FLUORINE ANALOGS OF SOME BIOLOGICALLY ACTIVE ADAMANTANE. I. THE SYNTHESIS OF 3-FLUORO-1-AMINOADAMANTANE AND SOME OF ITS DERIVATIVES.

A THESIS

SUBMITTED TO THE FACULTY OF ATLANTA UNIVERSITY

IN PARTIAL FULLFILLMENT OF THE REQUIREMENTS

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BY

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DEPARTMENT OF CHEMISTRY

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DEDICATION

To my grandmother, Jessie Goodson, for her never ending faith -

W.A.B.

ACKNOWLEDGEMENT

I wish to thank Dr. Gloria L. Anderson of Morris Brown College for her aid in completing this study. Also I would like to thank BISRIP and the National Institutes of Health Minority Schools Biomedical Support Program. I would like to thank Dr. Thomas Cole, Jr., Atlanta University, for mass spectral measurements and assistance.

W.A.B.

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INTRODUCTION

During recent years, a considerable amount of interest has been generated in the application of organic fluorine chemistry to biological and medicinal research. There have been studies which show that fluorine substituents in some biologically active molecules frequently enhance their activity and, in many instances, reduce undesirable side effects.

Smith[1] has reviewed the biological properties of some compounds containing the C-F bond. According to Smith, there is no unique or specific biological effect brought about by the introduction of fluorine into the molecule. Although the steric and electronic effects introduced into an organic molecule by fluorine substitution can be explained by current theory, details of chemical-biological interactions are not always clear.[1] However, most fluoro organics have shown some biological activity. Filler,[2] in a review of fluorinated compounds of medicinal interest, gave numerous examples of fluoro organics that are useful, and pointed out that there are many others that show potential in medicinal chemistry. These include:

1. Fluorine containing bioactive molecules show increased oxidative and thermal stability and higher lipid solubility over their hydrogen substituted analogs.

2. Fluoro compounds often mimic their non-fluorinated analogs, for example, the amino acid antagonists trifluoroleucine and p-fluoro-phenylalanine, which can be incorporated into proteins.

3. 5-Fluorouracil, a nucleic acid antagonist, is used in the treatment of cancer.

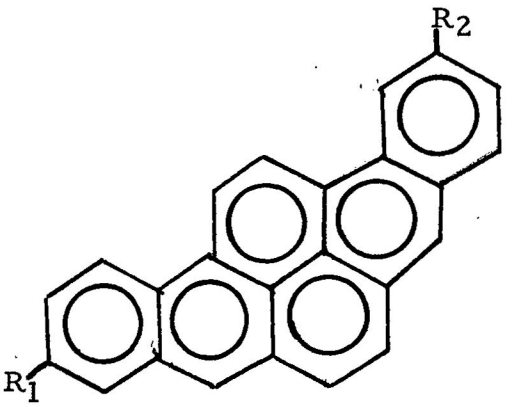
4. Halocarbons and fluorine-containing ethers are important inhalation anesthetics.

5. Fluorinated phenothiazines are among the most useful tranquilizers.

6. Fluorine-containing steroids have proven invaluable as adrenocortical and anti-inflammatory drugs, as progestational agents and in androgenic hormone therapy.

There have been a large number of studies done on biologically active compounds containing fluorine.[2] One such study on the effect of fluorine substitution on a biologically active compound was done by Eliahu Boger on Benzo (RST) Pentaphene (1), (R_1 R_2 H).[3] The parent compound is carcinogenic, but fluorine substitution reduced or destroyed carcinogenic activity completely. Moreover, Boger discovered that in the presence of the fluorine analog the parent compound, in some instances, in-

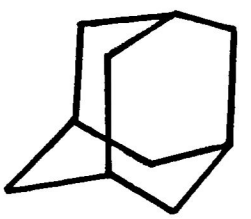
hibited carcinogenic behavior. These results are summarized in Table 1. No explanation for the effect of fluorine substitution was given. Clearly, fluorine substitution has a positive effect on the biological activity of organic molecules.



1

Benzo (RST) Pentaphene (R_1=R_2=H)

The adamantane structure (2) has generated considerable interest



2

Adamantane

among chemists who are engaged in research related to drug design. Several biologically active adamantane derivatives have been described. The biological activity of adamantoyl penicillin[4], N-p-tolylsulfonyl N'-adamantyl urea,[5] and the ester of 19-nortestosterone and 1-adamantane

TABLE 1

THE EFFECT OF FLUORINE SUBSTITUTION ON THE CARCINOGENIC BEHAVIOR OF BENZO (RST) PENTAPHENE[a]

COMPOUND (1)	R_1	R_2	BIOLOGICAL ACTIVITY	EFFECT OF FLUORINE
A	H	H	Carcinogenic	----------
B	F	H	Slightly carcinogenic 57% inhibition of activity of A.	Decrease of carcinogenicity.
C	F	F	Not carcinogenic; Activity of A almost completely inhibited.	Loss of carcinogenicity.
D	H	F	Non-carcinogenic; Does not inhibit A.	Loss of carcinogenicity.

[a]Eliahu Boger, Abstracts, 162nd National Meeting of the American Chemical Society, Washington, D.C., Sept., 1971.

carboxylic acid[6,7] has been examined. Some other examples of adamantane derivatives which are biologically active are shown in Table 2.

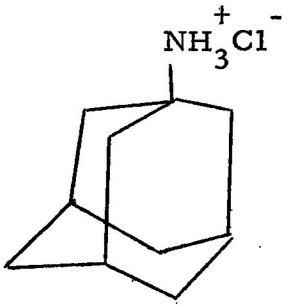
As indicated above, several biologically active adamantane derivatives are known. However, the effect of fluorine substitution on the biological activity of adamantane derivatives has not been reported. The observation that fluorine substitution in organic molecules has a positive effect on biological activity, and the apparent important biological activity observed in some adamantane derivatives suggested that the incorporation of fluorine into biologically active adamantanes might influence their activity. Moreover, structure-reactivity relationship studies might provide needed information on the mechanism whereby fluorine transmits its influence. The purpose of this work was to develop a synthetic method for the preparation of fluorine analogs of biologically active adamantane derivatives. This thesis reports a synthetic method developed to prepare the first in a series of fluorine analogs of biologically active adamantanes.

Initially, the well known prescription drug, Symmetrel (3), discovered in the DuPont Laboratories, was selected as the biologically active adamantane of interest. This compound has been found to be effective against influenza A, A_1, A_2, and C in tissue culture, chick embryos, and mice.[8] Antiviral activity has also been found in humans.[8] The synthesis of the fluorine analog, 4 became the focus of this work. This thesis describes the preparation of this compound and some of its derivatives.

TABLE 2

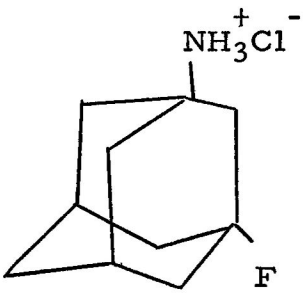
SOME BIOLOGICALLY ACTIVE ADAMANTANES

COMPOUND 2 SUBSTITUENTS				BIOLOGICAL ACTIVITY	REFERENCES
1	3	5	7		
NH HCl	H	H	H	Antiviral Activity; Effective against influenza A_2 virus in humans.	(8)
$CHCH_3NH_2$ HCl	H	H	H	Antiviral activity	(9)
$CONH_2$	CH_3	CH_3	CH_3	Sedative Action	(10)
OH	CH_3	CH_3	CH_3	Sedative Action	(10)
OH	CH_3	CH_3	CH_2CH_3	Antiviral Activity	(11)
OCH_3	H	CH_3	CH_3	Antiviral Activity	(11)



3

1-Aminoadamantane Hydrochloride
(Symmetrel)

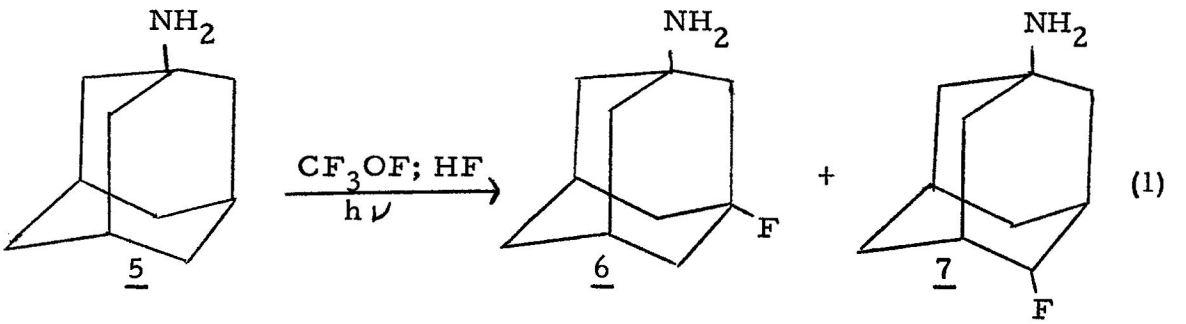


4

3-Fluoro-1-Aminoadamantane Hydrochloride

RESULTS AND DISCUSSION

In 1970, Kollonitsch and co-workers[12] at the Merck Sharpe and Dohme Research Laboratories reported the synthesis of 3-fluoro-1-aminoadamantane as one of two products obtained from a photochemical process on 1-aminoadamantane (equation 1). The photofluorination was accomplished

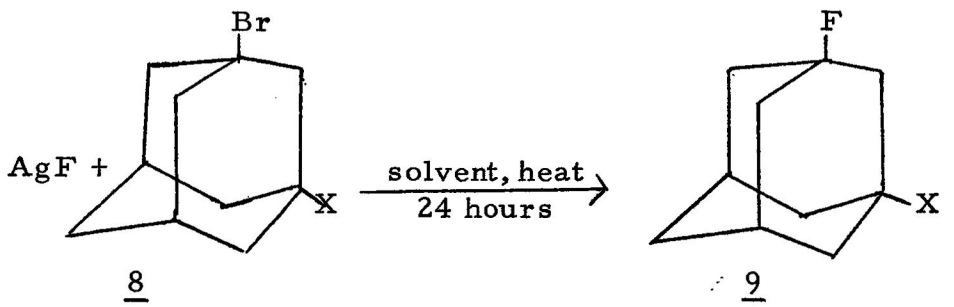


5 6 7 (1)

by means of ultraviolet light irradiation of a solution of the compound in fluorotrichloromethane, liquid hydrogen fluoride or trifluoroacetic acid at -78° in the presence of trifluoromethyl hypofluorite. No experimental details were given, nor did they describe the physical and chemical properties of 6 and 7. This method was not pursued as synthetic procedure for the following reasons: (1) the type of reagents that were used, (2) the reaction conditions that were required, (3) the techniques that were involved, and (4) the product comes out as a mixture which is probably difficult to separate. Therefore, another method was sought for the preparation of 6.

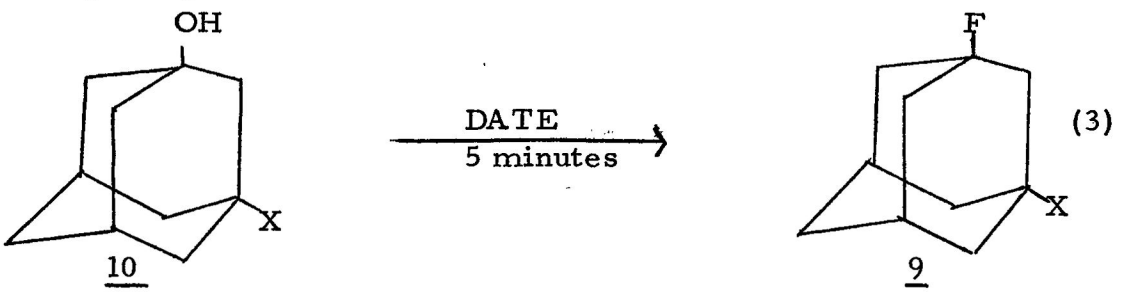
In general, organic fluorine compounds, unlike other halogen containing compounds are difficult to synthesize even though there are several fluorinating methods available.[13] This fact, coupled with the resistance of many polycyclic compounds to undergo transformation at the bridgehead make bridgehead fluorination the most challenging aspect of the proposed synthesis. Therefore a method of adding fluorine was sought.

Adamantane derivatives are well known.[14] However, only a relatively few fluoroadamantanes have been reported.[14,15] These have been prepared according to equation 2.



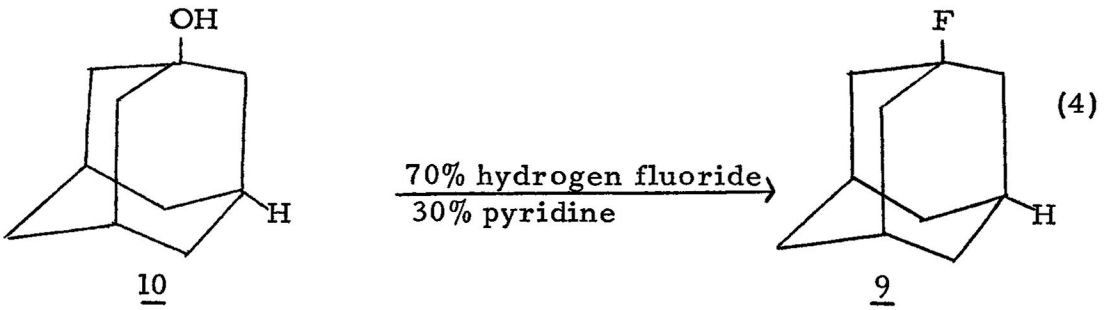
8 9 (2)

Several years ago, it was discovered in these laboratories that fluoroadamantanes can be synthesized readily from the corresponding alcohol and 1-(N, N-Diethylamino)-1, 1, 2-Trifluoro-2-Chloroethane (DATE),[16] according to equation 3.[17]



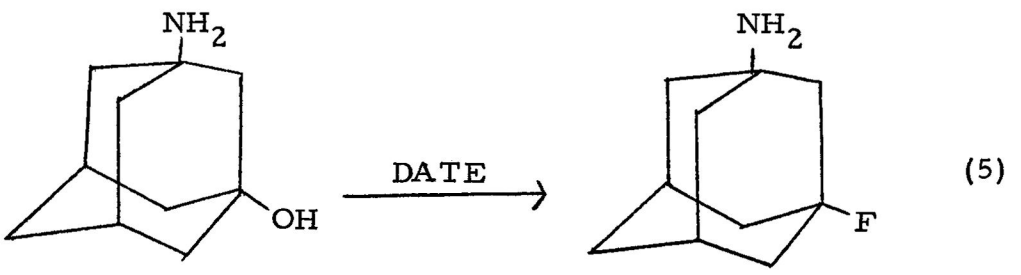
10 9 (3)

More recently, Olah[18] has described the preparation of 1-fluoroadamantane and several other fluorine-containing compounds from the corresponding alcohol and pyridinium polyhydrogen fluoride (equation 4).



10 9 (4)

Our method (equation 3) compared to equation 2 and equation 4 is difficult to purify. Therefore, the method described in equation 3 would be the method of choice because of the ease with which DATE transformed a variety of adamantyl alcohols into the corresponding fluoroadamantanes. This prompted consideration of the adaptation of this method for the preparation of 3-fluoro-1-aminoadamantane. (equation 5).

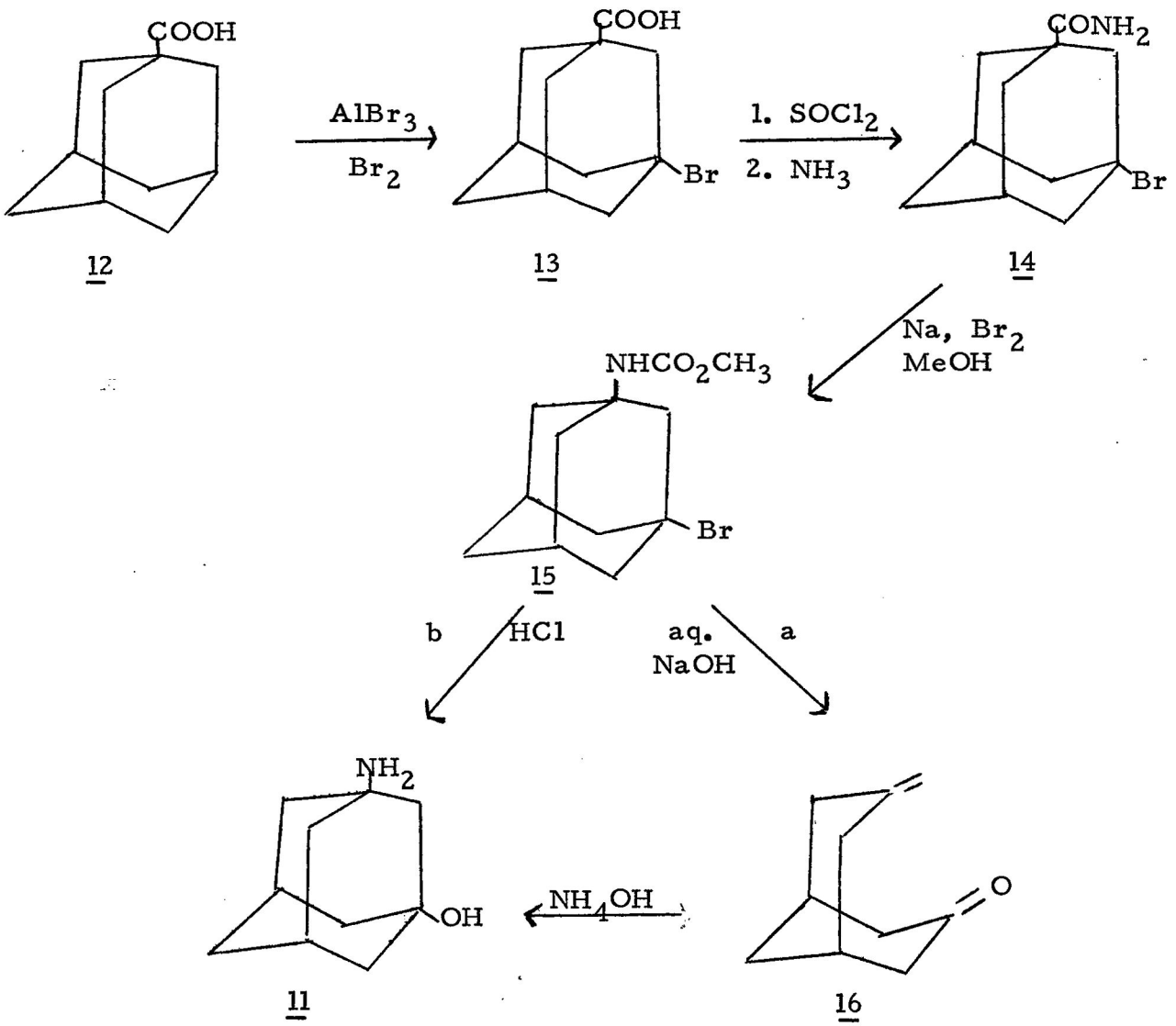


11 6 (5)

Thus, the synthesis of the corresponding amino alcohol 11 became the major problem.

The preparation of 3-hydroxy-1-aminoadamantane (11) has been described. Stetter, Gartner and Tacke,[19] and Grob and Schwarz[20] have prepared 11 according to procedures a and b, respectively (Chart 1).

Chart 1



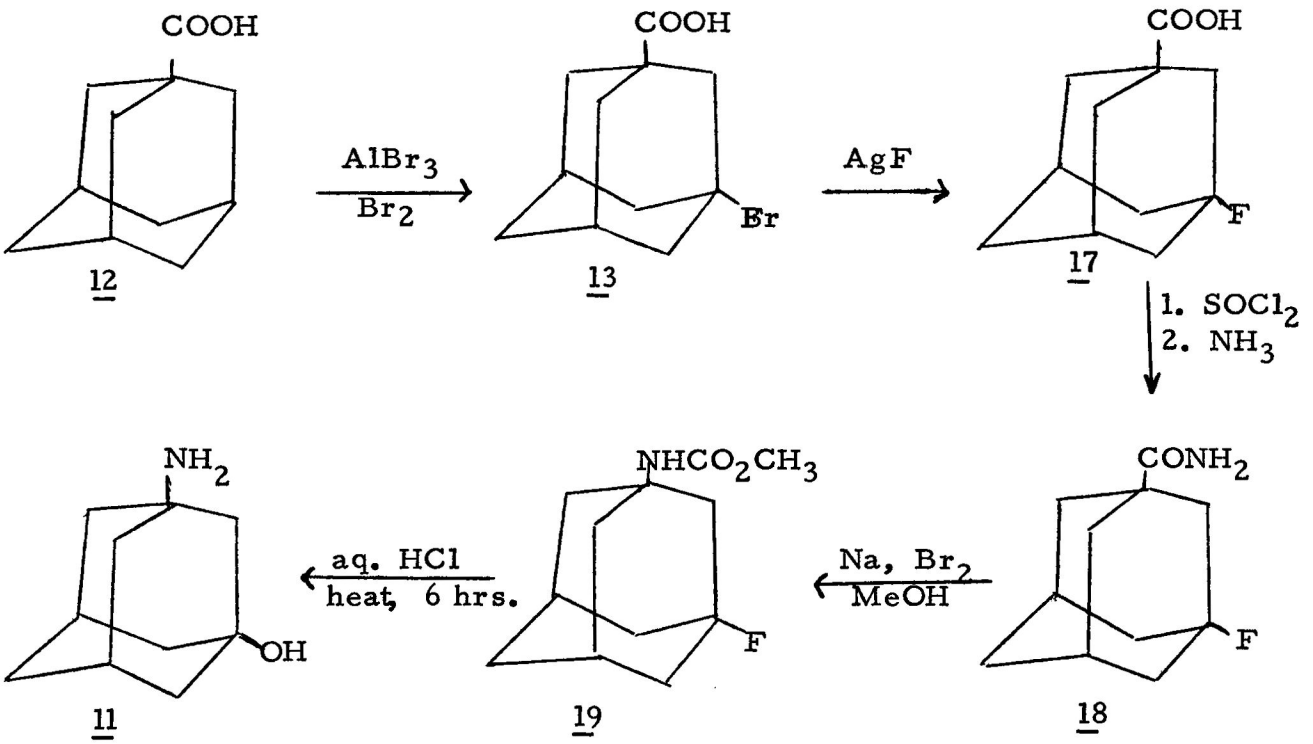
The procedure in Chart 1 suffers from the disadvantage that in the preparation of 3-bromo-1-adamantane carboxylic acid:

1. A large amount of aluminum bromide and bromine are required,

2. Rather carefully controlled conditions are required such as that of keeping the bromine and aluminum bromide at 0° while the acid 12 is added over a period of 4 hours. In addition, the mixture must stand at 0° to 10° for 48 hours, and then an additional 5 hours at 20°.

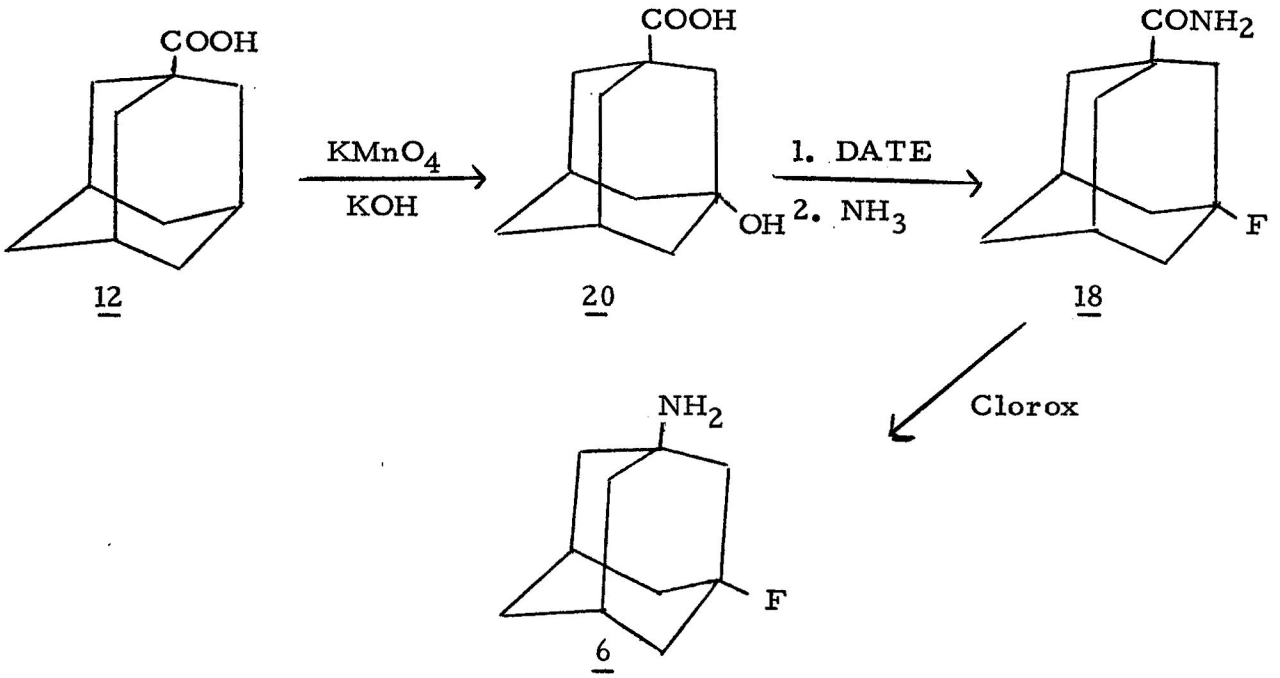
In general, the entire procedure is long and drawn out. Therefore, another synthetic approach was sought. The hydroxy amine 11 has been prepared by an alternative route by Stepanov and Srebrodol'skii,[21] according to the sequence described in Chart 2. This procedure presents the same problems as those in Chart 1. These less than desirable features prompted the search for a more convenient method. To prepare 6, further consideration led to the conclusion that a process not involving the amino alcohol, 11 was required.

Chart 2

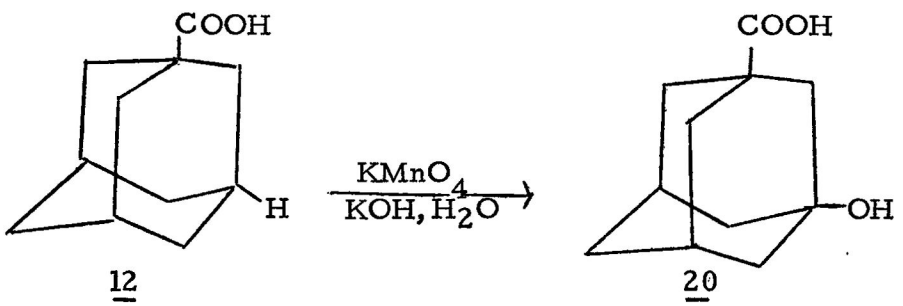


The desired compound, 3-fluoro-1-aminoadamantane, has been synthesized in relatively good yield in a simple and rapid sequence as described in Chart 3.

Chart 3

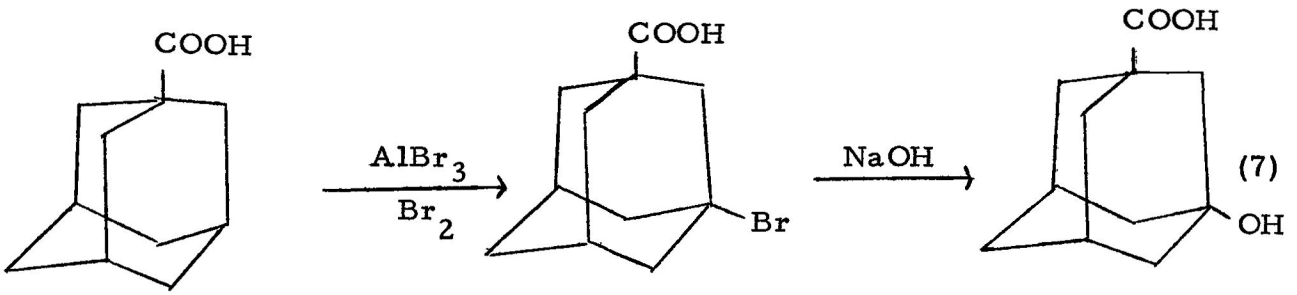


3-Hydroxy-1-adamantane carboxylic acid (20) was prepared from commercially available 1-adamantane carboxylic acid (12) by oxidation of the acid 12 with alkaline potassium permanganate. The oxidation and isolation process required no more than one hour.



(6)

This method is better for the preparation of 20 than that previously reported by Stetter and Mayer.[22]

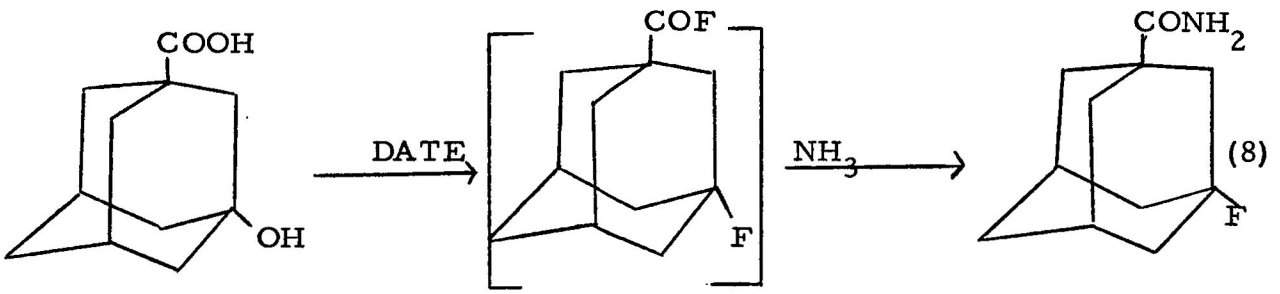


(7)

Stetter's synthesis, as previously pointed out, the bromination of the acid required a large amount of aluminum bromide and bromine and took about three days under rather carefully controlled conditions. Direct oxidation of 12 gives 20 in 83 per cent yield from 12 . The reaction can be carried out conveniently in a beaker on a hot plate.

3-Fluoro-1-adamantane carboxamide (18) was prepared according to equation 8. The hydroxy acid 20 reacts rapidly (exothermic) with DATE to form the intermediate acid fluoride 21. The acid fluoride 21 was not isolated. However, evidence for its presence was obtained from the typical $-\overset{O}{\overset{\|}{C}}-F$ ^{19}F signal at -20 ppm (relative to chlorine trifluoride, CCl_3F) and the rapid conversion to the fluoroamide 18 with cold concentrated

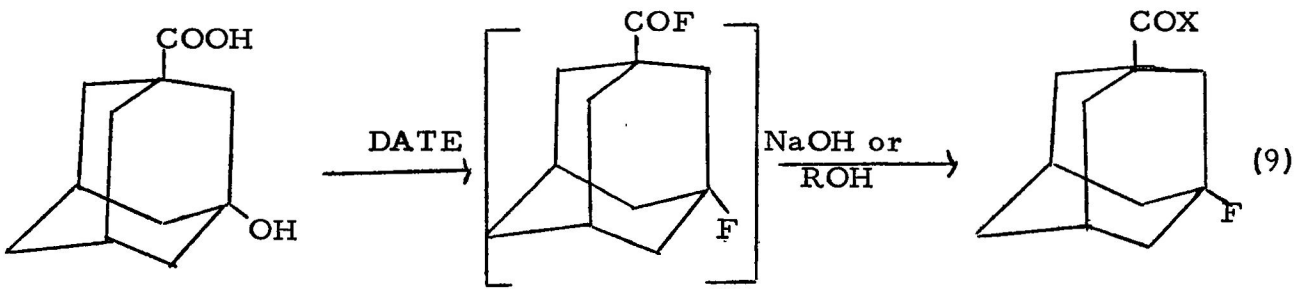
ammonium hydroxide. The product 18 is obtained in 69 per cent yield from 20.



(8)

20 21 18

The preparation of the fluoroamide 18 has been described by Stepanov and Srebrodol'skii[21] as outlined in Chart 2 on page 13 . This procedure using DATE is much simpler. In addition, the intermediate acid fluoride 21 can be converted to the fluoro acid 17 or the ester 22 by adding the appropriate reagent (equation 9).

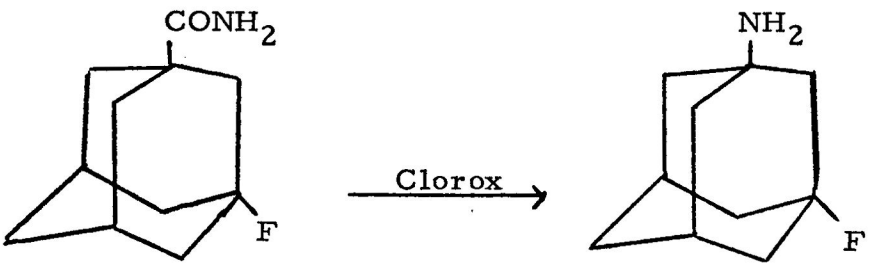


(9)

20 21 17 X = -OH

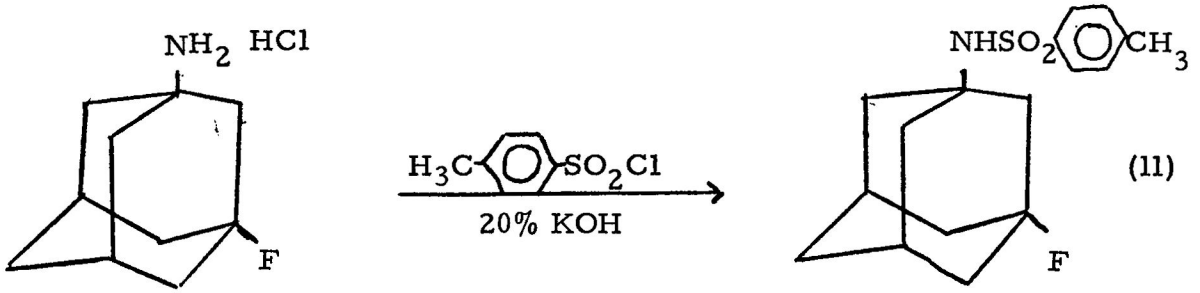
22 -OR

3-Fluoro-1-aminoadamantane (6), (isolated as the hydrochloride in 80 per cent yield) was prepared via a Hofmann rearrangement, utilizing household Clorox.



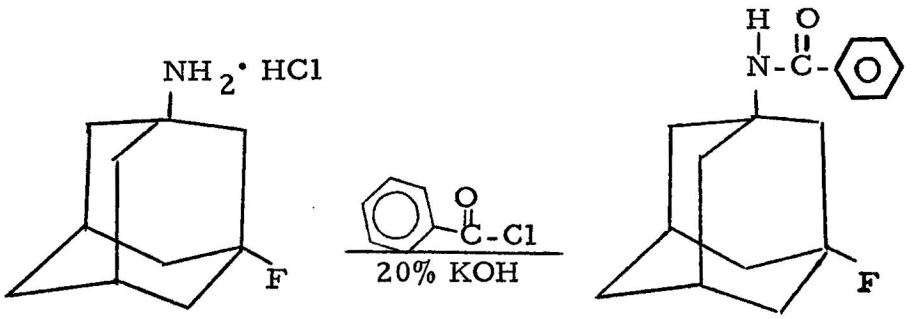
18 6 (10)

This reaction was carried out conveniently in a beaker on a hot plate which does not require a great deal of time. In addition to spectroscopic evidence, the following derivatives were prepared to support the structural assignment of 3-fluoro-1-aminoadamantane. The toluene sulfonamide (23) was prepared by treating the amine hydrochloride with p-toluene sulfonyl chloride and potassium hydroxide giving the product in 69 per cent yield.



4 23 (11)

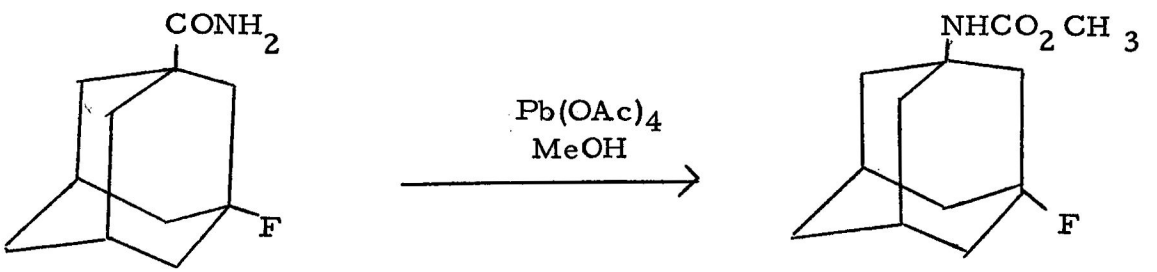
Similarly, the benzamide (24) was prepared, using the same procedure as that for the toluene sulfonamide derivative, in 61 per cent yield.



(12)

4 24

3-Fluoro-1-methyl N-adamantyl carbamate 19, unlike the other derivatives, was not prepared from the fluoro amine hydrochloride (4). This compound 19 was prepared from the fluoro amide (18) via a Hofmann rearrangement using lead tetraacetate in methanol. The reaction gave 19 in 61 per cent yield.



(13)

18 19

3-Fluoro-1-Aminoadamantane Hydrochloride has been sent to the National Institutes of Health for a study of the biological activity. This compound has been assigned a NSC # 245469. No preliminary results are available at this time.

EXPERIMENTAL

Infrared (ir) spectra were recorded on a Perkin-Elmer IR 567 spectrophotometer and calibrated against the 6.24 μ band of a polystyrene film. Melting points were determined in sealed tubes on a Thomas-Hoover melting point apparatus, except as noted, and are uncorrected. ^{19}F nuclear magnetic resonance (nmr) spectra were recorded on a Varian T-60 spectrometer. ^{19}F Chemical shifts are reported in parts per million relative to the parent compound, 3-fluoroadamantane. Positive ^{19}F chemical shifts indicate upfield shifts relative to the parent compound as an internal reference. A Varian aerograph series 2700 gas chromatograph was used to monitor the reactions. The temperature was kept at 175° at a flow rate of 17.5 seconds on a OV-101 column.

1-(N, N-Diethylamino)-1, 1, 2-Trifluoro-2-Chloroethane. -- This compound was prepared according to the procedure of Yarovenko and Raksha.[16] Chlorotrifluoroethylene gas was bubbled through diethylamine (70g, 0.95 mole), cooled by means of an ice bath, for seven hours. The reaction mixture was left to stand overnight. The product was vacuum distilled. (32°C/1mm) to give 110g (61%) of a clear colorless liquid. (Lit.[16] 33°C/6mm).

3-Hydroxy-1-Adamantane Carboxylic Acid (20). -- 1-Adamantane carboxylic acid (40g, 0.22 mole) was added portionwise to a warm solution of potassium permanganate (40g) in a potassium hydroxide solution (500 ml, 2%). After all of the acid had been added, the mixture was heated until it turned brown. The mixture was allowed to cool to room temperature, and concentrated aqueous hydrochloric acid (HCl) was added until the mixture became strongly acidic (pH paper). Solid sodium bisulfite was added until all of the manganese dioxide was destroyed. The white precipitate was collected, washed with water, washed three times with ether, and dried in vacuo to give 36.2g (83.1%) of crude 3-hydroxy-1-adamantane carboxylic acid. m.p. 198-199° (Lit.[22] 202-203°). The crude product was recrystallized from acetone: water (9:1) to give 26.3g (72.37%). Analytical sample was sublimed m.p. 202-203°: ir, λ(KBr)=3200-2500 cm^{-1} (-OH stretch), 1700-1600 cm^{-1} (C=O), 1250-1150 cm^{-1} (C-O); Mol. wt. 196 (mass spec.).

Anal. Calcd. for $C_{11}H_{16}O$: C, 67.35; H, 8.16.

Found: C, 67.25; H, 8.24

3-Fluoro-1-Adamantane Carboxamide (18). -- 3-Hydroxy-1-Adamantane Carboxylic Acid (20g, 0.102 mole) was added portionwise to 1-(N, N-Diethylamino)-1, 1, 2-Trifluoro-2-Chloroethane (40g. 0.210 mole). A highly exothermic reaction occurred, during which time all of the starting material dissolved. The reaction mixture was allowed to cool to room temperature. The reaction mixture was dissolved in ether and poured into cold ammonium hydroxide (200 ml) cooled by means of an ice bath. A yellowish precipitate formed. The precipitate was collected, washed successively with water followed by ether, and dried in vacuo to give 13.8g (69%) of crude 3-fluoro-1-adamantane carboxamide. m.p. 140-143° (Lit.[21] 147-148°). The crude product was recrystallized from cyclohexane/hexame mixture and sublimed, m.p. 147-148°; ir, λ ($CHCl_3$)=3500, 3419 cm^{-1} (NH stretch), 1670 cm^{-1} (C-O stretch), 1587 cm^{-1} (NH bend), 1240 cm^{-1} (C-O bend), 1040 cm^{-1} (CN stretch), 1110 cm^{-1} (C-F); ^{19}F nmr ϕ(EtOH) = +3.0 ppm; Mol. wt. 197 (mass spec.).

Anal. Calcd. for $C_{11}H_{16}FNO$: C, 67.01; H, 8.12; F, 9.64; N, 7.11

Found: C, 65.34; H, 8.35; N, 6.99.

The carboxamide has been analyzed four times, but these results were closest to the theoretical calculations. The compounds which were derived

from the amide provides evidence that this compound had the expected structure even though satisfactory elemental analysis was not obtained.

3-Fluoro-1-Aminoadamantane Hydrochloride (4). -- 3-Fluoro-1-adamantane carboxamide (6g, 0.03 mole) was added to a household Clorox solution (150 ml). The reaction mixture was heated rapidly until a yellowish oily layer began to form. After the oily formed, the mixture was allowed to cool to room temperature. The reaction mixture was extracted with ether; the ethereal extract was washed with water; and dried over anhydrous potassium carbonate. Hydrogen chloride gas was bubbled into the dried ethereal extract and a white solid precipitated. The solid was collected and washed several times with ether to give 3.3g (80.2%) of 3-fluoro-1-aminoadamantane hydrochloride. m.p. 282° (dec.): ir, λ(KBr)= 3300-2800 cm^{-1} (NH stretch, broad), 1600-1575 cm^{-1} (NH_3^+), 1010 cm^{-1} (CN stretch). Mol. wt. 169 (mass spec.); ^{19}F nmr δ(EtOH)= +5.8 ppm.

Anal. Calcd. for $C_{10}H_{17}ClFN$: C, 58.39; H, 8.27; Cl, 17.24; F, 9.25; N, 6.81.

Found: C, 58.33; H, 8.32; Cl, 17.37; N, 6.89.

3-Fluoro-1-Aminoadamantane (6). -- 3-Fluoro-1-aminoadamantane hydrochloride (5g. 0.024 mole) was suspended in a potassium hydroxide solution (80 ml, 20%). The reaction mixture was allowed to stir at room temperature for 1 hour. The reaction mixture was extracted with ether; the ethereal extract was washed several times with water; then dried over anhydrous potassium carbonate. Evaporation of the solvent gave 3.0g (79%) of 3-fluoro-1-aminoadamantane, m.p. 190-200°: ir, $\lambda(CCl_4)$=3300 cm^{-1} (NH stretch), 1550 cm^{-1} (NH bend), 1095 cm^{-1} (CN stretch), 1095 cm^{-1} (C-F); ^{19}F nmr δ(EtOH)= +3.9 ppm.

Anal. Calcd. for $C_{10}H_{16}FN$: C, 71.01; H, 9.47; F, 11.24; N, 5.24.
Found: C, 69.93; H, 9.50; N, 7.97.

The C and H analysis data were incorrect probably due to the fact that the compound was impure.

3-Fluoro-1-(N-Adamantyl)-p-Toluenesulfonamide (23). -- This compound was prepared according to the procedure of Grob and Schwarz.[20] 3-Fluoro-1-aminoadamantane hydrochloride (2g, 0.009 mole) was suspended in a potassium hydroxide solution (40 ml, 20%) with the addition of ether (100 ml). p-Toluenesulfonyl chloride (5g) was added to the alkaline/ethereal solution. After the reaction mixture was allowed to stir at room temperature overnight, the ether was evaporated and the basic solution was acidified with hydrochloric acid. The precipitate that formed was

collected and washed with ether several times to give 2.0g (68.7%) of crude 3-fluoro-1-(N-adamantyl)-p-toluenesulfonamide. The product was recrystallized from absolute ethanol and sublimed, m.p. 271-273°. The melting point was taken in an oil bath. ^{19}F nmr δ(EtOH) = +5.8 ppm.

Anal. Calcd. for $C_{17}H_{22}FNO_2S$: C, 63.16; H, 6.81; F, 5.88; N, 4.33.
Found: C, 59.77; H, 7.11; N, 4.10.

The C and H analysis of this compound was incorrect, due probably to the fact that the product was impure.

3-Fluoro-1-(N-Adamantyl) Benzamide (24). -- 3-Fluoro-1-amino-adamantane hydrochloride (2g, 0.009 mole) was suspended in a potassium hydroxide solution (40 ml, 20%). Benzoyl chloride (5g) was added to the alkaline reaction mixture, which was stirred constantly for several hours at room temperature. The precipitate that formed was dissolved in ether, washed with water several times and dried over anhydrous potassium carbonate. Evaporation of the solvent gave 1.5g (61%) of 3-fluoro-1-(N-adamantyl) benzamide. The product was sublimed. m.p. 115-117°.
^{19}F nmr δ(EtOH) = +3.5 ppm.

Anal. Calcd. for $C_{17}H_{20}FNO$: C, 74.73; H, 7.33; F, 6.96; N, 5.13.
Found: C, 74.61; H, 7.36; N, 5.10.

3-Fluoro-1-Methyl N-Adamantyl Carbamate (19). -- The carbamate was prepared according to the procedure of Acott and co-workers.[24] 3-Fluoro-1-adamantane carboxamide (1g, 0.004 mole) and lead tetraacetate (3.8g) in methanol (50 ml) were stirred at 55-60°. After 30 minutes, the mixture was diluted with aqueous sodium carbonate (Na_2CO_3, 10%) and extracted with ether. The ethereal extract was washed with water several times, then dried over magnesium sulfate. Evaporation of the solvent gave 3-fluoro-1-methyl-N-adamantyl carbamate (0.7g, 61%), m.p. 105° (Lit.[21] 115-116°). After sublimation, the compound had a m.p. of 110-112°. ^{19}F nmr δ(EtOH) = +3.7 ppm.

Anal. Calcd. for $C_{12}H_{18}FNO_2$: C, 63.44; H, 7.93; F, 8.37; N, 6.17. Found: C, 63.40; H, 8.20; F, 8.71; N, 6.12.

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