

THE SYNTHESIS OF ORGANIC MEDICINALS CONTAINING FLUORINE



by

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TABLE OF CONTENTS

	PAGE
INTRODUCTION.....	1
I. Development of Chemotherapy.....	1
II. Drug Antagonism and Isosterism.....	6
III. Scope of the Present Project.....	10
EXPERIMENTAL.....	12
Ia. Attempted synthesis of 3,4-difluorophenyl- arsonic acid. Method I.....	12
p-Fluoronitrobenzene.....	13
p-Fluoroaniline.....	14
3-Nitro-4-fluoroaniline.....	14
3-Nitro-4-fluoroacetanilide.....	16
3-Amino-4-fluoroacetanilide.....	16
2-Fluoro-5-acetamidobenzene diazonium fluoborate.....	17
Attempted preparation of 3,4-difluoroacet- anilide.....	18
Ib. Synthesis of 3,4-difluorophenylarsonic acid. Method II. An attempted alternate route to 3,4-difluoro aniline.....	21
2-Amino-4-nitrofluorobenzene.....	22
2-Fluoro-5-nitrobenzene diazonium fluoborate.	24
Attempted preparation of 3,4-difluoronitro- benzene by decomposition of 2-fluoro- 5-nitrobenzene diazonium fluoborate.....	24
Ic. Successful synthesis of 3,4-difluorophenyl- arsonic acid. Method III.....	26
2-Methylcarboxybenzene diazonium fluoborate..	27
2-Fluoromethyl benzoate.....	28

	PAGE
2-Fluorobenzamide.....	28
2-Fluoroaniline.....	29
2-Fluorobenzene diazonium fluoborate.....	30
<u>o</u> -Difluorobenzene.....	31
3,4-Difluoronitrobenzene from <u>o</u> -difluoro- benzene.....	32
3,4-Difluoroaniline.....	33
3,4-Difluorophenylarsonic acid.....	34
Id. Synthesis of 3,4-difluorophenylarsonic acid.	
Method IV. An alternate route to <u>o</u> - fluoroaniline.....	36
2-Nitrobenzene diazonium fluoborate.....	37
2-Fluoronitrobenzene.....	37
2-Fluoroaniline from 2-fluoronitrobenzene...	38
IIa. Synthesis of 5-fluoro-7-diethylaminomethyl-8- hydroxyquinoline and 5-fluoro-7-iodo-8- hydroxyquinoline. Method I.....	
5-Nitroso-8-hydroxyquinoline.....	41
5-Amino-8-hydroxyquinoline.....	42
8-Hydroxyquinolyl-5 diazonium fluoborate hydrofluoborate.....	43
5-Fluoro-8-hydroxyquinoline.....	44
5-Fluoro-7-diethylaminomethyl-8-hydroxy- quinoline.....	45
5-Fluoro-7-iodo-8-hydroxyquinoline.....	46
IIb. Synthesis of 5-fluoro-7-diethylaminomethyl- 8-hydroxyquinoline. Method II. An alter- nate route to 5-fluoro-8-hydroxyquinoline	
4-Methoxybenzene diazonium fluoborate.....	49
<u>p</u> -Fluoroanisole.....	50

	PAGE
2-Nitro-4-fluoroanisole.....	50
2-Amino-4-fluoroanisole.....	53
5-Fluoro-8-methoxyquinoline.....	55
5-Fluoro-8-hydroxyquinoline from 5-fluoro-8-methoxyquinoline.....	59
IIc. Synthesis of 5-fluoro-7-diethylaminomethyl-8-hydroxyquinoline. Method III. Attempted alternate route to 5-fluoro-8-methoxyquinoline.....	
	61
8-Methoxyquinoline.....	62
5-Nitro-8-methoxyquinoline.....	63
Attempted preparation of 5-amino-8-methoxyquinoline.....	64
IIIa. Synthesis of 2-trifluoromethyl-1,4-naphthoquinone, an analog of Menadione (2-methyl-1,4-naphthoquinone). Method I.....	
	66
3-Nitrobenzotrifluoride.....	67
3-Aminobenzotrifluoride.....	67
3-Acetamidobenzotrifluoride.....	69
2-Nitro-5-acetamidobenzotrifluoride.....	69
2,5-Diacetamidobenzotrifluoride.....	72
2,5-Diaminobenzotrifluoride hydrosulfate....	73
Trifluoromethylbenzoquinone.....	74
2-Trifluoromethyl-5,8,9,10-tetrahydro-1,4-naphthoquinone.....	75
2-Trifluoromethyl-5,8,9,10-tetrahydro-1,4-naphthohydroquinone.....	76
2-Trifluoromethyl-1,4-naphthoquinone.....	77
IIIb. Synthesis of 2-trifluoromethyl-1,4-naphthoquinone. Method II. An alternate route to trifluoromethylbenzoquinone.....	
	78

	PAGE
Method III. An attempted route to tri- fluoromethyl benzoquinone.....	78
2,5-Diaminobenzotrifluoride hydrochloride...	79
2,5-Diaminobenzotrifluoride.....	80
2,5-Diaminobenzotrifluoride hydrosulfate....	80
Trifluoromethylbenzoquinone.....	81
3-Hydroxybenzotrifluoride.....	82
Attempted preparation of 2-nitroso-5-hydroxy- benzotrifluoride.....	83
DISCUSSION OF EXPERIMENTAL RESULTS.....	84
I. SYNTHESIS OF 3,4-DIFLUOROPHENYLARSONIC ACID...	84
Method I.....	84
Method II.....	85
Method III.....	86
Method IV.....	87
II. SYNTHESIS OF 5-FLUORO-7-DIETHYLAMINOMETHYL-8- HYDROXYQUINOLINE AND 5-FLUORO-7-IODO-8- HYDROXYQUINOLINE.....	88
Method I.....	88
Method II.....	89
Method III.....	91
III. SYNTHESIS OF 2-TRIFLUOROMETHYL-1,4-NAPHTHO- QUINONE.....	92
Method I.....	92
Method II.....	95
Method III.....	96
PHARMACOLOGICAL TESTING.....	97
SUMMARY.....	98
BIBLIOGRAPHY.....	100

INTRODUCTION

I. DEVELOPMENT OF CHEMOTHERAPY.

Chemotherapy is defined as the treatment of diseases by administering chemicals which affect the causative organism unfavorably but do not injure the patient. The science of chemotherapy is relatively new and, although it is now an exceedingly widespread and valuable method of combating systemic infections, nevertheless, it is only since the turn of the century that appreciable progress has been made in this field.

The earliest of the chemotherapeutic agents were, as might be expected, naturally-occurring products. The use of Cinchona bark for the treatment of malaria was introduced into Europe in 1638 and quinine, its principal alkaloid, was isolated by Pelletier in 1820. Ipecac was introduced into Europe in 1658 from Brazil where the natives used a decoction of the root in the treatment of diarrheas. Emetine, the most active of the ipecac alkaloids, was first described by Pelletier in 1817. The more recent use of ipecac dates from the 1840's when it was employed in India as an efficient symptomatic treatment for certain types of dysentery. Rogers (1), in 1912, demonstrated that emetine was a valuable drug in the therapy of amebiasis.

Paul Ehrlich, often referred to as the "father of chemotherapy," made spectacular advances in this field and devoted the major portion of his scientific career to the principle

that a molecule can be constructed which will act as a specific agent against a parasite without undue injury toward the host. His early leads with Methylene Blue and Trypan Red were followed by investigations of comparable substances containing arsenic which resulted in the synthesis of the spirocheticide arsphenamine in 1912 (2). Although this drug is not entirely specific for the pathogenic organism, Ehrlich's discovery represented a tremendous triumph in the field of chemotherapy, particularly so since it was the result of planned research.

The successes attendant upon the brilliant achievements of Ehrlich were followed by a period of widespread investigation of the arsenicals and other heavy metals. Hundreds of new compounds were prepared and tested many of which have proved of great value in the treatment of previously incurable infectious diseases. Treponemiasis, amebiasis and trypanosomiasis yielded to organic arsenicals, leishmaniasis to compounds of antimony.

Until 1920, synthetic chemotherapy was chiefly interested in organo-metallic trypanocidal or spirocheticidal drugs. The introduction, in that year, of Germanin, a strictly organic compound, marked an important departure from this field. This drug has proved to be an extraordinarily useful trypanocidal agent having a very high therapeutic index (300 in mice) and a prolonged period of action. A single dose may confer immunity to sleeping sickness for several months (3).

The selective action of dyes on various tissues, an early phase of Ehrlich's work, formed the basis for an extensive investigation of similar compounds in an effort to produce drugs which would attack the common pathogenic microorganisms such as staphylococcal, streptococcal and pneumococcal bacteria. In 1934, Domagk (4) announced the remarkable effectiveness of Prontosil in curing streptococcal and staphylococcal infections in test animals. Soon after this epoch-making discovery, investigators found that Prontosil breaks down in the tissues to p-aminobenzenesulfonamide (now commonly called sulfanilamide), a compound as effective as Prontosil in curing infections. Within a few years, more than one thousand sulfa compounds had been synthesized, although only a few have shown outstanding promise in chemotherapy. Thus, to the list of pathogenic microorganisms vulnerable to chemical agents were added the streptococcus, meningococcus, pneumococcus, gonococcus, gas bacillus, and others.

Other successful investigations originating from the work of Ehrlich were in the antimalarial field. The synthesis of a large number of compounds related to Methylene Blue was undertaken by German chemists who, in 1924, produced Plasmoquine (5), and, in 1933, Atebrine (6). Plasmoquine was found to possess curative properties against both benign and malignant tertiary malaria although it has proved too toxic for general clinical use. Atebrine, a drug of low toxicity, is a very effective prophylactic

against benign and malignant tertiary malaras, and a cure for the malignant tertiary form.

Further progress in the fight against the malaria parasite was achieved by the monumental effort put forth in the recent wartime program of the Office of Scientific Research and Development during the course of which some 14,000 compounds were tested. Of these, the most outstanding are structurally related to either Atebrine or Plasmoquine and have been assigned the following names (7): Chloroquine, Oxychloroquine, Santochin, Camoquine and Pentaquine. All of these compounds have shown activity surpassing that of Atebrine as suppressive drugs while Pentaquine has also been shown to have curative action exceeding that of Plasmoquine.

Paludrine (8), a biguanide compound, the result of a search by British investigators for antimalarial drugs among pyrimidine derivatives, has proven to be a potent and non-toxic antimalarial drug. It is active against all three forms of malaria and possesses the property, absent from other antimalarials, of preventing the development of parasites in the pre-erythrocytic stage.

Lately, the development of a new type of chemotherapeutic agent, the "Antibiotics," has become increasingly important. These are soluble antibacterial substances produced by micro-organisms during growth on suitable media.

Inhibition of growth of one bacterial species by the presence of another had been observed since the beginning of bacteriology. Emmerich and Low (9), in 1899, prepared

an extract of a certain species which was found to have a destructive effect against pathogenic cocci but it was too toxic for clinical use.

In 1929, Fleming (10) discovered that the broth on which a mold known as *Penicillium* was growing had bactericidal properties. The name Penicillin was given to active filtrates of the broth and the active compound itself was isolated in 1940 (11). This antibiotic has remarkable antibacterial activity. It is bacteriostatic against almost all Gram-positive organisms, but completely non-toxic. The constitution of the drug has been elucidated and its synthesis accomplished (12) but yields are too low for commercial production. Today, it has attained widespread use against a variety of infections.

Since the wonderful success of Penicillin, a drug which approximates the ideal chemotherapeutic agent, several other antibiotics have been discovered and clinically tested. Streptomycin, discovered by Waksman (13) in 1943, is active against Gram-negative organisms. The structure of streptomycin has not been elucidated as yet. Chloromycetin, an antibiotic effective against Rocky Mountain spotted fever, rickettsia, typhus and typhoid fever, was discovered by Burkholder (14) in 1947. Its structure and synthesis are known (15) and the drug is commercially available. Yet another antibiotic of considerable importance is Aureomycin (16). This compound has been found effective against

Lymphogranuloma Venereum, Rickettsia and certain viruses. However, so far, very little information is available concerning its chemical structure.

From this brief discussion of the subject, it is readily apparent that the science of chemotherapy has had a relatively short but remarkably fruitful past and it is safe to predict an even more brilliant and productive future during which the goal of Ehrlich, the synthesis of a specific molecule to combat every infectious disease, will be largely realized.

II. DRUG ANTAGONISM AND ISOSTERISM.

In the present work, the most important theoretical guides for the selection of a method of attack on the problem of synthesizing drugs of a high degree of therapeutic activity have been the principles of drug antagonism and isosterism.

The theory of drug antagonism (17) has been a recent avenue of advance for the science of chemotherapy and deserves some comment. It is frequently observed that the addition of a second drug to a system already containing an active drug causes reversal of the action of the first drug. This is known as drug antagonism. It may be direct, in that the antagonist combines chemically with the drug to form a physiologically inactive complex, or indirect, in that no chemical interaction between drug and antagonist is possible, but each is capable of displacing the other from its biolog-

ical point of action.

All essential metabolites, whether they function as co-enzymes, prosthetic groups, activators or building blocks, are usable by cells by reason of the fact that some protein structure in the cell is specifically designed to "fit" their particular electronic configuration. Any substance made available to the living cell, which penetrates the cell wall and is closely similar in electronic configuration to an essential metabolite, will be liable to be caught up in the metabolic wheel at the point specifically designed to accommodate the related metabolite. If the analog "fits" but cannot undergo conversion to a functional form, then it may act as a growth inhibitor.

This is the present theory of the action of the sulfa drugs. The essential metabolite which they displace is p-aminobenzoic acid. The discovery of this mechanism of action of the sulfa drugs is chiefly responsible for the present theory of drug antagonism.

This theory has led to a flurry of activity on the part of pharmaceutical chemists to construct molecules of similar configuration to that of known essential metabolites in order to test their properties as antagonists. Some of the antagonists or "anti-vitamins" which have been developed include pyridine-3-sulfonic acid as an antagonist of nicotinic acid (18), phenylpantothenone as an antagonist of pantothenic acid (19) and pyrithiamin as an antagonist of thiamin (20).

The concept of isosterism was originally defined by Langmuir (21) in 1919. He proposed that molecules or groups which have the same numbers of atoms and the same total number of electrons arranged in the same manner are "isosteric," and, further, he called attention to the fact that when isosteres are also isoelectric (possess the same total charge), then they have strikingly similar properties. Classic examples of pairs of isosteres are carbon monoxide-nitrogen and carbon dioxide-nitrous oxide.

Grimm (22) broadened the concept to include molecules or groups possessing the same number of valence electrons, whether or not the same number of atoms were involved. According to this definition, groups of the following types are isosteric: fluoride, hydroxyl, amino, and methyl; oxide, methylene, and imide; acetylide and cyanide.

Erlenmeyer, investigating applications of Grimm's interpretation, pointed out (23) that certain dyes differing in structure only by the substitution of a methylene group for its isostere, an oxide group, exhibited almost identical absorption spectra. He also extended the concept of isosterism by proposing (24) that the aromatic $-\text{CH}=\text{CH}-$ group and the ring sulfur atom are isosteric, since only the outer electrons of the group can be considered significant in determining isosterism. As evidence he pointed out that benzene and thiophene possess very similar physical properties and, in a striking investigation (24), he showed that, even in the exceedingly specific antigen-antibody

reactions, certain corresponding derivatives of benzene and thiophene proved to be indistinguishable.

Since, in the final analysis, the practical use of the concept of isosterism requires a similarity of chemical and physical properties between corresponding compounds containing isosteric groups, the suggestion of Erlenmeyer that only outer electrons should be considered is too sweeping to accept without taking account of other factors. Benzene, thiophene and furane should be isosteric according to the unrestricted definition, but furan exhibits properties quite dissimilar to the other two. The same considerations apply to thiazole and oxazole in their relation to pyridine.

Hence, for practical applications of the concept in predicting the properties of isosteres, it is clear that one must be mindful of such influences as resonance and opportunities for hydrogen bonding. It is also noteworthy that only in cases where the groups involved differ but slightly in weight are similar properties observed (25).

As applied to certain specific groups whose similar effects have been well established, however, the concept of isosterism is playing an important role in suggesting the possibilities of new physiologically active agents which differ from compounds of tested value only in the substitution of one such isosteric group for another.

A classic illustration of this approach is that of sulfapyridine, sulfadiazine, and sulfathiazole (26). The replacement of the benzene by the thiophene ring in cocaine

produced a compound closely resembling cocaine in its physiological effect (27). Another interesting example is that of the alkylamine esters of p-fluorobenzoic acid which have anesthetic properties similar to those of the corresponding derivative of p-hydroxybenzoic acid (28).

III. SCOPE OF THE PRESENT PROJECT

As pointed out in the discussion of the concept of isosterism, fluoride is isosteric with hydroxyl, amino, and methyl. Hence, as a rationale for the present undertaking, it was postulated that replacement of an amino or hydroxyl group on a drug of proven activity should result in a compound whose physiological properties should be similar to the parent compound but, it was hoped, intensified or enhanced without excessively increasing the toxicity. Furthermore, since the size of the fluorine atom is comparable to that of the hydrogen atom, it is conceivable that replacement of one or more of the hydrogen atoms of a compound known to be an essential metabolite, vitamin, or vitamin substitute by a fluorine atom, would produce a reversal of the activity characteristic of the parent compound, or, in other words, an antagonist of the parent compound.

With these two principles in mind, the synthesis of the following compounds was undertaken:

a. 3,4-Difluorophenylarsonic acid.--This compound is an analog of atoxyl (4-aminophenylarsonic acid), an arsenical of recognized spirocheticidal activity.

b. 5-Fluoro-7-diethylaminomethyl-8-hydroxyquinoline.--

The high antimalarial activity of a type of compound developed by Burckhalter, et al., (29)(30), (2-diethylaminomethyl-4-aminophenol and derivatives) suggested the synthesis of a similar compound substituting a quinoline nucleus for the benzene ring and a fluorine atom for the amino group.

c. 5-Fluoro-7-iodo-8-hydroxyquinoline.--The similarity

of structure of the compound synthesized under (b.) to the amebicidal agent Vioform (5-chloro-7-iodo-8-hydroxyquinoline) suggested the synthesis and testing of this compound as an amebicide. A further reason for choosing this compound lies in the fact that its activity can be compared with that of a series of halogenated 8-hydroxyquinolines recently prepared by Edgerton (31).

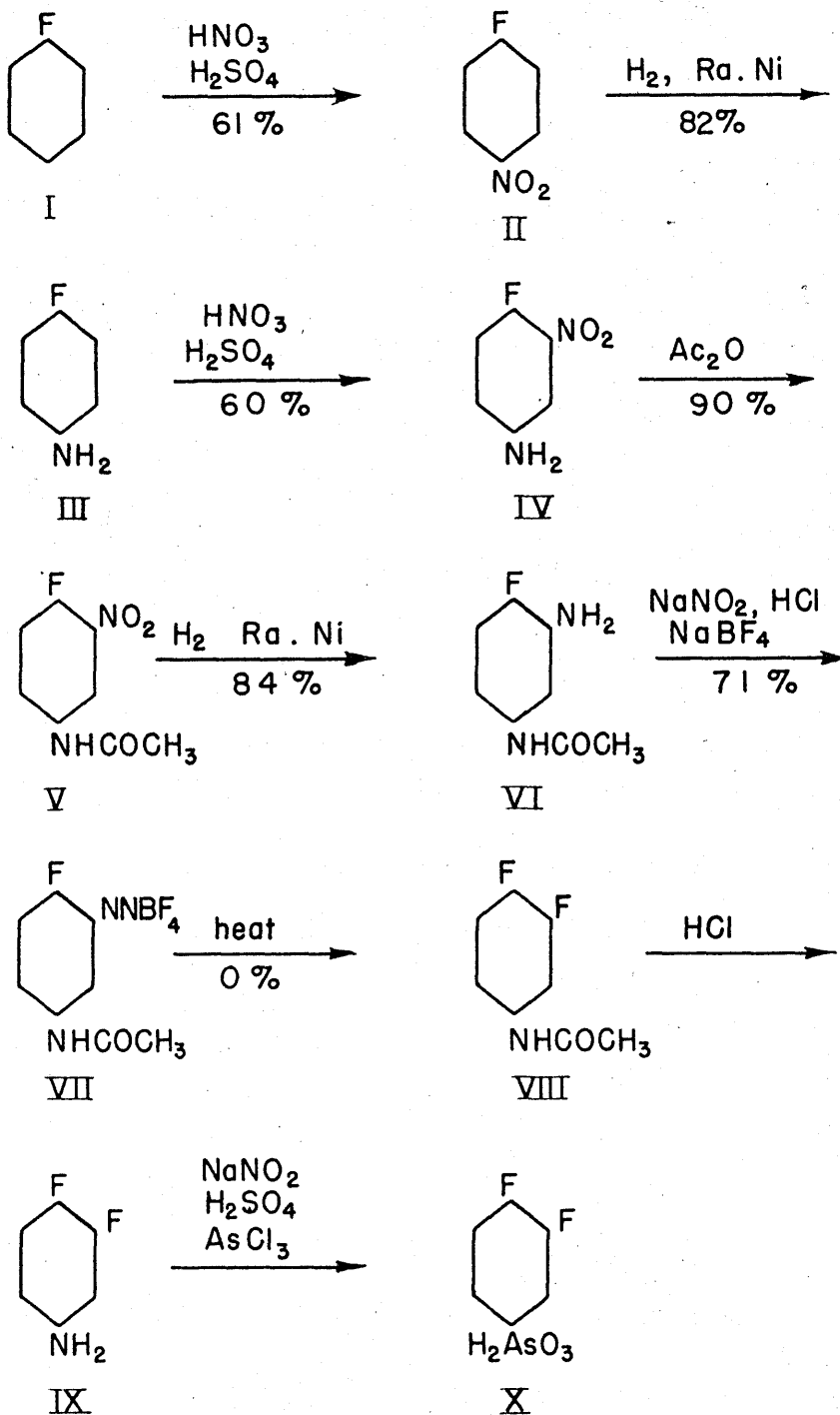
d. 2-Trifluoromethyl-1,4-naphthoquinone.--The substitu-

tion of fluorine atoms for hydrogen in the methyl group of Menadione (2-methyl-1,4-naphthoquinone), a vitamin K substitute, could conceivably result in a vitamin K antagonist.

EXPERIMENTAL

I. a. Attempted synthesis of 3,4-difluorophenylarsonic acid.

Method I.



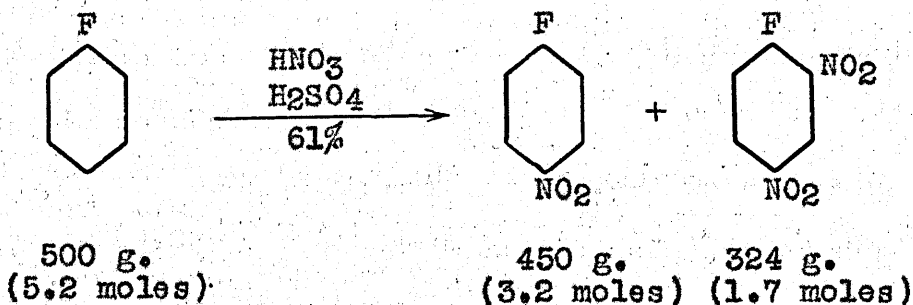
p-Fluoronitrobenzene (II).--This compound was prepared by the method of Bradlow and VanderWerf (32) as follows:

A 3 l. beaker equipped with a stirrer, thermometer, and dropping funnel was set in an ice-salt bath and charged with 1350 ml. of a 2:1 mixture (by volume) of concentrated sulfuric acid and nitric acid (density 1.5). Additional cooling was provided by intermittent addition of powdered Dry Ice. A 500 g. portion (5.22 moles) of fluorobenzene was added dropwise over the course of five hours while the temperature was kept at about -10° . The reaction mixture was poured over 4500 g. of ice.

The product was extracted with ether and the ether extract washed twice with water, once with sodium carbonate solution and again with water, dried over sodium sulfate.

The ether was removed and the residue was distilled under reduced pressure. A total of 450 g. of p-fluoronitrobenzene boiling at $78^{\circ 1}$ under 3 mm. pressure was obtained corresponding to a 61% yield.

The residue was further distilled to yield 324 g. (33%) of 2,4-dinitro-fluorobenzene boiling at 136° under 3 mm. pressure.

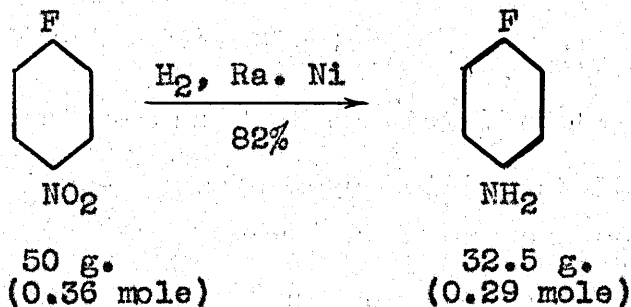


¹ All boiling points uncorrected, all melting points corrected.

p-Fluoroaniline (III).--The method of Bradlow and Vanderwerf (32) was used in preparing this compound.

A 50 g. (0.36 mole) portion of p-fluoronitrobenzene diluted with 50 ml. of redistilled absolute alcohol was placed in a hydrogenator and 0.5 g. of Raney nickel together with a drop of platinum chloride solution was added. The mixture was shaken with hydrogen under a pressure of 2-3 atmospheres while heat was applied by means of an infra-red lamp. Absorption of hydrogen started shortly and the theoretical amount was absorbed in four hours.

The solution was filtered through a sintered glass funnel to remove the catalyst and the solvent distilled, the last traces being removed under the reduced pressure provided by a water pump. Distillation of the residue under reduced pressure gave 32.5 g. (82%) of p-fluoroaniline boiling at 69° under 6 mm. pressure.



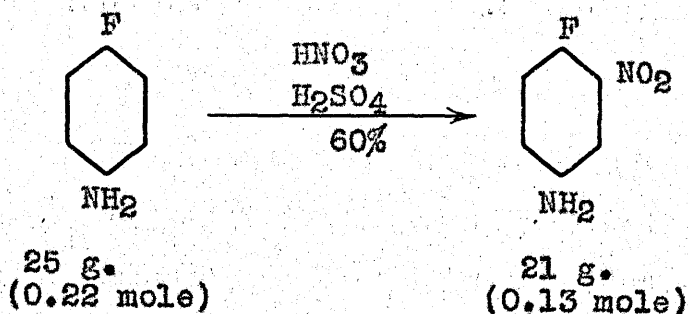
3-Nitro-4-fluoroaniline (IV).--The procedure of Bradlow and Vanderwerf (32) for nitrating p-fluoroaniline was employed.

A 600 ml. beaker equipped with a stirrer, thermometer, and addition funnel was charged with 118 ml. of concentrated

sulfuric acid and set in an ice-salt bath. A 25 g. (0.22 mole) portion of p-fluoroaniline was added cautiously in small portions. A mixture of 9.4 ml. (0.21 mole) of nitric acid (density 1.5) and 50 ml. of concentrated sulfuric acid was added slowly while the temperature was maintained at about -5° by the addition of Dry Ice powder. Addition required forty minutes and stirring was continued for another $1\frac{1}{2}$ hours.

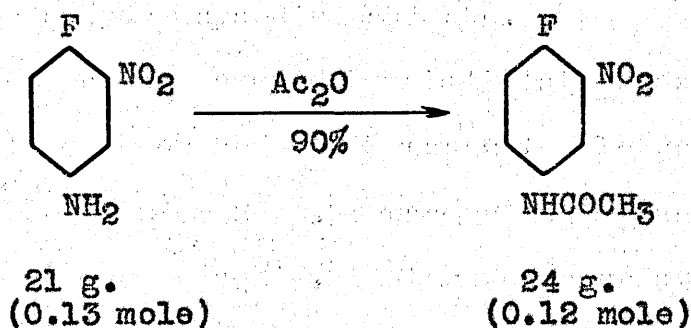
The reaction mixture was poured over 1 kg. of ice and neutralized with dilute ammonium hydroxide while the temperature was held below 30° by further addition of ice. The dark orange precipitate which formed was filtered off, washed with water, and taken up in ether. The filtrate was extracted with ether, the ether solutions were combined and dried over anhydrous sodium sulfate.

The ether was removed by distillation and the residue was distilled under reduced pressure. The crude product boiled at 150° under 2 mm. pressure and appeared in the receiver as an orange solid. After one recrystallization from a 1:1 ethanol-water solution, 21 g. (60%) of 3-nitro-4-fluoroaniline melting at $94.8-95.2^{\circ}$ was obtained.



3-Nitro-4-fluoroacetanilide (V).--A modification of the procedure described by Fieser (33) for the preparation of acetanilide was used.

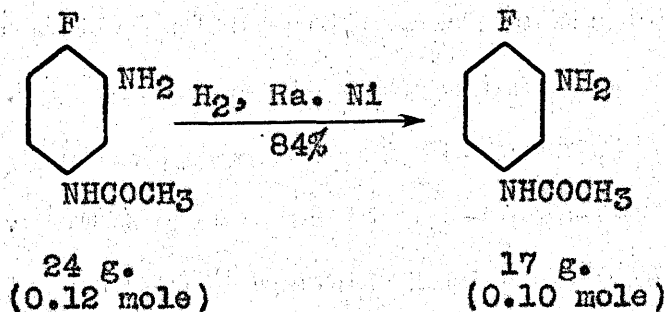
Exactly 21 g. (0.13 mole) of 3-nitro-4-fluoroaniline was added to 50 ml. of benzene in a 250 ml. Erlenmeyer flask and to this was added in 1 ml. portions 15 g. (0.15 mole) of acetic anhydride. The mixture became quite warm and a lemon-yellow solid appeared as a thick paste, replacing the orange starting material. The solvent was removed by heating on a steam bath and the yellow solid residue was recrystallized from 100 ml. of 3:1 ethanol-water solution. After a single washing with water and an overnight drying in a vacuum desiccator, 24 g. (90%) of crystalline 3-nitro-4-fluoroacetanilide melting at 139.0-139.6° was obtained.



3-Amino-4-fluoroacetanilide (VI).--A hydrogenation bottle was charged with 24 g. (0.12 mole) of 3-nitro-4-fluoroacetanilide, 125 ml. of absolute alcohol, 0.2 g. of Raney nickel, and a drop of platinum chloride solution. The mixture was shaken with hydrogen under a pressure of about 3 atmospheres. Absorption of hydrogen started shortly and

continued smoothly until the theoretical amount had been taken up.

The solution was filtered hot to remove the catalyst and the filtrate was cooled, causing a quantity of white crystals to separate. After concentration of the mother liquor to about 1/4 its volume and cooling, a second crop of crystals was obtained. These were dried under vacuum to give 17 g. (84%) of pure 3-amino-4-fluoroacetanilide, m.p. 154.9-157.1°.



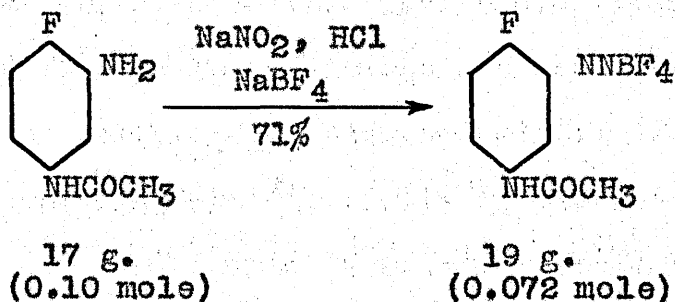
2-Fluoro-5-acetamidobenzene diazonium fluoborate (VII).---

The Schiemann reaction (34) for the preparation of diazonium fluoborates was used.

A 250 ml. beaker equipped with a stirrer and thermometer was set in an ice-salt bath and charged with 17 g. (0.10 mole) of 3-amino-4-fluoroacetanilide and 21 ml. (0.24 mole) of concentrated hydrochloric acid diluted with 30 ml. of water. The mixture was cooled to 0° and diazotized by the gradual addition over a period of forty-five minutes of 7.0 g. (0.10 mole) of sodium nitrite in the form of moist balls. At the conclusion of the diazotization, a cold solution of 22 g.

(0.20 mole) of sodium fluoborate in 20 ml. of water was added all at once causing an orange precipitate to form. After stirring for another thirty minutes, the precipitate was filtered off, washed with 30 ml. of cold water, then with 50 ml. of cold alcohol, and finally with 50 ml. of cold ether.

Dried in air, the 2-fluoro-5-acetamidobenzene diazonium fluoborate weighed 19 g. (76% of the theoretical).



Attempted preparation of 3,4-difluoroacetanilide (VIII).--

Two methods were used in attempts to obtain this compound.

a. The Schiemann method (34) involving heating of the dry diazonium fluoborate salt was carried out as follows:

A 19 g. (0.07 mole) portion of 2-fluoro-5-acetamidobenzene diazonium fluoborate was placed in a 250 ml. flask equipped with a reflux condenser. The flask was cautiously heated at a spot next to the edge of the pile of material within. Decomposition started quickly and continued without further application of heat. A rapid evolution of thick white smoke accompanied the decomposition. After the initial reaction had subsided, the flask was heated with a flame

until no more fumes were evolved.

The reflux condenser was replaced with a distilling head and the reaction flask was heated strongly with a flame. About one ml. of a liquid boiling at 134-137° was obtained.

The residue, consisting of a black tar, was treated with ether, in which it was partially soluble, forming an orange solution which was decanted, dried over sodium sulfate and evaporated to dryness leaving a brown tar. The residue after the ether treatment was extracted with benzene and the benzene solution was evaporated to dryness leaving a reddish-brown tar.

The residue after the benzene treatment was refluxed with 6M hydrochloric acid for two hours, neutralized with sodium hydroxide and steam distilled. Only one phase appeared in the receiver.

No 3,4-difluoroacetanilide could be isolated from any of the materials obtained.

b. The modification described by Hartung (35) involving heating the diazonium fluoborate salt in an inert solvent was attempted as follows:

To a 400 ml. beaker containing 100 ml. of kerosene heated to 170° by means of a hot plate was added in small portions from a spatula 15 g. of 2-fluoro-5-acetamidobenzene diazonium fluoborate. Decomposition occurred as the material was added, a puff of white smoke accompanying the addi-

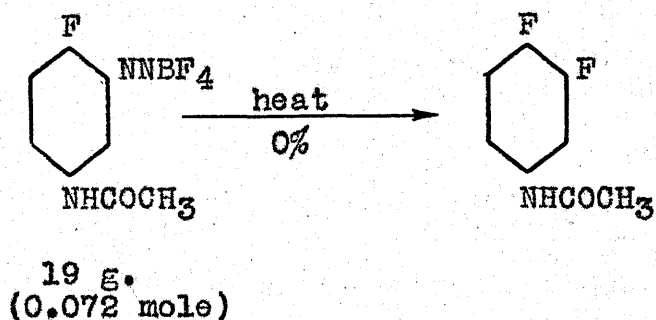
tion of each portion of the dry powder. A lump of dark red tar accumulated in the bottom of the beaker.

After the cooled solution had stood overnight, a few scattered crystals separated from the kerosene. These were removed and, after being dried in a vacuum desiccator, melted at 122.0-124.6°. There was not enough of this material to attempt an identification.

The tarry residue was transferred to a 500 ml. flask, 200 ml. of water was added and the mixture was steam distilled to remove the kerosene traces.

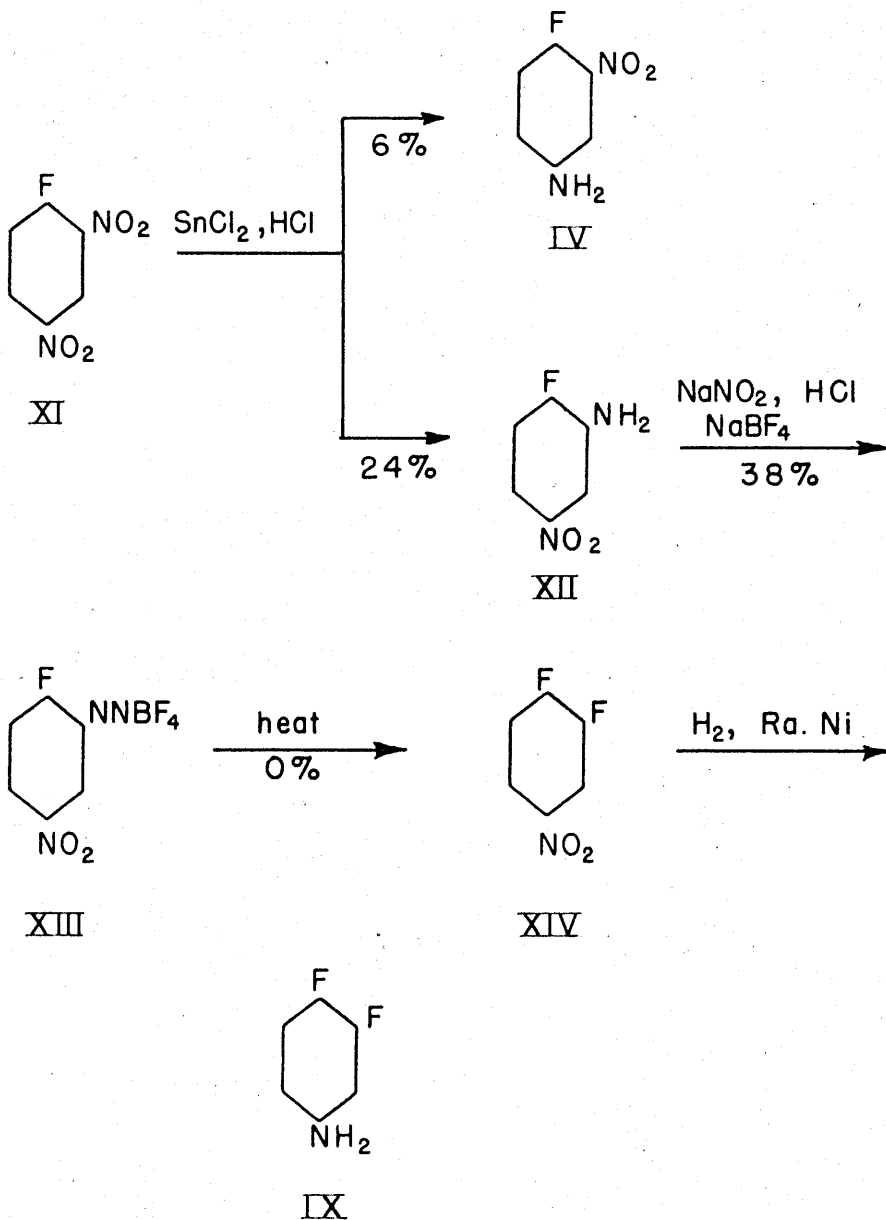
The residue was cooled, 100 ml. of concentrated hydrochloric acid was added and the mixture was refluxed for three hours. It was cooled, neutralized with 50% sodium hydroxide solution and steam distilled. The distillate was extracted with ether, the ether extract dried over sodium sulfate and evaporated. Only a smear of oily material remained from the evaporation.

No further products were obtained.



I. b. Synthesis of 3,4-difluorophenylarsonic acid.

Method II. An attempted alternate route to 3,4-difluoroaniline:



2-Amino-4-nitrofluorobenzene (XII).--This preparation was carried out by two methods:

a. By catalytic hydrogenation:

Exactly 22 g. (0.12 mole) of 2,4-dinitrofluorobenzene [obtained as a by-product from the preparation of p-fluoronitrobenzene (II)] was dissolved in 20 ml. of absolute alcohol and placed in a hydrogenation vessel. About 0.2 g. of Raney nickel and 1 drop of platinum chloride solution were added and the mixture was shaken with hydrogen under a pressure of 2-4 atmospheres while heat was applied by means of an infra-red lamp. Absorption of hydrogen started shortly and at the end of six hours, the calculated amount necessary to reduce one nitro group had been taken up.

The contents of the vessel were transferred to a 250 ml. flask and steam distilled. A small quantity of orange-red needles appeared in the distillate which, dried in air, weighed 0.02 g., m.p. 101.2-101.4°. (Recorded m.p. of 2-amino-4-nitrofluorobenzene: 102°) (36). The distillate was acidified with hydrochloric acid and evaporated to dryness to yield 0.8 g. of brownish-orange crystals, a yield of 4.3% calculated as 2-amino-4-nitrofluorobenzene hydrochloride.

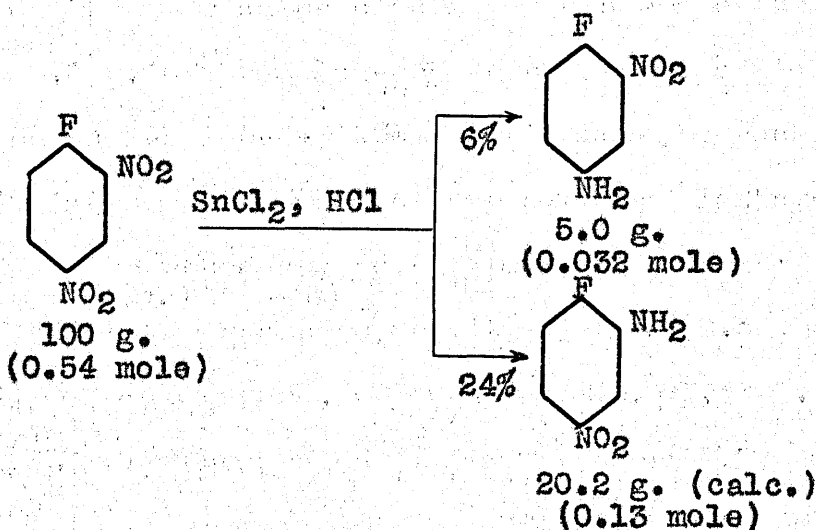
b. This compound has been prepared by Blanksma et al. (36) and their procedure was employed as follows:

A 4 l. beaker was charged with 100 g. (0.54 mole) of 2,4-dinitrofluorobenzene, 500 ml. of ethanol, 1 l. of water and 100 ml. of concentrated hydrochloric acid. The solution was heated to 65° and a mixture of 280 g. (1.48 moles) of

stannous chloride, 360 ml. of concentrated hydrochloric acid and 300 ml. of ethanol was added slowly over a forty-five minute period.

The cooled solution was made basic with sodium bicarbonate and steam distilled. Orange-red crystals of 2-amino-4-nitrofluorobenzene separated from the distillate which, after filtration and air-drying, melted at 100.5-101.1°. Weight of this material was 8.3 g. Evaporation of the forerun, which consisted mostly of alcohol, yielded an additional 2.5 g. Acidification of the remainder of the distillate with hydrochloric acid followed by evaporation yielded 11 g. of the hydrochloride. The total yield was 24% of the theoretical.

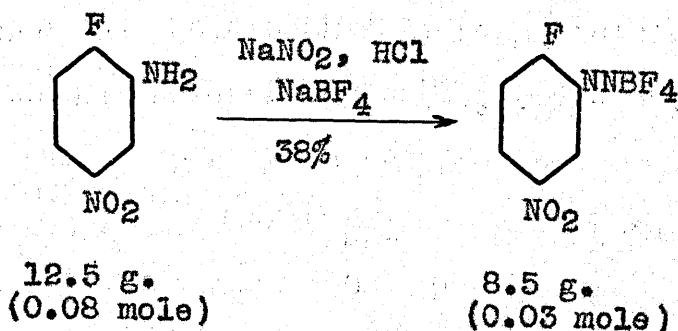
The residue from the steam distillation was extracted with ether, the ether extract was dried over anhydrous sodium sulfate and evaporated to dryness. The residue was recrystallized from an alcohol solution yielding 5.0 g. (6%) of 2-nitro-4-aminofluorobenzene, m.p. 72-79°.



2-Fluoro-5-nitrobenzene diazonium fluoborate (XIII).--

To a 250 ml. flask set in an ice-salt bath and equipped with a stirrer and thermometer was added 17 ml. (0.20 mole) of concentrated hydrochloric acid diluted with 30 ml. of water and 12.5 g. (0.08 mole) of 2-amino-4-nitrofluorobenzene. A creamy mixture resulted which was diazotized by addition of 5.5 g. (0.08 mole) of sodium nitrite in the form of moist balls while the temperature was kept below 5°.

It was stirred for about thirty minutes and a cold solution of 20 g. (0.18 mole) of sodium fluoborate in 20 ml. of water was added at once. The mixture was stirred for an hour in the cold and filtered. The bright yellow filter cake was washed with 50 ml. of ice water, then with 50 ml. of cold alcohol and finally with 50 ml. of cold ether. Dried in air, the 2-fluoro-5-nitrobenzene diazonium fluoborate weighed 8.5 g. (42% of the theoretical).



Attempted preparation of 3,4-difluoronitrobenzene (XIV)
by decomposition of 2-fluoro-5-nitrobenzene diazonium fluo-
borate (XIII).--This preparation was attempted by two methods:

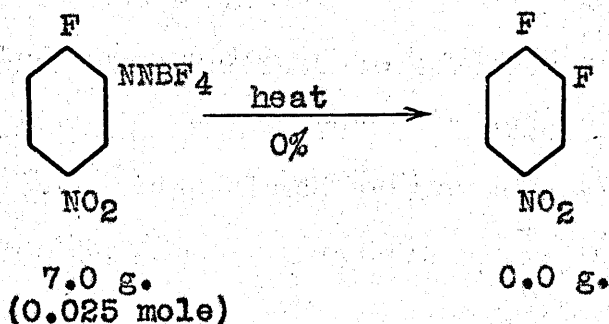
a. By heating the dry powder:

A mixture of 1 g. of 2-fluoro-5-nitrobenzene diazonium fluoborate and 5 g. of sand was placed in a 125 ml. flask connected to a reflux condenser. A small flame was applied to the flask and almost at once a violent explosion ensued, shattering the flask into small pieces. No further work was done on this method.

b. By heating in an inert liquid:

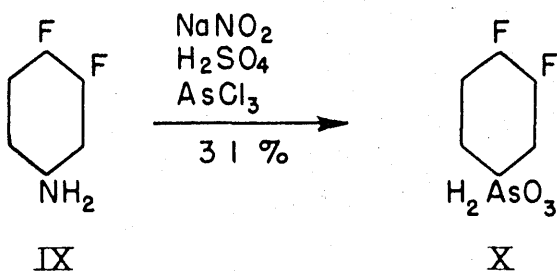
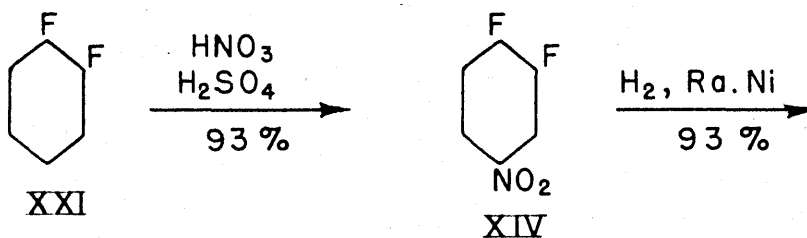
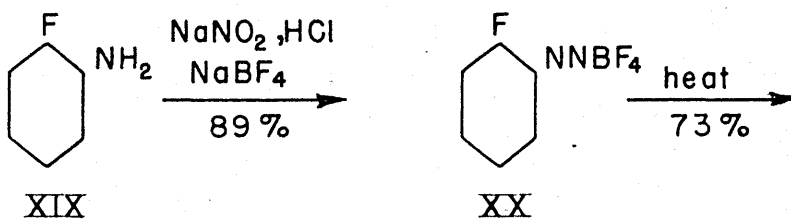
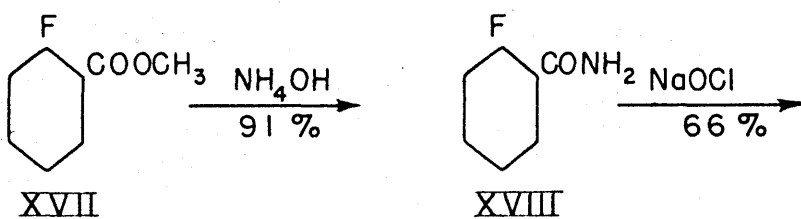
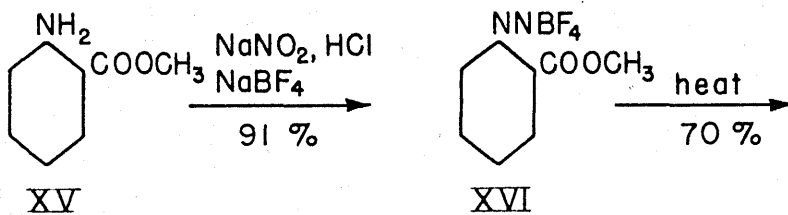
To 100 ml. of kerosene heated to 135° was added in small portions 7 g. (0.03 mole) of 2-fluoro-5-nitrobenzene diazonium fluoborate. The material decomposed as it was added forming gray, sooty smoke and leaving a black, cokey residue.

The mixture was steam distilled, the distillate was extracted with ether, and the ether extract was dried over anhydrous sodium sulfate. The ether was removed and the residue was run through a chromatographic adsorption column using alumina as the adsorbing medium. A dark orange color appeared in the upper part of the column. It was elutriated with acetone, the acetone was removed by evaporation and the residue was distilled under reduced pressure. No product was obtained having a boiling point comparable to the desired product, 3,4-difluoronitrobenzene.



I. c. Successful synthesis of 3,4-difluorophenylarsonic acid.

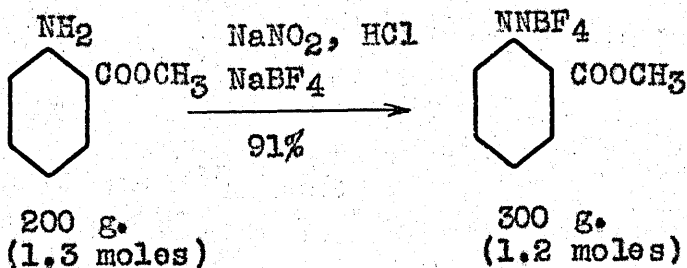
Method III.



2-Methylcarboxybenzene diazonium fluoborate (XVI).--

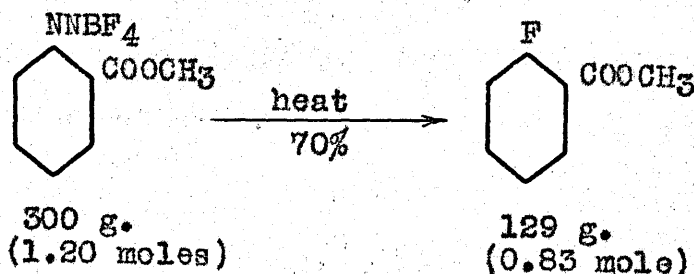
A 2 l. stainless steel beaker fitted with a thermometer and stirrer was set in an ice-salt bath and charged with 275 ml. (3.3 moles) of concentrated hydrochloric acid diluted with 300 ml. of water. A 35 g. portion of methyl anthranilate was added, the mixture was cooled to 0° and diazotization was started by addition of sodium nitrite in the form of moist balls. As diazotization progressed, more methyl anthranilate was added until a total of 200 g. (1.3 moles) of methyl anthranilate and 90 g. (1.3 moles) of sodium nitrite had been added.

The solution was stirred for 15 minutes and a cold solution of 288 g. (2.6 moles) of sodium fluoborate in 400 ml. of water was added all at once. The mixture was stirred for one hour and filtered. The filter cake was washed with 150 ml. of ice water, then with 200 ml. of cold alcohol and, finally, with 200 ml. of cold ether. Dried in air, the 2-methylcarboxybenzene diazonium fluoborate weighed 300 g. (91% of the theoretical).



2-Fluoromethyl benzoate (XVII).--A 1 l. flask connected to a condenser and receiver was charged with 300 g. (1.20 moles) of 2-methylcarboxybenzene diazonium fluoborate and heated with a small flame. The dry salt gradually melted and decomposed smoothly. The residue was heated strongly with a flame until all of the product had distilled over.

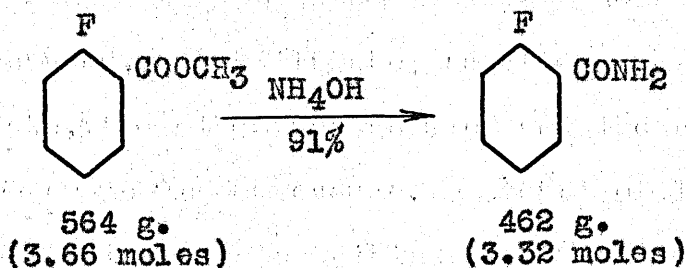
The distillate was washed with water, the water was extracted with ether, and the organic portions were combined. Another 150 ml. of ether was added and dry ammonia gas was bubbled through the solution to remove any dissolved BF_3 . A white, crystalline precipitate formed which was filtered off and discarded. The filtrate was dried over anhydrous sodium sulfate, the ether was removed and the residue was distilled under reduced pressure. A total of 129 g. (70%) of 2-fluoromethyl benzoate boiling at 89° under 15 mm. pressure was obtained.



2-Fluorobenzamide (XVIII).--This compound was prepared by the method of Bergmann et al. (37) as follows:

A 100 g. portion of 2-fluoromethylbenzoate was added to 1 l. of 28% ammonium hydroxide and shaken for six hours. The

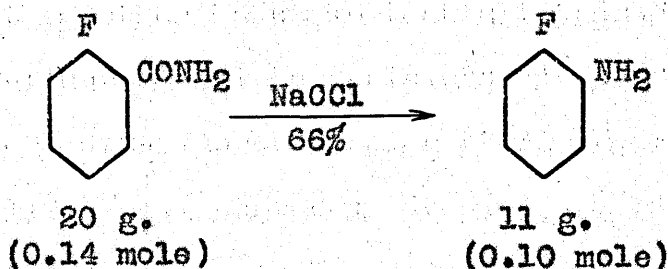
white crystalline precipitate which formed was filtered off and another 100 g. of 2-fluoromethyl benzoate was added to the filtrate which was then shaken overnight. The product which formed was filtered off and by cooling the filtrate in ice, a second crop was obtained. The whole process was repeated with another batch so that a total of 564 g. (3.66 moles) of 2-fluoromethyl benzoate was used. The total weight of the air-dried 2-fluorobenzamide obtained was 462 g. (91%), m.p. 117.2-117.8°. (Recorded: 118) (37). Saturation of the filtrate with ammonia gas yielded no additional product.



2-Fluoroaniline (XIX).--The method of Rinke and Bolswald (38) was used to prepare this compound.

A 400 ml. beaker set in an ice bath was charged with 186 ml. of a solution of sodium hypochlorite made by passing the chlorine generated from the reaction of 50 g. of potassium permanganate with 500 ml. of concentrated hydrochloric acid into 1 l. of 10% sodium hydroxide. The solution was cooled to 3° and 20 g. (0.14 mole) of 2-fluorobenzamide was added. The solution was allowed to warm up to room temperature and stand for 20 hours, after which it was steam distilled. The

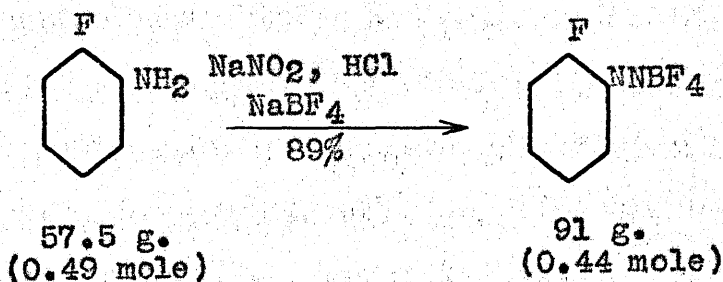
distillate was extracted with ether and the ether extract was dried over sodium sulfate. The ether was removed and the residue was distilled under reduced pressure. A total of 11.2 g. (66%) of 2-fluoroaniline boiling at 62-63° under 12 mm. pressure was obtained.



2-Fluorobenzene diazonium fluoborate (XX).---To a 500 ml. stainless steel beaker fitted with a stirrer and thermometer and set in an ice-salt bath was added 103 ml. (1.23 moles) of concentrated hydrochloric acid and 100 ml. of water. About 10 g. of 2-fluoroaniline was added, the mixture was cooled to 0°, and diazotization was started by the gradual addition of sodium nitrite in the form of moist balls. As diazotization progressed, more of the starting material was added until a total of 57.5 g. (0.49 mole) of 2-fluoroaniline and 35 g. (0.50 mole) of sodium nitrite had been added.

The solution was transferred to a 1 l. glass beaker and a cold solution of 109 g. (1.0 mole) of sodium fluoborate in 150 ml. of water was added all at once. A heavy paste formed which was stirred by hand until a homogeneous mixture was obtained. The precipitate was filtered off, washed with 50

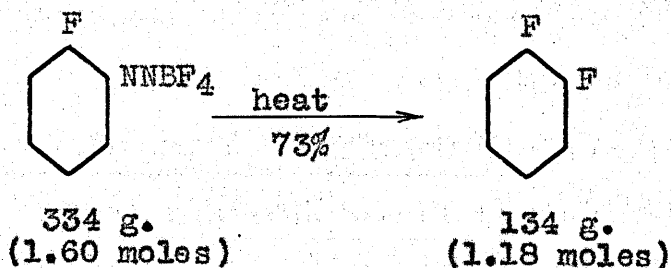
ml. of ice water followed by 50 ml. of alcohol. It was slurried with 100 ml. of ether, filtered, and washed with another 50 ml. of ether. Dried in air, 2-fluorobenzene diazonium fluoborate weighed 91 g. (89% of the theoretical).



o-Difluorobenzene (XXI).---A 334 g. (1.60 moles) quantity of 2-fluorobenzene diazonium fluoborate was decomposed in two batches as follows:

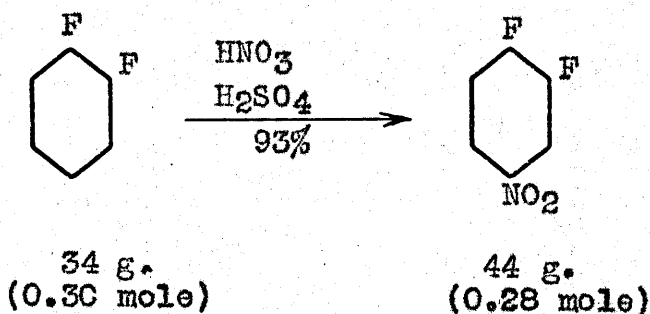
A 167 g. portion was placed in a 1 l. flask connected to a condenser and a receiver set in an ice bath with a reflux condenser serving as an outlet. The dry solid was decomposed by heating the flask with a small flame. When the decomposition reaction was nearly complete, the flask was heated strongly with the flame until the temperature of the vapors rose to 150°. The product in the receiver was taken up in ether, washed twice with water, dried over anhydrous sodium sulfate and distilled.

From the two batches, a total of 134 g. (73%) of o-difluorobenzene boiling at 91-92° (740 mm.) was obtained.



3,4-Difluoronitrobenzene (XIV) from *o*-difluorobenzene (XXI).---This compound was prepared by McNally and Byers (39) and their procedure was followed in the present work.

To 60 ml. of a 2:1 (by volume) mixture of concentrated sulfuric acid and fuming nitric acid (density 1.5) at -10° was added dropwise with stirring 34 g. (0.30 mole) of *o*-difluorobenzene. Cooling was provided by an ice-salt bath aided by internal addition of Dry Ice. The solution was poured over 120 g. of ice and extracted with ether. The ether extract was washed twice with water, once with dilute sodium bicarbonate solution and again with water. It was dried over anhydrous sodium sulfate, the ether was removed and the residue was distilled under reduced pressure. A total of 44 g. (93%) of 3,4-difluoronitrobenzene boiling at 85° under 15 mm. pressure was obtained.



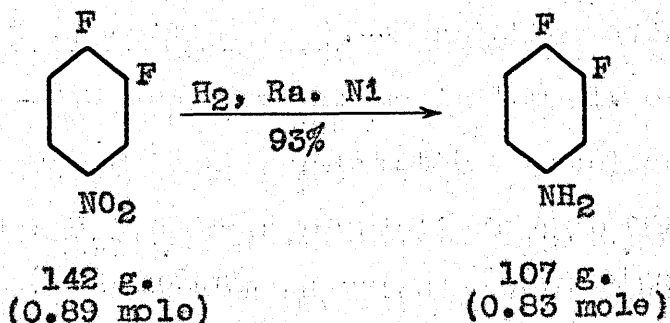
3,4-Difluoroaniline (IX).---A solution of 142 g. (0.89 mole) of 3,4-difluoronitrobenzene in 150 ml. of absolute ethanol was placed in a hydrogenation vessel and 2 g. of Raney nickel and two drops of platinum chloride solution were added. Hydrogen was admitted under a pressure of 2-3 atmospheres, the vessel was agitated and an infra-red heat lamp was directed on the vessel. Reduction proceeded slowly and it was necessary to add more catalyst twice during the course of the reaction when it appeared that absorption had stopped. The entire process required about forty-eight hours. The catalyst was filtered off, the solvent was removed and the residue was distilled at reduced pressure to yield 107 g. (93%) of 3,4-difluoroaniline boiling at 77° under 7 mm. pressure, n_{25}^D 1.5110.

Anal. Calcd. for $C_6H_5NF_2$: C, 55.8; H, 3.9; N, 10.9.
Found: C, 55.7; H, 3.9; N, 11.0.¹

3,4-Difluoroaniline hydrochloride was prepared by passing dry hydrogen chloride gas into an ether solution of the free base. The white crystalline product sublimed rapidly above 220°.

Anal. Calcd. for $C_6H_5NF_2Cl$: C, 43.5; H, 3.6; N, 8.5.
Found: C, 43.9, 43.8; H, 3.6, 3.6; N, 8.6.

¹ All analyses carried out by Clark Microanalytical Laboratory, Urbana, Illinois.

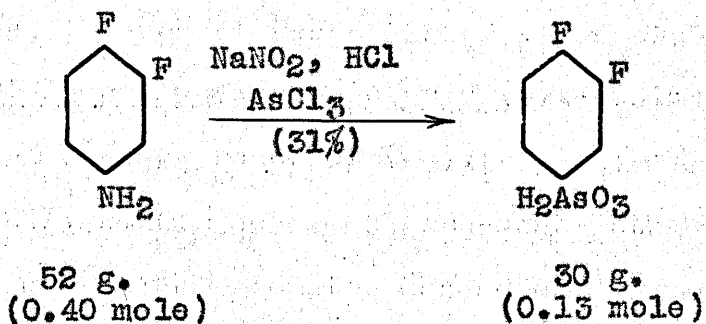


3,4-Difluorophenylarsonic acid (X).---This compound was prepared by the Bart reaction (40).

To a 2 l. beaker set in an ice-salt bath and equipped with a stirrer and thermometer was added 1 l. of absolute ethanol, 52 g. (0.40 mole) of 3,4-difluoroaniline, 40 g. of concentrated sulfuric acid and 112 g. (0.62 mole) of arsenous chloride. The mixture was cooled to 0° and diazotized by the addition of 28 g. (0.40 mole) of sodium nitrite in a saturated aqueous solution, at such a rate that the temperature did not rise above 5°. When diazotization was complete, 4.0 g. of cuprous bromide was added, the solution was stirred thoroughly in the cold, and then heated on a steam bath until evolution of nitrogen ceased. The mixture was steam distilled, the distillate being discarded. The residue was evaporated to about 200 ml. and allowed to stand overnight. A quantity of white crystals appeared which was filtered off. By evaporation of the filtrate to about 100 ml. with subsequent cooling, a second crop was obtained. The crystals were washed with alcohol and ether and air-dried to yield 30 g. (31%) of 3,4-difluorophenylarsonic acid which did not melt below 300°.

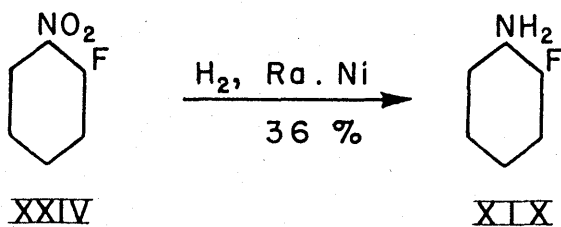
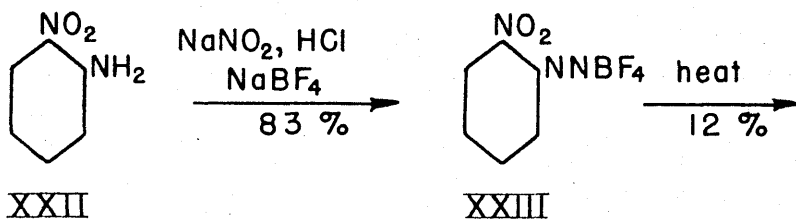
An analytical sample was purified by two recrystallizations from water.

Anal. Calcd. for $C_6H_5O_3F_2As$: C, 30.3; H, 2.1. Found: C, 30.4; H, 2.3.



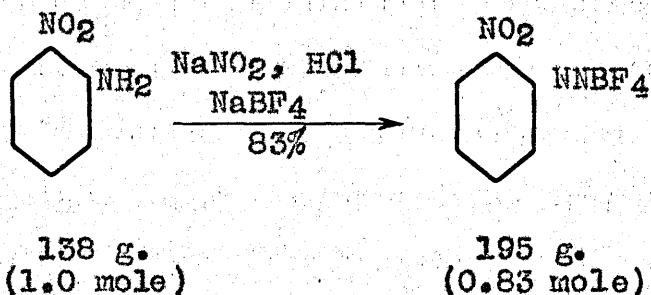
I. d. Synthesis of 3,4-difluorophenylarsonic acid.

Method IV. An alternate route to o-fluoroaniline:



2-Nitrobenzene diazonium fluoborate (XXIII).---This material was prepared by the Schiemann reaction (34) as follows:

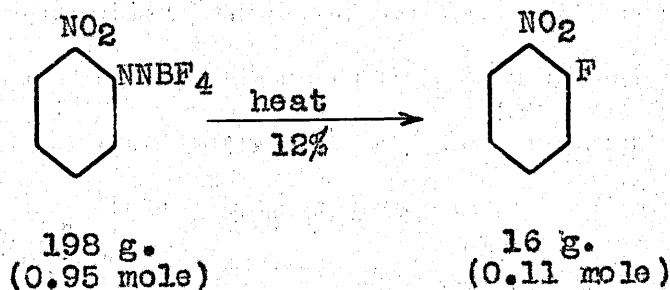
A 1500 ml. beaker charged with 170 ml. (2.0 moles) of concentrated hydrochloric acid diluted with 200 ml. of water was set in an ice-salt bath and 138 g. (1.0 mole) of o-nitroaniline was added. The mixture was cooled to 0° and diazotized by the addition over a period of 1 hour of 69 g. (1.0 mole) of sodium nitrite in the form of moist balls, at 0-5°. It was stirred for another thirty minutes and a cold solution of 238 g. (2.2 moles) of sodium fluoborate in 250 ml. of water was added all at once. The thick slurry which formed was stirred for thirty minutes and filtered. The filter cake was washed with 100 ml. of ice water, then with 100 ml. of cold alcohol. It was slurried with 200 ml. of ether, filtered and washed with 50 ml. of ether. Dried in air the weight of the 2-nitrobenzene diazonium fluoborate was 195 g. (83% of the theoretical).



2-Fluoronitrobenzene (XXIV).---The method of Schiemann and Pillarsky (41) was used in the preparation of this compound.

A 10 g. sample of 2-nitrobenzenediazonium fluoborate was mixed with 20 g. of sand and placed in a 125 ml. flask connected to a condenser and receiving flask. The fluoborate decomposed rapidly when heated with a small flame. When the initial reaction had subsided, the flask was heated strongly until no more decomposition appeared to take place. The tarry residue was steam distilled. The contents of the receiving flask were also steam distilled and the distillates were combined.

Several batches were decomposed in this manner in quantities of 10-30 g. until a total of 198 g. had been treated. The steam distillates were combined and extracted with ether. The ether extract was dried over sodium sulfate, the ether was removed and the residue was distilled under reduced pressure. A total of 16 g. (12%) of 2-fluoronitrobenzene boiling at 87° under 8 mm. pressure was obtained.

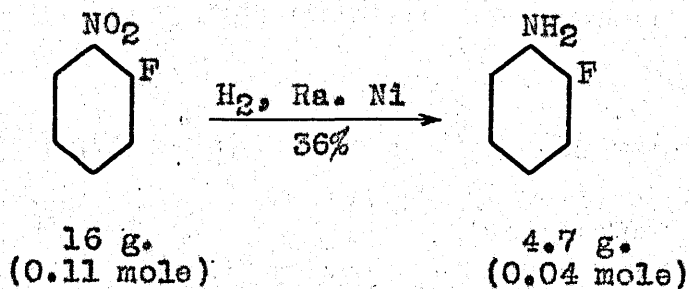


2-Fluoroaniline (XIX) from 2-fluoronitrobenzene (XXIV).--

A solution of 16 g. (0.11 mole) of 2-fluoronitrobenzene in 15 ml. of absolute alcohol was placed in a hydrogenation vessel and 0.2 g. of Raney nickel and a drop of platinum chloride solution were added. Hydrogen was admitted at a pressure of

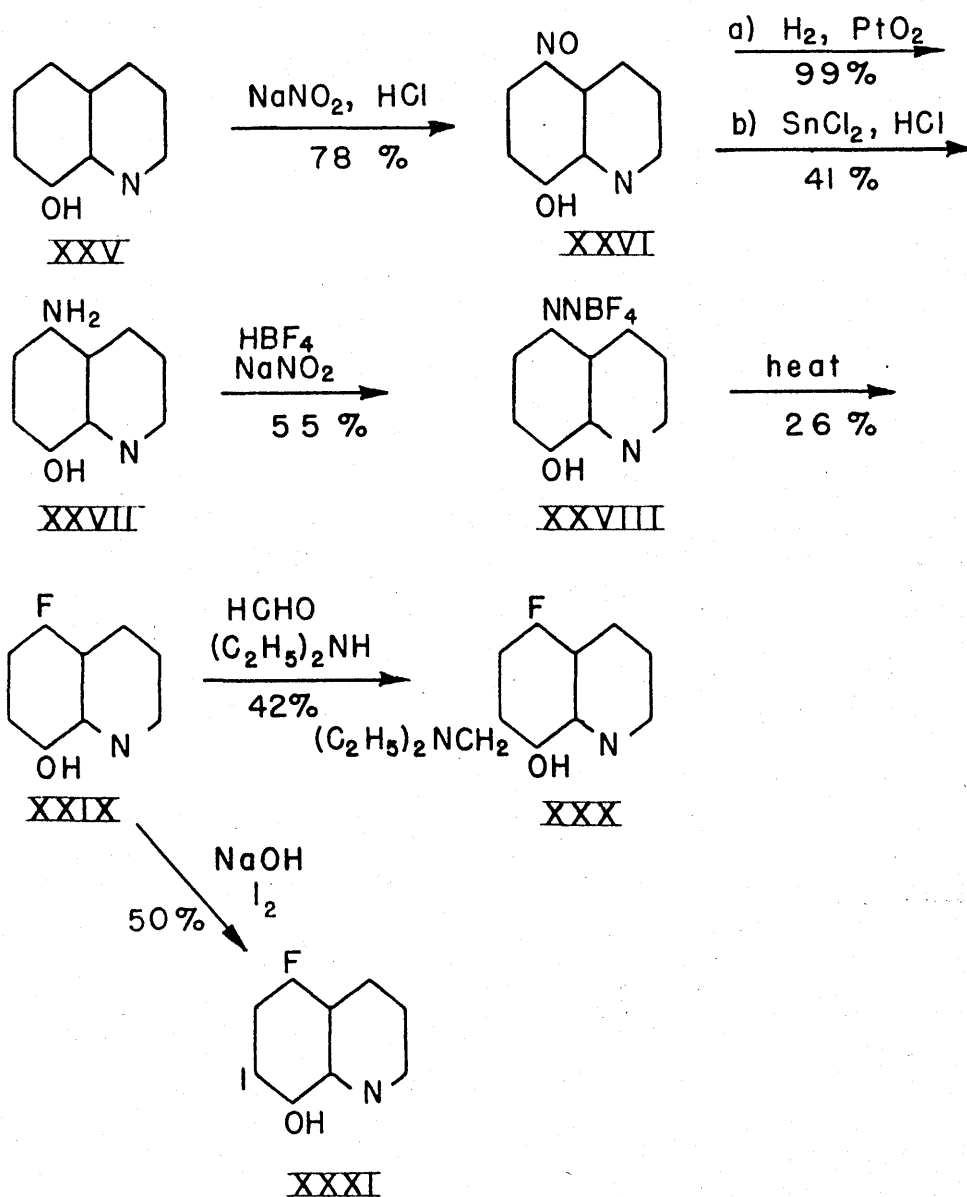
2-3 atmospheres while the vessel was agitated. An infra-red heat lamp was directed on the vessel. Absorption of hydrogen started after thirty minutes and was complete in another two hours.

The cooled solution was filtered into a distilling flask, the solvent was removed and the residue was distilled under reduced pressure. When distillation was about half complete, a white paste formed inside the flask and began to spatter. The distillate was combined with the residue and purified by washing an ether solution of the product with sodium bicarbonate solution. The ether solution was then treated with dilute hydrochloric acid and the layers separated, the ethereal portion being discarded. The aqueous portion was made basic with sodium hydroxide solution, extracted with ether and the ether solution was dried over sodium sulfate, the ether removed and the residue distilled under reduced pressure. A total of 4.7 g. (36%) of o-fluoroaniline boiling at 67° under 15 mm. pressure was obtained.



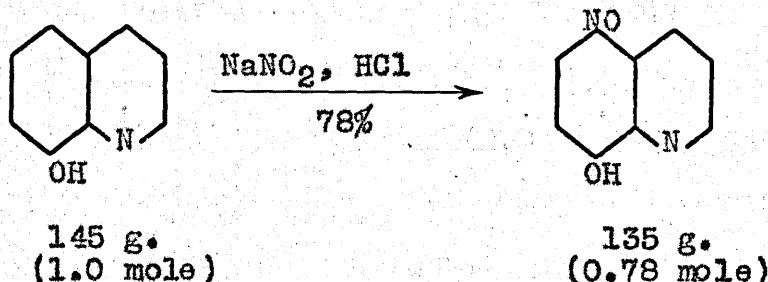
II. a. Synthesis of 5-fluoro-7-diethylaminomethyl 8-hydroxyquinoline, a potential anti-malarial, and 5-fluoro-7-iodo-8-hydroxyquinoline, a potential amebicidal agent.

Method I.



5-Nitroso-8-hydroxyquinoline (XXVI).--This material was prepared by the method of Kostanecki (42) as follows:

To a 4 l. beaker set in an ice-salt bath and equipped with a stirrer and thermometer was added a solution of 166 ml. (2.0 moles) of concentrated hydrochloric acid in 2 l. of water and 145 g. (1.0 mole) of 8-hydroxyquinoline (Eastman Kodak Co.). The solution was cooled to 0° and nitrosated by the gradual addition of 69 g. (1.0 mole) of dry sodium nitrite. The slurry which formed was stirred for an hour in the cold and filtered. The filter cake, consisting of the hydrochloride salt of 5-nitroso-8-hydroxyquinoline, was washed with water. For use in a reduction with stannous chloride and hydrochloric acid, this material could be used directly without drying. The free base was precipitated by addition of glacial acetic acid to a solution of the hydrochloride in dilute sodium hydroxide. The stiff gel which formed was broken up into a thin paste by beating and stirring and then filtered. Dried in air, the 5-nitroso-8-hydroxyquinoline weighed 135 g. (78% of the theoretical).



5-Amino-8-hydroxyquinoline (XXVII).--This preparation was carried out by two methods:

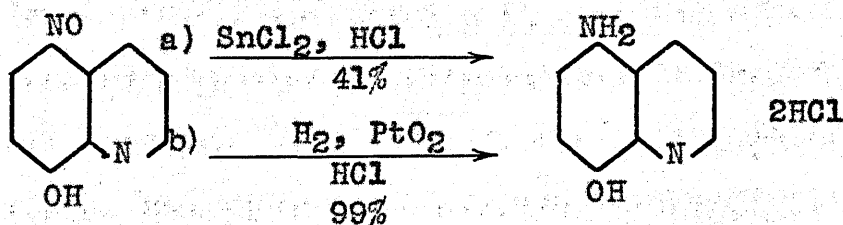
a. Reduction with stannous chloride and hydrochloric acid as used by Kostanecki (42).

The entire amount of 5-nitroso-8-hydroxyquinoline hydrochloride obtained from the nitrosation of 145 g. (1.0 mole) of 8-hydroxyquinoline as described above was added slowly while still moist to a solution of 500 g. of stannous chloride in 600 ml. of concentrated hydrochloric acid, while the temperature was kept below 20° by means of an ice bath. When addition was complete, the mixture was heated to 60° then cooled and filtered. The filter cake was washed with concentrated hydrochloric acid and dissolved in 3 l. of hot water. Hydrogen sulfide gas was passed into the solution for about 12 hours, the precipitate which formed being filtered off from time to time. The filtrate was placed in a 5 l. flask and evaporated under vacuum. When the flask was almost dry, the residue was transferred to a vacuum desiccator to complete the drying process. The weight of the 5-amino-8-hydroxyquinoline hydrochloride obtained was 95 g. (41% of the theoretical yield based on the 8-hydroxyquinoline).

b. Reduction by catalytic hydrogenation:

A mixture of 20 g. (0.10 mole) of 5-nitroso-8-hydroxyquinoline and 150 ml. of absolute alcohol was placed in a hydrogenation vessel and 0.1 g. of platinum oxide was added. Hydrogen was admitted at about 3 atmospheres pressure and

agitation was started. Absorption of hydrogen was complete in five hours. The shaking apparatus was disconnected and dry hydrogen chloride gas was passed into the solution in the reaction vessel until it was saturated. After addition of 100 ml. of ether, the mixture was cooled in an ice bath and filtered. The filter cake was washed with ether and dried in air. Total weight of the 5-amino-8-hydroxyquinoline hydrochloride was 23 g. (99%).

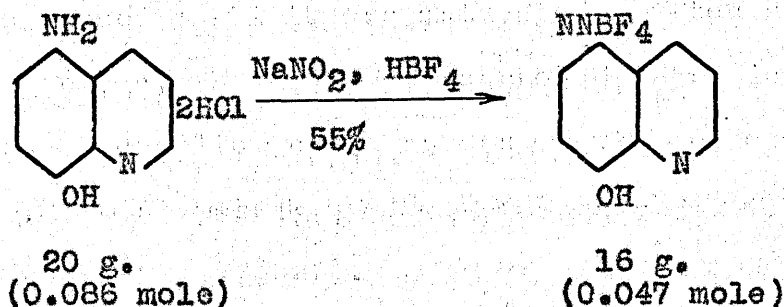


8-Hydroxyquinolyl-5 diazonium fluoborate hydrofluoborate

(XXVIII).--This compound was prepared by the general method of Roe and Hawkins (43) for fluorinating heterocyclic nuclei.

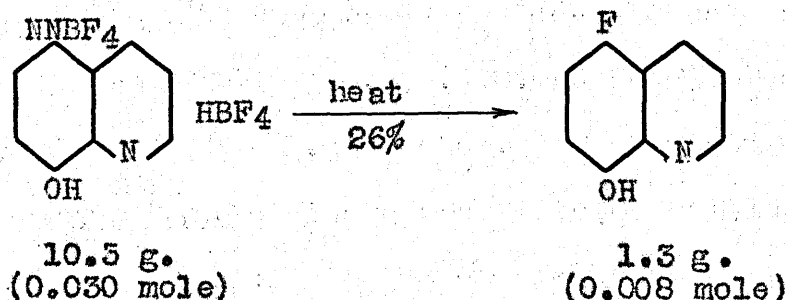
To a solution of 67 ml. (0.47 mole) of 45% fluoboric acid diluted with 20 ml. of water was added 20 g. (0.086 mole) of 5-amino-8-hydroxyquinoline hydrochloride. The solution was cooled to 5° by means of an ice-salt bath and diazotized by the addition of 6.0 g. (0.086 mole) of sodium nitrite dissolved in 20 ml. of water. After standing for about 1½ hours, the precipitate was filtered off, washed with 30 ml. of a cold 1:1 mixture of alcohol and ether and

three times with 30 ml. of cold ether. Dried in air, the 8-hydroxyquinolyl-5 diazonium fluoborate hydrofluoborate weighed 16 g. (55% of the theoretical).



5-Fluoro-8-hydroxyquinoline (XXIX).--A 10.5 g. (0.030 mole) portion of 8-hydroxyquinolyl-5 diazonium fluoborate was decomposed by sprinkling into a beaker set on a hot plate and heated to 130°. The tarry residue which remained after the decomposition was dissolved in hot water, filtered hot, and the filtrate was neutralized with sodium acetate. The resulting precipitate was filtered off, dried in air and sublimed in a vacuum sublimator at 105° under 5 mm. pressure. A total of 1.3 g. (26%) of white, crystalline 5-fluoro-8-hydroxyquinoline melting at 110.0-110.3° was obtained.

Anal. Calcd. for C₆H₉ONF: C, 66.3; H, 3.7; N, 8.6.
Found: C, 66.5; H, 3.8; N, 8.5.



5-Fluoro-7-diethylaminomethyl-8-hydroxyquinoline (XXX).--

This compound was prepared by the Mannich reaction (44) as follows:

To a solution of 1.2 g. (0.013 mole) of paraformaldehyde and 3.1 g. (0.042 mole) of diethylamine in 25 ml. of ethanol was added dropwise a solution of 5.5 g. (0.034 mole) of 5-fluoro-8-hydroxyquinoline in 100 ml. of 1:1 ether-ethanol. The mixture was allowed to stand for thirty minutes and the solvent was distilled off under vacuum provided by the water pump. A dark amber oil remained which solidified on cooling. After two recrystallizations from ether and one recrystallization from ligroin followed by a vacuum sublimation to remove a trace of a white impurity, bright yellow crystals of (XXX) melting at 80.0-80.5° was obtained.

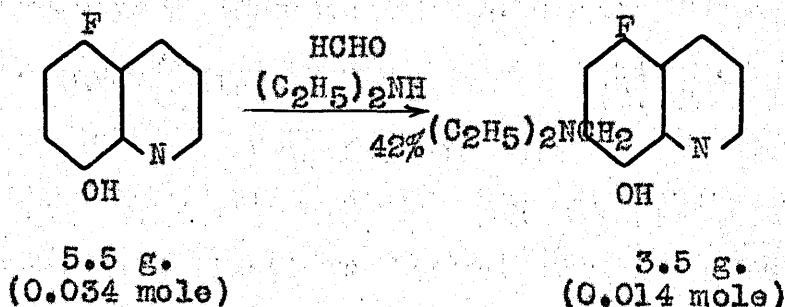
The original mother liquid was evaporated to dryness, the resulting oil was dissolved in dilute hydrochloric acid and extracted with ether. The aqueous portion was neutralized with sodium acetate. A white precipitate resulted which was filtered off, dried, and sublimed. A total of 0.5 g. of 5-fluoro-8-hydroxyquinoline melting at 109° was recovered by this process.

Addition of sodium hydroxide to the filtrate resulted in a yellow precipitate which was taken up in ether. The ether was evaporated and the product was subjected to sublimation. The residue was redissolved in ether, filtered with charcoal and evaporated, yielding an oil which solid-

ified on cooling into bright yellow crystalline (XXX) melting at 77.0-79.0°.

A total of 3.5 g. (42%) of purified 5-fluoro-7-diethylaminomethyl-8-hydroxyquinoline was obtained.

Anal. Calcd. for $C_{14}H_{17}ON_2F$: C, 67.7; H, 6.8; N, 11.3.
Found: C, 67.7; H, 6.8; N, 11.1.

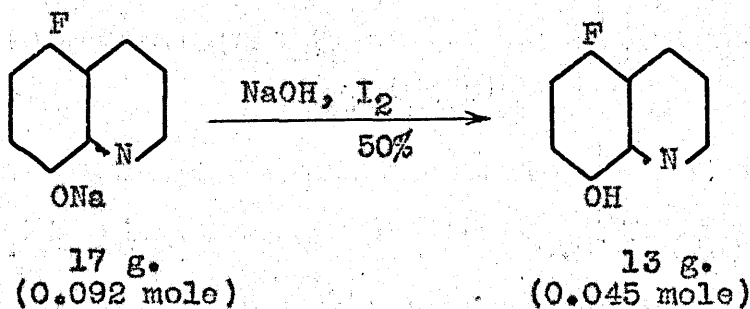


5-Fluoro-7-iodo-8-hydroxyquinoline (XXXI).---A 32 g.

(0.13 mole) portion of iodine was dissolved in a solution of 10 g. of sodium hydroxide in 200 ml. of water and to this was added 17 g. (0.092 mole) of the sodium salt of 5-fluoro-8-hydroxyquinoline. The mixture was diluted to 500 ml. and heated on the steam bath for five hours. After standing overnight, the mixture was filtered. A small amount of precipitate was collected and discarded. The filtrate was acidified with dilute hydrochloric acid and extracted with ether. The ethereal portion was washed with four 100 ml. quantities of 6 M hydrochloric acid which were combined and added to the aqueous portion. This acid solution was exactly neutralized with ammonium hydroxide. A light-colored, fluffy precipitate formed which was filtered off and dried

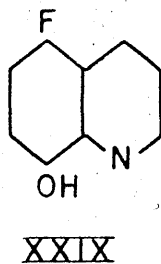
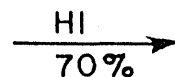
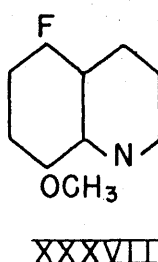
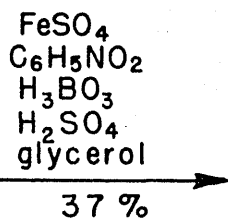
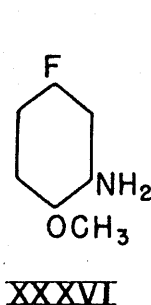
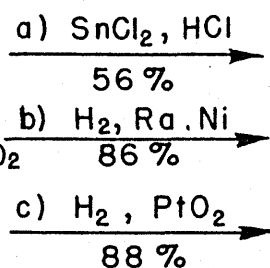
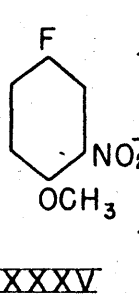
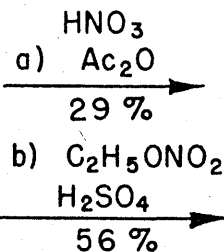
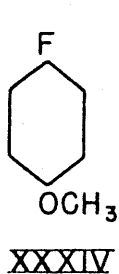
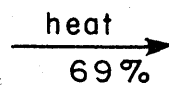
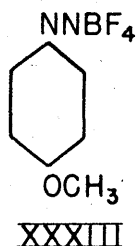
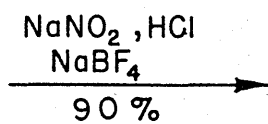
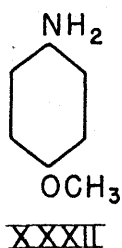
under vacuum. The weight of this crude 5-fluoro-7-iodo-8-hydroxyquinoline melting at 144.0-145.1° was 13 g. (50%). After purification by vacuum sublimation and recrystallization from ligroin, m.p. was 147.7-148.5°.

Anal. Calcd. for C₉H₅NOFI: C, 37.4; H, 1.7; N, 4.8; I, 43.9. Found: C, 37.4; H, 1.9; N, 4.9; I, 43.7.



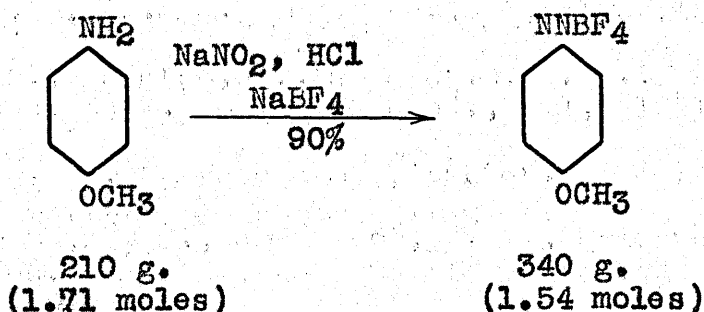
II. b. Synthesis of 5-fluoro-7-diethylaminomethyl-8-hydroxyquinoline.

Method II. An alternate route to 5-fluoro-8-hydroxyquinoline:



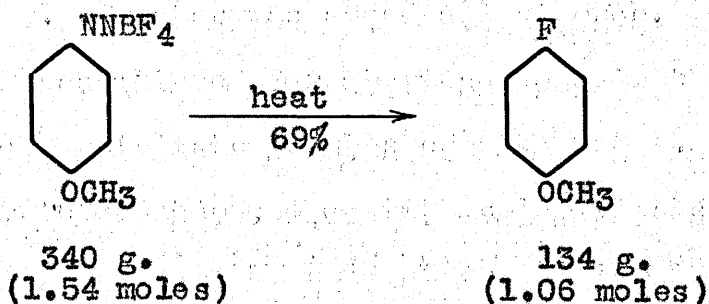
4-Methoxybenzene diazonium fluoborate (XXXIII).--This compound was prepared by the Schiemann process (34) as follows:

To a 3 l. beaker set in an ice-salt bath and equipped with a thermometer and mechanical stirrer were added 210 g. (1.71 moles) of *p*-anisidine (Monsanto Chemical Co.) and 340 ml. (4.1 moles) of concentrated hydrochloric acid diluted with 585 ml. of water. The solution was cooled to 0° which caused some crystals to separate and the mixture was diazotized by the addition of 118 g. (1.71 moles) of sodium nitrite in the form of moist balls. Small lumps of Dry Ice were added from time to time to aid the cooling process. The diazotized solution was stirred for 15 minutes and a cold solution of 373 g. (3.43 moles) of sodium fluoborate dissolved in 300 g. of water was added all at once. The resulting slurry was stirred for about an hour in the cold and filtered. The precipitate was washed with 200 g. of 10% sodium fluoborate solution, then with cold 1:1 alcohol-ether solution, and, finally, with cold ether. Dried in a vacuum desiccator, the weight of the 4-methoxybenzene diazonium fluoborate obtained was 340 g. (90% of the theoretical).



p-Fluoroanisole (XXXIV).--A 340 g. (1.54 moles) portion of 4-methoxybenzene diazonium fluoborate was placed in a 1 l. round-bottomed flask connected to a condenser and receiver. The flask was heated carefully with a small flame and the material decomposed smoothly. At intervals the condenser became plugged with white crystals. These were flushed into the receiving flask by means of a stream of water. Towards the end of the decomposition, the flask was heated strongly to distill over the last traces of the product.

The distillate was taken up in ether, washed with 15% sodium hydroxide solution and dried over sodium sulfate. The ether was removed and the residue was distilled at atmospheric pressure. A total of 134 g. (69%) of p-fluoroanisole boiling at 156° (738 mm.) was obtained.



2-Nitro-4-fluoroanisole (XXXV).--This compound was prepared by two different methods as follows:

a. The procedure of Swarts (45) involving nitration with nitric acid in acetic anhydride was used.

To a 2 l. three-necked, round-bottomed flask equipped with an addition funnel, mechanical stirrer and thermometer,

was added 336 g. (2.66 moles) of p-fluoroanisole and 400 g. of acetic anhydride. The flask was placed in an ice-salt bath and cooled to -10° by addition of small pieces of Dry Ice. A 210 ml. (3.15 moles) portion of concentrated nitric acid (density 1.42) was added dropwise at a temperature of $-5-0^{\circ}$. Addition was complete in about $1\frac{1}{2}$ hours and stirring was continued for another hour in the cold. The solution was allowed to warm up to room temperature with constant stirring over a two hour period. It was then poured into 3 l. of ice water. An oil separated and shortly formed a yellow solid.

The mixture was neutralized with sodium carbonate under a layer of ether. A small amount of a red solid formed which was filtered off and subsequently identified as the sodium salt of 2,6-dinitro-4-fluorophenol. The identification was accomplished by treating the dry solid with hydrochloric acid, extracting with ether, distilling the ethereal solution under reduced pressure and recrystallizing the distillate, which solidified on standing, from alcohol. A bright yellow material melting at $49.0-49.5^{\circ}$ was obtained. Recorded melting point of 2,6-dinitro-4-fluorophenol is 50.2° . (46)

The filtrate was extracted with ether, the ethereal layer separated and dried over sodium sulfate. After removal of the ether on the steam bath, the residue was distilled under reduced pressure. At 7 mm. pressure, 160 g. of a liquid boiling at 48° was obtained which was identified as

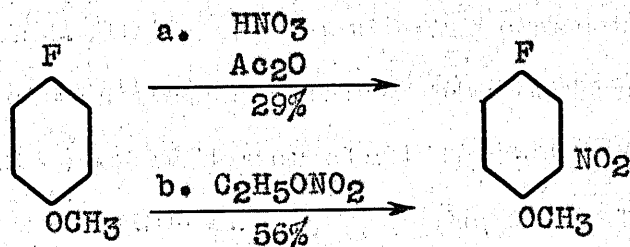
the starting material. The residue which solidified on cooling weighed 172 g. corresponding to a 38% yield based on a total starting material or 71% based on unrecovered starting material.

The product was recrystallized from ethyl alcohol to yield 132 g. (29%) of white crystalline 2-nitro-4-fluoroanisole melting at 60.0-61.5°.

b. Nitration with ethyl nitrate.

A 400 ml. beaker equipped with a mechanical stirrer, thermometer and addition funnel was charged with 50 ml. of concentrated sulfuric acid and 25 g. (0.20 mole) of *p*-fluoroanisole was poured in carefully. A moderate evolution of heat was observed. The solution was cooled to -10° by means of an ice-salt bath aided by internal cooling with Dry Ice. Dropwise addition of 18 g. (0.20 mole) of ethyl nitrate was carried out at rate such that the temperature did not rise above 0°. When addition was about half complete, the mixture became quite stiff and viscous so an additional 25 ml. of concentrated sulfuric acid was added. After the reaction was complete, the mixture was poured over 250 g. of ice. A dark yellow precipitate formed which was filtered off and dissolved in ether. The ethereal solution was washed with 10% sodium hydroxide solution, filtered through charcoal, dried over sodium sulfate and evaporated. The residue was a red oil which solidified on cooling. The weight of this crude product was 32 g. corresponding to a

93% yield. Recrystallization from alcohol produced 19 g. (56%) of white, crystalline 2-nitro-4-fluoroanisole melting at 62.5-63.0°. (Recorded: 61.6°) (45).



2-Amino-4-fluoroanisole (XXXVI).--This preparation was carried out by three methods as follows:

a. Reduction with stannous chloride and hydrochloric acid.

A 12 g. (0.07 mole) portion of 2-nitro-4-fluoroanisole was added to 60 ml. (0.72 mole) of concentrated hydrochloric acid and 50 g. (0.27 mole) of stannous chloride. The mixture was heated on a steam bath and, during the course of about 20 minutes, it became homogeneous while undergoing an exothermal reaction. It was cooled in ice and a gray precipitate formed which was filtered off, dissolved in water and neutralized with sodium carbonate solution under a layer of ether. After thorough shaking, the ether layer was separated, dried over sodium sulfate and evaporated. The residue was distilled under reduced pressure. A total of 5.5 g. (56%) of 2-amino-4-fluoroanisole boiling at 105-106° under 8 mm. pressure was obtained.

b. Reduction by catalytic hydrogenation using Raney

nickel:

A 58 g. (0.34 mole) portion of 2-nitro-4-fluoroanisole was dissolved in 350 g. of redistilled absolute alcohol and placed in a low pressure hydrogenator. About 0.5 g. of Raney nickel and 2 drops of platinum chloride solution were added. The mixture was agitated for four hours during which no hydrogen was absorbed. After addition of more catalyst, the reaction started and was complete in another 14 hours. The catalyst was filtered off, the solvent evaporated and the residue distilled under reduced pressure. A total of 41 g. (86%) of 2-amino-4-fluoroanisole boiling at 104° under 7 mm. pressure was obtained.

c. Reduction by catalytic hydrogenation using Adams catalyst:

A 40 g. (0.23 mole) portion of 2-nitro-4-fluoroanisole was dissolved in 150 ml. of hot redistilled absolute alcohol and placed in a low pressure hydrogenator. Adams catalyst was added and hydrogen was admitted under 50 lb. pressure. After shaking was started, reduction began at once and was complete in about 5 hours. The catalyst was filtered off, the solvent evaporated and the residue distilled under reduced pressure. A total of 29 g. (88%) of 2-amino-4-fluoroanisole boiling at 104° under 7 mm. pressure was obtained.

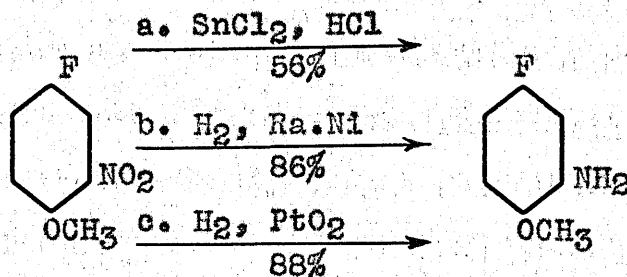
Anal. Calcd. for C_7H_8ONF : C, 59.5; H, 5.7; N, 9.9.
Found: C, 59.5; H, 5.7; N, 10.76, 10.51.

The hydrochloride was prepared by passing dry hydrogen chloride gas into an ether solution of the free base and

submitted for analysis.

Anal. Calcd. for C_7H_9ONClF : C, 47.3; H, 5.1; N, 7.9.

Found: C, 47.5; H, 5.2; N, 7.7.



5-Fluoro-8-methoxyquinoline (XXXVII).---Three variations

of the Skraup reaction as modified by Cohn (47) were tried in the preparation of this compound.

a. Using nitrobenzene as the oxidizing agent:

A sample of 2-amino-4-fluoroanisole was purified by dissolving in dilute hydrochloric acid, extracting the acid mixture with ether, the ethereal portion being discarded, neutralizing with sodium hydroxide and extracting again with ether after which the ethereal solution was dried over sodium sulfate, the ether removed, and the residue distilled under reduced pressure. A clear, colorless product was obtained.

An 82 g. (0.58 mole) portion of this material, 20 g. of ferrous sulfate, and 43 g. (0.35 mole) of nitrobenzene were placed in a 1 l. round-bottomed flask and to this mixture was added a cold solution of 36 g. (0.59 mole) of boric acid in 196 g. (1.75 moles) of glycerine which had been made

up hot. A 100 ml. portion of concentrated sulfuric acid was added slowly with cooling. A reflux condenser was attached and the mixture was refluxed for 24 hours at an oil bath temperature of 150°.

The mixture was cooled and neutralized by the addition of 460 g. of 50% sodium hydroxide solution added slowly with cooling. The basic mixture was extracted with ether, the ethereal portion was separated, filtered through charcoal and dried over sodium sulfate. After removal of the ether, the residue was distilled under reduced pressure.

The distillate was treated with 30 ml. of 20% sodium hydroxide solution and 20 g. of benzoyl chloride. The mixture became quite hot. It was cooled, shaken thoroughly, acidified with hydrochloric acid and extracted with ether, the ethereal portion being discarded. The aqueous portion was made basic and extracted with ether, the ethereal portion separated and dried over sodium sulfate. After removal of the ether, the residue was distilled under reduced pressure to yield 38 g. (37%) of 5-fluoro-8-methoxyquinoline boiling at 144-147° under 9 mm. pressure.

b. Using 2-nitro-4-fluoroanisole as the oxidizing agent:

A 500 ml. three-necked flask equipped with a stirrer, thermometer and reflux condenser was charged with 25 g. (0.18 mole) of 2-amino-4-fluoroanisole, 19 g. (0.11 mole) of 2-nitro-4-fluoroanisole, 6 g. of ferrous sulfate and a solution of 95 g. of anhydrous glycerol and 11 g. of boric

acid. The mixture was heated to 75° and 30 ml. of concentrated sulfuric acid was added dropwise. It was then refluxed for 34 hours at an oil bath temperature of 145°.

The cooled reaction mixture was poured over 500 g. of ice, nearly neutralized by addition of 38 g. of sodium hydroxide in 50% solution and made basic by addition of sodium bicarbonate. The resulting dark, oily mixture was placed in a continuous extractor and extracted with benzene for 36 hours.

The benzene layer was separated and the benzene was distilled off leaving a dark, oily residue. Upon treatment with 25 ml. of concentrated hydrochloric acid diluted to 75 ml. with water, a clear yellow solution was obtained which separated into two layers. The organic layer was separated, washed with water, and discarded, the washings being added to the aqueous layer.

The aqueous layer was made basic with sodium bicarbonate and extracted with ether. The ether extract was dried overnight over sodium sulfate, the ether was distilled off and the residue was distilled under reduced pressure. A total of 2.8 g. (9.0%) of 5-fluoro-8-methoxyquinoline boiling at 128-132° under 4 mm. pressure was obtained.

The reaction mixture was extracted further with ether for 24 hours and the ether extract was worked up in a similar manner but no more product was obtained.

c. Using nitroethane as the oxidizing agent:

A 250 ml. flask was charged with 25 g. (0.18 mole) of 2-amino-4-fluoroanisole, 8.3 g. (0.11 mole) of nitroethane and 6 g. of ferrous sulfate. To this was added a solution of 11 g. of boric acid in 94 g. of anhydrous glycerol, and 30 ml. of concentrated sulfuric acid was added carefully with intermittent cooling under the tap. The mixture was refluxed for 40 hours at an oil bath temperature of 150°.

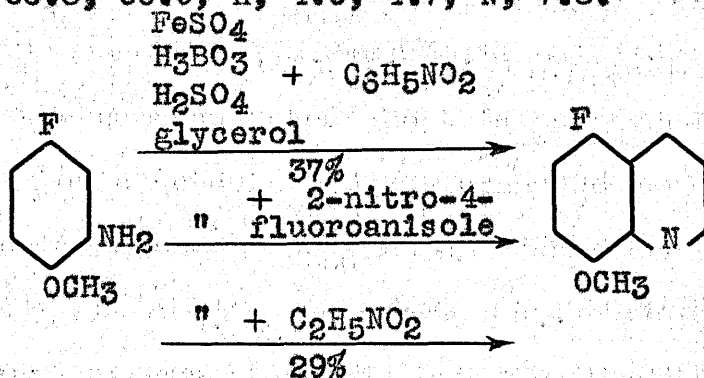
The cooled reaction mixture was poured over 250 g. of ice, nearly neutralized by addition of 38 g. of sodium hydroxide in 50% solution and then made basic with sodium bicarbonate. The mixture was placed in a continuous extractor equipped with a stirrer and extracted with benzene for 40 hours. The benzene extract was evaporated to 50 ml. and the residue was extracted with dilute hydrochloric acid. The organic layer was discarded. The acid layer was made basic with sodium bicarbonate and extracted with ether. A black tar which was present in the acid solution did not dissolve in the ether but was taken up when extracted with benzene.

The benzene and ether extracts were combined, dried over sodium sulfate and the solvent was removed. The residue was distilled at reduced pressure yielding 9.0 g. (29%) of 5-fluoro-8-methoxyquinoline boiling at 120-122° at 3 mm.

After standing for twelve days at room temperature, the product solidified. Melting point was 34.0-36.5°.

Anal. Calcd. for $C_{10}H_8ONF$: C, 67.8; H, 4.6; N, 7.9.

Found: C, 66.8, 66.9; H, 4.6, 4.7; N, 7.8.



5-Fluoro-8-hydroxyquinoline (XXIX) from 5-fluoro-8-

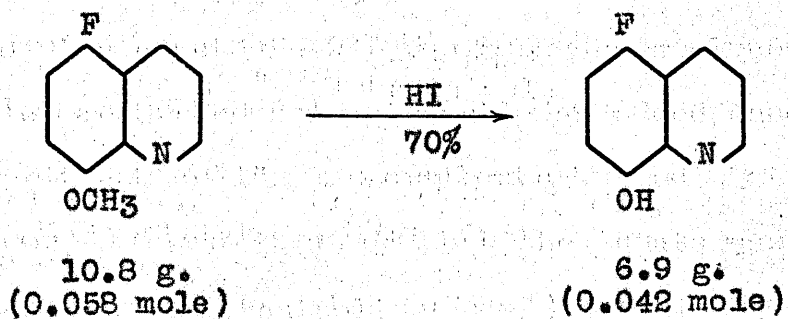
methoxyquinoline (XXXVII).—A 10.8 portion (0.058 mole) of 5-fluoro-8-methoxyquinoline was refluxed with 150 g. (0.58 mole) of 50% hydriodic acid for 24 hours. The cooled solution was diluted with 150 ml. of water and neutralized with sodium bicarbonate. The precipitate which formed was filtered off, washed with water and dried in a vacuum desiccator.

The dry product was sublimed at 105° under 5 mm. pressure. A total of 7.7 g. (77%) of 5-fluoro-8-hydroxyquinoline was obtained as the sublimate.

This product was further purified as follows: It was dissolved in dilute hydrochloric acid, the solution was extracted with ether and the ethereal portion discarded. The aqueous portion was made basic with sodium hydroxide and extracted with ether, the ethereal portion again being discarded. The solution was acidified again with hydrochloric acid and finally neutralized with sodium bicarbonate.

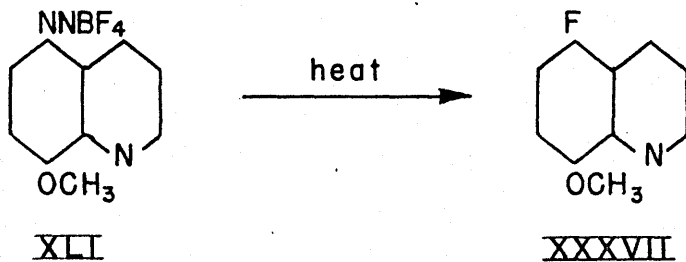
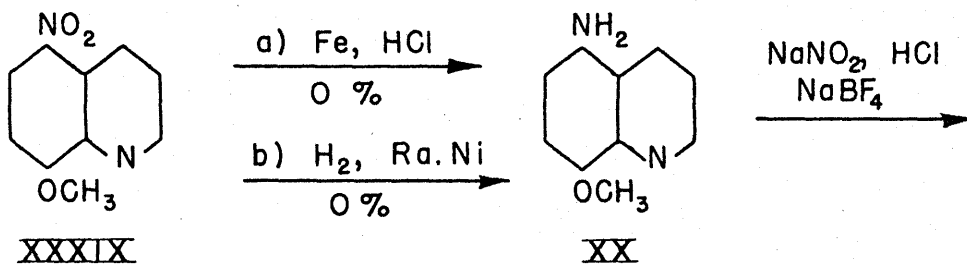
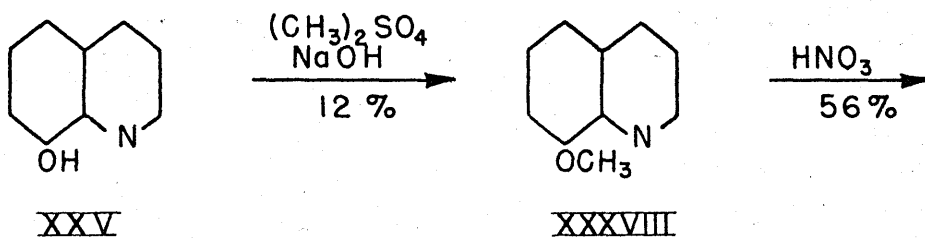
The precipitate which formed was filtered off, dried

under vacuum and sublimed as before to yield 6.9 g. (70%)
of purified 5-fluoro-8-hydroxyquinoline, m.p. 109.8-110.2°.



II. c. Synthesis of 5-fluoro-7-diethylaminomethyl-8-hydroxyquinoline.

Method III. Attempted alternate route to 5-fluoro-8-methoxyquinoline:

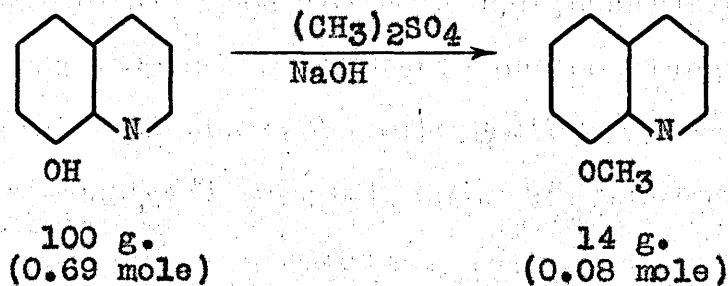


8-Methoxyquinoline (XXXVIII).--This compound has been prepared by Kaufman and Rothlin (48) and their procedure was used as follows:

A solution of 55 g. (1.38 moles) of sodium hydroxide in 300 ml. of water was added to a mixture of 100 g. (0.69 mole) of 8-hydroxyquinoline (Eastman Kodak Co.) in 500 ml. of water which was heated to about 70°. To the hot solution was added 44 g. (0.35 mole) of dimethyl sulfate. The solution was kept hot for one hour, cooled, extracted with benzene and the benzene extract dried overnight over sodium sulfate.

The benzene was distilled off and the residue was distilled under reduced pressure yielding 14 g. (12%) of 8-methoxyquinoline boiling at 134-137° at 5 mm. pressure.

The aqueous portion of the reaction mixture was acidified with glacial acetic acid, the resulting precipitate was filtered off, dried under vacuum and sublimed at 65° under a pressure of 12 mm. A total of 70 g. of purified starting material (8-hydroxyquinoline) was recovered.

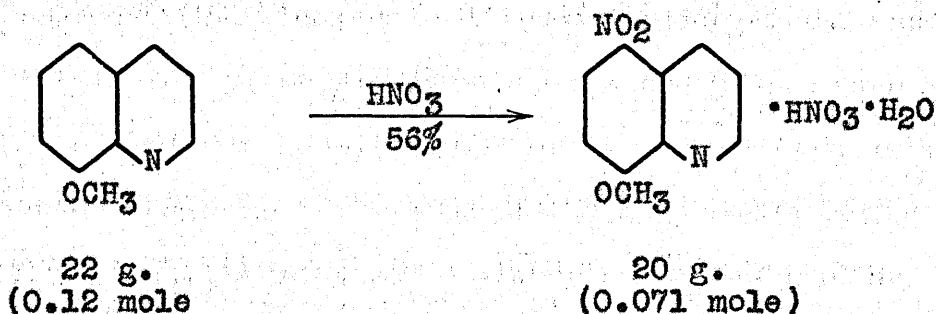


5-Nitro-8-methoxyquinoline (XXXVIII).---The method of Balaban (49) was used for preparing this compound.

A 250 ml. beaker equipped with a thermometer and stirrer was set in an ice-salt bath and charged with 55 ml. (1.24 moles) of fuming nitric acid (density 1.50). A 22 g. portion (0.12 mole) of 8-methoxyquinoline was added gradually over a period of $1\frac{1}{2}$ hours at a temperature of $-5-0^{\circ}$.

The mixture was stirred for another hour, poured over 75 g. of ice and diluted to 250 ml. with ice water. A yellow precipitate appeared which was filtered off, washed with water and dried in a vacuum desiccator. The weight of the 5-nitro-8-methoxyquinoline nitrate hydrate thus obtained was 20 g. (56% of the theoretical).

The nitrate hydrate was decomposed by treatment with dilute sodium hydroxide solution. The 5-nitro-8-hydroxyquinoline, which appeared as a yellow precipitate, was filtered off and washed with water. Dried in air, the product melted at $148.8-149.2^{\circ}$. (Recorded: 151°) (49).



Attempted preparation of 5-amino-8-methoxyquinoline

(XL).--This preparation was attempted by two methods:

a. By catalytic hydrogenation:

An 8.4 g. (0.041 mole) sample of 5-nitro-8-methoxyquinoline (m.p. 147.8-148.3°) was placed in a hydrogenation bottle and 30 ml. of redistilled absolute alcohol, 0.5 g. of Raney nickel and a drop of platinum chloride solution were added. The mixture was shaken with hydrogen under a pressure of 2-3 atmospheres while heat was applied by means of an infra-red heat lamp. After an induction period of forty-five minutes, absorption of hydrogen started. It was complete after two hours at which time the theoretical amount of hydrogen had been absorbed.

The catalyst was removed by filtration through a sintered glass funnel and the solvent was distilled off leaving a reddish-black tar. This residue was dissolved in dilute hydrochloric acid and the solution was extracted with ether, the ethereal portion being discarded. The aqueous portion was neutralized with sodium hydroxide and extracted first with ether, then with benzene. The ether and benzene extracts were dried over sodium sulfate.

Nothing but tarry residues could be obtained from these solutions.

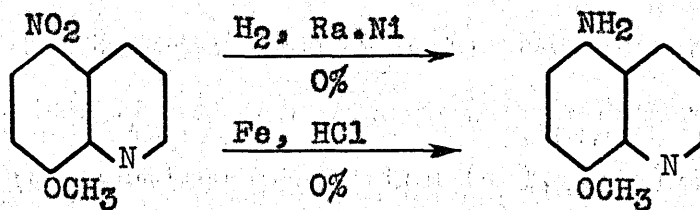
b. By the procedure of Balaban (49), involving reduction with iron and hydrochloric acid:

To a 500 ml. three-necked flask equipped with a reflux

condenser, mercury-sealed stirrer and a flexible tube for addition of solids was added 20 g. (0.075 mole) of 5-nitro-8-methoxyquinoline nitrate hydrate, 150 ml. of ethyl alcohol and 2.0 ml. of concentrated hydrochloric acid. The mixture was heated to reflux temperature by means of an oil bath and 20 g. of powdered iron was added in small portions over the course of thirty minutes. Refluxing was continued for three hours.

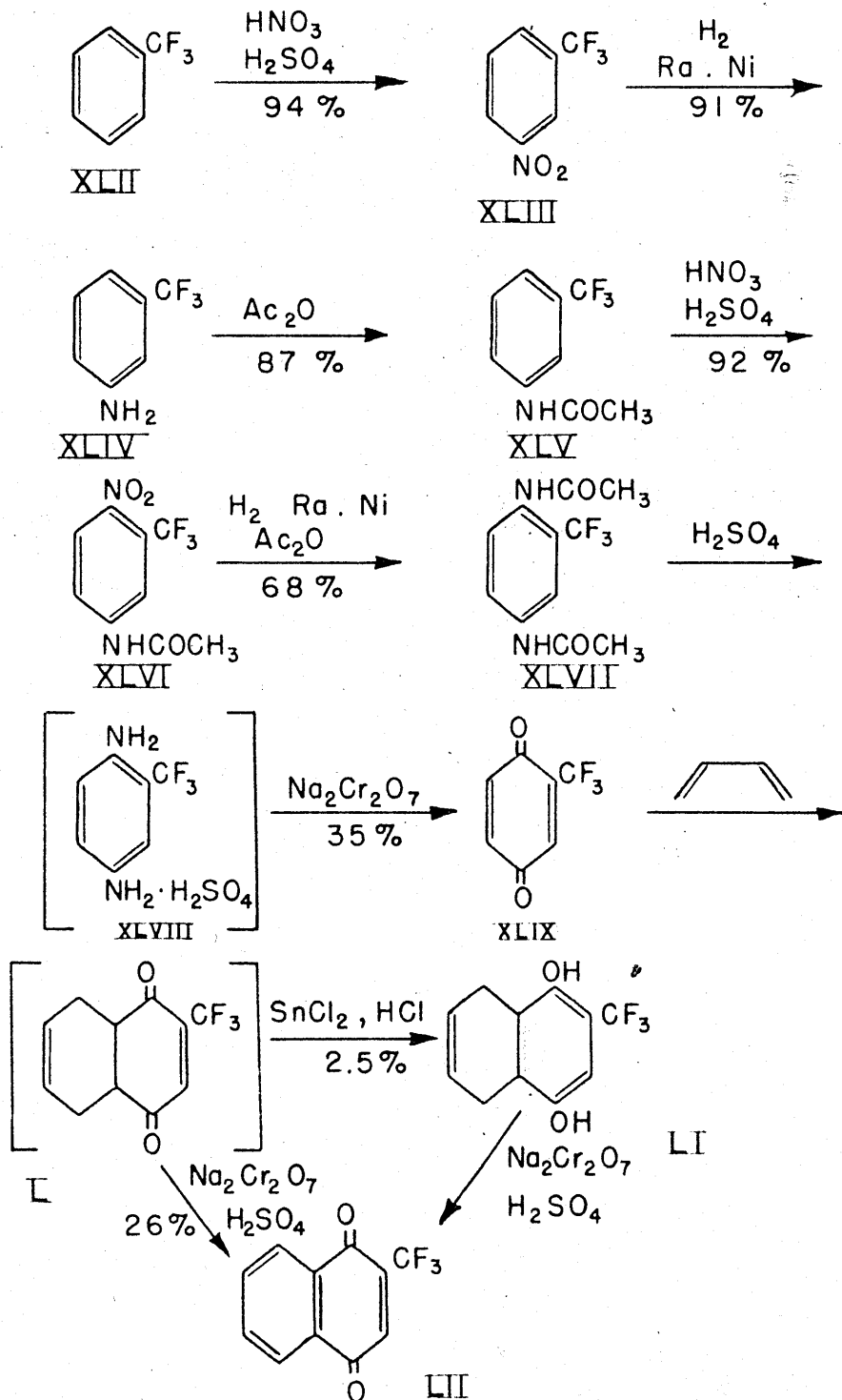
The solvent was distilled off leaving a dark tar which was dried under vacuum and extracted with benzene. From this benzene extract nothing but a tar could be obtained.

The residue from the benzene extraction was treated with dilute hydrochloric acid and filtered. The filtrate was made basic with sodium hydroxide producing a bluish-black precipitate. The basic mixture was treated with hydrogen sulfide gas causing a black precipitate to form. This was filtered off, dried and boiled in benzene. Upon cooling, a trace of yellow crystals appeared along with a reddish-brown lumpy solid residue. No 5-amino-8-methoxyquinoline was isolated from this reaction.



III. a. Synthesis of 2-trifluoromethyl-1,4-naphthoquinone, an analog of Menadione (2-methyl-1,4-naphthoquinone).

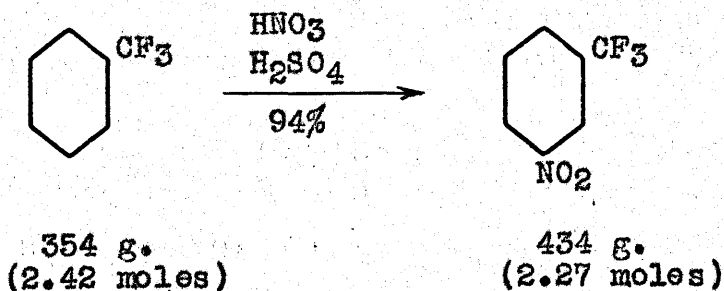
Method I:



3-Nitrobenzotrifluoride (XLII).--This material was prepared by the procedure of Swarts (50) as follows:

A 1500 ml. beaker set in an ice-salt bath and equipped with a mechanical stirrer and thermometer was charged with 354 g. (2.42 moles) of benzotrifluoride (Hooker Chemicals), cooled to -10° , and 600 ml. of a 3:2 mixture (by volume) of concentrated sulfuric acid and fuming nitric acid (density 1.5) was added dropwise over a two hour period. The temperature was kept near -5° by the periodic addition of small lumps of Dry Ice. The solution was stirred in the cold for three hours, then poured over 1200 g. of ice and extracted with three 250 ml. portions of ether. The ether extract was washed with three 150 ml. portions of water and dried overnight over anhydrous sodium sulfate.

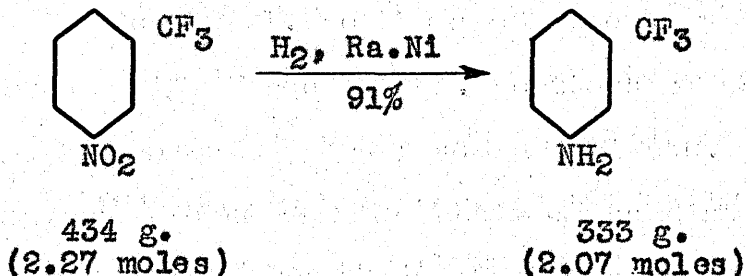
The ether was removed and the residue was distilled at reduced pressure to yield 434 g. (94%) of 3-nitrobenzotrifluoride boiling at 79° (6 mm.).



3-Aminobenzotrifluoride (XLIV).--A solution of 434 g. (2.27 moles) of 3-nitrobenzotrifluoride in 450 ml. of absolute alcohol was placed in a 2 l. hydrogenation vessel

together with 3 g. of Raney nickel and two drops of platinum chloride solution. The solution was shaken with hydrogen at a pressure of 1-3 atmospheres while heat was supplied by means of an infra-red lamp. Absorption of hydrogen started after two hours and was complete after another twenty hours.

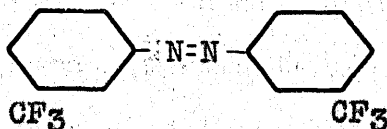
The solution was filtered through a sintered glass funnel to remove the catalyst, the solvent was removed and the residue was distilled at reduced pressure. A total of 333 g. (91%) of 3-aminobenzotrifluoride was obtained boiling at 68° (5 mm.).



The residue in the distillation flask was dissolved in ethanol, heated to 60°, and filtered with charcoal. The filtrate was chilled in ice and a quantity of bright orange needles separated. Dried in air, the weight of the crystals was 2.0 g., m.p. 75.6-78.0°. An analytical sample prepared by successive recrystallizations from ethanol melted at 82.2-82.5°. The composition of the material was shown to correspond to $\text{C}_7\text{H}_4\text{NF}_3$.

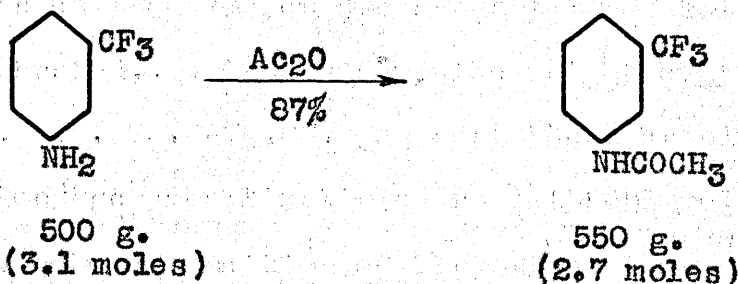
Anal. Calcd. for $\text{C}_7\text{H}_4\text{NF}_3$: C, 52.8; H, 2.5; N, 8.8.
Found: C, 53.0; H, 2.6; N, 8.8.

On the basis of the analytical results and melting point, the compound was identified as m,m'-trifluoroazoluene:



Recorded melting point of m,m'-trifluoroazotoluene: 82.5° (51).

3-Acetamidobenzotrifluoride (XLV).--To a solution of 500 g. (3.1 moles) of 3-aminobenzotrifluoride in 600 ml. of benzene was added 315 g. (3.1 moles) of acetic anhydride. The solution was refluxed for two hours on a steam bath, the benzene was distilled off and the residue was allowed to stand overnight. White crystals of 3-acetamidobenzotrifluoride separated which, dried in air, weighed 550 g. (87%), m.p. 103.7-104.5°. (Recorded m.p.: 103°) (50).



2-Nitro-5-acetamidobenzotrifluoride (XLVI).--This compound was prepared using the conditions described by Jones (52) for the preparation of 2-nitro-5-aminobenzotrifluoride.

To a 3 l., three-necked flask set in an ice-salt bath and equipped with a stirrer and thermometer was added 1 l. of concentrated sulfuric acid and 200 g. (0.99 mole) of 3-acetamidobenzotrifluoride. The solution was cooled to -5° and a solution of 80 g. (1.2 moles) of fuming nitric acid (density 1.5) in 100 ml. of concentrated sulfuric acid was added dropwise over a forty minute period at $-5-0^{\circ}$. The solution was brought to room temperature, stirred for three hours, heated to 40° , stirred for one hour, and then poured over ice. A voluminous yellow precipitate separated which was filtered off, washed thoroughly with water, and dried, first in air, then under vacuum. The weight of the crude product was 309 g. (126%).

A careful investigation of the crude product was made in the following manner:

The entire amount was dissolved in about 2 l. of boiling benzene. Two crops of orange-yellow crystals of 2-nitro-5-acetamidobenzotrifluoride melting at $121.2-123.0^{\circ}$ were obtained by cooling first to room temperature and later in ice. The combined weight of these crystals was 160 g.

The mother liquor was evaporated to about half its volume and cooled in ice. Light yellow crystals separated which were filtered off and recrystallized from alcohol to yield 6 g. of a white crystalline solid melting at $163-166^{\circ}$. An analytical sample was purified by successive recrystallizations from alcohol followed by sublimation under vacuum.

Melting point of the final product was 172.0-172.4°. Analysis of this material showed the composition to be $C_9H_7O_3N_2F_3$.

Anal. Calcd. for $C_9H_7O_3N_2F_3$: C, 43.6; H, 2.9; N, 11.3.
Found: C, 44.0; H, 3.0; N, 11.7.

From the analytical data and melting point, this compound was identified as 2-nitro-3-acetamidobenzotrifluoride. (Recorded m.p.: 171°) (53).

Addition of water to the alcohol mother liquor and subsequent chilling yielded 13 g. of yellow crystals, m.p. 104-115°, later identified by melting point of a purified sample as 2-nitro-5-acetamidobenzotrifluoride.

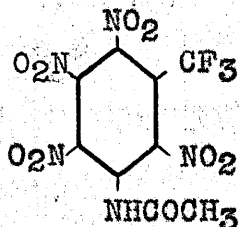
Further evaporation of the benzene mother liquor from the third crop of crystals resulted in a fourth crop which, after one recrystallization from alcohol and water, weighed 51 g., melting point 80-95°. This material was also identified by the melting point of a purified sample as 2-nitro-5-acetamidobenzotrifluoride.

A fifth crop of crystals from the benzene solution was deep orange in color and weighed 6 g., m.p. 118-165°. After one recrystallization from alcohol, the melting point was 188-189°. An analytical sample was prepared by a second recrystallization from alcohol followed by vacuum sublimation to yield bright orange crystals melting at 191.2-192.2°. The composition of the material was shown by analysis to correspond to $C_9H_4N_5O_9F_3$.

Anal. Calcd. for $C_9H_4N_5O_9F_3$: C, 28.2; H, 1.0; N, 18.2

Found: C, 28.5; H, 0.8; N, 18.5.

From this information, the following structure was postulated for the compound:

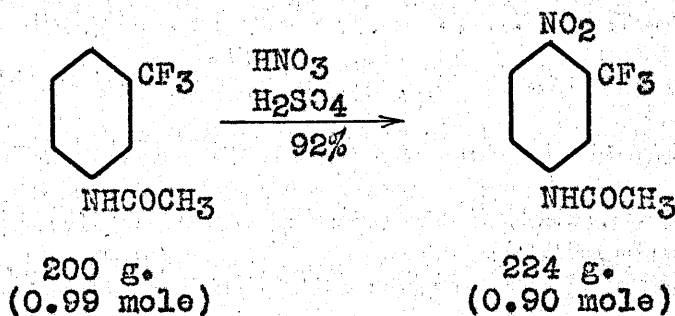


2,3,4,6-tetranitro-5-acetamidobenzotrifluoride.

The total weight of 2-nitro-5-acetamidobenzotrifluoride was 224 g. (92%).

A sample was prepared for analysis by recrystallization from aqueous ethanol, dilute acetic acid and again from aqueous ethanol to yield a pure material melting at 123.2-123.9°. Recorded m.p. of 2-nitro-5-acetamidobenzotrifluoride: 123.5° (53).

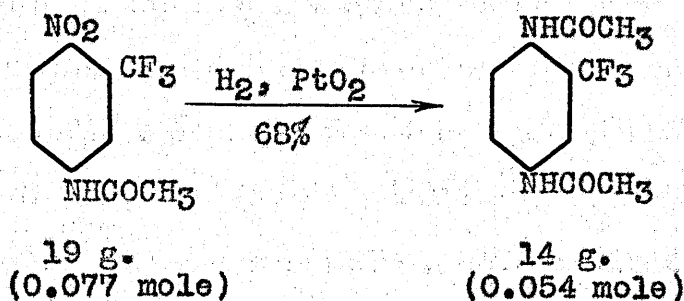
Anal. Calcd. for C₉H₇O₃N₂F₃: C, 43.56; H, 2.84; N, 11.29. Found: C, 43.81; H, 3.02; N, 11.29.



2,5-Diacetamidobenzotrifluoride (XLVII).---A 19 g.

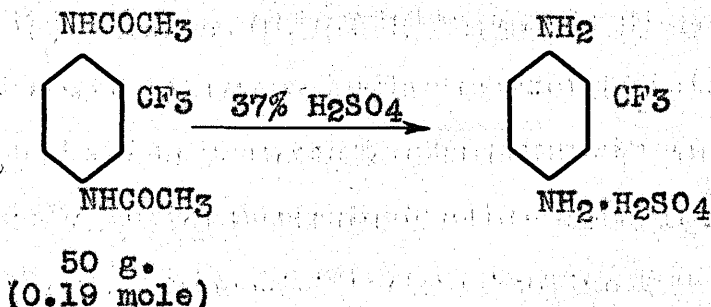
(0.77 mole) portion of 2-nitro-5-acetamidobenzotrifluoride,

purified by recrystallization from benzene, dilute ethanol and dilute acetic acid, was dissolved in 50 ml. of acetic anhydride and the solution was placed in a hydrogenating apparatus. About 0.2 g. of platinum oxide was added and the solution was shaken with hydrogen under a pressure of 1-3 atmospheres while heat was applied by means of an infra-red lamp. Absorption of hydrogen started at once and was complete in two hours. The cooled solution was filtered to remove the catalyst, diluted with 100 ml. of water and set in an ice bath for 40 hours. White crystals separated which were dried in air to yield 14 g. (70%) of 2,5-diacetamidobenzotrifluoride, m.p. 184-187°.



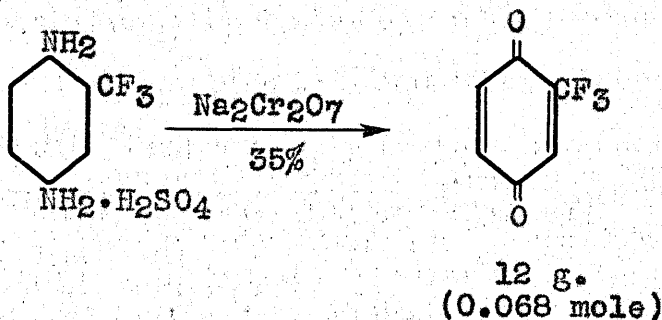
2,5-Diaminobenzotrifluoride hydrosulfate (XLVIII).--

A 50 g. (0.19 mole) portion of 2,5-diacetamidobenzotrifluoride was heated with stirring in a solution of 255 ml. of concentrated sulfuric acid diluted with 770 ml. of water until it dissolved. The hot solution was decolorized by filtering with charcoal. The product, 2,5-diaminobenzotrifluoride hydrosulfate, was not isolated but was oxidized in the sulfuric acid solution as described below.



Trifluoromethylbenzoquinone (XLIX).---The sulfuric acid solution of 2,5-diaminobenzotrifluoride hydrosulfate prepared as above from 50 g. (0.19 mole) of 2,5-diacetamidobenzotrifluoride was set in an ice bath and 750 ml. of benzene was added. The heterogeneous system was cooled to 8° and stirred vigorously while a solution of 68 g. (0.26 mole) of sodium dichromate dihydrate in 125 ml. of water was added at such a rate that the temperature did not rise above 10°. The reaction mixture was stirred for two hours in the cold and the benzene layer was separated. It was dried over anhydrous sodium sulfate and concentrated to about 30 ml. by distilling off the benzene under reduced pressure provided by the water pump. About 100 ml. of Skellysolve C was added and the solution was chilled in a Dry Ice-chloroform bath. Reddish-orange crystals of trifluoromethylbenzoquinone separated together with white crystals of benzene. The benzene crystals dissolved upon slight warming and the trifluoromethylbenzoquinone was filtered off. By addition of another 100 ml. of Skellysolve C to the filtrate and subsequent cooling as before, another crop was obtained. Dried

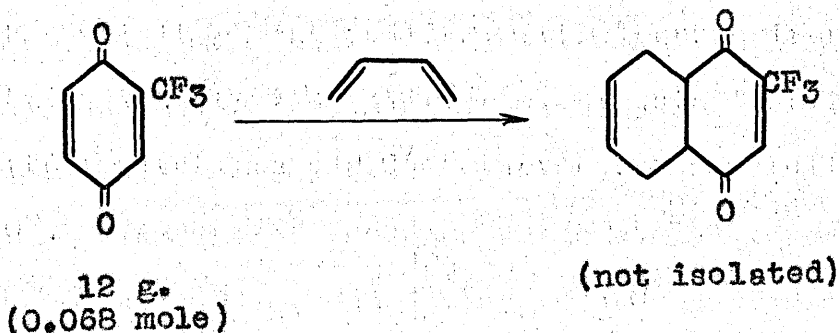
in air, the weight of the trifluoromethylbenzoquinone was 12 g. (35%), m.p. 48-49°. After one recrystallization from alcohol the product was a dull yellow color and melted at 51.2-54.0°.



2-Trifluoromethyl-5,8,9,10-tetrahydro-1,4-naphthoquinone

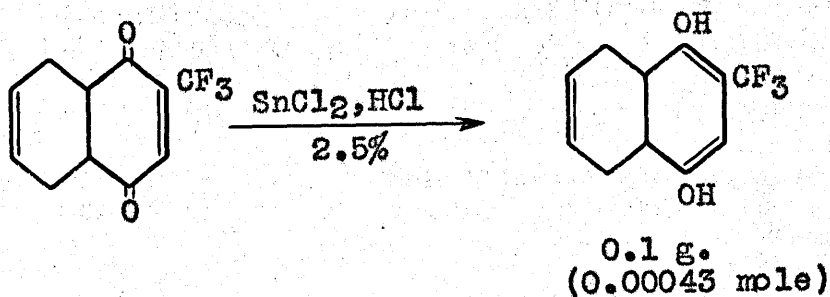
(L).---This compound was prepared by the general method described by Fieser (54) for the preparation of substituted naphthoquinones from substituted benzoquinones.

A solution of 12 g. (0.068 mole) of trifluoromethylbenzoquinone in 35 ml. of acetic acid was placed in a pressure flask and cooled in ice water. A 4.3 g. (0.08 mole) portion of butadiene which had been condensed out of a tank into a graduated cylinder set in Dry Ice was added, the stopper was clamped on, and the flask was immersed in running water for forty hours. The solution was filtered with acetic acid washed charcoal and reserved for the next reaction. The product, 2-trifluoromethyl-5,8,9,10-tetrahydro-1,4-naphthoquinone, was not isolated.



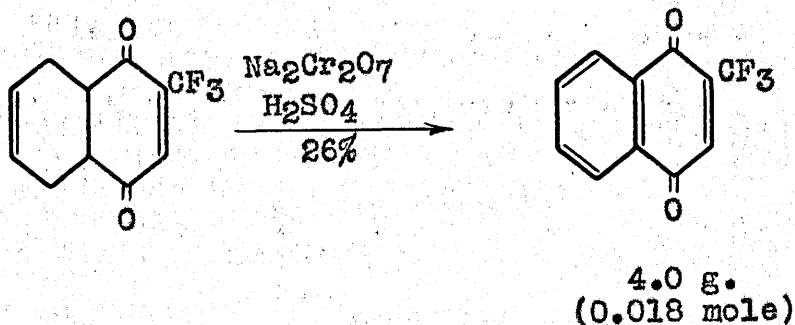
2-Trifluoromethyl-5,8,9,10-tetrahydro-1,4-naphthohydroquinone (LI).--An acetic acid solution of 2-trifluoromethyl-5,8,9,10-tetrahydro-1,4-naphthoquinone prepared as described above from 3.0 g. (0.017 mole) of trifluoromethylbenzoquinone was heated on a steam bath for twenty minutes and to the hot solution was added 2.8 ml. of concentrated hydrochloric acid and 0.42 g. of stannous chloride in 14 ml. of water. The solution was allowed to stand overnight at room temperature and was then chilled in ice. After several hours, light-colored crystals separated which were filtered off and dried in air. Weight of the 2-trifluoromethyl-5,8,9,10-tetrahydro-1,4-naphthohydroquinone obtained was 0.1 g. (2.5%), m.p. 163-167°. After recrystallization from alcohol, the product melted at 176.8-177.0°.

Anal. Calcd. for $C_{11}H_{11}O_2F_3$: C, 56.9; H, 4.8. Found: C, 57.0, 56.9, 57.2, 56.9; H, 5.0, 4.9, 4.6, 4.8.



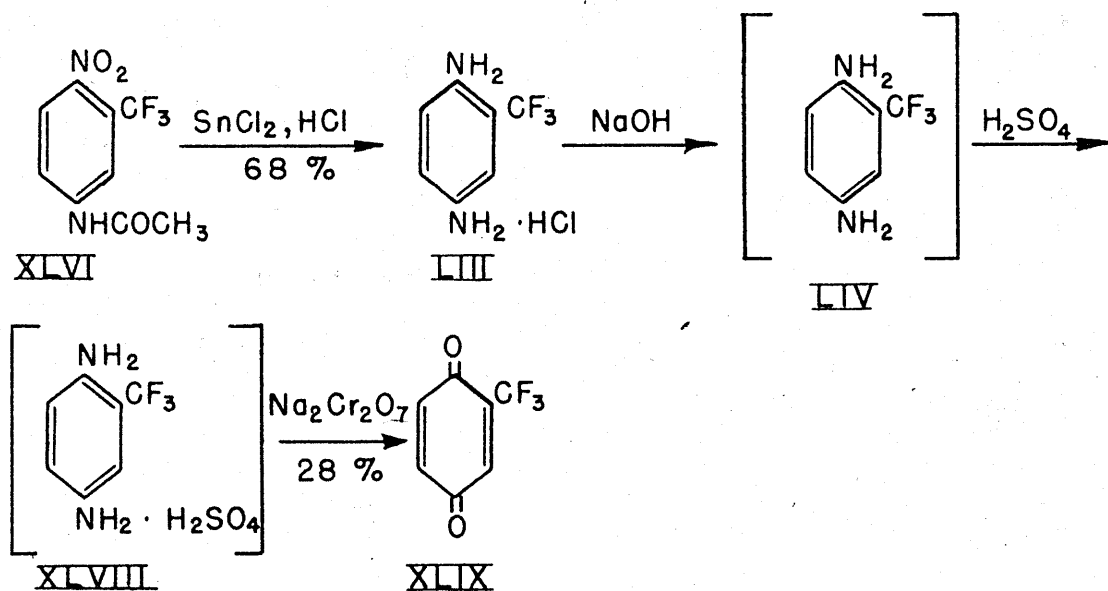
2-Trifluoromethyl-1,4-naphthoquinone (LII).--An acetic acid solution of 2-trifluoromethyl-5,8,9,10-tetrahydro-1,4-naphthoquinone (I) prepared as described above from 12 g. (0.068 mole) of trifluoromethylbenzoquinone was placed in a 500 ml. three-necked flask equipped with a Hershberg stirrer and thermometer. It was heated to 50° and treated with a solution of 27.3 g. (0.092 mole) of sodium dichromate dihydrate and 1.4 ml. of concentrated sulfuric acid in 17 ml. of water at 50°. The mixture was heated to 65° over a hot plate and maintained at 65-70°. After about twenty minutes, the temperature suddenly began to rise and cooling was provided by means of an ice bath. The mixture was maintained at 65-70° for another half hour, then poured into a mixture of 70 g. of ice and 70 ml. of water. The yellow solid which appeared was filtered off, washed with water, and dried in air. Weight of the 2-trifluoromethyl-1,4-naphthoquinone was 4.0 g. (26%), m.p. 73.0-83.5°. After two recrystallizations from ethanol, the product melted at 104.3-105.0°.

Anal. Calcd. for $C_{11}H_5O_2F_3$: C, 58.4; H, 2.2. Found: C, 58.7; H, 2.2.

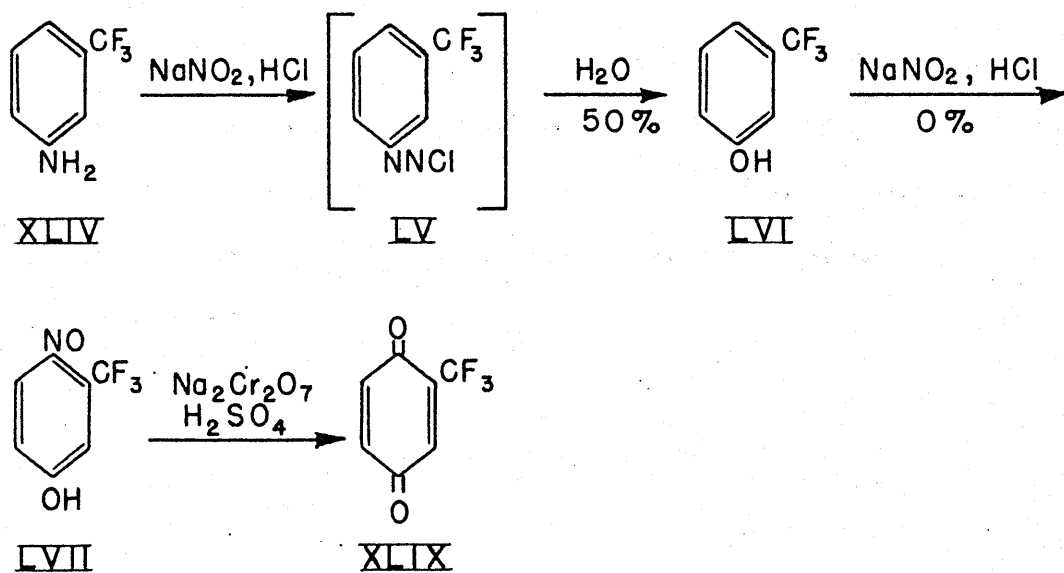


III. b. Synthesis of 2-trifluoromethyl-1,4-naphthoquinone.

Method II. An alternate route to trifluoromethylbenzoquinone:



Method III. An attempted route to trifluoromethylbenzoquinone:

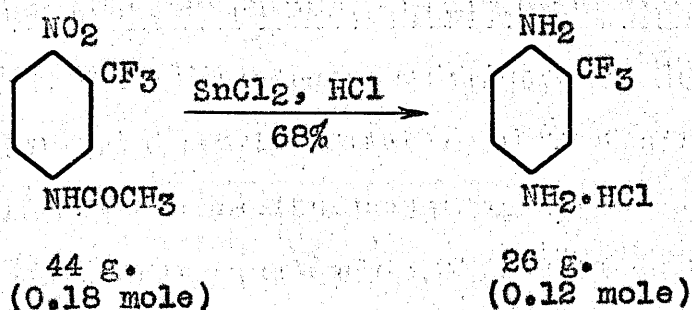


2,5-Diaminobenzotrifluoride hydrochloride (LIII).---To 44 g. (0.18 mole) of 2-nitro-5-acetamidobenzotrifluoride in a 1 l. beaker was added a solution of 147 g. of stannous chloride in 168 ml. of concentrated hydrochloric acid. The temperature of the mixture rose slowly to 60° and it was heated on a hot plate to about 90° and kept hot for two hours. It was filtered to remove some insoluble impurities and H₂S gas was passed into the hot solution for several hours. The heavy yellow precipitate of stannic sulfide was filtered off and the filtrate was evaporated to dryness. The weight of the crude product was 37 g.

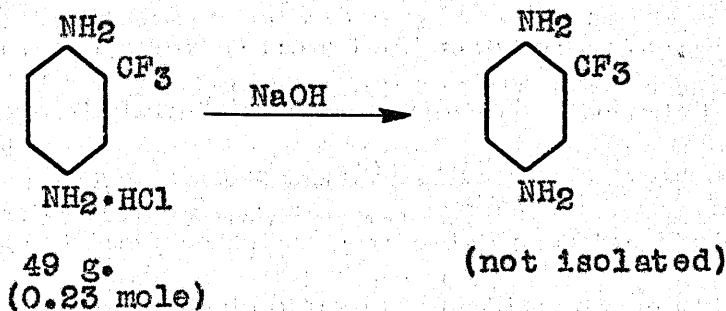
This material was sublimed at 210° under 5 mm. pressure to yield 30 g. of sublimate which was somewhat brownish in color. It was dissolved in water, filtered with charcoal, evaporated to dryness and resublimed to give 26 g. (68%) of 2,5-diaminobenzotrifluoride hydrochloride which did not melt below 250°.

An analytical sample was prepared by neutralizing the hydrochloride with dilute sodium hydroxide, extracting the free base with ether and reprecipitating the hydrochloride by passing in dry hydrogen chloride gas. The precipitated salt was filtered off, dried, and resublimed.

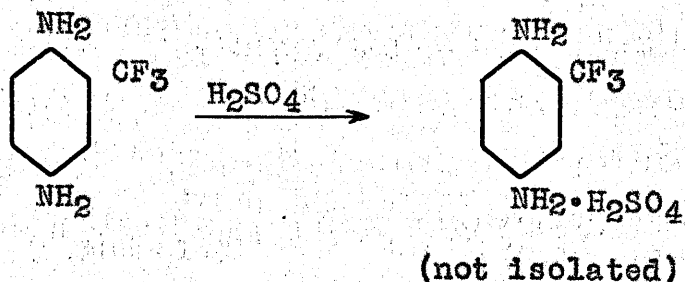
Anal. Calcd. for C₇H₈N₂ClF₃: C, 39.5; H, 3.8; N, 13.2.
Found: C, 39.4; H, 3.8; N, 13.4.



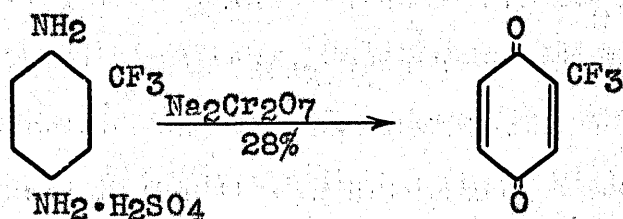
2,5-diaminobenzotrifluoride (LIV).--A solution of 49 g. (0.23 mole) of 2,5-diaminobenzotrifluoride hydrochloride in 200 ml. of water was made basic with 10% sodium hydroxide solution and extracted with ether. The ethereal solution began to darken at once. The 2,5-diaminobenzotrifluoride was not isolated but was used in the ether solution for the next reaction.



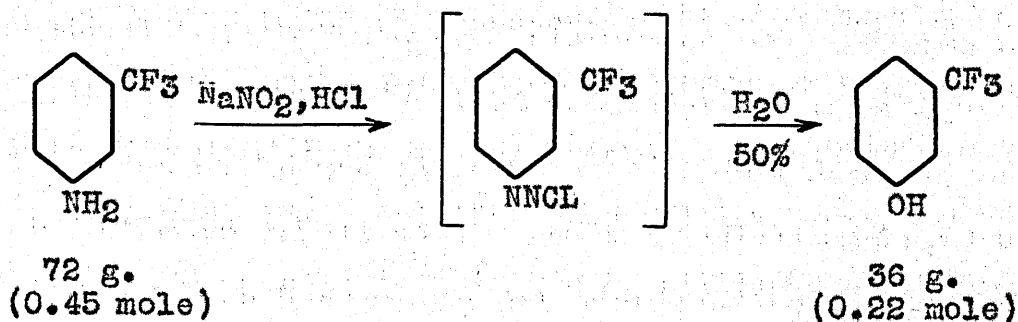
2,5-diaminobenzotrifluoride hydrosulfate (XLVIII).--The ethereal solution of 2,5-diaminobenzotrifluoride described above was extracted with a solution of 250 ml. of concentrated sulfuric acid in 775 ml. of water. The acid solution was clarified by filtration with charcoal and used directly for the oxidation reaction described below without isolating the 2,5-diaminobenzotrifluoride hydrosulfate.



Trifluoromethylbenzoquinone (XLIX).--The sulfuric acid solution prepared as above from 49 g. (0.23 mole) of 2,5-diaminobenzotrifluoride hydrochloride was placed in a 3 l. beaker equipped with a thermometer and mechanical stirrer and cooled in an ice bath. Approximately 750 ml. of benzene was added, the mixture was cooled to 8° and oxidized by the addition of a solution of 68 g. (0.23 mole) of sodium dichromate dihydrate in 125 ml. of water at such a rate that the temperature did not rise above 10°. After addition was complete, the mixture was stirred for two hours in the cold and the benzene layer was separated. It was dried over anhydrous sodium sulfate, filtered, and concentrated to about 40 ml. by distilling off the benzene under reduced pressure provided by the water pump. The residue was diluted with 100 ml. of Skellysolve C and cooled in a Dry Ice-chloroform mixture. Reddish-orange crystals separated which were filtered off. Further addition of Skellysolve C with cooling as before produced a second crop of crystals. Total weight of the trifluoromethylbenzoquinone obtained was 11.5 g. (28% based on the diamine hydrochloride), m.p. 49.5-51.3°.

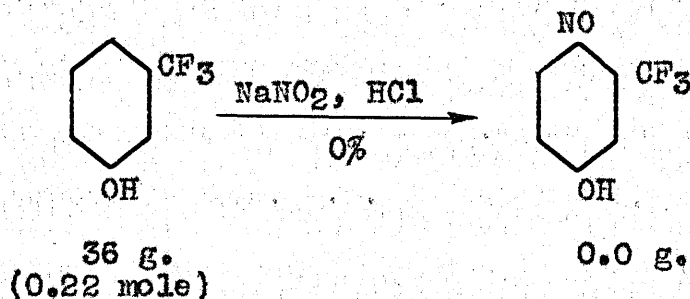


3-Hydroxybenzotrifluoride (LVI).—A 72 g. (0.45 mole) portion of 3-aminobenzotrifluoride was added to a solution of 49 ml. of concentrated sulfuric acid in 225 ml. of water. The solution was cooled to 0° and diazotized by the gradual addition of 34 g. (0.49 mole) of sodium nitrite in the form of moist balls at a temperature below 5°. The excess nitrous acid was destroyed by the addition of 10 g. of urea. The 3-trifluoromethylbenzene diazonium chloride (LV) formed in the reaction mixture was hydrolyzed and removed by steam distillation from a dilute sulfuric acid solution. About 500 ml. of distillate was collected which was extracted with ether. The ether extract was dried over anhydrous sodium sulfate, the ether was removed and the residue was distilled under reduced pressure to yield 36 g. (50%) of colorless 3-hydroxybenzotrifluoride, b.p. 75° at 14 mm.



Attempted preparation of 2-nitroso-5-hydroxybenzotrifluoride (LVII).--The method described by Kremers et al. (55) for the preparation of nitrosothymol was used.

A 36 g. (0.22 mole) portion of 3-hydroxybenzotrifluoride dissolved in 166 ml. of 95% ethanol was placed in a 1 l. beaker set in an ice-salt bath, 166 ml. of concentrated hydrochloric acid was added and the solution was cooled below 0°. Dry sodium nitrite was added in about 5 g. portions until a total of 23 g. (0.33 mole) had been introduced. There was no evidence of a reaction. No precipitate was obtained when a small sample was poured into water. The reaction mixture was allowed to stand at room temperature for twenty-four hours without apparent effect. It was heated for three hours on the steam bath at about 60° but no reaction was observed. When it was poured into 2 l. of water, a reddish oil separated which was removed and identified as the starting material. No 2-nitroso-5-hydroxybenzotrifluoride was obtained.



DISCUSSION OF EXPERIMENTAL RESULTS

I. SYNTHESIS OF 3,4-DIFLUOROPHENYLARSONIC ACID

Method I (Flow sheet I a, page 12).--The steps involved in this synthetic scheme were comparatively straightforward and were carried out with good yields up to the proposed decomposition of 2-fluoro-5-acetamidobenzene diazonium fluoborate (VII) to produce 2,4-difluoroacetanilide (VIII), a reaction resulting in zero yield.

The first step, the preparation of *p*-nitrofluorobenzene (II), was carried out in 61% yield while at the same time a 33% yield of 2,4-dinitrofluorobenzene was obtained. Bradlow (56) reports that the use of a smaller quantity of sulfuric acid increases the yield of the mono-nitro compound by 10-15%.

The decomposition of 5-acetamidobenzene diazonium fluoborate (VII) was attempted several times but each time a hopeless mass of tar was obtained from which no products could be isolated. Roe (34), in his discussion of the Schiemann reaction, lists the preparation of only one fluoroacetanilide from the corresponding fluoborate but no yield is reported. He also makes the statement that amino groups lower the yield of fluoride obtained. These facts indicate that the presence of the acetamido group practically eliminates the possibility of obtaining a good yield from a Schiemann reaction.

Hence, it was necessary to abandon the approach.

Method II (Flow sheet I b, page 21).---In an effort to avoid the presence of the acetamido group during the Schiemann reaction a scheme was devised whereby a nitro group would be in the place of the acetamido group.

The first step, reduction of 2,4-dinitrofluorobenzene (XI) with stannous chloride and hydrochloric acid produced the desired isomer, 2-amino-4-nitrofluorobenzene (XII), in a favorable ratio (4:1) to the other isomer, 2-nitro-4-aminofluorobenzene (IV), but yields were discouraging (24% and 6% respectively). The observation of Blanksma (36) that 2-amino-4-nitrofluorobenzene (XII) had a sweet taste was confirmed by this investigator. A sweet odor could be detected also during evaporation of solutions of this compound.

A rather low yield (38%) of 2-fluoro-5-nitrobenzene diazonium fluoborate (XIII) was obtained by a Schiemann reaction on 2-amino-4-nitrofluorobenzene (XII). This bright yellow compound was quite sensitive to light and would darken on the surface when exposed for only a few minutes although shaded areas remained bright. The attempted decomposition of 2-fluoro-5-nitrobenzene diazonium fluoborate (XIII) to obtain 3,4-difluoronitrobenzene by heating the dry salt resulted in a violent explosion. Even though "diluted" with sand, 1 g. of the fluoborate detonated with sufficient force to shatter a 125 ml. flask into small pieces. It was deemed too dangerous to pursue the investigation of this

type of decomposition further and heating in an inert solvent was attempted. This procedure resulted in a tarry mass from which no product could be isolated. This approach also was abandoned.

Method III (Flow sheet I c, page 26).---In this synthetic scheme, fluorine atoms were introduced into the benzene ring first, to be followed by nitration, reduction and arsonation. Happily, this procedure produced good yields at every step, except, perhaps, the Bart reaction in the last step.

In performing a Schiemann reaction on methyl anthranilate (XV), two slight modifications of the usual procedure, suggested by the experience of other workers (57) on this type of reaction, were introduced. The initial diazotization was conducted in a stainless steel beaker. This had the advantage of speeding up the cooling process due to more rapid heat interchange between the solution and the ice-salt bath, and, in addition, the yield was increased from a reported 66% (58) to 91%. It has been found in this laboratory that, in general, an increase of 10% in the overall yield is frequently obtained by the use of a stainless steel beaker.

Following the decomposition of the fluoborate, the product was taken up in ether, dried, and dissolved boron trifluoride was removed by precipitating out an ammonia-boron trifluoride complex by passing in dry ammonia gas. This eliminated the possibility of complex-formation sometimes

encountered during the distillation process. The yield of 2-fluoromethyl benzoate obtained by this method was 70% while the reported yield was 53% (58).

Several variations of the Hofmann reaction were tried in the preparation of 2-fluoroaniline (XIX) from 2-fluorobenzamide (XVIII). The use of sodium hypobromite following several different procedures produced yields of 10-48%. Sodium hypochlorite consistently gave 58-66% yields of 2-fluoroaniline (XIX).

The Schiemann reaction with 2-fluoroaniline (XIX) produced 2-fluorobenzene diazonium fluoborate (XX) in 89% yield as compared with a reported 45% (37). Decomposition of this fluoborate salt proceeded smoothly to give a 73% yield of *o*-difluorobenzene (XXI) although the reported yield is only 30% (37). No special variations from the customary methods were used in the decomposition.

Nitration of *o*-difluorobenzene (XXI) gave 3,4-difluoronitrobenzene (XIV) in 93% yield as compared to a reported 85% (39) and catalytic reduction of the nitro compound gave 3,4-difluoroaniline (IX) in 93% yield.

The Bart reaction on 3,4-difluoroaniline (IX) gave 3,4-difluorophenylarsonic acid in 31% yield without serious complications.

Method IV (Flow sheet I d, page 36).--A potentially shorter method of obtaining 2-fluoroaniline wherein *o*-nitroaniline is used as the starting material was attempted

according to this scheme. The yields on all steps were unsatisfactory and, furthermore, the decomposition of 2-nitrobenzene diazonium fluoborate was a very laborious and time-consuming task. The scheme was therefore discarded in favor of Method III.

II. SYNTHESIS OF 5-FLUORO-7-DIETHYLAMINOMETHYL-8-HYDROXYQUINOLINE AND 5-FLUORO-7-iodo-8-HYDROXYQUINOLINE

Method I (Flow sheet II a, page 40).---The preparation of 5-nitroso-8-hydroxyquinoline (XXVI) was carried out in good yield (78%) without difficulty. Reduction of 5-nitroso-8-hydroxyquinoline (XXVI) to 5-amino-8-hydroxyquinoline (XXVII) by chemical means using stannous chloride and hydrochloric acid was accomplished in rather low yield (41%) at the cost of considerable time and effort, the product being obtained as the hydrochloride. When reduced by catalytic methods, yields were high (85-99%) but the identity and purity of the product was questionable. 5-Amino-8-hydroxyquinoline (XXVII) was so unstable that it was found best to isolate the hydrochloride and carry the work forward with that material.

The preparation of the diazonium fluoborate of 5-amino-8-hydroxyquinoline (XXVIII) was carried out by diazotization in 45% fluoboric acid. The yield was somewhat low but this is not unusual for quinoline compounds.

The decomposition of 8-hydroxyquinolyl-5 diazonium fluoborate (XXVIII) gave a low yield (26%) of 5-fluoro-8-hydroxy-

quinoline (XXIX) which could not be improved by repeated attempts.

By means of a Mannich reaction on 5-fluoro-8-hydroxyquinoline (XXIX), 5-fluoro-7-diethylaminomethyl-8-hydroxyquinoline was obtained in 42% yield without serious trouble.

Treatment of 5-fluoro-8-hydroxyquinoline (XXIX) with iodine in alkaline solution produced 5-fluoro-7-iodo-8-hydroxyquinoline in 50% yield.

In general, the whole process outlined on flow sheet IIa was deemed quite unsatisfactory due to low yields on several steps and the instability of some of the intermediates which made the work very difficult and tedious.

Method II (Flow sheet II b, page 48).--It was decided to avoid the use of the unstable aminoquinoline intermediates by introducing the fluorine atom into a benzene nucleus which could be converted later into a quinoline ring.

A Schiemann reaction on *p*-anisidine (XXXII) produced *p*-fluoroanisole (XXXIV) in 62% overall yield. Nitration of the latter was carried out by two methods, a.) with nitric acid and b.) with ethyl nitrate. The yields of 2-nitro-4-fluoroanisole (XXXV) reported by Swarts (45) from the nitration of *p*-fluoroanisole (XXXIV) with nitric acid in acetic anhydride could not be duplicated. An appreciable amount of the starting material remained unreacted. Furthermore, this procedure gave a considerable amount of 2,6-dinitro-4-fluorophenol which was difficult to deal with in working

up the product. Nitration with ethyl nitrate was more satisfactory giving 2-nitro-4-fluoroanisole (XXXV) in 56% yield. However, it was found necessary to use fresh reagent for this reaction.

Reduction of 2-nitro-4-fluoroanisole (XXXV) was readily accomplished either with stannous chloride and hydrochloric acid or catalytically. Catalytic reduction gave higher yields (86-88% vs. 56%) and platinum oxide caused the reaction to proceed much faster than Raney nickel.

A detailed study of the Skraup reaction used to convert 2-amino-4-fluoroanisole (XXXVI) to 5-fluoro-8-methoxyquinoline (XXXVI) was conducted. When nitrobenzene was used as an oxidizing agent, a yield of 37% was obtained. The yield obtained by using nitroethane was in the same range (29%).

In the Skraup reaction, the nitro compound used as an oxidizing agent is itself reduced to an amine, which, in the case of an aromatic compound, can then also undergo a Skraup reaction, thereby competing with the progress of the desired reaction and contaminating the product. In an effort to remove this possibility, a reaction was conducted using 2-nitro-4-fluoroanisole (XXXV) as the oxidizing agent which, if reduced, would yield 2-amino-4-fluoroanisole (XXXVI), the starting material. However, the reverse effect was achieved. The yield, instead of increasing, dropped to 9%.

It was concluded that there are inherent limitations

to the yield obtainable from this reaction, probably due to such factors as steric hindrance and hydrogen bonding.

Cleavage of 5-fluoro-8-methoxyquinoline (XXXVII) with hydriodic acid went smoothly to produce 5-fluoro-8-hydroxyquinoline (XXIX) in 70% yield.

Method III (Flow sheet II c, page 61).---It was felt that a large part of the difficulty in synthesizing 5-fluoro-8-hydroxyquinoline by Method I was due to the presence of the hydroxyl group. By blocking this group through formation of an ether, a less reactive compound would be obtained from which higher yields might be obtained in a Schiemann reaction.

The methylation of 8-hydroxyquinoline (XXV) with methyl sulfate produced an unexpectedly low yield (12%) of 8-methoxyquinoline (XXXVIII) with a high (70%) recovery of starting material. The 70% yield reported by Kaufman and Rothlin (48) could not be duplicated, possibly because the description of their procedure was incomplete and ambiguous.

Nitration of 8-methoxyquinoline (XXXVIII) was carried out in reasonable yield (56%) but attempted reduction of 5-nitro-8-methoxyquinoline (XXXIX) produced dark tars from which none of the desired 5-amino-8-methoxyquinoline (XX) could be isolated.

After several attempts, this method was abandoned as definitely inferior to Method II, although, perhaps, not impossible if given sufficient study.

III. SYNTHESIS OF 2-TRIFLUOROMETHYL-1,4-NAPHTHOQUINONE

Method I (Flow sheet III a, page 66).--The sequence of reactions proposed in this scheme was carried out effectively up to the nitration of 3-acetamidobenzotrifluoride (XLV). Although no trouble was encountered during this reaction, it was difficult to obtain a product pure enough to be reduced catalytically. To obtain such a material, it was found necessary to perform successive recrystallizations from benzene, alcohol and acetic acid.

A study was made of the products of the nitration. In addition to the desired 2-nitro-5-acetamidobenzotrifluoride (XLVI), a small quantity (2.5%) of the colorless (!) isomer 2-nitro-3-acetamidobenzotrifluoride and a small quantity (1.5%) of the highly nitrated compound 2,3,4,6-tetranitro-5-acetamidobenzotrifluoride were obtained. It is possible that small amounts of these and other products, removable by the triple recrystallization employed, inhibited the catalytic reduction.

Once purified sufficiently, reduction of 2-nitro-5-acetamidobenzotrifluoride (XLVI) with hydrogen and platinum oxide proceeded smoothly to completion with little trouble. The use of acetic anhydride as a solvent resulted in acetylation of the amine as it was formed. Difficulty was sometimes experienced in isolating the 2,5-diacetamidobenzotrifluoride (XLVII) from the solution due to the formation, after the solvent had been removed, of an orange oil which interfered with the recrystallization.

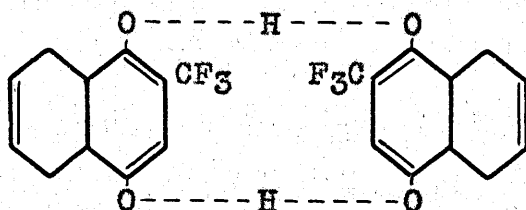
The hydrolysis of 2,5-diacetamidobenzotrifluoride (XLVII) with dilute sulfuric acid took place readily. The product, 2,5-diaminobenzotrifluoride hydrosulfate (XLVIII), which was not isolated, is written as the mono-hydrosulfate of 2,5-diaminobenzotrifluoride by analogy with the composition of the hydrochloride which will be mentioned later.

Oxidation of 2,5-diaminobenzotrifluoride hydrosulfate (XLVIII) with sodium dichromate seemed to take place quite easily but the isolation of the product, trifluoromethylbenzoquinone (XLIX) was not a simple task. The reaction mixture was kept in intimate contact with benzene, thus extracting the product as it was formed. This procedure was apparently effective, but frequently an emulsion was obtained from the mixture which required several hours to separate. For best results, it was desirable that the solutions be kept as cold as possible without causing the benzene to crystallize. Hence, the reaction was run between 6 and 10° and the benzene was removed under vacuum at 10-20°. Yields were from 15-35%. This particular reaction was rather unsatisfactory and was a bottleneck in the general scheme. Variations were attempted using ferric chloride and hydrogen peroxide. However, no improvement over the method described was obtained although a critical study was not made.

The reaction of trifluoromethylbenzoquinone (XLIX) with butadiene apparently took place with reasonable yields al-

though the product, 2-trifluoromethyl-5,8,9,10-tetrahydro-naphthoquinone (L) was not isolated.

Reduction of this material with stannous chloride and hydrochloric acid gave 2-trifluoromethyl-5,8,9,10-tetrahydro-naphthohydroquinone (LI) in very low yield (2.5%). The melting point of this compound was 176° which is close to that of a non-halogenated related compound, 2-methyl-5,8-dihydro-1,4-naphthohydroquinone, m.p. 171° (59). A second compound, purple in color, and melting at 133° was isolated from this reaction but not identified. By analogy to the structure of an intermediate reduction compound isolated by Okahara and Murata (59), the following quinhydrone structure is postulated for this material.



The material described by Okahara and Murata was purple in color and melted at 126°.

Oxidation of 2-trifluoromethyl-5,8,9,10-tetrahydro-naphthoquinone (L) with sodium dichromate and sulfuric acid gave the desired final product, 2-trifluoromethyl-1,4-naphthoquinone. Oxidation of 2-trifluoromethyl-5,8,9,10-tetrahydro-naphthohydroquinone (LI) or of the quinhydrone

described above would also be expected to yield 2-trifluoromethyl-1,4-naphthoquinone.

Method II (Flow sheet III b, page 78).---The time, trouble, and loss of material entailed in the repeated recrystallization of 2-nitro-5-acetamidobenzotrifluoride (XLVI) required for catalytic reduction prompted the trial of another scheme using reduction with stannous chloride and hydrochloric acid.

The reduction with stannous chloride was readily accomplished with accompanying hydrolysis of the acetamido group to yield 2,5-diaminobenzotrifluoride hydrochloride. Analysis showed the presence of only one hydrochloride. The analytical sample was prepared by passing anhydrous hydrochloric acid into an ether solution of the amine. It is conceivable that under such circumstances, a salt is formed more readily with one amino group than the other and the compound is thereupon precipitated out of solution before the other group is affected. Perhaps in aqueous solution, the dihydrochloride is formed and could be isolated by evaporation. A test made with o-aminobenzotrifluoride shows this compound to form a hydrochloride readily under the same conditions, thus eliminating the possibility that steric hindrance, hydrogen bonding or inductive effect could offer complete explanations of the lack of formation of the dihydrochloride.

By conversion of the hydrochloride to the hydrosulfate,

followed by oxidation with sodium dichromate, the desired trifluoromethylbenzoquinone is obtained.

In the absence of an easier and faster way to purify 2-nitro-5-acetamidobenzotrifluoride, the procedure of Method II is recommended.

Method III (Flow sheet III b, page 78).--The relative ease of preparation of thymoquinone from thymol (55) suggested that a similar method of attack on m-trifluoromethylphenol might produce equally good results.

Accordingly, m-trifluoromethylphenol (LVI) was prepared from m-trifluoromethylaniline in 50% yield by diazotization and hydrolysis. However, the proposed nitrosation of the phenol (LVI) could not be forced to go. Most nitrosations are performed either in the cold or at room temperature, but no reaction seemed to occur in this case even when heated to 60° for several hours. Hence, the scheme had to be abandoned.

PHARMACOLOGICAL TESTING

Pharmacological testing of the four potentially active compounds prepared is largely incomplete.

1. 5-Fluoro-7-diethylaminomethyl-8-hydroxyquinoline. This compound was intended for an antimalarial. In vitro tests¹ showed it to have an activity of less than 0.075 times that of quinine. As an amebicidal agent, it was found to be as effective in dilutions of 1:150,000 as emetine in dilutions of 1:1,000,000.

2. 5-Fluoro-7-iodo-8-hydroxyquinoline. This compound, an analog of Vioform, was prepared for testing as an amebicidal agent. No reports of its activity are available as yet.

3. 3,4-Difluorophenylarsonic acid. This compound, a potential spirocheticide, has not been tested as yet.

4. 2-Trifluoromethyl-1,4-naphthoquinone. This compound has been submitted for testing as a potential anti-vitamin K material. Pharmacological testing is incomplete as yet.

¹ Carried out by Parke, Davis & Company.

SUMMARY

The synthesis of the following new fluorine-containing compounds is reported:

3-nitro-4-fluoroacetanilide

3-amino-4-fluoroacetanilide

2-fluoro-5-acetamidobenzene diazonium fluoborate

3,4-difluoraniline

3,4-difluorophenylarsonic acid

2-fluoro-5-nitrobenzene diazonium fluoborate

8-hydroxyquinolyl-5 diazonium fluoborate

5-fluoro-8-hydroxyquinoline

5-fluoro-7-diethylaminomethyl-8-hydroxyquinoline

5-fluoro-7-iodo-8-hydroxyquinoline

2-amino-4-fluoroanisole

5-fluoro-8-methoxyquinoline

2,5-diacetamidobenzotrifluoride

2,5-diaminobenzotrifluoride hydrochloride

trifluoromethyl-1,4-benzoquinone

2,3,4,6-tetranitro-5-acetamidobenzotrifluoride

2-trifluoromethyl-5,8,9,10-tetrahydro-1,4-naphthohydroquinone

2-trifluoromethyl-1,4-naphthoquinone

Four of the above-listed compounds are potentially active therapeutic agents.

5-Fluoro-7-diethylaminomethyl-8-hydroxyquinoline, an analog of aminoalkylphenols known to possess high anti-

malarial activity, was synthesized for testing as an anti-malarial agent.

5-Fluoro-7-iodo-8-hydroxyquinoline, an analog of Vioform (5-chloro-7-iodo-8-hydroxyquinoline), a valuable amebicide, is a potential amebicidal agent.

3,4-Difluorophenylarsonic acid, an analog of Atoxyl, an arsenical of known activity, was prepared for testing as a spirocheticide.

2-Trifluoromethyl-1,4-naphthoquinone, an analog of the vitamin K substitute Menadione (2-methyl-1,4-naphthoquinone), is a potential vitamin K antagonist.

In vitro tests on 5-fluoro-7-diethylaminomethyl-8-hydroxyquinoline indicate an antimalarial activity of less than 0.075 times that of quinine, and an amebicidal activity of about 1/7 that of emetine.

Pharmacological tests are incomplete on the other three compounds.

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