

but does not dissolve in acetone (compare No. 37 with 36). This solvent completely disintegrates cellulose triacetate at -50° (No. 38).

Methyl acetate swells the cellulose triacetate fibers at -50° (No. 40) much more than at room temperature (No. 39).

Solutions (1:1000) of materials insoluble in a solvent or solvent mixture at room temperature, but completely soluble at low temperature, show the formation of finely divided, swollen particles by increasing the temperature from -50 to -20 or to -10° .

The solution of an ester or ether of cellulose in a solvent is preceded by a swelling effect and the development of heat. The influence of lower temperatures on this swelling and solution effect can be explained by the formation of soluble molecular compounds which dissociate at higher temperatures. The exothermic character of swelling reactions also works in the direction of an increased solubility at low temperatures.

It is known that certain mono alkyl derivatives of cellulose dissolve in water at room temperature and become insoluble in boiling water. Here also a molecular compound is formed between the unsubstituted OH groups containing monoalkylcellulose and water. This molecular compound is soluble in water at room temperature. At higher temperatures this molecular compound dissociates; the alkyl-cellulose, therefore, becomes insoluble in hot water.

Summary

Cellulose esters insoluble in certain solvents or solvent mixtures at room temperature may become soluble at lower temperatures (-50°). This can be explained by the formation of soluble molecular compounds, which dissociate at elevated temperatures, and by the exothermic character of the swelling reactions.

PITTSBURGH, PENNA.

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[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

Carcinogenic Hydrocarbons. III. 20-Isopropylcholanthrene. A Comparison of the Fluorescence and Crystal Forms of Methylcholanthrene, Ethylcholanthrene and Isopropylcholanthrene^{1,2}

BY WILLIAM F. BRUCE AND FLOYD TODD

Cholanthrene and its 20-methyl derivative are particularly interesting carcinogenic hydrocarbons because they are among the most active cancer producing materials.³ The 20-*t*-butyl member of this group of substituted cholanthrenes has been prepared,⁴ and more recently the 20-ethyl homolog has been reported.¹ The present paper describes the preparation of the 20-isopropyl member of this series. In addition, the fluorescence of the methyl, ethyl and isopropyl members under comparable conditions has been measured. A detailed description of the crystal properties of these three substances is included in the experimental part, having been determined microscopically by Professor C. W. Mason, to whom we give hearty thanks for his collaboration.

A comparison of the fluorescence of these three cholanthrene derivatives shows that the intensity of fluorescence, measured under comparable conditions, is strongest for the methyl and weakest for the isopropyl member. From the data

now available for this series, fluorescence and carcinogenic activity appear to be roughly parallel. A more extensive comparison will be available when the series is completed.

Study of the crystal form of 20-methyl, ethyl and isopropyl cholanthrenes shows that the methyl derivative has two forms.⁵ The most common form is acicular, belonging to the triclinic system. Above approximately 140° , however, a platelet or monoclinic form is more stable. Since the conversion of one form to the other is not rapid, it is possible by rapid cooling to secure chiefly the platelet form. This is particularly easy in *n*-propyl alcohol, as Bachmann has pointed out. From a concentrated benzene solution by rapid cooling, both forms can be obtained together. The ethyl and isopropyl members of this group have been observed in only a plate-like form. The crystal system differs, however, for the former has been assigned to the monoclinic system and the latter to the orthorhombic. The characteristic constants for these substances are included in the experimental part.

The preparation of isopropylcholanthrene was accomplished by the general synthesis of Fieser and Seligman, with modifications like those made

(1) Preceding paper, Bruce and Kahn, *THIS JOURNAL*, **60**, 1017-1019 (1938).

(2) Taken in part from the Thesis of Floyd Todd submitted in partial fulfillment of the requirements for the degree of M.S. at Cornell University.

(3) For a recent survey of the literature see Fieser, *Am. J. Cancer*, **34**, 37-124 (1938).

(4) Fieser and Snow, *THIS JOURNAL*, **60**, 176 (1938).

(5) Cf. Bachmann, *J. Org. Chem.*, **1**, 352 (1936).

in the preparation of ethylcholanthrene.¹ Starting with *p*-bromocumene (I), 4-bromo-7-isopropylhydrindene (II) was prepared by the same method as the corresponding ethyl homolog. For the preparation of the ketone (III), the hydrindene (II) was most advantageously converted to the nitrile, then by α -naphthylmagnesium bromide to the ketimine hydrochloride and ketone. By pyrolysis of the ketone, isopropylcholanthrene (IV) was formed. This series of reactions was patterned after the improved procedure of Fieser and Seligman.⁶

In some experiments the bromohydrindene was converted to a Grignard reagent and treated with α -naphthoyl chloride. The yield of ketone by this reaction was less than that by the alternate method. An interesting by-product was observed however, after the addition of dilute bicarbonate to the Grignard- α -naphthoyl chloride solution and removal of some of the ether-benzene solvent. A yellow granular precipitate separated. The substance melted at 145° and proved to be α -naphthoic anhydride.⁷ The production of an anhydride by the addition of water to any combination of reagents is a curious reaction. A similar reaction in another system already has been reported.⁸ Other investigators who have used the acid chloride route in the preparation of a cholanthrene⁹ have noticed the large amount of hydrindene produced from the Grignard reagent in spite of all precautions to exclude traces of water and ensure complete reaction. They have also experienced difficulty in the removal of α -naphthoic acid from the product. Possibly an-

hydride was formed but not detected, for in our experiments it was accompanied by the hydrocarbon in approximately equimolecular amount and did not crystallize until a suitable concentration and solvent combination was accidentally discovered. The difficulty with which it is hydrolyzed may explain the unusual difficulty in removing α -naphthoic acid in these reactions.

Experimental Part

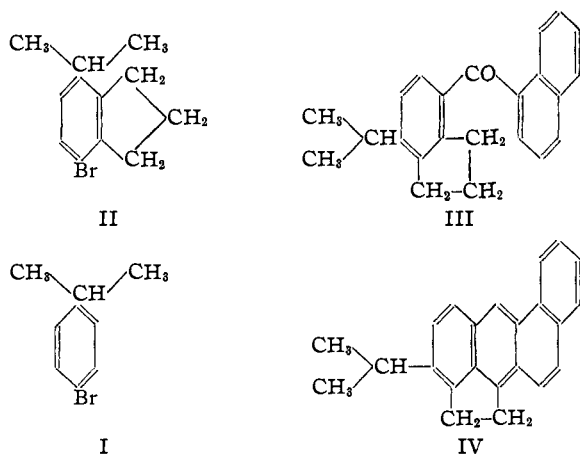
4-Bromocumene (4-Bromo-1-isopropylbenzene) (I).—This substance, boiling at 217°, was prepared by Boedtker by the action of propyl chloride on bromobenzene in the presence of aluminum chloride.¹⁰ In order to be more sure that the product is not contaminated by the *n*-isomer, which boils at 220°,¹¹ the substance was made by the action of isopropyl chloride on bromobenzene in the presence of aluminum chloride. To a mixture of 2240 g. (14.2 moles) of bromobenzene and 110 g. of powdered aluminum chloride in a 5-liter flask immersed in an ice-bath was added with stirring 750 g. (9.6 moles) of isopropyl chloride. After standing at 0° for half an hour the reaction mixture was heated on a steam-bath for fifteen minutes. It was then cooled and poured on 2 kg. of ice. When the dark color of the complex had disappeared, the lower layer was separated and washed repeatedly with concentrated sulfuric acid until the acid was only slightly colored. The material was then washed with water until neutral and was dried with calcium chloride. Upon distillation, the excess bromobenzene was recovered, and the 4-bromocumene boiled at 75–90° at 9 mm. On redistillation this fraction gave 1300 g. (67%) of material boiling from 87–89° at 9 mm. (215–216° at 744 mm.).

From the residue was isolated 240 g. (20%) of a substance boiling from 115–118° at 9 mm. Analysis showed that this material has the composition of a diisopropylbromobenzene.

*Anal.*¹² Calcd. for C₁₂H₁₇Br: C, 59.73; H, 7.05; Br, 33.13. Found: C, 59.68; H, 7.17; Br, 33.12.

Since this substance is presumably 1,3-diisopropyl-4-bromobenzene, upon oxidation it should give 4-bromoisophthalic acid melting at 287°.¹³ Accordingly 1 g. of the material was boiled for five hours with 10 g. of sodium bichromate, 10 cc. of sulfuric acid, 25 cc. of acetic acid and 10 cc. of water. The reaction mixture was poured into 50 cc. of water. The white precipitate which formed after an hour was collected on a filter and washed with methyl alcohol. This substance melted with decomposition at 285–286° (corr.) and therefore is 4-bromoisophthalic acid. The yield was low (0.1 g.) because oxidation is slow under these conditions. Most of the original material was recovered unchanged.

The Isopropylbromobenzyl Chlorides.—The procedure in the preparation of the benzyl chloride mixture was very similar to the corresponding preparation of the ethylbromobenzyl chlorides.¹ From 1300 g. of 4-bromocumene, 250



(6) Fieser and Seligman, *THIS JOURNAL*, **58**, 2482 (1936).

(7) Hofmann, *Ber.*, **1**, 42 (1868).

(8) Bruce, *THIS JOURNAL*, **60**, 2277 (1938).

(9) Fieser and Seligman, *ibid.*, **57**, 942 (1935).

(10) Boedtker, *Bull. soc. chim.*, [3] **35**, 829 (1906).

(11) Meyer, *J. prakt. Chem.*, [2] **34**, 101 (1886).

(12) Semimicroanalyses by F. T.

(13) Schöpf, *Ber.*, **24**, 3777 (1891); Claus, *J. prakt. Chem.*, [2] **43**, 359 (1891).

g. of trioxymethylene and 1000 g. of zinc chloride were secured 280 g. of unchanged 4-bromocumene, 960 g. (76%) of the purified isopropylbenzyl chloride mixture, boiling from 136–139° at 9 mm., and 65 g. (8%) of the dichloromethyl product melting at 86–87.5°.

Anal. Calcd. for $C_{10}H_{12}BrCl$: C, 48.49; H, 4.88. Found: C, 48.51; H, 4.89.

The Isopropylbromobenzylmalonic Esters.—To a solution of 70 g. of sodium in 2000 cc. of methyl alcohol distilled over magnesium methylate was added 960 g. of malonic ester and 400 g. of the isopropylbromobenzyl halide mixture. After two hours of refluxing, most of the alcohol was removed by distillation, water was added after cooling and after neutralization the product was separated. The aqueous portion was extracted with benzene. Upon distillation, 510 g. (85%) of the malonic ester mixture was secured, boiling from 163–168° at 1 mm.

Anal. Calcd. for $C_{17}H_{23}O_4Br$: C, 54.7; H, 6.25; Br, 21.56. Found: C, 55.29; H, 6.57; Br, 19.20.

The Isopropylbromobenzylmalonic Acids.—Hydrolysis of the ester with sodium hydroxide, using the same procedure followed in hydrolyzing the ethylbromobenzylmalonic esters, gave the malonic acids in 88% yield. A sample of the acid purified from acetic acid melted at 124–126°.

Anal. Calcd. for $C_{15}H_{15}O_4Br$: C, 49.54; H, 4.79; Br, 25.36; equiv. wt., 158. Found: C, 49.29; H, 4.59; Br, 25.31; equiv. wt., 157.

Upon incomplete acidification after hydrolysis, the monosodium salt of the malonic acids separated in lustrous flaky crystals which melted with decomposition at 236–237°.

Anal. Calcd. for $C_{15}H_{14}O_4BrNa$: C, 46.31; H, 4.18; Br, 23.71. Found: C, 46.18; H, 4.23; Br, 19.28.¹⁴

The Isopropylbromopropionic Acids.—By heating 175 g. of the malonic acid mixture at 150–170° until no more evolution of gas occurred, a residue of the propionic acid mixture weighing 162 g. (99%) was obtained. A sample on distillation boiled at 216–218° at 22 mm. and solidified to a material melting at 56–58°.

Anal. Calcd. for $C_{12}H_{15}O_2Br$: C, 53.12; H, 5.54; equiv. wt., 271. Found: C, 53.07; H, 5.61; equiv. wt., 269.

The Isopropylbromohydrindones.—The acid chloride prepared from 163 g. of the propionic acid and 100 g. of thionyl chloride was added to a mixture of 100 g. of aluminum chloride and 2500 cc. of carbon bisulfide under the usual conditions.⁹ The product boiled from 162–170° at 3 mm. (168–170° at 9 mm., 170–172° at 13 mm.). After distillation the mixture of hydrindones solidified to a material melting from 90–94°. The yield was 98 g. (64%), but in another similar experiment using 235 g. of propionic acid, 165 g. of thionyl chloride (removed on an oil-bath at 140° and 20 mm.), 150 g. of aluminum chloride and 3000 cc. of carbon bisulfide, the yield was 176 g. (82%).

(14) The sample (68.80 mg.) taken for halogen determination proved too large for effective decomposition in the semi-micro procedure used. In view of the satisfactory carbon-hydrogen results, the bromine analysis was not repeated.

Anal. Calcd. for $C_{12}H_{13}OBr$:¹⁵ C, 56.93; H, 5.19. Found: C, 57.02; H, 5.39.

4-Bromo-7-isopropylhydrindene (II).—From 40 g. of the hydrindones was secured by Clemmensen reduction 33 g. of the hydrindene boiling at 120–123° at 3 mm.; yield, 87%.

Anal. Calcd. for $C_{12}H_{15}Br$: C, 60.25; H, 6.28; Br, 33.34. Found: C, 60.15; H, 6.26; Br, 33.23.

4-Cyano-7-isopropylhydrindene.—In an open tube 1 m. long provided with a coil of heavy copper wire as stirrer and an electric heater covering the lower third was put 50 g. of the hydrindene and 30 g. of dry cuprous cyanide. After thorough mixing, 25 cc. of dry pyridine was added. The mixture was stirred and heated at 180° (inside temperature) for fifteen hours. The hot fluid product was poured into a flask and shaken with 75 cc. of ammonium hydroxide (1:1). The cyanohydrindene was extracted with 300 cc. of benzene. Upon distillation there resulted 35 g. (91%) of twice distilled product boiling from 113–115° at 0.8 mm. (120–123° at 2 mm., 125–128° at 3 mm.). This material, unlike the bromohydrindene, gave no Beilstein test. A forerun of 2.5 g. boiling from 93–98° at 0.8 mm. consisted of unchanged bromohydrindene.

Anal. Calcd. for $C_{13}H_{15}N$: N, 7.5. Found: N, 7.2.

4- α -Naphthoyl-7-isopropylhydrindene.—To the Grignard reagent prepared from 22 g. of α -bromonaphthalene, 3 g. of magnesium and 80 cc. of ether was added 50 cc. of benzene and 13 g. of 4-cyano-7-isopropylhydrindene. After the reaction mixture was heated overnight it was poured on 100 g. of ice with 50 cc. of hydrochloric acid. After two hours 25 g. of the ketimine hydrochloride, a yellow crystalline solid, was collected on a filter. A sample crystallized from 70% acetic acid melted at 262° with decomposition; yield 100%.

Anal. Calcd. for $C_{23}H_{24}NCl$: N, 4.00. Found: N, 4.15.

By hydrolysis of 24.5 g. of the ketimine hydrochloride, 18.5 g. (82%) of the 4- α -naphthoyl-7-isopropylhydrindene resulted, boiling from 210–212° at 0.8 mm.

Anal. Calcd. for $C_{23}H_{22}O$: C, 87.7; H, 7.1. Found: C, 87.6; H, 7.2.

20-Isopropylcholanthrene.—Pyrolysis of 4.5 g. of the ketone at 410–415° for thirty minutes gave after distillation 3 g. of a yellow oil. The ether solution of this oil soon deposited 1 g. (24%) of a yellow solid melting at 165–173°. By three crystallizations from benzene and one from propyl alcohol, 0.109 g. of very pure 20-isopropylcholanthrene resulted. The melting point, 188–189° (corr.), was unchanged during the last two crystallizations.

Anal. Calcd. for $C_{23}H_{20}$: C, 93.2; H, 6.8. Found: C, 92.9; H, 6.8.

Formation of α -Naphthoic Anhydride.—A Grignard reagent was prepared from 10 g. of 4-bromo-7-isopropylhydrindene, 60 cc. of ether and 2 g. of magnesium. The cooled Grignard solution was added slowly with stirring to a solution of 15 g. of pure α -naphthoyl chloride (m. p. 20–21°) in 200 cc. of absolute ether at –5°. The solution was warmed to boiling and was refluxed for four hours. An equal volume of saturated sodium bicarbonate solution

(15) Microanalyses by W. F. B.

was added with stirring to remove unchanged acid chloride. Upon removing the ether and cooling, a yellow granular solid was obtained. This material, collected on a filter, weighed 3 g. and melted at 145°. A mixed melting point with an authentic sample of α -naphthoic anhydride gave no depression. Upon distillation of the filtrate, 2 g. of isopropylhydrindene boiling at 88–90° at 1 mm. was obtained as a forerun.

Anal. Calcd. for $C_{12}H_{16}$: C, 90.0; H, 10.00. Found: C, 89.9; H, 10.47.

The main portion, containing the ketone, distilled from 225–235° at 1.2 mm.; yield, 7.3 g. (55.5%).

When a sample of α -naphthoic chloride in ether was stirred with sodium bicarbonate solution for two hours, evaporation of the ether left no residue, showing that the acid chloride contained no anhydride, and that no anhydride was formed by the reaction between the acid chloride and water ($2RCOCl + H_2O \rightarrow (RCO)_2O + 2HCl$).

Comparison of the Fluorescence of Methylcholanthrene, Ethylcholanthrene and Isopropylcholanthrene.—A solution of 0.05 mg. of each hydrocarbon in 40 cc. of thiophene-free benzene was placed in the container of a fluorometer to be described elsewhere.¹⁶ The incident light was passed through a Corning 585 filter to remove nearly all the visible light, and the strong blue fluorescent light which resulted was passed at right angles to the incident light through a Corning 038 filter to remove any yellow light. The solutions were compared with a standard block of uranium glass. The intensity of the transmitted fluorescent light was measured by a galvanometer attached to a sensitive copper oxide photoelectric cell. The results are shown in Table I.

TABLE I
FLUORESCENCE OF THREE CHOLANTHRENES

Substance	Galvanometer reading	Relative ^a fluorescence
Water	0.5	0.05
Benzene	.8	.08
Uranium glass	8.4	.86
20-Methylcholanthrene	10.6 (9.8 corr.)	1.00
20-Ethylcholanthrene	9.3 (8.5 corr.)	0.88
20-Isopropylcholanthrene	8.8 (8.0 corr.)	.83

^a A blank of 0.8 was subtracted from the reading of each benzene solution.

Description of the Crystal Form of Three Cholanthrenes.—Since knowledge of the crystal constants of these substances may on occasion be valuable for identifying small amounts of these materials, aside from the intrinsic interest of such data in this series, a detailed study made by Professor C. W. Mason is reported here.¹⁷

20-Methylcholanthrene is capable of crystallizing in two forms. The phase stable at room temperature, obtained by slow cooling, appears as needles, described as follows: oblique-ended

(16) Private communication from D. B. Hand.

(17) Cf. Chamot and Mason, "Handbook of Chemical Microscopy," John Wiley and Sons, Inc., New York, 1938, pp. 261 ff.

prisms and lath-shaped forms, and rhomboidal plates. No views show parallel extinction; the maximum extinction angle is about 20°. The acute angle of the rhomb-shaped plates is 60°, and the vibrations 20° to the acute diagonal have the lower refractive index, about 1.51. The other refractive index, for this view, is very high.

Some of the prisms give good optic axis interference figures, biaxial, +, $r > v$ marked, $2V$ large (75° or more), β about 1.63. Birefringence is dispersed, with anomalous polarization colors. The prisms are 6-sided or more in cross section, and their comparable side views are not easily obtained, but the refractive index for vibrations lengthwise is about 1.65, and for vibrations crosswise very much higher, probably 1.75 or more. Aqueous liquids are necessary for refractive index determinations.

On the basis of symmetry and optical properties, this modification is probably triclinic. There is no reason for considering the plates and prisms as being other than variations of habit, depending on conditions of growth.

The phase which is stable at high temperatures is obtained by rapid cooling of the solutions, particularly from *n*-propyl alcohol. It appears as rhomb-shaped plates, the acute angle being 68°. There is symmetrical extinction, with higher refractive index for vibrations parallel to the acute diagonal of the rhombs. The plates yield a biaxial acute bisectrix interference figure, with Bx_a inclined in the plane of the acute diagonal (plane of symmetry) and the axial plane crosswise of this plane. Birefringence is +, much weaker than the triclinic form, $r < v$ marked, $2V$ about 60°.

The refractive index, for vibrations parallel to the acute diagonal (approximately β) is about 1.640; for vibrations parallel to the obtuse diagonal (approximately α) is about 1.7. Edge views of the plates were not obtained. The crystals are monoclinic.

The triclinic (I) and monoclinic (II) crystals described above are enantiotropic modifications, with a transition temperature of about 140°, observed microscopically by means of a hot stage. The transformation of II to I is very sluggish at lower temperatures, especially in the absence of a solvent. II are frequently observed in the midst of I after rapid crystallization from a solvent on a microscope slide. The transformation of I to II takes place readily on heating. When both phases are close together in the presence of a sol-

vent, the growth of I and the solution of II at room temperature is evident. Needles of I bore through plates of II in growing.

20-Ethylcholanthrene appears in the form of thin rhomb-shaped plates, with the acute angle 70° . The extinction is symmetrical or nearly so. The plates yield a biaxial interference figure, $+$, $r < v$ marked, $2V$ about 40° . Bx_a is inclined to the normal to the plate in the plane of the obtuse diagonal, which is the axial plane. Edge views, obtained with difficulty, show oblique extinction. The crystals are probably monoclinic. The refractive index for vibrations parallel to the acute diagonal (approximately β) is 1.660; for vibrations parallel to the obtuse diagonal (approximately α) 1.640. No evidence of polymorphism was obtained, either on heating or on crystallization from the melt or from solution.

20-Isopropylcholanthrene appears as thin lath-shaped crystals, rectangular in habit, which exhibit parallel extinction flatwise and edgewise. Viewed normal to the principal face, the crystals

yield centered biaxial interference figures, $+$, $2V$ about 40° , with the axial plane crosswise of the crystals, and weak birefringence. Viewed edgewise, the birefringence is stronger. For light vibrating crosswise of the crystals, and travelling normal to their principal face, the refractive index α is about 1.67; for vibrations lengthwise β is 1.69; γ , exhibited by edge views, is higher, estimated at 1.72. No evidence of polymorphism was obtained. The crystals are probably orthorhombic.

Summary

The preparation of 20-isopropylcholanthrene by the method of Fieser and Seligman is described. The formation of α -naphthoic anhydride by the addition of water to an organometallic complex system encountered in this preparation is described. The fluorescence and crystal form of the methyl, ethyl and isopropyl members of this series are recorded.

Ithaca, N. Y.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

The Synthesis and Germicidal Properties of Some Alkylfluorophenols

BY C. M. SUTER, ELMER J. LAWSON AND PERRIN G. SMITH

While the synthesis and bactericidal properties of chloro- and bromoalkylphenols have been investigated extensively,¹ little is known about the corresponding fluorine or iodine derivatives. Because of the marked difference in physiological properties between aliphatic fluorine compounds and those containing other halogens² it is of interest to obtain similar information in the aromatic series. The present study deals with the preparation and properties of a series of 2-*n*-alkyl-4-fluorophenols.

Two methods of synthesis were investigated, both starting with *p*-fluorophenetole obtained from *p*-phenetidine by a modification of the method employed by Schiemann and Kühne.^{3,4} In the first method, *p*-fluorophenol obtained by deethylation of *p*-fluorophenetole with aluminum chloride in benzene was utilized in obtaining esters of the normal fatty acids. The esters were

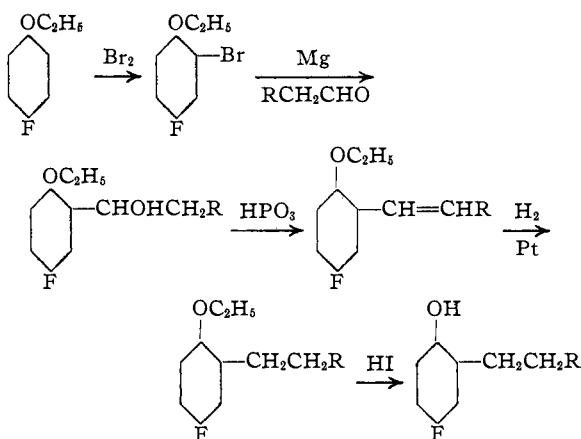
(1) Klarman, Shternov and Gates, *THIS JOURNAL*, **55**, 2576 (1933); Klarman, Gates, Shternov and Cox, *ibid.*, **55**, 4657 (1933).

(2) Henne, *ibid.*, **59**, 1201, 1400 (1937).

(3) Schiemann and Kühne, *Z. physik. Chem.*, **156A**, 414 (1931).

(4) Schiemann, *et al.*, *J. prakt. Chem.*, **143**, 18 (1935).

converted into hydroxy ketones by the Fries reaction and the latter were reduced with zinc amalgam. Since the yields were poor, particularly for the higher members of the series, a more satisfactory synthesis was sought; the steps involved in the method finally adopted are shown by the accompanying equations.



Bromination of *p*-fluorophenetole gave a crys-