

The Preparation of 8,11-Heptadecadienoic (Nor-Linoleic) Acid

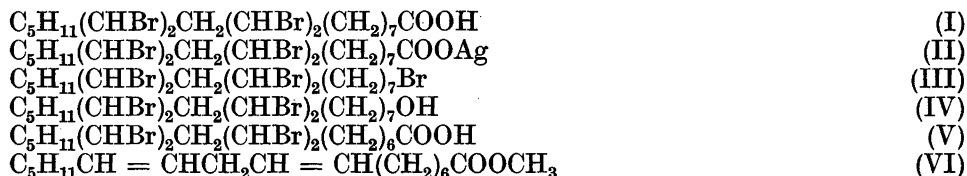
SUNE BERGSTRÖM, KARIN PÄÄBO and MAX ROTTENBERG

Department of Physiological Chemistry, University of Lund, Lund, Sweden

For metabolic studies concerning the specificity of essential fatty acids it was deemed of interest to prepare a close structural analogue of linoleic acid, *viz.*, one containing the same *cis-cis*-1,4-dienoic system but with one carbon atom less in the polymethylene chain carrying the carboxyl group. The sequence of reactions used in this synthesis is shown schematically I—VI.

Pure linoleic acid tetrabromide¹ I was used as starting material. Its silver salt (II) was treated with bromine and the resulting primary-tetrsecondary pentabromide (III) selectively solvolysed to form tetrabromoheptadecanol (IV). This primary alcohol was oxidised to the tetrabromo carboxylic acid (V). This acid after esterification and treatment with zinc gave the final product, methyl nor-linoleate (VI).

The scheme adopted and the procedures employed were not straightforward and require comment. The common alkali metal salts of acid (I) are insoluble in water so that the silver salt (II) could not be prepared by the usual technique².



A satisfactory procedure using the triethanolamine salt is described in the experimental part. A large number of individual silver salt-bromine decarboxylations have been carried out. The early experiments were run in carbon tetrachloride in the standard fashion² with yields ranging from 18 to 59 % of pure neutral pentabromide. Later on the procedure developed by Rottenberg for degrading steroid carboxylic acids³ was applied which gave a substantial increase in yield (up to 90 %). One such run is described.

The partial debromination procedure as described by Silberman⁴ appeared to be a promising means for converting the primary bromide (III) into a primary alcohol *via* the intermediate di-unsaturated bromide. On our substance,

however, this heterogeneous reaction gave very inconsistent results, and only in one experiment could a product be obtained which gave correct analytical values for halogen and unsaturation. Since this result could not be duplicated on subsequent attempts the method was abandoned. We next turned our attention to partial hydrolysis and solvolysis of the pentabromide. The polyhalide was treated with the solvolytic agent for different periods of time, the progress of the reaction was checked by mercurimetric titration of the liberated halide ion, and on appearance of one equivalent the reaction was stopped. The product was analysed for bromine and unsaturation. Stirring or shaking with potassium carbonate in methanol gave unchanged pentabromide. Potassium acetate in either ethanol or acetic acid, or silver acetate in acetic acid gave products showing considerable unsaturation after a one-equivalent stage of solvolysis. Sodium iodide in acetone turned out to be a highly selective agent which smoothly converted the pentabromide into an analytically pure tetrabromo iodide. No appreciable improvement in specificity could be achieved, however, when the solvolysis experiments were run on the iodide. It can be concluded that the solvolytic systems commonly used for transforming bromides into alcohols are too "basic", so that solvolysis is always accompanied by concurrent dehydrobromination. It was obvious therefore to try an alcohol-soluble salt of a very strong carboxylic acid as the solvolytic agent. The sodium or potassium salts of trifluoroacetic acid were indeed found to be the desired reagents. They are soluble in acetone or ethanol and turned out to be strictly selective toward the primary bromide group whereas the dissecondary, vicinal dihalide groupings remained unattacked even after extended reaction periods. A disadvantage is that the replacement reaction is rather slow. Thus it was found by mercurimetric titration that it took 8 days boiling with sodium trifluoroacetate in ethanol to bring about a 90 % conversion. The titration values are shown in Table 1. No attempt was made to isolate the intermediate trifluoroacetic esters. They are little known as yet and stated to be extremely susceptible to alcoholysis⁵. Accordingly the tetrabromo alcohol (IV) was obtained directly on short after-treatment with methanolic HCl. The yields of material giving correct bromine analyses were almost quantitative but the amounts of crystallisable material ultimately obtained were much smaller. This point requires further investigation.

Table 1.

Time, hours	% Br ⁻ liberated
0.6	2.0
1.5	2.5
4.3	4.0
22	15.0
46	28.7
124	58.7
166	82.5
190	92.7

The oxidation of the tetrabromo alcohol (IV) to the acid (V) had to be carried out under non-alkaline conditions. The excellent method developed by the Curtis, Heilbron *et al.*⁸ for oxidising higher molecular primary alcohols in acetone-water- H_2SO_4 was not published at the time this problem was worked on. Among the methods then known the procedure described by Crombie and Harper⁶ (oxidation with acid permanganate), which appeared most promising, gave only 46 % yield. We therefore approached the problem from the analytical side with the method that we have used earlier for the quantitative analytical oxidation of alcohols with chromium trioxide^{9,7}. We then found that with chromium trioxide in 95 % acetic acid at 80° the tetrabromo acid was obtained directly from the alcohol in 97 % yield. The method described therefore compares favourably with that of Curtis and Heilbron⁸. The tetrabromo acid (V) was smoothly converted to methyl nor-linoleate IV by standard procedures, *cf.*⁴ (VI) was obtained as a colourless oil, b.p. 139° at 0.7 mm Hg. The purity of (VI) was checked by comparison with the purest available specimen of authentic methyl linoleate (see Table 2), and by infrared spectroscopy.

Table 2.

	Methyl linoleate	Methyl nor-linoleate
B. p.	148°/0.5	139°/0.7
Unsat.	1.78	1.79
ϵ 231 $m\mu$	34	516
% Conjug. diene *	0.1	1.67

* Calc. on the basis of $\epsilon = 3.1 \times 10^4$ (J.F. Mead, *Science* **115** (1952) 471).

Dr. D. H. Wheeler, of General Mills, Inc., Minneapolis, Minn., U.S.A., has kindly co-operated with us by running infrared analysis on this material. He comments on the results of these two samples as follows: "Both seem to have about the same amount of *trans* double bond as is found in debromination linoleate. The band at 3.30 μ is very close in intensity to that of ordinary or debromination linoleate and falls in line with the expected intensity of the series oleate, linoleate, linolenate."

EXPERIMENTAL

All m.p.'s are corrected. Microanalysis by the Microanalytical Laboratory, Department of Medical Chemistry, Uppsala.

Silver salt. 24 g (= 40 millimoles) of linoleic acid tetrabromide (I) m.p. 114–115°, was dissolved in 100 ml of acetone, 40 ml of 1.0 *N* triethanolamine in water added followed by 3 liters of boiling water whereupon part of the acetone escaped. At *ca.* 90° there was then added, in small portions, 40 ml of 1.0 *N* AgNO_3 with swirling. The mixture was filtered hot and the white precipitate washed with 10 liters of boiling water. After drying, finally over P_2O_5 , the yield was 25.2 g (89 %). Found: AgBr 24.5, 26.0 %. $\text{C}_{18}\text{H}_{31}\text{O}_2\text{Br}_4\text{Ag}$: AgBr 26.6 %.

1.8.9.11.12-pentabromo heptadecane (III) (silver salt bromine decarboxylation). 53 g of silver tetrabromostearate (75 millimoles) was combined with 12 g of silver acetate (72 millimoles); the mixture was finely ground and rigorously dried. After addition of 250 ml of pure, dry ethyl bromide it was treated with 7.8 ml (147 millimoles) of dry bromide at the b.p. of the solvent (38°), the operation taking ten minutes. The mixture was boiled for a further 90 min., then filtered and washed as described earlier⁹. The solution containing the total neutral plus acidic material was taken to dryness, the residue was taken up in petrol ether and filtered through a column of Al_2O_3 (200 g). Extraction of the column with petrol ether gave, after drying, 42.7 g (90 % yield) of white, crystalline neutral product that contained 62.9 % Br (calc. 62.93 %). A specimen was recrystallised from acetone-ethanol, m.p. 66–67°. Found: C 32.02, 32.01; H 5.01, 4.83; Br 63.50, 62.22. Calc. for $C_{17}H_{31}Br_5$ (635.00): C 32.15; H 4.92; Br 62.93.

Tetrabromo heptadecyl iodide. 3.85 g of pentabromoheptadecane (6.06 millimoles) in 10 ml of acetone was mixed with a solution of 1.1 g of sodium iodide in 10 ml of acetone. After 24 hours a crystalline precipitate had formed which after washing with acetone weighed 530 mg and on titration was equivalent to 52.1 ml of 0.1 N $Hg(NO_3)_2$. The orange-coloured filtrate was taken to dryness *in vacuo*, the residue in ether was washed with SO_2 -water, $KHCO_3$, and water, dried over sodium sulphate, filtered, and the solvent removed. After drying, the residue weighed 4.05 g (= 98 % yield). A specimen after recrystallisation from petroleum ether had m.p. 57–60°. Found: C 29.58; H 4.49; Br 47.05, 47.08. Calc. for $C_{17}H_{31}Br_4I$ (682.00): C 29.94; H 4.58; Br 46.87 %.

Tetrabromoheptadecanol IV from pentabromide III.

Early experiment. 556 mg of pentabromide in 15 ml of acetone was added to a solution of sodium, potassium trifluoroacetates⁸ in 5 ml of acetone and left in a glass-stoppered flask in the dark. After 22 months at room temperature a crust of colourless, cubic crystals had deposited which were soluble in water and gave a copious precipitate with acidified $AgNO_3$ solution. The acetone solution was concentrated, the residue which was sparingly soluble in petroleum ether was taken up in methylene chloride, washed several times with water, dried over Na_2SO_4 , and filtered, yielding 0.55 g of waxy crystals. Crude product, found: Br 55.0; 54.7. Calc. for $C_{16}H_{29}Br_4CH_2OCOCF_3$: Br 46.7; for $C_{16}H_{29}Br_4CH_2OH$: Br 55.9 %.

Treatment with $CH_3OH-HCl$ did not change the bromine content.

Preparative procedure. 1.725 g of pentabromide and 0.92 g of sodium potassium trifluoroacetate were dissolved in 99 per cent ethanol and made up to a total volume of 375 ml. The mixture was refluxed on a boiling water-bath. 5 ml aliquots were withdrawn at intervals listed in Table 1, and titrated for bromide ion using mercuric nitrate and diphenylcarbazide¹⁰. After 190 hours the titration value corresponded to 93 % conversion of primary halide. The alcohol solution was concentrated *in vacuo*, taken into ether, thoroughly washed with $KHCO_3$ and water, dried over Na_2SO_4 and the solvent distilled off. Drying *in vacuo* over KOH and paraffin gave 0.97 g of colourless crystalline wax, m.p. 76–78° after two recrystallisations from ethanol-petroleum ether. Found: C 35.9, 36.2; H 5.78, 5.59; Br 55.92. Calc. for $C_{17}H_{32}OBr_4$ (572.09): C 35.69; H 5.64; Br 55.87.

The following procedure has now been adopted: 6.2 g of pentabromide and 5.1 g of pure sodium trifluoroacetate were boiled under reflux with 10 ml of bromobenzene and 40 ml of 99 per cent ethanol during 12 days. 1 ml of methanol-HCl (ca. 8 N) was added and the mixture boiled for a further 4 hours. Working up gave 5.8 g of greasy colourless crystals. Recrystallisation from ether-ligroin furnished 2.2 g of needles, m.p. 83–85°. The highest observed melting point was 88°.

Tetrabromoheptadecanoic acid.

A. *Micro-quantitative oxidations*. Analytical oxidations were run exactly as described earlier⁷. The best and most clearcut results were obtained when the temperature was about 80° and the acetic acid concentration 95 % (Fig. 1). At lower temperatures and higher acid concentrations the oxidations usually stopped at an earlier stage.

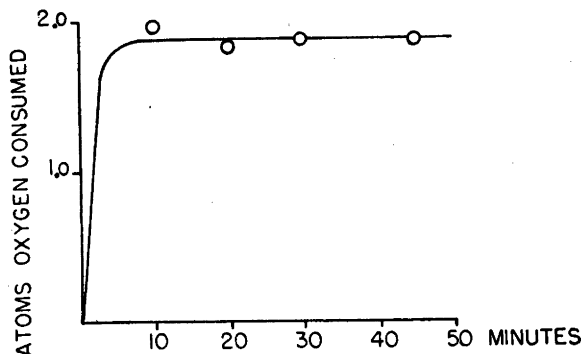


Fig. 1. Each point represents a sample of 1.543 mg tetrabromoheptadecanol dissolved in 1 ml of glacial acetic acid to which 0.794 mg of chromium trioxide in 0.1 ml of 95 per cent acetic acid had been added. Temperature 80°.

B. *Preparative run.* 3.2 g (5.6 millimoles) of tetrabromoheptadecanol in 342 ml of glacial acetic acid + 18 ml of water was placed in a water-bath maintained at 80–90°. At an inside temperature of 80–83° a solution of 2 g of chromium trioxide in 5 ml of water and 95 ml of acetic acid were added during five minutes and the mixture kept at 80–83°. After one hour 10 ml of methanol was added, followed by 500 ml of water and taken to dryness *in vacuo* in a water-bath at about 55°. The green residue was taken up in chloroform, the chloroform solution washed with HCl, water, NaH_2PO_4 , and water, dried over Na_2SO_4 , and filtered. Evaporation gave 3.34 g of slightly greenish crystalline wax, m.p. 101–102°, neut. eq. calc. 586; found 615, 606. One recrystallisation from ligroin gave 2.98 g of material, m.p. 99°, neut. eq. 601, 596, 599. The analytical specimen was obtained after two recrystallisations m.p. 105–106° (long needles). Found: C 35.09; H 5.09; Br 54.58, 54.74; neut. eq. 585. Calc. for $\text{C}_{17}\text{H}_{30}\text{Br}_4\text{O}_2$: C 34.84; H 5.16; Br 54.54; neut. eq. 586.08.

Methyl nor-linoleate VI. 1.5 g of tetrabromoheptanoic acid, m.p. 100–102° in 20 ml of methylene chloride was treated with ethereal diazomethane. Evaporation gave waxy crystals, m.p. 44–46° after one recrystallisation from acetone. 4 g of powdered zinc and 10 ml of 99 per cent ethanol were boiled in an atmosphere of CO_2 . 0.15 ml of 48 % HBr were added and the mixture refluxed for 4 minutes. 1.4 g of tetrabromo ester in 5 ml of benzene and 20 ml of ethanol was added to the boiling mixture which was refluxed for one hour more. The mixture was filtered through “super-cel” and the filter extracted with petroleum ether. The combined filtrates were washed with HCl, KHCO_3 , and water, dried over Na_2SO_4 , and filtered. The solution was concentrated under CO_2 and distilled. Main fraction, 282 mg, b.p. 139° at 0.7 mm Hg. Unsat. calc. 2.00; found 1.79. (Best available linoleate 1.78).

The infra-red curve shows a band at 3.30 μ very close in intensity to that of linoleate. In the UV a weak absorption maximum ($\epsilon = 516$) is observed at 231 $\text{m}\mu$, corresponding to about 1.3 % of conjugated diene.

SUMMARY

Linoleic acid tetrabromide has been converted into methyl nor-linoleate by the following sequence of reactions: (a) silver salt-bromine decarboxylation, (b) selective solvolysis with trifluoroacetate of the primary bromine atom to tetrabromoheptadecanol, (c) chromic acid oxidation of this alcohol to the carboxylic acid in practically quantitative yield followed by debromination of the methyl ester.

We are most grateful to Dr. Wheeler, General Mills Inc., Minneapolis, and to Dr. W. Lundberg, Hormel Institute, Austin, Minn., U.S.A., for the help with the IR analysis. We are also indebted to Professor Maurice Stacey, F.R.S., Birmingham, for a gift of trifluoroacetate.

This work is part of an investigation supported by "Statens Medicinska Forskningsråd", "Knut och Alice Wallenbergs Stiftelse" and "Magn. Bergvalls Stiftelse".

REFERENCES

1. Mc Cutchon, J. W. *Org. Syntheses* **22** (1942) 75.
2. Allen, C. F. H., and Wilson, C. V. *Org. Syntheses* **26** (1946) 52.
3. Rottenberg, M. *Helv. Chim. Acta* **35** (1952) 1286.
4. Silberman, H., and Silberman-Martyncewa, S. *J. Org. Chem.* **13** (1948) 707.
5. Bourne, E. J., Tatlow, C. E. M., and Tatlow, J. C. *J. Chem. Soc.* **1950** 1367.
6. Crombie, L., and Harper, S. H. *J. Chem. Soc.* **1950** 2685.
7. Bergström, S., and Lindstedt, S. *Acta Chem. Scand.* **5** (1951) 157.
8. Curtis, R. G., Heilbron, I., Jones, E. R. H., and Woods, G. F. *J. Chem. Soc.* **1953** 457.
9. Bergström, S., Theorell, H., and Davide, H. *Arkiv Kemi* **23 A** (1946) No. 13.
10. Pääbo, K., and Rottenberg, M. *Acta Chem. Scand.* **3** (1949) 1444.

Received April 24, 1953.