red 1-amino-6-nitronaphthalene, mp 167–170° (lit.[18] 172–173°). The amine was converted *via* the diazonium hexafluorophosphate, mp 134–135° dec, to 1-fluoro-6-nitronaphthalene, which after steam distillation crystallized from Skellysolve B in lemon yellow needles, mp 109–110.5°.

Anal. Calcd for $C_{10}H_6O_2NF$: C, 62.83; H, 3.16; N, 7.33. Found: C, 62.97; H, 3.12; N, 7.35.

2-Amino-5-fluoronaphthalene. Reduction of the nitro compound in the usual way gave 2-amino-5-fluoronaphthalene as a colorless oil, bp 95–96° (0.3–0.4 mm), $n^{25}D$ 1.6440, homogeneous to glpc.

Anal. Calcd for $C_{10}H_8NF$: mol wt, 161. Found: mol wt (mass spectroscopy), 161.

2-Acetamido-5-fluoronaphthalene. The acetyl derivative crystallized from aqueous ethanol (Norit) and then from Skellysolve B–ethyl acetate as a white powder, mp 135.5–137°.

Anal. Calcd for $C_{12}H_{10}ONF$: C, 70.92; H, 4.96; N, 6.89. Found: C, 70.86; H, 5.13; N, 6.88.

2-Cyano-5-fluoronaphthalene. Prepared from the corresponding amine in the usual manner and isolated by steam distillation, the amine crystallized from Skellysolve B (Norit) in needles, mp 102–103°.

Anal. Calcd for $C_{11}H_6NF$: C, 77.18; H, 3.53. Found: C, 77.04; H, 3.72.

2-Bromo-5-fluoronaphthalene. Prepared from the corresponding amine in the usual manner and purified by preparative glpc (SE on Chromosorb W), this formed a colorless oil, $n^{25}D$ 1.6300.

Anal. Calcd for $C_{10}H_6FBr$: mol wt, 225. Found: mol wt (mass spectroscopy), 224, 226.

6-Fluoro-1-naphthoic Acid. Ethyl 6-nitro-1-naphthoate, mp 109–110° (lit.[18] 111.5–112°), was reduced in the usual manner, and the amine was converted to the diazonium hexafluorophosphate, mp 110.5–111.5° dec. This salt was decomposed by heating alone, and the resulting residue was treated overnight with alcoholic potassium hydroxide. The solution was then diluted, filtered, and acidified, giving 6-fluoro-1-naphthoic acid which after sublimation at 200° (1 mm) crystallized from aqueous ethanol in needles, mp 238–240.5°.

Anal. Calcd for $C_{11}H_7O_2F$: C, 69.47; H, 3.68. Found: C, 69.26; H, 3.71.

2-Fluoro-8-nitronaphthalene. 2-Amino-8-nitronaphthalene[3] was converted to the diazonium hexafluorophosphate, mp 134–136° dec; this on decomposition in mineral oil at 150° gave 2-fluoro-8-nitronaphthalene which crystallized from hexane in yellow needles, mp 85–86.5°.

Anal. Calcd for $C_{10}H_6O_2NF$: C, 62.83; H, 3.16; N, 7.33. Found: C, 63.00; H, 3.27; N, 7.41.

Substituent Effects. IX.[1] ^1H and ^{19}F Nuclear Magnetic Resonance Spectra of 4-Substituted 3,5-Dimethylfluorobenzenes[2]

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Contribution from the Department of Chemistry, The University of Texas, Austin, Texas 78712. *Received August 15, 1966*

Abstract: ^{19}F chemical shifts are reported for a series of 4-substituted 3,5-dimethylfluorobenzenes (I); comparison of these values with ones for *para*-substituted fluorobenzenes show differences that can be attributed to steric hindrance of mesomerism. Combined with the arguments of part VII,[4] these results suggest that the π-inductive effect is not important, π polarization being mainly due to mesomeric interactions. The proton nmr spectra of I are also reported; it is pointed out that proton SCS values cannot be interpreted in terms of "normal" substituent theory, because of complications due to long-range magnetic interactions.

Previous papers[4–6] of this series have presented evidence suggesting that substituents influence the ^{19}F nmr chemical shifts of aryl fluorides in two main ways: first, by a direct electrostatic polarization of the C–F bond (field effect); secondly, by altering the π density at the carbon atom adjacent to fluorine. As one might expect on this basis, the field effect depends not only on the distance separating the substituent from fluorine, but also on its angular orientation; the factor determining the degree of polarization of the C–F bond is apparently the vector potential along its axis.

One point which still remains to be settled is the manner in which substituents can polarize the π system of an adjacent aromatic ring. Such a polarization could be produced either by a normal mesomeric interaction in cases where the substituent carries *para* or π electrons, or by a π-inductive effect; both these effects should lead to a qualitatively similar[7] π polarizations and it is therefore difficult to distinguish between them.

In part V,[6] an attempt was made to assess the importance of the π-inductive effect by studying the influence of CF_3, a powerful $+I$ substituent which cannot undergo normal mesomeric interactions; the results presented there seemed to suggest that the π-inductive effect is not important. The same conclusion follows from the success of the modified *FM* treatment of substituent effects in part VII,[4] where the π polarization was assumed to follow quantitatively the pattern calculated for a mesomeric effect.

However, neither of these arguments was conclusive, and we therefore decided to study the relative roles of the mesomeric and π-inductive effects by a more direct method. This can be done in the case of bulky substituents such as NO_2 or NMe_2 by introducing groups into the positions *ortho* to them; the resulting steric hindrance twists the substituent out of coplanarity with the ring and so interrupts conjugative interaction between the ring and the substituents. We have accordingly prepared a number of 4-substituted 3,5-

(1) Part VIII: W. Adcock and M. J. S. Dewar, *J. Am. Chem. Soc.*, 89, 386 (1967).

(2) This work was supported by a grant from The Robert A. Welch Foundation.

(3) On leave of absence from the Department of Chemistry, College of General Education, University of Tokyo, Komaba, Meguro, Tokyo, Japan.

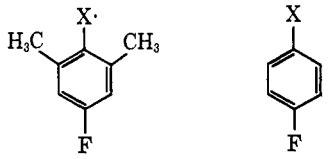
(4) W. Adcock and M. J. S. Dewar, *J. Am. Chem. Soc.*, 89, 379 (1967).

(5) M. J. S. Dewar and A. P. Marchand, *ibid.*, 88, 354 (1966).

(6) M. J. S. Dewar and A. P. Marchand, *ibid.*, 88, 3318 (1966).

(7) See M. J. S. Dewar, *ibid.*, 74, 3350 (1952).

dimethylfluorobenzenes (I) and measured their ^{19}F nmr spectra; we also measured their proton nmr spectra in the hope that these might throw further light on the nature of substituent effects.



I II

Results and Discussion

Tables I and II list ^{19}F substituent chemical shifts[4,8] (SCS) for the substituted 3,5-dimethylfluorobenzenes in carbon tetrachloride and in dimethylformamide, respectively; values[9] for the corresponding fluorobenzenes (II) are included for reference.

Table I. ^{19}F Substituent Chemical Shifts for I and II in CCl_4

Substituent	SCS I	SCS II[a]
NH_2	12.84	14.20
NMe_2	3.86	15.65
Cl	2.29	3.10
Br	1.83	2.50
I	1.45	1.55
COOMe	−2.47	−6.20
NO_2	−4.68	−9.55
CN	−8.87	−9.20

[a] R. W. Taft, S. Ehrenson, I. C. Lewis, and R. E. Glick, *J. Am. Chem. Soc.*, **81**, 5353 (1959).

Table II. ^{19}F Substituent Chemical Shifts for I and II in DMF

Substituent	SCS I	SCS II[a]
NH_2	13.12	14.05[b]
OH	10.88	12.95[c]
NMe_2	3.90	15.05[b]
NHAc	2.05	6.85
Cl	1.41	2.70
Br	1.32	2.00
I	1.24	1.35[b]
$CONH_2$	−0.13	−4.15[d]
COOH	−1.73	−6.05
COOMe	−2.80	−6.70[e]
NO_2	−5.51	−10.30
CN	−9.67	−9.80

[a] See Table I, footnote *a*. [b] SCS in methanol; SCS values in methanol and dimethylformamide are usually similar, except for substituents that act as donors to protic solvents. [c] Measured by us. [d] SCS in monomethylformamide. [e] Value for ethyl ester.

It will be noticed that the SCS for NO_2 and $COOCH_3$ are much less in the case of I than in II, whereas the two values for CN are almost identical; this would be expected if the differences were due to steric inhibition of mesomerism, CN being axially symmetric and so insensitive to steric effects. The differences between the two sets of SCS values can therefore be taken as measures of the effect of decreased mesomeric interactions in I between the substituent and the ring.

(8) The ^{19}F nmr spectra were measured by the procedure described in part VII.[4]

(9) R. W. Taft, E. Price, I. R. Fox, I. C. Lewis, K. K. Andersen, and G. T. Davis, *J. Am. Chem. Soc.*, **85**, 3146 (1963).

Many lines of evidence[10] indicate that the nitro group in compounds such as I is twisted right out of the plane of the ring, the angle of twist in nitromesitylene for example being[10a] 66°; resonance interactions between the ring and nitro should therefore be suppressed—and the same should be true for groups of similar geometry, *e.g.*, carboxyl. The differences between the SCS values for these substituents in I and II (see Tables I and II) should therefore be measures of the over-all contributions of mesomeric interactions in the unhindered fluorobenzenes (II).

Now the modified *FM* treatment in part VII[4] provided estimates of the relative contributions of the field effect, and of total π polarization, to the SCS for these substituents; these values, for SCS of II measured in DMF, are shown in Table III. If we accept these estimates, we can then use the values for I listed in Table I to calculate π-inductive contributions, for, as we have seen, the mesomeric contribution to π polarization should then be small. The values so calculated are shown in the last column of Table III.

Table III. Estimated Contributions of Various Effects to ^{19}F SCS in II

Substituent	Field effect	Total π polarization effect	π-Inductive effect
NO_2	−4.35	−5.95	−1.16
COOH	−1.32	−4.73	−0.41

It will be seen that the calculated π-inductive contribution is only a small fraction of the total π polarization; these results therefore support the earlier suggestion that the π-inductive effect is not important. Indeed, the π-inductive contributions shown in Table III are likely to be too large since they ignore possible mesomeric effects in I; these will be significant unless the substituent is held rigidly orthogonal to the ring, which appears[10a] not to be the case. Similar residual resonance seems to occur with dimethylamino; since the shift for I (X = NMe_2) is upfield (SCS negative), it seems clear that there is still a significant mesomeric interaction ($-M$) between the substituent and the ring, for the field effect of NMe_2 should lead to a downfield shift. Reversing the argument, one might expect there also to be a significant mesomeric contribution in the nitro and carboxyl derivatives (I; X = NO_2, COOH).

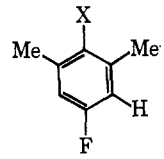
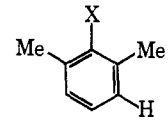
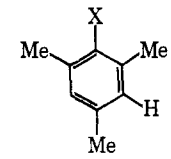
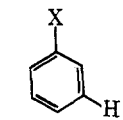
The results for the hydroxy and amino derivatives (I; X = OH, NH_2) are also interesting; here the SCS's are almost the same as in the corresponding benzene derivatives (II). Apparently two *o*-methyl groups are insufficient to push these groups out of conjugation with the ring, a conclusion which also seems to follow from other chemical and physical properties of compounds containing this structure.

We also measured the proton nmr spectra of the substituted fluoro-*m*-xylenes I, in the hope of obtaining additional information concerning the nature of substituent effects, the results[11] are shown in the first column of Table IV.

(10) (a) J. Trotter, *Can. J. Chem.*, 37, 1487 (1959); (b) B. M. Wepster in "Steric Effects in Conjugated Systems," G. H. Gray, Ed., Academic Press Inc., New York, N. Y., 1958, p 82; J. W. Smith, *ibid.*, p 141.

(11) The proton nmr spectra were measured in carbon tetrachloride at room temperature, using a Varian A60 spectrometer.

Table IV. Proton SCS in Various Substituted Benzenes

X	^{1}H SCS for indicated proton in 			
NH_2	0.06	0.070[a]	0.05;[b] 0.08[c]	0.203;[e] 0.237[f]
NMe_2	0.06	0.020[a]	0.02[d]	0.010[e]
OH	0.00	0.017[a]	0.02;[b] 0.06[c]	0.140[f]
Cl	−0.03	...	−0.10[b]	0.025;[e] 0.063[f]
Br	−0.13	−0.133[a]	−0.10;[b] −0.12[c]	0.085;[e] 0.125[f]
I	−0.09	−0.173[a]	−0.09[b,c]	0.250;[e] 0.257[f]
CO_2H	−0.20	−0.147[a]	...	0 −0.135[f]
CO_2Me	−0.10	...	...	0 −0.073[f]
CN	−0.20	−0.198[a]	...	0 −0.105[f]
NO_2	−0.24	−0.205[a]	−0.21;[c] −0.20[d]	−0.208;[e] −0.173[f]

[a] R. R. Fraser, *Can. J. Chem.*, **38**, 2226 (1960). [b] P. Diehl and S. Svegliano, *Helv. Chim. Acta*, **46**, 461 (1963). [c] W. A. Gibbons and V. M. S. Gil, *Mol. Phys.*, **9**, 167 (1965). [d] E. Bullock, *Can. J. Chem.*, **41**, 711 (1963). [e] H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 731 (1961). [f] F. Langenbucher, R. Mecke, and E. D. Schmidt, *Ann. Chem.*, **669**, 11 (1963).

Table IV also lists SCS values taken from the literature for protons *meta* to substituents in various series of benzene derivatives. It will be noticed that the values in the first three columns agree closely with one another; these refer to substituents hindered by pairs of *o*-methyl groups.

The last column of Table IV lists corresponding values for unhindered substituents; if proton SCS's could be interpreted in the kind of terms used for other substituent effects, or for ^{19}F SCS's (see part VII[4]), the differences between the hindered and unhindered SCS values should be a measure of the π polarization of *meta* positions by substituents, due to the mesomeric effect. However, it is immediately obvious that the differences cannot be interpreted in this way. Thus the largest differences appear in the case of bromine and iodine, where *o*-methyl groups should have no effect on conjugative interactions with an adjacent ring, while the difference for the equally unhinderable cyano group is greater than that for COOMe or NO_2. Moreover, the differences *increase* in the series Cl < Br < I, while conjugative interactions between halogen and the ring are known to *decrease* in this order.

SCS values for atoms *meta* to a substituent in benzene are known to show little correlation with the corresponding σ constants; this can be seen very clearly from the data for the halogens in Table IV, the σ constants for Cl, Br, and I being similar and *positive*, which should correspond to *negative* SCS values. Moreover, the sets of SCS values for different atoms (^{1}H, ^{19}F, ^{13}C) show little correlation with one another.[4] In part VII,[4] it was shown that the ^{19}F SCS values could be interpreted in terms of a general treatment of substituent effects if allowance is made for the anisotropic polarizability of the C–F bond; the arguments given above suggest that no such interpretation can be possible for the ^{1}H SCS values.

It is of course well recognized that proton chemical shifts are particularly hard to interpret, on account of their sensitivity to long-range magnetic interactions. Magnetic interactions with distant groups produce chemical shifts that are independent of the nucleus being studied; the relative importance of these disturbing effects is therefore greater, the smaller the shifts due to changes in the local electron distribution. Since the shifts produced by changes in the local electron distribution are about 20-fold greater for ^{19}F than ^{1}H, long-range magnetic interactions are correspondingly less important in the case of fluorine—and ^{19}F SCS can therefore be interpreted reasonably well in terms of "normal" substituent effect theory where long-range magnetic interactions are neglected. On this basis, one would not expect a similar treatment to be successful in the case of proton SCS.

It is true that fair correlations exist between the SCS for protons *para* to a substituent in benzene and the σ constant of the substituent;[12] however, the effects of substituents on the local electron distribution is greater for the *para* position than for the *meta* position, while the effect of long-range magnetic interactions should be correspondingly smaller. In this case the effects of local electron distribution, as determined by "normal" substituent interactions, may well dominate. In the case of *meta* protons, the long-range magnetic effects seem relatively much more important.

The anomalous SCS of protons *meta* to halogen seem to illustrate this point rather clearly. The positive SCS values for halogen can be attributed to magnetic shielding by the clouds of unshared electrons around the halogen atom, this increasing, as expected, with the size of the atom, *i.e.*, in the series Cl < Br < I. Long-range magnetic shielding by halogen is known to be an important factor in determining proton chemical shifts.[9,13] The large decrease in the SCS on introducing methyl groups *ortho* to halogen may then well be due to steric interactions between the substituent and the electronic atmosphere of the halogen atom.[14] A substituent *ortho* to a large atom such as bromine or iodine should tend to produce a "dent" in its electronic atmosphere; this will hinder the circulation of electrons about the axis of the C–Br or C–I bond, and so reduce the diamagnetic shielding effect due to this

(12) H. Spiesecke and W. G. Schneider, *J. Chem. Phys.*, **35**, 731 (1961).
(13) *Cf.* A. A. Bothner-By and C. Naar-Colin, *J. Am. Chem. Soc.*, **80**, 1728 (1958); G. S. Reddy and J. H. Goldstein, *J. Chem. Phys.*, **38**, 2736 (1963).
(14) *Cf.* M. J. S. Dewar, R. C. Fahey, and P. J. Grisdale, *Tetrahedron Letters*, 343 (1963).

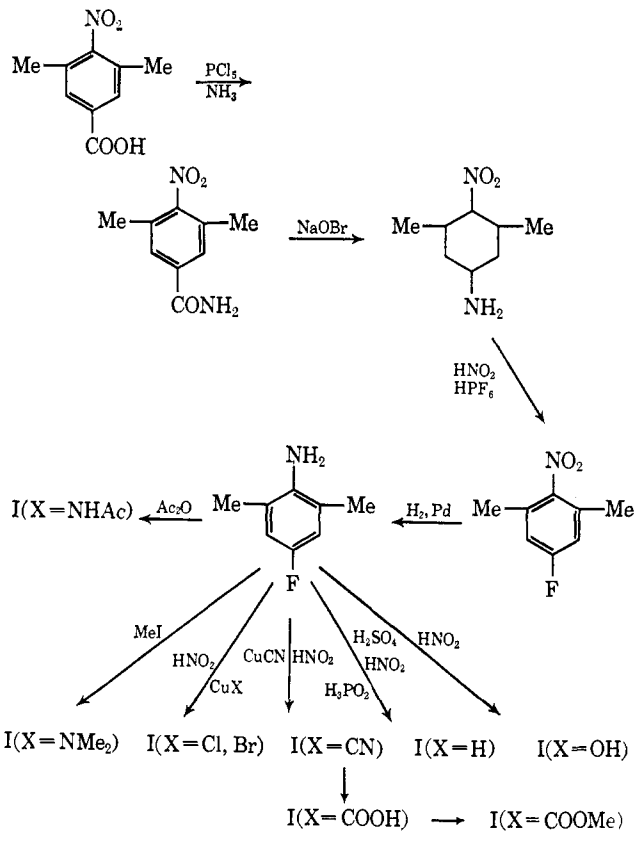
Table V. Proton SCS for Methyl Groups in I

X in I	NH_2	NMe_2	OH	Cl	Br
SCS	0.22	0.02	0.07	−0.03	−0.10
X in I	I	CO_2H	CO_2Me	CN	NO_2
SCS	−0.15	−0.20	0.00	−0.23	−0.07

circulation. Such an effect might be described as *steric inhibition of diamagnetism.*

In the case of unsymmetrical substituents such as NO_2, steric effects could influence the long-range magnetic interactions in two different ways. First, they may perturb direct magnetic interactions between the substituent and proton by altering their relative geometry, in view of the anisotropic magnetic susceptibility of such groups;[15] secondly, the normal aromatic ring current in benzene should be perturbed to a greater or less extent by conjugation with mesomeric substituents, and this perturbation will be decreased if the conjugation is sterically inhibited. At present it is unfortunately impossible to estimate the magnitude of these effects quantitatively; however, the available evidence suggests that they must lead to chemical shifts large enough to be very significant in proton nmr. For instance, Yamaguchi[15] and Bullock[16] have found that the SCS for protons in the methyl group *para* to nitro is unchanged if the nitro group is forced out of coplanarity with the ring by *ortho* substituents; since our results for I show that the effect of nitro on the local electron distribution at the *para* position is greatly reduced by such noncoplanarity, the results for *p*-nitrotoluene derivatives indicate that noncoplanarity must also lead to some opposite compensating effect. We also measured the SCS for methyl protons in I; these values (Table V) need no comment since they closely resemble those reported for other 6-nitro-*m*-xylene derivatives (*cf.* references in Table IV).

Chart I



Synthetic Procedures

The 4-substituted 3,5-dimethylfluorobenzenes (I) were prepared as indicated in Chart I.

Experimental Section

Proton nmr and infrared spectra of all the new compounds described here were consistent with the assumed structures.

3,5-Dimethyl-4-nitrobenzamide. A mixture of 3,5-dimethyl-4-nitrobenzoic acid[17] (8.2 g) and phosphorus pentachloride (9.4 g) was heated 30 min at 120–130°, then evaporated to dryness, and the residue was added to cold concentrated aqueous ammonia (100 ml), giving 3,5-dimethyl-4-nitrobenzamide (7.8 g, 95%), which after recrystallization from 50% ethanol had mp 169–170°.

Anal. Calcd for $C_9H_{10}N_2O_3$: N, 14.43. Found: N, 14.34.

3,5-Dimethyl-4-nitroaniline. A slurry of 3,5-dimethyl-4-nitrobenzamide (86 g) in cold aqueous sodium hydroxide (350 ml of 10%) was added to a solution of sodium hydroxide (85 g) and bromine (80 g) in water (350 ml) below 0°. The mixture was then heated slowly to 100° and kept there for 3 hr; after cooling, the 3,5-dimethyl-4-nitroaniline (64.5 g, 88%) was collected as a yellow powder, which crystallized from benzene–Skellysolve C (1:1) in yellow flakes, mp 132–134°.

Anal. Calcd for $C_8H_{10}N_2O_2$: C, 57.82; H, 6.07; N, 16.86. Found: C, 57.70; H, 6.16; N, 16.75.

3,5-Dimethyl-4-nitrofluorobenzene (I; X = NO_2). A mixture of 3,5-dimethyl-4-nitroaniline (44.2 g), concentrated hydrochloric acid (60 ml), and water (60 ml) was diazotized with sodium nitrite (26.0 g) in water (75 ml), and the diazonium hexafluorophosphate (75 g, mp 123–124° dec) precipitated by adding hexafluorophosphoric acid (100 ml). After washing and drying, the salt was added in portions to mineral oil (150 ml) at 120°. After 1 hr, I (X = NO_2) was isolated by steam distillation and extraction with ether, mp 56–57° after crystallization from Skellysolve B (27.6 g, 61%).

Anal. Calcd for $C_8H_8FNO_2$: C, 56.80; H, 4.77; F, 11.23; N, 8.28. Found: C, 56.81; H, 4.94; F, 11.05; N, 8.07.

2,6-Dimethyl-4-fluoroaniline (I; X = NH_2). 3,5-Dimethyl-4-fluoronitrobenzene (27.6 g) in ethanol (200 ml) was reduced catalytically over palladized charcoal (500 mg) with hydrogen (10 psi) overnight. I (X = NH_2) distilled at 60–62° (3 mm) as a colorless oil (22.8 g, 97%), $n^{25}D$ 1.5298.

Anal. Calcd for $C_8H_{10}FN$: C, 69.04; H, 7.24; F, 13.65; N, 10.06. Found: C, 68.93; H, 7.14; F, 13.74; N, 10.15.

4-Acetamido-2,6-dimethyl-4-fluorobenzene (I; X = NHAc). Acetylation of I (X = NH_2) with acetic anhydride in benzene gave I (X = NHAc), mp 167.5–168.5° after crystallization from aqueous ethanol (50%).

Anal. Calcd for $C_{10}H_{12}FNO$: C, 65.99; H, 7.09; F, 10.44; N, 7.70. Found: C, 66.18; H, 6.58; F, 10.56; N, 7.82.

2,6,N,N-Tetramethyl-4-fluoroaniline (I; X = NMe_2). A mixture of I (X = NH_2) (3.40 g), methyl iodide (14.1 g), and anhydrous sodium carbonate (8.4 g) was boiled under reflux for 4 days. Water was then added and I (X = NMe_2) was isolated with ether and distilled, bp 110–115° (90 mm), $n^{22}D$ 1.4916 (1.15 g, 28%).

Anal. Calcd for $C_{10}H_{14}FN$: C, 71.82; H, 8.44; F, 11.36; N, 8.38. Found: C, 71.96; H, 8.54; F, 11.40; N, 8.38.

4-Chloro-2,6-dimethylfluorobenzene (I; X = Cl). A solution of I (X = NH_2) (4.6 g) in concentrated hydrochloric acid (5 ml) and water (5 ml) was diazotized with sodium nitrite (2.8 g), and the solution was filtered into one of cuprous chloride (20 g) in concentrated hydrochloric acid (200 ml) at 60°. After 1 hr, I (X = Cl) was steam distilled, isolated with ether, and fractionated, bp 63–64° (10 mm), $n^{23}D$ 1.5044 (2.45 g, 47%).

Anal. Calcd for C_8H_8ClF: C, 60.58; H, 5.08; mol wt, 158.5. Found: C, 60.45; H, 4.74; mol wt (mass spectroscopy), 158, 160 (= ^{35}Cl, ^{37}Cl).

4-Bromo-2,6-dimethylfluorobenzene (I; X = Br). I (X = NH_2) (4.17 g) in 6 *N* sulfuric acid (25 ml) was diazotized with sodium nitrite (2.45 g), and the filtered solution was added to a boiling solution of cuprous bromide (7.2 g) in 48% hydrobromic acid (10

(15) *Cf.* I. Yamaguchi, *Mol. Phys.*, 6, 105 (1963).
(16) E. Bullock, *Can. J. Chem.*, 41, 711 (1963).
(17) J. P. Schaefer and T. J. Milaglia, *J. Am. Chem. Soc.*, 86, 64 (1964).

g) and water (20 ml) in a rapid current of steam. The distillate was extracted with ether and the extract distilled; I (X = Br) was collected at 45–47° (5 mm), $n^{25}D$ 1.5293 (3.45 g, 53%).

Anal. Calcd for C_8H_8BrF: C, 47.32; H, 3.97; Br, 39.35; F, 9.36. Found: C, 47.48; H, 4.05; Br, 39.28; F, 9.43.

3,5-Dimethyl-4-fluoroiodobenzene (I; X = I). Nitrosylsulfuric acid, prepared from concentrated sulfuric acid (12 ml) and sodium nitrite (30 g), was added to I (X = NH_2) (4.2 g) in concentrated sulfuric acid (15 ml) at 20°, and the mixture was poured into a solution of potassium iodide (20 g) in water (40 ml). After 30 min at 50°, I (X = I) was isolated with ether and distilled, bp 90° (0.5 mm).

Anal. Calcd for C_8H_8FI: C, 38.43; H, 3.22; F, 7.60; mol wt, 250. Found: C, 38.50; H, 3.11; F, 7.33; mol wt (mass spectroscopy), 250.

3,5-Dimethyl-4-fluorobenzonitrile (I; X = CN). Sodium nitrite (14 g) was added to a cold solution of I (X = NH_2) (22.8 g) in concentrated hydrochloric acid (40 ml) and water (40 ml). The solution was neutralized with sodium carbonate and then added dropwise to cuprous cyanide (18 g) dissolved in water (100 ml) containing potassium cyanide (18 g). The resulting mixture was warmed to 50° for 2 hr and extracted with ether; the extract was steam distilled. Ether extraction gave I (X = CN) (12.9 g, 55%), mp 97–97.5° after crystallization from methanol.

Anal. Calcd for C_9H_8FN: C, 72.47; H, 5.41; F, 12.74; N, 9.39. Found: C, 72.67; H, 5.41; F, 12.52; N, 9.20.

2,6-Dimethyl-4-fluorobenzoic Acid (I; X = COOH). A solution of I (X = CN) (4.5 g) in concentrated sulfuric acid (12.5 ml) was heated 5 hr at 80°; water (50 ml) was then added and the crystalline amide (4.0 g) collected, mp 140–147°. The amide (3.8 g) was heated 30 min at 150° with phosphoric acid (10 ml), then cooled, made alkaline with potassium hydroxide solution, filtered, and acidified. I (X = COOH) (2.25 g, 50%) was crystallized from benzene, mp 146.5–148°.

Methyl 2,6-Dimethyl-4-fluorobenzoate (I; X = COOMe). Methylation of I (X = COOH) with diazomethane in ether gave I (X = COOMe), bp 57–58° (4 mm), mp 29–30°.

Anal. Calcd for $C_{10}H_{11}FO_2$: C, 65.92; H, 6.09; F, 10.43; mol wt, 182. Found: C, 65.70; H, 5.96; F, 10.40; mol wt (mass spectroscopy), 182.

2,6-Dimethyl-4-fluorophenol (I; X = OH). Sodium nitrite (3.5 g) was added to a solution of I (X = NH_2) (5.6 g) in 3 *N* sulfuric acid (40 ml), and the resulting solution was filtered and added dropwise to boiling 70% sulfuric acid (200 ml) in a current of steam. Ether extraction of the distillate, followed by sublimation at 46–47° (0.1 mm), gave I (X = OH) (0.96 g), mp 72–76°, raised by recrystallization from Skellysolve B to 81–82°.

Anal. Calcd for C_8H_9FO: mol wt, 140. Found: mol wt (mass spectroscopy), 140.

Nucleosides. XXXVIII. Proton Magnetic Resonance Studies of Acetylated Nucleosides[1]

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Abstract: The proton magnetic resonance (nmr) spectra of 36 acetylated derivatives of 3′-aminohexosyl and pentosyl nucleosides were examined. The results show that chemical shifts of acetyl signals are unreliable for determining configuration of the sugar moiety. The effect of conformation and neighboring anisotropy on the acetyl chemical shifts was studied. Removal of the anisotropy of the 5,6 double bond of the aglycon by hydrogenation produced an effect on specific signals which, together with evidence from partially acetylated compounds, enabled individual resonances to be assigned. A general rule based on the effect of the anisotropy of the 5,6 double bond on the C_2′-acetoxy resonance is proposed which may have wide application in the assignment of anomeric configuration to pyrimidine nucleosides. Upon hydrogenation of the 5,6 double bond, a diamagnetic (upfield) shift of the $C_{2'}$-acetoxy resonance signal is observed in pyranosyl pyrimidine nucleosides having *cis*-$C_{1'}$–$C_{2'}$ substituents and pentofuranosyl pyrimidine nucleosides having a *trans*-$C_{1'}$–$C_{2'}$ relationship. Removal of the 5,6 double bond in pyranosyl pyrimidine nucleosides having a *trans*-$C_{1'}$–$C_{2'}$ relationship and pentofuranosyl pyrimidine nucleosides having a *cis*-$C_{1'}$–$C_{2'}$ relationship causes a paramagnetic (downfield) shift in the $C_{2'}$-acetoxy resonance signal. Several new acetylated nucleoside derivatives were prepared.

Previous reports from this laboratory[2–5] dealt with the synthesis and structure proof of several 3′-amino-3′-deoxy-β-D-*aldo*-hexopyranosyl nucleosides of purines and pyrimidines. Because of inconsistencies in the acetyl resonance signals in the nmr spectra of several of these nucleoside derivatives, we resorted to *chemical* studies to determine the configuration of the glycosyl moieties.

In 1958, Lemieux and co-workers[6] studied the nmr spectra of a number of acetylated pyranoses and inositols of known configuration and found that, as a rule, axial acetoxy groups absorb at lower field than equatorial acetoxy groups. These studies have been largely confirmed by other investigators.[7–10]

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