TABLE I (*Concluded*)

Name Ethylacetomalonate-monothio-	Formula	M. p. °C.	Decomp. °C.	Cryst. form	Analysis Calcd. %	Analysis Found %	Remarks
p-Phenetide[a]	.....	113–114	.....	yellow needles	..	...	
p-Chloro-anilide	.....	141–142	.....	slender needles	...	...	First prepared by S. and L.
p-Iodo-anilide	C_8H_8NSCl	149	.....	needles	Cl,19.1	Cl,18.8	
α-Naphthylamide	.....	111	.....	pale yellow needles	...	...	Prepared also by Jacobsen[4]

[a] This substance has been prepared by Sachs and Loeng [*Ber.*, **37**, 876 (1904)] who describe it as yellow plates from acetic acid melting at 99–100°.

This work was aided by a generous grant from the Cyrus M. Warren Fund of the American Academy.

Summary

A number of substituted aromatic mustard oils have been found to react with sodium ethylaceto-acetate, forming thio-amides of ethyl acetyl-malonate.

The resulting amides easily hydrolyze with alkali to form monothio-amides of malonic acid. Carbon dioxide is evolved on heating the latter so that thio-amides of acetic acid are formed.

The non-existence of thio-aceto-acetyl-*o*-(and *m*)-toluides has been indicated.

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THE SYNTHESIS OF SOME POSSIBLE PRECURSORS OF LYSINE

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RECEIVED AUGUST 11, 1924 PUBLISHED DECEMBER 13, 1924

It is generally known that the animal body can synthesize certain amino acids such as glycine. However, the so-called "essential" amino acids must be present in the diet and are not synthesized in the body from the ordinary products of metabolism. Perfusion experiments with surviving livers have indicated that α-hydroxy acids can be converted to α-amino acids and *vice versa*. If this is a normal reaction in the body, then a diet containing the hydroxy acids corresponding to the essential amino acids should be equivalent to a diet containing the amino acids themselves.

Lysine, *l*-α,ε-diaminocaproic acid, is one of the essential amino acids. It was thought that considerable evidence concerning possible synthetic reactions in the animal body could be obtained by supplementing a diet deficient in lysine with various caproic acid derivatives

[4] Jacobsen, *Ber.*, **20**, 1897 (1887).

substituted in the alpha and epsilon positions. Accordingly the synthesis of the following series of caproic acid derivatives was undertaken; α-hydroxycaproic acid, ε-aminocaproic acid, ε-hydroxycaproic acid, α-amino-ε-hydroxycaproic acid, ε-amino-α-hydroxycaproic acid, α,ε-diaminocaproic acid (*dl*-lysine) and α,ε-dihydroxycaproic acid.

All of these compounds have been described in the literature with the exception of ε-hydroxycaproic acid. In general the methods previously used are satisfactory for these preparations. ε-Aminocaproic acid[1] and *dl*-lysine dihydrochloride[2] were prepared by essentially the methods described by J. v. Braun. A few changes were made in this procedure and these will be considered in the experimental part. ε-Amino-α-hydroxy caproic acid was made by the method of Fischer and Zemplin[3] and the physical properties of the product obtained agreed with those recorded in the literature.

α-Hydroxycaproic acid was made by a combination of two methods previously described. Ley[4] prepared this compound by the hydrolysis of α-bromocaproic acid with sodium carbonate solution. Abderhalden and Weil[5] prepared it by the action of nitrous acid on α-amino caproic acid and purified the product by means of the copper salt. The method used in this work was to hydrolize α-bromocaproic acid and purify the crude acid by the copper salt method.

Helferich and Malkomes[6] in converting cyclohexanone into δ-hexenic acid, obtained a by-product which they have considered to be the lactone of ε-hydroxycaproic acid, but they do not claim to have definitely established the position of the hydroxyl group. The sodium salt of this acid has now been prepared by the following series of reactions.

$$C_6H_5O(CH_2)_4Br \xrightarrow[C_2H_5ONa]{CH_2(CO_2C_2H_5)_2} C_6H_5O(CH_2)_4CH(CO_2C_2H_5)_2$$

$$\xrightarrow{\text{Hydrolysis}} C_6H_5O(CH_2)_4CH(CO_2H)_2 \xrightarrow{\text{Heat}}$$

$$C_6H_5O(CH_2)_4CH_2CO_2H \xrightarrow{HBr} Br(CH_2)_5CO_2H \xrightarrow[\text{Water, then HCl}]{Ag_2O}$$

$$HO(CH_2)_5CO_2H \text{ and lactone} \xrightarrow{NaOH} HO(CH_2)_5CO_2Na$$

The free acid was not isolated, as it always contained some lactone.

α-Amino-ε-hydroxycaproic acid and α,ε-dihydroxycaproic acid have been reported as having been isolated from the products formed by

[1] v. Braun, *Ber.*, **40**, 1839 (1907). See also Ruzicka, *Helvetica chim. Acta*, **4**, 479 (1921).

[2] v. Braun, *Ber.*, **42**, 839 (1909).

[3] Fischer and Zemplin, *Ber.*, **42**, 4878 (1909).

[4] Ley, *Ber.*, **10**, 230 (1877).

[5] Abderhalden and Weil, *Z. physiol. Chem.*, **84**, 51 (1913).

[6] Helferich and Malkomes, *Ber.*, **55B**, 702 (1922).

the action of nitrous acid on lysine.[7] This reaction is not a satisfactory method of preparation for these compounds. It was thought that they could be prepared from some of the intermediate compounds in the above synthesis. This part of the work has not been completed as yet. However, since the report on the physiological experiments with the other compounds is now ready for publication[8] it was thought desirable to present the method used in their preparation. None of the compounds proved to be a substitute for lysine in the diet.

Experimental Part

α-Hydroxycaproic Acid.—A solution of 70 g. of α-bromocaproic acid and 70 g. of sodium carbonate in 1 liter of water was boiled for an hour, and to the hot solution 35 g. of copper acetate was added. The copper salt of α-hydroxycaproic acid precipitated as a light green powder. The solution was cooled and the salt was collected on a filter, washed with water and dried in the air; yield, 40 g. or 60%. A suspension of the copper salt in hot water was treated with hydrogen sulfide, the copper sulfide filtered off and the filtrate concentrated under reduced pressure. The hydroxy acid was extracted with ether and recrystallized from petroleum ether; m. p., 60–62°. Considerable loss of product occurs in the conversion of the copper salt to the pure free acid.

ε-Aminocaproic Acid.—As mentioned before, this compound was prepared by the method of J. v. Braun[1] starting with benzoyl-piperidine which was converted in turn to ε-benzoylamyl chloride, ε-benzoylamyl iodide, ε-benzoylamyl cyanide and this by hydrolysis with hydrochloric acid into ε-aminocaproic acid hydrochloride. The free amino acid was obtained from the salt by treatment with silver oxide and removal of the silver by hydrogen sulfide. The acid was purified by repeated washing with absolute alcohol. It melted at 203° as mentioned by J. v. Braun. Considerable loss occurred in the last step due to the formation of an inner amide or lactam.

***dl*-Lysine Dihydrochloride.**—J. v. Braun's method[2] was also followed in general for this preparation. However, better yields of ε-benzoyl-aminocaproic acid were obtained from ε-benzoylamino-amyl cyanide by complete hydrolysis with hydrochloric acid to ε-aminocaproic acid hydrochloride and subsequent treatment with alkali and benzoyl chloride than could be obtained by direct hydrolysis of the amide cyanide to the amide acid with alkalies. In the bromination of ε-benzoyl-aminocaproic acid to give α-bromo-ε-benzoyl-aminocaproic acid great care must be taken to have all of the reagents dry if good yields are to be expected. The conversion of the bromo acid to the amino acid and subsequent hydrolysis to lysine hydrochloride ran according to the directions given. The salt was washed with alcohol and ether. It melted at 192–193°, which is slightly higher than the melting point previously recorded.

Diethyl-ε-phenoxybutyl Malonic Ester.—Eighteen g. of sodium was dissolved in 500 cc. of absolute alcohol, and 128 g. of diethyl malonate and 160 g. of δ-phenoxybutyl bromide were added. The mixture was refluxed for about four hours, when the reaction was complete. Most of the alcohol was removed by distillation from a steam-bath and water was added to dissolve the sodium bromide. The ester layer was collected in a little benzene and the solution was distilled under reduced pressure. The ester was collected at 224–228° (20 mm.); yield, 144 to 166 g., or 65–75%; $n_D^{22°}$, 1.4879; d_4^{20}, 1.081.

Anal. Subs., 0.1948: CO_2, 0.4751; H_2O, 0.1352. Calc. for $C_{17}H_{24}O_5$: C, 66.21; H, 7.85. Found: C, 66.53; H, 7.77.

[7] Szydlowski, *Monatsh.*, **27**, 826 (1906).

[8] Detailed description of the physiological experiments have been published by Lewis and others, *J. Biol. Chem.*, about November, **1924.**

ϵ-Phenoxybutyl Malonic Acid.—Thirty g. of phenoxybutyl malonic ester was refluxed with 100 cc. of 20% sodium hydroxide for about five hours. The solution was then cooled and acidified with concd. hydrochloric acid. The ϵ-phenoxybutyl malonic acid separated was filtered off and recrystallized from hot water; yield, 22.8 to 23.2 g., or 93–95%; m. p., 152° (with some decomposition).

Anal. Subs., 0.2886: CO_2, 0.6543; H_2O, 0.1680. Calc. for $C_{13}H_{16}O_5$: C, 61.88; H, 6.40. Found: C, 61.85; H, 6.51.

ϵ-Phenoxycaproic Acid.—Twenty-five g. of phenoxybutyl malonic acid was placed in a 250cc. round-bottom flask and heated in an oil-bath held at 225°. The acid melted and carbon dioxide was given off. When the evolution of gas ceased, the remaining material was cooled and recrystallized from petroleum ether; yield, 18–19 g., or 87–91%; m. p., 69°. The melting point is given in the literature[9] as 71°.

ϵ-Bromocaproic Acid.—A mixture of 20 g. of ϵ-phenoxycaproic acid and 100 cc. of 48% hydrobromic acid was refluxed for five hours. The oily upper layer was separated and the hydrobromic acid layer was diluted with several times its volume of water and then extracted with ether. The oily material was added to the ether solution. The ϵ-bromocaproic acid was separated from the ether solution of phenol by extraction with a cold saturated solution of sodium carbonate. The acid was then precipitated with hydrochloric acid, collected in ether and distilled under reduced pressure; yield, 9.7–10.3 g., or 52–55%; b. p., 165–170° (20 mm.). On cooling, the acid crystallized. After crystallization from petroleum ether, it melted at 35°.

Anal. Subs., 0.1883: 9.53 cc. of 0.0922 *N* $AgNO_3$. Calc. for $C_6H_{11}O_2Br$: Br, 40.97. Found: 40.13.

This acid was also prepared from ϵ-benzoylamino-amyl cyanide. A mixture of 55 g. of phosphorus tribromide, 32 g. of bromine and 35 g. of ϵ-benzoylamino-amyl cyanide was refluxed for two hours over a free flame. The mixture was distilled under ordinary pressure until the phosphorus oxybromide boiling at 150–160° was removed, and the residue was distilled under reduced pressure. No constant-boiling fraction was obtained, the boiling point varying from 80° to 130° (6 mm.). This fraction was hydrolyzed by boiling for ten hours with 48% hydrobromic acid. The reaction mixture was steam-distilled and the ϵ-bromocaproic acid was isolated from the residue by extraction with ether. Five g. of acid boiling at 165–170° at 20 mm. was obtained.

Another method for the preparation of ϵ-bromocaproic acid was tried, in which pentamethylene bromide was the starting point. To a solution of 42 g. of pentamethylene bromide in 100 cc. of alcohol was added a solution of 9 g. of sodium cyanide. The mixture was refluxed for five hours, the alcohol removed by distillation and the residue was hydrolyzed by boiling it with 200 cc. of 48% hydrobromic acid for ten hours. On cooling the solution ammonium bromide separated. This was removed by filtration and the filtrate, consisting of an oil and water, was extracted with ether. The ether layer was dried over anhydrous sodium sulfate and then distilled under reduced pressure. Two fractions and a residue were thus obtained; the first fraction boiling at 100–105° (6 mm.) weighed 12 g. and was found to be unchanged pentamethylene bromide; the second fraction boiling at 130–170° (6 mm.) weighed 4 g. and was found to be impure ϵ-bromocaproic acid; the residue was recrystallized from benzene and there was obtained 7 g. of pimelic acid; m. p., 102°.

ϵ-Hydroxycaproic Acid.—A mixture of 10 g. of ϵ-bromocaproic acid, 15 g. of silver oxide and 100 cc. of water was refluxed until the bromine was completely precipitated. The excess of silver was then precipitated by adding 4.5 g. of sodium chloride and heating the solution for a few minutes. The mixture was filtered and the filtrate was cooled and

[9] v. Braun, *Ber.*, **38**, 965 (1905).

acidified with hydrochloric acid. In one run a white waxy solid which melted at 54° was obtained. In most cases, an oil separated and was collected in ether; yield, 2–2.5 g. Analysis indicated that this was a mixture of ε-hydroxycaproic acid and its lactone.

Three g. of this oil was exactly neutralized with sodium hydroxide, using phenolphthalein as an indicator. The solution was evaporated to dryness and the sodium salt of ε-hydroxycaproic acid was washed with alcohol and ether.

Anal. Subs., 0.3130: Na_2SO_4, 0.1462. Calc. for $C_6H_{11}O_3Na$: Na, 14.93. Found: 15.13.

α-Bromo-ε-phenoxybutyl Malonic Acid.—A solution of 28 g. of δ-phenoxybutyl malonic acid in 200 cc. of dry ether was treated with 7.5 cc. (18 g.) of bromine. The bromination proceeded very smoothly. The ether solution was washed with water, then dried and the ether removed by evaporation. The residual yellow solid was purified by dissolving in a small volume of hot benzene, cooling the solution and treating it with four or five volumes of petroleum ether. A white, crystalline product melting at 108–113° with some decomposition was thus obtained; yield, 26 g., or 71%. The neutral equivalent of the acid was found to be 161.1 as compared with a calculated value of 165.5. No further attempt was made at purification but this product was used at once for the next preparation.

α-Bromo-ε-phenoxycaproic Acid.—Twenty-five g. of crude α-bromo-ε-phenoxybutyl malonic acid was heated in an oil-bath at 150° until the evolution of carbon dioxide ceased. On cooling, the product solidified. This residue was first purified by one crystallization from hot 50% acetic acid. This treatment gave plates melting at 112–117°. The partially purified compound was then recrystallized from petroleum ether, yielding a white solid; m. p., 116–117°; yield, 23 g., or 80%.

Anal. Subs., 0.0805: 2.85 cc. of 0.1000 *N* $AgNO_3$. Calc. for $C_{12}H_{15}O_3Br$: Br, 27.53. Found: 27.96.

α,ε-Dibromocaproic Acid.—A mixture of 20 g. of α-bromo-ε-phenoxycaproic acid and 200 cc. of 45% hydrobromic acid was refluxed for about eight hours. The phenol was removed by steam distillation. On cooling the solution, the dibromo acid separated as an oil which slowly crystallized. On recrystallization from an ether-alcohol mixture and then from water, the acid was obtained in colorless needles; m. p., 144–146°.

Anal. Subs., 0.0725: 5.21 cc. of 0.1000 *N* $AgNO_3$. Calc. for $C_6H_{10}O_2Br_2$: Br, 58.32. Found: 58.40.

Summary

Several substituted caproic acids have been prepared for use in physiological experiments.

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