dimethyl ester of 2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene-1-butyric acid as obtained from the reaction was a liquid. From 5.52 g. of propionic acid ester was obtained 4.56 g. (75%) of the product which "sublimed" at 190–200° at 0.5 mm.

Four and six-tenths grams of the aforementioned ester was cyclized in a nitrogen atmosphere by means of sodium methoxide in exactly the same manner as described for the previous cyclizations to give **11-methyl-1-keto-2-carbomethoxy-1,2,3,4,9,10,11,12-octahydrophenanthrene** (X), which was a liquid at room temperature but which solidified on standing at about −10°. The cyclized product which was "sublimed" at 170–180° at 0.5 mm. was not obtained analytically pure.

The cyclized keto-ester obtained above was hydrolyzed in an atmosphere of nitrogen in the manner previously described to give 1.9 g. (59% yield from the butyric ester) of the methylketoöctahydrophenanthrene which "sublimed" at 100–150° at 0.6 mm. The product was a liquid which was not obtained analytically pure.

The **semicarbazone** of XI formed small colorless crystals; m. p. 210.5–212.5° with decomposition in a preheated bath.

Anal. Calcd. for $C_{16}H_{21}ON_3$: N, 15.5. Found: N, 15.9.

The Wolff–Kishner reduction of 0.26 g. of semicarbazone with sodium ethoxide from 0.35 g. of sodium and 10 cc. of absolute alcohol at 175° for twenty-four hours yielded **11-methyl-1,2,3,4,9,10,11,12-octahydrophenanthrene**, a colorless liquid which was "sublimed" at 0.4 mm. but was not obtained analytically pure. When it was heated with 0.6 g. of selenium at 310–320° for twenty hours it yielded phenanthrene.

Summary

The synthesis of the *cis* and *trans* forms of 3′-keto-2-methyl-1,2-cyclopentano-1,2,3,4-tetrahydronaphthalene from 1-tetralone is described. These compounds possess the B, C and D rings of the sex hormone equilenin including the angular methyl group, but lack the phenolic A ring. In addition, a homolog possessing a six-membered D ring has been synthesized.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

Some Fluorinated Amines of the Pressor Type

BY C. M. SUTER AND ARTHUR W. WESTON[1]

The study of physiologically active compounds containing fluorine in the aromatic nucleus[2] has now been extended to include a number of pressor amines. *m*-Fluorophenethylamine and 3-fluoro-4-hydroxyphenethylamine have been described[3] previously but their physiological action was not reported. *p*-Fluorophenylpropanolamine[4] has an ephedrine-like action except that it probably does not show tachyphylaxis.

p-Fluorophenethylamine and its N-methyl derivative were prepared from fluorobenzene by the reactions indicated.

$$C_6H_5F \xrightarrow{Br_2} p\text{-}BrC_6H_4F \xrightarrow[CH_2CH_2\,\diagdown O\diagup]{Mg} p\text{-}FC_6H_4CH_2CH_2OH \xrightarrow{PBr_3} p\text{-}FC_6H_4CH_2CH_2Br \xrightarrow[n\text{-}C_4H_9OH]{CH_3NH_2} p\text{-}FC_6H_4CH_2CH_2NHCH_3$$

The liquid dibromide that constitutes most of the dibromide fraction obtained as a by-product in the bromination of fluorobenzene is chiefly 2,4-dibromofluorobenzene as shown by its synthesis from 2,4-dibromoaniline. The solid isomer is then probably 3,4-dibromofluorobenzene. *p*-Fluorophenethyl alcohol has been obtained previously[5] by another method. Reduction of *p*-fluorobenzyl cyanide with sodium and alcohol gave only a trace of *p*-fluorophenethylamine.

α-Methyl-*p*-fluorophenethylamine was prepared from *p*-fluorobenzyl methyl ketone and formamide. The ketone was obtained in 37% yield by rearrangement of the addition product obtained from chloroacetone and *p*-fluorophenylmagnesium bromide.

The physiological tests on the fluoroamines[6] have produced some interesting results. The toxicity of each amine hydrochloride was determined by oral administration in a 0.5% suspension of tragacanth to female white mice of the Carworth strain. The toxicities of the unfluorinated amines were determined for comparison purposes. The results are summarized in Table I and were obtained from a total of 280 mice, five

(1) Sharp and Dohme post-doctorate Fellow, 1938–1939.

(2) (a) Suter, Lawson and Smith, THIS JOURNAL, **61**, 161 (1939); (b) Suter and Weston, *ibid.*, **61**, 2317 (1939).

(3) Schiemann and Winkelmüller, *J. prakt. Chem.*, **135**, 101 (1932).

(4) Zenitz and Hartung, "Medicinal Chemistry Abstracts," Baltimore meeting of the American Chemical Society, April, 1939, p. 10.

(5) Baddeley and Bennett, *J. Chem. Soc.*, 1819 (1933).

(6) We are much indebted to Dr. Paul A. Mattis and Mr. Albert R. Latven of the Medical-Research Division, Sharp and Dohme, for these results.

at each dose level, with a sufficient number of levels to encompass the LD. 0 and LD. 100. The LD. 50 was calculated in each instance by the use of Behren's method.

TABLE I

TOXICITY OF SUBSTITUTED PHENETHYLAMINES

Amine	Toxicity in mg./kg. LD. 0	LD. 50	LD. 100
$C_6H_5CH_2CH_2NH_2$	200	400	600
p-$FC_6H_4CH_2CH_2NH_2$	200	300	450
$C_6H_5CH_2CH(NH_2)CH_3$	15	45	80
p-$FC_6H_4CH_2CH(NH_2)CH_3$	15	25	50
$C_6H_5CH_2CH_2NHCH_3$	600	685	800
p-$FC_6H_4CH_2CH_2NHCH_3$	400	520	700

The effects of the amine hydrochlorides on blood pressure were determined in rabbits, dogs and guinea pigs. In general, the effect of the compounds was depressor in rabbits and pressor in dogs and guinea pigs. In the experiments with rabbits, although there was considerable variation, similar doses of N-methyl-p-fluorophenethylamine, α-methyl-p-fluorophenethylamine and α-methylphenethylamine showed the same depressor activity which was on the average greater than for p-fluorophenethylamine. In the experiments on dogs p-fluorophenethylamine, α-methyl-p-fluorophenethylamine and α-methylphenethylamine showed similar pressor activity while N-methyl-p-fluorophenethylamine was slightly less active. In the experiments on guinea pigs, α-methyl-p-fluorophenethylamine showed greater pressor activity than p-fluorophenethylamine, and N-methyl-p-fluorophenethylamine was more active than α-methylphenethylamine. Because of its low toxicity and its pressor activity N-methyl-p-fluorophenethylamine was the most promising of the compounds studied.

Experimental

Bromination of Fluorobenzene.—Bromination of 135.6 g. (1.41 moles) of fluorobenzene with 287 g. (1.79 moles) of bromine in the presence of iron filings[7] gave besides 178 g. of the p-fluorobromobenzene fraction, b. p. 153–161°, 73 g. of dibromofluorobenzene, b. p. 105–110° (22 mm.), and a small (3.6 g.) crystalline residue. Careful fractionation of the dibromofluorobenzene gave a product b. p. 102–103 (23 mm.), 214.6° (745 mm.), $n^{20}D$ 1.5830, d^{20}_4 2.053, M_D calcd. 41.73, observed 41.32. The crystalline residue after three crystallizations from alcohol melted at 66.5–67°. Previously 69° has been given[7] as the m. p. of this product.

2,4-Dibromofluorobenzene.—A mixture of 85.3 g. (0.34 mole) of 2,4-dibromoaniline, 69 ml. of concentrated hydrochloric acid and 100 ml. of water was heated on the steam-bath for an hour, cooled to 0° and diazotized with 24.8 g. of sodium nitrite in 35 ml. of water. A cold solution of 68 g. of commercial 40% fluoboric acid was then added rapidly, the temperature remaining below 0°. After twenty minutes stirring the thick yellow paste was filtered by suction and washed successively with 100 ml. of water, 100 ml. of methanol and 70 ml. of ether. The yield was 77.8 g. (65.5%). It decomposed at 182°. Pyrolysis in a 1-liter distilling flask (very little product passed into the receiver) followed by steam distillation gave a heavy colorless oil which upon separation and distillation came over at 110–110.5° (30 mm.). The yield was 20.6 g. or 24% based on the original dibromoaniline. It had the properties b. p. 215.4–216° (745 mm.), $n^{20}D$ 1.5840, d^{20}_4 2.047, M_D calcd. 41.73, observed 41.51.

Anal.[8] Calcd. for $C_6H_3Br_2F$: Br, 63.0. Found: Br, 63.3.

p-Fluorophenethyl Alcohol.—To a Grignard reagent prepared from 100 g. (0.571 mole) of p-bromofluorobenzene in 250 ml. of dry ether was added slowly a solution of 52.8 g. (1.2 mole) of ethylene oxide in 60 ml. of dry benzene from a dropping funnel surrounded by ice. The temperature of the reaction mixture was kept below 10° during the addition and was then raised slowly. At 45° a vigorous reaction occurred with separation of solid material. After two hours of refluxing the mixture was added to ice and dilute sulfuric acid. The benzene–ether layer was separated, combined with the ether extract of the aqueous layer, washed with water and sodium bicarbonate solution and dried. Fractionation of the ether layer gave 54.8 g. (68.5% yield) of product distilling at 114–122° (20 mm.), most of which came over at 117–118°. The properties of this fraction were $n^{20}D$ 1.5081, d^{20}_4 1.137, M_D obsd., 36.76, calcd. 36.96. The alcohol has been reported[5] as a colorless oil, b. p. 110° (20 mm.). Conversion of 0.5 g. of the alcohol to the benzoate gave a product melting at 54.5–55.5°. Previously[5] this has been reported to have the m. p. 43–44°, and hence was analyzed.

Anal. Calcd. for $C_{15}H_{13}O_2F$: C, 73.76; H, 5.36. Found: C, 73.73; H, 5.69.

p-Fluorophenethyl Bromide.—A procedure similar to that of Speer and Hill[9] for phenethyl bromide was employed. To a stirred solution of 56 g. (0.4 mole) of p-fluorophenethyl alcohol in an equal weight of dry benzene kept in ice and salt was added slowly 84 g. (0.31 mole) of phosphorus tribromide. The mixture was heated slowly to 100° and then cooled, treated with ice water and then washed with bicarbonate solution and with water. There was obtained 65 g. (80% yield) of product, b. p. 101–102° (17 mm.), $n^{20}D$ 1.5323, d^{20}_4 1.456, M_D calcd. 43.21, obsd. 43.31. Although this material had satisfactory physical constants the bromine analysis was low. It was used in the next experiment without further purification.

Anal.[8] Calcd. for C_8H_8FBr: Br, 39.4. Found: Br, 38.5.

p-Fluorophenethylamine.—To 700 ml. of absolute alcohol containing about 112 g. (6.6 moles) of ammonia was added 20.3 g. (0.1 mole) of p-fluorophenethyl bromide. The alcohol solution was kept in a tightly stoppered bottle at room temperature for ten days. The residue from evapo-

(7) Schiemann and Pillarsky, *Ber.*, **64B**, 1343 (1931).

(8) Analysis by Mr. E. Washburn of this Laboratory.

(9) Speer and Hill, *J. Org. Chem.*, **3**, 143 (1938).

ration of the alcohol was treated with 10% sodium hydroxide, the amine extracted with ether and the solution dried with potassium hydroxide. Fractionation of the ether solution gave 9.5 g. of amine (68% yield) b. p. 99–100° (24 mm.), $n^{20}D$ 1.5080, d^{20}_4 1.069, M_D calcd. 38.86, obsd. 38.79. The residue from the distillation, probably secondary and tertiary amines, amounted to 4–5 g.

Anal. Calcd. for $C_8H_{10}NF$: neut. eq., 139. Found: neut. eq., 138.3.

The hydrochloride was prepared by passing hydrogen chloride gas into a dry ether solution of the amine and crystallizing the precipitate from dry isopropyl alcohol. It is soluble in absolute ethanol and insoluble in acetone, chloroform and carbon tetrachloride. From 7.4 g. of amine there was obtained 6.3 g. of pure hydrochloride, silvery plates melting[10] at 206–208°.

Anal. Calcd. for $C_8H_{11}NClF$: Cl, 20.20. Found: Cl, 20.26.

N-Methyl-*p*-fluorophenethylamine.—To a solution of 20.3 g. (0.1 mole) of *p*-fluorophenethyl bromide in 15.5 g. of dry *n*-butyl alcohol in a magnesium citrate bottle was added 15.5 g. (0.5 mole) of dry methylamine gas. The bottle was stoppered and heated on the steam-bath for twenty-four hours, cooled and the contents made alkaline with 30% sodium hydroxide. The mixture was extracted three times with ether, the ether dried over potassium hydroxide and the solution fractionated. The product distilling at 105–107° (26 mm.) amounted to 9 g. or 59% of the theoretical amount. Its properties were $n^{20}D$ 1.4964, d^{20}_4 1.027, M_D calcd. 43.66, observed 43.57.

Anal. Calcd. for $C_9H_{12}NF$: neut. eq., 153. Found: neut. eq., 153.7, 153.3.

The hydrochloride was prepared as for that of *p*-fluorophenethylamine. After crystallization from acetone the m. p. was 163–164°.

Anal. Calcd. for $C_9H_{13}NClF$: Cl, 18.71. Found: Cl, 18.78, 18.75.

***p*-Fluorobenzyl Cyanide.**—To a solution of 11 g. (0.24 mole) of sodium cyanide in 10 ml. of water was added 25.3 g. (0.173 mole) of crude *p*-fluorobenzyl chloride[11] b. p. 79–83° (22 mm.) dissolved in 25 g. of 95% alcohol. The mixture was refluxed for four hours, cooled, and the insoluble sodium chloride filtered off and washed with alcohol. The combined alcohol solutions were partially distilled and the residue and diluted alcoholic distillate extracted with ether. Fractionation of the dried ether solution gave 9.3 g. of nitrile distilling at 118–122° (20.5 mm.). A pure sample, b. p. 122–123° (21 mm.), had $n^{20}D$ 1.5007, d^{20}_4 1.139, M_D calcd. 34.98, obsd. 34.93.

Anal. Calcd. for C_8H_6NF: N, 10.37. Found: N, 10.10.

Lower boiling fractions from the distillation contained a solid, m. p. 183–184°. *p*-Fluorobenzoic acid melts at 182–184°.

An attempt to reduce *p*-fluorobenzyl cyanide with sodium and alcohol according to the procedure of Adams and Marvel[12] gave only a little basic material which could not be purified.

(10) Melting points are corrected.

(11) Schiemann, *Ber.*, **65B**, 1438 (1932).

(12) Adams and Marvel, THIS JOURNAL, **42**, 310 (1920).

***p*-Fluorobenzyl Methyl Ketone.**—A Grignard reagent was prepared from 35 g. (0.20 mole) of *p*-fluorobromobenzene and 4.6 g. (0.19 mole) of magnesium. To this was added 18.5 g. (0.2 mole) of chloroacetone in 50 ml. of ether as rapidly as the refluxing of the reaction mixture would allow. The ether was removed by heating the reaction flask in an oil-bath and at 100° the residue foamed with formation of a gel from which ether was removed slowly by heating at 135–140° for forty-five minutes. The flask was cooled, ice and dilute acid were added, the heavy oil which separated was removed with ether and the ether solution dried and fractionated. There was obtained 11.2 g. (37%) of practically pure ketone distilling at 106–107° (18 mm.).

A variation of this procedure in which the reaction mixture was not heated above 100° gave a product that could not be satisfactorily fractionated. Substantially pure ketone was finally obtained by conversion to the sodium bisulfite addition compound followed by regeneration with dilute sodium carbonate. It distilled at 108° (18 mm.) as a light yellow oil with $n^{20}D$ 1.4965, d^{20}_4 1.107, M_D calcd. 40.07, obsd. 40.17. After a few days of standing, crystals of *p*-fluorobenzoic acid were deposited. Carbon and hydrogen analyses gave low results even with material kept in a sealed ampoule. A solid derivative was therefore prepared. The dinitrophenylhydrazone did not form but the semicarbazone, m. p. 200.5–201.5°, separated readily. Analysis by the Jamieson method[13] of titrating with potassium iodate gave only fair results.

Anal. Calcd. for $C_{10}H_{12}ON_3F$: eq. wt., 52.30. Found: eq. wt., 51.50.

In this analysis the end-point was not stable, probably due to the reaction of the liberated ketone with iodine.

α-Methyl-*p*-fluorophenethylamine.—A mixture of 8.7 g. (0.057 mole) of *p*-fluorobenzyl methyl ketone and 16 g. (0.36 mole) of formamide was heated in a 100-ml. round-bottomed flask attached to an air condenser for twelve hours at a temperature where vigorous bubbling occurred.[14] The amide was hydrolyzed by refluxing with 35 ml. of 30% sodium hydroxide for eleven hours, and the amine layer separated. Distillation gave 3.6 g. (41% yield) of pure amine, b. p. 95–96° (17 mm.), $n^{20}D$ 1.4979, d^{20}_4 1.028, M_D calcd. 43.49, observed 43.65. The amine rapidly took up carbon dioxide from the air forming a solid salt.

Anal. Calcd. for $C_9H_{12}NF$: neut. eq., 153. Found: neut. eq., 152.2, 152.4.

The amine was converted into the hydrochloride in the usual manner. After crystallizing from dry acetone it melted at 156–157°.

Anal. Calcd. for $C_9H_{13}NFCl$: Cl, 18.71. Found: Cl, 18.73.

Summary

1. Three new fluorinated amines of the phenethylamine type have been prepared.

2. Physiological tests with white mice indi-

(13) Smith and Wheat, *Ind. Eng. Chem., Anal. Ed.*, **11**, 2000 (1939).

(14) Johns and Burch, THIS JOURNAL, **60**, 919 (1938).

cate that the fluorinated phenethylamines are slightly more toxic than the unsubstituted compounds. Toward dogs and guinea pigs the amines showed pressor activity while with rabbits the effect was depressor.

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[CONTRIBUTION FROM THE WILLIAM H. CHANDLER CHEMISTRY LABORATORY OF LEHIGH UNIVERSITY]

The Acid Catalyzed Esterification of Normal Fatty Acids

BY HILTON A. SMITH AND C. H. REICHARDT

In a recent article[1] the study of the effect of the length of the carbon chain on the rate of the catalyzed esterification of normal aliphatic acids in dry methanol was reported. It was demonstrated that an increase in the hydrocarbon chain length of the acid from one to three carbon atoms caused a lowering of the value of the specific reaction rate constant, while further increase in the number of carbon atoms had no effect. It was further demonstrated that the activation energy is, within experimental error, the same (about 10,000 cal./mole) for all normal acids.

In a subsequent publication, Fairclough and Hinshelwood[2] also reported a study of the esterification of normal fatty acids, including the catalyzed reaction in dry methanol. Their findings differ from those already published. Their activation energies are consistently higher by some 15–20%, and E for the esterification of acetic acid is also considerably greater than for acids of larger molecular weight. Also, their results indicate that, instead of remaining the same with increasing chain length, the reaction velocity constants for esterification of butyric and higher acids go through a minimum at a chain length of approximately ten carbon atoms.

The high activation energies in general and also the low k's for pelargonic acid as reported by Fairclough and Hinshelwood, are a direct result of their choice of the values of r in Goldschmidt's equation

$$k = \frac{(a + r)\ln[a/(a - x)] - x}{rt\ (\text{catalyst})} \qquad (1)$$

where a is the original concentration of organic acid, x is the concentration of ester formed after time t, and the catalyst is hydrogen chloride. The constant r, although determined experimentally by choosing that figure which gives the most consistent reaction rate constants, is defined theoretically by the equation

$$r = (CH_3OH_2^+)(H_2O)/(H_3O^+) \qquad (2)$$

and hence should be essentially independent of the particular organic acid present or of its concentration. Nevertheless, these authors have used different r values for each acid studied. The low reaction velocity constant for pelargonic acid is due to their choice for this acid of an r which is approximately twice as great as that chosen for either hexoic or palmitic acids. (No intervening acids were studied.) Their high activation energies are caused by the fact that their values of r decrease with temperature. The nonconstancy of r for different acids and its decrease with temperature are quite the opposite from the results not only of Smith[1] but also of Goldschmidt,[3] Williamson and Hinshelwood,[4] Hinshelwood and Legard,[5] Hartman and co-workers[6] and others. Fairclough and Hinshelwood explain the difference in their values of r for acetic acid esterification from those found by Williamson and Hinshelwood as being due to the change from 0.5 to 0.1 N solution. Considering the theoretical significance of r, it seems questionable that this dilution could decrease the value of this constant from 0.345 to 0.11 at 45°, and at the same time cause it to increase from 0.125 to 0.27 at 0°.

Because of these discrepancies, the study of the catalyzed esterification of normal fatty acids in dry methanol under the conditions described by Fairclough and Hinshelwood has been repeated.

Experimental

As in previous work,[1] dry methanol was prepared by distillation in a 5-ft. (1.5-meter) spiral column. All organic acids, with the exception of lauric acid, were purified by fractionation in efficient fractionating columns. Eastman Kodak Co. lauric acid was used without purification.

(1) Smith, THIS JOURNAL, **61**, 254 (1939).

(2) Fairclough and Hinshelwood, *J. Chem. Soc.*, 593 (1939).

(3) Goldschmidt and co-workers, *Z. physik. Chem.*, **60**, 728 (1907); **81**, 30 (1912); **143**, 139, 278 (1929).

(4) Williamson and Hinshelwood, *Trans. Faraday Soc.*, **30**, 1145 (1934).

(5) Hinshelwood and Legard, *J. Chem. Soc.*, 587 (1935).

(6) Hartman and Borders, THIS JOURNAL, **59**, 2107 (1937); Hartman and Gassmann, *ibid.*, **62**, 1559 (1940).