[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

Some α-Alkylthio Aliphatic Acids

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The studies of Adams and his co-workers relating to chaulmoogric and hydnocarpic acids have shown that the position of the carboxyl group and the total number of carbon atoms in an acid have more effect on its physiological activity against *B. leprae* than does the presence of a cyclic structure. In fact, many of the branched chain purely aliphatic acids synthesized by them were more effective *in vitro* against this organism than were chaulmoogric, hydnocarpic and other acids containing cyclic structures. The most active acids synthesized by them contained a total of sixteen to eighteen carbon atoms and had the carboxyl group near the center of the molecule.[2] Acids containing more carbon atoms showed less activity. They did not synthesize acids containing more than nineteen carbon atoms. It is possible that another peak of activity exists above this point.

The sulfide linkage has frequently been found to enhance antiseptic activity.[3]

The work described in this paper was based on a recognition of the facts just presented. A series of aliphatic acids substituted at the alpha position by an alkythio group was prepared to determine their antiseptic properties. Because the high molecular weight thiols were easily prepared,[4] and showed a minimum of the objectionable properties of mercaptans, the condensation of their potassium mercaptides with the sodium salts of the appropriate alpha-bromo acids was employed as shown by the following example

$$C_{16}H_{33}SK + BrCH(C_{10}H_{21})COONa \longrightarrow C_{16}H_{33}SCH(C_{10}H_{21})COONa + KBr$$

The products were all waxy white solids. Those prepared from the lower acids (acetic to caproic) crystallized well from low boiling petroleum ether. The products obtained from the higher acids (capric to palmitic) formed unfilterable gels in all solvents tried. Purification of these compounds was effected through their barium salts. This method was doubly advantageous in that an analysis of the salts for barium provided additional evidence of identity.

It will be noted in Table I that the melting points of the higher acids show no regular sequence. High vacuum sublimation, selective adsorption on Darco G-60 and the use of the ether-soluble lead salts caused little change in the melting points. When absolutely pure these compounds would probably melt in the range 45–60°. Because of their tendency toward gel formation, their waxy nature and their high molecular weights, they might be expected to be especially prone to the adsorption and inclusion of impurities. As the probable impurities possess similar properties, it might be expected that their removal would be very difficult of accomplishment. It was therefore decided that the analyses should be taken as reasonable evidence of identity and purity despite the unsatisfactory nature of the melting points.

Pharmacological testing of the compounds is in progress.

Experimental

1. Preparation of the α-Alkylthio Acids

A solution of 0.03 mole of potassium hydroxide and 0.03 mole of the appropriate mercaptan in 25 cc. of 95% ethanol was heated to boiling under nitrogen. A few crystals of potassium iodide were added. An exactly neutralized solution of 0.03 mole of the desired α-bromo acid in 20 cc. of 50% ethanol was added dropwise to the boiling mercaptide solution. Reaction was evidenced by the formation of a white suspension at the point of contact of the two solutions. Digestion was continued for four hours after all of the acid solution had been added. The material was then transferred to a Claissen flask, the alcohol was removed under reduced pressure and the solid residue was suspended in water. Amyl alcohol prevented serious foaming during removal of the ethanol. The aqueous suspension was heated for fifteen minutes. Excess 12 *N* hydrochloric acid was then added and the heating continued until the product had been completely liberated from its salt. This was evidenced by the formation of a clear layer of oily material on the surface of the solution. The reaction mixture was then poured into a beaker and cooled. The solidified product was filtered, washed thoroughly with water and dried. Yields of the crude dry products were 70–80% of the theoretical.

2. Purification

(a) The lower α-alkylthio acids (R′ = H-, CH_3-, C_2H_5-, C_3H_7-, C_4H_9-) were crystallized from low boiling petroleum ether.

(b) The crude products from the preparation of the higher α-alkylthio acids (R′ = C_8H_{17}-, C_9H_{19}-, $C_{10}H_{21}$-, $C_{12}H_{25}$-, $C_{14}H_{29}$-) were dissolved in boiling methanol (200–300 cc.) and decanted from some insoluble residue (this residue was proven to be the disulfide arising from oxidation of the mercaptan used in the synthesis). A hot concentrated solution of barium hydroxide in methanol was filtered into the solution of the crude acid until it was basic to phenolphthalein. The curdy white barium salt was filtered, air dried and then dissolved in boiling dry benzene (75–100 cc.) to which had been added 1 cc. of methanol to prevent gel formation. The salt was precipitated from this solution by addition of an equal volume of methanol. It was then filtered and dried.

The acids were liberated from their barium salts by digestion with excess 0.24 *N* hydrochloric acid.

(1) This communication contains material from a thesis presented by Edward W. Fager to the Graduate School of Yale University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June, 1942.

(2) R. Adams, *et al.*, THIS JOURNAL, **51**, 1261 (1929); **52**, 2540 (1930).

(3) E. Klarmann, L. W. Gates and V. A. Shternov, *ibid.*, **54**, 1204 (1932); C. M. Suter and H. L. Hansen, *ibid.*, **54**, 4100 (1932).

(4) "Organic Syntheses," **21**, 36 (1941).

TABLE I

MELTING POINTS, NEUTRALIZATION EQUIVALENTS AND ANALYSES OF ACIDS OF THE TYPE: $RSCHCOOH$ (R′)

	M. p., °C.	Neutralization equivalent Calculated	Found	S % Calcd.	Found	Ba % (of salt) Calcd.	Found
R = $C_{12}H_{25}$-							
R′ = C_9H_{19}-	46–48	386.4	387.0[a]	8.28	8.03	15.13	15.14[a]
R = $C_{14}H_{29}$-							
R′ = C_2H_5-	38–39	316.4	318.0[a]	10.10	10.26[a]	...	...
R = $C_{16}H_{33}$-							
R′ = H-	73.5–74	316.4	316.5[a]	10.10	10.20	...	...
CH_3-	58–59	330.4	330.5[a]	9.70	9.82	...	...
C_3H_7-	47.5–49	358.3	357.8[a]	8.94	8.87[a]	...	...
C_4H_9-	48.5–49.5	372.3	372.0[a]	8.60	8.81	...	...
C_8H_{17}-	42–43	428.5	430.0[a]	7.46	7.27	13.86	13.70[a]
C_9H_{19}-	47–49	442.5	443.3[a]	7.24	6.79	13.46	13.49[a]
$C_{10}H_{21}$-	46–48	456.5	457.5[a]	7.00	6.95	13.10	13.28[a]
$C_{12}H_{25}$-	46–48	484.5	483.5[a]	6.62	6.45	12.44	12.60[a]
$C_{14}H_{29}$-	46–48	512.6	511.5[a]	6.26	5.97	11.83	11.63[a]

[a] Average of two analyses.

The writers are indebted to Dr. R. J. Anderson for suggesting the procedure followed in the preparation of the barium salts.

3. Analysis

(a) Sulfur and barium were determined gravimetrically by conventional methods.

(b) Neutralization equivalents were determined by titration of benzene solutions of the acids with .02 *N* alcoholic potassium hydroxide using thymolphthalein as an indicator.

Summary

1. Some new aliphatic acids of the type: $RSCHCOOH$ (R′) with molecular weights above 300 have been synthesized as possible antiseptic agents.

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Thermal Decomposition of Lard

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During the course of an investigation into the effects of ingested heated lard on the gastro-intestinal tract of the rat,[1] we studied some of the chemical changes which occurred in lard as a result of heating. It had been noted that our experimetal rats fared well on a diet containing 50% of unheated lard. Other groups of rats, which were fed diets in which the unheated lard was replaced by lard that had been heated up to and including 300°,[2] likewise consumed adequate quantities of food and grew reasonably well. On the other hand, when 50% of the diet consisted of lard that had been heated at 340–350°, the animals found the diet unpalatable, ate poorly and lost weight rapidly. It seemed probable, therefore, from the biological experiments, that more extensive chemical changes had occurred in the most drastically heated lard than in samples heated at lower temperatures. This assumption was subsequently verified.

Banzon[3] heated coconut oil at its boiling point (*ca.* 300°), in the presence of various catalysts, and reported the formation of much unsaponifiable material. A distillate was collected and a white crystalline powder was isolated from the unsaponifiable fraction. Banzon suggested that the material might be a ketone. Holleman and Koolhaas[4] confirmed the report of Banzon and extended the study of the unsaponifiable fraction obtained from both the distillate and from the residue of coconut oil heated at 300–320° with the aid of a reduced iron powder as catalyst. They reported the isolation of *n*-12-pentacosanone, which resulted from the pyrolysis of lauric and myristic acid glycerides, as well as considerable quantities of other ketonic material. Roffo[5] reported that the heating of lard to 350° for thirty minutes destroyed all of the cholesterol, to the extent that it was no longer precipitated by digitonin. Mauthner and Suida,[6] Veldstra,[7] Waterman and van Vlodrop,[8] and others, pyrolyzed cer-

(1) Morris, Larsen and Lippincott, *J. Natl. Cancer Inst.*, in press.

(2) All temperature values in this paper are on the centigrade scale.

(3) Banzon, *Philippine Agr.*, **25**, 817 (1937); **26**, 399 (1937).

(4) Holleman and Koolhaas, *Rec. trav. chim.*, **58**, 666 (1939).

(5) Roffo, *Bol. inst. med. exptl. estud. cancer*, **15**, 407 (1938).

(6) Mauthner and Suida, *Monatsh.*, **17**, 29 (1896).

(7) Veldstra, *Nature*, **144**, 246 (1939).

(8) Waterman and van Vlodrop, *Rec. trav. chim.*, **57**, 629 (1938).