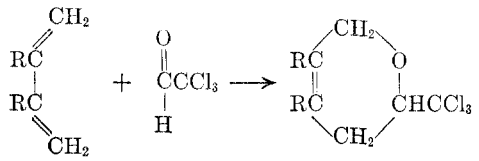
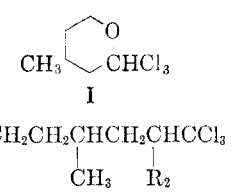
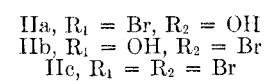


In the present study, an additional reaction of this type and a partial structural study of a previously reported cleavage product were undertaken. It has now been found that chloroacetaldehyde reacts with 2,3-dimethylbutadiene in a sealed tube, heated at 100° for 24 hr., to give 3,4-dimethyl-6-chloromethyl-5,6-dihydro-1,2-pyran (30% yield), from which the corresponding tetrahydropyran is obtained on hydrogenation. It was not possible under these conditions to effect a reaction between cyclopentadiene and chloral.

We have also observed that when the hydrogenated chloral-isoprene adduct (I), obtained in our first study[1] was treated with dry hydrogen bromide in acetic acid according to the method of Paul,[2] it suffered cleavage to give a bromoalcohol (IIa or IIb), rather than the dibromo derivative IIc, even though the work of Paul had shown that under these conditions, tetrahydropyrans undergo cleavage to give the dibromo derivatives. The explanation undoubtedly lies in the steric and electronegative influence of the neighboring trichloromethyl group during the cleavage process.



I



IIa, R_1 = Br, R_2 = OH
IIb, R_1 = OH, R_2 = Br
IIc, R_1 = R_2 = Br

When I was subjected to oxidative cleavage with chromic oxide in acetic acid, a white solid was obtained which, in addition to the acid function, contains an α-ketotrichloromethyl group. Further work is being done on these compounds to confirm the assignments of structure of the original diene-chloral adducts, tentatively made on the basis of polarizations present in the combining molecules.

EXPERIMENTAL

Cleavage of the hydrogenated isoprene-chloral adduct. Into a 125-ml. round bottomed flask were placed 12 g. (0.055 mole) of hydrogenated adduct (I)[1] and 50 ml. of glacial acetic acid. Dry hydrogen bromide gas was passed into the solution for a period of 2 hr., during which time the reaction solution was cooled intermittently with an ice bath. An insoluble oil began to separate after 1 hr. The oil was removed and triturated with 95% ethanol, after which a white solid separated. Recrystallization from ethanol yielded 8.1 g. (50%) of white crystalline material, m.p. 51.5–52°.

Anal. Calcd. for $C_7H_{12}OBrCl_3$: C, 28.15; H, 3.90. Found: C, 28.19; H, 3.55.

(2) R. Paul, *Bull. soc. chim. France* [4], **53**, 1489 (1933).

Ceric nitrate reagent and various acylating agents confirmed the presence of the hydroxy group.

Oxidation of the hydrogenated isoprene-chloral adduct. Into a 500-ml. three necked round bottomed flask, equipped with mechanical stirrer, were placed 10 g. (0.045 mole) of the saturated adduct (I), 20 ml. of concentrated hydrochloric acid, and sufficient acetic acid to produce a homogeneous solution. To this was added, very slowly and with stirring, a solution of 40 g. of chromic oxide dissolved in a minimum amount of acetic acid and water. The temperature of the reaction solution was not allowed to rise above 50°. After all the chromic acid had been added, the reaction mixture was allowed to stand 2 days at room temperature. The solution was then poured onto ice and water, which caused a flaky solid to separate. The solid was recrystallized from hot water, after which it melted at 79.5–80°. A total of 6 g. was obtained, which corresponded to 48% of the theoretical amount. Molecular wt., calcd., 247; neut. equiv., 243 and 245. Reaction with sodium hydroxide solution released chloroform, indicating the presence of the α-ketotrichloromethyl group.

Condensation of chloroacetaldehyde with 2,3-dimethylbutadiene. 3,4-Dimethyl-6-chloromethyl-5,6-dihydro-1,2-pyran. Into a Carius tube were placed 18 ml. (0.15 mole) of 2,3-dimethylbutadiene, 20 ml. (containing 0.15 mole) of 80% chloroacetaldehyde, and a few milligrams of hydroquinone. (The chloroacetaldehyde used was a Dow product, containing 40% chloroacetaldehyde in water. Upon distillation, an 80% solution was obtained.) The sealed tube was heated in an oven at 100° for 21 hr. Upon fractionation of the reaction mixture, a clear, colorless liquid was obtained, b.p. 86–88° (20 mm.), n_D^{25} 1.4960. Yield, 7.73 g. (30%). The product became yellow after a few days. Number of double bonds, 1.02, 1.04 (hydrogenation).

Anal. Calcd. for $C_8H_{13}OCl$: C, 60.00; H, 8.13. Found: C, 60.21; H, 8.90.

Hydrogenation of 3,4-dimethyl-6-chloromethyl-5,6-dihydro-1,2-pyran. 3,4-Dimethyl-6-chloromethyltetrahydropyran. Six g. (0.037 mole) of 3,4-dimethyl-6-chloromethyl-5,6-dihydro-1,2-pyran, dissolved in 50 ml. of 95% ethanol, was hydrogenated as previously described, using 50 lb. of pressure and 20 mg. of platinum oxide. Distillation of the product yielded 5.87 g. (98%) of a stable, clear, colorless liquid, b.p. 95–97° (20 mm.) n_D^{25} 1.4560.

Anal. Calcd. for $C_8H_{15}OCl$: C, 58.88; H, 9.20; mol. wt. 162.5. Found: C, 58.50; H, 8.70; mol. wt. (Rast) 160.

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Direct Condensation of Dipalmitoxypantoic Acid with Ethyl β-Alanate[1]

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A previously unsuccessful attempt to condense dipalmitoxypantoic acid with ethyl β-alanate[2] proved feasible with the aid of dicyclohexyl carbodiimide. This condensation, representing a successful application of Sheehan's method of peptide

(1) Supported by research grant No. A-257 from the National Institutes of Health, U. S. Public Health Service, Department of Health, Education, and Welfare.

(2) T. Sakuragi and F. A. Kummerow, *J. Am. Chem. Soc.*, **78**, 838 (1956).

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.

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(3) J. C. Sheehan and G. P. Hess, *J. Am. Chem. Soc.*, **77**, 1067 (1955).
(4) T. Sakuragi and F. A. Kummerow, *J. Nutrition*, **59**, 327 (1956).

p-Fluorotropic Acid and *p*-Fluoroatropine

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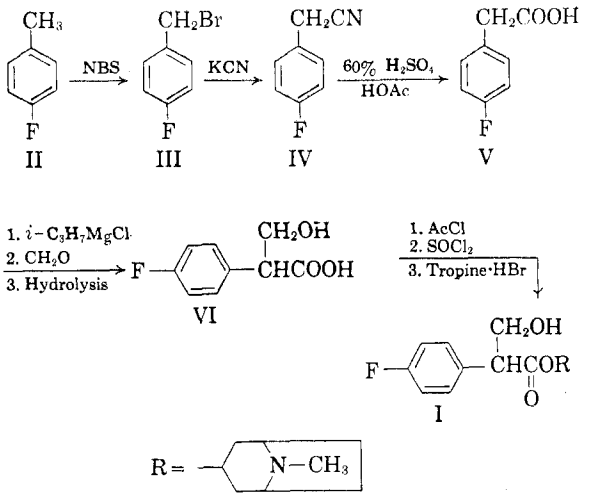
Received October 1, 1956

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

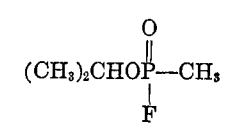


slight modifications[4] was found to be satisfactory for the preparation of *p*-fluorotropic acid (VI) in 65% yield.

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

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(1) J. R. Vaughan, Jr., *et al.*, *J. Org. Chem.*, **14**, 228 (1949).
(2) G. P. Hager and E. B. Starkey, *J. Am. Pharm. Assoc.*, **32**, 44 (1943).
(3) F. F. Blicke, H. Raffelson, and B. Barna, *J. Am. Chem. Soc.*, **74**, 253 (1952).
(4) Unpublished communication from the Colgate-Palmolive Company, Jersey City, N. J., August 31, 1955.
(5) S. P. Findlay, *J. Am. Chem. Soc.*, **75**, 3204 (1953).
(6) R. Wolffenstein and L. Mamlock, *Ber.*, **41**, 723 (1908).
(7) R. Foster and H. R. Ing, *J. Chem. Soc.*, 938 (1956).
(8) The authors are indebted to Mr. Peter Zvirblis for these results.