formation,[3] could not be brought about through the conventional halogenation of the acyl group with subsequent condensation with an amino compound.

The melting point of the ethyl DL-dipalmitoxypantothenate thus prepared was 61.5–63.0° in comparison with 57.0–58.5° for the same compound prepared by the *in situ* palmitoylation of ethyl DL-pantothenate.[2] Upon single dose assay with rats,[4] the newly synthesized ethyl DL-dipalmitoxypantothenate was found to be fully active as a source of pantothenic acid.

EXPERIMENTAL

Ethyl DL-*N*-[*α,γ-dipalmitoxy-β,β'-dimethylbutyryl*] *β-aminopropionate* (*ethyl* DL-*dipalmitoxypantothenate*). Six hundred twenty-five milligrams (1 mmole) of DL-dipalmitoxypantoic acid[2] was dissolved in 40 ml. of dry pyridine which contained 200 mg. (excess) of ethyl β-alanate and 208 mg. (1 mmole) of dicyclohexyl carbodiimide. The clear mixture was set aside at room temperature for 96 hr. The precipitate was removed by filtration, and the filtrate was evaporated to dryness under reduced pressure. The residue was taken up into ether, and washed with 1*N* hydrochloric acid, a cold 5% potassium carbonate solution and with water. After drying over anhydrous sodium sulfate, the solvent was removed and the residue recrystallized twice from 95% ethanol. Yield: 540 mg. (74.6%), m.p. 61.5–63.0°.

Anal. Calcd. for $C_{43}H_{81}NO_7$: C, 71.31; H, 11.28; N, 1.93. Found: C, 71.64; H, 11.06; N, 1.95.

DEPARTMENT OF FOOD TECHNOLOGY
UNIVERSITY OF ILLINOIS
URBANA, ILL.

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p-Fluorotropic Acid and *p*-Fluoroatropine

RICHARD S. BERGER,* ARTHUR E. JACOBSON, AND ALBERT A. KONDRITZER

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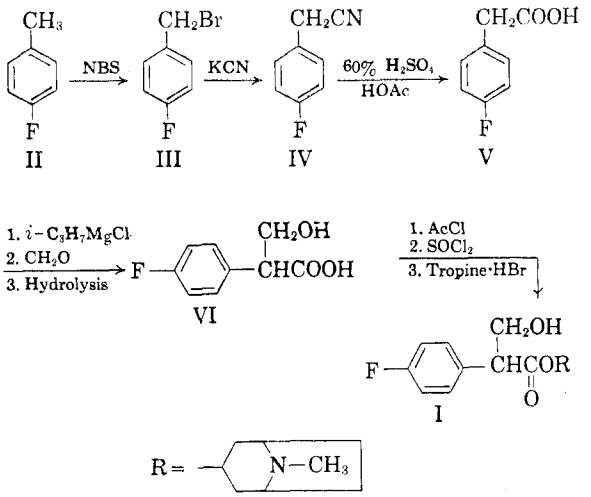
The synthesis of *p*-fluoroatropine (I) through a series of reactions starting with *p*-fluorotoluene is reported here. To our knowledge there have been no previous reports of atropine modified by substituents on the aromatic ring.

p-Fluorobenzylbromide (III) was prepared by the Wohl-Ziegler reaction from *p*-fluorotoluene (II) and N-bromosuccinimide. This method is simpler to carry out and results in a higher yield (81%) of III than previous methods[1,2] employing elementary bromine. The conversion of the bromide (III) to *p*-fluorophenylacetic acid (V) was accomplished *via* the corresponding nitrile (IV); the nitrile (IV) and the acid (V) have previously been reported by Hager and Starkey.[2] The method of Blicke[3] with

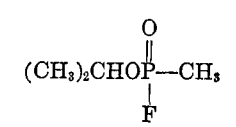


slight modifications[4] was found to be satisfactory for the preparation of *p*-fluorotropic acid (VI) in 65% yield.

Tropine was obtained by the basic hydrolysis of atropine in almost quantitative yield essentially by the method of Findlay.[5] The tropine was converted to the previously unreported hydrobromide[4] for use in the esterification of VI.

The esterification step was carried out in a manner similar[4] to the original atropine synthesis[6] and *p*-fluoroatropine (I) was obtained from the reaction in 26% yield. The reaction mixture darkened considerably during the heating which followed the addition of the tropine hydrobromide. An attempt to improve the yield of I by lowering the temperature about twenty degrees during this part of the reaction resulted in no yield of the product. The preparation of I by ester interchange between tropine and the ethyl ester of VI by the method of Foster and Ing[7] was tried without success.

p-Fluoroatropine was tested in rats for activity as compared with atropine against Sarin (VII), one of the so called "nerve gases." It showed a therapeutic activity approximately the same as atropine.[8]



VII

* Present address: Shell Development Company, Emeryville, California.

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EXPERIMENTAL[9]

p-Fluorobenzyl bromide. To a solution of 11.0 g. (0.10 mole) of *p*-fluorotoluene (Eastman) in 10 ml. of carbon tetrachloride was added 15.0 g. (0.084 mole) of N-bromosuccinimide (Eastman). The mixture was refluxed for 2 hr., and at the end of that time the N-bromosuccinimide which had been at the bottom of the flask had disappeared, and a layer of succinimide was floating on top. The mixture was filtered and the filter cake washed with several portions of carbon tetrachloride.

The filtrate was distilled at atmospheric pressure to remove solvent and a small amount of unreacted *p*-fluorotoluene. Distillation of the remaining liquid at 27 mm. gave 12.8 g. (80.5%) of colorless *p*-fluorobenzyl bromide, b.p. 92–102°, n_D 1.547 (lit.[1] b.p. 93–95°/20 mm., n_D 1.548).

p-Fluorobenzyl cyanide. To a solution of 6.5 g. (0.10 mole) of potassium cyanide dissolved in 12 ml. of water was added, dropwise, 11.9 g. (0.063 mole) *p*-fluorobenzyl bromide dissolved in 30 ml. of 95% ethanol. The mixture was refluxed for 3 hr. The solution was cooled overnight in the refrigerator, and the precipitated inorganic salts were filtered and washed with 95% ethanol. Most of the alcohol was distilled leaving two liquid phases. The aqueous layer was separated and washed with ether and the ether extracts were combined with the organic layer. The solution was dried, the solvent was removed, and the residual oil was distilled at 25 mm. to give 5.3 g. (62%) of *p*-fluorobenzyl cyanide, b.p. 120–129°, n_D 1.499 (lit.[2] b.p. 100–103°/3 mm., n_D 1.501).

p-Fluorotropic acid. Isopropylmagnesium chloride was prepared from 4.2 g. (0.081 mole) of isopropyl chloride and 1.2 g. (0.05 mole) of magnesium in 30 ml. of dry ether. After the addition of the halide, the mixture was refluxed for 45 min. The fluorophenylacetic acid[2] (3.3 g., 0.021 mole) dissolved in 50 ml. of benzene was added to the stirred Grignard reagent during a 20-min. period. The mixture was stirred and refluxed for 3.5 hr. after this addition.

Paraformaldehyde (1.72 g., 0.057 mole), which had previously been dried for several days over phosphorous pentoxide, was heated in an oil bath at 180–200° and the gaseous formaldehyde was carried over the reaction surface in a slow stream of dry nitrogen. The reaction mixture was stirred and ice-cooled during this part of the reaction. Stirring was continued for 30 min. after all of the formaldehyde had been carried over.

The Grignard complex was hydrolyzed by pouring onto a mixture of 100 ml. ice and 7 ml. concentrated sulfuric acid. After standing overnight in the refrigerator, the mixture was stirred for 45 min. and filtered. The layers of the filtrate were separated and the aqueous layer and solid returned to the original reaction flask and heated to boiling. The aqueous layer was then cooled and extracted with five 20 ml. portions of ether. The ether extracts were combined with the benzene layer and the solution concentrated to approximately 25 ml. at which point crystallization occurred.

Filtration and further concentration of the mother liquors gave 2.56 g. (65%) *p*-fluorotropic acid, m.p. 97–100°. Two recrystallizations from benzene gave fine white needles, m.p. 99.5–100°.

Anal. Calcd. for $C_9H_9FO_3$: C, 58.7; H, 4.9; neut. equiv., 184. Found: C, 59.1; H, 5.2; neut. equiv., 189.

Tropine. The method of Findlay[5] was employed with the exception that the sublimation step was omitted. After removal of the ether, white needle-like crystals of tropine were obtained in almost quantitative yield, m.p. 63–64.5° (Findlay reports 87% yield, m.p. 63–65.5°).

Tropine hydrobromide was prepared in 95% yield by passing dry gaseous hydrogen bromide into an ethereal solution of the base. The product may be recrystallized from absolute alcohol–petroleum ether. The hydrobromide does not have a sharp characteristic melting point, melting with decomposition between 235° and 260°.

(9) All melting points are uncorrected.

Anal.[4] Calcd. for $C_8H_{16}BrNO$: Br, 36.10. Found: Br, 35.84.

p-Fluoroatropine. *p*-Fluorotropic acid (0.74 g., 0.004 mole) and a magnetic stirrer were placed in a 20-ml., two necked flask to which a reflux condenser was attached. Freshly distilled acetyl chloride (2 ml.) was added, the mixture was stirred, and after the initial reaction had subsided, it was heated and stirred for 20 min. at 90–95°. After removal of the excess acetyl chloride under reduced pressure, 4 ml. of freshly distilled thionyl chloride was added and the mixture was stirred and heated for 1.5 hr. at 90–95°. The excess thionyl chloride was removed under reduced pressure, 0.80 g. (0.0036 mole) of tropine hydrobromide was added and the mixture was stirred and heated for 1 hr. A drop of concentrated hydrochloric acid and 2 ml. of water were added to the reddish oil and the mixture was heated for 1 hr. at 90–95°. After cooling in ice, 10% sodium hydroxide solution was added until the mixture reached *p*H 10, whereupon an oil precipitated. After standing overnight in the refrigerator, the oil together with the aqueous layer was extracted several times with chloroform. After removal of the solvent from the combined extracts, the oily residue was dissolved in ether and the solution was placed in a refrigerator for several days. The precipitated, crystalline *p*-fluoroatropine (m.p. 87–93°, 0.29 g., 26%) melted at 94–95° after recrystallization from chloroform–petroleum ether (32–63°).

Anal. Calcd. for $C_{17}H_{22}FNO_3$: C, 66.4; H, 7.2. Found: C, 66.5; H, 7.5.

The *picrate* was prepared from a sample of the atropine and recrystallized from ethanol to give yellow powdery crystals, m.p. 181–183°.

Anal. Calcd. for $C_{23}H_{25}FN_4O_{10}$: C, 51.5; H, 4.7. Found: C, 51.0; H, 4.7.

PHYSIOLOGY DIVISION
DIRECTORATE OF MEDICAL RESEARCH
CHEMICAL WARFARE LABORATORIES
ARMY CHEMICAL CENTER, MD.

Synthesis of Some Organic Arsonites and Arsonates[1]

LESLIE M. WERBEL, THOMAS P. DAWSON, JOHN R. HOOTON, AND THEODORE E. DALBEY

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Although organic arsenical research has been quite extensive, extending back to the work of Cadet[2] in 1760, little work has been done on alkylarsonate esters. The purpose of this work was to prepare certain methylarsonate esters of the type $CH_3As(O)(OR)_2$ (I).

Several methods for their synthesis appeared to be available: (*1*) reaction of dichloromethylarsine oxide with alcohols, (*2*) alkylation of metallic salts of alkylarsonic acids with alkyl halides, and (*3*) oxidation of alkylarsonites.

Although dichloroarylarsine oxides are known[3,4]

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