in place of the angular methyl group. The estrogenic activity of one of the racemic forms is

of the same order as that of racemic equilenin. ANN ARBOR, MICHIGAN RECEIVED DECEMBER 11, 1940

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

The Synthesis of Analogs of the Sex Hormones. An Analog of Equilenin Lacking the Phenolic A Ring

BY W. E. BACHMANN AND DONALD G. THOMAS

As part of a program concerned with the synthesis of sex hormones we have undertaken the preparation of relatively simple analogs of the estrogenic hormones in order to determine the effect of a simplification of structure on the estrogenic activity. We have synthesized 3'-keto-2-methyl-1,2-cyclopentano-1,2,3,4-tetrahydronaph-thalene (I, R = H), which possesses the B, C and D rings of the sex hormone equilenin (II) including the angular methyl group but lacks the phenolic A ring.

This compound was synthesized in cis and trans forms from 1-tetralone by employing the procedures developed in this Laboratory for the synthesis of equilenin.¹ The 2-glyoxalate (III), which was formed by condensation of 1-tetralone with dimethyl oxalate, was decarbonylated smoothly when heated with powdered glass and 2-carbomethoxy-1-tetralone (IV) was obtained in 94% yields. This result is in contrast to that obtained by Hückel and Goth² in the pyrolysis of the corresponding ethyl ester without the use of powdered glass. Under their conditions, considerable resinification and decomposition of the glyoxalate occurred which reduced the yield of product to 58%. Methylation of IV followed by a Reformatsky reaction using methyl bromoacetate yielded a hydroxy ester (V) which was dehydrated and hydrolyzed to a mixture of the geometrical isomers of the unsaturated acid (VI). The latter were reduced smoothly by sodium amalgam in alkaline solution to a mixture of the cis and trans forms of 2-methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene-1-acetic acid (VII). The diastereoisomeric forms of the acid were formed in a ratio of about 4:1; this proportion was not appreciably changed when catalytic hydrogenation was employed. Since the configurations of the acids are not known, the prefix α is assigned to one and β to the other, and

(1) Bachmann, Cole and Wilds, THIS JOURNAL. 62. 824 (1940).

(2) Hückel and Goth, Ber., 57, 1285 (1924).

these prefixes are given to the intermediates and the final products obtained from each of the two forms.

The cyclopentanone ring was constructed by lengthening the acetic acid side chain of VII to a propionic acid group through the Arndt-Eistert reaction, cyclizing the dimethyl ester of the dicarboxylic acid (VIII) and hydrolyzing and decarboxylating the cyclic keto-ester (IX) to I. One of the forms of I is a liquid at ordinary temperature, the other a crystalline solid.

We have also built up a six-membered ring to give 11-methyl-1-keto-octahydrophenanthrene (XI, R = H) by lengthening the propionic





acid side chain on the acid ester of VIII to a butyric acid group, cyclizing the resulting dimethyl ester of the dicarboxylic acid to X and hydrolyzing and decarboxylating the latter. Proof of the presence of a reduced phenanthrene nucleus was obtained by reducing the cyclic ketone to XII which on selenium dehydrogenation yielded phenanthrene. The hydrocarbon (XII) is an isomer of the 12-methyloctahydrophenanthrene prepared by Kon.³ Tests on the estrogenic activity of these compounds are not yet complete.

The synthesis of the 6-methoxy derivative of I (R = OCH₃) and the corresponding phenolic compound (I, R = OH) will be described in a future communication. The preparation of XI (R = H) serves as an exploratory reaction for the corresponding methoxy derivative (XI, R = OCH₃) which we propose to employ as the starting ketone for the synthesis of 8-methyl estrone.

We are grateful to the Horace H. Rackham Fund for a generous grant which made possible this investigation.

Experimental

In some of the reactions we employed the procedures used on analogous compounds in the synthesis of equilenin¹; these will be indicated by a reference to the page of the equilenin article where the details may be found.

Methyl 1-Keto-1,2,3,4-tetrahydronaphthalene-2-glyoxalate (III).—1-Tetralone (5.84 g.) in 20 cc. of benzene was condensed with 9.44 g. of dimethyl oxalate by means of sodium methoxide from 1.84 g. of sodium in 40 cc. of benzene. The reaction was carried out in an atmosphere of nitrogen according to the procedure described (ref. 1, p. 831). The mixture was allowed to stand for about four or five hours in a water-bath slightly below room temperature; usually within an hour the contents of the flask had solidified almost completely. From the reaction mixture there was obtained 8.46 g. (91%) of the glyoxalate which without recrystallization melted at $64-66^{\circ}$ and was sufficiently pure for use in the next step. A sample crystallized from methanol in stout yellow prisms; m. p. $65.5-66.5^{\circ}$. With a 2% alcoholic solution of ferric chloride it gave an immediate deep red color.

Anal. Calcd. for $C_{18}H_{12}O_4$: C, 67.2; H. 5.2. Found: C, 67.0; H, 5.2.

Methyl Ester of 1-Keto-1,2,3,4-tetrahydro-2-naphthoic Acid (IV).—Twelve grams of finely powdered soft glass was added to 24 g. of molten glyoxalate at 150° and the temperature was raised to 180° until evolution of carbon monoxide was complete (fifteen to twenty minutes). After cooling, the product was dissolved in acetone and the solution was decanted from the glass, treated with Norit and allowed to evaporate. The residue crystallized readily when scratched with 30–40° petroleum ether. The crude dried product weighed 20.1 g. (95%) and was satisfactory for methylation without further purification. The average yield of several runs of varying sizes was 94%.

A sample crystallized in large colorless prisms from $60-75^{\circ}$ petroleum ether containing a small amount of acetone; m. p. $84.5-86.5^{\circ}$ in a preheated bath, the value depending on the rate of heating. With alcoholic ferric chloride it gave a violet color in the course of a few minutes.

Anal. Calcd. for $C_{12}H_{12}O_3$: C, 70.6; H, 5.9. Found: C, 70.5; H, 5.8.

2 - Methyl - 2 - carbomethoxy - 1 - keto - 1.2.3.4 - tetrahydronaphthalene.--To a solution of sodium methoxide prepared from 10 g. of sodium and 200 cc. of anhydrous methanol was added a solution of 20.4 g. of the aforementioned compound in 100 cc. of dry, thiophene-free benzene and 100 cc. of anhydrous methanol. The mixture was refluxed for ten to fifteen minutes, cooled and treated with 30 cc. of methyl iodide. After standing at room temperature for two hours the solution was refluxed for thirty to forty-five minutes, cooled, neutralized with acetic acid and evaporated nearly to dryness on a steambath. Benzene and water were added and after separation the water was extracted twice with benzene. The combined benzene solution was washed with sodium bicarbonate solution, with water, treated with Norit and allowed to evaporate spontaneously. The product which solidified was recrystallized from 60-75° petroleum etheracetone, from which it separated in long, colorless rectangular prisms; yield, 19.2 g. (2 crops) (88%)⁴; m. p. 56-57.5°. A sample after two further recrystallizations melted at 56.5-57.5°. It was found convenient to combine second crops from several runs and purify them by vacuum distillation followed by recrystallization and in some runs the entire product was purified in this manner.

Anal. Calcd. for C₁₈H₁₄O₃: C, 71.5; H, 6.5. Found: C, 71.9; H, 6.4.

Dimethyl Ester of 2-Methyl-2-carboxy-1-hydroxy-1,2,3,-4-tetrahydronaphthalene-1-acetic Acid (V).—To 35-40 g. of 20-mesh zinc (washed with dilute hydrochloric acid, water, acetone and dried immediately prior to use) and 0.2 g. of iodine in 150 cc. of anhydrous ether and 150 cc. of

⁽³⁾ Kon, J. Chem. Soc., 1081 (1933). See also Kon and Narracott, *ibid.*, 672 (1938).

⁽⁴⁾ Kloetzel [THIS JOURNAL, 62, 1708 (1940)] likewise obtained excellent yields of these compounds by our procedure.

dry, thiophene-free benzene was added 21.8 g. of the aforementioned methyl keto-ester and 16 cc. of methyl bromoacetate. When the mixture was refluxed on a water-bath, the iodine color faded, the solution became cloudy and within a few minutes a colorless addition product was deposited. At the end of one-half hour another addition of 35-40 g. of zinc and a trace of iodine was made and after one hour 35-40 g. of zinc, a trace of iodine and 16 cc. of methyl bromoacetate were added. Further additions of zinc were made at forty-five minute intervals thereafter. The mixture was refluxed for a total of five to six hours with frequent vigorous shaking in order to free the zinc from the rather gummy precipitate of the addition product.

The addition product was dissolved in a little acetic acid and methanol and the solution was decanted from the zinc into water which had been acidified with acetic acid. After separation of the ether-benzene layer, the aqueous solution was extracted twice with benzene and the combined extracts were washed with dilute ammonium hydroxide three or four times (which removed most of the color) and finally with water. Evaporation of the etherbenzene left an oily residue which crystallized readily when treated with $30-40^{\circ}$ petroleum ether and scratched; yield, 28.5 g. (97%); m. p. $51-58^{\circ}$. Although the product melted considerably lower than a purified sample, it was sufficiently pure for the next step. After three recrystallizations from $60-75^{\circ}$ petroleum ether-acetone a sample separated as colorless crystals; m. p. $63.5-64.5^{\circ}$.

Anal. Calcd. for C₁₆H₂₀O₅: C, 65.7; H, 6.9. Found: C, 65.9; H, 6.9.

Conversion of the Reformatsky Ester to the Unsaturated Acids (VI).—Dehydration of 5.84 g. of the crude Reformatsky ester was carried out by means of 5 cc. of thionyl chloride and 2.5 cc. of pyridine in 10 cc. of benzene, followed by treatment with 6 g. of potassium hydroxide in 100 cc. of methanol which removed the elements of hydrogen chloride. The ester groups were hydrolyzed by adding 20 cc. of 45% potassium hydroxide solution and refluxing (ref. 1, p. 833). Acidification of the alkaline solution precipitated a mixture of unsaturated acid and acid anhydride which weighed 4.0 g. From the filtrate was obtained another 0.24 g. which raised the yield to 86%.

Four grams of the mixture was treated successively with two 25 cc. portions of a 6% solution of sodium bicarbonate in water at room temperature. The insoluble residue which remained was the anhydride of syn-2-methyl-2carboxy-1,2,3,4-tetrahydronaphthylidene-1-acetic acid (anhydride of syn form of VI). From benzene the anhydride formed colorless crystals melting at 139.5-141°.

Anal. Calcd. for C₁₄H₁₂O₈: C, 73.7; H, 5.3. Found: C, 73.3; H, 5.3.

The first bicarbonate extract upon acidification produced quite pure *anti-2*-methyl-2-carboxy-1,2,3,4-tetrahydronaphthylidene-1-acetic acid (VI). From acetone it crystallized in colorless prisms; m. p. in a preheated bath, 194-195° with evolution of gas.

Anal. Calcd. for C₁₄H₁₄O₄: C, 68.3; H, 5.7. Found: C, 68.1; H, 5.7.

Preparation of the Reduced Acids (VII).—Since experiment showed that the aforementioned unsaturated acids yielded the same reduced acids, in subsequent work reduc-

tion was carried out on the mixture of acids obtained on dehydration and hydrolysis of the Reformatsky ester. The aqueous solution of the mixture of the potassium salts of the two unsaturated acids obtained from 23.36 g. of Reformatsky ester was shaken vigorously for thirty minutes with 400 g. of 2% sodium amalgam (ref. 1, p. 833). Acidification of the nearly colorless solution yielded a precipitate which weighed 12.7 g. and consisted largely of the α -acid. Recrystallization from carbon tetrachlorideacetone gave a first crop of fairly pure α -acid; wt. 10.75 g.; m. p. 163-168°; and a second crop weighing 1.2 g. and melting at about 135-150°. The first crop was sufficiently pure for conversion to the dimethyl ester with diazomethane and recrystallization of combined second crops gave a further yield of α -acid. A sample of α -2-methyl-2carboxy - 1,2,3,4 - tetrahydronáphthalene - 1 - acetic acid prepared by hydrolysis of the pure α -acid ester (described below) was recrystallized from carbon tetrachloride-acetone from which it separated in needle-like prisms; m. p. 167.5-169°.

Anal. Calcd. for C₁₄H₁₆O₄: C, 67.7; H, 6.5. Found: C, 67.3; H, 6.4.

Ether extraction of the filtrate from the precipitated α acid gave an oil which crystallized from carbon tetrachloride. The first crop of β-2-methyl-2-carboxy-1,2,3,4tetrahydronaphthalene-1-acetic acid weighed 3.75 g. and melted at about 100-115° with bubbling, indicating the presence of solvent of crystallization; the second crop weighed 1.24 g. and melted at about 135-150°. The first crop was used for conversion to the dimethyl ester with diazomethane. Recrystallization of the second crop gave a further amount of the α -acid. An attempt was made to obtain a sample of pure β -acid by hydrolysis of the pure β -acid ester (described below). The product was "sublimed"⁵ at 0.5 mm. rather than recrystallized since it tends to take up solvent of crystallization. This treatment, however, resulted in dehydration, for the analysis of the compound which was formed corresponded to that of the anhydride. The compound formed colorless crystals when recrystallized from 60-75° petroleum etherether; m. p. 141.5-143°.

Anal. Calcd. for C₁₄H₁₄O₃: C, 73.0; H, 6.1. Found: C, 72.7; H, 6.0.

Dimethyl Ester of 2-Methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene-1-acetic Acid.—The α -form prepared from 10 g. of the acid by means of diazomethane crystallized from 60–75° petroleum ether in long colorless rectangular prisms; yield, 10.5 g. (94%); m. p. 62–63.5°. A sample after a second recrystallization melted at 62.5– 64°.

Anal. Calcd. for C₁₆H₂₀O₄: C, 69.5; H, 7.3. Found: C, 69.1; H, 7.3.

The β -form prepared from 6.3 g. of the crude acid was a liquid which did not crystallize; yield, 6.5 g. (90%).

2 - Methyl - 2 - carbomethoxy - 1,2,3,4 - tetrahydronaphthalene-1-acetic Acid.—The α -form of the acid ester was prepared by refluxing a mixture of 8.28 g. of the dimethyl ester and 30 cc. of 1.03 N sodium hydroxide in 100

⁽⁵⁾ This term is used to indicate that the compound was evaporated under reduced pressure below its boiling point in a sublimation apparatus, the vapor being condensed in a cool part of the apparatus.

cc. of methanol for one hour and forty-five minutes. After the methanol had been removed by a current of air, the residue was dissolved in water and the solution acidi-fied with hydrochloric acid. The oil which precipitated soon crystallized; yield, 7.72 g. After one recrystallization from $60-75^{\circ}$ petroleum ether containing a small amount of acetone, the acid ester was obtained in practically pure form as colorless rectangular prisms; m. p. 113.5–114.5°. A sample after a second recrystallization melted at 114.5–115°.

The β -form was prepared by refluxing a mixture of 6.5 g. of the liquid dimethyl ester, 26 cc. of N sodium hydroxide solution and 125 cc. of methanol for one and one-half hours; yield, 5.37 g. After recrystallization from 60–75° petroleum ether-acetone the acid ester melted at 106–108°. After two more recrystallizations a sample formed colorless prisms; m. p. 107.5–109°.

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.7; H, 6.9. Found: C, 68.5; H, 6.8 (α -form); C, 68.6; H, 6.9 (β -form).

Dimethyl Ester of 2-Methyl-2-carboxy-1,2,3,4-tetrahydronaphthalene-1-propionic Acid (VIII).-The acid chloride of the α -acid ester was prepared by adding 5.24 g. of the acid ester to 4 cc. of thionyl chloride and 2 drops of pyridine in 8 cc. of anhydrous ether (ref. 1, p. 834). After removal of ether and excess thionyl chloride under reduced pressure at about 40° a benzene solution of the acid chloride was added dropwise to a cooled (5-10°) ethereal solution of diazomethane. The latter had been prepared from 15 g. of N-nitrosomethyl urea, 45 cc. of 45% potassium hydroxide solution and 150 cc. of reagent ether and dried for two to three hours over soda lime in the refrigerator. Addition of the acid chloride produced an evolution of nitrogen. After half an hour, the ether and excess diazomethane were removed at room temperature under reduced pressure. The diazoketone usually crystallized in yellow needles.

The diazoketone was dissolved in 60 cc. of dry methanol and treated at 60–70° with one-half of the silver oxide obtained from 10 cc. of 10% silver nitrate solution. Within fifteen minutes the remainder of the silver oxide was added in two portions. After refluxing one to two hours longer the mixture was boiled with Norit, filtered and concentrated. After passage through a short column of alumina to remove colloidal silver the solution was evaporated to dryness and the liquid propionic ester was "sublimed" at 0.6 mm. at 140–160° prior to cyclizing. The α -ester was not obtained analytically pure even when prepared from the pure propionic acid ester with diazomethane.

The β -propionic ester prepared in a similar fashion was also a liquid which was not obtained analytically pure. It was used directly for cyclization.

2' - Carbomethoxy - 3' - keto - 2 - methyl - 1,2 - cyclopentano-1,2,3,4-tetrahydronaphthalene (IX).—The liquid propionic ester obtained from the Arndt-Eistert reaction on 1.31 g. of the α -acetic acid ester was dissolved in 20 cc. of dry, thiophene-free benzene and cyclized in a nitrogen atmosphere by sodium methoxide prepared from 0.25 g. of sodium and 5 cc. of anhydrous methanol (ref. 1, p. 835). The cyclic keto-ester was a liquid which did not crystallize. With 2% alcoholic ferric chloride solution it gave an immediate violet color.

The β -form was obtained in exactly the same manner

in 68% yield (based on the β -acetic acid ester employed to make the β -propionic ester). The crude product melted at 78-85°; after recrystallization from 60-75° petroleum ether containing a small amount of acetone it was obtained as clusters of large dense colorless crystals; m. p. 86-88°. After standing several months the same sample melted at 97-99.5°. With 2% alcoholic ferric chloride a violet color developed in the course of a few minutes.

Anal. Calcd. for $C_{16}H_{18}O_8$: C, 74.4; H, 7.0. Found: C, 74.7; H, 7.0 (α -form); C, 74.4; H, 7.0 (β -form).

3'-Keto-2-methyl-1,2-cyclopentano-1,2,3,4-tetrahydronaphthalene (I, $\mathbf{R} = \mathbf{H}$).—The α -form of the cyclic keto-ester obtained above was refluxed for one and onehalf hours in a nitrogen atmosphere with 20 cc. of acetic acid, 10 cc. of hydrochloric acid and 2 cc. of water (ref. 1, p. 835). The solvents were removed under reduced pressure on the steam-bath and the oily residue was dissolved in benzene. The solution was washed with sodium bicarbonate solution and water, treated with Norit and dried. Evaporation of the benzene yielded the ketone which was "sublimed" at 110–160° at 0.5 mm. and obtained as a colorless liquid. It solidified on prolonged standing at about -10°, but the solid melted below room temperature.

Anal. Calcd. for $C_{14}H_{16}O$: C, 84.0; H, 8.1. Found: C, 83.4; H, 7.9.

The **semicarbazone** formed fine colorless crystals; m. p. 241-242° with decomposition in a preheated bath.

Anal. Calcd. for $C_{15}H_{19}ON_3$: N, 16.4. Found: N, 16.8.

The β -form prepared in exactly the same manner from 0.5 g. of crude cyclic keto-ester yielded 0.34 g. (88%) of crystalline ketone. This was "sublimed" at 110–150° at 0.5 mm. and recrystallized from 30–40° petroleum ether in which it is appreciably soluble. A sample after recrystallization formed colorless crystals; m. p. 57–58°.

Anal. Calcd. for C₁₄H₁₆O: C, 84.0; H, 8.1. Found: C, 83.8; H, 8.0.

2 - Methyl - 2 - carbomethoxy - 1,2,3,4 - tetrahydronaphthalene-1-propionic Acid .--- The propionic ester obtained from the Arndt-Eistert reaction on 5.24 g. of the α -acetic acid ester was refluxed for two hours with 21.1 cc. of N sodium hydroxide solution in 100 cc. of methanol. The methanol was evaporated and the residue was dissolved in water and precipitated with hydrochloric acid. The acid ester, isolated by means of benzene, weighed 4.25 g. (77% from acetic acid ester to propionic acid ester); m. p. 72-77°. Although this material could be used in the next Arndt-Eistert reaction, it was preferable to recrystallize it from 60-75° petroleum ether-ether before use. A sample prepared for analysis was "sublimed" at 0.5 mm. and recrystallized three times from 60-75° petroleum ether-ether. It crystallized in colorless prisms which melted at 78-80.5°.

Anal. Calcd. for $C_{16}H_{20}O_4$: C, 69.5; H, 7.3. Found: C, 69.5; H, 7.3.

11 - Methyl - 1 - keto - 1,2,3,4,9,10,11,12 - octahydrophenanthrene (XI).—The propionic side chain of the above acid ester was lengthened by means of the Arndt-Eistert reaction in the manner previously described. The

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 $100-150^{\circ}$ 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 11methyl-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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Some Fluorinated Amines of the Pressor Type

By C. M. Suter and Arthur W. Weston¹

The study of physiologically active compounds containing fluorine in the aromatic nucleus² has now been extended to include a number of pressor amines. *m*-Fluorophenethylamine and 3-fluoro-4-hydroxyphenethylamine have been described³ previously but their physiological action was not reported. p-Fluorophenylpropanolamine⁴ 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.

$$C_{6}H_{6}F \xrightarrow{Br_{2}} p \cdot BrC_{6}H_{4}F \xrightarrow{Mg} CH_{2}CH_{2}CH_{2}$$

$$p \cdot FC_{6}H_{4}CH_{2}CH_{2}CH_{2}OH \xrightarrow{PBr_{3}}$$

$$p \cdot FC_{6}H_{4}CH_{2}CH_{2}Br \xrightarrow{CH_{3}NH_{2}} p \cdot FC_{6}H_{4}CH_{2}CH_{2}NHCH_{3}$$

The liquid dibromide that constitutes most of the dibromide fraction obtained as a by-product in

(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. the bromination of fluorobenzene is chiefly 2,4dibromofluorobenzene as shown by its synthesis from 2,4-dibromoaniline. The solid isomer is then probably 3,4-dibromofluorobenzene. p-Fluorophenethyl alcohol has been obtained previously⁵ 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 fluoroamines⁶ 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

⁽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.