2; (*E,E*)-2-methyl-5-phenyl-2,4-pentadienoic acid, 20414-94-2; (*E*)-cinnamaldehyde, 14371-10-9; (*E,E*)-2,5-diphenyl-2,4-pentadienoic acid, 23848-94-4; 2-cyclohexylidenepropionic acid, 77124-22-2; 3,3-diphenylacrylic acid, 606-84-8; benzophenone, 119-61-9; 2-methylpropionaldehyde, 78-84-2; (*E*)-2,4-dimethyl-2-pentenoic acid, 3876-52-6; (*Z*)-2,4-dimethyl-2-pentenoic acid, 3876-51-5; (*E*)-2-ethyl-4-methyl-2-pentenoic acid, 77124-23-3; (*Z*)-2-ethyl-4-methyl-2-pentenoic acid, 77124-24-4; (*E*)-ethyl cinnamate, 4192-77-2; **1a**, 53243-58-6.

Aromatic Fluorinations Suitable for Fluorine-18 Labeling of Estrogens

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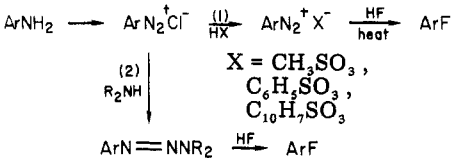
Two aromatic fluorination methods, the decomposition of aryl azides and the decomposition of aryltriazenes, were investigated as methods potentially suitable for fluorine-18 labeling of estrogens. The aryltriazene method gives moderate yields in many systems but fails with *o*-methoxy or (methanesulfonyl)oxy groups. The aryl azide method gives good yields of *p*-fluoroanilines, which can be deaminated readily, but oxygen or large alkyl groups ortho to the azide interfere with the fluorination. The synthesis of *m*-fluorohexestrol via the aryltriazene decomposition approach is reported.

Introduction

The changes in physical and chemical properties resulting from the introduction of fluorine into organic compounds have long been recognized by organic chemists, and fluorinated substituents have been used as labels, probes, and controlling substituents for mechanistic studies.[1] The isosteric replacement of hydrogen by fluorine has been used by pharmacologists to elevate hydrophobicity and to retard metabolism.[1d] Recently, interest in the preparation of radiopharmaceuticals labeled with short-lived isotopes as imaging agents and physiological probes has rekindled an interest in developing methods for the introduction of fluorine that would be suitable for isotope incorporation.[2]

Fluorine-18 is a 110-min half-life positron emitter that can be produced readily and in large quantities by medical cyclotrons and is an excellent radionuclide for studies by positron-emission transaxial tomography.[3] Methods for the introduction of fluorine-18 into organic molecules need to be convenient and rapid and should also be of reasonably high yield. In addition, the preparation of radiopharmaceuticals whose distribution is based on uptake by high-affinity, limited capacity binding systems (receptor binding) requires labeling methods that will operate without added carrier fluorine and will produce agents of high specific activity.[4] For the preparation of aliphatic fluorine-containing compounds, the modification of methods based on displacements by fluoride ion appear to be suitable,[2f,5] but the preparation of high specific activity fluorine-labeled aromatic compounds presents additional challenges.

Scheme I



While there are a number of methods for aromatic fluorination, the traditional Balz–Schiemann reaction[6] is the only commonly used method in the syntheses of fluorine-18 labeled aromatic compounds.[2c,7] This reaction is very inefficient from a radiochemical point of view, because the maximum radiochemical yield is only 25%. But, more importantly, since fluorine is introduced by exchange labeling of an aryldiazonium tetrafluoroborate precursor, the dilution of specific activity by the unlabeled fluorine in the counterion is enormous. In fact, the low specific activity of some radiopharmaceuticals synthesized by this method can account for their failure to localize in target organs.[7b]

In conjunction with studies toward the development of γ-emitting estrogen analogues as receptor-based agents for imaging breast tumors,[8] we realized the need for new methods for the synthesis of fluorine-18 labeled aromatic compounds of high specific activity, particularly methods that would be suitable for the preparation of fluoroaromatics containing phenolic oxygen functions, as are found in estrogens. Here, we report two methods for aromatic fluorination: fluoride trapping of arylnitrenium

(1) (a) Schlosser, M. *Tetrahedron* **1978**, *34*, 3. (b) Hudlicky, M. "Chemistry of Organic Fluorine Compounds", 2nd ed.; Ellis Horwood Ltd.: England, 1976; Chapters 7 and 9. (c) Sheppard, W. A.; Sharts, C. M. "Organic Fluorine Compounds"; W. A. Benjamin, Inc.: New York, 1969; Chapters 8 and 9. (d) "Carbon-Fluorine Compounds: Chemistry, Biochemistry and Biological Activities"; Ciba Foundation Symposium, Associated Scientific Publishers: Amsterdam, 1972.

(2) (a) Welch, M. J. "Radiopharmaceuticals and Other Compounds Labeled with Short Lived Radionuclides", Pergamon: Oxford, 1977. (b) McAfee, J. G. "Radiopharmaceuticals"; Subramanian, G., Rhodes, B. A., Cooper, J. F., Sodd, V. J., Eds.; The Society of Nuclear Medicine: New York, 1975; p 3. (c) Robinson, G. D., Jr. *Ibid.* p 141. (d) Wolf, A. P.; Christman, D. R.; Fowler, J. S.; et al. "Radiopharmaceuticals and Labeled Compounds"; IAEA: Vienna, 1973; Vol 1, p 345. (e) Maeda, M.; Tewson, T. J.; Welch, M. J. 3rd International Symposium of Radiopharmaceutical Chemistry, St. Louis, MO, 1980; Abstract 17.8. (f) Tewson, T. J.; Welch, M. J.; Raichle, M. E. *J. Nucl. Med.* **1978**, *19*, 1339.

(3) (a) Ter-Pogossian, M. M.; Raichle, M. E.; Sobel, B. E. *Sci. Am.* **1980**, *243*, 170. (b) Ter-Pogossian, M. M.; Phelps, M. E.; Hoffman, E. J.; Mullani, N. A. *Radiology* **1975**, *114*, 89.

(4) Katzenellenbogen, J. A.; Heiman, D. F.; Carlson, K. E.; Lloyd, J. E. In "Receptor Binding Radiopharmaceuticals"; Eckelman, W. C., Ed., Vol. X in "Radiotracers in Biology and Medicine"; Colombetti, L. G., Series Ed.; CRC Press, in press.

(5) (a) Heiman, D. F. Ph.D. Thesis, University of Illinois, Urbana, IL, 1980. (b) Gately, S. J.; Shaughnessy, W. J. *Int. J. Appl. Radiat. Isot.* **1980**, *31*, 339. (c) Tewson, T. J.; Welch, M. J. *J. Org. Chem.* **1978**, *43*, 1090.

(6) Balz, G.; Schiemann, G. *Chem. Ber.* **1927**, *60*, 1186.

(7) (a) De Kleijn, J. P. *J. Fluorine Chem.* **1977**, *10*, 341. (b) Palmer, A. J.; Eakins, M. N.; Waters, S. L. *Int. J. Appl. Radiat. Isot.* **1977**, *30*, 695.

(8) (a) Katzenellenbogen, J. A.; Senderoff, S. G.; McElvany, K. D.; O'Brien, H. A. Jr.; Welch, M. J. *J. Nucl. Med.* **1981**, *22*, 42. (b) Heiman, D. F.; Senderoff, S. G.; Katzenellenbogen, J. A.; Neeley, R. J. *J. Med. Chem.* **1980**, *23*, 944. (c) Goswami, R.; Harsy, S. G.; Heiman, D. F.; Katzenellenbogen, J. A. *Ibid.* **1980**, *23*, 1002.

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Table I. Preparation of Piperidino Triazenes from Anilines

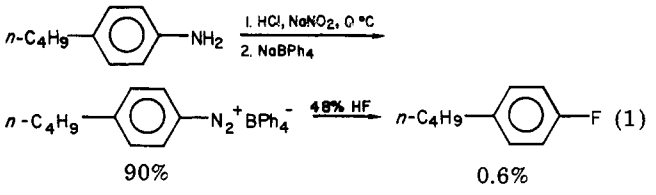
compd	R	% yield of triazenes
1	4-CH_3	97
2	4-$CH_3(CH_2)_3$	95
3	4-$(CH_3)_2CH$	90
4	3-CH_3O	90
5	2-CH_3O-5-phenyl	100
6	2-CH_3SO_2O	100
7	2-CH_3O	90
8	2-CH_3O-5-CH_3	94

ions generated by the acid decomposition of aryl azides, and fluoride reaction with aryldiazonium ions generated by the acid decomposition of aryltriazenes.[9] Both methods are exemplified in several systems and can be used successfully with certain patterns of oxygen and alkyl substitution in the aromatic ring, and the triazene method has been used in the synthesis of *m*-fluorohexestrol, a nonsteroidal estrogen with high binding affinity for the estrogen receptor.[10] Since both of these methods do not depend upon precursors that contain unlabeled fluorine, they should be readily adaptable to the synthesis of fluorine-18 labeled compounds with high specific activity. The synthesis of fluorine-18 labeled estrogens and investigations of their biological properties are currently underway.

Results and Discussions

Aryltriazene Decompositions. Two approaches were taken in attempts to modify the Schiemann reaction in order to provide efficient incorporation of fluoride (Scheme I).

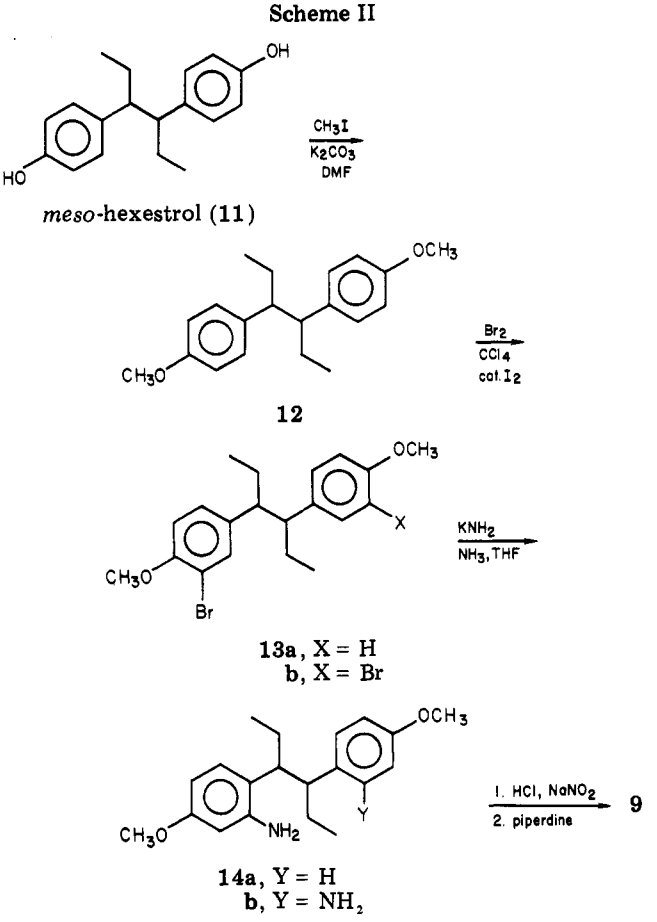
The first approach involves the decomposition of a diazonium salt prepared with a nonfluorine-containing counterion, in the presence of a fluoride source. However, the instability of such diazonium salts (e.g., phenyldiazonium methanesulfonates, phenyldiazonium benzenesulfonates, 4-butylphenyldiazonium naphthalenesulfonates, etc.) made their isolation and purification very difficult. Only when tetraphenylborate was used as the counteranion (4-butylphenyldiazonium tetraphenylborate) were we able to isolate a low yield (0.6%) of the fluorinated product after decomposition (eq 1).



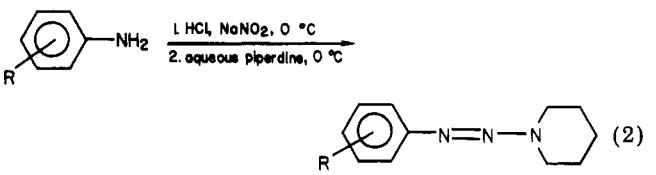
The second approach involves trapping a diazonium ion with a secondary amine to form a triazene. The purified triazenes can then be decomposed in the presence of hydrofluoric acid to give the corresponding fluoroaromatics. This was in fact the first reported method for aryl fluorination (1888).[11] However, this reaction fell into disuse with the development of the more elegant Schiemann reaction (1927).[6]

We synthesized several piperidinotriazenes (1-aryl-3,3-(1,5-pentanediyl)triazenes) bearing alkyl and/or oxygen

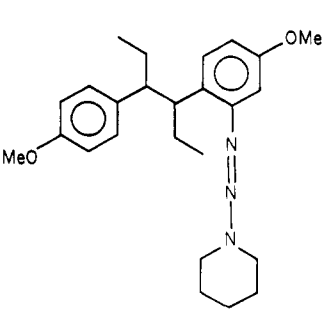
Scheme II



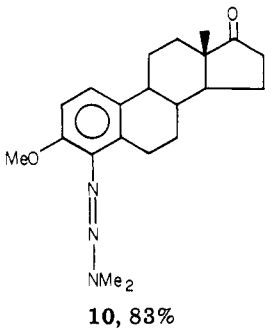
functions in the ring as models for estrogen systems (Table I, eq 2).



All the triazenes were prepared in good yields. More importantly, these triazenes are stable at room temperature and can be vigorously purified by recrystallization or chromatography before fluorination. Similarly, two triazeno estrogens, 2'-piperidinoazohexestrol dimethyl ether (9) and 4-(dimethylamino)azoestrone 3-methyl ether (10) were prepared and recrystallized to analytical purity.



9, 51%



10, 83%

The triazene 10 was prepared from the known 4-aminoestrone 3-methyl ether, but the hexestrol triazene 9 was prepared from the corresponding amine, prepared from *meso*-hexestrol (11) according to Scheme II. Hexestrol dimethyl ether (12) was treated with bromine in carbon tetrachloride in presence of catalytic amount of

(9) Preliminary reports of the use of the aryltriazene decomposition approach to aromatic fluorination and radiofluorination have appeared: (a) Widdowson, D. A.; Rosenfeld, M. N. *J. Chem. Soc., Chem. Commun.* **1979**, 914; (b) Tewson, T. J.; Welch, M. J. *Ibid* **1979**, 1149.

(10) Ng, J.; Katzenellenbogen, J. A.; Carlson, K. E., unpublished results.

(11) Wallach, O. *Justus Liebigs Ann. Chem.* **1888**, 235, 242, 255.

Table II. Decomposition of Aryltriazenes in Hydrogen Fluoride

triazene	fluorination condn, (room temperature, 30 min)	% yield of isolated fluorinated product[a]
1	(1) anhydrous HF/THF,	15
	(2) HF-pyridine/benzene,	15
	(3) 48% aqueous HF	27
2	48% aqueous HF	16
3	HF-pyridine/benzene	22
4	(1) HF-pyridine/benzene,	19
	(2) 48% aqueous HF,	17
	(3) anhydrous HF/benzene,	18
	(4) anhydrous HF/CH_2Cl_2	trace
5	(1) 48% aqueous HF,	0[b]
	(2) HF-pyridine/benzene	0[b]
6	48% aqueous HF	0[b]
7	48% aqueous HF	0[b]
8	48% aqueous HF	0[b]
9	(1) 48% aqueous HF,	41[c]
	(2) HF-pyridine/benzene,	43[c]
	(3) HF-pyridine/HOAC	25
10	(1) HF-pyridine/HOAC,	0[d]
	(2) HF-pyridine/benzene,	0[d]
	(3) 48% aqueous HF	0[d]

[a] Yields were determined by weight after isolation and purification by distillation (except for 9 and 10). The isolated yields of volatile products may be lowered by evaporative losses. Comparable yields were determined by ^{19}F NMR, using internal standards (fluorobenzene or *p*-fluorotoluene). [b] The absence of fluorinated products was established by ^{19}F NMR. With fluorobenzene or *p*-fluorotoluene as internal standard, the detection limit by ^{19}F NMR is $<0.5\%$. [c] The yields based on GLC analysis were 47% and 46%, respectively. [d] The absence of fluorinated product was determined by comparison with authentic 4-fluoroestrone 3-methyl ether by GLC and ^1H NMR, ^{19}F NMR, and mass spectra (see text).

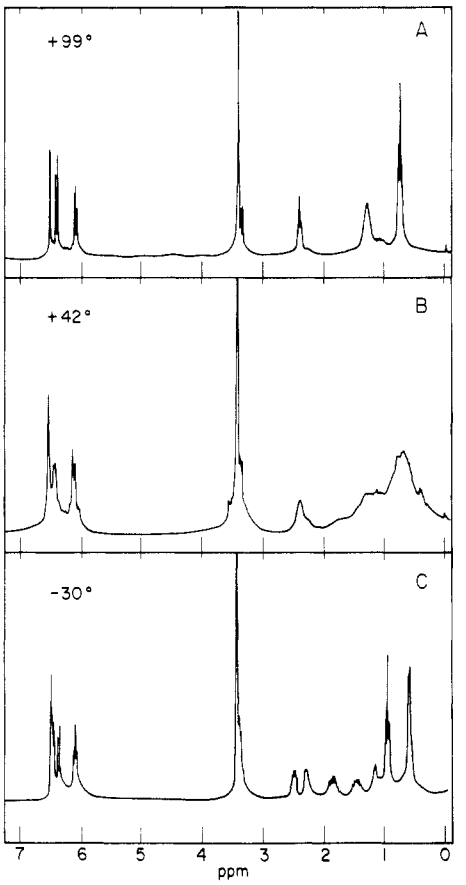


Figure 1. Variable-temperature ^1H NMR spectra of *cis*-3,6-dimethoxy-9,10-diethyl-9,10-dihydrophenanthrene (**16**). Spectra were obtained in $CDCl_3$ at the temperatures indicated by using a Varian HR-220 instrument in the FT mode.

iodine. The mixture of unreacted starting material (**12**), monobromo (**13a**), and dibromo (**13b**) species could be separated chromatographically with difficulty at this point but was more conveniently carried through the synthesis. Treatment of the bromohexestrol methyl ether mixture (**12, 13a, 13b**) with potassium amide in liquid ammonia–THF produced 2′-aminohexestrol dimethyl ether (**14a**) by a benzyne reaction.[12] Hexestrol dimethyl ether (**12**) and the diamine **14b** could be very readily removed by chromatography at this point.

These triazenes were decomposed under various conditions to give the corresponding fluorinated aromatic compounds (Table II). All of the triazenes bearing only alkyl groups (**1–3**) underwent fluorination in reasonable yields, as did those bearing alkoxy groups oriented meta with respect to the triazene group (**4, 9**). None of the triazenes bearing an *o*-methoxy group (**5, 7, 8, 10**) gave any detectable yield of the fluorinated product. (The detection limit by ^{19}F NMR analysis is >0.5%; see Table II, footnote *b*). Even the *o*-(methanesulfonyl)oxy triazene (**6**), which is less electron rich and lacks reactive carbinol hydrogens, failed to undergo fluorination.

The yields of fluorinated product varied somewhat depending upon the conditions of triazene decomposition, but the use of sources of anhydrous hydrogen fluoride (anhydrous hydrogen fluoride or hydrogen fluoride–pyridine complex) did not give higher yields than did 48% aqueous hydrogen fluoride. The fact that phenols did not constitute a significant fraction of the byproducts when aqueous HF was used suggests that the availability of free water in this reagent is very low.

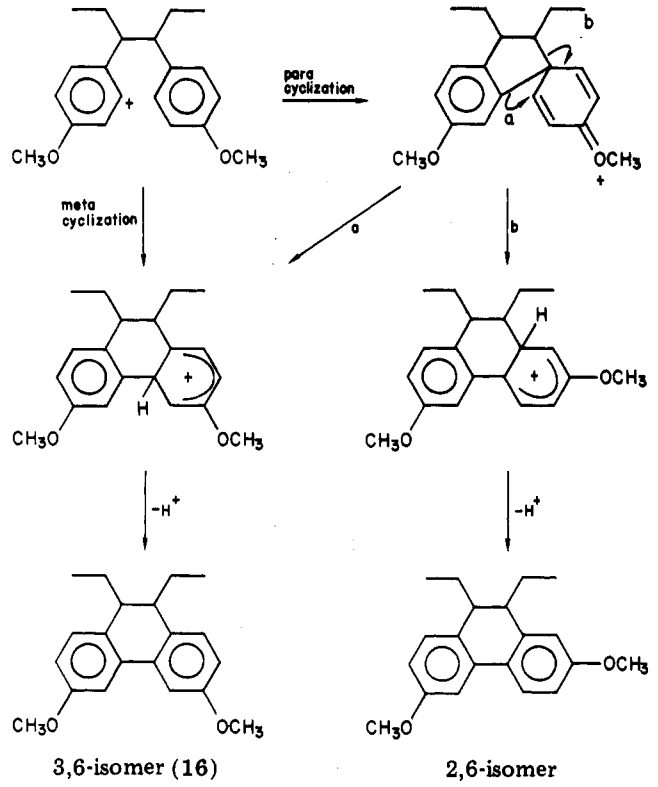
The choice of solvents, however, is extremely important. Methylene chloride is a poor solvent, as it facilitates the homolytic decomposition of triazenes. Polar solvents such as THF often led to a more complex product mixture, and acidic solvents such as acetic acid led to decomposition of triazenes before the fluorinating agent was added. The best solvents found were aromatic hydrocarbons such as benzene or bromobenzene. They are polar enough to dissolve the triazenes but are relatively inert to the aryl cations generated when the acid was added. In some cases, good yields of fluorinated product were obtained with the fluorinating agent itself as solvent.

Decomposition of the hexestrol triazene **9** under various conditions (see Table II) gave 2′-fluorohexestrol dimethyl ether (**15a**) in 25–43% yield. This compound could be demethylated smoothly by refluxing with boron tribromide in dry chloroform for 20 min to give the fluorinated nonsteroidal estrogen, 2′-fluorohexestrol (**15b**), in 83% yield.

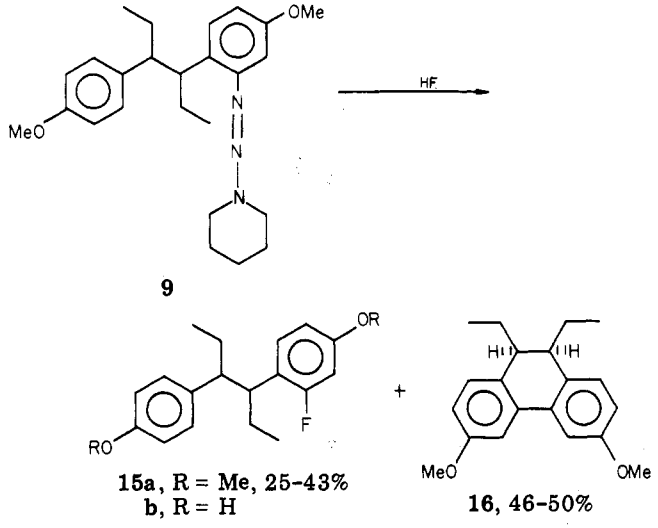
In the decomposition of hexestrol triazene **9**, a major byproduct constituting 46–50% of the mass balance was also isolated. In the mass spectrum, this material showed a molecular ion of m/e 296 and a fragmentation pattern showing consecutive losses of two ethyl groups; no benzylic–benzylic bond cleavage, which is very characteristic of the fragmentation of hexestrol derivatives, was observed. Proton NMR (42 °C) shows two very broad adsorptions (δ 0.7–1.6) for the methyl and methylene protons. Variable-temperature NMR studies (Figure 1) revealed two different ethyl groups at low temperatures (−35 °C) which become equivalent upon warming (99 °C). This suggested

(12) (a) Heaney, H. *Chem. Rev.* **1962**, *62*, 81. (b) Roberts, J. D.; Vaughan, C. W.; Carlsmith, L. A.; Semenow, D. A. *J. Am. Chem. Soc.* **1956**, *78*, 611.

Scheme III

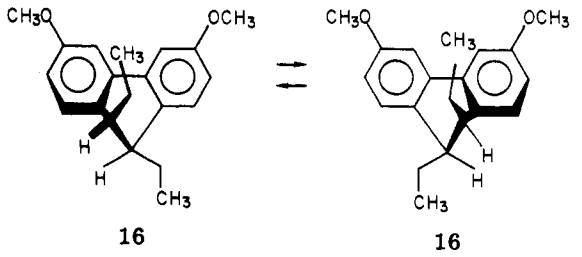


that the structure of the byproduct was *cis*-3,6-dimethoxy-9,10-diethyl-9,10-dihydrophenathrene (16). Rotation

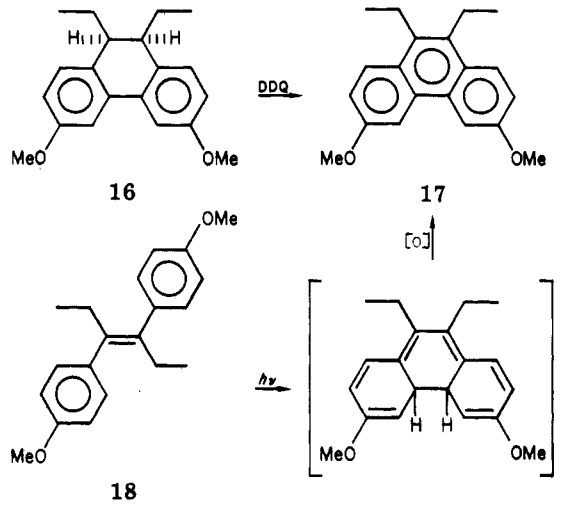


about the biphenyl bond in this molecule should be relatively restricted;[13] so, the two ethyl groups, which have quite different dihedral angles with respect to the plane of the benzene ring, would be expected to be nonequivalent at lower temperatures where interconversion of the atropisomers is slow.

Further evidence of the structure of 16 comes from its oxidation to known 3,6-dimethoxy-9,10-diethylphenathrene (17) with dichlorodicyanoquinone (DDQ). Proton NMR shows the disappearance of the two methine protons, and the two ethyl groups shift downfield and become equivalent. The mass spectrum shows a prominent molecular ion of m/e 297 with consecutive losses of two methyl groups



in the fragmentation pattern. The melting point and UV spectrum of the oxidation product 17 are identical with those reported for this compound, prepared by oxidation of the photocyclization product of diethylstilbestrol dimethyl ether (18).[14]



Compound 16 could arise from the cyclization of the intermediate diazonium cation (from the decomposition of triazene) in a reaction similar to that of the Pschorr phenanthrene synthesis.[15] In fact a very similar reaction without the methoxy groups had been reported.[16] At this point, however, it is unclear whether the cyclization proceeds directly by electrophilic attack of the aryl carbenium ion on the carbon atom meta to the methoxy group in the other ring or whether cyclization first takes place at the more electron rich center para to the methoxy group. The latter cyclization would afford a spiroarenium ion intermediate that could rearrange and lose a proton to form either the 3,6-dimethoxy (Scheme III, bond a migrates) or the 2,6-dimethoxy isomer (bond b migrates). Significant amounts of the 2,6-isomer were not isolated, but additional methoxy resonances were observed in crude samples of the byproducts; so, it is very possible that smaller amounts of the 2,6-isomer might have been lost during the purification of the 3,6-isomer.

As was mentioned before, the position of the oxygen function on the ring seems to be crucial in the fluorination of triazenes, as no fluorinated product was observed in all triazenes bearing oxygen functions in the ortho position. This is in agreement with the results originally reported by Wallach.[11] In contrast to our findings and the results of Wallach, however, 4-(dimethylamino)azoestrone 3-methyl ether (10) was reported to give 4-fluoroestrone 3-methyl ether in 85% yield upon treatment with hydrogen

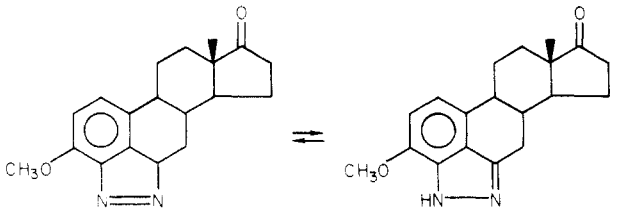
(13) (a) Hall, D. M.; Turner, E. E. *J. Chem. Soc.* **1955**, 1242. (b) Armarego, W. L. F.; Turner, E. E. *Ibid.* **1956**, 3668. (c) Eliel, E. L. "Stereochemistry of Carbon Compounds"; McGraw Hill Book Co.: New York, 1962; p 164.

(14) (a) Doyle, T. D.; Benson, W. R.; Filipescu, N. *J. Am. Chem. Soc.* **1976**, *98*, 3262. (b) Collins, D. J.; Hobbs, J. J. *Aust. J. Chem.* **1967**, *20*, 1905. (c) Hugelshofer, P.; Kalroda, J.; Schaffner, K. *Helv. Chim. Acta* **1960**, *165*, 1322.

(15) Pshorr, R. *Chem. Ber.* **1896**, *29*, 496.

(16) Ruggli, P.; Straub, A. *Helv. Chim. Acta* **1936**, *19*, 1288; *Ibid.* **1937**, *20*, 37.

fluoride–pyridine complex in acetic acid.[9a] We have repeatedly tried to reproduce this result using analytically pure triazene **10** under a variety of conditions. The reaction products were compared (GLC, ^{1}H NMR, ^{19}F NMR, mass spectra, and elemental analysis) with an authentic sample of 4-fluoroestrone 3-methyl ether, and it was clear that no fluorine was incorporated under any of the conditions. Instead, 15% estrone 3-methyl ether was isolated, along with a pale, pink solid (36%), which shows a prominent molecular ion at m/e 310 and has a molecular formula of $C_{19}H_{22}N_2O_2$ by elemental analysis. Inspection of other spectroscopic data (UV, IR, ^{1}H NMR) suggests that the product may have the structure **19**. The formation of indazoles (benzpyrazoles) from the decomposition of *o*-alkyldiazonium ions is in fact quite common.[17]

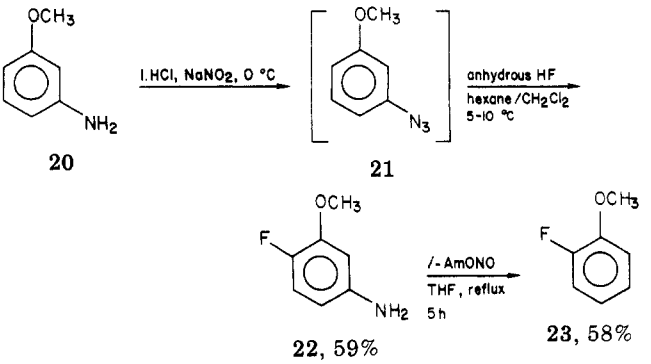


19

The yields of fluorinated products based on the starting triazenes are not excellent, though in many cases they are comparable to the yields obtained by the Schiemann reaction on the same or similar systems (see also, Table II, footnote *a*). However, for the purpose of labeling with fluorine-18, where a small amount of labeled fluoride in a nonnucleophilic acid would be treated with an excess of triazene, this reaction is potentially a much more effeicient way for fluorine-18 incorporation than the Schiemann reaction. Thus, theoretically, all of the labeled fluoride could be utilized, and compounds of very high specific activity could be produced. Another attractive feature of this method is that, in contrast to most diazonium salts, the starting triazenes are usually very stable compounds that can be purified to analytical purity before fluorinations. This helps to minimize the contamination of the fluorine-labeled products with impurities from the precursors or their decomposition products. In fact, in preliminary studies, we have successfully synthesized fluorine-18 labeled *m*-fluorohexestrol by the triazene method and have obtained good yields of fluorine-18 incorporation.[18] Finally, the triazene method has recently been extended to aromatic brominations[9b,19] and iodinations[20] and as such can be used to incorporate radioisotopes of these elements (such as ^{77}Br, ^{123}I, ^{125}I, ^{131}I). In the applications to aromatic substitution with halogens other than fluorine, however, it is not all clear that the triazene method is superior, either in terms of yields, product purity, or potential product specific activity, to the traditional Sandmeyer reaction.[21]

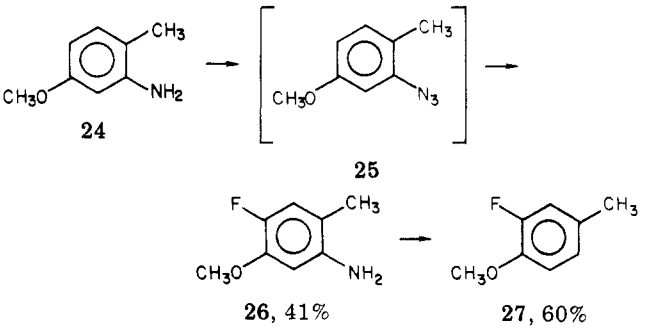
Aryl Azide Decomposition. It has long been known that aryl hydroxylamines and aryl azides, when treated with hydrogen halides (bromides and chlorides), undergo decomposition to give *o*- and *p*-haloanilines,[22] presumably via the intermediacy of an arylnitrenium ion. More recently, this reaction has been extended to fluorination with anhydrous hydrogen fluoride, giving moderate yields of *p*-fluoroanilines.[23] We have adapted the decomposition of aryl azides in anhydrous hydrogen fluoride, together with a recently reported deamination procedure,[24] to develop a method for monofluorination of oxygen-containing aromatic compounds that may be suitable for labeling with fluorine-18.

m-Anisidine can be diazotized and converted to the corresponding azide **21** by reaction with sodium azide. This azide, without isolation, was added to anhydrous hydrogen fluoride, to furnish a 59% yield of the desired *p*-fluoro-*m*-anisidine (**22**). The amino group in **22** can then be removed by refluxing the anisidine **21** with isoamyl nitrite in tetrahydrofuran for 5 h, affording a 58% yield of *o*-fluoroanisole (**23**).



20 21 22, 59% 23, 58%

This reaction sequence was also applied to another model system, 2-methyl-5-methoxyaniline (**24**), and resulted in a 41% yield of 2-methyl-4-fluoro-5-methoxyaniline (**26**) which was successfully deaminated to 2-fluoro-4-methylanisole (**27**) in 60% yield.



24 25 26, 41% 27, 60%

In additional studies, however, we have found that the azide rearrangement approach is not successful with an *o*-methoxy group (azide **28**). Furthermore, although fluorination proceeded well in the model system **24**, decomposition of *m*-azidohexestrol dimethyl ether (**29**), followed by nitrite deamination, failed to produce any *o*-fluorohexestrol dimethyl ether. In this latter case, it is possible that with ortho-situated alkyl groups larger than methyl (**29** vs. **25**), the nitrenium ion is intercepted by an intramolecular hydride transfer reaction from the adjacent alkane chain.

The fluorination of aryl azides is an attractive approach for the preparation of certain *p*-fluoroanilines that is potentially directly adaptable to labeling with fluorine-18.

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(18) The synthesis of fluorine-18 labeled 2′-fluorohexestrol and investigations of its in vivo behavior will be described in another paper.

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(21) Sandmeyer, T. *Chem. Ber.* **1884**, *17*, 1633, 2650.

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(23) (a) Titov, A. I.; Baryshnikova, A. N. *Zh. Obshch. Khim.* **1953**, *23*, 361. (b) Patrick, T. B.; Schield, J. A.; Kirchner, D. G. *J. Org. Chem.* **1974**, *39*, 1758. (c) Mulvey, D. M.; DeMarco, A. M.; Weinstock, L. M. *Tetrahedron Lett.* **1978**, *16*, 1419.

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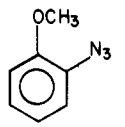
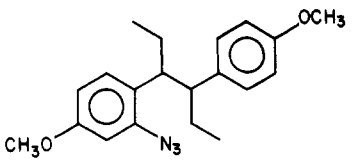


28



29

However, at this point, the reductive deamination step that we have used requires longer reaction times (ca. 5 h) than is desirable for use with fluorine-18 (110-min half-life). It is possible that higher temperature modifications or the use of a more effective hydrogen donor as solvent in the deamination may accelerate the reaction rates so as to make the azide decomposition–deamination sequence a viable method for aromatic radiofluorination. In fact, an example of a more rapid reductive deamination has been reported in the recent literature.[25]

Conclusion

Two methods of aromatic fluorination have been explored in terms of their suitability for aromatic radiofluorination with the 110-min half-life radioisotope fluorine-18 and their applicability to the preparation of oxygen-substituted fluoroaromatics, such as are found in estrogens. Aromatic triazenes, which are stable, readily purified, and easily produced from the corresponding aromatic amines, undergo fluorine substitution when decomposed by acid in the presence of fluoride ion. This method tolerates certain ring substituents, but not *o*-alkoxy or sulfonyloxy groups, and in some cases major byproducts resulting from intramolecular reaction of the diazonium ion or aryl cation are obtained. The decomposition of aryl azides in acidic fluorine-containing medium produces *p*-fluoroanilines which can be reductively deaminated. This reaction also fails with oxygen substituents ortho to the azide, and also with larger *o*-alkyl groups. Both of these methods are potentially adaptable to labeling with fluorine-18, and since, unlike the Schiemann reaction, they do not involve fluorine-containing precursors, they should be capable of producing radiofluorinated products with high specific activity in a no-carrier-added synthesis.

Experimental Section

General Procedures. All starting anilines were obtained frm Aldrich except the following: 48% aqueous hydrogen fluoride was purchased from J. T. Baker Chemical Co.; 2-aminophenyl methanesulfonate was prepared from 2-nitrophenol by methanesulfonation of the phenol and reduction of the nitro group with stannous chloride in hydrochloric acid. 4-Aminoestrone 3-methyl ether was prepared from estrone by a nitration, methylation, and reduction sequence, similar to one we have published earlier.[26] All solvents are analytical reagent grade except those used in fluorinations, which were further purified by distillation.

Transfer of anhydrous hydrogen fluoride gas was accomplished by using a Toho Kasei Model I HF-Reaction Apparatus constructed primarily of Diaflon (polytrifluoromonochloroethylene). The apparatus was purchased from Peninsula Laboratories, Inc., San Carlos, CA. Isolation of reaction products was also done in apparatus made of polyethylene.

Caution: Anhydrous hydrogen fluoride is an extremely toxic and hazardous substance that must be handled with great care, using appropriate equipment deployed in efficient fume hoods, and with adequate protection of personnel against inhalation or skin contact. Aqueous hydrogen fluoride and HF–pyridine are also very hazardous. Information on proper safety precautions is available.[27]

Proton magnetic resonance spectra were recorded on a Varian Associates EM-390 or HR 220 spectrometer and chemical shifts are reported in parts per million downfield from an internal tetramethylsilane signal. Fluorine-19 nuclear magnetic resonance spectra were recorded on an EM-390 spectrometer and chemical shifts were reported in parts per million downfield from an internal Freon signal. Infrared spectra were obtained on a Perkin-Elmer 173B or Beckman IR-12 spectrometer.

Elemental analyses were done by the University of Illinois microanalytical laboratory. Melting points were taken on a Fisher-Johns melting-point apparatus and are corrected. Chromatography columns were packed with Brinkmann 0.05–0.3-mm silica gel. Low- and high-resolution electron-impact mass spectra were obtained on Varian Models CH-5 and 731 spectrometers in the Mass Spectrometry Laboratory, School of Chemical Sciences, University of Illinois, supported in part by a grant from the National Institute of General Medical Sciences (GM 27029).

1-(4-Methylphenyl)-3,3-(1,5-pentanediyl)triazene (1). *p*-Toluidine (15 g, 0.15 mol) was mixed with 100 mL of water and cooled in an ice bath, and hydrochloric acid (30 g, 37%, 0.3 mol) in 200 mL of water was added with stirring at 0 °C. After 10 min, sodium nitrite (9.66 g, 0.15 mol) in 60 mL of water was added slowly, keeping the temperature below 5 °C. The mixture slowly turned yellow, and after another 30 min, piperidine (60 g, 0.69 mol) in 50 mL of water was added. A pale yellow precipitate was collected by filtration, washed, and dried under vacuum overnight: yield 27.5 g (97%); mp 42–44 °C; ^{1}H NMR ($CDCl_3$) 1.6 (br s, 6 H, CH_2), 2.3 (s, 3 H, Ar CH_3), 3.82 (br s, 4 H, NCH_2), 7.2 (d, J = 9 Hz, 4 H, Ar H).

Anal. Calcd for $C_{12}H_{17}N_3$: C, 70.94; H, 8.37; N, 20.7. Found: C, 70.37; H, 8.47; N, 20.52.

1-(4-Butylphenyl)-3,3-(1,5-pentanediyl)triazene (2). 4-Butylaniline was treated with hydrochloric acid and sodium nitrite under similar conditions as in the preparation of 1. Upon addition of piperidine, a red oil that formed was extracted into ether. The extract was washed repeatedly with water, dried over $MgSO_4$, and then concentrated at reduced pressure to a red oil that was further dried under vacuum: yield 95%; ^{1}H NMR ($CDCl_3$) δ 0.9 (t, 3 H, CH_3), 1.5 (m, 4 H, butyl CH_2), 1.55 (br s, 6 H, piperidine CH_2), 2.58 (t, 2 H, Ar CH_2), 3.6 (br s, 4 H, NCH_2), 7.25 (d, J = 9 Hz, 4 H, Ar H).

Anal. Calcd for $C_{15}H_{23}N_2$: C, 74.47; H, 9.39; N, 17.14. Found: C, 74.07; H, 9.36; N, 17.24.

1-(4-Isopropylphenyl)-3,3-(1,5-pentanediyl)triazene (3). The general procedure used in the preparation of 2 was followed, but anhydrous tetrahydrofuran was also added as cosolvent in the diazotization. 4-Isopropylaniline gave the desired product (3) as a dark red oil: yield 90%; ^{1}H NMR ($CDCl_3$) δ 1.2 (d, 6 H, CH_3), 1.65 (br s, 6 H, CH_2), 2.85 (m, 1 H, CH), 3.65 (br s, 4 H, NCH_2), 7.2 (dd, 4 H, Ar H).

Anal. Calcd for $C_{14}H_{21}N_3$: C, 72.73; H, 9.09; N, 18.18. Found: C, 72.77; H, 9.15; N, 18.01.

1-(3-Methoxyphenyl)-3,3-(1,5-pentanediyl)triazene (4). The general procedure used for the preparation of 2 was followed. *m*-Anisidine gave the desired product (4) as a dark red oil: yield 90%; ^{1}H NMR ($CDCl_3$) δ 1.65 (br s, 6 H, CH_2), 3.75 (br s, 4 H, NCH_2), 3.80 (s, 3 H, OCH_3), 6.6–7.3 (m, 4 H, Ar H).

Anal. Calcd for $C_{12}H_{17}N_3O$: C, 65.75; H, 7.76; N, 19.17. Found: C, 66.08; H, 7.78; N, 18.76.

1-(2-Methoxy-5-phenylphenyl)-3,3-(1,5-pentanediyl)triazene (5). The procedure used for the preparation of 1 was followed. 2-Methoxy-5-phenylaniline gave a quantitative yield of the desired triazene (5) as a pale yellow solid: mp 129–131 °C; ^{1}H NMR ($CDCl_3$) δ 1.65 (br s, 6 H, CH_2), 3.75 (br s, 4 H, NCH_2), 3.85 (s, 3 H, OCH_3), 6.9–7.6 (m, 9 H, Ar H).

Anal. Calcd for $C_{18}H_{22}N_3O$: C, 72.97; H, 7.43; N, 14.19. Found: C, 73.71; H, 7.31; N, 14.79.

1-(2-(Methanesulfonyloxy)phenyl)-3,3-(1,5-pentanediyl)-

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(27) (a) Pieters, H. A. "Safety in the Chemical Laboratory"; Butterworths Scientific Publications: London, 1951; p 56. (b) Manufacturing Chemists Assoc. "Guide for Safety in the Chemical Laboratory"; D. Van Nostrand: New York, 1954. (c) Reinhardt, C. F.; Hume, W. G.; Linch, A. L.; Wetherhold, J. M. *Am. Ind. Hyg. Assoc. J.* **1966**, *27*, 166.

triazene (6). The procedure used for the preparation of 1 was followed. 2-(Methanesulfonyloxy)aniline gave a quantitative yield of the desired triazene (6) as a brown solid: mp 82–84 °C; ^{1}H NMR ($CDCl_3$) δ 1.70 (br s, 6 H, CH_2), 3.08 (s, 3 H, CH_3), 3.75 (br s, 4 H, NCH_2), 7.0–7.5 (m, 4 H, Ar H).

Anal. Calcd for $C_{12}H_{17}N_3SO_3$: C, 50.88; H, 6.01; N, 14.84. Found: C, 50.74; H, 6.06; N, 14.69.

2′-Piperidinoazohexestrol Dimethyl Ether (9). 2′-Aminohexestrol dimethyl ether (**14a**, 1.4 g, 4.47 mmol) was dissolved in 40 mL of a 1:1 acetone–water mixture and diazotized by treatment with concentrated hydrochloric acid (2 mL) and sodium nitrite (308 mg, 4.47 mmol) at 0 °C. The mixture was stirred for 30 min, and aqueous piperidine (3.8 g, 44.7 mmol) was added. After being stirred for another 30 min, the mixture was partitioned between ether and water, and the ether layer was washed twice with water, dried ($MgSO_4$), and concentrated in vacuo. Chromatography on silica gel (eluted with 1:2 ether–hexane) afforded the desired triazene (9) as a yellow oil (0.939 g, 51% yield) that was crystallized from petroleum ether and then from ethanol–water to give a pale yellow solid: mp 122–124 °C; ^{1}H NMR ($CDCl_3$) δ 0.58 (t, 6 H, CH_3), 1.35 (m, 4 H, CH_2), 1.75 (br s, 4 H, piperidino CH_2), 2.65 (m, 2 H, CH), 3.65 (br s, 4 H, NCH_2), 3.70 (s, 6 H, OCH_3), 6.4–7.1 (m, 7 H, Ar H); mass spectrum, m/e 409 (4, M^+), 260 (100), 149 (5).

Anal. Calcd for $C_{25}H_{35}N_3O_2$: C, 73.35; H, 8.56; N, 10.27. Found: C, 73.11, H, 8.72, N, 10.12.

4-(Dimethylamino)azoestrone 3-Methyl Ether (10). 4-Aminoestrone 3-methyl ether (244 mg, 0.816 mmol) was dissolved in 25 mL of dioxane, and 0.56 mL of concentrated hydrochloric acid in 10 mL of water was added. After the mixture was cooled to 0 °C, sodium nitrite (56.4 mg, 0.817 mmol) in 4 mL of water was added dropwise. After the mixture was stirred for 30 min, aqueous dimethylamine (40%, 0.96 mL, 8 mmol) was added at 0 °C. Water was added 20 min later, and the resulting pink precipitate was collected by filtration, washed, dried under vacuum, and recrystallized from ethanol/water to give 0.24 g (83%) of **10** as yellowish-orange crystals: mp 151–153 °C; ^{1}H NMR ($CDCl_3$) δ 0.90 (s, 3 H, CH_3), 1.5–2.85 (m, 15 H, CH_2 envelope), 3.4 (s, 6 H, NCH_3), 3.85 (s, 3 H, OCH_3), 7.05 (dd, 2 H, Ar H); mass spectrum, m/e 355 (M^+, 72), 311 (49), 283 (100).

Anal. Calcd for $C_{21}H_{29}N_3O_2$: C, 71.00; H, 8.17; N, 11.83. Found: C, 70.92; H, 8.19; N, 11.83.

***meso*-Hexestrol Dimethyl Ether (12).** Methyl iodide (25 g, 176 mmol) was added to a heterogeneous mixture of *meso*-hexestrol (11, 5 g, 18.5 mmol) and potassium carbonate (25 g, 181 mmol) in 100 mL of dimethylformamide, and the mixture was stirred overnight. Volatile material was evaporated under reduced pressure at 40 °C, and the residue was partitioned between water and ether. The ether layer was repeatedly washed with water, dried ($MgSO_4$), and evaporated to yield a white solid, which was recrystallized from ethanol to yield 5.4 g (97%) of *meso*-hexestrol dimethyl ether (12), mp 144–145 °C (lit.[28] 144–145 °C).

Bromination of Hexestrol Dimethyl Ether (12). 3′-Bromohexestrol Dimethyl Ether (13a). To a solution of hexestrol dimethyl ether (**12**, 4 g, 13.3 mmol) in 175 mL of carbon tetrachloride was added a few crystals of iodine, and the solution cooled (ice–water bath). With rapid stirring, a solution of bromine in carbon tetrachloride (13.3 mL of a 1 M solution, 1 equiv) was added over a 30-min period. When addition was complete, the brown solution was stirred for 30 min at 0–5 °C and the n poured into a dilute aqueous solution of sodium bisulfite. The organic layer was separated, washed with 5 N aqueous sodium hydroxide, dried ($MgSO_4$), and evaporated to give a colorless oil which gave a white solid (4.4 g, 87%) upon trituration with ethanol. Analysis by TLC and ^{1}H NMR indicated the product was approximately 80% of the desired monobromination product (**13a**) and small, equal amounts of hexestrol dimethyl ether (**12**) and the symmetrical dibromination product (**13b**).

Compound **13a** was also synthesized in a pure form by the methylation of 3′-bromohexestrol which in turn was prepared from the bromination ofhexestrol followed by separation by preparative TLC. Pure **13a** is a white solid: mp 108–109 °C; ^{1}H NMR (CCl_4) δ 0.46 (t, 6 H, 2 CH_2CH_3), 1.1–1.6 (m, 4 H, 2 CH_2CH_3), 2.24–2.48 (m, 2 H, 2 Ar CH), 3.71 (s, 3 H, $ArOCH_3$), 3.8 (s, 3 H, $ArOCH_3$), 6.63–6.95 (m, 6 H, Ar H), 7.2 (d, 1 H, Ar H ortho to Br); mass spectrum (10 eV), m/e 378 (1.61, M^+), 376 (1.69, M^+), 180 (2.7), 149 (100).

2′-Aminohexestrol Dimethyl Ether (14a). A solution of potassium amide in liquid ammonia was prepared by the following procedure. Ammonia (100 mL) was condensed into an oven-dried round-bottom flask outfitted with a dry ice condenser and magnetic stirrer. A small piece of potassium was added, and the bright blue solution stirred for 5 min. A trace amount (1 mg) of ferric nitrate was added; the blue color immediately disappeared and was replaced by a light brown color. The remainder of the potassium (500 mg) was then added in small pieces, and the solution stirred until the blue color became dull gray; some suspended solid material was also present. This preparation of potassium amide was then stirred an additional 15 min to ensure complete reaction of the metal with the solvent.

To the potassium amide preparation was added a solution of crude 3′-bromohexestrol dimethyl ether (mixture of **12**, **13a**, and **13b**; 1.2 g, 3.18 mmol) in 30 mL of tetrahydrofuran. The solution was stirred for 1.5 h, at which time the color had gradually changed to brown. Ammonium nitrate (1.0 g) was added; the condenser was removed, and the ammonia allowed to evaporate. The remaining solution of crude amine in tetrahydrofuran was diluted with 100 mL of water, and the products were extracted into ethyl acetate. The organic layer was washed with water, dried ($MgSO_4$), and evaporated under reduced pressure to yield 1.3 g of a dark brown oil. After purification by chromatography on silica gel (CH_2Cl_2) and recrystallization from ether/petroleum ether, 547 mg (55%) of amine **14a** was obtained as a white solid:[29] mp 119–120 °C; ^{1}H NMR (CCl_4) δ 0.56 (t, 3 H, CH_2CH_3), 0.6 (t, 3 H, CH_2CH_3), 1.5 (m, 4 H, CH_2), 2.65 (m, 2 H, CH), 3.55 (br s, 2 H, NH_2), 3.8 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 6.4–7.3 (m, 7 H, Ar H); IR (neat) 3300–3400 cm^{-1} (NH); mass spectrum (10 eV), m/e 313 (4.69, M^+), 298 (4.85), 164 (68), 149 (100).

Anal. Calcd for $C_{20}H_{27}H_1O_2$: mol wt 313.2035. Found: mol wt 313.2040.

General Procedures for Fluorination of Triazenes. Method A. Concentrated Hydrofluoric Acid. Concentrated hydrofluoric acid (49%; 1–10 equivs) was added slowly to the triazene neat or dissolved in benzene at room temperature. Vigorous evolution of gas was usually seen, accompanied by the darkening of the substrate. The mixture was stirred for 30 min and then warmed to 50 °C for 10 min. The mixture was then cooled, neutralized with aqueous sodium hydroxide, and partitioned between ether and water. The ether layer was washed with dilute hydrochloric acid and water and dried ($MgSO_4$). Removal of solvent leaves th fluorinated product as an oil which can be purified by distillation or chromatography.

Method B. Hydrogen Fluoride–Pyridine Complex. The triazene was dissolved in a minimum amount of benzene in a Diaflon (polytrifluoromonochloroethylene) vessel, and hydrogen fluoride–pyridine complex (1–10 equivs) was added slowly. After being stirred for 30 min at room temperature and 10 min at 50 °C, the product mixture was worked up according to method A.

Method C. Anhydrous Hydrogen Fluoride. The triazene was dissolved in a minimum amount of benzene (or other solvent) in a Diaflon vessel connected to the hydrogen fluoride manifold and frozen with liquid nitrogen. Anhydrous hydrogen fluoride (6 equivs) was distilled into another graduated vessel and then transferred by condensation into the vessel containing the solution of triazene. This vessel was warmed to room temperature, and the reaction mixture was then stirred for 30 min, neutralized, and worked up according to method A.

4-Fluorotoluene (From 1). 4-Fluorotoluene was prepared by fluorination of 1 using all the three procedures described.

Method A. After workup and isolation by distillation, 27% 4-fluorotoluene was obtained as a colorless liquid: bp 116–118 °C (lit.[30] bp 116 °C); ^{19}F NMR (CCl_4) 117.1 ppm (m); ^{1}H NMR (CCl_4) δ 2.2 (s, 3 H, CH_3), 6.9 (m, 4 H, Ar H). The product has a retention time identical with that of an authentic sample of

(28) Solmssen, U. V. *Chem. Rev.* **1945**, *37*, 481.

(29) The 55% yield of **14a** was based on the mixture of bromohexestrol methyl esters (**12**, **13a**, **13b**); when based on pure **13a**, the yield of **14a** is 69%.

(30) Prager, B.; Jacobson, P. *Beilstein, 4th ed.* **1922**, *5*, 290.

4-fluorotoluene (Aldrich) on GLC (OV-17 column, 6 ft).

Methods B and C. (See Table II.) The isolated products were identical with to the material produced by method A.

4-Fluorocumene (From 3). 4-Fluorocumene was prepared from **3** by using method B. After distillation, 22% 4-fluorocumene was obtained as a colorless liquid: bp 156–159 °C; ^{1}H NMR (CCl_4) δ 1.25 (d, 6 H, CH_3), 2.89 (m, 1 H, CH), 6.9–7.4 (m, 4 H, Ar H); ^{19}F NMR (CCl_4) 121.3 ppm (m); mass spectrum, *m/e* 138 (46, M^+), 123 (100), 120 (25), 105 (58), 103 (17).

Anal. Calcd for $C_9H_{11}F$: mol wt 138.0847. Found: mol wt 138.0846.

4-Butylfluorobenzene (From 2). 4-Butylfluorobenzene was prepared from **2** according to method A. Distillation under vacuum gave 16% 4-butylfluorobenzene (1 mmHg, 50 °C) as a colorless liquid: ^{1}H NMR ($CDCl_3$) 0.8 (t, 3 H, CH_3), 1.4 (m, 4 H, CH_2), 2.45 (m, 2 H, Ar CH_2), 6.8 (m, 4 H, Ar H); ^{19}F NMR (CCl_4) 117 ppm (m); mass spectrum, *m/e* 152 (76, M^+), 134 (51), 110 (25), 109 (100), 92 (62), 91 (34), 58 (21), 43 (25), 31 (15).

Anal. Calcd for $C_{10}H_{13}F$: mol wt 152.0999. Found: mol wt 152.1000.

3-Fluoroanisole (From 4). 3-Fluoroanisole was prepared from the fluorination of **4** according to the three procedures described (see Table I). All three methods gave similar yields (17–19%) of 3-fluoroanisole after purification by distillation: bp 160–162 °C; ^{1}H NMR (CCl_4) δ 3.85 (s, 3 H, OCH_3), 6.6–7.4 (m, 4 H, Ar H); ^{19}F NMR (ether) δ 111.3 ppm (m); mass spectrum, *m/e* 126 (100, M^+), 96 (35), 83 (4).

Anal. Calcd for C_7H_7FO: mol wt 126.0485. Found: mol wt. 126.0483.

2′-Fluorohexestrol Dimethyl Ether (15a). Triazene **9** was fluorinated according to method A. After product isolation and evaporation of solvent, a pale yellow oil was obtained which was subjected to preparative TLC on silica gel. Development with 1:2 chloroform–carbon tetrachloride gave 2′-fluorohexestrol dimethyl ether (**15a**, 41%) as the most mobile band. This material was recrystallized from ether (trace)/hexane to give analytically pure white crystals: mp 122–124 °C; ^{1}H NMR ($CDCl_3$) δ 0.6 (t, 6 H, CH_3), 1.45 (m, 4 H, CH_2), 2.75 (m, 2 H, CH), 3.90 (s, 6 H, OCH_3), 6.8–7.4 (m, 7 H, Ar H); ^{19}F NMR ($CDCl_3$) δ 119.7 (m); mass spectrum, *m/e* 316 (2, M^+), 167 (20), 149 (100), 139 (13), 121 (23).

Anal. Calcd for $C_{20}H_{25}O_2F$: C, 75.95; H, 7.91. Found: C, 75.67; H, 8.28.

2′-Fluorohexestrol (15b). 2′-Fluorohexestrol dimethyl ether (21 mg, 0.066 mmol, **15a**) was dissolved in dry chloroform as 2 mmol of boron tribromide in dry chloroform was added. After refluxing for 20 min, the reaction mixture was cooled to −78 °C and quenched with methanol. The product was partitioned between ethyl acetate and water. The organic layer was washed with water and dried ($MgSO_4$) and ethyl acetate was evaporated to give a colorless oil which was subjected to preparative TLC. Development with 33% ether/hexane furnished 19 mg (99%) of a white solid as the only UV-active mobile band, which was further purified by recrystallization from ethanol/water to give 16 mg (83%): ^{1}H NMR (acetone-d_6) δ 0.49 (t, 6 H, CH_3), 1.35 (m, 4 H, CH_2), 2.75 (m, 2 H, CH), 6.6–7.3 (m, 7 H, Ar H), 8.35 (br s, 2 H, OH); ^{19}F NMR (acetone-d_6) 120.4 ppm (m); mass spectrum, *m/e* 288 (3, M^+), 153 (5), 135 (45), 120 (33), 118 (95), 116 (100).

Anal. Calcd for $C_{18}H_{21}O_2F$: C, 74.97; H, 7.34; mol wt 288.1522. Found: C, 74.49; H, 7.64; mol wt 288.1519.

3,6-Dimethoxy-9,10-diethyl-9,10-dihydrophenanthrene (16) and 3,6-Dimethoxy-9,10-diethylphenanthrene (17). The dihydrophenanthrene (**16**) was isolated in 45–50% yield as a byproduct in the synthesis of 2-fluorohexestrol dimethyl ether (**15a**) described above. It was obtained as a colorless oil, migrating as the second most mobile component on silica gel preparative TLC: ^{1}H NMR ($CDCl_3$, sealed tube, 99 °C) δ 0.95 (t, 6 H, CH_3), 1.44 (m, 4 H, CH_2), 2.64 (m, 2 H, CH), 3.80 (s, 6 H, OCH_3), 6.7–7.2 (m, 6 H, Ar H); mass spectrum, *m/e* 296 (78, M^+), 267 (100), 238 (9), 147 (11), 73 (11).

Oxidation of **16** with dichlorodicyanoquinone in benzene gave 54% 3,6-dimethoxy-9,10-diethylphenathrene (**17**) as a white solid: ^{1}H NMR ($CDCl_3$) δ 1.2 (t, 6 H, CH_3), 2.95 (q, 4 H, CH_2), 3.75 (s, 6 H, OCH_3), 6.8–7.7 (m, 6 H, Ar H); mass spectrum, *m/e* 294 (100, M^+), 279 (35), 264 (7). This compound also has a melting point (95–97 °C) and UV spectrum identical with those of reported for 3,6-dimethoxy-9,10-diethylphenathrene.[13b]

Attempted Fluorination of 4-(Dimethylamino)azoestrone 3-Methyl Ether (10). 4-(Dimethylamino)azoestrone 3-methyl ether (**10**) was treated with HF/pyridine according to method B. After the reaction, water was added to precipitate a pinkish-white solid, which was subjected to preparative TLC on silica gel. Development with 10% ethyl acetate in benzene gave two UV-active bands. The uppermost band was identified by ^{1}H NMR and mass spectroscopy to be strone 3-methyl ether. The second UV-active band was isolated as a pinkish-white solid that was identified as 4,6-diazaethenoestrone 3-methyl ether (**19**): ^{1}H NMR (Me_2SO-d_6, 220 Mz) δ 0.82 (s, 3 H, CH_3), 1.48–2.68 (m, 13 H, methylene envelope), 3.00 (dd, 1 H, methione H at 6 position), 3.88 (s, 3 H, OCH_3), 6.7 (s, 2 H, Ar H); mass spectrum, *m/e* 310 (M^+, 100), 185 (14), 28 (7); IR (KBr) 1740 (C=O), 1545 cm^{-1} (N=N); UV (EtOH) λ_{max} 306 nm (ϵ 9610), 294 (11 367), 264 (10 953), 256 (11 263).

Anal. Calcd for $C_{19}H_{22}O_2N_2$: C, 73.5; H, 7.10; N, 9.03. Found: C, 72.38; H, 7.09; N, 9.14.

3-Methoxy-4-fluoroaniline (22). *m*-Anisidine (10 g, 81.2 mmol) was dissolved in 100 mL of methylene chloride and 100 mL of hexane. Hydrochloric acid (100 mL, 10%) was added, and the mixture was cooled to 5 °C. Sodium nitrite (6.16 g, 89.3 mmol) was dissolved in 25 mL of water and was added dropwise to the solution. After the mixture was stirred for 20 min, sodium azide (52.78 g, 0.812 mol) in water was added to the solution slowly and with vigorous stirring, keeping the temperature below 5 °C. Vigorous gas evolution was evident during the addition. After 3 h, the methylene chloride layer was separated and dried over $MgSO_4$.

This solution of azide **21** was then added slowly to a Diaflon vessel containing anhydrous hydrogen fluoride (16.5 g, 812 mmol) at 5 °C. Vigorous gas evolution was evident, and the solution turned reddish black. After 1 h, aqueous sodium hydroxide was added slowly to neutralize the mixture. The product was extracted into ethyl acetate, which was washed twice with water and dried ($MgSO_4$). Evaporation of solvent left a black oil that was distilled under vacuum [bp 120 °C (3 mm)] to give 6.76 g (59%) of 3-methoxy-4-fluoroaniline (**22**) which solidified as a pale yellow solid on cooling: ^{1}H NMR ($CDCl_3$) δ 3.65 (s, 2 H, NH_2), 3.70 (s, 3 H, OCH_3), 6.0–7.0 (m, 3 H, Ar H); ^{19}F NMR ($CDCl_3$) 147.1 ppm (m).

2-Fluoroanisole (23). 3-Methoxy-4-fluoroaniline (**22**, 0.675 g, 4.78 mmol) was dissolved in 10 mL of THF and was added dropwise to a boiling solution of isoamyl nitrite (1.12 g, 9.56 mmol) in 15 mL of THF. The mixture was heated under reflux for 5 h. Removal of solvent by rotary evaporation left a brown oil which was partitioned between benzene and cold sulfuric acid. The benzene layer was washed repeatedly with brine and dried over $MgSO_4$. Removal of benzene by rotary evaporation left a pale yellow oil which was chromatographed on silica gel to give 350 mg of 2-fluoroanisole (**23**) as a colorless oil (58%): ^{1}H NMR (CCl_4) δ 3.92 (s, 1 H, OCH_3), 7.15 (m, Ar H); ^{19}F NMR (THF) 134.1 ppm (m); ^{19}F NMR (CCl_4) 132 ppm; mass spectrum, *m/e* 126 (M^+, 100), 111 (56), 83 (62).

Anal. Calcd for C_7H_7OF: mol wt 126.0481. Found: mol wt 126.0481.

2-Methyl-4-fluoro-5-methoxyaniline (26). 2-Methyl-5-methoxyaniline (**24**) was converted to 2-methyl-4-fluoro-5-methoxyaniline (**26**) according to the procedures used in the preparation of 3-methoxy-4-fluoroaniline (**23**). After isolation by vacuum distillation, the solid obtained was recrystallized from ether–hexane to give 41% 2-methyl-4-fluoro-5-methoxyaniline (**26**) as a white solid: ^{1}H NMR ($CDCl_3$) δ 2.1 (s, 3 H, CH_3), 3.5 (br s, 2 H, NH_2), 3.85 (s, 3 H, OCH_3), 6.25 (d, J = 6 Hz, 1 H, Ar H ortho to F), 6.75 (d, 12 Hz, 1 H, Ar H meta to F); ^{19}F NMR ($CDCl_3$) 147.3 ppm (dd, F–*o*-H, J = 9.5 Hz, F–*m*-H, J = 6.5 Hz).

2-Fluoro-4-methylanisole (27). The procedure used in the deamination of 3-methoxy-4-fluoroaniline (**22**, see above) was applied to 2-methyl-4-fluoro-5-methoxyaniline (**26**). After isolation and purification by chromatography, 2-fluoro-4-methylanisole (**27**) was obtained as a colorless oil in 60% yield: ^{1}H NMR (CCl_4) δ 2.2 (s, 3 H, CH_3), 3.85 (s, 3 H, OCH_3), 6.8–7.05 (m, 3 H, Ar H); ^{19}F NMR (CCl_4) 134 ppm (m); mass spectrum, *m/e* 140 (M^+, 100), 125 (68), 97 (35).

Anal. Calcd for C_8H_9OF: mol wt 140.0638. Found: mol wt 140.0637.

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Structure Elucidation with Lanthanide-Induced Shifts. 10. Generation of Atomic Coordinates: Empirical Force Field Calculations vs. Other Methods[1]

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Structure analysis by methods such as lanthanide-induced shifts requires a mathematical description of a molecular structure. The validity of the final results depends upon the particular model used to generate atomic coordinates for the proposed structure. We have evaluated several different models which have been employed by workers in the field of lanthanide shift reagents. Three of the models are based on X-ray crystallographic data, one utilizes standard bond lengths and bond angles, and a last model uses empirical force field calculations. The results clearly show that empirical force field calculations provide the most reliable model for molecular structure. The dangers of using other less accurate structural models are also demonstrated, since incorrect structures can fortuitously result in excellent statistical agreement with experimental data.

In the last 10 years lanthanide shift reagents (LSR's) have proved to be a valuable development in the use of NMR spectroscopy for organic structure determination.[2] While LSR's can be used qualitatively to simplify and interpret spectral patterns, more recent work has been directed at a quantitative comparison of experimental lanthanide-induced shifts (LIS) with values predicted via the pseudocontact equation[3] (eq 1 and Figure 1). The

$$\text{LIS} = k(3\cos^2\theta - 1)/r^3 \qquad (1)$$

predicted LIS for some proposed structure are compared with the experimental LIS, and a statistical comparison (usually with the crystallographic agreement factor)[4] is used to assess the validity of the proposed structure. We have found considerable success in applying this technique to the analysis of both nitriles[5] and ketones.[1,6] The prediction of induced shifts with eq 1 requires a mathematical description of the complex in terms of interatomic distances and angles. In this paper we present an evaluation of various models which have been used to calculate these geometric parameters. Our results demonstrate that calculation of substrate geometry by using empirical force field calculations affords the most accurate and reliable method available.

Caution must be exercised in the rigorous analysis of structures with LIS, since substantial errors may arise in both the determination of experimental LIS and in the calculation of predicted LIS. The difficulties in determining experimental LIS have been discussed at length,[7,8] and the importance of using bound shifts corresponding to the 1:1 complex[7] has also been emphasized.[5a,9] Questions regarding the validity of eq 1 for calculating predicted LIS have been evaluated elsewhere.[2,5a] A major problem still remains in the application of eq 1, however, and that is the determination of atomic coordinates for a proposed structure. Hinckley[10] has shown that errors in these co-

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