# *Notes* A department for short papers of immediate interest.

## A Simplified Procedure for Synthesis of Oleic-1-$C^{14}$ Acid[1]

SUSANNE VON SCHUCHING AND ERNEST STUTZMAN

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It became of interest to prepare oleic-1-$C^{14}$ acid in the course of metabolic studies. Bergström *et al.*[2] have published a short report describing the introduction of a $C^{14}$-atom in the carboxyl position by means of the nitrile synthesis. During attempts to follow their procedure, certain steps were found difficult to carry out on a small scale and were modified as described in this note. For example, the silver salt degradation method[3] for the preparation of 1-bromo-8,9-diacetoxyheptadecane was improved through exposure of the reactants to ultraviolet light; in addition, the temperature was kept low during the degradation step and the product was purified over a column of Celite mixed with silicic acid. Furthermore, a purer product was obtained when the addition of cyanide was carried out in a sealed tube. The preparation of ethyl 9,10-dibromostearate-1-$C^{14}$ and the debromination[4] of this compound were modified to give a better recovery of radioactive material. It was found also that when the intermediates are prepared in pure form as described later, the ethyl 9,10-dibromostearate-1-$C^{14}$ does not require micro distillation; its purification over a column of aluminum oxide is sufficient. The synthetic steps up to the nitrile addition were carried out on a semimicro scale. The yield of radioactivity at this point was calculated to be in excess of experimental requirements, and enough inactive dihydroxystearic acid was added to give a total of 5 g.

### EXPERIMENTAL

Merck U.S.P. oleic acid was used as the starting material. Melting points were determined on a Fisher-Johns melting point apparatus and are reported as uncorrected. Double bonds were determined by the Wijs method. Bromine determinations were made by the procedure of Stepanow.[5]

*The 9,10-dihydroxystearic acid* (I) was prepared according to the method of Coleman *et al.*,[6] modified through the use of 2.5 times the recommended amount of potassium hydroxide. The yield of dihydroxystearic acid was 50%.

*Anal.* Calcd. for $C_{18}H_{36}O_4$: C, 68.3; H, 11.4. Found: C, 68.0; H, 11.3.

Neutralization equivalent, calculated 324, and found, 315; m.p. 127.5°.

*9,10-Diacetoxyoctadecanoic acid* (II). Dihydroxystearic acid, 13.5 g., was acetylated with 15 ml. of acetic anhydride in 30 ml. of purified pyridine. The yield of II, obtained as a light colored oil, was 16.1 g. (94%).

*Silver salt of 9,10-diacetoxyoctadecanoic acid* (III). Of II, 16.1 g. were taken up in 150 ml. of ethanol and neutralized to a phenolphthalein end point with sodium hydroxide. With vigorous stirring, 6 g. of silver nitrate in 90 ml. of 60% ethanol were added, light being carefully excluded. The heavy precipitate was collected, washed with water and acetone, and thoroughly dried. The white sticky product was obtained in 80% yield.

*1-Bromo-8,9-diacetoxyheptadecane* (IV). Degradation of 16.4 g. of silver salt (III) was carried out after suspending the material in 300 ml. of dry carbon tetrachloride and 16 ml. of methylene chloride. With magnetic stirring, 150 ml. of the solvent mixture were distilled off. After the residual material was cooled, 3 g. of dry silver acetate was added followed by 3.6 ml. of dry bromine dissolved in 9 ml. of carbon tetrachloride. An ultraviolet light[7] was placed close to the flask and the mixture was heated gradually under reflux. Carbon dioxide started to evolve at 40° and the reaction was brought to completion by raising the temperature and heating at 80° for 1 hr. Silver bromide was removed from the cooled mixture and the filtrate was washed with 2*N* potassium iodide, 2*N* sodium thiosulfate, and finally water and then was dried. This washing procedure averted troublesome emulsions. For further purification, the product was passed over a column of a mixture of 125 g. of silicic acid and 125 g. of Celite. The mixture of Celite and silicic acid had been prepared by being washed with acetone, ether, and carbon tetrachloride. Since the filtration is very slow, two chromatographic tubes, 40 × 600 mm., were employed. Adsorption was carried out in carbon tetrachloride solution and followed by elution with petroleum ether. The petroleum ether was dried down and yielded 8.9 g. (64%) of a light yellow oil. It was hydrolyzed without further purification to V.

*1-Bromo-8,9-dihydroxyheptadecane* (V). In a solution of 300 mg. of dry hydrogen chloride in 45 ml. of dry methanol, 8.9 g. of IV was refluxed for 3 hr. Water was added and V was dissolved in ether. The solution was washed with water, dried over sodium sulfate, and gave, after evaporation, 6.9 g. of V. On recrystallization from hexane, there resulted 3.5 g. (48%) of V; m.p. 101–102°.

*Anal.* Calcd. for $C_{17}H_{35}O_2Br$: C, 58.4; H, 10.0; Br, 22.3. Found: C, 58.7; H, 10.1; Br, 22.3.

*9,10-Dihydroxystearic-1-$C^{14}$ acid* (VI) was prepared under conditions to give a pure product and a high recovery of radioactivity. Potassium cyanide (3 mmoles) containing 4 mc. of carbon$^{14}$ were dissolved in 1 ml. of water and 10 ml. of ethanol in a 100 ml. Kjeldahl flask. A small excess, 1.1 g., of V was added to the flask. The flask was sealed and heated at 100° for 48 hr. The resulting nitrile was transferred to an

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[1] Supported in part by grants from the United States Public Health Service (H-1897) and The American Heart Association to C. R. Treadwell and L. Swell.

[2] S. Bergström, K. Pääbo, and M. Rottenberg, *Acta Chem. Scand.*, **6**, 1127 (1952).

[3] H. Hunsdiecker and C. Hunsdiecker, *Ber.*, **75**, 291 (1942).

[4] D. E. Ames and R. E. Bowman, *J. Chem. Soc.*, 1079 (1951).

[5] A. Stepanow, *Ber.*, **39**, 4056 (1906).

[6] J. E. Coleman, C. Ricciuti, and D. Swern, *J. Am. Chem. Soc.*, **78**, 5342 (1956).

[7] 6 Amp. "Mineralight," Ultra-Violet Products, Inc.

alkali-resistant flask[8] and 2 g. of potassium hydroxide dissolved in 3 ml. of ethanol was added. Hydrolysis of the nitrile was carried out by refluxing for 48 hr. The mixture was acidified with 2*N* hydrochloric acid and washed with water. After being dried, VI was recrystallized from methanol. The yield was 730 mg. (82%), m.p. 127°. In order to increase the recovery of dihydroxystearic acid, the mother liquors were reextracted with 3 g. of unlabeled dihydroxystearic acid. The total recovery of radioactivity was 3.552 mc. (88.8%).

*Ethyl 9,10-dibromostearate-1-$C^{14}$* (VII). Enough inactive dihydroxystearic acid was added to VI to make a total of 5 g. Conversion to the dibromo-compound was carried out according to Ames and Bowman[4] with the use of hydrogen bromide–acetic acid and sulfuric acid. The yield of the crude dibromide ester was 6.5 g. (88.6%). The product was esterified by refluxing in a device diagrammed in Fig. 1 with 4 ml. of absolute alcohol, 10 ml. of benzene, and 0.17 ml. of concentrated sulfuric acid, water being removed azeotropically. The ester VII was run over a short column of activated alumina which retained most of the impurities. A sample had a b.p. of 235° at 1 mm.; bromine content calculated for $C_{20}H_{38}O_2Br_2$: Br, 34%. Found: 34.5%. The ester was a pale yellow oil. The yield was 5.1 g. (85%). It was used for the preparation of oleic-1-$C^{14}$ acid without further purification.

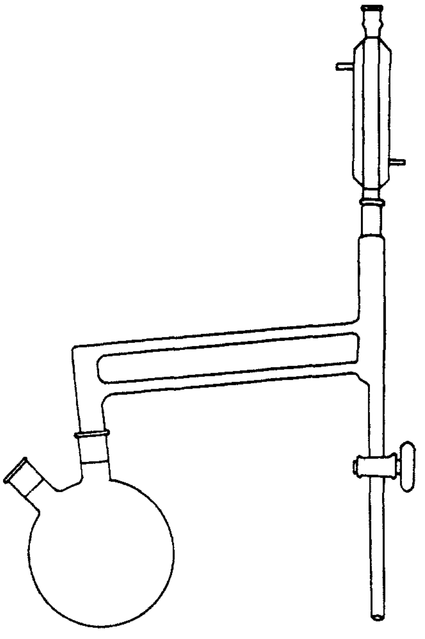

Figure 1

*Oleic-1-$C^{14}$ acid* (VIII). Of zinc, 3 g. were activated by being boiled 5 min. with 15 ml. of ethanol and 1 ml. of 60% aqueous hydrobromic acid. The ethyl ester of VII was added to the zinc and the mixture refluxed under nitrogen for 2 hr. The zinc was removed by filtration and extracted with 1 g. of carrier ethyl oleate in petroleum ether for a more complete recovery of radioactive material. The combined filtrates were washed with 5% sulfuric acid and water and the solution was dried. Product VIII can be saponified directly without distillation. Saponification of the ethyl oleate was carried out with sodium ethoxide in absolute alcohol, followed by acidification with 2*N* hydrochloric acid. The yield of oleic-1-$C^{14}$ acid was 3.7 g., m.p. 12°; iodine number calculated, 89.9. Found: 91.6. Radioactivity was determined by counting an infinitely thick sample after diluting with cold oleic acid in a gas-flow chamber.[9] The total activity was 2.4 mc. (60%) based on $C^{14}$-cyanide. The specific activity of the final product was 0.65 $\mu$c. per mg.

RADIOISOTOPE SERVICE AND
GENERAL MEDICAL RESEARCH
VETERANS ADMINISTRATION CENTER
MARTINSBURG, W. VA.
AND
DEPARTMENT OF BIOCHEMISTRY
THE GEORGE WASHINGTON UNIVERSITY
SCHOOL OF MEDICINE
WASHINGTON 5, D. C.

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[8] Corning "Boron Free."

[9] RCL Nucleometer, Scaler Type, Mark 9, Model 4.

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## Derivatives of Piperazine. XXXI. Salts of Piperazine and *N*-Phenylpiperazine for Utilization in Identification of Perfluoro-Organic Acids

WARNER H. CHRISTIE, JOAN B. CHRISTIE,
JOHN A. WETHINGTON, JR., AND C. B. POLLARD

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In research work involving the syntheses of fluorine organic compounds, the rapid identification of perfluoro-organic acids presented a problem as suitable derivatives have not been reported. Pollard *et al.*[1–5] have found the piperazine and *N*-phenylpiperazine salts of organic acids to be easily prepared and useful for identification. Haszeldine[6] reported the preparation of the piperazinium salt of perfluorobutyric acid.

It has been found that piperazine and *N*-phenylpiperazine react readily with perfluoro acids to form stable crystalline salts which can be readily purified. The monocarboxylic acids form piperazinium salts having a molecular ratio of 2 acid to 1 base. The dicarboxylic acid combines in a 1 to 1 molecular ratio. It is to be noted that the piperazinium salts of the 3, 4, 6, and 8 carbon acids melt within about 2° of each other. Mixed melting points of various combinations of these salts (approximately 50–50) show depressions of about 6°. The *N*-phenylpiperazinium salts of the 3 carbon acid and Kel F 8114 melt within 3° of each other. A mixture of these two salts (approximately 50–50) shows a depression of about 30°. The *N*-phenylpiperazinium salts of the 4, 6, and 8 carbon acids melt close together. Mixtures of various combinations of these salts (approximately 50–50) show depressions of from 15 to 20°. The mixed melting points were determined in sealed tubes.

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[1] C. B. Pollard and D. E. Adelson, *J. Am. Chem. Soc.*, **56**, 150 (1934).

[2] C. B. Pollard, D. E. Adelson, and J. P. Bain, *J. Am. Chem. Soc.*, **56**, 1759 (1934).

[3] C. B. Pollard and D. E. Adelson, *J. Am. Chem. Soc.*, **58**, 532 (1936).

[4] M. Prigot and C. B. Pollard, *J. Am. Chem. Soc.*, **70**, 2758 (1948).

[5] C. B. Pollard and N. S. Gidwani, *J. Org. Chem.*, **22**, 992 (1957).

[6] R. N. Haszeldine, *J. Chem. Soc.*, 2789 (1950).