CH_3OCH_2COO$– | 110[c] | 97 | 16.8 | 240–241 | 84.6 | 27 | 73.33 | 73.01 | 8.96 | 8.96 | | | $C_{22}H_{32}O_4$ |
| $C_2H_5OCH_2COO$– | 122.5–124 | 121 × 7* | 17.1 | 240–241 | 77.9 | 25 | 73.76 | 73.96 | 9.15 | 9.16 | | | $C_{23}H_{34}O_4$ |
| *n*-$C_3H_7OCH_2COO$– | 88–89 | 103 | 17.0 | 240 | 75.9 | 29 | 74.20 | 74.33 | 9.35 | 9.23 | | | $C_{24}H_{36}O_4$ |
| *i*-$C_3H_7OCH_2COO$– | 81–82 | ... | 16.5 | 240–241 | ... | .. | 74.20 | 73.88 | 9.35 | 9.03 | | | $C_{24}H_{35}O_4$ |
| *n*-$C_4H_9OCH_2COO$– | 61.5–63 | 111 | 15.6 | 240 | 63.0 | 29 | 74.58 | 74.66 | 9.51 | 9.43 | | | $C_{25}H_{38}O_4$ |
| $CH_3OCH_2CH_2COO$– | 110–112 | 93 ± 6* | 17.0 | 239–242 | 79.6 | 25 | 73.76 | 73.83 | 9.15 | 9.06 | | | $C_{23}H_{34}O_4$ |
| $C_2H_5OCH_2CH_2COO$– | 53–55 | 102 | 16.6 | 240 | 74.7 | 29 | 74.20 | 74.40 | 9.35 | 9.12 | | | $C_{24}H_{36}O_4$ |
| *i*-$C_3H_7OCH_2CH_2COO$– | 62–63.5 | 88 | 16.8 | 241 | 76.0 | 29 | 74.58 | 74.78 | 9.51 | 9.38 | | | $C_{25}H_{38}O_4$ |
| $CH_3OCH_2CH_2CH_2COO$– | 55–57 | 123 ± 4* | 17.1 | 240–241 | 88.4 | 26 | 74.20 | 74.03 | 9.35 | 9.19 | | | $C_{24}H_{36}O_4$ |
| $CH_2CH_2CHCOO$–<br>└———┘ | 149–151 | <100 | 16.7 | 240–241 | 84.4 | 26 | 77.27 | 77.28 | 9.30 | 9.00 | | | $C_{23}H_{32}O_3$ |
| $CH_2CH_2CH_2CH$—COO–<br>└——————┘ | 110–111 | <100 | 16.5 | 240–241 | 80.7 | 24 | 77.79 | 77.83 | 9.25 | 9.11 | | | $C_{24}H_{34}O_3$ |
| $CH_2CH_2CH_2CHCOO$–<br>└——O——┘ | 116–117 | <100 | 16.7 | 240–241 | 76.6 | 26 | 74.57 | 74.46 | 8.82 | 8.68 | | | $C_{24}H_{34}O_4$ |
| CH=CH—CH=C—COO–<br>└————O————┘ | 221[c] | <100 | 29.5 | 244–246 | 170.5 | 27 | 75.13 | 74.87 | 7.89 | 8.42 | | | $C_{24}H_{30}O_4$ |
| $CH_3COOCH_2COO$– | 110–112[c] | *ca.* 100 | 16.5 | 240–241 | 65.3 | 27 | 73.76 | 73.83 | 9.15 | 9.06 | | | $C_{23}H_{32}O_5$ |
| $CH_3COOCH_2CH_2COO$– | 112[c] | *ca.* 100 | 16.8 | 240–241 | 62.8 | 27 | 71.64 | 71.64 | 8.86 | 8.52 | | | $C_{24}H_{34}O_5$ |
| $CH_3SCH_2COO$– | 100–101 | 133 ± 3* | 17.3 | 239–240 | 82.5 | 26 | 70.17 | 70.19 | 8.57 | 8.59 | 8.52 | 8.77 | $C_{22}H_{32}O_3S$ |
| $C_2H_5SCH_2COO$– | 99–100 | 123 ± 5* | 17.1 | 240–241 | 84.4 | 25 | 70.73 | 70.68 | 8.77 | 8.64 | 8.21 | 8.18 | $C_{23}H_{34}O_3S$ |
| *n*-$C_3H_7SCH_2COO$– | 69.5–70.5 | 121 ± 6* | 17.4 | 240 | 85 | 26 | 71.24 | 71.10 | 8.97 | 8.98 | 7.91 | 8.02 | $C_{24}H_{36}O_3S$ |
| *i*-$C_3H_7SCH_2COO$– | 75–76 | 111 ± 2* | 17.2 | 240–242 | 87.5 | 29 | 71.24 | 71.30 | 8.97 | 8.87 | 7.91 | 7.84 | $C_{24}H_{36}O_3S$ |
| $C_6H_5SCH_2COO$– | 120.5–122 | 99 | 22.7 | 240 | 76.1 | 29 | 73.93 | 73.29 | 7.81 | 7.54 | 7.31 | 7.56 | $C_{27}H_{34}O_3S$ |
| $C_6H_5CH_2SCH_2COO$– | 80.5–82 | 46 | 18.2 | 239–241 | 76.4 | 26 | 74.29 | 74.37 | 8.03 | 8.01 | 7.09 | 7.20 | $C_{28}H_{36}O_3S$ |
| $CH_3SCH_2CH_2COO$– | 85–86 | <100 | 16.9 | 239–241 | 84.4 | 29 | 70.73 | 70.76 | 8.77 | 8.67 | | | $C_{23}H_{34}O_3S$ |
| $CH_3CH(SCH_3)COO$– | 125–126 | <100 | 17.7 | 240–241 | 76.7 | 24 | 70.73 | 70.70 | 8.77 | 8.81 | | | $C_{23}H_{34}O_3S$ |
| $CH_3CH(SC_2H_5)COO$– | 84–86 | 81 | 17.3 | 240–242 | 87.1 | 29 | 71.24 | 71.18 | 8.97 | 8.86 | 7.91 | 7.77 | $C_{24}H_{36}O_3S$ |
| $CH_3SCH_2CH_2CH_2COO$– | 64–66 | 75 | 16.8 | 240–241 | 86.0 | 27 | 71.24 | 70.97 | 8.97 | 8.92 | 7.91 | 7.90 | $C_{24}H_{36}O_3S$ |
| $CH_3CH_2CH(SCH_3)COO$– | 118–119.5 | 27 | 17.9 | 241 | 72.8 | 29 | 71.24 | 71.14 | 8.97 | 9.02 | 7.91 | 7.63 | $C_{24}H_{36}O_3S$ |

[a] Activity is measured by the effect on growth of seminal vesicles and prostate of castrated male rats. Daily subcutaneous injection for 3 days sacrificed 24 hours after last injection. Estimated activity based on testosterone propionate as 100%. All results based on 3 rats except starred results which indicate 10 rats were used. [b] All run in 1% w/v solution in U. S. P. grain alcohol except the rotation of the furoate ester which was run in the same concentration of C. P. chloroform. [c] Uncorrected m. p. [d] Yield varied from 30 to 90%.

The solution was passed through a column of activated alumina (Aluminum Ore Co., minus 80 mesh). The absorbed product was then washed off the alumina with 1:1 Skellysolve A-ether. This process of adsorption and elution was repeated several times giving 0.5 g. of a white crystalline mass. This was recrystallized from Skellysolve A to give one fraction, m. p. 61.5-63° (0.32 g.), a second fraction, m. p. 58-59° and a residual sirup. Analysis of the first fraction showed it to be pure ester.

**Testosterone Ethylmercaptoacetate.**—A mixture of 0.75 g. of testosterone in 1 cc. of ethylmercaptoacetic anhydride was heated for two hours on a steam-bath. The reaction mixture was poured into water and allowed to stand overnight. It was then extracted with ether and the extract washed with dilute sodium carbonate solution. The ether was diluted with three parts of Skellysolve A and the solution passed through a column of activated alumina. The adsorbed ester was eluted from the alumina with 1:1 ether–Skellysolve. This process was repeated three times. The solvent was evaporated, almost to dryness, diluted with a little Skellysolve A, and the product allowed to crystallize. These crystals were filtered off and recrystallized from Skellysolve B; yield 0.80 g., m. p. 99-100°.

## Summary

A series of new alkoxy and alkylmercapto acids and their acid chlorides have been prepared. These have been used in the preparation of the corresponding testosterone esters.

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