Selective Substitution of Aliphatic Remote Tertiary Hydrogens by Fluorine

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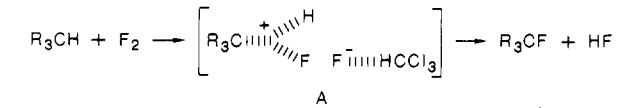
Substitution of saturated hydrogens is a very desirable but difficult task. Elemental fluorine under suitable conditions, including a polar solvent and low temperatures, acts as an electrophile strong enough to react with saturated tertiary CH bonds of various aliphatic compounds. The regioselectivity and the readiness of the hydrogen substitution by fluorine are functions of the p-orbital contribution to the bond, in agreement with the electrophilic nature of the reaction. Apart from branched paraffins, oxygen- as well as nitrogen-containing aliphatic molecules can participate in the reaction, and various protecting groups and their effectiveness were examined. The role of the electron-withdrawing group on the selectivity was also evaluated.

One of the most attractive fields in organic chemistry is the activation of unreactive sites in an organic molecule. An important and promising approach has been the activation of CH bonds with soluble organic transition-metal complexes, although the lack of the desired catalytic effect proved a serious deficiency.[1] Other conditions that have been applied sporadically include radical chlorination,[2] ozone oxidation,[3] tertiary hydroxylation with peroxy compounds,[4] iodosylbenzene coupled with tetraphenylporphyrin,[5] or employment of iodine tris(trifluoroacetate).[6]

Recently we demonstrated that various steroidal and cyclic unactivated tertiary hydrogens can be substituted by fluorine through a very uncommon type of reaction involving diluted F_2.[7] There are many differences, however, between such rigid systems and the more flexible aliphatic molecules, particularly in the ease of approach to the relevant tertiary hydrogens. Still, this novel and unusual reaction for activation of tertiary positions far away from any activating moiety has been shown to be fully operative in the aliphatic field as well.[8]

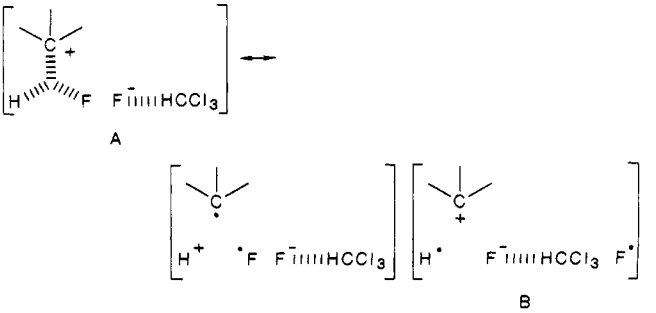
Elemental fluorine can react directly with organic molecules in either a radical or an electrophilic mode. The radical pathway is facilitated by the ease of the homolytic cleavage for the F–F bond (39 kcal/mol), and this has been extensively used for perfluorination purposes[9] and formation of stable perfluoro radicals.[10] Under suitable reaction conditions, however, dilute fluorine shows a tendency to react mainly in an ionic mode. Similar to the other halogens, the reactive end of the F–F dipole is the positive one. In contrast, fluorine has proved to be such a strong electrophile that it can even react with the electrons of certain saturated C–H bonds, resulting in electrophilic substitutions, a rapidly developing field.[14]

As we have shown,[7b] among saturated bonds the most suitable for an electrophilic attack are the tertiary ones. We believe that this preference is connected with the bond highest p-orbital character (p hybridization), providing that it is far away from any electron-withdrawing moiety such as oxygen, nitrogen, or a halogen. The reaction is not operable under nonpolar conditions (e.g., $CFCl_3$, hexane, or heptane serving as solvents) where only indiscriminate, rapid, radical fluorination takes place. Increasing the polarity by adding CH_3COOH, CH_3NO_2, and especially $CHCl_3$ ensures a high degree of ionic type reaction initiated by the positive pole of the fluorine molecule. This leads to a fluorinated product through intermediate A.[14]



A

Chloroform plays an important role in this reaction, since it acts as a radical scavenger. It also provides the necessary polar medium, including a somewhat acidic hydrogen that through hydrogen bonding serves as an acceptor for the F^-, thus lowering the activation energy of the transition state. Nonpolar solvents, with no such acidic hydrogens, cannot solvate the fluoride ion and therefore are not suitable for this reaction. The transition state A can be considered as a resonant form in a fast charge-transfer process, which explains the retention of configuration that was found in all relevant cases.[7] According to such a representation, the farther the C–H bond is from an electron-withdrawing moiety, the easier the charge transfer will be. The alternative configuration B is not likely to contribute much, since the solvated fluoride ion would not attack the carbocation as fast as in the first case. Such a delay would allow some rearrangements and eliminations that actually have never been detected.



A B

Although fluorine is considered to be one of the most reactive agents, its selectivity when reacting in an ionic mode is quite impressive.[11] Thus, passing fluorine through

(1) Parshall, G. W. *Catalysis (London)* **1977**, *1*, 335. Crabtree, R. H.; Demou, P. C.; Eden, D.; Mihelcic, J. M.; Paruell, C. A.; Quirk, J. M.; Morris, G. E. *J. Am. Chem. Soc.* **1982**, *104*, 6994. Crabtree, R. H. *ChemTech.* **1982**, 506. Bergman, R. G. *Science (Washington, D.C.)* **1984**, *223*, 902 and references therein.

(2) See, for example: Deno, N. C. In *Methods in Free Radical Chemistry*; Huyser, E. S., Ed.; Marcel Dekker: New York, 1972; Vol. 3, p 135. Deno, N. C.; Meyer, M. D. *J. Org. Chem.* **1979**, *44*, 3383 and references therein.

(3) Cohen, Z.; Mazur, Y. *J. Org. Chem.* **1979**, *44*, 2318 and references therein.

(4) Zadok, E.; Mazur, Y. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 303. Schneider, H. J.; Muller, W. *Ibid.* **1981**, *21*, 146. Takaishi, N.; Takahashi, H.; Inamoto, Y. *Tetrahedron Lett.* **1985**, *26*, 2361.

(5) Groves, G. T.; Nemo, T. E. *J. Am. Chem. Soc.* **1983**, *105*, 6243.

(6) Buddrus, J.; Plettenberg, H. *Angew. Chem., Int.* Ed. *Engl.* **1976**, *15*, 436.

(7) (a) Rozen, S.; Ben-Shushan, G. *J. Org. Chem.* **1986**, *51*, 3522. (b) Rozen, S.; Gal, C. *J. Org. Chem.* **1987**, *52*, 2769.

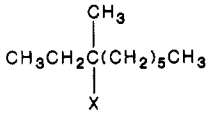
(8) For a preliminary communication, see: Gal, C.; Ben-Shushan, G.; Rozen, S. *Tetrahedron Lett.* **1980**, *21*, 5067. Gal, C.; Rozen, S. *J. Fluorine Chem.* **1982**, *20*, 689.

(9) (a) Lin, W. H.; Bailey, W. I., Jr.; Lagow, R. J. *J. Chem. Soc., Chem. Commun.* **1985**, 1350. (b) Adcock, J. L.; Cherry, M. L. *Ind. Eng. Chem. Res.* **1987**, *26*, 208.

(10) Scherer, K. V., Jr.; Ono, T.; Yamanouchi, K.; Fernandez, R.; Henderson, P. *J. Am. Chem. Soc.* **1985**, *107*, 718.

0022-3263/87/1952-4928$01.50/0

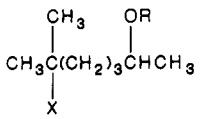
a cold (−78 °C) 1:1 $CFCl_3/CHCl_3$ solution of 3-methylnonane (1) with its 22 hydrogens resulted in substitution of only one of them (the tertiary one) and produced 3-methyl-3-fluorononane (2) in 65% yield. No other single



1: X = H
2: X = F

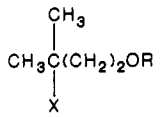
compound was obtained in higher than a few percent yield. The ^{19}F NMR of the residual mixture indicated a complex of many fluorinated compounds, resulting from random radical fluorination. The presence of fluorine radicals could not be completely suppressed, and they remain a yield limiting factor in any fluorination process. This is evident from monitoring the reaction. At first, the ionic substitution proceeds smoothly, but with time it slows down as the monofluorinated product is prevented from additional electrophilic reaction by the strong electron-withdrawing effect of the fluorine atom. Thus, if the reaction is allowed to continue after the yield of the desired product reaches its maximum, the nonspecific radical side reactions continue to take their toll up to the point where the products as well as the reactants are destroyed.

An oxygen function a few bonds away from the tertiary center, as in 6-methyl-2-heptyl *p*-nitrobenzoate (3), slowed down the reaction compared with 1, but eventually 6-fluoro-6-methyl-2-heptyl *p*-nitrobenzoate (4) was obtained in 65% yield. Reducing the gap between the reaction



3: X = H; R = $COC_6H_4NO_2$-*p*
4: X = F; R = $COC_6H_4NO_2$-*p*
16: X = H; R = $CH_2O(CH_2)_2OMe$
17: X = F; R = $CH_2O(CH_2)_2OMe$

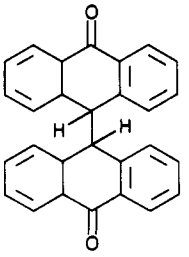
center and the protected alcohol from three to two methylene units, as in 3-methylbutyl *p*-nitrobenzoate (5), slowed the reaction even further, but the yield of the expected fluorinated product 6 was still 60%.



5: X = H; R = $COC_6H_4NO_2$-*p*
6: X = F; R = $COC_6H_4NO_2$-*p*
7: X = H; R = Ac
8: X = H; R = $COCCl_3$
9: X = F; R = Ac
10: X = F; R = $COCCl_3$
11: X = H; R = COC_6H_5

Several types of protecting groups for the alcohol moiety have been examined. *p*-Nitrobenzoates were used when the volatility of the product presented a problem. However, since these derivatives are not always soluble enough under the reaction conditions, acetates and trichloroacetates were also used with similar efficiency, as demonstrated with 7 and 8 where the fluorinated derivatives 9 and 10 were produced in 70% and 65% yields, respectively.

Apart from decreasing the volatility and forming crystalline derivatives, the role of the nitro group in the *p*-nitrobenzoates is also to protect the aromatic ring from electrophilic fluorination. Thus, esters of unsubstituted benzoic acid, exemplified by 2-methylbutyl benzoate (11), are destroyed quite rapidly. The IR spectra of the crude reaction mixtures revealed an ester moiety, but no aromatic protons were detected in the ^1H NMR, while the ^{19}F NMR spectra showed many peaks with a wide range of chemical shifts. It should be noted at this point that, in the presence of aromatic rings that are not strongly deactivated, clean tertiary fluorination could not be achieved. This was demonstrated when fluorine, even in concentrations lower than 1%, was passed through dianthrone (12), 1,5-diacetoxy-3-phenylpentane (13), *trans*-4-phenylcyclohexyl acetate (14), and even *trans*-4-(*p*-nitrophenyl)cyclohexyl acetate (15). In all cases aromaticity was lost before any



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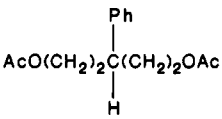

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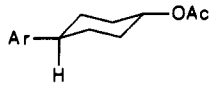
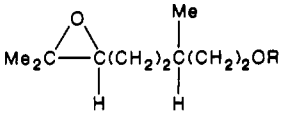


14: Ar = Ph
15: Ar = $C_6H_4NO_2$-*p*

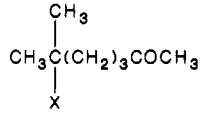
other fluorination process could take place. Unlike the *p*-nitrobenzoates, all the above cases contain only one or no deactivating moiety, insufficient for a strong electrophile such as fluorine.

Protection of an alcohol as an ether is possible but not efficient. Thus, from the ether 16 the corresponding fluoro derivative 17 was obtained in a low 20% yield. It seems that the positive end of the fluorine dipole can tear out the hydridelike hydrogen α to the etheric oxygen. Eventually carbonyl compounds are formed as evidenced by the IR spectrum of the crude reaction mixture. In a similar case where the epoxide 18 was reacted, several rearranged carbonyl derivatives could be detected after the hydrogen α to the epoxy group was abstracted by the fluorine. It



18: R = $COC_6H_4NO_2$-*p*

is worth contrasting these reactions with Lagow's perfluorinations, conducted under radical conditions, where ethers constitute one of the most robust groups toward fluorine.[9a] The carbonyl moiety in a ketone reduces the yield more than would be expected from its electron-withdrawing power, probably because of side reactions originating from its enol form. As an example 6-methyl-2-heptanone (19) indeed produced the expected 6-methyl-6-fluoro-2-heptanone (20), but only in 35% yield.

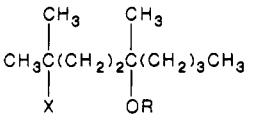


19: X = H
20: X = F

Primary and secondary hydroxyls have to be protected against the oxidative power of the fluorine, but tertiary alcohols do not require such protection. When either 2,5-dimethyl-5-nonanol (21) or its acetate 22 was treated with F_2, similar results were obtained, and the corresponding fluoro derivatives 23 and 24 were formed in 45%

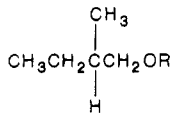
(11) Recently, the link between reactivity and selectivity has been reevaluated: Pross, A. *Isr. J. Chem.* **1985**, *26*, 390 and references therein.

and 50% yields, respectively.



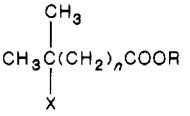
21: X = H; R = H
22: X = H; R = Ac
23: X = F; R = H
24: X = F; R = Ac

As mentioned, electrophilic substitution of a hydrogen on a saturated carbon depends on the *p*-orbital contribution to its bond. It is obvious, either by intuitive means or through semiempirical calculations, that the nearer the tertiary center is to an electron-withdrawing group the lower the p character of the bond will be. The limit for an effective electrophilic fluorination seems to be the distance of one CH_2 group. Thus, while the tertiary hydrogen in the 3-methylbutanol derivatives (**5**, **7**, **8**) could be selectively substituted by fluorine, this could not be done with the 2-methylbutanol derivative **25**, where only slow radical-induced deterioration of the starting material was observed. In the case of carboxylic acid derivatives,



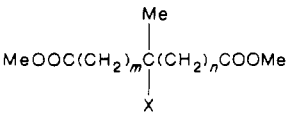
25: R = $COC_6H_4NO_2$-*p*

however, the requirement for at least two CH_2 groups between the reaction center and the electron-withdrawing moiety is less strong. There is only one methylene group between the reacting center and the carboxyl moiety in 2,2,2-trichloroethyl 3-methylbutanoate (**26**), and yet it reacts with fluorine to form **27**, although slowly and with moderate yield of 30%. The yield and the rate improved considerably with an additional interposed methylene, and the yield for the transformation of **28** to **29** was 55%.



26: *n* = 1; X = H; R = CH_2CCl_3
27: *n* = 1; X = F; R = CH_2CCl_3
28: *n* = 2; X = H; R = CH_2CCl_3
29: *n* = 2; X = F; R = CH_2CCl_3

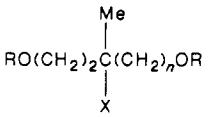
The effect of an electron-withdrawing moiety upon the hybridization of the tertiary hydrogen seems to be additive. This is quite well demonstrated when fluorination of **26** is compared with the fluorination of dimethyl 3-methylglutarate (**30**). In both cases only one methylene separates



30: *m* = *n* = 1; X = H
31: *m* = *n* = 1; X = F
32: *m* = 1; *n* = 2; X = H
33: *m* = 1; *n* = 2; X = F
34: *m* = *n* = 2; X = H
35: *m* = *n* = 2; X = F

the carboxylic group from the tertiary hydrogen, but in **30** there are two such groups. This reduced the yield of the electrophilic substitution product **31** by 1 order of magnitude to a mere 2%. Increasing gradually the gap as in dimethyl 3-methyladipate (**32**) resulted in a slightly improved ease of fluorination, and the corresponding fluoro derivative **33** was obtained in 10% yield. In both cases the reaction proceeded very slowly, and many randomly fluorinated compounds were also formed by various radical processes. The yield was not much improved even when working with dimethyl 4-methylpimelate (**34**), which yielded **35** in only 25% yield.

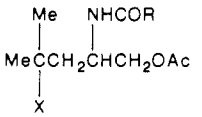
When more than one electron-withdrawing group is present, their nature also has a dominant influence on the electrophilic substitution. The differences in yields between molecules with one *p*-nitrobenzoate, acetate, or trichloroacetate group are not drastic, as can be seen when comparing the fluorination of **5**, **7**, and **8**. When, however, these differences are found in more than one place in a molecule, the effect is strongly felt. Thus, while 1,5-bis(trichloroacetoxy)-3-methylpentane (**36**) was converted to the 3-fluoro derivative **37** in only 20% yield, the corresponding bis(acetate) **38** reacted with fluorine to form 1,5-diacetoxy-3-methyl-3-fluoropentane **39** in 40% yield.



36: *n* = 2; X = H; R = $COCCl_3$
37: *n* = 2; X = F; R = $COCCl_3$
38: *n* = 2; X = H; R = Ac
39: *n* = 2; X = F; R = Ac
40: *n* = 3; X = H; R = Ac
41: *n* = 3; X = F; R = Ac
42: *n* = 3; X = H; R = $COC_6H_4NO_2$-*p*
43: *n* = 3; X = F; R = $COC_6H_4NO_2$-*p*

Adding an additional methylene between the reacting center and the electronegative oxygen atoms as in 1,6-diacetoxy-3-methylhexane (**40**) raised the yield of the fluorinated product **41** to 55%, but replacing acetoxy by *p*-nitrobenzoxy, as in **42**, reduced the yield of the corresponding **43** to only 20%. Not surprisingly, in all these cases the rate of the reactions followed the same pattern as the yields, also in accordance with semiempirical calculations, which show lower hybridization in the p orbital for the tertiary CH bond in compounds with stronger electron-withdrawing groups.

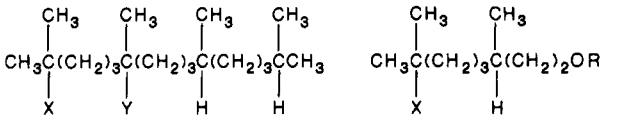
Nitrogen functions have also to be protected. Leucine was reduced to the corresponding alcohol, and both the hydroxyl and the amine groups were then acetylated to give **44**. The nitrogen however was still too basic and



44: X = H; R = CH_3
45: X = H; R = CF_3
46: X = H; R = CCl_3
47: X = F; R = CCl_3

reacted with the elemental fluorine. Changing to the trifluoroacetamide **45** entirely deactivated the tertiary hydrogen because of the accumulative effect of the two electron-withdrawing groups. The only amide that inhibited electrophilic reaction on the nitrogen, but still permitted substitution of a remote tertiary hydrogen, was the trichloroacetamide **46**, which was converted into **47**.

We have seen that electron-withdrawing groups usually have an inhibiting effect on the substitution of tertiary hydrogens by fluorine, but there are cases when it can have a beneficial role. When 2,6,10,14-tetramethylpentadecane (**48**) was reacted with fluorine, the two different tertiary hydrogens were substituted equally, forming **49** and **50** in 25% yield. The selectivity was improved, however, when an oxygenated function was present as in 3,7-dimethyloctyl *p*-nitrobenzoate (**51**). Only one monofluorinated com-



48: X = Y = H
49: X = F; Y = H
50: X = H; Y = F

51: X = H; R = $COC_6H_4NO_2$-*p*
52: X = F; R = $COC_6H_4NO_2$-*p*

pound was then obtained and identified as 3,7-dimethyl-7-fluorooctyl *p*-nitrobenzoate (**52**). Quite impressively, despite the two tertiary hydrogens the fluorine substitutes only the one more remote from the oxygenated function.

In conclusion, this work shows that the 100-year-old elemental fluorine, which was practically banned by organic chemists, can be used in a very selective mode on sites that are practically inert to any other known organic reagent.

Experimental Section

^1H NMR spectra were recorded with Bruker WH-90 and Bruker WH-360 spectrometers at 90 and 360 MHz, respectively, with $CDCl_3$ as a solvent and are reported (δ) downfield from Me_4Si, which served as internal standard. The ^{19}F NMR spectra were measured at 84.67 and 338.8 MHz, respectively, and are reported also in δ upfield from the internal standard $CFCl_3$. Mass spectra were measured with a Du Pont 21-491B spectrometer. IR spectra were recorded as neat films, in $CHCl_3$ solution, or as KBr pellets on a Perkin-Elmer 177 spectrophotometer.

General Fluorination Procedure. Fluorine is of course a strong oxidizer and a very corrosive material. An appropriate vacuum line made from copper or Monel in a well-ventilated area should be constructed for working with this element. Variations of such vacuum lines are described for example in Matheson Report No. G-115B or in a recent review.[12] The reactions themselves can be carried out in glass vessels. If elementary precautions are taken, work with fluorine is relatively simple, and we have had no bad experiences working with it. The reactions were usually carried out at −75 °C on scales of 1–6 mmol of substrate in 400 mL of 1:1 $CFCl_3/CHCl_3$. The reactions were monitored by ^1H NMR, TLC, and/or GC on 20% SE-30 or 10% OV-17 columns. They were usually stopped when the conversion reached about 90–95%. The fluorine concentration varied between 1 and 10% F_2 in N_2, according to the type of substrate. It should be held to the minimum needed, since higher concentrations encourage nonselective radical reactions. The gas mixture was prepared in a secondary container[13] before the reaction was started. This mixture was first passed through a dry NaF column serving as a HF scavenger (Matheson) and then in a slow stream of about 15 mL/min through a vigorously stirred solution of the substrate containing NaF. An efficient mixing, which is a very important factor, was achieved by using a Vibromixer (Chemapec), which also ensures a fine dispersion of the gas bubbles. Since absolute rates of these reactions are very difficult to measure because of the poor solubility of the fluorine and because of other difficulties, the referred rates are relative and derived from the amount of fluorine passed through the reaction mixture. For compounds such as paraffins, which react fast and efficiently with fluorine, about 1 mol equiv of the halogen was bubbled through the solution in order to achieve a full conversion. Other compounds needed much more fluorine, and in certain cases up to 100 mol equiv was passed through. The unreacted fluorine was trapped in a soda lime trap connected to the outlet of the reaction vessel. In most cases competitive reactions of a mixture of two relevant substrates were also conducted, revealing more reliable information about the relative reactivities of such compounds.

(12) Vyplel, H. *Chimia* **1985**, *39*, 305.
(13) Various mixtures of fluorine in inert gases such as N_2 or He are commercially available.
(14) For an excellent book on various types of electrophilic substitutions on a saturated carbon see: Olah, G. A.; Prakash, G. K. S.; Williams, R. E.; Field, L. D.; Wade, K. *Hypercarbon Chemistry*; Wiley: New York, 1987. Prof. Olah was also one of the first to generally suggest the type of the pentacoordinated carbonium ion presented in intermediate A. For a detailed reference see the above book.

The term "worked up as usual" means stopping the reaction by pouring it into 500 mL of water, washing the organic layer with $NaHCO_3$ solution followed by water until neutral, drying the organic layer over $MgSO_4$, and finally evaporating the solvent, preferably at room temperature. The crude product was usually purified by vacuum flash chromatography using silica gel 60-H (Merck). It should be noted that often the volatility and the polarity of the fluorine-containing compounds are quite similar to those of the starting materials, and only very careful chromatography will yield pure compounds. In many cases final purification was achieved by HPLC (Waters) on LiChrosorb Si-100 (Merck). If the crude reaction mixture is not immediately purified, it is advisable to add a drop or two of pyridine or hexamethyldisilazane to capture the small amount of HF that may be formed with time. Otherwise the HF will autocatalyze additional elimination, and the compounds will eventually decompose.

Preparation of Starting Materials. Some of these preparations are described briefly in the respective sections. In general, alcohols were treated with Ac_2O/py for acetate preparation, with CCl_3COCl/py for trichloroacetates, and with freshly prepared *p*-nitrobenzoyl chloride/pyridine for the preparation of the *p*-nitrobenzoates. The crude products were usually purified by short-column chromatography using 2–4% EtOAc in petroleum ether (PE) as eluent. Methyl esters were prepared by using diazomethane, while the trichloroethyl carboxylates were prepared by refluxing the corresponding acyl halide (RCOOH + $(COCl)_2$), CCl_3CH_2OH, and pyridine for 12 h. The yields of all esterifications varied from 85% to nearly quantitative. In general, when no melting point is given, the product is liquid at room temperature.

Fluorination of 3-methylnonane (**1**) was performed on 1.0 g (7 mmol) using 1% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with pentane, followed by HPLC using cyclohexane as eluent. The pure **2** was thus isolated in 65% yield: ^1H NMR 1.27 (CH_3CF, 3 H, d, J_{HF} = 22 Hz), 1.7–1.1 (12 H, m), 0.91 (Me, 3 H, t, J = 6 Hz), 0.89 (Me, 3 H, t, J = 4.2 Hz); ^{19}F NMR −146.1 (octet, J_{HF} = 22 Hz, $W_{h/2}$ = 80 Hz); MS, m/e 160 (M^+), 112 [$(Me(CH_2)_4CH{=}CHMe)^+$] 69 [$(MeCH{=}CMeCH_2)^+$].

Fluorination of 6-methyl-2-heptyl *p*-nitrobenzoate (**3**) was performed as described above on 0.5 g (1.8 mmol) using 4% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 4% EtOAc in PE, followed by HPLC using 3% EtOAc in cyclohexane as eluent. The pure **4** was thus isolated in 65% yield: mp 43 °C (from hexane); ^1H NMR 8.24 (4 H, AB, J = 8 Hz), 5.20 (CHO, 1 H, sextet, J = 6.1 Hz), 1.41 (CH_3CH, 3 H, d, J = 7 Hz), 1.33 (Me_2CF, 6 H, d, J_{HF} = 20 Hz); 2.1–0.8 (6 H, m); ^{19}F NMR −138.8 (heptet, J_{HF} = 20 Hz); MS, m/e 297 (M^+), 277 [$(M - HF)^+$], 282 [$(M - CH_3)^+$]. Anal. Calcd for $C_{15}H_{20}FNO_4$: C, 60.61; H, 6.73. Found: C, 60.86; H, 6.79.

Fluorination of 3-methylbutyl *p*-nitrobenzoate (**5**) was performed on 0.5 g (2.1 mmol) using 4% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 5% EtOAc in PE, followed by HPLC using 5% EtOAc in cyclohexane as eluent. The pure **6** was thus isolated in 60% yield: ^1H NMR 8.25 (4 H, AB, J = 8 Hz), 4.55 (CH_2O, 2 H, t, J = 6.7 Hz), 2.14 (CH_2CF, 2 H, dt, J_{HF} = 19.7 Hz, J = 6.7 Hz), 1.46 (Me_2CF, 6 H, d, J_{HF} = 21.4 Hz); ^{19}F NMR −132.0 (quintet, J_{HF} = 24 Hz); MS, m/e 235 [$(M - HF)^+$]. Anal. Calcd for $C_{12}H_{14}FNO_4$: C, 56.47; H, 5.49. Found: C, 56.50; H, 5.72. A similar procedure was followd when working with the acetate of the above compound **7**. The yield of the fluorinated derivative **9** was 70%: ^1H NMR 4.22 (CH_2O, 2 H, t, J = 6.7 Hz), 2.10 (CH_2CF, 2 H, dt, J_{HF} = 20 Hz, J = 6 Hz), 2.04 (Ac, 3 H, s), 1.42 (Me_2CF, 6 H, d, J_{HF} = 20 Hz); ^{19}F NMR −139.0 (quintet, J_{HF} = 20 Hz); MS, m/e 148 (M^+). The trichloroacetate **10** was also obtained in a similar way from **8** in 65% yield: ^1H NMR 4.53 (CH_2O, 2 H, t, J = 6.7 Hz), 2.11 (CH_2CF, 2 H, dt, J_{HF} = 19 Hz, J = 6.8 Hz), 1.43 (Me_2CF, 6 H, d, J_{HF} = 21 Hz); ^{19}F NMR −141.6 (quintet, J_{HF} = 24 Hz); MS, m/e 251.5 (M^+), 231.5 [$(M - HF)^+$]. Anal. Calcd for $C_7H_{10}Cl_3FO_2$: C, 33.40; H, 3.98. Found: C, 32.95; H, 3.62.

Preparation and Fluorination of (β-Methoxyethoxy)methyl Ether of 6-Methyl-2-heptanol (**16**). The ether was prepared by adding 6-methyl-2-heptanol to NaH in THF, refluxing for 2 h, and cooling to room temperature. β-Methoxyethoxy methyl chloride (MEM chloride) was added dropwise, and the resulting mixture refluxed for an additional 2 h. After the usual

workup, the reaction mixture was chromatographed with 8% EtOAc in PE, resulting in a 50% yield of pure liquid **16**. The fluorination of **16** was performed on 0.5 g (2.3 mmol) using 3% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 5% EtOAc in PE, followed by HPLC using 5% EtOAc in cyclohexane as eluent. The pure **17** was thus isolated in 20% yield: ^{1}H NMR 4.75 (OCH_2O, 2 H, d, J = 1.5 Hz), 3.63 (CHO, CH_2CH_2O, 5 H, m), 3.39 (CH_3O, 3 H, s), 1.33 (Me_2CF, 6 H, d, J_{HF} = 21 Hz), 1.17 (CH_3CO, 3 H, d, J = 7 Hz), 2.0–0.5 (6 H, m); ^{19}F NMR −130.0 (heptet, J_{HF} = 20 Hz); MS, m/e 236 (M^+). Anal. Calcd for $C_{12}H_{25}FO_3$: C, 61.02; H, 10.59. Found: C, 60.50; H, 10.13.

Fluorination of 6-methyl-2-heptanone (19) was performed on 0.4 g (3.1 mmol) using 4% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 10% EtOAc in PE, followed by HPLC using 10% EtOAc in cyclohexane as eluent. **20** was thus isolated in 35% yield: ^{1}H NMR 2.14 (CH_3CO, 3 H, s), 1.35 (($CH_3)_2CF$, 6 H, d, J_{HF} = 21.4 Hz), 2.5–0.9 (6 H, m); ^{19}F NMR −138.6 (heptet, J_{HF} = 22 Hz); MS, m/e 126 [$(M - HF)^+$], 111 [$(M - HF - CH_3)^+$].

Preparation of 2,5-Dimethyl-5-nonanol (21) and Its Acetate 22 and Their Fluorination. **21** was prepared in 80% yield by reacting 5-methyl-2-hexanone with BuMgBr and purified by flash chromatography using 5% EtOAc in PE as eluent. Part of the alcohol was acetylated by Ac_2O/py to produce **22** in 90% yield. **21** (0.6 g, 3.5 mmol) was fluorinated with 5% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 8% EtOAc in PE, followed by HPLC using 8% EtOAc in cyclohexane as eluent. The fluoro derivative **23** was thus isolated in 45% yield: IR 3300 cm^{-1}; ^{1}H NMR 1.17 (CH_3CO, 3 H, s), 1.35 (Me_2CF, 6 H, d, J_{HF} = 21 Hz), 1.7–0.9 (13 H, m); ^{19}F NMR −138.7 (heptet, J_{HF} = 21 Hz); MS, m/e 155 [$(M - HF - CH_3)^+$], 152 [$(M - HF - H_2O)^+$]. Anal. Calcd for $C_{11}H_{23}FO \cdot {}^1/_2H_2O$: C, 66.33; H, 12.06. Found: C, 66.00; H, 11.90. The acetate **22** (0.6 g, 2.8 mmol) was also fluorinated with 4% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 1% EtOAc in PE, followed by HPLC using 1% EtOAc in cyclohexane as eluent. **24** was thus isolated in 50% yield: ^{1}H NMR 1.96 (Ac, 3 H, s), 1.39 (CH_3CO, 3 H, s), 1.33 (Me_2CF, 6 H, d, J_{HF} = 21 Hz), 1.9–1.1 (13 H, m); ^{19}F NMr −138.0 (heptet, J_{HF} = 20 Hz); MS, m/e 155 [$(M - HF - Bu)^+$], 112 [$(M - HF - Bu - Ac)^+$]. Anal. Calcd for $C_{13}H_{25}FO_2$: C, 67.24; H, 10.77. Found: C, 66.96; H, 10.33.

Fluorination of 2,2,2-trichloroethyl 3-methylbutanoate (26) was performed on 0.5 g (2.1 mmol) using 8% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 5% EtOAc in PE, followed by HPLC using 5% EtOAc in cyclohexane as eluent. The pure **27** was thus isolated in 30% yield: ^{1}H NMR 4.70 (CH_2CCl_3, 2 H, s), 2.77 (CH_2CF, 2 H, d, J_{HF} = 15 Hz) 1.53 (Me_2CF, 6 H, d, J_{HF} = 20 Hz); ^{19}F NMR −134.5 (heptet, J_{HF} = 19 Hz); MS, m/e 251.5 (M^+).

Fluorination of 2,2,2-trichloroethyl 4-methylpentanoate (28) was performed on 0.5 g (2.0 mmol) using 4% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 5% EtOAc in PE, followed by HPLC using 5% EtOAc in cyclohexane as eluent. The pure **29** was thus isolated in 55% yield: ^{1}H NMR 4.75 (CH_2CCl_3, 2 H, s), 2.63 (CH_2CO, 2 H, t, J = 8 Hz), 2.01 (CH_2CF, 2 H, dt, J_{HF} = 20.5 Hz, J = 6.7 Hz) 1.38 (Me_2CF, 6 H, d, J_{HF} = 21 Hz); ^{19}F NMR −141.9 (heptet, J_{HF} = 21 Hz); MS, m/e 245.5 [$(M - HF)^+$]. Anal. Calcd for $C_8H_{12}Cl_3FO_2$: C, 36.16; H, 4.52. Found: C, 36.39; H, 4.46.

Fluorination of dimethyl 3-methyladipate (32) was performed on 0.5 g (2.66 mmol) using 9% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 10% EtOAc in PE, followed by HPLC using 12% EtOAc in cyclohexane as eluent. The fluoro derivative **33** was isolated in 10% yield: ^{1}H NMR 3.69 (COOMe, 6 H, s), 2.69 ($CFCH_2CO$, 2 H, d, J_{HF} = 15 Hz), 1.47 (CH_3CF, 3 H, d, J_{HF} = 22 Hz), 2.5–1.8 (4 H, m); ^{19}F NMR −144.3 (sextet, J_{HF} = 22 Hz); MS, m/e 175 [$(M - OMe)^+$]. Anal. Calcd for $C_9H_{15}FO_4$: C, 52.43; H, 7.28. Found: C, 51.96; H, 7.40.

Fluorination of dimethyl 4-methylpimelate (34) was performed on 0.4 g (1.98 mmol) using 7% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 5% EtOAc in PE, followed by HPLC using 8% EtOAc in cyclohexane as eluent. The fluoro derivative **35** was isolated in 25% yield: ^{1}H NMR 3.71 (COOMe, 6 H, s), 2.50 (CH_2CO, 4 H, t, J = 6 Hz), 2.20 ($CFCH_2CO$, 4 H, dt, J_{HF} = 20 Hz, J = 6 Hz), 1.46 (CH_3CF, 3 H, d, J_{HF} = 23 Hz), ^{19}F NMR −144.3 (sextet, J_{HF} = 23 Hz); MS, m/e 199 [$(M - OMe)^+$].

Fluorination of 1,5-Bis(trichloroacetoxy)-3-methylpentane (36). Compound **36** and the corresponding acetate **38** were prepared from 3-methyl-1,5-pentandiol, which in its turn was synthesized by reduction of dimethyl 3-methylglutarate (**30**) with $LiAlH_4$ in 75% yield. The fluorination of **36** was carried on 0.55 g (1.34 mmol) using 8% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 10% EtOAc in PE, followed by HPLC using 8% EtOAc in cyclohexane as eluent. The fluoro derivative **37** was isolated in 20% yield: ^{1}H NMR 4.52 (CH_2O, 4 H, t, J = 6.1 Hz), 2.10 ($CFCH_2$, 4 H, dt, J_{HF} = 19 Hz, J = 6 Hz), 1.35 (CH_3CF, 3 H, d, J_{HF} = 21 Hz); ^{19}F NMR −147.4 (octet, J_{HF} = 21 Hz); MS, m/e 407 [$(M - HF)^+$]. Similarly 1,5-diacetoxy-3-methyl-3-fluoropentane (**39**) was obtained from **38** in 40% yield and purified by HPLC using 13% EtOAc in cyclohexane. **39**: ^{1}H NMR 4.22 (CH_2O, 4 H, t, J = 6.7 Hz), 2.05 (Ac, 6 H, s), 2.01 ($CFCH_2$, 4 H, dt, J_{HF} = 19 Hz, J = 6.5 Hz), 1.41 (CH_3CF, 3 H, d, J_{HF} = 21 Hz); ^{19}F NMR −145.7 (octet, J_{HF} = 20 Hz); MS, m/e 200 [$(M - HF)^+$]. Anal. Calcd for $C_{10}H_{17}FO_4$: C, 54.54; H, 7.73. Found: C, 54.36; H, 7.71.

Preparation and Fluorination of 1,6-Diacetoxy-3-methylhexane (40) and the Corresponding Bis[(*p*-nitrobenzoyl)oxy] Derivative 42. Both compounds were prepared by acylation of citronelol followed by reductive ozonolysis ($NaBH_4$) and additional acetylation. The fluorination of **40** was carried on 0.50 g (2.31 mmol) using 6% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 8% EtOAc in PE, followed by HPLC using 10% EtOAc in cyclohexane as eluent. The fluoro derivative **41** was isolated in 55% yield: ^{1}H NMR 4.13 and 4.08 (CH_2O, 4 H, t, J = 6. Hz), 2.05 (Ac, 6 H, s), 1.37 (CH_3CF, 3 H, d, J_{HF} = 22 Hz), 2.4–1.3 (6 H, m); ^{19}F NMR −145.8 (sextet, J_{HF} = 22 Hz); MS, m/e 148 [$(M - 2Ac)^+$]. Anal. Calcd for $C_{11}H_{19}FO_4$: C, 56.41; H, 8.12. Found: C, 56.29; H, 8.58.

Similarly 0.5 g (1.16 mmol) of 1,6-bis(*p*-nitrobenzoxy)-3-methylhexane (**42**; mp 193 °C, from hexane) was fluorinated with 6% F_2 in N_2 to give **43** in 20% yield after purification by HPLC using 25% EtOAc in cyclohexane: mp 57 °C (from hexane); ^{1}H NMR 8.24 (4 H, AB, J = 8 Hz), 4.48 and 4.42 (CH_2O, 4 H, t, J = 6 Hz), 1.48 (CH_3CF, 3 H, d, J_{HF} = 20 Hz), 2.4–0.95 (6 H, m); ^{19}F NMR −147.2 (sextet, J_{HF} = 20 Hz); MS, m/e 254 [$(M - (CH_2)_2OCOC_6H_4NO_2)^+$], 234 [$(254 - HF)^+$], 220 [$(M - HF - (CH_2)_3OCOC_6H_4NO_2)^+$], 122 [$(C_6H_4NO_2)^+$]. Anal. Calcd for $C_{21}H_{21}FN_2O_8$: C, 56.25; H, 4.69. Found: C, 55.42; H, 4.51.

Preparation and Fluorination of 2-(Trichloroacetamido)-4-methylpentyl Acetate (46). Leucine was esterified with CH_2N_2 and then reduced with $LiAlH_4$. The alcohol was dissolved in MeOH and treated with $(CCl_3CO)_2O$ at room temperature for 12 h. The resulting amide was then acetylated with Ac_2O/py to give **46**, which was purified by flash chromatography using 35% EtOAc in PE. This compound (0.24 g, 0.78 mmol) was fluorinated with 6% F_2 in N_2 and, after the usual workup, the crude reaction mixture was flash chromatographed with 40% EtOAc in PE, followed by HPLC using 40% EtOAc in cyclohexane as eluent. The fluoro derivative **47** was isolated in 30% yield: IR 3410, 1715, 1690, 1510 cm^{-1}; ^{1}H NMR 7.0 (NH, 1 H, br s), 4.25 (CH_2O, 2 H, d, J = 4 Hz), 2.10 (Ac, 3 H, s), 1.57 and 1.33 (Me_2CF, 6 H, d, J_{HF} = 21 Hz), 2.0–1.6 (3 H, m); ^{19}F NMR −137.1 (heptet, J_{HF} = 20 Hz); MS, m/e 322.5 (M^+). Anal. Calcd for $C_{10}H_{15}Cl_3FNO_3$: C, 37.21; H, 4.65. Found: C, 36.85; H, 4.37.

Fluorination of 2,6,10,14-tetramethylpentadecane (48) was performed on 0.6 g (2.2 mmol) using 2.5% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 5% EtOAc in PE, followed by HPLC using 2% EtOAc in cyclohexane as eluent. Two compounds were isolated. The less polar one obtained in 25% yield proved to be 6-fluoro-2,6,10,14-tetramethylpentadecane (**50**): ^{1}H NMR 1.29 (CH_3CF, 3 H, d, J_{HF} = 22 Hz), 0.87 (CH_3, 15 H, d, J = 6.1 Hz), 1.7–1.2 (21 H, m); ^{19}F NMR −143.8 (sextet, J_{HF} = 19 Hz, $W_{h/2}$ = 70 Hz); MS, m/e 266 [$(M - HF)^+$]. The more polar isomer was identified as 2-fluoro-2,6,10,14-tetramethylpentadecane (**49**): 25% yield; ^{1}H NMR 1.33 (Me_2CF, 6 H, d, J_{HF} = 21 Hz), 0.88 (CH_3, 12 H, d, J = 6.1 Hz), 2.0 – 1.0 (21 H, m); ^{19}F NMR −144.3 (heptet, J_{HF} = 19 Hz, $W_{h/2}$ = 93 Hz); MS, m/e 256 [$(M - 2\ Me)^+$]; 236 [$(M -$

2 Me - HF)$^+$]. Anal. Calcd for $C_{19}H_{39}F$: C, 79.72; H, 13.63. Found: C, 79.93; H, 13.30.

Fluorination of 3,7-dimethyloctyl *p*-nitrobenzoate (51) was carried as described above on 0.5 g (1.6 mmol) using 3% F_2 in N_2. After the usual workup, the crude reaction mixture was flash chromatographed with 3% EtOAc in PE, followed by HPLC using 1% EtOAc in cyclohexane as eluent. The pure **52** was thus isolated in 30% yield: ^{1}H NMR 8.25 (4 H, AB, J = 8 Hz), 4.24 (CH_2O, 2 H, t, J = 6.7 Hz), 1.34 (Me_2CF, 6 H, d, J_{HF} = 19 Hz), 0.99 (CH_3CH, d, J = 6 Hz), 1.8-1.0 (9 H, m); ^{19}F NMR -138.3 (heptet, J_{HF} = 18 Hz); MS, m/e 139 [(M - HF - $OCOC_6H_4NO_2$)$^+$]. Anal. Calcd for $C_{17}H_{24}FNO_4$: C, 62.77; H, 7.38. Found: C, 63.08; H, 7.72.

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Registry No. 1, 5911-04-6; **2**, 90304-30-6; **3**, 77894-20-3; **4**, 110318-88-2; **5**, 38120-06-8; **6**, 77894-24-7; **7**, 123-92-2; **8**, 57392-55-9; **16**, 77894-22-5; **17**, 77894-27-0; **19** (alcohol), 4730-22-7; **19**, 928-68-7; **20**, 110318-89-3; **21**, 42842-12-6; **22**, 110330-30-8; **23**, 110318-90-6; **24**, 110318-91-7; **26**, 1617-04-5; **27**, 77894-29-2; **28**, 57392-48-0; **29**, 77894-28-1; **32**, 54576-13-5; **33**, 82953-27-3; **34**, 4751-49-9; **35**, 110318-92-8; **36**, 110318-93-9; **37**, 110318-94-0; **38**, 40065-27-8; **39**, 82953-29-5; **40**, 82953-26-2; **41**, 82953-30-8; **42**, 110318-95-1; **43**, 110318-96-2; **46**, 110318-98-4; **47**, 110318-99-5; **48**, 1921-70-6; **50**, 90304-32-8; **51**, 77894-21-4; **52**, 110319-00-1; MEM chloride, 3970-21-6; $Me_2CHCH_2CH(NH_2)CH_2OH$, 502-32-9; $Me_2CHCH_2CH(NHCOCl_3)CH_2OH$, 110318-97-3; $MeCO(CH_2)_2CHMe_2$, 110-12-3; citronellol, 106-22-9; leucine, 61-90-5.

Novel Synthesis and Spectral Characterization of an *N*-Acetoxyarylamine: *N*-Acetoxy-2,4-dinitrophenylamine

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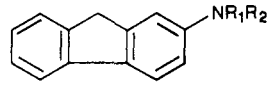
N-Acetoxyarylamines have been proposed as reactive metabolites of carcinogenic aromatic amines. As a model compound to investigate the synthesis and spectral characteristics of these proposed intermediates, stable crystalline *N*-acetoxy-2,4-dinitrophenylamine (**5**) was prepared on condensation of *O*-acetylhydroxylamine with 2,4-dinitrofluorobenzene. Its physical and spectroscopic properties (IR, UV, NMR, MS) were identical with those of the product prepared on acetylation of *N*-hydroxy-2,4-dinitrophenylamine (**6**) with acetic anhydride. The *N*-acetoxy compound **5** could also be prepared by treatment of the hydroxylamine **6** with *p*-nitrophenyl acetate. Under more strenuous acetylating conditions with acetic anhydride the *N,O*-diacetate derivative **8** was produced from the hydroxylamine **6**. The acetylation site in the stable monoacetate derivative differs from that formed on acetylation of other *N*-hydroxyarylamines. The unstable *N*-hydroxy-*N*-acetyl-2,4-dinitrophenylamine was prepared by transesterification of the *N,O*-diacetate **8** with methanol/sodium acetate. Acetic anhydride and *p*-nitrophenyl acetate, under mild conditions, converted *N*-hydroxy-2-aminofluorene to *N*-hydroxy-2-(acetylamino)fluorene and to 2,2'-azoxyfluorene, respectively. *N*-Acetoxy-2-aminofluorene could not be detected in either case.

Introduction

N-Acetoxyarylamines have been proposed as ultimate reactive metabolites of carcinogenic aromatic amines.[1] The mutagenicity of the well-documented carcinogen, 2-(acetylamino)fluorene (**1**) is believed to result from an electrophilic interaction of a putative intermediate, such as *N*-acetoxy-2-aminofluorene (**2**) with DNA.[2] This metabolite is thought to be formed by an enzyme-mediated transacetylation of *N*-hydroxy-2-(acetylamino)fluorene (**3**) a cytochrome P-450 catalyzed oxidative metabolite of 2-(acetylamino)fluorene.[3] *N*-Hydroxyarylamines are also converted to *N*-acetoxyarylamines apparently by acetyl CoA dependent enzymatic O-esterification.[4] Evidence for such a mechanism is based solely on indirect experiments. *N*-Acetoxy-2-aminofluorene has never been synthesized or isolated as a metabolite due to its apparent instability, and attempts to isolate other similar derivatives from metabolic mixtures have not been successful. However, the chemical preparation of a number of *N*-acetoxyarylamines have been reported,[1b,c,5] although only the 4-aminoquinoline 1-oxide derivatives have been fully characterized.[6]

The first synthesis of an *N*-acetoxyarylamine was reported in 1923.[7] In that work *N*-acetoxy-2,4-dinitrophenylamine (**5**) was prepared by the acetylation of *N*-



1, R_1 = $COCH_3$, R_2 = H
2, R_1 = H, R_2 = $OCOCH_3$
3, R_1 = $COCH_3$, R_2 = OH
4, R_1 = $COCH_3$, R_2 = $OCOCH_3$

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