Fluorinated Azo Dyes.[1a] I. Synthesis and Spectral Properties of 3,5-Difluoro-4-N-methylaminoazobenzene, 2,6-Difluoroacetanilide, and Related Compounds

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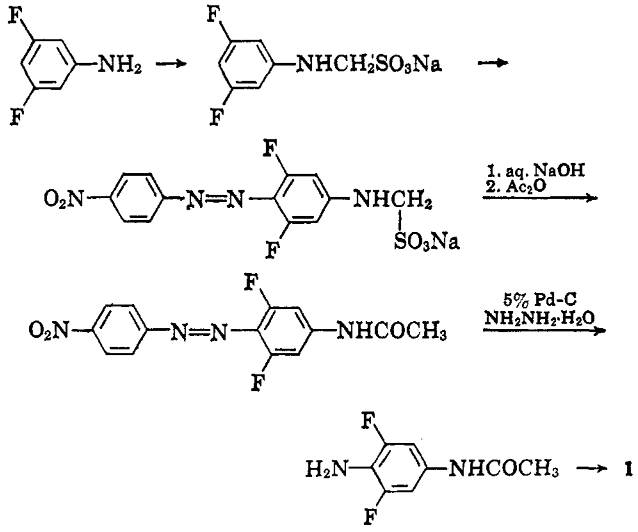
Synthesis of 3,5-difluoro-4-N-methylaminoazobenzene and related azo dyes is described. The named dye was made from 2,6-difluoro-1,4-phenylenediamine. A practical synthesis for the latter was devised by coupling sodium 3,5-difluoroanilinomethanesulfonate with *p*-nitrobenzenediazonium chloride and reductively splitting this, as the 4-acetyl derivative, with palladium on carbon and 85% hydrazine hydrate to give a high yield within a short time. Condensation of the difluorodiamine with nitrosobenzene took place exclusively at the 4-position. Lithium aluminum hydride reduction of 3,5-difluoro-4-(N-formyl)aminoazobenzene gave an unexpectedly poor yield of N-monomethylated dye; reaction with methyl iodide and alkali proved much superior. Synthesis of the new 2,6-difluoroacetanilide is also reported. Ultraviolet, visible, and infrared spectral data are presented with a discussion of steric effects and the marked photochromic properties of these dyes.

Systematic study of the carcinogenicity of various ring-substituted derivatives of 4-dimethylaminoazobenzene (DAB) has led to considerable insight into structure–activity relations. This knowledge has been most significantly built up by Drs. J. A. and E. C. Miller, McArdle Laboratory, University of Wisconsin, who have summarized much of what is known about many of these compounds,[2] particularly a series of DAB derivatives substituted with one or more fluorine atoms.[3] In general, an open 2-position [*ortho* to the azo linkage, *meta* to the $-N(CH_3)_2$ group] has seemed to be required for activity. However, only one of the positions (3 and 5) *ortho* to the amine group was blocked in any of the tested compounds and there is still a question as to whether an open 3- (or 5-) position is required for carcinogenicity. Accordingly, we have undertaken the synthesis of some further compounds. This report deals with the chemistry of the dye named in the title (3,5-difluoro-MAB) and related substances. It was felt, since for most dyes of this general structure N-monomethyl derivatives are carcinogenically as potent as the N-dimethyl dyes,[4] that the monomethylated-3,5-difluoro dye would offer the best chance to realize planarity and, therefore, a valid test of this compound blocked in both positions *ortho* to the amine function.

A key intermediate, 2,6-difluoro-1,4-phenylenediamine (1), has been isolated in a related synthesis as the N,N′-diacetyl derivative,[5] and its structure confirmed. Synthesis of 1 was accomplished in this study beginning with sodium 3,5-difluoroanilinomethanesulfonate which was coupled with *p*-nitrobenzenediazonium chloride. The resulting dye was hydrolyzed to the free amine and this was acetylated to facilitate separation of the two phenylene diamines after reductive splitting of the azo group. The reduction, in 77% yield, with preservation of the acetamido group, was accomplished in refluxing ethanol with 85% hydrazine hydrate and palladium on carbon as catalyst. This method appears to be new for reductive splitting of the azo group and is rapid and convenient. Hydrolysis gave 1, as shown in Chart I, in 45–47% over-all yields based on 3,5-difluoroaniline. Preparation of the latter from 2,4-difluoroaniline was done essentially as described[6]; however, the deamination step was modified by substituting an ether extraction for the steam-distillation step with improvement of over-all yields.

CHART I



Sulfomethylation of 3,5-difluoroaniline proved more difficult than is usual for this type of reaction. However, with excess reagents and heating for a relatively long time, yields are almost quantitative.

p-Nitrobenzenediazonium chloride couples as shown in Chart I, since the difluorophenylenediamine, m.p. 91–92°, obtained upon reduction was shown to be different from the only possible isomer.[2]

Chart II shows the steps leading from 1 to 3,5-difluoro-MAB (named in the title). The condensation with nitrosobenzene is smooth and in good yield (75%)

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(2) J. A. Miller, E. C. Miller, and G. C. Finger, *Cancer Res.*, **17**, 387 (1957).

(3) Use of the fluorine atom as a probe for finding active sites in carcinogens has been used in other series of compounds: see E. C. Miller, T. L. Fletcher, A. Margreth, and J. A. Miller, *ibid.*, **22**, 1002 (1962).

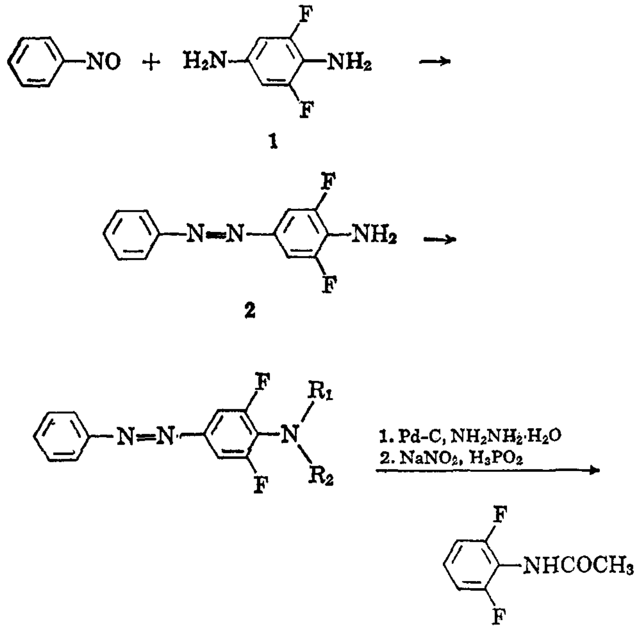
(4) The primary amines are, in general, much less carcinogenic, but an exception to this is found with 3-methoxy-4-aminoazobenzene which is a very weak liver carcinogen but is active toward sites unaffected by DAB derivatives having other substituents: J. A. Miller and E. C. Miller, *ibid.*, **21**, 1068 (1961). These authors suggest that the 3-methoxy dye may constitute a link between the aromatic amines and the azo dyes and thus show that the latter are in the same general class of carcinogens.

(5) This diamine was required[2] for structure proof of 2,6-difluoro-4-dimethylaniline, a component of 2,6-difluoro-DAB.

(6) G. C. Finger, F. H. Reed, and J. L. Finnerty, *J. Am. Chem. Soc.* **73**, 153 (1951).

with no other product being detected. The structure of 2 was confirmed by deamination which gave 3,5-difluoroazobenzene. This was also obtained, in only moderate yield, from a condensation between nitrosobenzene and 3,5-difluoroaniline,[7] a lethargic reaction which was not improved by raising the temperature.

CHART II



a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = R_2 = CH_3$
c, $R_1 = CHO$; $R_2 = CH_3$
d, $R_1 = COCH_3$; $R_2 = H$

Mono-N-methylated 2 was made in two ways from the N-formyl derivative: by lithium aluminum hydride (which gave unexpectedly low[8] yields, apparently because of the proximity of the fluorine atoms); and by methylation with methyl iodide in alkali,[9] followed by alkaline hydrolysis of the formyl group (76% based on the formamide).

Di-N-methylation of 2 was accomplished in moderate yield with methyl iodide and trimethyl phosphate.[10] Attempted reduction of the N-methylformamido dye with lithium aluminum hydride gave a mixture of N-monomethyl and N-dimethyl derivatives.

Synthesis of the new compound, 2,6-difluoroacetanilide, starting with 2 is described below. Acetylation and reductive splitting (which was complete in less than 5 min.) by the method just described followed by deamination gave a yield of 50% based on 2.

The absorption spectra of 4-amino-3,5-difluoroazobenzene and its N-monomethyl and N-dimethyl derivatives were run in alcohol and in acidic alcohol. In general, the resulting curves are similar to those reported earlier for various N- and ring-substituted derivatives of 4-aminoazobenzene.[11–13] As noted[14] for dyes of this type in acidic ethanol, there is a reciprocal relationship (indicating tautomeric forms) between the K′ and Q[13,15] (designated B and A in ref. 14) bands, which are located at 320–330 and 520–540 mμ, respectively, and which are due, respectively, to protonation of the amino group and to protonation of the β-nitrogen atom of the azo group. As seen in Table I, the data for the primary amine (3,5-difluoro-4-aminoazobenzene) shows that the equilibrium heavily favors the azonium form. In contrast, 3,5-difluoro-DAB, with considerable steric hindrance, has almost no absorption above 440 mμ and must be almost completely in the ammonium form. The monomethylated dye is intermediate with evidence of some hindrance; perhaps N—H···F bonding is sufficiently strong to allow planarity in spite of the bulk of one N-methyl group. The nitrogen is sufficiently basic to allow a moderate degree of protonation in 4 *N* acid.

All three dyes are markedly photochromic[16] (phototropic) in neutral ethanol. Table I gives maxima both for the relaxed (*trans*) state, after the solutions had been kept in the dark until no further increase in the density of maxima was observed, and for the illuminated (*cis*) state. The latter solutions had been illuminated until no further decrease in maxima was observed. Comparison of spectra which had been scanned rapidly with spectra for the same solutions run at ordinary speed showed that no significant change took place during the latter. At room temperature, it took approximately 2 hr. for the fully illuminated solution of 3,5-difluoro-MAB to return, in the dark, to the highest maxima. Of the three dyes, only the MAB showed a significant photochromic effect (albeit rather small) in acidic ethanol. Maxima were displaced a little hypsochromically by illumination. This was most noticeable with the N-monomethylated dye.

Although ethanol and other hydroxylic solvents are reported to promote an increased rate of *cis–trans* isomerism, so much so that many *p*-aminoazo compounds have not been observed to be photochromic in such media,[17] the relatively slow tautomerization of these fluorinated dyes makes them particularly interesting to study.

Infrared data is given in Table II with tentative assignments based on our own work and references as cited. The band near 927 cm.⁻¹, assigned to the —C—N=N—C— skeleton, does not appear in the two substances which have a 4′-nitro substituent.

Experimental Section[18]

3,5-Difluoronitrobenzene.—This was prepared by Finger's method[6] from 2,4-difluoroaniline, through 2,4-difluoro-6-nitroaniline. The deamination procedure was modified at several points, especially because steam distillation of crude 3,5-difluoronitrobenzene gave very poor yields in our hands. To a nitrosylsulfuric acid solution (19 g. of sodium nitrite in 200 ml. of concentrated sulfuric acid), 43 g. of 2,4-difluoro-6-nitroaniline was added portionwise with mechanical stirring at 15–20°, and the resulting solution was not used directly but was kept in the refrigerator overnight. It was then diluted by slowly

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[7] Similar results will be reported shortly (T. L. Fletcher and N. Ishikawa) in the synthesis of 4-amino-3,5-dichloroazobenzene.

[8] See ref. 4.

[9] Suggested by J. A. Miller.

[10] H. L. Pan and T. L. Fletcher, *J. Org. Chem.*, **27**, 3639 (1962).

[11] J. A. Miller, R. W. Sapp, and E. C. Miller, *J. Am. Chem. Soc.*, **70**, 3458 (1948).

[12] G. Cilento, J. A. Miller, and E. C. Miller, *Acta, Unio Intern. Contra Cancrum*, **11**, 632 (1955).

[13] A. J. Ryan, *Tetrahedron*, **20**, 1547 (1964).

[14] G. Cilento, E. C. Miller, and J. A. Miller, *J. Am. Chem. Soc.*, **78**, 1718 (1956).

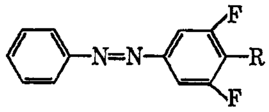
[15] G. E. Lewis, *Tetrahedron*, **10**, 129 (1960).

[16] R. Lovrien and J. C. B. Waddington, *J. Am. Chem. Soc.*, **86**, 2315 (1964).

[17] M. N. Inscoe, J. H. Gould, and W. R. Brode, *ibid.*, **81**, 5634 (1959).

[18] Melting points were determined on a Fisher-Johns block and are corrected to standards. Microanalyses were determined by Schwarzkopf Microanalytical Laboratories, Woodside, N. Y., and by A. Bernhardt, Mülheim (Ruhr), Germany.

TABLE I
ABSORPTION MAXIMA[a] FOR



Solvent	R	Band designation *b*	*c*	For solutions kept in the dark (*trans*), λ_{max}, mμ (log ϵ)	Solutions after illumination (*cis*), λ_{max}, mμ (log ϵ)
Ethanol	$\mathrm{N}{<}^{\mathrm{H}}_{\mathrm{H}}$			242 (4.06)	245 (4.08)
				377[d] (4.46[d])	366 4.20
	$\mathrm{N}{<}^{\mathrm{H}}_{\mathrm{CH_3}}$			244 (3.96)	251 (4.02)
				290 (shoulder) (3.63)	379 (4.15)
				397[d] (4.42)	
	$\mathrm{N}{<}^{\mathrm{CH_3}}_{\mathrm{CH_3}}$			235 (4.12)	239 (4.02)
				297 (4.00)	292 (3.76)
				387[d] (4.27[d])	381 (4.00)
Ethanol–hydrochloric acid	$\mathrm{N}{<}^{\mathrm{H}}_{\mathrm{H}}$		D	231 (3.74)	231 (3.77)
			C	262 (3.78)	262 (3.80)
		K′	B	324 (4.06)	324 (4.07)
		Q	A	517 (4.55)	517 (4.55)
	$\mathrm{N}{<}^{\mathrm{H}}_{\mathrm{CH_3}}$		D	229 (3.83)	228 (3.76)
		K′	B	322 (4.19)	322 (4.14)
		Q	A	538 (4.31)	539 (4.26)
	$\mathrm{N}{<}^{\mathrm{CH_3}}_{\mathrm{CH_3}}$		D	231 (3.95)	230 (3.94)
		K′	B	325 (4.38)	323 (4.37)
		?	?	425–450 (3.00)	440–450 (2.83)

[a] Ultraviolet and visible absorption spectra were obtained on a Beckman DK-1 automatic recording spectrophotometer in neutral absolute ethanol and in approximately 4 *N* hydrochloric acid in absolute ethanol. The latter solutions were conveniently made by adding 28.56 ml. of 7 *N* HCl to an alcoholic solution of the dye in a 50-ml. volumetric flask and then filling to the mark with alcohol. The concentration of the dye was 4×10^{-5} *M* in all cases. To obtain the highest possible maxima, solutions were kept in the dark overnight; λ_{max} values were checked several times in this way for reproducibility. Normal scanning speed (15 mμ/in. min.) for these spectra was altered for several runs to 150 mμ/in. min. in order to detect possible changes during the usual scan; there were no significant differences. Solutions were illuminated with 100-w. bulbs or in bright daylight until no further decreases in maxima were observed. [b] See ref. 12 and 13. [c] See ref. 15. [d] The corresponding data for the unfluorinated dyes are for $-NH_2$, λ_{max} 390 mμ (log ϵ 4.40) [L. Pentimalli, *Ann. chim.* (Rome), **49**, 187 (1959); "Organic Electronic Spectral Data," Vol. 4, J. P. Phillips and F. C. Nachod, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 393]; for $-N(CH_3)_2$, λ_{max} 410 mμ (log ϵ 4.44) [L. Pentimalli, *Tetrahedron*, **5**, 27 (1959); "Organic Electronic Spectra Data," Vol. 4, p. 519]. The contrast of the latter figures with the data for the fluorinated DAB is a measure of the hindrance to planar configuration caused by the two fluorine atoms *ortho* to the bulky dimethylamino group. The corresponding data for the unfluorinated MAB, λ_{max} 410 mμ (log ϵ 4.36) [G. M. Badger, R. G. Buttery, and G. E. Lewis, *J. Chem. Soc.*, 1888 (1954); "Organic Electronic Spectral Data," Vol. II, 1960] compared with those for 3,5-difluoro-MAB show significantly less steric effect.

adding 200 ml. of 85% phosphoric acid during 2 hr. keeping the temperature below 20°.

Into the rapidly stirred and cooled diazonium solution, 250 ml. of 45% hypophosphorous acid was added dropwise, while 18 g. of cuprous oxide was added in small portions keeping the temperature below 30°. There was vigorous evolution of nitrogen. After dilution with an equal volume of water, the oily product was extracted twice with 200-ml. portions of ether. The ether layer was filtered, washed with water, and dried ($MgSO_4$). The ether was then evaporated and the residue was distilled, b.p. 74–75° (15 mm.), 29 g. (73%), lit.[6] b.p. 78–79° (20 mm.). This was then reduced to 3,5-difluoroaniline.[6]

Sodium 3,5-Difluoroanilinomethanesulfonate.—To a solution of 19 g. of sodium bisulfite in 45 ml. of water, 15 g. of 38% formalin was added, and a mixture of this solution with 16 g. of 3,5-difluoroaniline was heated to reflux for 40 min. with vigorous stirring. Upon cooling to room temperature the clear solution deposited white crystals which were filtered off and washed with a small amount of ethanol, 29 g. (95%). An analytical sample was prepared by recrystallization from water.

Anal. Calcd. for $C_7H_6F_2NNaO_3S$: N, 5.71. Found: N, 5.46.

2,6-Difluoro-4′-nitro-4-aminoazobenzene.—A fine suspension of *p*-nitroaniline hydrochloride was prepared by pouring a warm solution of 28 g. (0.203 mole) of *p*-nitroaniline into a mixture of 60 ml. of concentrated hydrochloric acid and 60 ml. of water in 160 g. of ice with stirring. To this at 5° was added, all at once, a solution of 15.8 g. (0.23 mole) of sodium nitrite in 40 ml. of water, with vigorous stirring. To the resulting clear solution 64 g. of sodium acetate hydrate crystals were added.

The buffered diazonium solution was then added dropwise, over a period of 1 hr., to a mechanically stirred solution of 48.5 g. (0.198 mole) of sodium 3,5-difluoroanilinomethanesulfonate in 600 ml. of water kept at 5°. After stirring 2 hr. (at 5°) the reaction mixture was kept overnight in the refrigerator. The voluminous mass of very soluble dye was filtered and washed with a little saturated sodium chloride solution.

This filter cake was mixed with 1400 ml. of 5% aqueous sodium hydroxide, warming slowly to 95° with mechanical stirring. After 1 hr. at this temperature, the fine precipitate of hydrolyzed

TABLE II

INFRARED ABSORPTION DATA[a]

Azobenzene derivatives					
	ν_{max}, cm.$^{-1}$				
Substituent	—N=N—[b,c]	—C—N=N—C[d]	—C—N=[c]	Aryl C—F[e]	
4-Amino-2,6-difluoro-4′-nitro	1427		1145	1221	1042
4-Acetamido-2,6-difluoro-4′-nitro	1418		1156	1263	1058
4-Amino-3,5-difluoro	1427	921.7	1156	1321	1031
4-Formamido-3,5-difluoro	1425	929.4	1181	1333	1047
4-Acetamido-3,5-difluoro	1427	925.9	1181	1263	1049
4-N-Methylamino-3,5-difluoro	1427	925.9	1151	1289	1100
4-N-Methylformamido-3,5-difluoro	1425	925.9	1179	1340	1120
4-Dimethylamino-3,5-difluoro	1425	921.7	1172	1287	1095
3,5-Difluoro	1427	923.4	1140	1302	1120

1,3-Difluorobenzenes		
	ν_{max}, cm.$^{-1}$	
Substituent	Aryl C-F[e]	
4-Acetamido	1261	1142
4-Amino-5-nitro	1256	1131
4,5-Diamino	1189	1115
5-Amino(N-methylsulfonate, sodium salt)	1250	1121
2-Amino-5-acetamido	1279	1159
2,5-Diamino	1166	1145
2-Acetamido-5-amino	1267	1160
5-Acetamido	1276	1114

[a] Obtained on a Beckman IR-5 in disks (~1.5 mg. of substance/300 mg. of KBr). [b] See L. J. Bellamy, "The Infrared Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 272. [c] See P. Bassignaa and C. Cogrossi, *Tetrahedron*, **20**, 2361 (1964). [d] Reference *b*, p. 273. [e] Tentative assignments; see also M. J. Namkung and T. L. Fletcher, *J. Org. Chem.*, **26**, 2243 (1961); K. Suzuki, E. K. Weisburger, and J. H. Weisburger, *ibid.*, **24**, 1511 (1959).

dye was filtered off, washed, and dried. The crude orange-red powder, m.p. 278–280°, weighed 37.8 g. (69%). A small sample was recrystallized from toluene, giving red needles, m.p. 280–281° dec.

Anal. Calcd. for $C_{12}H_8F_2N_4O_2$: N, 20.14. Found: N, 20.13.

2,6-Difluoro-4′-nitro-4-acetamidoazobenzene.—A mixture of 21.7 g. of the foregoing water-washed azo compound, 400 ml. of glacial acetic acid, and 40 ml. of acetic anhydride was heated to boiling and refluxed for 1 hr. The solution was then treated with Darco and cooled, giving 17.5 g., m.p. 267–268°. A further 2.5 g., m.p. 265–266°, was obtained from the filtrate. Recrystallization from chlorobenzene gave red needles, m.p. 268–269°.

Anal. Calcd. for $C_{14}H_{10}F_2N_4O_3$: C, 52.50; H, 3.15; N, 17.50. Found: C, 52.76; H, 3.32; N, 17.38.

3,5-Difluoro-4-aminoacetanilide.—A mixture of 32.2 g. of 2,6-difluoro-4′-nitro-4-acetamidoazobenzene, 81 ml. of 85% hydrazine hydrate, 5% palladium-on-carbon catalyst, and 960 ml. of ethanol was gently warmed to boiling with mechanical stirring. After refluxing for 0.5 hr., the catalyst was filtered off and the filtrate was boiled down to small volume until crystals came out. After addition of 50 ml. of water, the crystals were filtered off and washed with cold water. This (18.4 g.) was recrystallized from dilute methanol giving tan needles, m.p. 155–156°, as a dihydrate.

Anal. Calcd. for $C_8H_8F_2N_2O \cdot 2H_2O$: C, 43.24; H, 5.47; F, 17.10; N, 12.60. Found: C, 43.50; H, 5.73; F, 17.30; N, 12.81.

2,6-Difluoro-1,4-phenylenediamine.—A mixture of 13 g. of 3,5-difluoro-4-aminoacetanilide, 25 ml. of concentrated hydrochloric acid, and 25 ml. of water was refluxed for 30 min., cooled, and made slightly basic with ammonium hydroxide. Tan crystals of the diamine were filtered off and washed with a small amount of cold water, 7.6 g. (90%), m.p. 91–92°.

Anal. Calcd. for $C_6H_6F_2N_2$: C, 50.00; H, 4.20; N, 19.44. Found: C, 50.10; H, 4.43; N, 19.30.

N,N′-Diacetyl-2,6-difluoro-1,4-phenylenediamine.—Into a warm suspension of 1.0 g. of 3,5-difluoro-4-aminoacetanilide in 10 ml. of benzene, 1.7 g. of acetic anhydride was added dropwise. After boiling a few minutes, white crystals came out. The mixture was cooled and filtered and the crystals were washed with benzene, giving 1.0 g. of diacetyl compound, m.p. 263–264°. Recrystallization from dilute acetic acid gave an analytical sample, m.p. 264–265°. (lit.[2] m.p. 250–252°).[19]

Anal. Calcd. for $C_{10}H_{10}F_2N_2O_2$: C, 52.63; H, 4.42; N, 12.28. Found: C, 52.33; H, 4.77; N, 12.30.

3,5-Difluoro-4-aminoazobenzene.—To 8.8 g. (0.061 mole) of 2,6-difluoro-1,4-phenylenediamine in 45 ml. of ethanol and 9 ml. of glacial acetic acid at room temperature, 7.0 g. (0.065 mole) of nitrosobenzene (Aldrich Chemical Co.) was added portionwise with stirring. Reaction occurred smoothly, the temperature rose to 35°, and yellow crystals came out. The mixture was kept at room temperature for 4 hr. and in a refrigerator overnight. The crystals were filtered off and washed with a small amount of ethanol giving 10.2 g., m.p. 127–128°. From the filtrate, after concentration *in vacuo* and recrystallization from ethanol, a further 0.6 g. of the same quality was obtained, making a total yield of 75%. Recrystallization from dilute ethanol gave orange rods, m.p. 128.5–129°.

Anal. Calcd. for $C_{12}H_9F_2N_3$: C, 61.80; H, 3.89; F, 16.29; N, 18.02. Found: C, 61.62; H, 3.98; F, 16.52; N, 18.12.

3,5-Difluoroazobenzene. A. Deamination.—A solution of 1 g. of 3,5-difluoro-4-aminoazobenzene in 10 ml. of glacial acetic acid was diazotized with 3.5 ml. of 10% solution of sodium nitrite in concentrated sulfuric acid. To this diazonium solution 20 ml. of 50% hypophosphorous acid was added and the mixture was was warmed gently. Nitrogen gas was evolved at about 40°, and gummy material came out which was separated by decantation. This residue was recrystallized from methanol (Darco) giving orange crystals melting at 50–55°. This was further purified by chromatography on alumina (benzene) followed by recrystallization from methanol, m.p. 58–59.5°. A mixture with the authentic sample obtained in B melted at 59–60°. The infrared spectra of this product and of the one obtained in B were identical.

B. Condensation of 3,5-Difluoroaniline with Nitrosobenzene.—To a solution of 1.29 g. (0.01 mole) of 3,5-difluoroaniline in 6.5 ml. of ethanol and 1.3 ml. of glacial acetic acid, 1.07 g. (0.01 mole) of nitrosobenzene was added, and the reaction mixture was allowed to stand at room temperature for 5 days. Orange-yellow needles (0.91 g.) were filtered off, m.p. 58–60°, and recrystallized from methanol giving m.p. 61–62°.

Anal. Calcd. for $C_{12}H_8F_2N_2$: C, 66.04; H, 3.70; F, 17.42; N, 12.84. Found: C, 65.90; H, 3.83; F, 17.28; N, 13.09.

3,5-Difluoro-4-formamidoazobenzene.—A mixture of 10.2 g. of 3,5-difluoro-4-aminoazobenzene and 50 ml. of formic acid (98–100%) was refluxed for 20 min., then 50 ml. of water was added. After cooling, the crystals were filtered off and washed giving 11.0 g., m.p. 158–160°. Recrystallization from 100 ml. of ethanol gave 10.0 g. of orange needles, m.p. 162–163°.

Anal. Calcd. for $C_{13}H_9F_2N_3O$: C, 59.77; H, 3.47; N, 16.09. Found: C, 59.57; H, 3.75; N, 16.30.

3,5-Difluoro-4-methylaminoazobenzene. A. Methylation with Methyl Iodide.—To a mixture of 7.8 g. (0.03 mole) of 3,5-difluoro-4-formamidoazobenzene and 70 ml. of ethanol was added a solution of 1.80 g. (0.032 mole) of potassium hydroxide in 3 ml. of water. To this solution, 4.7 g. (0.033 mole) of methyl iodide was added. The mixture was refluxed for 5 hr., then 20 ml. of 20% sodium hydroxide was added and the mixture was refluxed a further 10 min. After cooling, it was stirred into ice-cold water and the precipitate was filtered off and washed, giving 7.5 g. of yellow powder, m.p. 52–54°. This was dissolved in 30 ml. of benzene and chromatographed (alumina) to give 86–88% yields, m.p. 60–61°. Recrystallization from methanol

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[19] This low melting point is understandable since the earlier work reports that only very small amounts of the diamine were prepared and acetylated for melting point and mixture melting point comparison with the only other possible isomer (m.p. 188–190°).

gave orange needles with the same melting point. About 10% of 4-amino-3,5-difluoroazobenzene was also recovered from the column making the recovery almost quantitative.

Anal. Calcd. for $C_{13}H_{11}F_2N_3$: C, 63.15; H, 4.49; F, 15.37; N, 17.00. Found: C, 63.24; H, 4.62; F, 15.46; N, 17.15.

B. Reduction with Lithium Aluminum Hydride.—To a suspension of 3.0 g. of pulverized lithium aluminum hydride in 120 ml. of dried ether under N_2, 6.6 g. of 3,5-difluoro-4-formamidoazobenzene was added portionwise during 30 min., at 30° with vigorous stirring. After the addition, the stirring was continued for 30 min. at the same temperature, and 10 ml. of ethyl acetate was then added dropwise to destroy excess hydride. Water (20 ml.) was added to decompose the aluminum-dye complex, and then 10 ml. of 20% aqueous sodium hydroxide was added. The ether layer was separated and the mixture was washed with ether. The combined extracts were evaporated to dryness and the residue was dissolved in benzene and chromatographed on alumina. The first (and principal) band was eluted with benzene and concentrated to small volume and rechromatographed, giving 2.5 g. (40%), m.p. 58–60°. Recrystallization from 5 ml. of methanol gave 1.85 g., m.p. 60–61°. A mixture melting point with the product from A showed no depression.

Anal. Calcd. for $C_{13}H_{11}F_2N_3$: C, 63.15; H, 4.49; F, 15.37; N, 17.00. Found: C, 62.89; H, 4.95; F, 15.17; N, 16.74.

3,5-Difluoro-4-N-methylformamidoazobenzene.—A solution of 2.0 g. of 3,5-difluoro-4-N-methylaminoazobenzene in 10 ml. of 98–100% formic acid was refluxed for 20 min. After dilution with water, the formamido compound, m.p. 95–96°, was obtained quantitatively. Recrystallization from dilute ethanol gave fine orange crystals of the same melting point.

Anal. Calcd. for $C_{14}H_{11}F_2N_3O$: C, 61.08; H, 4.03; F, 13.81; N, 15.27. Found: C, 61.32; H, 4.07; F, 13.53; N, 15.52.

3,5-Difluoro-4-dimethylaminoazobenzene. A. Dimethylation of the Amine.—To a solution of 5.0 g. of 3,5-difluoro-4-aminoazobenzene in 20 ml. of trimethyl phosphate were added 2.5 g. of anhydrous sodium carbonate and 5 ml. of methyl iodide.[10] The mixture was gently heated to 160° with stirring for 15 min., then cooled below 40°. A further 5 ml. of methyl iodide was added and the mixture was heated again. After repeating this procedure a third time, the reaction mixture was cooled and diluted with ice-water, and the precipitate was filtered and washed, giving 5.6 g. of yellow powder, m.p. 33–40°. This was dissolved in 15 ml. of benzene and chromatographed (alumina). The first band was eluted with benzene. Evaporation of the solvent gave 2.0 g. (36%) of the product, m.p. 43–44°. Recrystallization from methanol gave orange needles with the same melting point.

Anal. Calcd. for $C_{14}H_{13}F_2N_3$: C, 64.36; H, 5.01; F, 14.55; N, 16.08. Found: C, 64.37; H, 5.09; F, 14.28; N, 16.24.

The second band was collected, giving 1.4 g., m.p. 51–55°. Recrystallization from methanol raised the melting point to 56–58°. This appeared to be the N-monomethylamino dye contaminated with a small amount of the dimethyl compound.

B. Reduction of 3,5-Difluoro-4-N-methylformamidoazobenzene with Lithium Aluminum Hydride.—Reduction of 1 g. of the named compound with lithium aluminum hydride in ether as described above gave a crude product which was dissolved in benzene and chromatographed on alumina. The principal band was eluted, and the solvent was evaporated to give 0.7 g., m.p. 46–48°, which was recrystallized from methanol giving orange needles, m.p. 48–49°. The analytical results were close to those calculated for the dimethylamino compound, but the material is apparently contaminated with the monomethylamino compound, and it was not purified further.

Anal. Found: C, 64.59; H, 5.00; F, 14.61; N, 16.34.

3,5-Difluoro-4-acetamidoazobenzene.—A mixture of 0.5 g. of 3,5-difluoro-4-aminoazobenzene and 3 ml. of acetic anhydride was boiled for 15 min. and cooled, giving orange needles, m.p. 186–187°. Recrystallization from ethanol gave an analytical sample, m.p. 187–188°.

Anal. Calcd. for $C_{14}H_{11}F_2N_3O$: N, 15.27. Found: N, 15.18.

4-Amino-2,6-difluoroacetanilide.—The reduction of 13.7 g. (0.05 mole) of 4-acetamido-3,5-difluoroazobenzene in 200 ml. of alcohol with 30 ml. of 100% hydrazine hydrate and 5% Pd–C gave 8.2 g. (88%) of the product, m.p. 191–192°. This reduction was complete in less than 5 min. An analytical sample was prepared by recrystallization from water giving white needles with unchanged melting point.

Anal. Calcd. for $C_8H_8F_2N_2O$: C, 51.61; H, 4.33; N, 15.05. Found: C, 51.77; H, 4.52; N, 15.31.

2,6-Difluoroacetanilide.—The above amine (4 g.) was added to a mixture of 15 ml. of concentrated HCl and 15 ml. of water at −2° with stirring and was diazotized with a saturated aqueous solution of 2 g. of $NaNO_2$ at 0–5°. The clear solution was stirred for 15 min. and poured into 30 ml. of hypophosphorus acid at 10°, and the mixture gradually warmed to 15° whereupon vigorous foaming occurred and a white precipitate began to form. The reaction mixture was then placed in an ice bath for 1 hr. with occasional stirring, and the precipitate was filtered off and dried, m.p. 142–145° (slight residue). Sublimation (120° bath) in a vacuum (1 mm.) gave 2.1 g. (57%) of the pure product, m.p. 144.5–145°.

Anal. Calcd. for $C_8H_7F_2NO$: C, 56.14; H, 4.12; F, 22.20; N, 8.19. Found: C, 56.29; H, 4.20; F, 22.14; N, 8.40.

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