tract was washed with water and evaporated to dryness. The residue was recrystallized from petroleum ether and identified as phenylboronic acid (m.p. 215°).

TNB was treated in the same way but the mixture was allowed to stand at room temperature for four days. The insoluble residue present was filtered and identified as a mixture of naphthalene and unreacted TNB. The filtrate was neutralized and extracted with ether. A small amount of α-naphthylboronic acid was obtained from the ether extract (m.p. 195°). TMB failed to react with 0.05 *N* sodium hydroxide after a period of 4 days at room temperature.

**Reaction with Sodium Metal.**—The procedures used were similar to those previously utilized for TPB[6] and TNB.[7] Since a detailed study recently has been described for the reaction of sodium with TMB,[3] we shall give only a brief summary of our observations.

A weighed sample of TMB was added to freshly prepared sodium amalgam in a dry glass bulb, and the bulb was swept out with dry nitrogen gas. Anhydrous ether was added and the bulb was sealed and set aside at room temperature. The bulb was shaken several times during the reaction period. The solution became pink, then purple and finally a yellow solid crystallized from the solution. At the end of the reaction period, the seal was broken and the ether solution was transferred to a flask containing distilled water. The bulb was rinsed several times with ether to remove all of the yellow solid adhering to the walls of the bulb. The rinses were added to the water and the ether was removed from the mixture by warming on a hot-plate. As the ether evaporated from the mixture, a white solid precipitated in the flask. The aqueous residue, containing the white precipitate, was titrated with standard hydrochloric acid to a phenolphthalein end-point. The insoluble residue was identified as TMB. The base was assumed to be sodium hydroxide. For samples that had been allowed to stand for 24 hr. the mole ratio of sodium to TMB varied from 1.09:1 to 1.53:1. A mixture of TMB and sodium amalgam which had been set aside for two months gave a 1.9 (Na) to 1 (TMB) mole ratio. No significant difference was noted between the ease of reaction of sodium with TMB as compared to TPB[6] or TNB.[7]

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# (±)-18-Fluoro-10-methyloctadecanoic Acid (Fluorotuberculostearic Acid)[1]

BY F. L. M. PATTISON AND R. G. WOOLFORD

RECEIVED NOVEMBER 5, 1956

Racemic fluorotuberculostearic acid (Vb) was prepared readily from 8-fluoroöctanoic acid by anodic coupling reactions. The sodium salt showed antitubercular activity *in vitro* but not *in vivo*.

From the knowledge gained from the study of fluoroacetates[2] and of other series of toxic compounds,[3] it has become increasingly apparent that certain biological systems are unable to differentiate between organic compounds containing the methyl group ($CH_3^-$) and the fluoromethyl group ($FCH_2^-$), respectively. Compounds containing the latter group, once assimilated, may then disturb or block the enzyme systems normally responsible for the metabolism of the non-fluorinated materials.

Occurring in the lipid sheath of the tubercle bacillus are a variety of fatty acids, including the levorotatory isomer of 10-methyloctadecanoic acid (tuberculostearic acid).[4] By applying the above observations regarding the fluoromethyl group to this acid, it was argued that 18-fluoro-10-methyloctadecanoic acid (fluorotuberculostearic acid) might readily be assimilated by the tubercle bacillus and that the toxic action of the fluorine atom might then result in its death. It was for this reason then that fluorotuberculostearic acid was prepared. If the racemic acid had shown high antitubercular activity, its resolution would have been undertaken; since its activity *in vivo* was low, this proved to be unnecessary. All compounds described in this article are therefore in the racemic form.

Fluorotuberculostearic acid was prepared by two routes, as is shown below. The work of Linstead, Lunt and Weedon[5] was of great value in selecting the experimental conditions. Some observations regarding symmetrical and unsymmetrical anodic coupling reactions of ω-fluorocarboxylic acids have been presented earlier.[6]

8-Fluoroöctanoic acid[6,7] (I) and methyl hydrogen β-methylglutarate[5] (II) (100% excess) on electrolysis formed a mixture of methyl 11-fluoro-3-methylundecanoate (IIIa), 1,14-difluorotetradecane and dimethyl β,β′-dimethylsuberate. The crude mixture, after hydrolysis with 10% sodium hydroxide, was separated into neutral and acidic fractions; the former gave 1,14-difluorotetradecane (20%), while the latter gave 11-fluoro-3-methylundecanoic acid (IIIb) (45%) and β,β′-dimethylsuberic acid (37%).

The anodic coupling of IIIb and methyl hydrogen azelate followed by hydrolysis of the resultant mixture gave the two symmetrical products, 1,20-difluoro-9,12-dimethyleicosane (23%) and hexadecanedioic acid (36%); a crude fraction of fluorotuberculostearic acid (Vb) also was obtained; this was found to be contaminated with azelaic acid, which had codistilled during attempted purification. Attempts to remove this impurity by preferential solubility in hot water and by treatment with alcoholic lead acetate[5] were unsuccess-

(1) Issued as DRB Report No. SW-35.

(2) See, for example, M. B. Chenoweth, *J. Pharmacol. Exptl. Therap.*, **97**, 383 (1949); R. A. Peters, *Endeavour*, **13**, 147 (1954).

(3) F. L. M. Pattison, *Nature*, **172**, 1139 (1953); **174**, 737 (1954); F. L. M. Pattison, W. C. Howell, A. J. McNamara, J. C. Schneider and J. F. Walker, *J. Org. Chem.*, **21**, 739 (1956), and subsequent papers in the series.

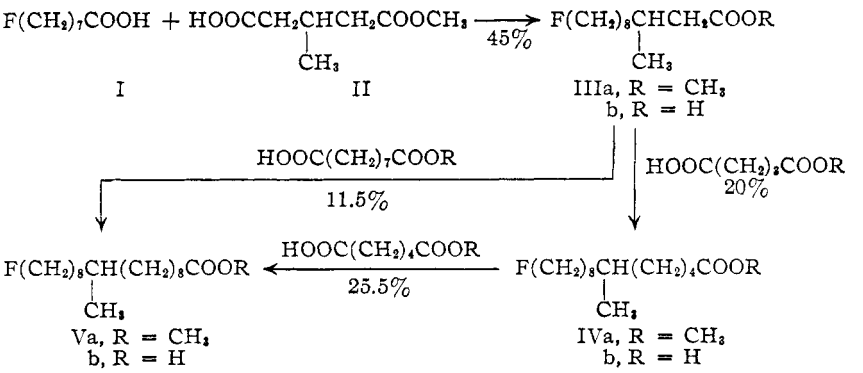
(4) R. J. Anderson and E. Chargaff, *J. Biol. Chem.*, **85**, 77 (1929); M. A. Spielman, *ibid.*, **106**, 87 (1934); F. S. Prout, J. Cason and A. W. Ingersoll, THIS JOURNAL, **70**, 298 (1948); S. Ställberg-Stenhagen, *Arkiv Kemi, Mineral. Geol.*, **26A**, No. 12, (1948); G. A. Schmidt and D. A. Shirley, THIS JOURNAL, **71**, 3804 (1949).

(5) R. P. Linstead, J. C. Lunt and B. C. L. Weedon, *J. Chem. Soc.*, 3331 (1950).

(6) F. L. M. Pattison, J. B. Stothers and R. G. Woolford, THIS JOURNAL, **78**, 2255 (1956).

(7) F. L. M. Pattison, S. B. D. Hunt and J. B. Stothers, *J. Org. Chem.*, **21**, 883 (1956).

ful. The crude acid was therefore re-esterified and fractionated to give methyl fluorotuberculostearate (Va) (11.5%). A portion of the pure ester was hydrolyzed with 10% sodium hydroxide and fractionated to give the pure fluorotuberculostearic acid (Vb). The acid was converted to the sodium salt for biological testing (see below).




Because of the above purification difficulties, methyl fluorotuberculostearate was prepared from 11-fluoro-3-methylundecanoic acid (IIIb) by a route involving two coupling reactions. The first of these, using methyl hydrogen glutarate, yielded on distillation methyl 14-fluoro-6-methyltetradecanoate (IVa) (20%), dimethyl suberate (57%) and 1,20-difluoro-9,12-dimethyleicosane (21%). The ester IVa was hydrolyzed to the acid IVb (93%), which in turn was coupled with methyl hydrogen adipate to give methyl fluorotuberculostearate (Va) (25.5%); dimethyl sebacate also was isolated (30%). This longer method, while proceeding in lower over-all yield, avoided some of the separation and purification difficulties encountered in the shorter method.

Sodium fluorotuberculostearate was screened[8] against virulent *Mycobacterium tuberculosis* var. *hominis* (strain H37Rv) both *in vitro* and *in vivo*. In the former, it caused complete inhibition of growth at a concentration of 1.25 γ/ml. in the absence of bovine serum but was inactive at a concentration of 20 γ/ml. in a medium containing 10% bovine serum. Because of the high toxicity, the diet concentration for the *in vivo* test was reduced from 0.125% to 0.0125%; at this lower concentration, the compound did not prolong the lives of tuberculous mice and is therefore inactive in what must be considered the crucial test.

Sodium fluorotuberculostearate was found to have an L.D. 50 of 2.7 mg./kg. (intraperitoneal injection into mice). The tolerated diet level of 0.0125% used on the tuberculous mice probably corresponds to just under 25 mg./kg./day. Of the other intermediates and by-products, 11-fluoro-3-methylundecanoic acid (L.D. 50, 2.42 mg./kg.) and 1,20-difluoro-9,12-dimethyleicosane (L.D. 50, 57 mg./kg.) were subjected to the usual toxicological screening by intraperitoneal injection into mice. Some of these results will be discussed in a future communication.

## Experimental[9]

**Procedure.**—The equipment, method and conditions were the same as previously described.[6]

**Intermediates.**—8-Fluoroöctanoic acid[6,7] was prepared by the oxidation of 8-fluoroöctanol.[10] Methyl hydrogen β-methylglutarate was prepared as described by Linstead, Lunt and Weedon.[5] Methyl hydrogen adipate (62%) and azelate (67%) were prepared by the modified procedure[10] of Swann, Oehler and Buswell.[11] Methyl hydrogen glutarate was prepared from glutaric acid by conversion to the anhydride, followed by treatment with methanol.

**11-Fluoro-3-methylundecanoic Acid (IIIb).**—A mixture of 8-fluoroöctanoic acid (20.0 g., 0.123 mole), methyl hydrogen β-methylglutarate (40.0 g., 0.25 mole), sodium (0.46 g., 0.02 g. atom) and methanol (70 ml.) was electrolyzed at 1.9 amp. for 6 hr. by the procedure described for unsymmetrical couplings.[6] The crude neutral product, having been isolated in the usual way,[6] was hydrolyzed by heating under reflux with 10% aqueous sodium hydroxide (300 ml.) for 3 hr. The product was separated into neutral and acidic fractions, and the ethereal extracts of each were dried over sodium sulfate. The neutral fraction yielded 1,14-difluorotetradecane (2.9 g., 20%), b.p. 146–147° (10 mm.), $n_D^{25}$ 1.4224. We have previously reported[6] b.p. 148° (11 mm.) and $n_D^{25}$ 1.4218. Fractionation of the acidic fraction through a modified Podbielniak column yielded 11-fluoro-3-methylundecanoic acid (12.0 g., 45%), b.p. 152–153° (2.7 mm.), $n_D^{25}$ 1.4393. *Anal.* Calcd. for $C_{12}H_{23}O_2F$: C, 66.02; H, 10.61. Found: C, 66.27; H, 10.81. Further distillation of the acidic residue through a short Vigreux column yielded β,β′-dimethylsuberic acid (9.3 g., 37%), b.p. 184–186° (1.0 mm.), m.p. 87–90°. Linstead, Lunt and Weedon[12] report m.p. 90–92° for a mixture of stereoisomeric β,β′-dimethylsuberic acids.

**14-Fluoro-6-methyltetradecanoic Acid (IVb).**—A mixture of 11-fluoro-3-methylundecanoic acid (IIIb) (15.0 g., 0.069 mole), methyl hydrogen glutarate (20.1 g., 0.138 mole), sodium (0.23 g., 0.01 g. atom) and methanol (70 ml.) was electrolyzed at 1.7 amp. for 4.5 hr. The cell contents were diluted with water, neutralized with acetic acid and thoroughly extracted with ether. The extracts were washed with sodium carbonate and with water and were dried over sodium sulfate. After removal of the ether, the residue yielded three products on careful fractionation: (1) dimethyl suberate (7.9 g., 57%) b.p. 142–144° (15 mm.), $n_D^{25}$ 1.4320; Vogel[13] reports b.p. 148° (20 mm.), $n_D^{20}$ 1.43370. (2) Methyl 14-fluoro-6-methyltetradecanoate (IVa) (3.8 g., 20%), b.p. 120–121° (0.10 mm.), $n_D^{25}$ 1.4387. *Anal.* Calcd. for $C_{16}H_{31}O_2F$: C, 70.04; H, 11.39. Found: C, 70.36; H, 11.26. (3) 1,20-Difluoro-9,12-dimethyleicosane (2.45 g., 21%), b.p. 156–157° (0.25 mm.), $n_D^{25}$ 1.4438. *Anal.* Calcd. for $C_{22}H_{44}F_2$: C, 76.23; H, 12.79. Found: C, 76.42; H, 12.55.

The ester IVa (3.0 g., 0.011 mole) was hydrolyzed with 10% sodium hydroxide (50 ml.) by heating under reflux until homogeneous (*ca.* 45 minutes). The solution was cooled, diluted with water, acidified with dilute hydrochloric acid and extracted with ether. The extracts were washed with water and dried over sodium sulfate. After removal of the ether, the residue on fractionation through a short Vigreux column yielded 14-fluoro-6-methyltetradecanoic acid (2.5 g., 93%), b.p. 146° (0.10 mm.), $n_D^{25}$ 1.4454.

*Anal.* Calcd. for $C_{15}H_{29}O_2F$: C, 69.20; H, 11.23. Found: C, 69.47; H, 11.25.

**Methyl 18-Fluoro-10-methyloctadecanoate (Methyl Fluorotuberculostearate) (Va). (a) From 11-Fluoro-3-methyl-**

(8) Carried out by Mr. Leonard Doub and Dr. M. W. Fisher, Parke, Davis and Co., Detroit, Mich.

(9) (a) The microanalyses were performed by Mr. J. F. Alicino, Metuchen, N. J., and by the Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.; (b) the melting points and boiling points are uncorrected.

(10) F. L. M. Pattison, W. C. Howell, A. J. McNamara, J. C. Schneider and J. F. Walker, *J. Org. Chem.*, **21**, 739 (1956).

(11) S. Swann, R. Oehler and R. J. Buswell, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 276.

(12) R. P. Linstead, J. C. Lunt and B. C. L. Weedon, *J. Chem. Soc.*, 3333 (1950).

(13) A. I. Vogel, THIS JOURNAL, 1758 (1934).

**undecanoic Acid.**—11-Fluoro-3-methylundecanoic acid (15.0 g., 0.069 mole), methyl hydrogen azelate (28.0 g., 0.139 mole), sodium (0.23 g., 0.01 g. atom) and methanol (70 ml.) were electrolyzed by the usual procedure at 1.7 amp. for 4.5 hr. The crude reaction product, after isolation in the usual way, was heated under reflux with 10% sodium hydroxide (200 ml.) for 3 hr. The mixture was separated into neutral and acidic fractions, and the extracts were dried over sodium sulfate. The neutral extract on distillation yielded 1,20-difluoro-9,12-dimethyleicosane (2.8 g., 23%), b.p. 149–150° (0.15 mm.), $n_D^{25}$ 1.4438. The acidic extract on distillation gave a fraction (3.6 g.) of b.p. 148–154° (0.025 mm.), presumed to be impure Vb, and hexadecanedioic acid (7.2 g., 36%), b.p. 184–188° (0.07 mm.), colorless crystals from methanol, m.p. 123–124°; Chuit[14] reports m.p. 124–124.2°. The sample of impure Vb was heated under reflux for 16 hr. with methanol (20 ml.), ethylene chloride (25 ml.) and concentrated sulfuric acid (0.2 ml.).[15] After dilution with water, the ethylene chloride layer was separated and distilled through a short Vigreux column to yield methyl fluorotuberculostearate (2.5 g., 11.5%), b.p. 149–150° (0.10 mm.), $n_D^{25}$ 1.4433.

*Anal.* Calcd. for $C_{20}H_{39}O_2F$: C, 72.68; H, 11.90. Found: C, 72.88; H, 11.90.

(b) **From 14-Fluoro-6-methyltetradecanoic Acid.**—A mixture of 14-fluoro-6-methyltetradecanoic acid (2.0 g., 0.0077 mole), methyl hydrogen adipate (2.5 g., 0.0156 mole), sodium (0.035 g., 0.0015 g. atom) and methanol (75 ml.) was electrolyzed at 1.5 amp. for 50 minutes. Isolation and distillation of the products in the usual way gave two fractions: (1) dimethyl sebacate (1.08 g., 30%), b.p. 76–78° (0.02 mm.), $n_D^{25}$ 1.4368; Stahl and Pessen[16] report $n_D^{25}$ 1.4368. (2) Methyl fluorotuberculostearate (0.62 g., 25.5%), b.p. 126–127° (0.02 mm.), $n_D^{25}$ 1.4433. The distillation residue was too small to allow of the isolation of pure 1,26-difluoro-9,18-dimethylhexacosane.

**18-Fluoro-10-methyloctadecanoic Acid (Fluorotuberculostearic Acid) (Vb).**—A portion of Va was hydrolyzed with 10% sodium hydroxide in the usual manner to yield the free acid, a colorless liquid of b.p. 159–160° (0.05 mm.), $n_D^{25}$ 1.4500. The acid solidified just below room temperature.

*Anal.* Calcd. for $C_{19}H_{37}O_2F$: C, 72.10; H, 11.79; F, 6.00; neut. equiv., 316.5. Found: C, 72.14; H, 11.68; F, 5.7; neut. equiv., 318.2.

The sodium salt was prepared as follows: the acid (1.3 g.), dissolved in ethanol (20 ml.), was titrated with 0.25 *N* sodium hydroxide to a faint pink end-point, using phenolphthalein as an external indicator. A few drops of Vb in ethanol were then added to return the solution to the acid side of the indicator. The solution was evaporated on a steam-bath, forming a colorless solid. After drying in a vacuum desiccator, the sodium salt was found to be non-hygroscopic and sufficiently soluble in water for biological testing.

**Acknowledgments.**—The work described herein was carried out under Contract (DRB X-24) with the Defence Research Board of Canada, to whom grateful acknowledgment is made for financial assistance and for permission to publish this work. The authors wish also to express their indebtedness to the National Research Council of Canada for the award of a bursary to R.G.W.; to Mr. J. B. Stothers for valuable help in the preliminary phases of the investigation; to Dr. I. G. Walker, Defence Research Medical Laboratories, Toronto, for carrying out the toxicity determinations; and to Parke, Davis and Co., Detroit, Mich., for screening sodium fluorotuberculostearate against *M. tuberculosis*.

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(14) P. Chuit, *Helv. Chim. Acta*, **9**, 264 (1926).

(15) R. O. Clinton and S. C. Laskowski, THIS JOURNAL, **70**, 3135 (1948).

(16) W. H. Stahl and H. Pessen, *ibid.*, **74**, 5487 (1952).

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# Toxic Fluorine Compounds. XVI.[1] Branched ω-Fluorocarboxylic Acids

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RECEIVED DECEMBER 3, 1956

Six branched ω-fluorocarboxylic acids, $F(CH_2)_nCHMe(CH_2)_mCOOH$, were prepared by anodic coupling reactions. The toxicological results may be explained on the basis of two modes of breakdown: (1) when *m* is odd, the compounds form intermediate oxidation products which in turn break down to give ω-fluorocarboxylic acids containing a total of *n* carbon atoms; (2) when *m* is even, β-oxidation occurs in the usual way, resulting in toxicity figures comparable to those of the unbranched ω-fluorocarboxylic acids, $F(CH_2)_{n+m+1}COOH$. Thus, compounds in which *n* is the same have approximately the same toxicity, irrespective of *m* and hence of the total length of the chain.

The unique pharmacological properties of the ω-fluorine atom in aliphatic compounds have been outlined in earlier reports in this series. By an examination of the toxicity of members of any series $F(CH_2)_nX$, it has been possible to deduce the probable metabolic fate of the group X. As an extension of this work, we have now prepared some branched ω-fluorocarboxylic acids (Table II), in order to obtain information regarding the metabolism of the corresponding unfluorinated branched-chain acids.

The value of unsymmetrical anodic coupling reactions in the synthesis of fluorine compounds has already been indicated.[2,3] The procedure used in the present work to obtain the compounds listed in Table I was essentially the same as that described earlier. In general, ω-fluorocarboxylic acids were electrolyzed in the presence of an excess of the appropriately substituted glutaric acid half-ester

$$F(CH_2)_{n-1}COOH + HOOCCH_2CHMeCH_2COOCH_3 \longrightarrow F(CH_2)_nCHMeCH_2COOCH_3 \longrightarrow F(CH_2)_nCHMeCH_2COOH$$

Simple homologation of II by means of the Arndt–Eistert synthesis yielded 11-fluoro-4-methylundecanoic acid (V). The preparation of 18-fluoro-10-methyloctadecanoic acid (VI) has been described in an earlier report.[3]

The results presented in Table II indicate that compounds in which *n* is odd are non-toxic whereas those in which *n* is even are toxic, irrespective of *m* and hence of the total length of the carbon chain. It is convenient to discuss this observation and the

(1) Part XV, THIS JOURNAL, **79**, 1959 (1957). Issued as DRB Report No. SW-36.

(2) F. L. M. Pattison, J. B. Stothers and R. G. Woolford, *ibid.*, **78**, 2255 (1956).

(3) F. L. M. Pattison and R. G. Woolford, *ibid.*, **79**, 2306 (1957).