SYNTHESIS OF FLUORINE SUBSTITUTED MEDICINALS

by

August Sveinbjornsson
B. S., University of Wisconsin, 1944
M. S., University of Wisconsin, 1945

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Advisory Committee:

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Redacted Signature

Redacted Signature

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It was found that some types of structural analogues of various vitamins would cause the appearance of characteristic signs of vitamin deficiency diseases in animals, and that these signs could be cured or prevented by adequate doses of the vitamin involved. Woolley and White (5) reported that the feeding of minute amounts of pyrithiamine to mice caused the appearance of typical signs of thiamin deficiency in these animals. Pyrithiamine is the analogue of thiamine in which the thiazole ring is replaced by the pyridine ring, or more specifically, the sulfur atom is replaced by -CH=CH-. It was then shown that glucoascorbic acid, a structural analogue of ascorbic acid, produced a scurvylike disease of rats, mice, and guinea pigs, and that, in guinea pigs, the disease was prevented by adequate amounts of ascorbic acid. Furthermore, signs of riboflavin deficiency was produced in rats by feeding isoriboflavin, and in mice by feeding 2,4-dinitro-7,8-dimethyl-10-ribityl-5,10-dihydrophenazine, the phenazine analogue of riboflavin. Moreover, manifestations of nicotinic acid deficiency were brought about in mice by feeding 3-acetylpyridine, and prevented with nicotinic acid (6).

It is necessary to bear in mind that the analogues of the vitamins known to be essential to animals including man, also show deficiency signs in animals as well as in bacteria. Thus, it is apparent that the analogues of the vitamins essential to man could not be employed as chemotherapeutic agents, if they harm the host more than the pathogenic

ACKNOWLEDGEMENTS

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C. Interest in Fluorine-Containing Organic Compounds.

The increasing interest in fluorine chemistry which has been evoked by the large scale use of fluorine and fluorine compounds on the Manhattan Project and by the important role of hydrofluoric acid in the production of high octane fuels, both of which developments have made fluorine a readily available commodity, have likewise focused attention on the aromatic fluorine-containing compounds. The field of the synthetic preparation of organic medicinals containing fluorine, particularly, appears to be virtually untouched, with few compounds of this type having been reported and still fewer adequately tested.

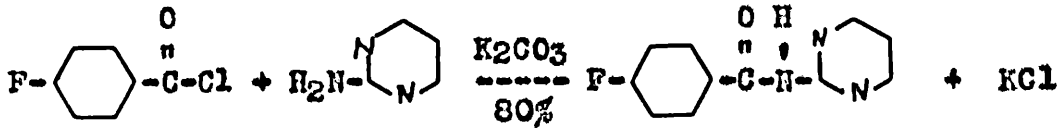
Several avenues of approach to the problem hold great interest. The first possibility is the exchange of fluorine for atoms of other members of the halogen family in important molecular structures. This approach appears less attractive, largely because there is considerable difference between the size of the fluorine atom and the other halogen atoms. In general, it appears that molecular size relationships are of importance in determining physiological and chemotherapeutic properties of organic compounds.

A second approach which is indicated is the substitution of fluorine for amino and hydroxyl groups in the molecules of compounds of importance in medicine. It may be pointed out that the fluorine atom is not only isosteric with the amino and hydroxyl groups, but is also of approximately the same weight. Therefore, the fluorine atom might be expected to

TABLE OF CONTENTS

reflux on a steam bath for three hours. The solid remaining after removal of the ether and addition of 50 ml. of water was filtered and air dried to give 5.6 g. (91%) of crude material. This was dissolved in benzene, extracted with 5% hydrochloric acid and the benzene solution dried over anhydrous sodium sulfate. Addition of Skellysolve C to the benzene solution gave 4.8 g. (80.0%) of 2-(p-fluorobenzamido)-pyrimidine melting at 224.4-226.0°.

Anal. Calcd. for $C_{11}H_8ON_3F$: C, 60.8, H, 3.7. Found: 60.6. Found: 3.6.



4.4 g. (0.028 mole) 2.7 g. (0.028 mole) 5.6 g. (0.025 mole)

2-(p-Fluorobenzamido)-pyridine.-- A 75 ml., conically shaped flask, equipped with a mechanical stirrer, a condenser and a dropping funnel was charged with 1.4 g. (0.015 mole) of 2-aminopyridine dissolved in 10 ml. of dry pyridine, and 2.4 g. (0.015 mole) of p-fluorobenzoyl chloride added dropwise with stirring. The mixture was heated on the steam bath for one hour, and 0.6 g. (0.015 mole) of sodium hydroxide dissolved in 5 ml. of water was then added slowly with continued heating. The pyridine was removed by distillation under reduced pressure, water being added from time to time to maintain the volume approximately constant. The resulting precipitate was filtered and washed repeatedly with water

TABLE OF CONTENTS (Continued)

TABLE OF CONTENTS (Continued)

hence does not retard the spreading of the disease.

When testing the anti-malarial activity of synthetic drugs, it soon became apparent that an exact quinine structure was not essential. In fact, recent research has revealed that a great variety of organic molecules show anti-malarial activity. Of these only a few are outstanding. Among them are (1) the acridine type, (2) the 6-alkoxy-8-amino substituted quinolines, and (3) the 2-alkyl-aminomethyl-4-amino substituted phenols.

The early development in chemotherapy dealt mainly with the production of drugs that would cure diseases caused by spirochetes and protozoa, but almost no progress had been made against bacilli or cocci until the discovery and application of Prontosil (4-sulfonamido-2',4'-diaminoazobenzene) by Mietzsch, Klarer, and Domagk (3).

The discovery of the action of Prontosil, sulfanilamide, and related compounds highlighted the developments in chemotherapy a decade ago. The effectiveness of the sulfa drugs in general was demonstrated against hemolytic streptococci, pneumococci, meningococci, gonococci, staphylococci and others.

Although more than a thousand sulfa compounds have been synthesized, only a few show outstanding promise in chemotherapy. All of these contain substituent groups on the amido nitrogen, (N'). Thus far, it has been demonstrated, that the activity is entirely lost, if the amino nitrogen (N^4) is substituted with a group that cannot be removed in the body. All nuclear substitution products of sulfanilamide tested to date are completely inactive, pointing to a remarkable

specificity (2).

During the last ten years, naturally occurring compounds, anti-microbial in action, and found in molds, yeasts and bacteria, have been isolated. They are bacteriostatic, although they may also and to a lesser extent, show bactericidal properties. These substances show a certain specificity in their action. Some act on gram-positive bacteria and show little action upon gram-negative ones. Others show selective action on some of each group. The two outstanding antibiotic substances used in chemotherapy today are Penicillin and Streptomycin.

Within the last decade, a new approach to the search of chemotherapeutic agents has taken form. In 1940, Woods and Fields (4) announced that p-aminobenzoic acid was active as an anti-sulfonamide agent. This suggested the possibility, that structural modifications of compounds known to function as essential metabolites, might result in the formation of compounds having specific antagonistic action toward the corresponding metabolites. This has indeed been shown to be the case. A few examples will suffice. It was found that 3-pyridinesulfonic acid and its amide would inhibit the growth of certain bacteria in a manner subject to reversal by nicotinic acid. Likewise, pantoyltaurine (N- , -dihydroxy-dimethylbutyryl)-taurine acted competitively with pantothenic acid to produce bacteriostasis, and several -aminosulfonic acids competed with -aminocarboxylic acids.

microorganism. In cases where their structures have been elucidated, however, growth factors not essential to man, but essential to certain pathogens, would seem to offer a feasible plan of attack.

B. The Concept of Isosterism.

The application of the concept of isosterism to the study of synthetic chemotherapeutic agents as well as to synthetic medicinals in general is to be found in increasing number in the current literature. The meaning of the term isostere has undergone considerable modification and extension, since its first introduction by Langmuir (7) in 1919. Langmuir proposed that molecules or groups which have the same number of atoms and the same total number of electrons arranged in the same manner be described as "isosteric". He called attention to the fact that when isosteres are also isoelectric, i.e., when they have the same total charge, then they possess strikingly similar physical properties. Classic examples of pairs of isosteres showing extraordinary close agreement in physical constants are carbon monoxide and nitrogen and carbon dioxide and nitrous oxide (8).

In his rather unsuccessful attempt to explain isomorphism, Grimm (9) 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 Grimm's definition, groups of the following types are classed as isosteric: fluoride, hydroxyl, amino, and methyl.

Shortly after Grimm's work appeared, Erlenmeyer began an extensive series of investigations dealing with the application of Grimm's interpretation of isosterism to organic chemistry. Erlenmeyer's major contribution in extending the concept of isosterism was his proposal that the aromatic -CH=CH- group and the ring sulfur atom are isosteric (8). Erlenmeyer arrived at this conclusion by arguing that only the boundary electrons, i.e., the outer electrons of the group, should be counted in determining isosterism. Thus, in the case of the -CH=CH- group, for example, the two electron pairs shared by the carbon atoms are not to be counted, as they are considered to be within the group or "pseudoatom". In this connection he called attention to the fact that benzene and thiophene possess very similar physical properties, such as boiling point, molecular refraction, parachor, certain crystallographic constants, and size and shape of the molecules in the liquid state. (8).

In a striking investigation, Erlenmeyer and co-workers (10) found that even in the exceedingly specific antigen-antibody reactions, certain corresponding derivatives of benzene and thiophene proved to be indistinguishable.

If we accept Grimm's and Erlenmeyer's broadened concept of isosterism, we find a reversal in activity in certain cases. Thus when the pyridine ring is substituted for the thiazole ring in thiamin, the resulting compound has anti-thiamin activity (11).

behave quite similarly to the amino and hydroxyl groups when occupying corresponding positions in an organic molecule. The therapeutic action of a compound in which these groups have been substituted for each other would probably be similar in nature and would effect a similar final result, but, at the same time, the variation in the electronegativity of the substituting groups would be expected to produce a definite change in the activity as well as in the toxicity of the compound. The direction and extent of such changes are unpredictable in the light of our present knowledge.

In a few instances the replacement of a hydroxyl or an amino group by a fluorine atom in therapeutic agents has been reported. Schiemann and Winkelmuller (12) prepared 3-fluoro-4-hydroxyphenylethylamine and 3-fluoro-phenylethylamine, compounds closely related to adrenaline. Physiological tests were not reported on these compounds.

Fosdick and Campaigne (13) prepared a number of alkamine esters of p-fluorobenzoic acid which were isosters of p-hydroxybenzoic acid esters previously reported (14) as good local anesthetics but quite toxic. They found that the fluoro-compounds were efficient anesthetics, equal to or better than procaine and also less toxic than the latter compound. They did, however, possess irritating qualities which rendered them unsuited for clinical use. Hansen (15) prepared 3-fluoro-4-hydroxy- methylaminoacetophenone, the 3-fluoro-derivative of adrenalone. This substance was found to possess weak vasopressor properties.

Except for the cases cited above, little is known concerning the effectiveness of fluorine-substituted analogues of medicinals of proved value.

A third line of attack on the general problem is based on the comparatively small atomic radius of the fluorine atom which is actually of the order of that of the hydrogen atom itself. Like hydrogen, fluorine requires only a single electron to complete its valence shell. These facts suggest the desirability of a study of the effect produced in various physiologically active compounds by the replacement of hydrogen with a fluorine atom. The work of Niemann (16,17) indicates that such a revision of structure in certain compounds produces a marked difference in physiological activity. Thus, 3-fluoro-4-hydroxyphenylalanine, in which a fluorine-atom replaces a single hydrogen atom of tyrosine (in the 3-position), exhibits pronounced insecticidal activity, whereas tyrosine itself plays the role of a metabolite. It is significant, that of all the non-metallic elements in the periodic table which regularly form single covalent bonds, the fluorine atom most closely approximates the hydrogen atom in its atomic radius. It is possible that the small atomic radius of fluorine may allow the fluoro-substituted compound to usurp the place of the tyrosine in the organism without, however, performing its metabolic functions. In other words, in the case cited, the fluoro-compound assumes the role of an anti-amino acid. The study of compounds in which a fluorine atom replaces a hydrogen atom in the molecules of substances possessing

important physiological action should open broad fields for fruitful and significant investigation.

D. Scope of the Present Work.

The scope of the research reported in this thesis includes the synthesis of isosteres of sulfa drugs and anti-malarials, in which an amino or a hydroxyl group has been replaced by the isosteric fluorine atom. In addition, a methoxy group has been replaced by a fluorine atom in anti-malarials of the 6-methoxy-8-amino substituted quinoline type. The synthesis of two analogues of menadione (2-methyl-1,4-naphthaquinone), a compound of high vitamin K activity in which the fluorine atom replaces a ring hydrogen or the hydrogens on the methyl group has been undertaken. Finally, the synthesis of a plant hormone, in which two chlorine atoms were replaced by fluorine atoms was accomplished.

The sulfa drugs selected for the N^4 amino group replacement with the isosteric fluorine atom were the following: sulfanilamide, sulfapyridine, sulfathiazole, and sulfadiazine. Thus, the synthesis of the following compounds was undertaken:

p-fluorobenzenesulfonamide (isostere of sulfanilamide)

2-(p-fluorobenzenesulfonamido)-pyridine (isostere of sulfapyridine),

2-(p-fluorobenzenesulfonamido)-thiazole (isostere sulfathiazole)

2-(p-fluorobenzenesulfonamido)-pyrimidine (isostere of sulfadiazine)

The fact that p-aminobenzoic acid has been found to be active as an anti-sulfonamide agent (4) prompted us to attempt synthesis of the corresponding p-fluorobenzamido analogues of the fluorine-containing sulfa drug isosteres, namely: p-fluorobenzamide, 2-(p-fluorobenzamido)-pyridine, 2-(p-fluorobenzamido)-thiazole, and 2-(p-fluorobenzamido)-pyrimidine.

The anti-malarials chosen for the attempted replacement of a hydroxyl or a methoxy groups with fluorine were as follows: plasmochin (6-methoxy-8-(1-methyl-4-diethylamino-butyl)-aminoquinoline)(I), 6-methoxy-8-(p-aminobenzenesulfonamido)-quinoline (II), 6-methoxy-8-(7-chloro-4-quinolyl)-aminoquinoline and 4-(7-chloro-4-quinolylamino)- -diethyl-amino-o-cresol) (IV). Hence, the synthesis of the following compounds was attempted: 6-fluoro-8-(1-methyl-4-diethyl-aminobutyl)-aminoquinoline (analogue of plasmoquine where the 6-methoxy group is replaced by fluorine), 6-fluoro-8-(p-fluorobenzenesulfonamido)-quinoline (analogue of II), 6-fluoro-8-(7-chloro-4-quinolyl)-aminoquinoline (analogue of III), and 2-diethylaminomethyl-4-7-chloro-4-quinolyl)-amino-fluorobenzene (isostere of camoquin).

The analogues of menadione selected for synthesis were as follows: 2-trifluoromethyl-1,4-naphthaquinone (analogue of menadione, where the 2-methyl group is replaced with a 2-trifluoromethyl group), and 2-methyl-3-fluoro-1,4-naphtha-quinone (analogue of menadione, where the hydrogen atom in 3 position is replaced with fluorine). It is of interest, that 2-methyl-3-fluoro-1,4-naphthaquinone is also an isostere

of phthiocol (2-methyl-3-hydroxy-1,4-naphthaquinone).

E. Standard Methods for Introduction of Fluorine into Aromatic Rings.

The introduction of a fluorine atom into an aromatic nucleus has been accomplished in several ways. Direct fluorination with elementary fluorine is not feasible, since the result of previous experiments (18) have shown that only polymeric materials are thus produced. This is presumably the result of the tendency of elementary fluorine to add to the aromatic double bond rather than to substitute for a nuclear hydrogen atom (19).

Diazotization of aromatic amines in aqueous solutions of hydrofluoric acid has led in a number of cases to the corresponding aromatic fluorides, but with poor yields (20).

Diazoamino compounds have been treated with aqueous hydrofluoric acid to yield aromatic fluorides (21). However, the diazamino compound must first be separately prepared, and twice the theoretical amount of initial amino-compound is required.

Aromatic diazopiperidides may be decomposed by heating with concentrated aqueous hydrofluoric acid to yield aromatic fluorides (22). Due to the vigorous nature of the reaction, it cannot be safely carried out with larger than 10 g. quantities.

The thermal decomposition of dry diazofluoborides (Schiemann reaction), which are prepared by precipitating a

diazotized aromatic amine from aqueous solution by the addition of either fluoboric acid or sodium fluoborate, gives the corresponding aromatic fluorides (23). In spite of the fact that the yields in most cases are satisfactory, the process is rather inconvenient, because of the time required to prepare and dry the solid diazofluoboride salt, and because of the care necessary to insure successful thermal decomposition.

Diazotization of the aromatic amine in anhydrous hydrogen fluoride with solid sodium nitrite at 0°-5°, followed by decomposition of the diazonium salt at an elevated temperature, has been found to give very satisfactory yields with a great number of aromatic amino compounds (24).

EXPERIMENTAL

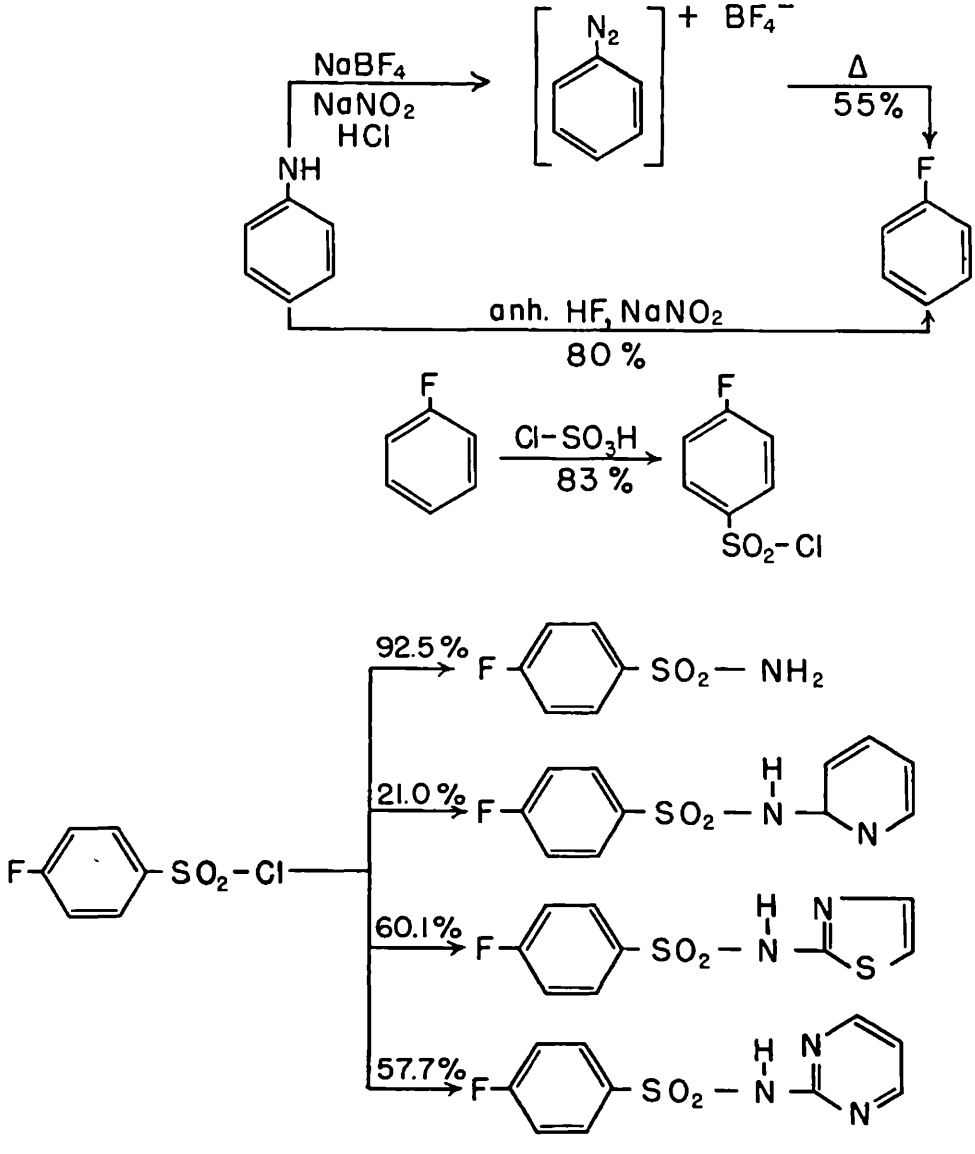
I. Synthesis of Isosteres of Sulfa Drugs.

The synthesis of p-fluorobenzenesulfonamide (isostere of sulfanilamide),

2-(p-fluorobenzenesulfonamido)-pyridine (isostere of sulfapyridine),

2-(p-fluorobenzenesulfonamido)-thiazole (isostere of sulfathiazole), and

2-(p-fluorobenzenesulfonamido)-pyrimidine, was accomplished according to the following flow sheet:



Fluorobenzene.-- (a) Application of the Schiemann method (25) gave 55% of fluorobenzene boiling at 84.1-85.2° at 740 mm. (b) Diazotization of aniline in anhydrous hydrogen fluoride to yield fluorobenzene was carried out as follows:

About 800 g. (40 moles) of hydrogen fluoride was slowly run into 186.2 g. (2 moles) of freshly distilled aniline, boiling point 181.5-181.7° at 736 mm., contained in a 2-l. copper flask cooled in an ice bath. This mixture was kept at -5° for two hours while 165.6 g. (2.4 moles) of granular sodium nitrite was slowly added with constant mechanical stirring. The reaction mixture was allowed to come to room temperature and then connected to an ice-cooled reflux coil to stand overnight at 35°.

Dilution with ice water followed by steam distillation gave an insoluble oil which was dried over calcium chloride and distilled to yield 154 g. (80%) of fluorobenzene, boiling at 84-85° at 735 mm.

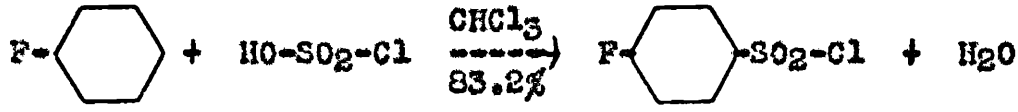
86.2 g.	800g.	165.6 g.	154 g.
(2 moles)	(40 moles)	(2.4 moles)	(1.6 moles)

p-Fluorobenzensulfonyl Chloride.-- The procedure of Bradlow and VanderWerf (26) was found to be satisfactory. A typical run was as follows:

To a 600 ml. beaker containing 250 ml. of chloroform was added 50.0 g. (0.52 mole) of fluorobenzene and the mix-

ture cooled to -5° C. To this mixture was added dropwise, with stirring, 250 g. (2.1 moles) of chlorosulfonic acid. The temperature was maintained at -5° to 0° during the addition. When all the chlorosulfonic acid had been added, the mixture was stirred for one hour in an ice bath and then allowed to come to room temperature overnight.

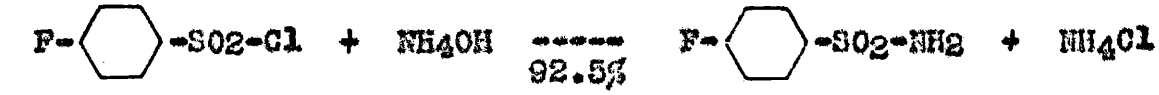
The mixture was then poured on ice, stirred vigorously, and the two layers separated. The aqueous layer was extracted twice with chloroform. The organic extracts were combined, washed with a small portion of cold water, then with saturated sodium chloride solution, and then dried over anhydrous sodium sulfate. The chloroform was removed and the residue purified by distillation at 105°-110° at 5 mm. to give a yield of 76.7 g. (83.2%) of p-fluorobenzenesulfonyl chloride.



50.0 g. (0.52 mole) 250.0 g. (2.1 moles) 76.7 g. (0.39 mole)

p-Fluorobenzenesulfonamide.-- A mixture of 19.4 g. (0.1 mole) of p-fluorobenzenesulfonyl chloride and 50 ml. of concentrated ammonium hydroxide contained in a 500 ml. Erlenmeyer flask was shaken vigorously. When the ensuing reaction had subsided, the mixture was heated on a steam bath for thirty minutes, cooled and filtered. A crude yield of 17.4 g. was obtained. After recrystallization from glacial

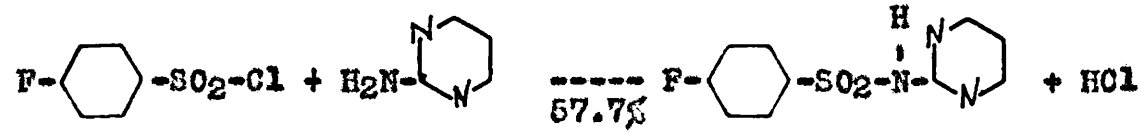
acetic acid, 16.2 g. (92.5%) of p-fluorobenzenesulfonamide melting at 123.1-124.0° was obtained (27).



19.4 g. (0.1 mole) | 50 ml. | 16.2 g. (0.092 mole)

2-(p-Fluorobenzenesulfonamido)-pyrimidine.-- To a 125 ml. conically shaped flask, equipped with a mechanical stirrer, a condenser, and a dropping funnel, and containing 9.5 g. (0.1 mole) of 2-aminopyrimidine in 30 ml. of dry pyridine, 19.4 g. (0.1 mole) of p-fluorobenzenesulfonyl chloride was added. The mixture was heated at 120° for two hours and a solution of 4.4 g. (0.11 mole) of sodium hydroxide in 25 ml. of water was then added slowly with continued heating. The pyridine was removed by distillation under reduced pressure, water being added from time to maintain the volume approximately constant. The 2-(p-fluorobenzenesulfonamido)-pyrimidine which separated was filtered, washed well with water, and air dried. The yield was 14.6 g. (57.7%) of product melting at 184.5-185.0°.

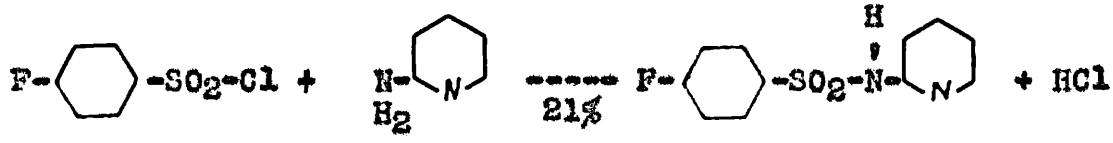
Anal. Calc. for $C_{10}H_8O_2N_3FS$: N, 16.6. Found: 16.6



19.4 g. (0.1 mole) | 9.5 g. (0.1 mole) | 14.6 g. (0.058 mole)

2-(p-Fluorobenzenesulfonamido)-pyridine.-- This product was prepared by the method used for 2-(p-fluorobenzenesulfonamido)-pyrimidine, except that 9.4 g. (0.1 mole) of 2-aminopyridine was used in place of 2-aminopyrimidine. The crude 2-(p-fluorobenzenesulfonamido)-pyridine (23 g.) was recrystallized repeatedly from glacial acetic acid to give 5.3 g. (21.0%) of pure material melting at 151.2-151.7°.

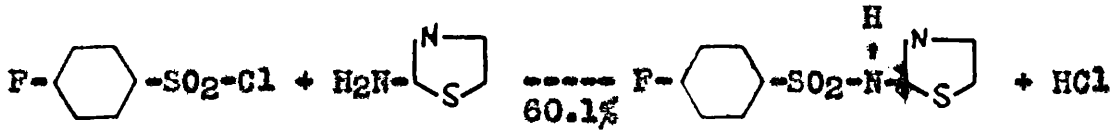
Anal. Calc. for $C_{11}H_9O_2N_2SF$: N, 11.1. Found: 11.0.



19.4 g.	9.4 g.	5.3 g.
(0.1 mole)	(0.1 mole)	(0.021 mole)

2-(p-Fluorobenzenesulfonamido)-thiazole.-- This compound was prepared by the method used for 2-(p-fluorobenzenesulfonamido)-pyrimidine except that 10.0 g. (0.1 mole) of 2-aminothiazole was substituted for the 2-aminopyrimidine. The crude 2-(p-fluorobenzenesulfonamido)-thiazole was recrystallized from glacial acetic acid to yield 15.5 g. (68.5%) of product melting at 171.2-172.0°.

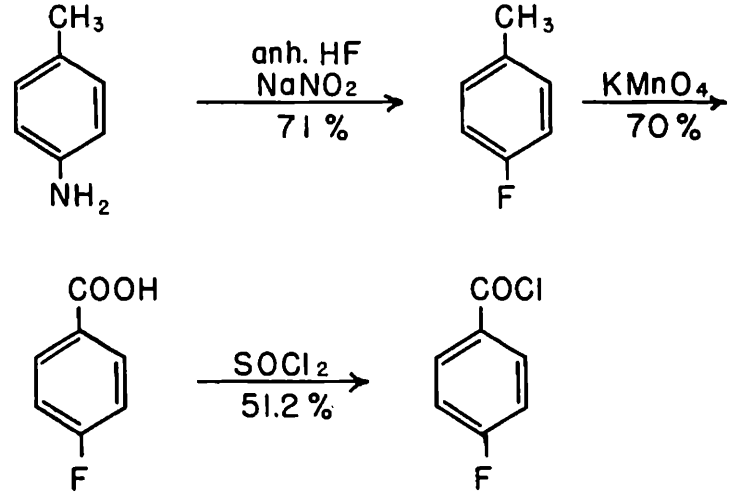
Anal. Calc. for $C_9H_7O_2N_2SF$: N, 10.9. Found: 10.7

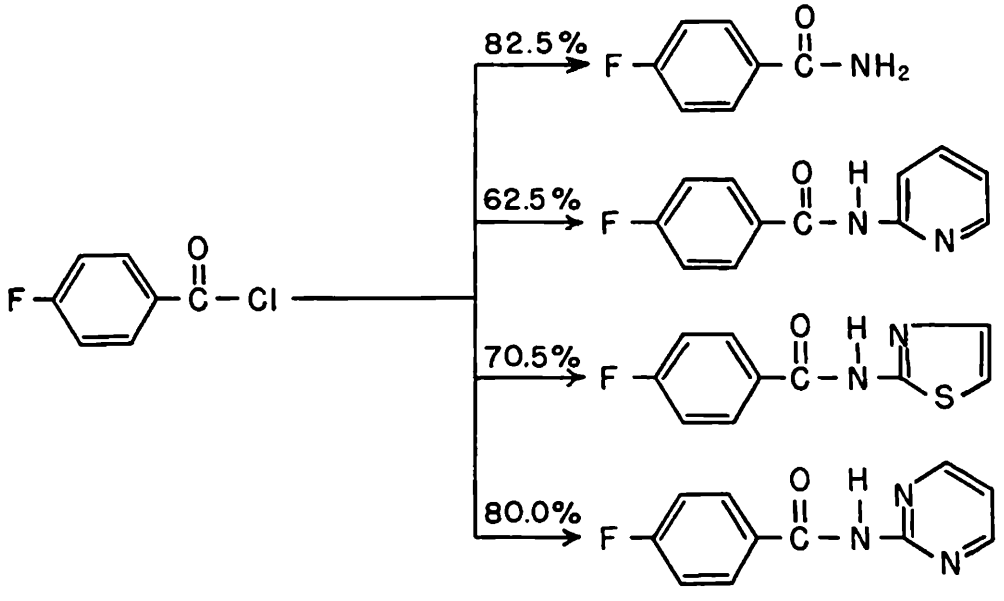


19.4 g.	10.0 g.	15.5 g.
(0.1 mole)	(0.1 mole)	(0.069 mole)

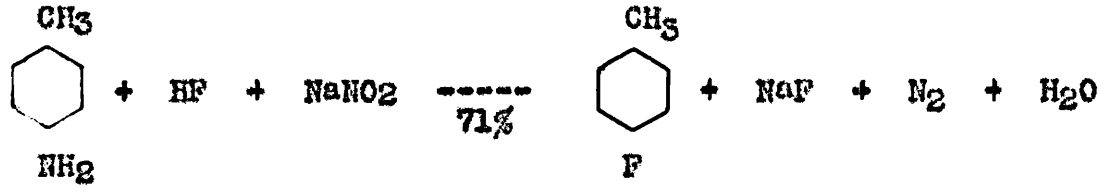
II. Synthesis of p-Fluorobenzamido Analogues of Sulfa-Drugs.

The synthesis of p-fluorobenzamide, 2-(p-fluorobenzamido)-pyridine, 2-(p-fluorobenzamido)-thiazole, and 2-(p-fluorobenzamido)-pyrimidine was accomplished in the following manner:





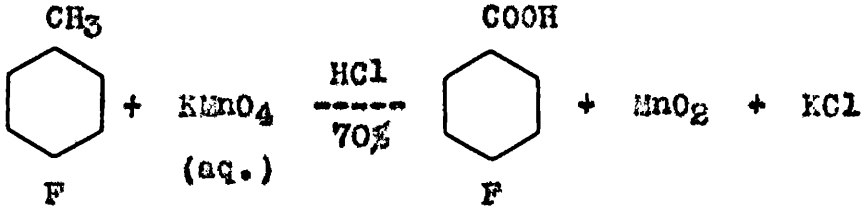
p-Fluorotoluene.-- About 800 g. (40 moles) of anhydrous hydrogen fluoride was slowly added to 214.0 g. (2 moles) of p-toluidine, contained in a 3-l., one-necked Monel metal flask which was cooled in an ice bath. This mixture was kept at 0° for 1½ hours while 165.6 g. (2.4 moles) of finely powdered sodium nitrite was slowly added with constant stirring. The reaction flask was then fitted with an ice-cooled reflux coil and allowed to stand overnight at room temperature. The decomposition was completed by warming at 55° for three hours. After dilution with ice water, the mixture was steam distilled to give an oil which was dried over calcium chloride and distilled to give 157.0 g. (71%) of p-fluorotoluene, boiling at 114-115° at 728 mm. Holleman and Beekman have reported the boiling point of p-fluorotoluene at 114° (28).



214.0 g. 800g. 157 g.
(2.0 moles) (40 moles) (1.4 moles)

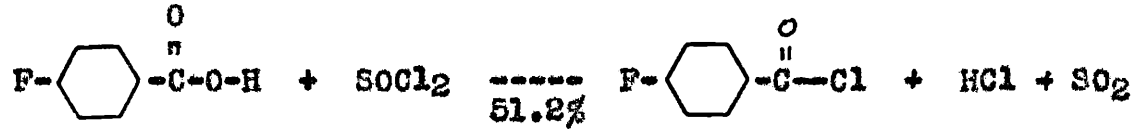
p-Fluorobenzoic Acid.-- A 5-l., three-necked flask, fitted with a stirrer, and a reflux condenser, was charged with 221 g. (1.4 moles) of potassium permanganate, 2600 ml. of water, and 64.5 g. (0.59 mole) of p-fluorotoluene. The mixture was refluxed for three hours, and the unoxidized p-fluorotoluene was distilled off under continuous stirring.

The recovered p-fluorotoluene amounted to 5.5 g. The manganese dioxide was filtered off while the reaction mixture was still hot, and the filtrate decolorized with few crystals of sodium hydrosulfite, and the solution refiltered. The filtrate was acidified with 100 ml. of concentrated hydrochloric acid. The resulting white crystalline precipitate was filtered, washed with cold water, and air dried. The yield of p-fluorobenzoic acid melting at 184.1-184.7° was 52.0 g. (70%) based on p-fluorotoluene that was oxidized. Schiemann and Winkelmuller have reported the melting point of p-fluorobenzoic acid at 185-186° (29).



59.0 g. 221 g. 52.0 g.
(0.53 mole) (1.4 moles) (0.37 mole)

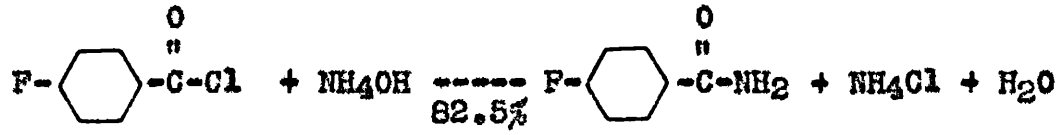
p-Fluorobenzoyl Chloride.-- A mixture of 52.0 g. (0.37 mole) of p-fluorobenzoic acid and 190 ml. of thionyl chloride was refluxed for six hours. The excess thionyl chloride was then taken off and the residue fractionally distilled, the fraction boiling between 98-100° at 32 mm. being collected. The yield of p-fluorobenzoyl chloride was 30.0 g. (51.2%).



52.0 g.
(0.37 mole)

30.0 g.
(0.19 mole)

p-Fluorobenzamide.-- A mixture of 8.7 g. (0.054 mole) of p-fluorobenzoyl chloride and 25 ml. of concentrated ammonium hydroxide was shaken vigorously until the reaction subsided. The mixture was then heated on a steam bath for thirty minutes, cooled and filtered. A crude yield of 6.2 g. (82.5%)was obtained. Recrystallization from glacial acetic acid gave pure p-fluorobenzamide melting at 154.2-154.5°. Slothouwer has reported a melting point of 154.5° for p-fluorobenzamide (30).



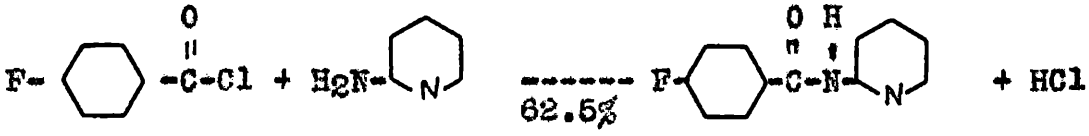
8.7 g.
(0.054 mole)

6.2 g.
(0.044 mole)

2-(p-Fluorobenzamido)-pyrimidine.-- To a mixture of 2.7 g. (0.028 mole) of 2-aminopyrimidine, 5.4 g. (0.028 mole) of powdered potassium carbonate, and 50 ml. of dry ether contained in a 200 ml. conically shaped 3-necked flask, fitted with a mechanical stirrer, a reflux condenser, and a dropping funnel, 4.4 g. (0.028 mole) of p-fluorobenzoyl chloride was added dropwise with stirring. The mixture was heated under

and then recrystallized from alcohol-water to give 2.0 g. (62.5%) of 2-(p-fluorobenzamido)-pyridine melting at 123.2-124.0°. Further recrystallization gave a pure product melting at 123.6-124.2°.

Anal. Calcd. for $C_{12}H_9ON_2F$: N, 12.9. Found N, 12.7



2.4 g. (0.015 mole)	1.4 g. (0.015 mole)	2.0 g. (0.0092 mole)

2-(p-Fluorobenzamido)-thiazole.-- This compound was prepared by the method described above, except that 1.5 g. (0.015 mole) of 2-aminothiazole was used in place of the 2-aminopyridine. The 2-(p-fluorobenzamido)-thiazole was recrystallized from alcohol-water to give 2.5 g. (74.7%) of pure compound melting at 196.2-186.8°.

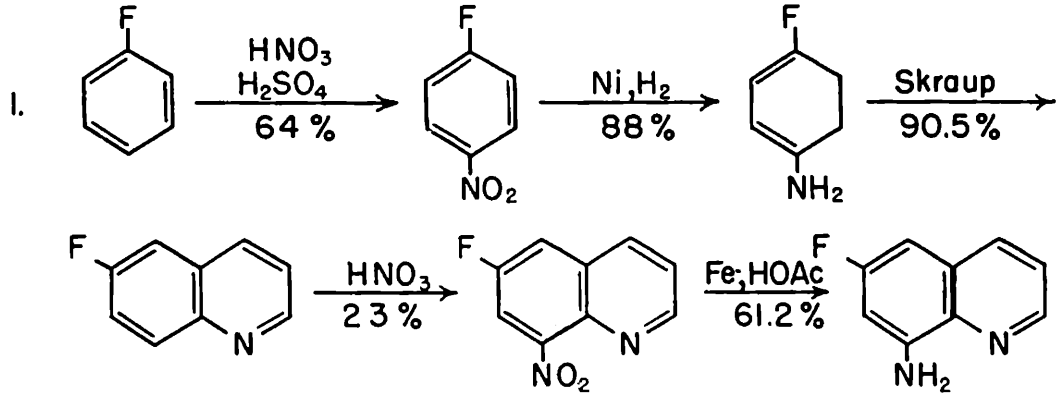
Anal. Calcd. for $C_{10}H_7ON_2FS$: N, 12.6. Found: N, 12.5.

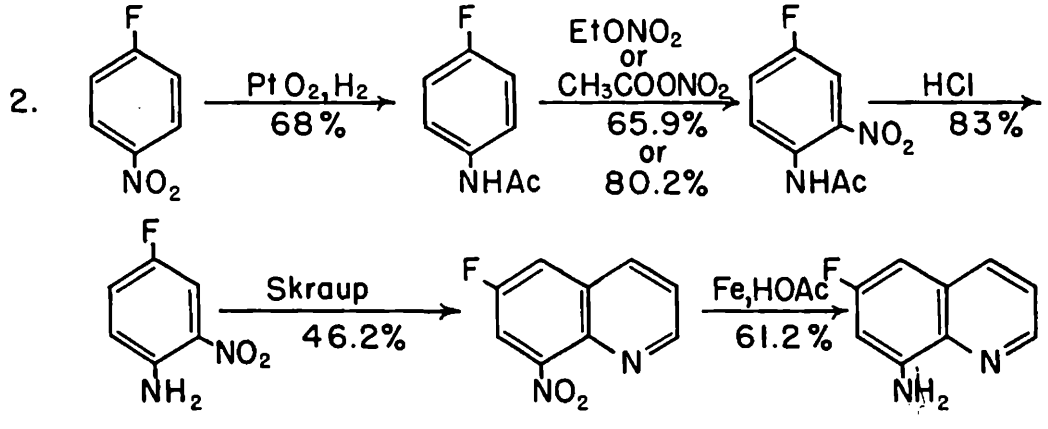
2.4 g. (0.015 mole)	1.5 g. (0.015 mole)	2.5 g. (0.011 mole)

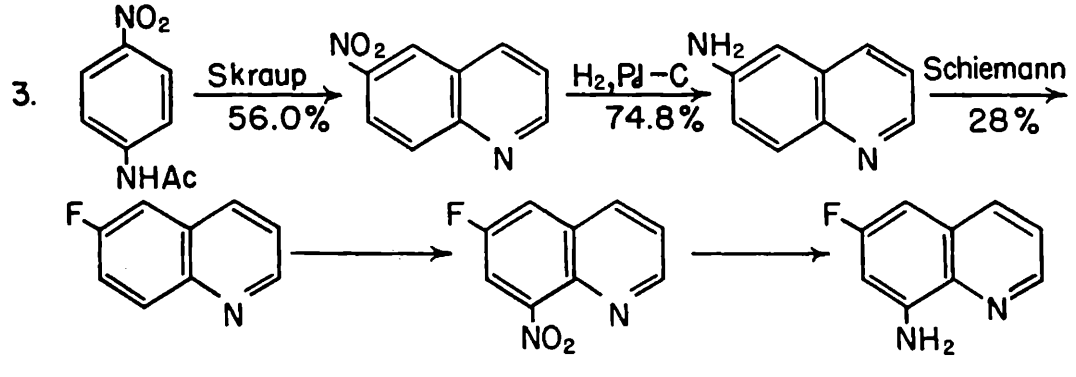
III. Synthesis of 6-Fluoro-8-amino Substituted Quinolines.

(a). Synthesis of 6-Fluoro-8-aminoquinoline.

The synthesis of 6-fluoro-8-aminoquinoline was accomplished in the following three different ways as shown on the following flow sheet:

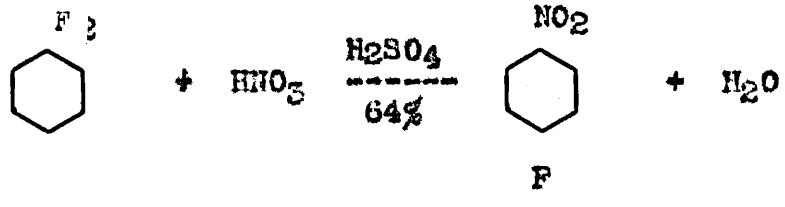






p-Nitrofluorobenzene.-- The procedure of Bradlow and VanderWerf (26) for the preparation of p-nitrofluorobenzene was followed. A typical run was as follows:

Direct nitration of fluorobenzene by dropwise addition with vigorous stirring of 140 g. (1.46 moles) to 300 ml. of a 2:1 (by volume) mixture of concentrated sulfuric acid and yellow fuming nitric acid (sp. gr. 1.5) at -10°, followed by addition of ice, ether extraction, and a careful fractionation through a packed column of the residue after removal of the ether, gave 130.6 g. (64%) of p-nitrofluorobenzene boiling at 103-104° at 28 mm. pressure.

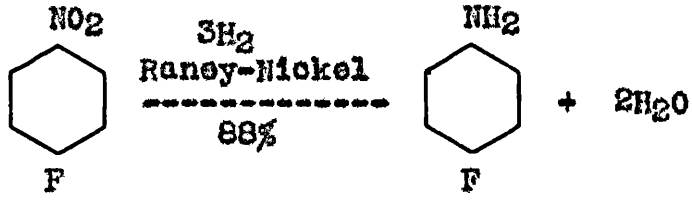


140 g. (1.46 moles) — 130.6 g. (0.92 mole)

p-Fluoroaniline.-- The procedure of Bradlow and VanderWerf (26) was followed in preparing p-fluoroaniline. A typical run is described:

A solution of 239 g. (1.7 moles) of p-nitrofluorobenzene in 500 ml. of absolute ethanol was hydrogenated at low pressure in the presence of Raney-Nickel catalyst and a trace of chloroplatinic acid as a promoter. The hydrogenation proceeded rapidly with evolution of heat. When the theoretical amount of hydrogen had been absorbed, the catalyst was filtered and the solvent removed by distillation. The residue was dissolved in aqueous hydrochloric acid, extracted with ether to remove the non-basic material,

neutralized with sodium hydroxide and extracted with ether. The ether extract was dried over anhydrous sodium sulfate, filtered, and the ether removed by distillation. The residue was fractionally distilled, and the cut at 95-96° at 28 mm. was collected. The yield of p-fluoroaniline was 165.5 g. (88%).



239 g.
(1.7 moles)

165.5 g.
(1.5 moles)

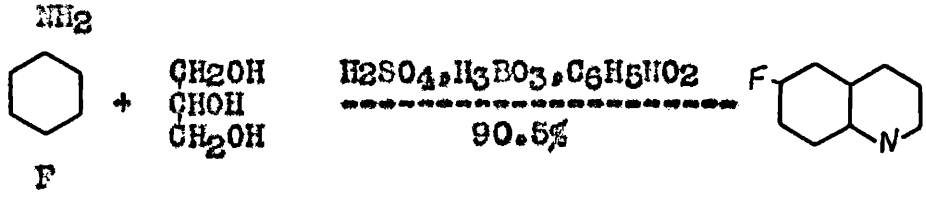
6-Fluoroquinoline.-- The modified procedure for the Skraup reaction described by Cohn (31) was used for this preparation. A typical run was as follows:

In a 2-liter flask were placed, in order, 31.5 g. of ferrous sulfate, 100 g. (0.9 mole) of p-fluoroaniline, 66.4 g. (0.54 mole) of nitrobenzene, and a cold solution of 55.6 g. (0.9 mole) of boric acid in 332 g. of glycerol. (The boric acid was dissolved in the glycerol by gentle heating.) Then 155 ml. of 95% sulfuric acid was added in portions with cooling. The contents of the flask were mixed, connected with a reflux condenser, heated over a free flame until the boiling point was reached and refluxed for twenty hours.

The mixture was cooled, diluted with water, neutralized with 565 cc. of 60% sodium hydroxide solution, and

steam distilled.

When all the organic material had been distilled, it was extracted from the water layer with ether and dried. The ether was removed and the residue was distilled through an efficient fractionating column. After a small forerun had been removed, 120 g. (90.5%) of 6-fluoroquinoline, distilling constantly at 125° under 30 mm. pressure, was obtained.

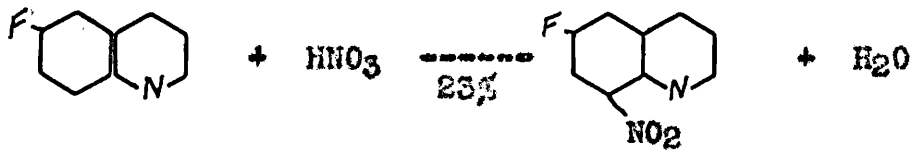


100 g. (0.9 mole) 332 g. 120 g. (0.8 mole)

6-Fluoro-8-nitroquinoline.-- This compound had previously been synthesized by Bradlow (32). General conditions for nitrations of this type are described by Meygen (33) and Dikshoorn (34). The procedure adopted was as follows:

A mixture of 315 ml. of fuming nitric acid (sp. gr. 1.5) and 71.5 g. (0.48 mole) of 6-fluoroquinoline was refluxed in a 2-liter one-necked round-bottom flask for ninety hours. The mixture was then poured onto ice and made just neutral to litmus with ammonium hydroxide. The flocculent yellow precipitate which was produced was filtered to give a crude yield of 91 g. The crude product was repeatedly crystallized from 95% alcohol and treated with Norite. There was finally obtained 17.5 g. (23%) of

6-fluoro-8-nitroquinoline melting at 118.7-119.0°.

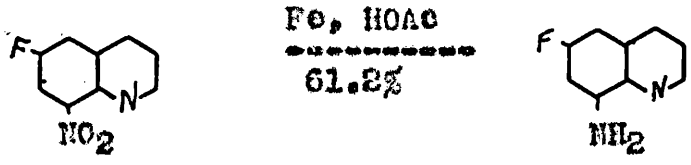


71.5 g.
(0.48 mole)

17.5 g.
(0.082 mole)

6-Fluoro-8-aminoquinoline.-- To a three-necked, round bottom flask containing 10.0 g. (0.052 mole) of 6-fluoro-8-nitroquinoline dissolved in 200 ml. of 50% aqueous acetic acid, 16.0 g. of finely powdered iron was added over a period of ninety minutes. During the addition the mixture was warmed on a steam bath. When the addition was completed, the mixture was cooled and neutralized with solid sodium hydroxide and extracted with ether. The ether extract was dried over anhydrous sodium sulfate, filtered, and the ether removed by distillation. The oily residue was fractionally distilled. The material distilling at 115-116° at 0.7 mm. pressure was collected. The yield of 6-fluoro-8-aminoquinoline obtained was 5.2 g. (61.2%). Sublimation of the solidified distillate gave pure 6-fluoro-8-aminoquinoline melting at 50.0-50.5°.

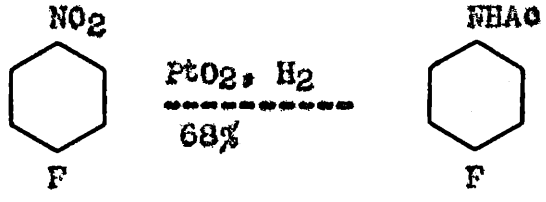
Anal. Calcd. for $C_9H_7N_2F$: N, 17.3. Found: N, 17.2



10.0 g.
(0.062 mole)

5.2 g.
(0.032 mole)

p-Fluoroacetanilide.-- A solution of 307 g. (2.2 moles) of p-nitrofluorobenzene in 500 ml. of acetic anhydride was hydrogenated at low pressure in the presence of platinum oxide catalyst. When the theoretical amount of hydrogen had been absorbed, the catalyst was filtered and the excess acetic anhydride removed by distillation. The remaining solid was dissolved in dilute hydrochloric acid, ether extracted and neutralized with sodium hydroxide. The grey-white precipitate yielded 225 g. (68%) of p-fluoroacetanilide melting at 149.5-150.6°.

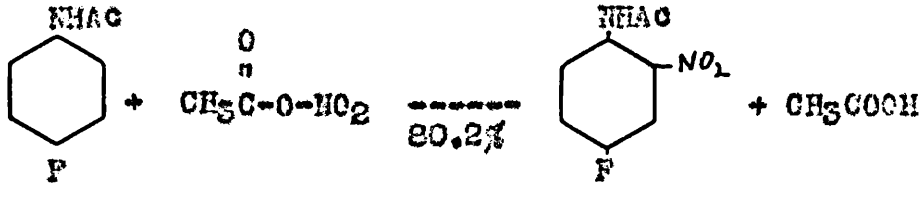


307 g.
(2.2 moles)

225 g.
(1.47 moles)

2-Nitro-4-fluoroacetanilide.-- This compound was prepared by two different methods, (a) by the nitration of p-fluoroacetanilide, with acetyl nitrate (35) as the nitrating agent, and (b) by the nitration of p-fluoroacetanilide, with ethyl nitrate as the nitrating agent (36).

(a). Acetyl nitrate Method.-- A solution of 30 g. (0.2 mole) of p-fluoroacetanilide, 60 g. of glacial acetic acid, and 30 g. of acetic anhydride was added to a three-necked flask, fitted with a thermometer, mechanical stirrer, and a dropping funnel. The mixture was cooled to 0° and a solution of 25 g. (0.25 mole) of acetyl nitrate in 25 ml. of acetic anhydride was added at such a rate as to maintain the temperature of the reaction mixture between 0-2°. After the addition was completed, the mixture was stirred for twenty hours. It was then poured onto ice, and the crude 2-nitro-4-fluoroacetanilide separated as a reddish oil which gradually crystallized on standing. The crude material (29 g., 89%) melted at 67-68°. Recrystallization from alcohol-water yielded 25 g. (80.2%) of 2-nitro-4-fluoroacetanilide melting at 69.3-69.9°. The reported melting point for this compound is 71° (36).

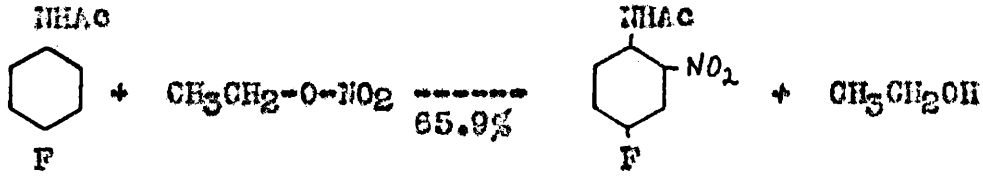


30.0 g.
(0.2 mole)

25.0 g.
(0.13 mole)

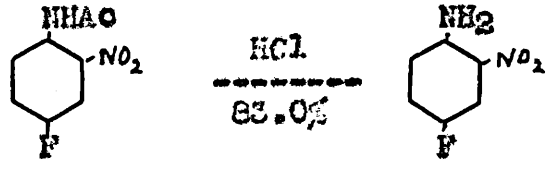
(b). Ethyl nitrate Method.-- A 500 ml., three-necked flask, fitted with a mechanical stirrer and a dropping funnel was charged with a solution of 55.0 g. (0.35 mole) of p-fluoroacetanilide in 160 ml. of concentrated sulfuric acid. The solution was cooled to 0°, and 29 g. of ethyl nitrate was added over a period of one hour. Stirring was

continued for fifteen minutes longer at 0°. The reaction mixture was then poured onto ice and the crude material filtered. The yield of crude 2-nitro-4-acetanilide melting at 65-66° was 60.0 g. Recrystallization from alcohol-water gave 45 g. (66.9%) of product melting at 69.5-70.5°.



53.0 g. (0.33 mole) — 46.0 g. (0.23 mole)

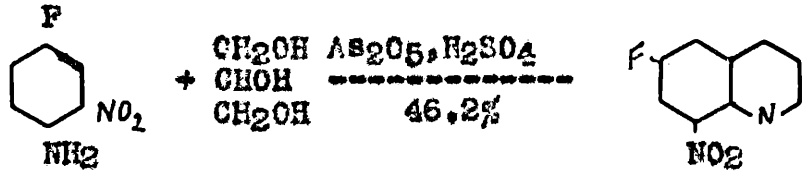
2-Nitro-4-fluoroaniline.-- To a 500 ml., one-necked flask, fitted to a reflux condenser was added 75.0 g. (0.38 mole) of 2-nitro-4-fluoroacetanilide and 190 ml. of 8N hydrochloric acid and the mixture refluxed for two hours. The solution was made basic with sodium hydroxide and ether extracted. The ether solution was dried over anhydrous sodium hydroxide, filtered, and the ether removed by distillation. There was obtained 48.2 g. (83.0%) of 2-nitro-4-fluoroaniline melting at 93.5-94.0°.



75.0 g. (0.38 mole) — 48.2 g. (0.31 mole)

6-Fluoro-8-nitroquinoline.-- The procedure of Wilkinson and Finar (36) was used. A typical run is described:

To a 500 ml., three-necked flask equipped with a stirrer, thermometer, and reflux condenser, was added 44.0 g. (0.28 mole) of 2-nitro-4-fluoroaniline, 100 g. of anhydrous glycerol, and 48.4 g. of arsenic pentoxide. The mixture was then treated with 58.6 g. of concentrated sulfuric acid at such a rate that the temperature did not exceed 130°. Next the material was heated at 130-135° for four hours, then at 160° for thirty minutes. The cooled solution was treated with water and neutralized with aqueous ammonia to precipitate the product which was collected and dried. Continuous extraction with benzene gave 25.2 g. (46.2%) of pure 6-fluoro-8-nitroquinoline melting at 119.2-120.0°.



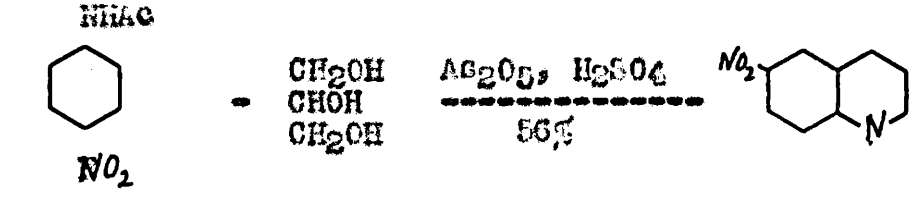
44.0 g.
(0.28 mole)

25.2 g.
(0.13 mole)

6-Nitroquinoline.-- The method of Haskelberg (37) was used to obtain 6-nitroquinoline. A run is described below:

A 5-liter flask equipped with a stirrer, thermometer, and reflux condenser was charged with 332 g. (1.8 moles) of p-nitroacetanilide, 663 g. of glycerol, and 310 g. of arsenic pentoxide, and 720 g. of concentrated sulfuric acid was added at such a rate that the temperature did not exceed 130°. The mixture was heated gently for four hours, cooled to room temperature, and poured into water. The product was

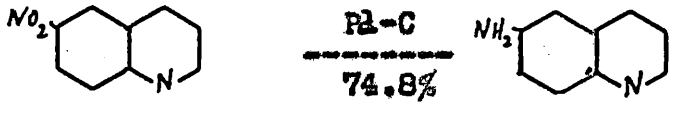
then decolorized with Norite, filtered and slowly neutralized with aqueous ammonia. After several recrystallizations from alcohol-water, the yield of 6-nitroquinoline melting at 140-150° was 175 g. (56%).



332 g.
(1.8 moles)

175 g.
(1.0 mole)

6-Aminoquinoline.-- A solution of 110 g. (0.63 mole) of 6-nitroquinoline in 250 ml. of absolute ethanol was hydrogenated at low pressure in the presence of 2% palladium-carbon catalyst. When the solution had absorbed the required amount of hydrogen, the catalyst was filtered, and the alcohol distilled off. The yield of 6-aminoquinoline obtained was 68.0 g. (74.8% melting at 115-116°.



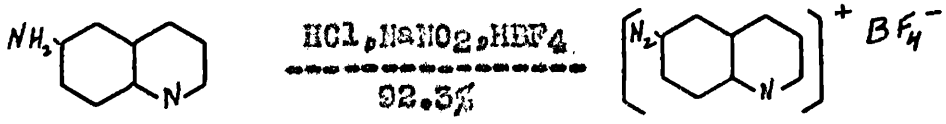
110.0 g.
(0.63 mole)

68.0 g.
(0.47 mole)

6-Fluoroquinoline.-- The procedure of Roe and Hawkins (38) was used. A typical run is described:

To a 800 ml. beaker was added a solution of 38.0 g. (0.26 mole) of 6-aminoquinoline in 225 ml. of 40% fluoboric

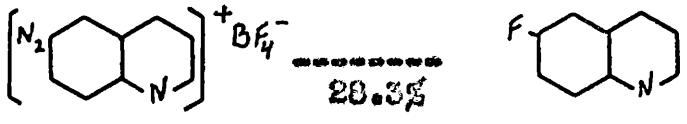
acid, and 120 ml. of water. Diazotization was effected by adding 19.0 g. of sodium nitrite to the solution, keeping the temperature below 15°. The solution was then cooled to -3° and filtered. The filter was washed with cold 50-50 alcohol-ether mixture, then three times with cold ether. There was obtained 58.0 g. (92.3%) of the diazonium fluoborate salt.



38.0 g.
(0.26 mole)

58.0 g.
(0.24 mole)

The diazonium fluoborate salt was added to a 2-liter, round-bottom flask and the salt heated until decomposition was complete. A dark red liquid remained which solidified on cooling. The residue was dissolved in water, and sodium hydroxide solution was added until the mixture was slightly alkaline to litmus. The reaction mixture was steam distilled and the crude 6-fluoroquinoline separated and fractionally distilled. The fraction boiling at 124-125° at 30 mm. was collected to give 10.0 g. (28.3%) of pure 6-aminoquinoline.

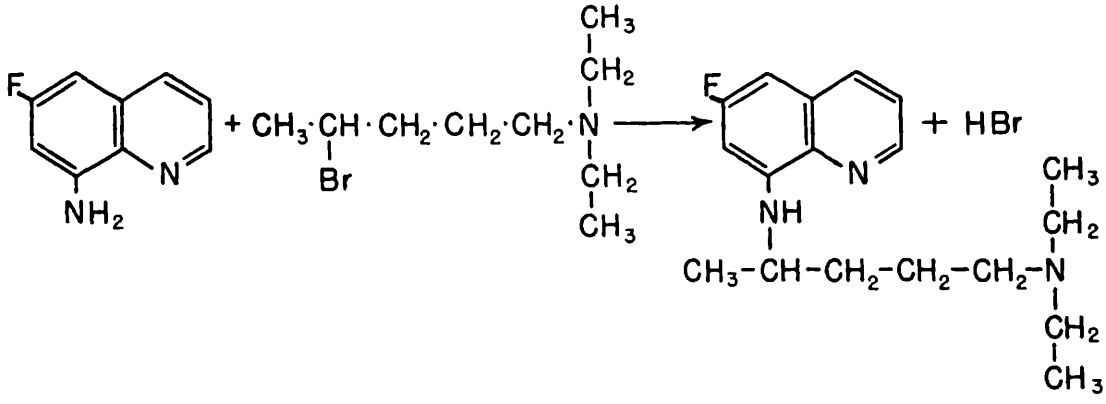


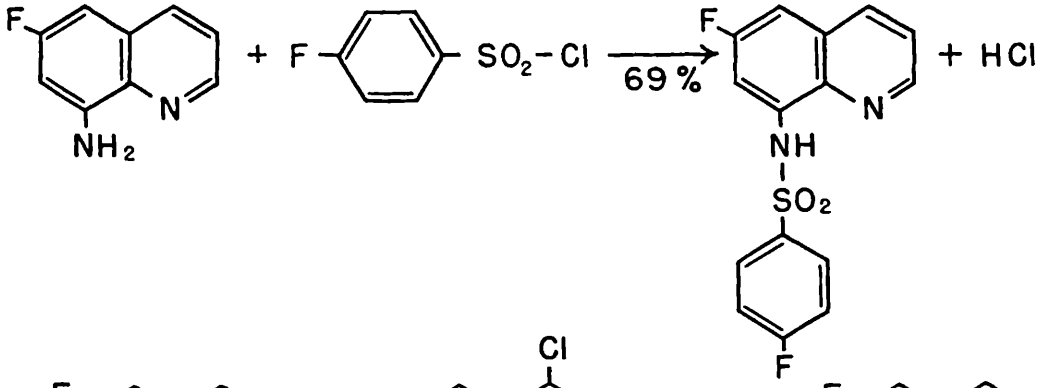
58.0 g.
(0.24 mole)

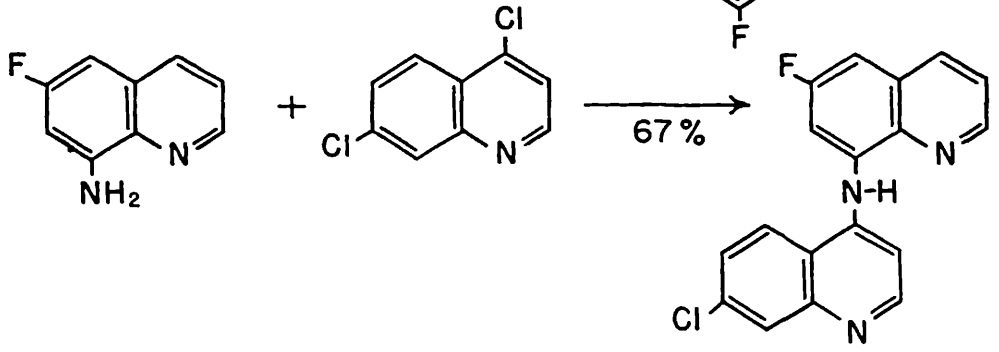
10.0 g.
(0.068 mole)

III. Synthesis of 6-Fluro-8-amino Substituted Quinolines.

(b) Attempted Synthesis of Fluorine Analogue of Plasmoquine and Other 6-Methoxy-8-aminosubstituted Quinoline Derivatives.

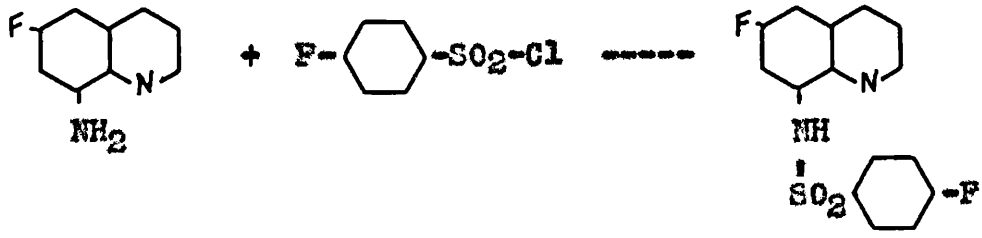






6-Fluoro-8-(p-fluorobenzenesulfonamido)-quinoline.-- To a 25 ml. Erlenmeyer flask was added 0.81 g. (0.005 mole) of 6-fluoro-8-aminoquinoline, 0.97 g. (0.005 mole) of p-fluorobenzensulfonyl chloride and 5 ml. of dry pyridine. The mixture was heated on the steam bath for thirty minutes and poured onto ice. The white, crystalline 6-fluoro-8-(p-fluorobenzenesulfonamido)-quinoline that separated was filtered, washed repeatedly with water and air dried. The yield was 1.1 g. (68%) of product melting at 125.2-125.7°.

Anal. Calcd. for $C_{15}H_{10}O_2N_2F_2S$: N, 8.7. Found: N. 8.5



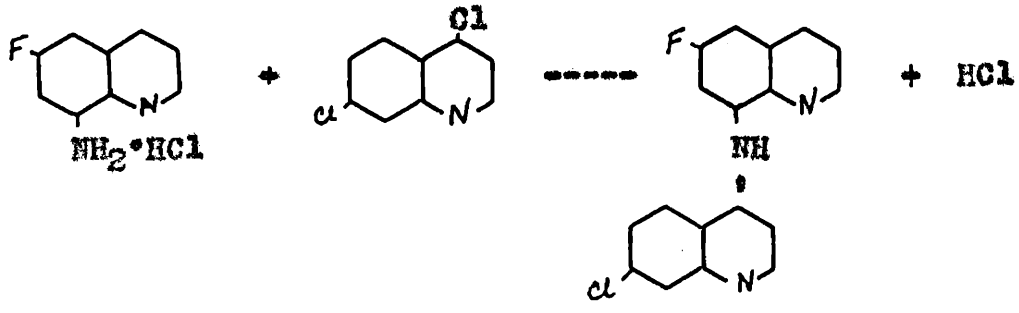
0.81 g.
(0.005 mole)

1.1 g.
(0.0034 mole)

6-Fluoro-8-(7-chloro-4-quinolylamino)-quinoline.-- A 100 ml. one-necked flask, fitted to a reflux condenser, was charged with 1.2 g. (0.006 mole) of 6-fluoro-8-aminoquinolinemonohydrochloride in 25 ml. of water and 1.2 g. (0.006 mole) of 4,7-dichloroquinoline. The mixture was heated on the steam bath for twenty-four hours. A small amount of water insoluble material was filtered, and the filtrate was made alkaline by adding aqueous ammonia. The grey-white precipitate which resulted was filtered and air dried to yield 1.3 g. (67%) of crude 6-fluoro-8-(7-chloro-4-quinolylamino)-quinoline melting at 185-186°. Recrystallization

from alcohol-water gave a pure product melting at 187.4-188.0°.

Anal. Calcd. for $C_{18}H_{11}N_3ClF$: N, 13.0. Found: N, 13.2.



1.2 g. (0.006 mole)

1.3 g. (0.004 mole)

Attempted preparation of 6-Fluoro-8-(1-methyl-4-diethylaminobutyl)-aminoquinoline.-- The method of Elderfield and his co-workers (38) for the preparation of 6-chloro-8-(5-diethylaminopentyl)-aminoquinoline from 6-chloro-8-aminoquinoline and diethylaminopentane was used. Thus far, none of the desired 6-fluoro-8-(1-methyl-4-diethylaminobutyl)-aminoquinoline has been obtained in large enough quantity to be identified. A typical run is described below:

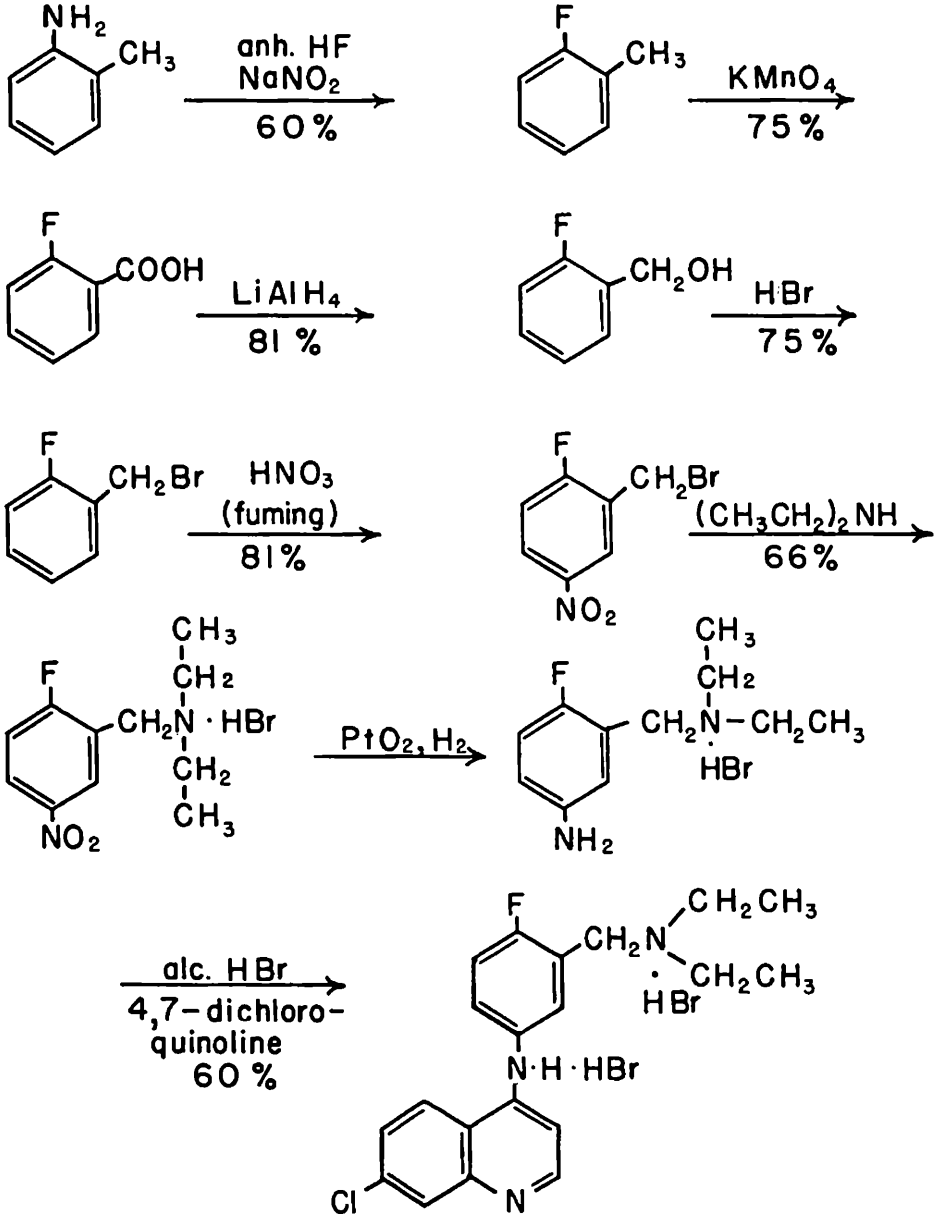
A mixture of 3.2 g. (0.02 mole) of 6-fluoro-8-aminoquinoline, 4.4 g. (0.02 mole) of 2-bromo-5-diethylaminopentane, and 1.6 g. (0.02 mole) of sodium acetate dissolved in 10 ml. of 50% alcohol was refluxed for seventy-two hours. It was then diluted with water, made strongly alkaline with sodium hydroxide and extracted with ether. The ether solution was dried over anhydrous sodium sulfate, filtered and the

ether removed by distillation. The oily residue was distilled under nitrogen. The forerun of the unreacted 6-fluoro-8-aminoquinoline distilling at 115° at 2 mm. was collected to give 2.5 g. The amount of the remaining residue was too small to be distillable.

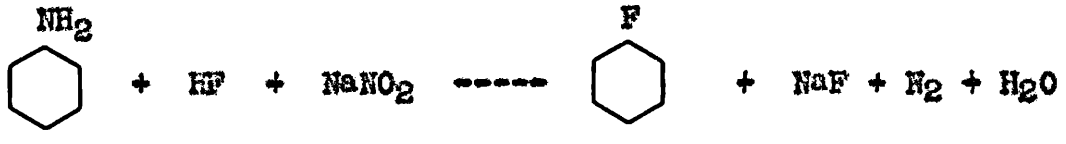
The chief difficulty encountered in obtaining enough of the desired 6-fluoro-8-(1-methyl-4-diethylaminobutyl)-aminoquinoline for proper identification lies in the inherent low yield obtained in coupling reactions of this type. In his preparation of 6-chloro-8-(5-diethylaminopentyl)-aminoquinoline, Elderfield reported a yield of only 10% for the coupling reaction. The small quantities of 6-fluoro-8-aminoquinoline available thus far have not been sufficient to make possible isolation of the desired product.

IV. Synthesis of Fluorine Isostere of Camoquin.

The synthesis of 4-(7-chloro-4-quinolyl)-amino-2-diethylaminomethylfluorobenzene was accomplished in the following manner:



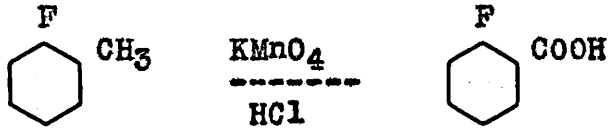
o-Fluorotoluene.-- About 1200 g. (60 moles) of anhydrous hydrogen fluoride was slowly added to 321.0 g. (3 moles) of o-toluidine, contained in a 3-liter, one-necked Monel metal flask which was cooled in an ice bath. This mixture was kept at 0° for 2½ hours while 248.4 g. (3.6 moles) of finely powdered sodium nitrite was slowly added with constant stirring. The reaction flask was then fitted with an ice-cooled reflux coil and allowed to stand overnight at room temperature. The decomposition was completed by warming at 55-60° for six hours. After dilution with ice water, the mixture was steam distilled to give an oil which was dried over calcium chloride and distilled to give 198.0 g. (60%) of o-fluorotoluene, boiling at 112-113° at 735 mm. pressure.



321.0 g. 1200 g. 248.4 g. 198.0 g.
(3.0 moles)(60 moles)(3.6 moles) (1.6 moles)

o-Fluorobenzoic Acid.-- A 5-liter, three-necked flask, equipped with a stirrer and a reflux condenser, was charged with 221 g. (1.4 moles) of potassium permanganate, 2600 ml. of water, and 64.5 g. (0.59 mole) of o-fluorotoluene. The mixture was refluxed for three hours, and the reflux condenser inverted so that any unoxidized starting material would be distilled. No o-fluorotoluene was recovered in this way. The manganese dioxide was filtered while the reaction

mixture was still hot, and the filtrate decolorized with few crystals of sodium hydrosulfite, and the solution refiltered. The filtrate was acidified with 100 ml. of concentrated hydrochloric acid. The resulting white crystalline precipitate was filtered, washed with cold water, and air dried. The yield of o-fluorobenzoic acid melting at 123.8-124.5° was 62.0 g. (75.1%). Cohen has reported the melting point of o-fluorobenzoic acid at 124° (39).



64.5 g. (0.59 mole) — 62.0 g. (0.44 mole)

o-Fluorobenzyl Alcohol.-- The general procedure of Nystrom and Brown (40) was used in reducing o-fluorobenzoic acid to o-fluorobenzyl alcohol by means of lithium aluminum hydride. The reduction was carried out as follows:

A 2-liter, three-necked flask, fitted with a reflux condenser, dropping funnel, and mechanical stirrer, was charged with 500 ml. of dry ether and 19.0 g. (0.5 mole) of lithium aluminum hydride. The mixture was vigorously stirred. When all the lithium aluminum hydride was well broken up and had formed a uniform suspension in the ether, 28.0 g. (0.2 mole) of o-fluorobenzoic acid dissolved in 350 ml. of dry ether was added at such a rate as to produce gentle reflux. When the addition of the ether solution of o-fluorobenzoic acid was complete, the reaction mixture was

refluxed for fifteen more minutes, followed by cautious addition of water to decompose the excess lithium aluminum hydride. This was followed with the addition of 10% sulfuric acid solution until the aqueous phase was clear. The aqueous layer was washed with ether and the combined ether solution dried over anhydrous sodium sulfate. After filtering, the ether was taken off. The crude yield of o-fluorobenzyl alcohol was 25.0 g. The crude material was fractionally distilled and the fraction distilling at 65-67° at 12 mm. pressure was collected. The yield of pure o-fluorobenzyl alcohol was 20.5 g. (81%).

28.0 g. (0.20 mole) → 20.5 g. (0.16 mole)

o-Fluorobenzyl Bromide.-- Into a solution of 25 ml. of benzene and 3.0 g. (0.024 mole) of o-fluorobenzyl alcohol was passed a steady stream of hydrogen bromide gas for three hours. The aqueous layer that separated was drawn off and the benzene solution dried over anhydrous sodium sulfate. After filtration, the benzene was removed by distillation. The liquid residue was fractionally distilled and the fraction boiling at 84-85° at 15 mm. pressure was collected to give 3.8 g. (75%) of pure o-fluorobenzyl bromide. (CAUTION, o-fluorobenzyl bromide is an extremely powerful lachrimator). The boiling point of o-fluorobenzyl bromide

was reported by Schoesmith and Slater (41) to be 84-85° at 15 mm. pressure.

3.0 g. (0.024 mole) — 3.8 g. (0.20 mole)

2-Fluoro-5-nitrobenzyl Bromide.-- A 600 ml. beaker was charged with 200 ml. of fuming nitric acid (sp. gr. 1.5). The nitric acid was mechanically stirred and cooled to 0°. To the acid was added dropwise 25.0 g. (0.13 mole) of o-fluorobenzyl bromide at a temperature of 0°. When the addition of the o-fluorobenzyl bromide was complete, the reaction mixture was allowed to come to room temperature with continued stirring. The mixture was poured onto ice and the yellow crystalline precipitate filtered and washed with cold water. The crude 2-fluoro-5-nitrobenzyl bromide (29 g.) melted at 74-75°. Recrystallization from ethanol gave 25.0 g. (81%) of pure product melting at 76.6-77.0°.

Anal. Calcd. for $C_7H_5O_2NFBr$: N, 6.0. Found; N,

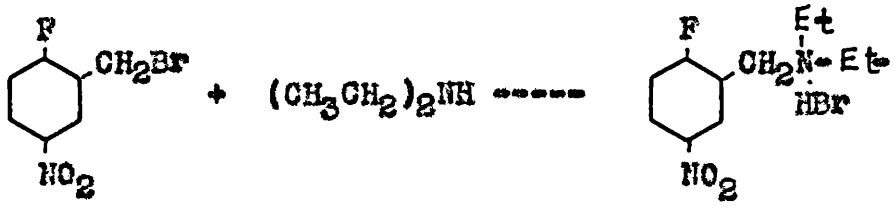
25.0 g. (0.13 mole) — 25.0 g. (0.11 mole)

2-Diethylaminomethyl-4-nitrofluorobenzene hydrobromide.-- The general procedure of Burckhalter and coworkers (42) for

the preparation of -alkylamino-4-nitro-o-cresols from -chloro-4-nitro-o-cresol and dialkyl amines was employed. A typical run, starting with 2-fluoro-5-nitrobenzyl bromide and diethyl amine was as follows:

A 500 ml., one-necked flask, equipped with a reflux condenser, was charged with 22.0 g. (0.094 mole) of 2-fluoro-5-nitrobenzyl bromide, 14.6 g. (0.2 mole) of diethyl amine and 150 ml. of absolute ethanol and the mixture refluxed for three hours. The volatile materials were removed by distillation under reduced pressure, and the residue was washed with water for the removal of recovered diethyl amine hydrobromide. The washed residue was dissolved in acetone and the solution dried over anhydrous sodium sulfate. After filtration, an equal volume of ether was added. Addition of excess alcoholic hydrogen bromide precipitated the yellow crystalline 2-diethylaminomethyl-4-nitrofluorobenzene hydrobromide. The yield was 19.0 g. (66%) of pure product melting at 162° (dec.).

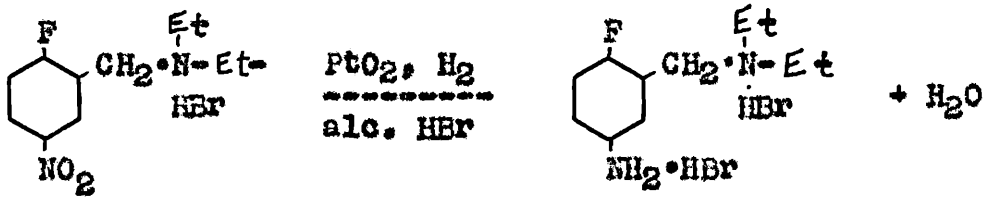
Anal. Calcd. for $C_{11}H_{15}N_2O_2F \cdot HBr$: C, 43.0. H, 5.2. N, 9.1. Found: C, 42.9. H, 5.2. N, 9.3.



22.0 g. (0.094 mole) | 14.6 g. (0.2 mole) | 19.0 g. (0.062 mole)

2-Diethylaminomethyl-4-aminofluorobenzene dihydrobromide.-- A suspension of 18.0 g. (0.06 mole) of 2-diethyl-

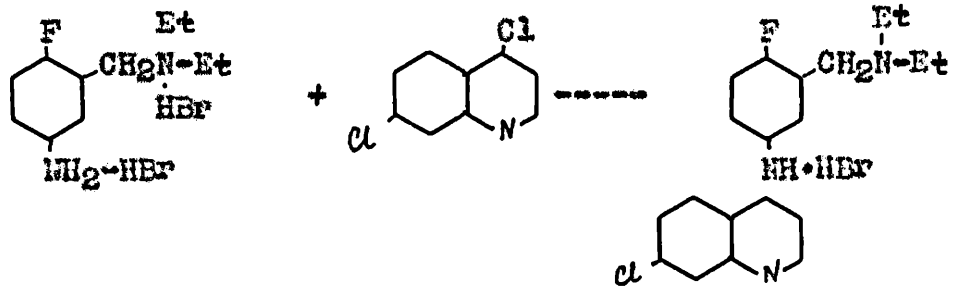
aminomethyl-4-nitrofluorobenzene hydrobromide in absolute ethanol was reduced catalytically using platinum oxide catalyst. When the solution had absorbed the theoretical amount of hydrogen it was filtered to remove the catalyst and the filtrate treated with a slight excess of alcoholic hydrogen bromide solution. The dihydrobromide salt of 2-diethylaminomethyl-4-aminofluorobenzene which was formed remained in solution. No attempt was made to isolate it in crystalline form. Rather, the alcoholic solution of 2-diethylaminomethyl-4-aminofluorobenzene dihydrobromide was used directly for the reaction with 4,7-dichloroquinoline for the preparation of 2-diethylaminomethyl-4-(7-chloro-4-quinolyl)-aminofluorobenzene dihydrobromide as shown below.



2-Diethylaminomethyl-4-(7-chloro-4-quinolyl)-aminofluorobenzene dihydrobromide.-- To the alcoholic solution of 2-diethylaminomethyl-4-aminofluorobenzene dihydrobromide above was added11.9 g. (0.06 mole) of 4,7-dichloroquinoline. The resulting mixture was heated on the steam bath for two hours. After cooling, and addition of ether, the dihydrobromide of 2-diethylaminomethyl-4-(7-chloro-4-quinolyl)-aminofluorobenzene precipitated as yellow crystals. The yield of the crude product melting at 201° (dec.) based on 2-diethylaminomethyl-4-nitrofluorobenzene was 19.0 g. (60%). Recrystallization

from methanol gave pure 2-diethylaminomethyl-4-(7-chloro-4-quinolyl)-aminofluorobenzene dihydrobromide melting at 203.8° (dec.).

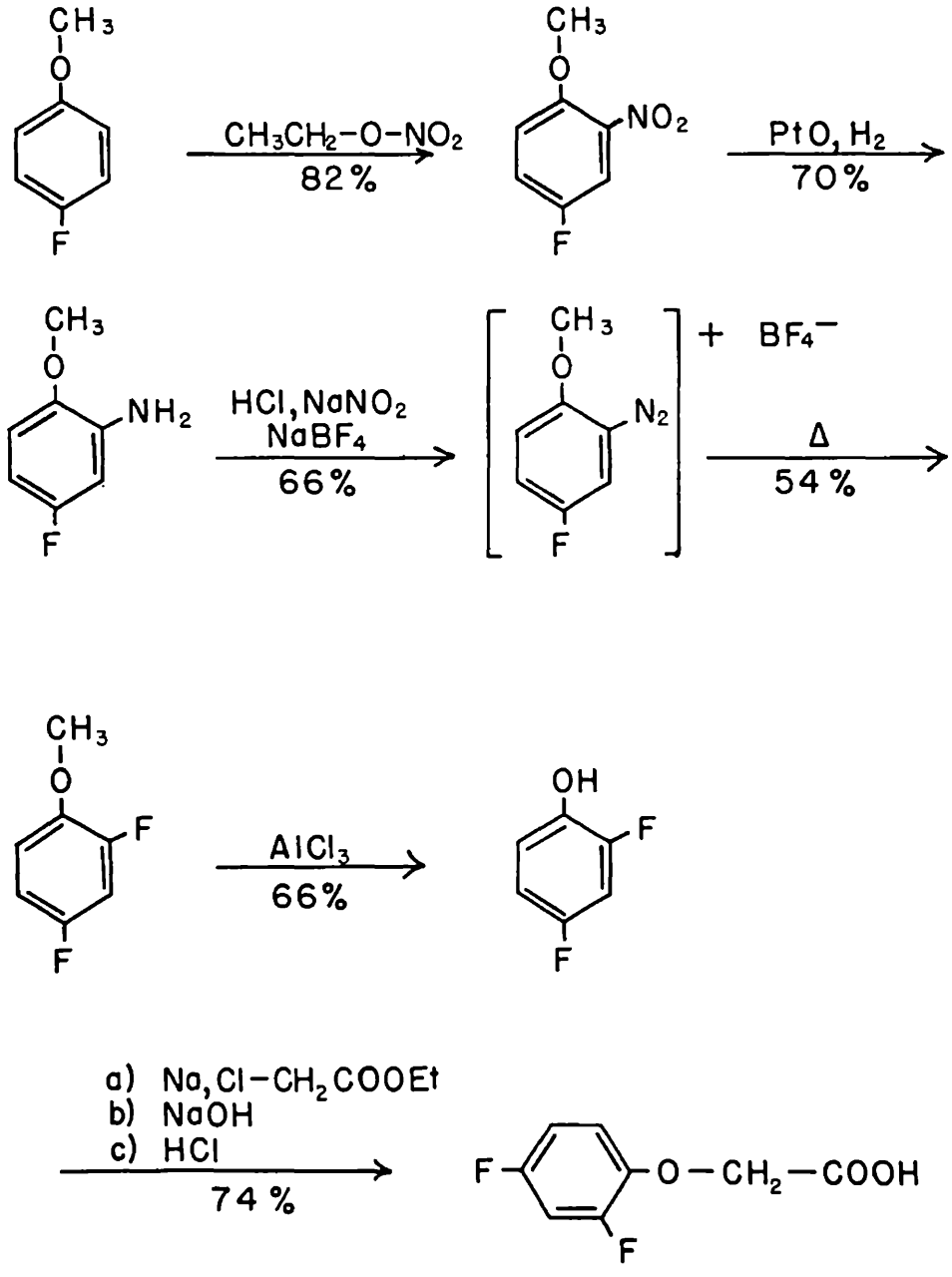
Anal. Calcd. for $C_{20}H_{21}N_3ClF \cdot 2HBr$: N, 8.1 C, 46.2 H, 4.4 Found: N, 7.9 C, 46.1 H, 4.7



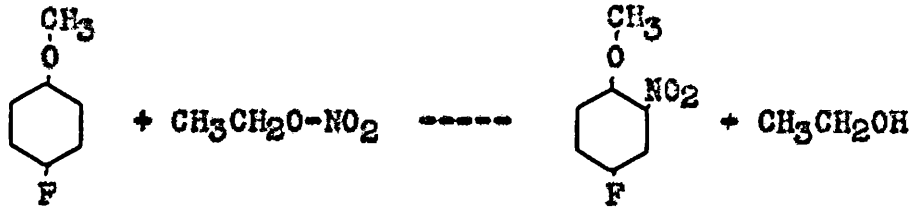
10.0 g.
(0.045 mole)

V. Synthesis of Fluorine Analogue of 2, 4-dichlorophenoxy-acetic acid.

The synthesis of 2, 4-difluorophenoxyacetic acid was carried out in the following manner:



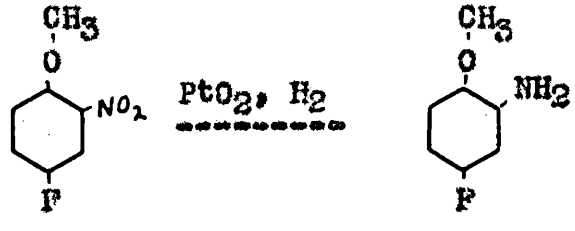
2-Nitro-4-fluoroanisole.-- A 600 ml. beaker was charged with 25.0 g. (0.19 mole) of p-fluoroanisole[1] dissolved in 95 ml. of concentrated sulfuric acid. The solution was mechanically stirred and cooled to 0°. To the solution, at 0-2°, 17.2 g. (0.19 mole) of ethyl nitrate was added dropwise. After the addition of all the ethyl nitrate the reaction mixture was stirred for fifteen minutes more and poured onto ice. The resulting yellow precipitate was filtered and washed well with cold water. There was obtained 28.0 g. (82%) of crude 2-nitro-4-fluoroanisole melting at 58-60°. The crude product was dissolved in ether and the ether solution washed with 10% sodium hydroxide solution in order to remove any phenolic components formed during the reaction. After thorough washing with water the ether solution was dried over anhydrous sodium sulfate, filtered and the pure 2-nitro-4-fluoroanisole was precipitated by the addition of Skellysolve C. The yield of the pure product was 25.1 g. (75%) melting at 59.2-60°. Swartz (35) has reported a melting point of 61.6° for 2-nitro-4-fluoroanisole.



25.0 g. (0.19 mole)	17.2 g. (0.19 mole)	25.1 g. (0.14 mole)

(1) Obtained through the kindness of A. F. Helin, University of Kansas.

2-Amino-4-fluoroanisole.-- A solution of 15.0 g. (0.088 mole) of 2-nitro-4-fluoroanisole in 100 ml. of absolute ethanol was reduced catalytically using platinum oxide catalyst. When the solution had absorbed the calculated amount of hydrogen, it was filtered to remove the catalyst and the alcohol removed by distillation. The oily residue was fractionally distilled and the fraction boiling at 93-95° at 2 mm. pressure was collected to give 8.0 g. (70%) of pure 2-amino-4-fluoroanisole.

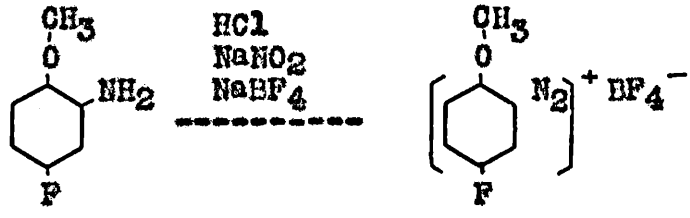


15.0 g.
(0.088 mole)

8.0 g.
(0.061 mole)

2-Methoxy-5-fluorodiazonium fluoborate.-- To a 800 ml. beaker, immersed in an ice-salt bath, and equipped with a stirrer and a thermometer, was added a solution of 56.4 g. (0.4 mole) of 2-amino-4-fluoroanisole and 80 ml. of concentrated hydrochloric acid in 140 ml. of water. The solution was cooled to 0°. This resulted in the precipitation of some of the amine hydrochloride. To the solution, cooled to 0°, 27.6 g. (0.4 mole) of solid sodium nitrite was added. When all the sodium nitrite had been added the reaction mixture was stirred at 0° for forty-five minutes. Then a solution of 87.3 g. (0.8 mole) of sodium fluoborate in 85 ml. of water was added slowly with continued stirring. The

resulting heavy precipitate was stirred for thirty minutes, filtered and washed with 50 ml. of 10% sodium fluoborate solution, followed by washing with 50-50 alcohol-ether mixture and finally with ether. The yield obtained was 63.1 g. (66%).

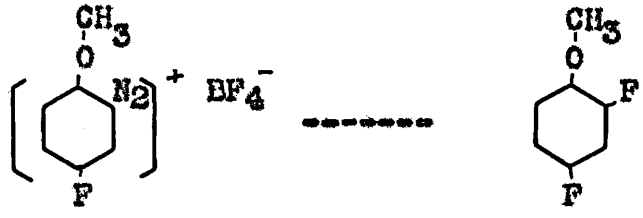


56.4 g.
(0.40 mole)

63.1 g.
(0.26 mole)

2,4-Difluoroanisole.-- A 500 ml., round bottom, one-necked flask was fitted with a knee joint leading to a straight condenser the end of which was fitted to a trap. The flask was charged with 63.1 g. (0.26 mole) of 2-methoxy-5-fluorodiazonium fluoborate and the solid thermally decomposed. The oily residue was dissolved in ether and the ether solution washed with sodium hydroxide solution and then with water. The ether solution was dried over anhydrous sodium hydroxide, filtered and the ether evaporated off. The residue was distilled and the fraction boiling at 155-156° at 734 mm. was collected to give 23.0 g. (54%) of pure 2,4-difluoroanisole.

Anal. Calcd. for $C_7H_6OF_2$: C, 58.4. H, 4.2 Found: C, 58.7 H, 4.4



63.1 g.
(0.26 mole)

23.0 g.
(0.14 mole)

2,4-Difluorophenol.-- A 200 ml., round bottom flask, equipped with a reflux condenser fitted with a calcium chloride drying tube, was charged with 10.0 g. (0.058 mole) of 2,4-difluoroanisole, 25 ml. of dry benzene and 24 g. of anhydrous aluminum chloride. The reaction mixture was refluxed for three hours, cooled and extracted with 100 ml. of 20% solution of sodium hydroxide. The aqueous solution was neutralized with dilute hydrochloric acid and ether extracted. The ether solution was dried over anhydrous sodium sulfate, filtered and the ether removed by evaporation. The liquid residue was distilled and the distillate boiling at 150-152° at 730 mm. pressure was collected to give 6.0 g. (66%) of pure 2,4-difluorophenol.

10.0 g.
(0.058 mole)

6.0 g.
(0.046 mole)

2,4-Difluorophenoxyacetic Acid.-- The general procedure of Haskelberg (43) was employed in coupling sodium 2,4-difluo-

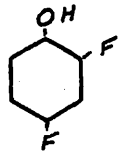
rophenolate and ethyl chloroacetate. The procedure was as follows:

In a conically shaped 100 ml., three-necked flask, fitted with a reflux condenser, was placed a solution of 2.4 g. (0.02 mole) of 2,4-difluorophenol in 15 ml. of n-butyl alcohol. To the solution was added 0.5 g. of finely cut sodium and 5.1 g. (0.04 mole) of ethyl chloroacetate.[1] The resulting grey gelatinous mixture was heated at 100° for one and one-half hours, cooled and diluted with water. The oil that separated was dissolved in ether, the ether solution dried over anhydrous sodium sulfate, filtered and the ether boiled off. An oily residue remained. No attempt was made to isolate the ethyl 2,4-difluorophenoxyacetate in pure form. The crude ester was subjected to hydrolysis in the following manner:

To the oily residue was added 0.8 g. of sodium hydroxide dissolved in 10 ml. of water. The mixture was heated on the steam bath overnight. The aqueous solution was extracted with ether and then acidified with dilute hydrochloric acid. The resulting grey crystalline precipitate was filtered and air dried to give 1.5 g. (44%) of 2,4-difluorophenoxyacetic acid melting at 121.5-122.5°. Recrystallization from benzene gave pure product melting at 124.0-124.5°.

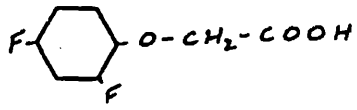
Anal. Calcd. for $C_8H_6O_3F_2$: C, 51.1. H, 3.2. Found: C, 51.5. H, 3.6.

(1) Kindly furnished us by H. L. Bradlow, University of Kansas.



2.4. g.
(0.02 mole)

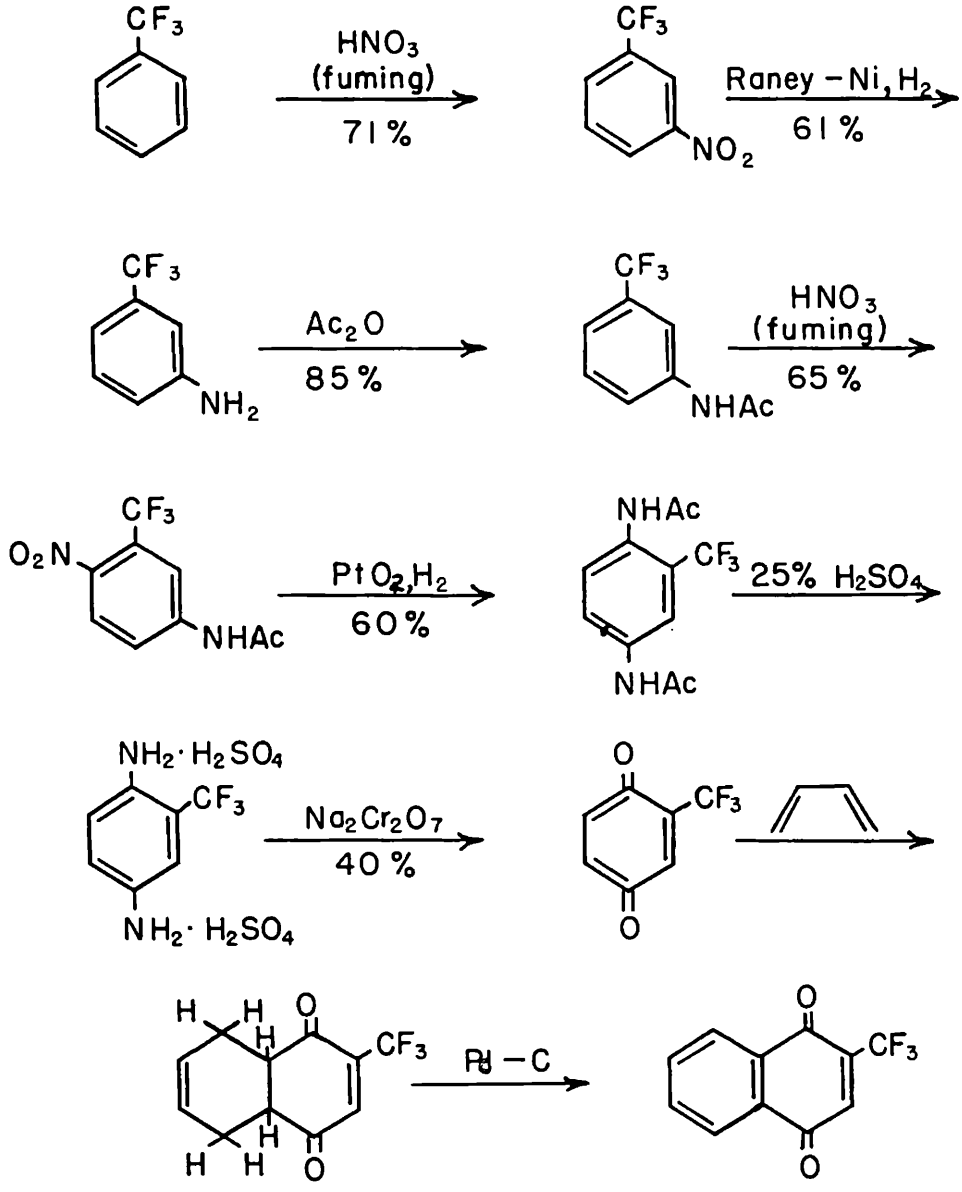
1) Na, $ClCH_2COOE$-
2) NaOH, HCl



1.5 g.
(0.008 mole)

VI. Attempted Synthesis of Fluorine Analogues of Menadione (2-Methyl-1.4-naphthaquinone).

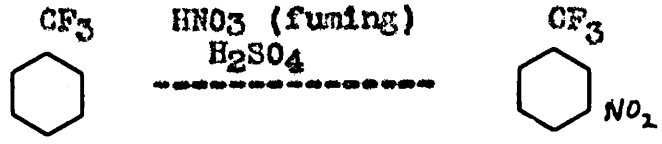
a) Proposed Synthesis of 2-Trifluoromethyl-1.4-naphthaquinone according to the following scheme:



m-Trifluoromethylnitrobenzene.-- The procedure of Swarts (44) was used to prepare this compound starting with benzotrifluoride and nitrating it with fuming nitric acid. A typical run is described;

To a 400 ml. beaker containing 35.0 g. (0.24 mole) of benzotrifluoride was added 60 ml. of a 1.5:1 mixture of concentrated sulfuric acid and fuming nitric acid. The solution was kept in an ice bath during the addition of the acid mixture. The reaction mixture was then allowed to come to room temperature and was held at that temperature for two hours.

The mixture was then poured on ice and extracted with ether. The ether layer was washed several times with water and dried over anhydrous sodium sulfate. After removal of the sodium sulfate, the ether was taken off and the residue fractionally distilled. The fraction boiling at 198-199° at 738 mm. was collected to give a yield of 31.5 g. (70.8%) of m-trifluoromethylnitrobenzene.



35.0 g.
(0.24 mole)

31.5 g.
(0.17 mole)

m-Trifluoromethylaniline.-- A solution of 31.5 g. (0.17 mole) of m-trifluoromethylnitrobenzene in 150 ml. of absolute ethanol was hydrogenated in the presence of Raney nickel, using a trace of platinic chloride as a promoter. When the theoretical amount of hydrogen had been absorbed,

the catalyst was filtered and the alcoholic filtrate solution distilled. The fraction boiling at 70-71° at 7 mm. pressure was collected to give 16.8 g. (60.6%) of m-trifluoromethylaniline.

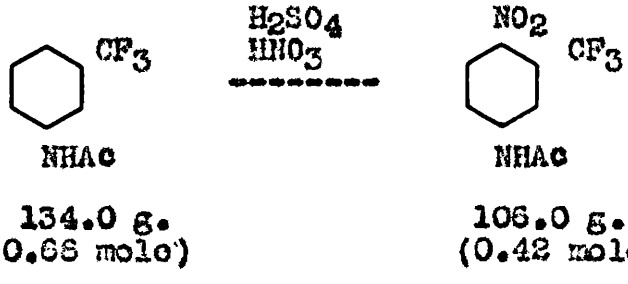
31.5 g. (0.17 mole) — 16.8 g. (0.11 mole)

m-Trifluoromethylacetanilide.-- To a solution of 42.0 g. (0.26 mole) of m-trifluoromethylaniline dissolved in 50 ml. of benzene was added 26.5 g. of acetic anhydride and a few drops of concentrated sulfuric acid. The mixture was heated on a steam bath for two hours and the benzene distilled off. The remaining crude m-trifluoromethylacetanilide was recrystallized from alcohol-water to give 45.0 g. (85%) of pure product melting at 104.5-105°. Swartz (44) has reported the melting point of m-trifluoromethylacetanilide to be 103°.

42.0 g. (0.26 mole) — 45.0 g. (0.22 mole)

3-Trifluoromethyl-4-nitroacetanilide.-- In a 2-liter, three-necked flask was placed 700 ml. of concentrated sulfuric acid. This was cooled to -5°, 134.0 g. (0.66 mole) of m-trifluoromethylacetanilide was added, and the mixture was stirred until a clear solution was formed. From a dropping

funnel was added a solution of 54 g. of fuming nitric acid in 67 ml. of concentrated sulfuric acid during forty-five minutes while the temperature was maintained at -5 to 0°. The solution was allowed to warm to room temperature and stand for three hours, then warmed to 40° for one hour, and poured onto ice. The yellow gummy precipitate gradually crystallized. It was collected and washed well with water. The crude 3-trifluoromethyl-4-nitroacetanilide was added to 500 ml. of acetic anhydride and the mixture refluxed for two hours in order to reacetylate any product that might have been deacetylated during the nitration. The acetic anhydride was removed by distillation and the residue washed well with water to give 106.0 g. (65%) of pure 3-trifluoromethyl-4-nitroacetanilide melting at

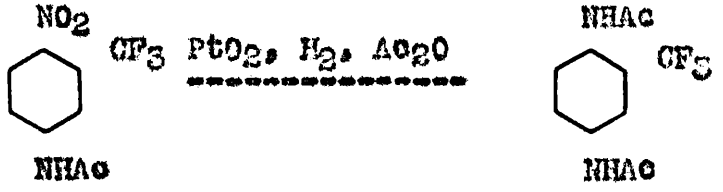


134.0 g. (0.68 mole) 106.0 g. (0.42 mole)

2,5-Diacetamidobenzotrifluoride.-- A solution of 50.0 g. (0.2 mole) of 3-trifluoromethyl-4-nitroacetanilide in 175 ml. of acetic anhydride was hydrogenated in the presence of platinum oxide catalyst. When the theoretical amount of hydrogen had been absorbed, the precipitated 2,5-diacetamidobenzotrifluoride and the platinum oxide catalyst were filtered. The mixed solid was added to 200 ml. of hot ethanol which dissolved

the organic material, and the catalyst was filtered. On cooling, 31.0 g. (60%) of pure 2,5-diacetamidobenzotrifluoride melting at 188.4-189.1° separated from the alcoholic filtrate.

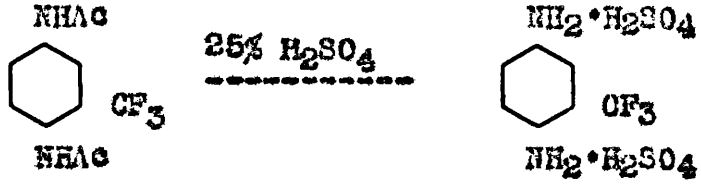
Anal. Calcd. for $C_{11}H_{11}O_2N_2F_3$: N, 11.3. Found: N, 11.1.



50.0 g.
(0.20 mole)

31.0 g.
(0.12 mole)

2,5-Diaminobenzotrifluoride dihydrosulfate.-- A 1-liter Erlenmeyer flask equipped with a mechanical stirrer was charged with 13.6 g. (0.052 mole) of 2,5-diacetamidobenzotrifluoride and 340 ml. of 25% sulfuric acid solution. The mixture was heated with stirring until hydrolysis was complete. No attempt was made to isolate the diamine salt. Rather, the aqueous solution was subjected to dichromate oxidation as indicated below.



13.6 g.
(0.052 mole)

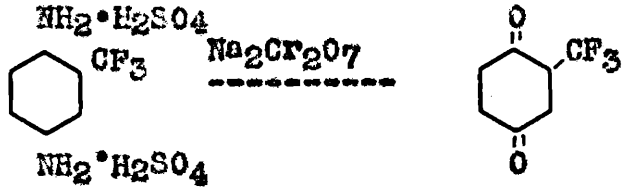
2-Trifluoromethyl-1,4-benzoquinone.-- The aqueous solution containing the dihyrosulfate salt of 2,5-diaminobenzotrifluoride

as indicated in the preceding experimental section was oxidized with sodium dichromate in the following manner:

The aqueous salt solution contained in a 1-liter Erlenmeyer flask equipped with a mechanical stirrer was cooled in an ice bath to a temperature below 10° and 250 ml. of benzene added. The heterogeneous mixture was stirred vigorously while 18.6 g. of sodium dichromate dissolved in 30 ml. of water was added at such a rate that the temperature did not rise above 10°. After the addition of the sodium dichromate solution was complete the reaction mixture was stirred for three hours at 10°. The benzene layer was separated and dried over anhydrous sodium sulfate. After filtration the benzene solution was stored in the dry ice chest overnight.

The solution was concentrated down to 40 ml. volume by distilling off the benzene. The addition of Skellysolve C and subsequent cooling of the solution in dry-ice chloroform precipitated yellow-orange crystals of 2-trifluoromethyl-1,4-benzoquinone. Upon filtration and air drying there was obtained 3.5 g. (40%) of pure 2-trifluoromethyl-1,4-benzoquinone melting at 51.2-52.0°.

Anal. Calcd. for $C_7H_3O_2F_3$: C, 47.7. H, 1.7. Found: C, 47.8. H, 2.0.

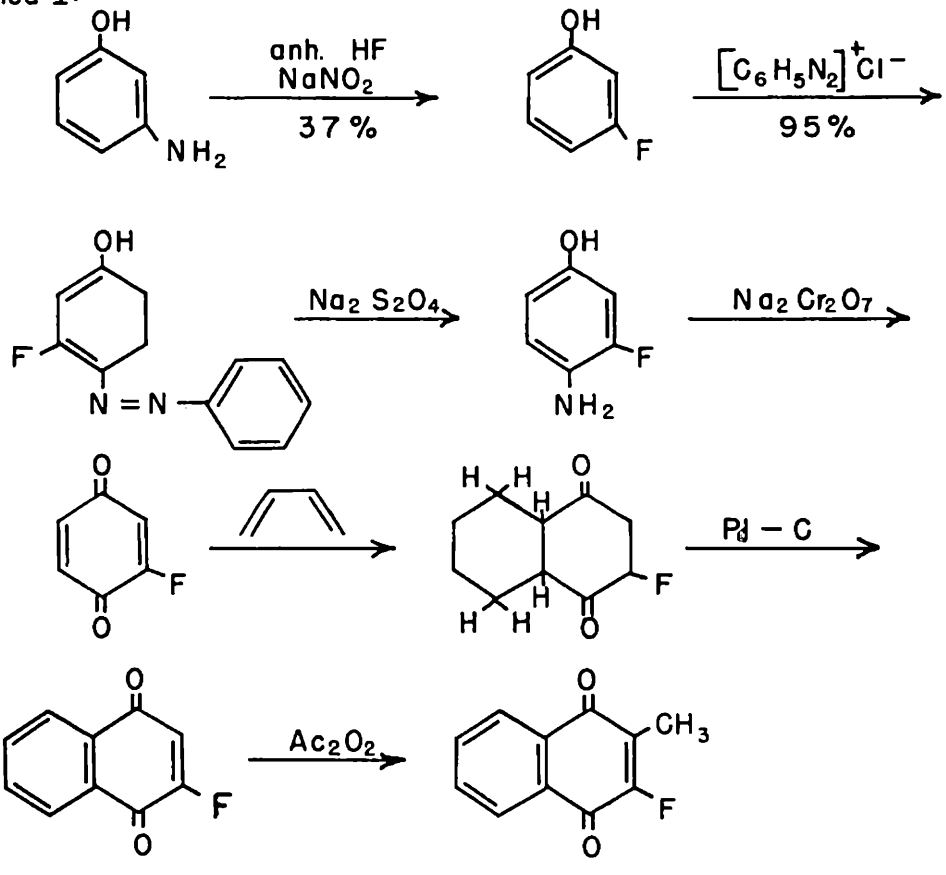


3.5 g.
(0.020 mole)

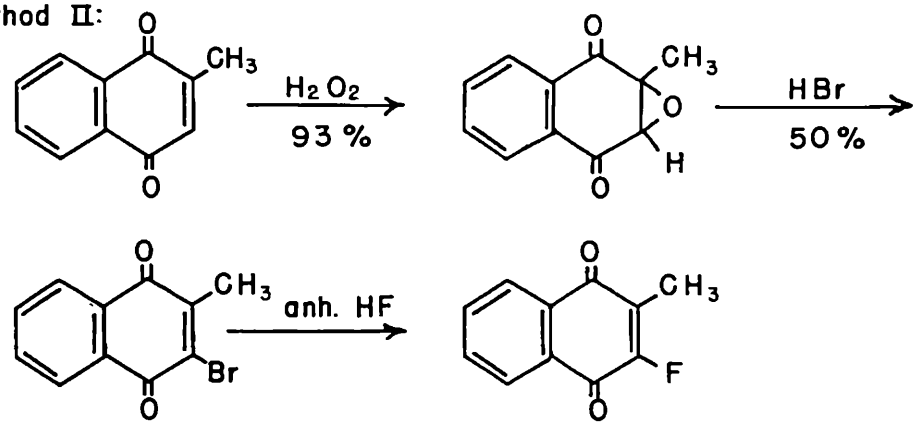
VI. Attempted Synthesis of Fluorine Analogues of Menadione (2-Methyl-1.4-naphthaquinone).

b) Proposed Synthesis of 2-Methyl-3-fluoro-1.4-naphthaquinone.

Method I:

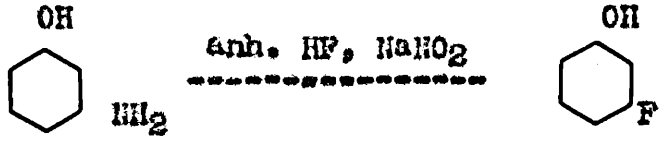


Method II:



m-Fluorophenol.-- About 640 g. (32 moles) of hydrogen fluoride was slowly run into 186.0 g. (1.7 moles) of m-aminophenol contained in a 2-liter copper flask cooled in an ice bath. This mixture was kept at -5° for two hours while 140.8 g. (2.0 moles) of granular sodium nitrite was slowly added with constant mechanical stirring. The reaction mixture was allowed to come to room temperature and then connected to an ice-cooled reflux coil and heated at 45-50° for three hours.

Dilution with ice water followed by steam distillation gave an insoluble oil which was dried over calcium chloride and distilled to yield 70.5 g. (37%) of m-fluorophenol boiling at 78-80° at 17 mm. pressure.



186.0 g.
(1.7 moles)

70.5 g.
(0.63 mole)

2-Fluoro-4-hydroxyazobenzene.-- The procedure of Hodgson (45) starting with 3-fluorophenol and diazotized aniline was used to obtain this compound. A typical run was as follows:

A 600 ml. beaker equipped with a mechanical stirrer was charged with a solution of 20.0 g. (0.22 mole) of aniline in 260 ml. of 25.8% of hydrochloric acid solution. The solution was cooled to 0° and diazotized by adding 20.0 g. (0.29 mole) of sodium nitrite dissolved in 200 ml. of water. Excess nitrous acid was destroyed by the addition of a small amount

of urea. To a 2-liter beaker, fitted with a mechanical stirrer was added 24.0 g. (0.21 mole) of 3-fluorophenol dissolved in 500 ml. of 6% sodium hydroxide solution. After cooling the solution to 0° the aqueous diazonium chloride was added with vigorous stirring. The resulting 2-fluoro-4-hydroxyazobenzene was filtered, washed well with cold water and air dried to give 43.0 g. (95%) of product melting at 138° (dec.). Hodgson has reported a melting point of 139° (dec.) for 2-fluoro-4-hydroxyazobenzene (45).

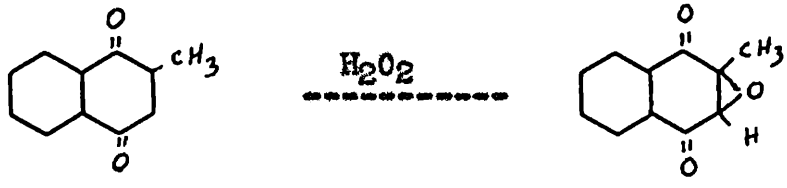
24.0 g.
(0.21 mole)

43.0 g.
(0.19 mole)

2-Methyl-2,3-epoxy-1,4,-naphthaquinone.-- The general procedure of Fieser (46) for the preparation of epoxides of 1,4-naphthaquinones was used for the preparation of 2-methyl-2,3-epoxy-1,4-naphthaquinone. A typical run was as follows:

A 1-liter Erlenmeyer flask was charged with 50.0 g. (0.29 mole) of 2-methyl-1,4-naphthaquinone and 500 ml. of absolute ethanol and the mixture heated until all of the 2-methyl-1,4-naphthaquinone was in solution. The alcoholic solution was allowed to cool while 10.0 g. of anhydrous sodium carbonate was dissolved in 250 ml. of water. Next, 50 ml. of 30% hydrogen peroxide solution was added. The quinone solution was cooled under the tap until crystallization began. The peroxide solution was then added all at once with

the subsequent discharge of the yellow color of the quinone solution. The reaction mixture was poured onto ice water and the colorless white crystals filtered and air dried. There was obtained 51.2 g. (93.1%) of 2-methyl-2,3-epoxy-1,4-naphthaquinone melting at 94.1-95.0°. Fieser (46) reports the melting point of pure 2-methyl-2,3-epoxy-1,4-naphthaquinone to be 95.5-96.5°.



50.0 g.
(0.29 mole)

51.2 g.
(0.27 mole)

2-Methyl-3-bromo-1,4-naphthaquinone.-- The method of Carrara and Bonacci (47) was employed in the preparation of this compound. A typical run was as follows:

To 150 ml. of 10% hydrogen bromide in glacial acetic acid contained in a 600 ml. beaker was added with stirring 15.0 g. (0.08 mole) of 2-methyl-2,3-epoxy-1,4-naphthaquinone. The quinone dissolved with a small evolution of heat. The stirring was continued for fifteen minutes and the mixture poured onto ice water. The resulting yellow precipitate was filtered and air dried. The crude product which was a mixture of 2-methyl-3-bromo-1,4-naphthaquinone and 2-methyl-3-hydroxy-1,4-naphthaquinone was dissolved in ether and extracted with 10% sodium hydroxide solution and then with water. The ether solution was dried over anhydrous sodium sulfate, filtered, and the ether distilled off. The remaining yellow

crystalline product yielded 10.0 g. (50%) of 2-methyl-3-bromo-1,4-naphthaquinone melting at 149.3-150.2°.

Upon acidification of the sodium hydroxide extract of the ether solution, there was obtained 5.0 g. of 2-methyl-3-hydroxy-1,4-naphthaquinone melting at 172.0-173.0°.

15.0 g.
(0.08 mole)

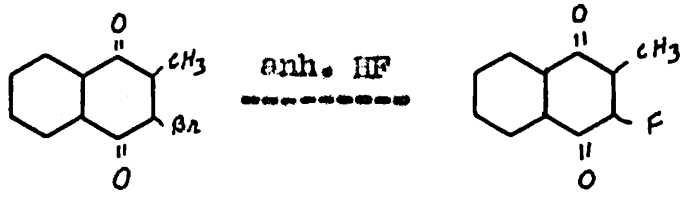
10.0 g.
(0.04 mole)

2-Methyl-3-fluoro-1,4-naphthaquinone.-- To 50.0 g. (2.5 moles) of anhydrous hydrogen fluoride contained in a stainless steel flask 5.0 g. (0.02 mole) of 2-methyl-3-bromo-1,4-naphthaquinone was added with stirring. Stirring was continued at 0° for three hours and the reaction mixture allowed to come to room temperature. The remaining hydrogen fluoride was boiled off. The residue was dissolved in ether and dried over anhydrous sodium sulfate. After evaporation of the ether, the remaining yellow precipitate was tested for fluorine. The zirconyl nitrate alizarin S test was positive. The product melted at 141-143° (softened at 135°). Mixed melting point of product with 2-methyl-3-fluoro-1,4-naphthaquinone gave a value of 145-146°.

Further evidence for a partial replacement of the bromine with fluorine in the reaction of hydrogen fluoride on 2-methyl-3-bromo-1,4-naphthaquinone was that hydrogen bromide

was given off during the reaction. This was demonstrated by passing the gaseous fumes given off during the reaction into an aqueous solution of silver nitrate. The resulting white precipitate was silver bromide since silver fluoride is very soluble in water.

It seems likely therefore that the product obtained from the reaction was a mixture of 2-methyl-3-fluoro-1,4-naphthaquinone and 2-methyl-3-bromo-1,4-naphthaquinone. No way has as yet been found to separate the two. Further work is under way in studying the conditions whereby a complete replacement of the bromine by the fluorine atom will be effected.



DISCUSSION OF EXPERIMENTAL RESULTS

Isosteres of Sulfa Drugs. (Sec. I, Experimental, p. 14-18).

The comparison of the synthesis of fluorobenzene by the Schiemann to that of the anhydrous hydrogen fluoride method is of interest. The obvious advantage of the anhydrous hydrogen fluoride method is that it gives a better yield of fluorobenzene. Another advantage of this method that is less apparent to one not familiar with the process is that it is less time consuming than the Schiemann. The most serious disadvantage of the method is the necessity of having to use special equipment for the handling of anhydrous hydrogen fluoride. The handling of hydrogen fluoride as a chemical does not introduce any serious problems if a well-ventilated hood is available for the experimentor.

In the synthesis of 2-(p-fluorobenzene sulfonamido)-pyridine (p. 17) the low yield obtained was due to the repeated recrystallization necessary to isolate the product in pure form. Our investigations have since revealed that alcohol-water is a better solvent than glacial acetic acid for the purification of the crude 2-(p-fluorobenzamido)-pyridine.

p-Fluorobenzamido Analogues of Sulfa Drugs. (Sec. II, Experimental, p. 18-23).

All attempts to prepare 2-(p-fluorobenzamido)-pyrimidine by the same method as that used for the preparation of 2-(p-fluorobenzamido)-thiazole and 2-(p-fluorobenzamido)-pyridine

were unsuccessful.

When a mixture of dry pyridine and triethyl amine was used as solvent in place of dry pyridine alone in the reaction of p-fluorobenzoyl chloride on 2-aminopyrimidine, a product melting at 160.8-161.4° that analyzed correctly for the 2-di-(p-fluorobenzamido)-pyrimidine was obtained.

Anal. Calcd. for $C_{18}H_{11}O_2N_3F_2$: C, 63.7. H, 3.3. N, 12.5. Found: C, 63.8. H, 3.8. N, 12.5.

The procedure of Schonberg and Mustafa (48) for the preparation of 1-acetamidonaphthalene from 1-(diacetyl)-aminonaphthalene by the action of diazomethane was attempted on this compound in the hope of obtaining the desired 2-(p-fluorobenzamido)-pyrimidine. This was unsuccessful, and the starting material was recovered.

Previous attempts to synthesize 2-(p-fluorobenzamido)-pyridine, 2-(p-fluorobenzamido)-thiazole and 2-(p-fluorobenzamido)-pyrimidine by the use of the general conditions of the Schotten-Bauman reaction, i.e., reacting a mixture of the heterocyclic amine and the p-fluorobenzoyl chloride in the presence of an aqueous sodium hydroxide solution, were unsuccessful. Difficultly separable mixtures of the corresponding amides and the starting materials were obtained.

6-Fluoro-8-aminoquinoline (Sec. III a, Experimental, p. 23-33).

The experimental investigation of the three different

methods for obtaining 6-fluoro-8-aminoquinoline with regard to their general applicability and overall yield indicates that method I (see flow sheet p. 25A) was most satisfactory. This method was formulated and partially completed by Bradlow (32). The author carried it to a successful completion and obtained 6-fluoro-8-aminoquinoline on July 2, 1947 (see p. 26). The publication of method II by Wilkinson and Finar (36) in March, 1948 included the preparation of 6-fluoro-8-aminoquinoline reported in the literature for the first time. The reported yields of the various steps of their synthesis could not be duplicated by the author. A notable extension of their method is the inclusion of an additional preparative route to 2-nitro-4-fluoroacetanilide (see flow sheet p. 23A). Nitration of 4-fluoroacetanilide when acetyl nitrate was used gave better yield than when ethyl nitrate was employed. However, the preparation of acetyl nitrate (49) from nitrogen pentoxide and acetic anhydride is difficult because of the great instability of nitrogen pentoxide. This makes the ethyl nitrate more desirable to use for this nitration in spite of the fact that the yield of the resulting 2-nitro-4-fluoroacetanilide is somwhat lower.

In method III (flow sheet p. 23A) we have carried the procedure of Haskelberg (43) beyond the preparation of 6-aminoquinoline to that of 6-fluoroquinoline following Roe and Hawkins' (50) modification of the Schiemann reaction. This sequence was found to give the least satisfactory results of all three methods.

6-Fluoro-8-amino Substituted Quinolines (Sec., IIIb, Experimental, p. 33-36).

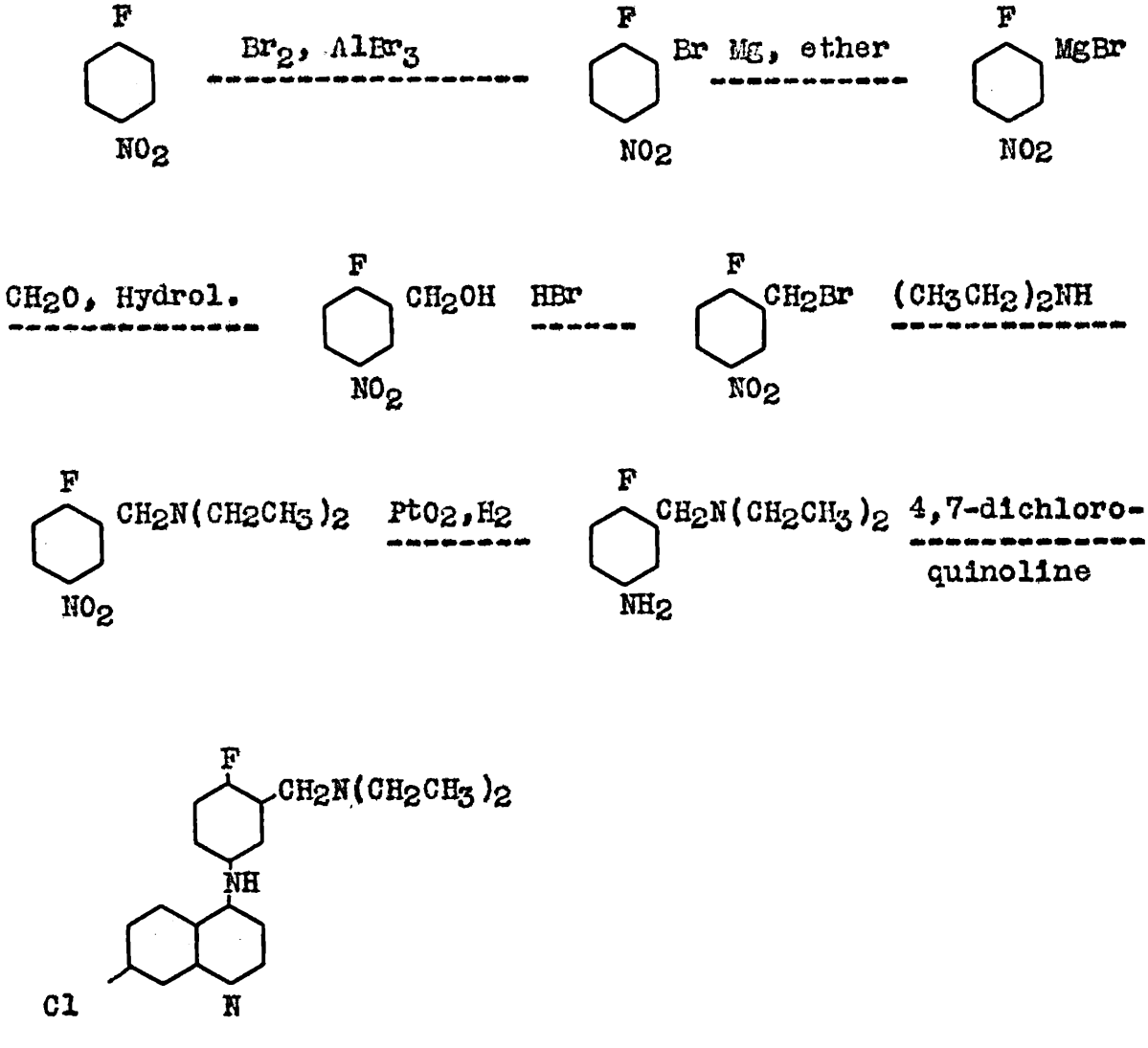
The inherent low yield in coupling reactions of the type attempted between 6-fluoro-8-aminoquinoline and 2-bromo-5-diethylaminopentane, along with the small quantities of 6-fluoro-8-aminoquinoline thus far available, have made it impossible to isolate and identify any of the desired 6-fluoro-8-(1-methyl-4-diethylaminobutyl)-aminoquinoline. The critical intermediate, 6-fluoro-8-aminoquinoline, has now been synthesized in large enough quantities so that the coupling reaction may be studied further.

The synthesis of 6-fluoro-8-(p-fluorobenzenesulfonamido)-quinoline and 6-fluoro-8-(7-chloro-4-quinolyl)-aminoquinoline as interesting hybrid structures was accomplished (see flow sheet 33A) in a conventional manner. Both of these compounds are reported for the first time.

Fluorine Isostere of Camoquin (Sec. IV, Experimental, p. 36-43)

Various unsuccessful attempts to synthesize 2-diethylaminomethyl-4-(7-chloro-4-quinolyl)-aminofluorobenzene (fluorine isostere of camoquin) were encountered before the one shown on flow sheet 36A was worked out.

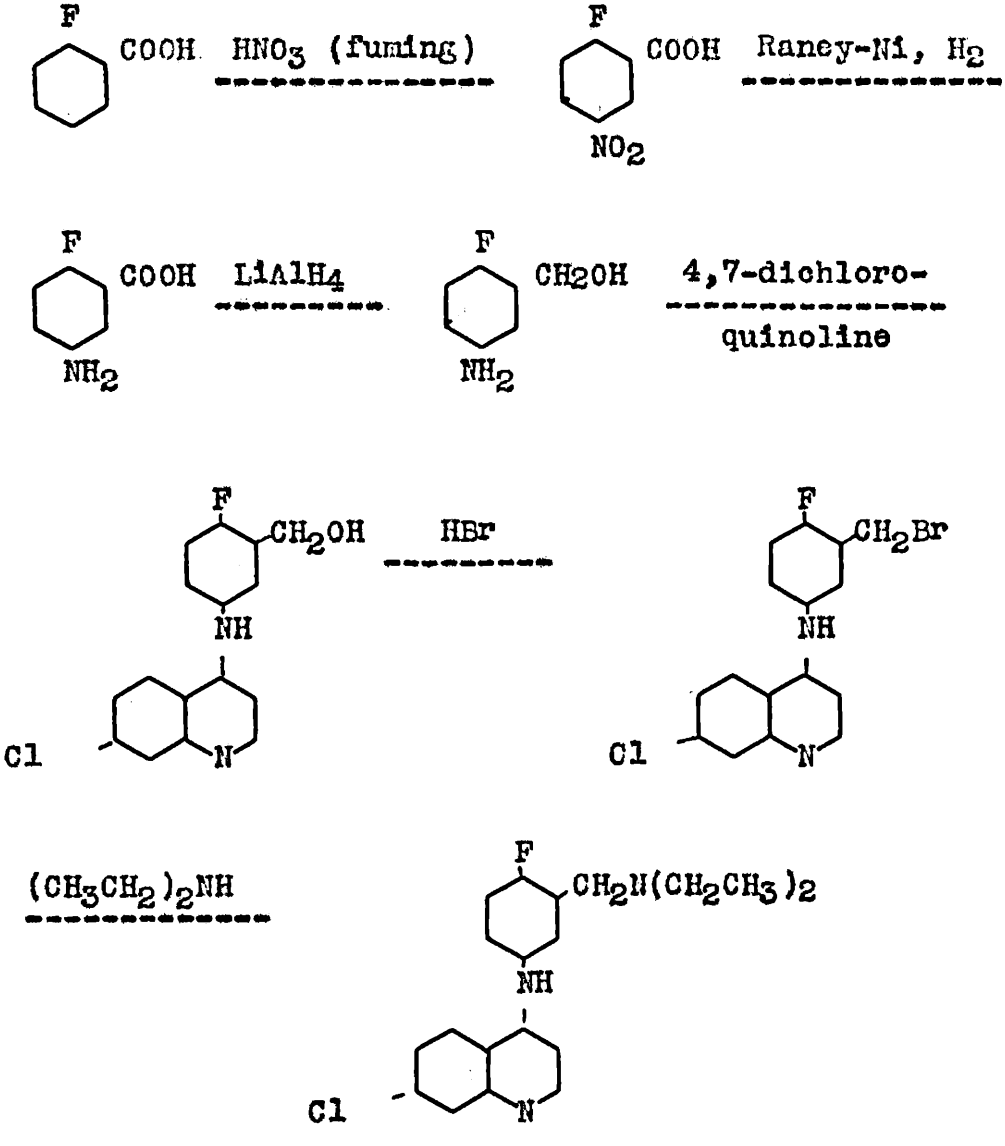
One of the first attempts to prepare the camoquin isostere was by the following proposed scheme:



2-diethylaminomethyl-4-(7-chloro-4-quinolyl)-aminofluorobenzene.

After preparation of 2-bromo-4-nitrofluorobenzene by the bromination of p-nitrofluorobenzene, we were unable to run a Grignard reaction on this compound for the purpose of obtaining 2-fluoro-5-nitrobenzyl alcohol. Several attempts were made by the use of di-n-butyl ether as a solvent in place of diethyl ether in the reaction, but these were also unsuccessful. Thus, this scheme was abandoned in favor of the following

synthetic approach:



This scheme too had to be abandoned. It was found that 2-fluoro-5-aminobenzoic acid could not be reduced by lithium aluminum hydride to the corresponding 2-fluoro-5-aminobenzyl alcohol. This was due to the extreme insolubility of 2-fluoro-5-aminobenzoic acid in ether, which is used as a solvent in the reduction. Even by employing the modified apparatus suggested by Nystrom and Brown (40) for use on compounds sparingly

soluble in ether, no reduction had taken place in eight days with the use of lithium aluminum hydride.

The successful synthesis of 2-diethylaminomethyl-4-(7-chloro-4-quinolyl)-aminofluorobenzene was carried out as shown by the scheme on flow sheet 36A. The reduction of 2-fluorobenzoic acid to 2-fluorobenzyl alcohol was accomplished in good yield only when a 2.5 to 1 molar ratio of lithium aluminum hydride to the acid was used. This is considerably in excess of what Nystrom and Brown (40) have used in reduction of substituted benzoic acids to the corresponding benzyl alcohols.

Prof of structure of 2-fluoro-5-nitrobenzyl bromide obtained by the nitration of 2-fluorobenzyl bromide was carried out as follows:

Oxidation with potassium permanganate of the nitration product melting at 76.6-77.0° resulted in the formation of crystalline product melting at 137.5-138.4°. Mixed melting point with an authentic sample of 2-fluoro-5-nitrobenzoic acid, prepared by the nitration of 2-fluorobenzoic acid according to the directions of Slothouwer (30), gave no depression. Thus, it was concluded that the nitration of 2-fluorobenzyl bromide resulted in the formation of 2-fluoro-5-nitrobenzyl bromide.

Fluorine Analogue of 2,4-dichlorophenoxyacetic Acid (Sec. V, Experimental, p. 43-49)

The nitration of p-fluoroanisole by the use of ethyl

nitrate to give 2-nitro-4-fluoroanisole was accomplished in better yield than previously reported (51) when other nitrating agents were used. The reduction of 2-nitro-4-fluoroanisole by the use of platinum oxide as a catalyst to yield 2-amino-4-fluoroanisole gave somewhat lower yield than obtained by Helin (52). The diazotization of 2-amino-4-fluoroanisole and the subsequent formation of the diazonium fluoborate salt by the general Schiemann reaction was accomplished in only 66% yield. This can undoubtedly be improved upon by further experimentation. In general, the yield of the fluoborate salt in the Schiemann reaction is over 90%. It is suggested that the cleavage of 2,4-difluoroanisole to 2,4-difluorophenol may be preferably carried out by the use of aluminum bromide or hydrogen iodide, rather than aluminum chloride. This would probably lead to somewhat better results.

Proposed Synthesis of 2-Trifluoromethyl-1,4-naphthaquinone.

(Sec. VIa, Experimental, p. 49-54)

The proposed synthesis of 2-trifluoromethyl-1,4-naphthaquinone as outlined on flow sheet VIa (p. 49A) has been carried as far as the preparation of 2-trifluoromethyl-1,4-benzoquinone. The remainder of the proposed synthesis consists of a Diels-Alder type condensation between butadiene-1, 3 and 2-trifluoromethyl-1,4-benzoquinone with the subsequent dehydration to give 2-trifluoromethyl-1,4-naphthaquinone.

Before succeeding in preparing 2-trifluoromethyl-1,4-benzoquinone we had met with numerous failures. The preparation of 2-trifluoromethyl-1,4-benzoquinone was first

attempted by the oxidation of m-trifluoromethylaniline. Analogous oxidation of m-toluidine to give 2-methyl-1,4-benzoquinone has been reported (53,54,55). Only resinous material was obtained when m-trifluoromethylaniline was subjected to oxidation under the same conditions. It seemed certain that a compound containing amino or hydroxyl groups para to each other in the molecule would oxidize with considerable more ease to give the desired benzoquinone structure. Therefore, we set out to prepare 2-trifluoromethyl-4-aminoaniline as a likely intermediate that would yield 2-trifluoromethyl-1,4-benzoquinone upon oxidation. It was hoped that nitration of m-trifluoromethylacetanilide would give the desired 3-trifluoromethyl-4-nitroacetanilide and subsequent deacetylation and reduction would yield 2-trifluoromethyl-4-aminoaniline. While the identification and proof of structure of the nitration product from m-trifluoromethylacetanilide was under way, there appeared a publication by Jones (56) describing the preparation of 2-nitro-5-aminobenzotrifluoride by the nitration of m-trifluoromethylacetanilide and subsequent deacetylation. After deacetylation, our nitration product gave an identical melting point with that reported by Jones for 2-nitro-5-aminobenzotrifluoride. Thus, it was established that nitration of m-trifluoromethylacetanilide gave 3-trifluoromethyl-4-nitroacetanilide. Jones had not reported the isolation of the pure 3-trifluoromethyl-4-nitroacetanilide. He had deactylated the crude nitration product--a mixture of 3-trifluoromethyl-4-nitroacetanilide

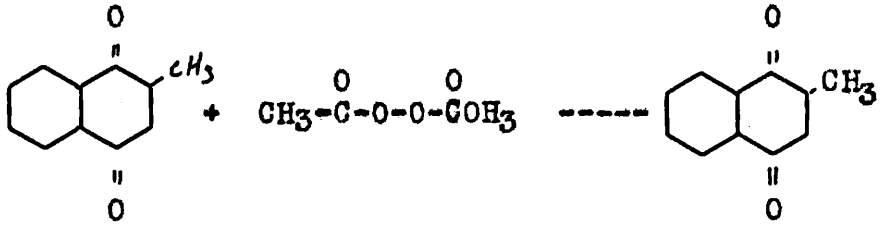
and 2-nitro-5-aminobenzotrifluoride to obtain 2-nitro-5-aminobenzotrifluoride.

In our attempt to prepare 2-trifluoromethyl-4-aminoaniline by the reduction of 2-nitro-5-aminobenzotrifluoride with Raney nickel as catalyst, it was found that the resulting 2-trifluoromethyl-4-aminoaniline was very unstable. It was impossible to isolate the desired material from the reduction mixture in pure form. This prompted us to change our synthetic scheme somewhat. Instead of attempting to obtain 2-trifluoromethyl-4-aminoaniline as the free base, it was decided to reduce and acetylate simultaneously 3-trifluoromethyl-4-nitroacetanilide, by employing platinum oxide in acetic anhydride, to give 2,5-diacetamidobenzotrifluoride (see flow sheet VIa, p. 49A). Subsequent hydrolysis in dilute sulfuric acid would then give an aqueous solution of the dihydrosulfate of 3-trifluoromethyl-4-aminoaniline which then could be subjected to dichromate oxidation directly. This is the successful preparative route to 2-trifluoromethyl-1,4-benzoquinone shown on flow sheet VIa (p. 49A).

In the dichromate oxidation of the amine dihydrosulfate, it was found necessary to maintain a layer of benzene on top of the aqueous oxidation mixture in order to extract the 2-trifluoromethyl-1,4-benzoquinone as it was formed. Otherwise, polymeric materials were formed.

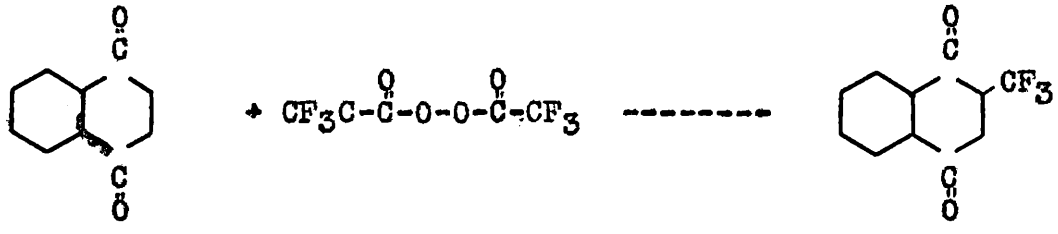
Work on the condensation of butadiene-1,3 with 2-trifluoromethyl-1,4-benzoquinone and the subsequent dehydration to give 2-trifluoromethyl-1,4-naphthaquinone is now in progress.

An entirely different approach to the synthesis of 2-trifluoromethyl-1,4-naphthaquinone was attempted. This approach was based on the work of Fieser and Oxford (57) on the alkylation of quinones by the use of diacylperoxides. Using 1,4-naphthaquinone and diacetyl peroxide as examples the general reaction can be illustrated as follows:



In general, the reaction with diacetyl peroxide is most satisfactory with naphthaquinones when either position 2 or 3 is already substituted.

It was of great interest to us to find out whether the peroxide of trifluoroacetic acid i.e., di-(trifluoroacetyl) peroxide could be made, and if so, whether the following alkylation could be carried out:



If successful, this would give us the desired 2-trifluoromethyl-1,4-naphthaquinone in a single step.

The attempt to make di-(trifluoroacetyl) peroxide from trifluoroacetyl chloride (58) or trifluoroacetic anhydride (59),

by the use of the general procedure of Gambarjan (60) for the preparation of diacetyl peroxide, has not met with success as yet. There was evidence of a chemical reaction taking place when the sodium peroxide was added to the etheral solution of the trifluoroacetic anhydride, but it was not possible to isolate the desired material.

Further work is under way in studying this reaction.

Proposed Synthesis of 2-Methyl-3-fluoro-1,4-naphthaquinone (Sec. VIb, Experimental, p. 54-59).

The synthesis of 2-methyl-3-fluoro-1,4-naphthaquinone in pure form has not been completed. The evidence for the successful replacement of bromine in 2-methyl-3-bromo-1,4-naphthaquinone with fluorine to give 2-methyl-3-fluoro-1,4-naphthaquinone has been presented previously (see p. 57). At best we have only been able to effect partial replacement of the bromine with fluorine under the conditions employed so far. We are hopeful that conditions for complete replacement will soon be worked out. It is suggested that the inclusion of mercuric fluoride in the reaction mixture may bring about completion of such a replacement.

Synthesis by method I as outlined on flow sheet VIb (p. 54A) for the preparation of 2-methyl-3-fluoro-1,4-naphthaquinone has been carried as far as the preparation of 2-fluoro-4-hydroxyazobenzene. The unexpected difficulties that have arisen in attempting to reduce this compound to the corresponding 3-fluoro-4-aminophenol by employing sodium hydrosulfite as the reducing agent, can not be logically

explained at present. This reduction has been reported by Hodgson (45) to proceed in a satisfactory manner. We are testing the feasibility of using high pressure reduction technique on 2-fluoro-4-hydroxyazobenzene for its conversion to 3-fluoro-4-aminophenol. The dichromate oxidation of this compound to give 2-fluoro-1,4-benzoquinone has been reported by Hodgson (45). The remainder of the synthetic scheme includes the Diels-Alder type condensation of butadiene-1,3 with 2-fluoro-1,4-benzoquinone followed by dehydrogenation to give 2-fluoro-1,4-naphthaquinone. We have proposed the use of diacetyl peroxide as a means of obtaining the desired 2-methyl-3-fluoro-1,4-naphthaquinone from 2-fluoro-1,4-naphthaquinone.

Various other unsuccessful attempts to obtain 2-methyl-3-fluoro-1,4-naphthaquinone have been carried out. Among these are the following:

Addition of hydrogen fluoride across the 2,3 double bond in 2-methyl-1,4-naphthaquinone to give 2-methyl-3-fluoro-1,4-naphthaquinone, was attempted. Analogous 1,4-additions of other halogen acids to the molecule have been reported (61) to yield the corresponding 3-substituted halogen derivatives. All attempts to isolate the desired 2-methyl-3-fluoro-1,4-naphthaquinone were unsuccessful, and the starting material was recovered unchanged.

Similarly, the attempted reaction of anhydrous hydrogen fluoride on 2-methyl-2,3-epoxy-1,4-naphthaquinone in a way analogous to that of hydrogen bromide (47) to give 2-methyl-

3-fluoro-1,4-naphthaquinone was unsuccessful, and the starting material was recovered.

DISCUSSION OF TESTING, AND FUTURE CHEMOTHERAPEUTIC EVALUATION, OF THE REPORTED FLUORINE-CONTAINING ORGANIC COMPOUNDS

Isosteres of Sulfa Drugs.

All of the sulfa compounds that have been found of chemotherapeutic value thus far contain an N^4 amino group or a group readily reduced to an amino group (such as an azo group like in prontosil). It was of great interest to us to ascertain whether the replacement of the N^4 amino group by fluorine would result in the formation of compounds that would retain their activity.

We have previously pointed out, that the fluorine atom is not only isosteric with the amino group, but is also of approximately the same weight. Therefore, the fluorine atom might be expected to behave quite similarly to the amino group when occupying corresponding positions in an organic molecule. The therapeutic action of a compound in which the amino group has been substituted with fluorine might possibly be similar in nature, but at the same time, the variation in the electronegativity of the substituting groups would be expected to produce a definite change in the activity as well as in the toxicity of the compound.

The following isosteres of the common type sulfa drugs have been submitted to chemotherapeutic evaluation:

p-fluorobenzenesulfonamide (isostere of sulfanilamide)

2-(p-fluorobenzenesulfonamido)-pyridine (isostere of sulfapyridine)

2-(p-fluorobenzenesulfonamido)-thiazole (isostere of sulfathiazole)

2-(p-fluorobenzenesulfonamido)-pyrimidine (isostere of sulfadiazine)

Preliminary in vitro testing of these compounds has been completed, using Escherichia coli as a test organism. The following is an insert from a report received (62) on this testing:

"The compounds were tested, using E. coli #550 as the test organism, in McLeod's synthetic media at pH 7.7. All compounds were insoluble at M/20 levels in distilled water. Solubility was effected very easily by the addition of 1 N NaOH to the suspension. When the drug was completely in solution, the excess alkali was neutralized by the addition of 1 N HCl. The solutions were then q.s.'ed to volume.

A simple dilution type assay was used and the end points were taken to be the lowest concentration of the drug that completely inhibited the growth of the culture of E. coli."

For comparison, the end points of sulfathiazole and sulfasuxadine were also given. The following end point values were reported:

	End Point
Sulfathiazole	1×10^{-2} M
Sulfasuxadine	2×10^{-2} M
p-Fluorobenzenesulfonamide	1×10^{-2} M
2-(p-fluorobenzenesulfonamido)-pyridine	1×10^{-3} M

2-(p-fluorobenzenesulfonamido)-thiazole $1x10^{-2}$ M

2-(p-fluorobenzenesulfonamido)-pyrimidine $1x10^{-2}$ M

The *in vivo* testing of these compounds is now under way. This testing will also include anti-malarial evaluation as well as bactericidal appraisal.

The p-fluorobenzamido analogues of the common type sulfa drugs could not be tested for their *in vitro* growth inhibition on E. coli because of their insolubility in the testing media. These included the following compounds:

p-fluorobenzamide

2-(p-fluorobenzamido)-pyridine

2-(p-fluorobenzamido)-thiazole

2-(p-fluorobenzamido)-pyrimidine

Anti-malarial Analogues.

The synthesis of the following fluorine containing organic compounds of possible anti-malarial activity has been completed:

2-Diethylaminomethyl-4-(7-chloro-4-quinolyl)-aminofluorobenzene (isostere of camoquin)

6-Fluoro-8-(p-fluorobenzenesulfonamido)-quinoline

6-Fluoro-8-(7-chloro-4-quinolyl)-aminoquinoline

The synthesis of 2-diethylaminomethyl-4-(7-chloro-4-quinolyl)-aminofluorobenzene has been accomplished in large enough quantity required for anti-malarial appraisal. The testing of this compound is now being arranged. The camoquin isostere has already been shown to be a highly successful anti-malarial (63). We await the outcome of the testing

of its fluorine isostere with great interest.

The synthesis of 6-fluoro-8-(7-chloro-4-quinolyl)-aminoquinoline was undertaken with the idea of studying its possible anti-malarial activity. This compound is an interesting hybrid type between 6-fluoro-8-aminoquinoline and 7-chloroquinoline. This compound is now being tested.

Finally, the synthesis of 6-fluoro-8-(p-fluorobenzenesulfonamido)-quinoline was carried out for the purpose of testing its anti-malarial activity as well as its bactericidal properties. It has been shown (64), that its analogue, 6-methoxy-8-(p-aminobenzenesulfonamido)-quinoline possessed slight anti-malarial action. Study of the in vitro growth inhibition against Staphylococcus aureus and E. coli of the 6-fluoro-8-(p-fluorobenzenesulfonamido)-quinoline has revealed moderate inhibition activity (65).

Fluorine Analogues of Menadione (2-Methyl-1,4-naphthaquinone)

The attempted synthesis of 2-trifluoromethyl-1,4-naphthaquinone and 2-methyl-3-fluoro-1,4-naphthaquinone was undertaken with the idea of testing these compounds for their possible anti-vitamin K action. This could be easily done by feeding these compounds to rats or dogs and measure the change in the animals' prothrombin level. If a vitamin K active compound such as menadione reversed such a change, it would be a strong indication for an anti-vitamin K mode of action.

There are numerous examples to be found in the recent literature of naphthaquinone structures that show anti-

vitamin K activity. This is usually evidenced by hemorrhagic conditions. A few examples will suffice:

Smith, Fradkin and Lackey (66) found that a fatal hemorrhagic syndrome accompanied by marked hypoprothrombinemia was produced in rats by administration of 2-(3-cyclohexylpropyl)-3-hydroxy-1,4-naphthaquinone, 2-(2-methyloctyl)-3-hydroxy-1,4-naphthaquinone and 2-(3-(decahydro-2-naphthyl)-propyl)-3-hydroxy-1,4-naphthaquinone. It is to be noted that all of these compounds are analogues of phthiocol (2-methyl-3-hydroxy-1,4-naphthaquinone), a compound which, itself, shows vitamin K activity. In all cases, the 2-methyl group is replaced by a bulkier group.

Meunier (67) has reported to have observed antagonistic relationship between 2-chloro-1,4-naphthaquinone and 2-methyl-1,4-naphthaquinone. Similarly, Mentzer and Buu Hoi (68) have shown that 2-chloro-1,4-naphthaquinone and 2-chloro-3-hydroxy-1,4-naphthaquinone have anti-vitamin K activity.

Fluorine Analogue of 2,4-Dichlorophenoxyacetic Acid (2,4-D).

The use of the plant hormone 2,4-dichlorophenoxyacetic acid (2,4-D) as a commercial weed killer prompted us to synthesize its fluorine analogue, 2,4-difluorophenoxyacetic acid, for the purpose of comparing its action with that of the dichloro compound. The testing of the fluoro analogue is now in progress.

SUGGESTION FOR FUTURE WORK

A. Completion of Work Already Started.

Proposed suggestions for the extension of the present work are as follows:

I. Completion of the synthesis of 6-fluoro-8-(1-methyl-4-diethylaminobutyl)-aminoquinoline by coupling of 1-diethylamino-4-bromopentane with 6-fluoro-8-aminoquinoline. The inherent low yield in coupling reactions of this type, and the small amount of 6-fluoro-8-aminoquinoline that has been available in the past, has prevented the isolation of the desired 6-fluoro-8-(1-methyl-4-diethylaminobutyl)-aminoquinoline. An ample supply of 6-fluoro-8-aminoquinoline has now been secured to carry this phase of the present work to a successful completion.

II. Completion of the synthesis of 2-trifluoromethyl-1,4-naphthaquinone by the condensation of butadiene-1,3 with 2-trifluoromethyl-1,4-benzoquinone, followed by dehydrogenation.

III. Further experimentation on the conditions necessary for the complete replacement of bromine with fluorine in 2-methyl-3-bromo-1,4-naphthaquinone to give 2-methyl-3-fluoro-1,4-naphthaquinone. The alternate synthetic approach to 2-methyl-3-fluoro-1,4-naphthaquinone as indicated on flow sheet VIb p. 64A should be continued.

IV. Synthesis of 2-diethylaminomethyl-4-(p-fluorobenzenesulfonamido)-fluorobenzene from p-fluorobenzenesulfonyl chloride and 2-diethylaminomethyl-4-aminofluorobenzene and

its testing for anti-malarial activity.

V. Interest in compounds formed by condensation of 2-methyl-3-bromo-1,4-naphthaquinone with the common sulfa drugs, as structures of potential value in tuberculosis therapy (69), has led us to undertake the synthesis of fluoroisosteres of the types of 2-methyl-3-(p-fluorobenzenesulfonamido)-1,4-naphthaquinone. Synthesis of this complex fluoro-sulfanilamide derivative, and the corresponding fluoro-sulfapyridine, sulfathiazole, and sulfadiazine derivatives has been started. The products isolated thus far have not been analyzed, and for that reason not reported in the experimental section of this thesis.

B. Work Contemplated But Not Started.

I. Replacement of the two -hydroxy groups in pyridoxine with fluorine. The resulting fluorine isostere of pyridoxine might be expected to show anti-vitamin B_6 activity. It is suggested that the replacement of the hydroxy group with bromine, using 48% hydrogen bromide, followed by the replacement of the bromine with fluorine by the use of mercuric fluoride, would be a feasible synthetic route.

II. Synthesis of -fluoroacids isosteric with some essential -amino acids. Such a synthesis could be carried out by the use of the Hell-Volhart-Felinsky reaction with the subsequent replacement of the halogen by means of mercuric fluoride.

III. It is suggested that p-fluorodimethyl aniline be

synthesized for the purpose of testing its carcinogenic properties. This compound, an isostere of p-aminodimethylaniline, might be expected to show similar physiological activities.

SUMMARY

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

2-(p-fluorobenzenesulfonamido)-pyridine

2-(p-fluorobenzenesulfonamido)-thiazole

2-(p-fluorobenzenesulfonamido)-pyrimidine

2-(p-fluorobenzamido)-pyridine

2-(p-fluorobenzamido)-thiazole

2-(p-fluorobenzamido)-pyrimidine

6-fluoro-8-aminoquinoline

6-fluoro-8-(p-fluorobenzenesulfonamido)-quinoline

6-fluoro-8-(7-chloro-4-quinolyl)-aminoquinoline

2-fluoro-5-nitrobenzyl bromide

2-diethylaminomethyl-4-nitrofluorobenzene hydrobromide

2-diethylaminomethyl-4-aminofluorobenzene dihydrobromide

2-diethylaminomethyl-4-(7-chloro-4-quinolyl)-amino-fluorobenzene dihydrobromide

2,4-difluoroanisole

2,4-difluorophenol

2,4-difluorophenoxyacetic acid

3-trifluoromethyl-4-nitroacetanilide

2,5-diacetamidobenzotrifluoride

2-trifluoromethyl-1,4-benzoquinone

II. The scope of the research reported in this thesis includes the synthesis of isosteres of sulfa drugs and anti-malarials, in which an amino or a hydroxy group has been replaced by the isosteric fluorine atom. In addition, a methoxy group has been replaced by a fluorine atom in anti-malarials of the 6-methoxy-8-amino substituted quinoline type. The synthesis of two analogues of menadione (2-methyl-1,4-naphthaquinone), a compound of high vitamin K activity, in which the fluorine atom replaces a ring hydrogen or the hydrogens on the methyl group was undertaken. Finally, the synthesis of a plant hormone, in which two chlorine atoms were replaced by fluorine atoms was accomplished.

A. The following sulfa drug isosteres were synthesized:

2-(p-fluorobenzenesulfonamido)-pyridine (isostere of sulfapyridine)

2-(p-fluorobenzenesulfonamido)-thiazole (isostere of sulfathiazole)

2-(p-fluorobenzenesulfonamido)-pyrimidine (isostere of sulfadiazine)

p-fluorobenzenesulfonamide (isostere of sulfanilamide)

Preliminary <u>in vitro</u> testing of the growth inhibition of these compounds against E. coli indicates that their growth inhibition activity is intermediate between that of sulfathiazole and sulfasuxadine.

The synthesis of the following sulfa drug analogues was also accomplished:

2-(p-fluorobenzamido)-pyridine

2-(p-fluorobenzamido)-thiazole

2-(p-fluorobenzamido)-pyrimidine

p-fluorobenzamide

These compounds could not be tested because of their insolubility in the microbial nutrients.

B. Synthesis of the following potential anti-malarials was completed:

2-diethylaminomethyl-4-(7-chloro-4-quinolyl)-aminofluorobenzene (isostere of camoquin)

6-fluoro-8-(p-fluorobenzenesulfonamido)-quinoline

6-fluoro-8-(7-chloro-4-quinolyl)-aminoquinoline

The pharmacological testing of these compounds is now being arranged.

C. Synthesis of the fluorine analogue of the plant hormone 2,4-dichlorophenoxyacetic acid (2,4-D) has been completed. Evaluation of its possible weed-killing activity is under way.

D. The attempted synthesis of fluorine analogues of menadione is reported. These analogues are:

2-trifluoromethyl-1,4-naphthaquinone

2-methyl-3-fluoro-1,4-naphthaquinone

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