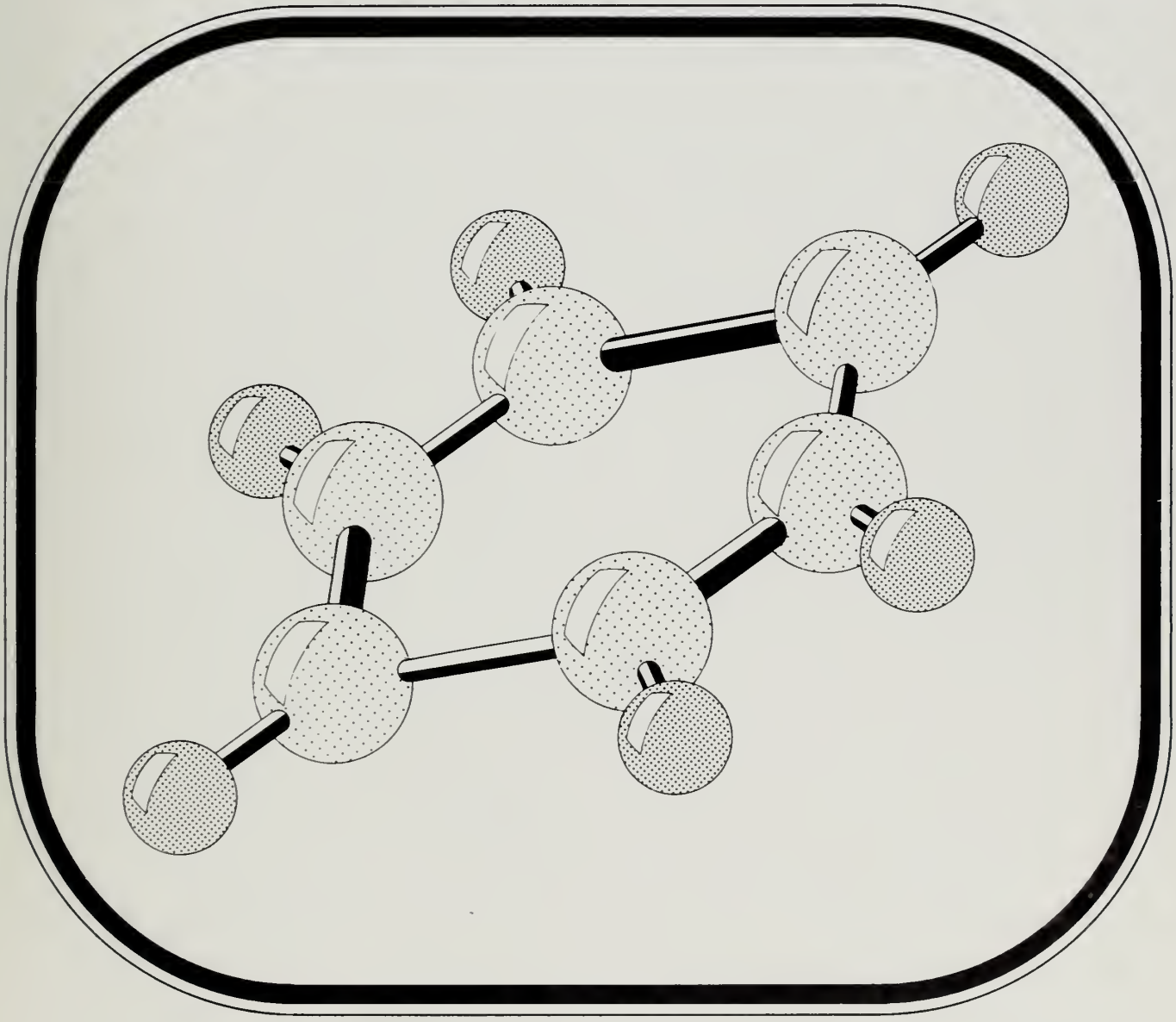
AROMATIC FLUORINE CHEMISTRY AT THE ILLINOIS STATE GEOLOGICAL SURVEY

Research Notes, 1934-1976

R. H. Shiley D. R. Dickerson G. C. Finger



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AROMATIC FLUORINE CHEMISTRY AT THE ILLINOIS STATE GEOLOGICAL SURVEY

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ABSTRACT

Forty years of research pertaining to the study of organic fluorine chemistry performed at the Illinois State Geological Survey is reviewed. The review consists of a tabulation of more than 1100 organic fluorine compounds with corresponding synthetic methods and physical constants and a bibliography.

INTRODUCTION

For many years Illinois has been the leading U.S. producer of the mineral fluorite (calcium fluoride), commercially called fluorspar. The fluorspar of Illinois occurs in Hardin and Pope Counties, in the extreme southeastern part of the state. These deposits are relatively shallow and are readily mined by standard procedures. In addition to being accessible, the mines are linked by excellent transportation facilities to major industrial centers, which manufacture chemicals, steel, aluminum, and ceramic products.

As early as 1851 the Geological Survey of Illinois (now the Illinois State Geological Survey) became interested in the geologic and economic aspects of fluorspar. In 1964, the Illinois State Legislature designated fluorspar as the state mineral.

Chemical research on Illinois minerals became an important activity of the Survey in 1931 when its chemical laboratories were established. In 1934 research on the synthesis, physical and chemical properties, and possible industrial uses of fluorine compounds was conceived. During the same period, the market debut of the new fluorocarbon refrigerants (Freons) influenced the Survey's decision to pioneer in an entirely new area of fluorine research, namely the synthesis of aromatic fluorine compounds.

Many of our more important chemical compounds have a halogen atom (F, Cl, Br, I) as one of their constituents. As a member of this family, fluorine is a unique element, i.e., it is the most reactive and electronegative element known. The outstanding effects of fluorine substitution for hydrogen in organic molecules are: (1) no appreciable change in boiling point, (2) decreased surface tension, (3) low heat of vaporization, and (4) increased volatility. In general, fluorine compounds are more stable than their sister halogen analogs, and in some instances fluorine may stabilize other groups. Intense labilization of fluorine is known also.

Today, the insignificant fluorine chemical industry of the 1930s has become a multibillion dollar business of diversified products. In addition to the refrigerants, the organic fluorine chemicals industry includes a wide variety of plastics, herbicides, insecticides, anesthetics, medicinals, dyes, lubricants, dielectrics, and other specialized items.

As fluorine became increasingly significant, the Illinois State Geological Survey has accumulated a wealth of experimental data on aromatic fluorine compounds and has built up an extensive collection of reference compounds and intermediates. This compendium is essentially a list of the compounds studied, including a record of their physical properties and a summary of the synthetic methods used in their preparation. Many of these synthetic procedures were developed in the Geological Survey laboratories; others are standard laboratory procedures which have been adapted or modified to suit the unique properties of aromatic compounds.

This publication is a brief review of over 40 years of both published and unpublished research on aromatic fluorine chemistry carried on by the Fluorine Chemistry Section of the Illinois State Geological Survey. The senior member of this group, Dr. G. C. Finger, has been associated with this research since its inception. This review may thus be considered a research biography of aromatic fluorine chemistry.

TABULAR SURVEY OF FLUORINE COMPOUNDS

A tabulated list of the aromatic fluorine compounds synthesized in the Illinois State Geological Survey laboratories, including those new to the published literature, follows. The table lists the compounds by their empirical formulas and for the most part consists of benzene derivatives. Other compound types are indicated by name. The physical constants listed are those observed at the time of synthesis; in nearly all cases they are uncorrected. These data may differ slightly from those observed for the analytically pure compounds; however, generally the compounds for which there are references can be assumed to be pure. The included references refer only to Illinois State Geological Survey publications. Some of these reprints are available upon request. An asterisk (*) indicates that a sample of the compound was available when the list was prepared.

The form of the information in the tabulated list is illustrated by the following two examples. (1) 2-Fluoro-3-chloro*pyridine* is found under its empirical formula C_5H_3ClFN. Its boiling point is 95° C at 100 mm pressure. An asterisk in the sample availability column indicates that a research sample is available. Additional information can be found in reference 1. (2)1,3,5-Trifluoro-2,4,6-tribromo*benzene* is found under its empirical formula $C_6Br_3F_3$. Its melting point is 99° C. A research sample is available (indicated by an asterisk), and additional information can be found in reference 6.

Because the available research samples vary greatly in their age and purity, no guarantee as to configuration or purity can be given with them. These samples are available in quantities of 0.1 g (analytical samples) and larger (i.e., 100 g). To obtain samples, please indicate the desired quantity and, if possible, the planned use. Direct all requests to the Geochemical Section, Illinois State Geological Survey, Urbana, Illinois 61801.

TABLE 1—AROMATIC FLUORINE COMPOUNDS SYNTHESIZED IN

Empirical formula	Ring substitution	Compound type or derivative
$C_5HCl_2F_2N$	$\frac{F_2\text{-}Cl_2}{2,6\text{-}3,5}$	pyridine
$C_5H_2BrFN_2O_2$	$\frac{F\text{-}Br\text{-}NO_2}{2\text{-}5\text{-}3}$	pyridine
$C_5H_2Cl_2FN$	$\frac{F\text{-}Cl_2}{2\text{-}3,5}$	pyridine
C_5H_3BrFN	$\frac{F\text{-}Br}{2\text{-}5}$	pyridine
C_5H_3ClFN	$\frac{F\text{-}Cl}{2\text{-}3}$	pyridine
	2-5	pyridine
$C_5H_3FN_2O_2$	$\frac{F\text{-}NO_2}{2\text{-}3}$	pyridine
	2-5	pyridine
$C_5H_3F_2N$	$\frac{F_2}{2,3}$	pyridine
	2,6	pyridine
C_5H_4FN	$\frac{F}{2}$	pyridine
$C_5H_5FN_2$	$\frac{F\text{-}NH_2}{2\text{-}5}$	pyridine
		acetyl
	2-6	pyridine
		phenyl isothiocyanate
	3-2	pyridine
		hydrochloride salt
$C_6Br_2F_4$	$\frac{F_4\text{-}Br_2}{1,2,4,5\text{-}3,6}$	—
$C_6Br_3F_3$	$\frac{F_3\text{-}Br_3}{1,3,5\text{-}2,4,6}$	—
$C_6Cl_2F_2N_2O_4$	$\frac{F_2\text{-}(NO_2)_2\text{-}Cl_2}{1,3\text{-}4,6\text{-}2,5}$	—
$C_6Cl_2F_2O_2$	$\frac{F_2\text{-}Cl_2}{2,5\text{-}3,6}$	1,4-quinone
$C_6Cl_2F_3NO_2$	$\frac{F_3\text{-}NO_2\text{-}Cl_2}{1,2,4\text{-}3\text{-}5,6}$	—
$C_6Cl_3FN_2O_4$	$\frac{F\text{-}(NO_2)_2\text{-}Cl_3}{1\text{-}3,5\text{-}2,4,6}$	—

(Continued on

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
46	—	—	—	—	—	1	*
61	—	—	—	—	—	2,3	*
43	—	—	—	—	—	1	*
—	63/15	—	—	—	—	1	*
—	95/100	—	—	—	—	1	*
—	89/100	—	1.4952/25	—	—	1	*
—	110/10	—	1.5255/25	—	—	2,3	*
—	87/7	19-21	1.5243/25	—	—	2,3	*
—	118	—	1.4420/25	—	—	4	—
—	125/743	—	1.4345/25	—	—	4,5	—
—	125	—	—	—	—	—	*
88	—	—	—	—	—	4	—
132	—	—	—	—	—	4	—
38	—	—	—	—	—	—	—
193	—	—	—	—	—	4	—
—	117/24	—	—	—	—	4	—
188	—	—	—	—	—	4	—
77	—	—	—	—	—	—	—
99	—	—	—	—	—	6	*
133	—	—	—	—	—	7	*
200-205d	—	—	—	—	—	8,9,10	—
—	—	—	—	—	—	—	—
141	—	—	—	—	—	—	*

next page)

Empirical formula	Ring substitution	Compound type or derivative
$C_6Cl_3F_2NO_2$	$\frac{F_2\text{-}NO_2\text{-}Cl_3}{1,4\text{-}6\text{-}2,3,5}$	—
$C_6Cl_3F_3$	$\frac{F_3\text{-}Cl_3}{1,3,5\text{-}2,4,6}$	—
$C_6Cl_4FNO_2$	$\frac{F\text{-}Cl_4\text{-}NO_2}{1\text{-}2,3,5,6\text{-}4}$	—
C_6Cl_5F	$\frac{F\text{-}Cl_5}{1\text{-}2,3,4,5,6}$	—
$C_6Cl_6F_6$	$\frac{F_6\text{-}Cl_6}{\text{symmetrical}}$	cyclohexane
$C_6F_3I_3$	$\frac{F_3\text{-}I_3}{1,2,4\text{-}3,5,6}$	—
$C_6F_4I_2$	$\frac{I_2\text{-}F_4}{2,3\text{-}1,4,5,6}$	—
C_6F_6	$\frac{F_6}{1,2,3,4,5,6}$	—
$C_6HBrClF_2I$	$\frac{F_2\text{-}Br\text{-}Cl\text{-}I}{1,4\text{-}2\text{-}6\text{-}3}$	—
$C_6HBrF_2N_2O_4$	$\frac{F_2\text{-}(NO_2)_2\text{-}Br}{1,2\text{-}3,5\text{-}4}$	—
$C_6HBr_2F_2NO_2$	$\frac{F_2\text{-}NO_2\text{-}Br_2}{1,2\text{-}3\text{-}4,5}$	—
$C_6HBr_2F_3$	$\frac{F_3\text{-}Br_2}{1,3,5\text{-}2,4}$	—
$C_6HClF_2N_2O_4$	$\frac{F_2\text{-}(NO_2)_2\text{-}Cl}{1,2\text{-}3,5\text{-}6}$	—
	1,3-2,4-6	—
	1,3-4,6-2	—
	1,4-2,6-3	—
$C_6HClF_2O_2$	$\frac{F_2\text{-}Cl}{2,5\text{-}3}$	1,4-quinone
	2,6-3	1,4-quinone
$C_6HCl_2FN_2O_4$	$\frac{F\text{-}Cl_2\text{-}(NO_2)_2}{1\text{-}2,3\text{-}4,6}$	—
	1-2,4-3,5	—
	1-2,6-3,5	—
$C_6HCl_2F_2NO_2$	$\frac{F_2\text{-}NO_2\text{-}Cl_2}{1,2\text{-}3\text{-}4,5}$	—

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
38	—	—	—	—	—	—	—
63	—	—	—	—	—	11,12	*
80	—	—	—	—	—	13	*
138	—	—	—	—	—	13	—
80	—	—	—	—	—	—	—
64	—	—	—	—	—	—	—
—	—	—	—	—	—	—	*
—	—	—	—	—	—	—	*
62	—	—	—	—	—	—	*
—	—	—	—	—	—	—	*
48	—	—	—	—	—	—	*
—	196-198	—	—	—	—	6	—
60	—	—	—	—	—	7	*
—	—	—	—	—	—	—	*
63	—	—	—	—	—	7	—
70	—	—	—	—	—	7	—
147	—	—	—	—	—	8,9,10	—
136	—	—	—	—	—	8	—
46	—	—	—	—	—	7	*
75	—	—	—	—	—	—	—
94	—	—	—	—	—	12	—
—	—	—	1.5255/25	—	—	—	—

next page)

TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
	1,3-4-2,6	—
	1,3-5-2,4	—
	1,3-5-4,6	—
$C_6HCl_2F_3$	$\frac{F_3\text{-}Cl_2}{1,2,5\text{-}3,4}$	—
	1,3,5-2,4	—
$C_6HCl_3FNO_2$	$\frac{F\text{-}Cl_3\text{-}NO_2}{1\text{-}2,4,5\text{-}3}$	—
	1-2,4,6-3	—
$C_6HCl_3F_2$	$\frac{F_2\text{-}Cl_3}{1,3\text{-}2,4,5}$	—
	1,3-2,4,6	—
	1,3-4,5,6	—
	1,4-2,3,5	—
C_6HCl_4F	$\frac{F\text{-}Cl_4}{1\text{-}2,3,4,5}$	—
	1-2,3,5,6	—
$C_6HF_2N_3O_3$	—	5,6-difluoro-4-nitrobenzo-1,2,3 oxadiazole
$C_6HF_3N_2O_4$	$\frac{F_3\text{-}(NO_2)_2}{1,2,3\text{-}4,6}$	—
	1,3,5-2,4	—
$C_6HF_3O_2$	$\frac{F_3}{2,3,5}$	1,4-quinone
$C_6HF_4NO_2$	$\frac{F_4\text{-}NO_2}{1,2,3,5\text{-}4}$	—
C_6HF_5	$\frac{F_5}{1,2,3,4,5}$	—
$C_6H_2BrClFNO_2$	$\frac{F\text{-}Br\text{-}Cl\text{-}NO_2}{1\text{-}5\text{-}2\text{-}3}$	—
$C_6H_2BrClF_2$	$\frac{F_2\text{-}Br\text{-}Cl}{1,4\text{-}2\text{-}5}$	—
$C_6H_2BrCl_2F$	$\frac{F\text{-}Cl_2\text{-}Br}{1\text{-}2,6\text{-}3}$	—
$C_6H_2BrFN_2O_4$	$\frac{F\text{-}(NO_2)_2\text{-}Br}{1\text{-}2,4\text{-}5}$	—
$C_6H_2BrFO_2$	$\frac{F\text{-}Br}{2\text{-}5}$	1,4-quinone

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
—	103/7.5	—	—	—	—	—	—
—	113/12.5	—	—	—	—	14	*
41	114/20	—	—	—	—	14	*
—	154	—	—	1.599	30.41	—	—
—	162	—	1.4870/20	—	—	6,14	*
57	—	—	—	—	—	—	—
—	94/2	—	1.5585/25	—	—	14	*
—	91/45	—	—	—	—	14	—
—	87/18	—	—	—	—	14	—
50	200	—	—	—	—	—	—
—	200	-11.5	1.5340/20	—	—	15	—
66	76/0.7	—	—	—	—	—	*
73	—	—	—	—	—	13,16	—
<350	—	—	—	—	—	—	—
70	—	—	—	—	—	7	—
54	—	—	—	—	—	7,13	—
sublimes	—	—	—	—	—	—	—
—	79/20	-5	1.46507/20	—	—	17,18	—
—	—	—	—	—	—	—	*
75	—	—	—	—	—	—	*
50	—	—	—	—	—	—	—
—	117/21	—	—	—	—	—	*
92	—	—	—	—	—	8,9,10	*
119	—	—	—	—	—	17,19	*

next page)

TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
$C_6H_2BrF_2NO_2$	$\frac{F_2\text{-}NO_2\text{-}Br}{1,2\text{-}3\text{-}5}$	—
	1,2-5-4	—
	1,3-6-4	—
	1,4-5-2	—
$C_6H_2BrF_3$	$\frac{F_3\text{-}Br}{1,2,3\text{-}4}$	—
	1,2,3-5	—
	1,2,4-5	—
	1,3,5-2	—
$C_6H_2Br_2F_2$	$\frac{F_2\text{-}Br_2}{1,2\text{-}4,5}$	—
	1,4-2,5	—
$C_6H_2Br_3FO$	$\frac{OH\text{-}F\text{-}Br_3}{1\text{-}3\text{-}2,4,6}$	—
$C_6H_2ClFN_2O_4$	$\frac{F\text{-}(NO_2)_2\text{-}Cl}{1\text{-}4,5\text{-}2}$	—
	1-2,4-5	—
$C_6H_2ClFO_2$	$\frac{F\text{-}Cl}{2\text{-}5}$	1,4-quinone
$C_6H_2ClF_2NO_2$	$\frac{F_2\text{-}Cl\text{-}NO_2}{1,2\text{-}3\text{-}4}$	—
	1,2-4-5	—
	1,3-2-4	—
	1,3-2-5	—
	1,3-4-5	—
	1,3-4-6	—
	1,3-5-4	—
	1,4-2-5	—
	1,4-3-5	—
$C_6H_2ClF_3$	$\frac{F_3\text{-}Cl}{1,2,3\text{-}4}$	—
	1,2,3-5	—
	1,3,4-2	—

[a] Bp 223° C

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
58	—	—	—	—	—	—	*
—	66/0.9	—	1.5465/20	—	—	—	—
—	97/5	—	—	—	—	20	—
58	—	—	—	—	—	—	—
—	149	—	—	—	—	—	—
—	146	-14	1.48173/20	—	—	21	—
—	144	-18	1.4862/20	—	—	15	—
—	140	4	—	—	—	6	—
34	—	—	—	—	—	—	*
66	—	—	—	—	—	15	—
90	—	—	—	—	—	—	—
63	—	—	—	—	—	7	*
77	—	—	—	—	—	8,9,10	—
127	—	—	—	—	—	8,9,10,17,19	*
—	132/43	—	—	—	—	—	—
—	118/31	—	—	—	—	22	*
47	—	—	—	—	—	13,21	—
42	—	—	—	—	—	21,22	*
—	206	—	1.5195/20	—	—	—	—
—	106/15[a]	6	1.5337/20	—	—	20	*
—	203	20	—	—	—	23	—
—	116/20	28	—	—	—	20	*
—	220	—	1.5281/20	—	—	—	—
—	130	—	—	—	—	23	*
—	—	—	—	—	—	23	—
—	131	—	—	—	—	24	*

next page)

TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
	1,3,4-5	—
	1,3,4-6	—
	1,3,5-2	—
$C_6H_2Cl_2FNO_2$	$\frac{F\text{-}Cl_2\text{-}NO_2}{1\text{-}2,3\text{-}4}$	—
	1-2,4-5	—
	1-2,5-4	—
	1-2,6-3	—
	1-2,6-4	—
	1-3,4-6	—
$C_6H_2Cl_2F_2$	$\frac{F_2\text{-}Cl_2}{1,2\text{-}3,4}$	—
	1,2-3,5	—
	1,2-3,6	—
	1,2-4,5	—
	1,3-2,4	—
	1,3-2,5	—
	1,3-4,5	—
	1,3-4,6	—
	1,4-2,3	—
	1,4-2,5	—
	1,4-3,5	—
$C_6H_2Cl_2F_2O$	$\frac{OH\text{-}F_2\text{-}Cl_2}{1\text{-}3,4\text{-}5,6}$	—
	—	benzoate
$C_6H_2Cl_2F_3N$	$\frac{NH_2\text{-}F_3\text{-}Cl_2}{1\text{-}2,3,6\text{-}4,5}$	—
	—	acetyl
$C_6H_2Cl_3F$	$\frac{F\text{-}Cl_3}{1\text{-}2,3,4}$	—
	1-2,3,5	—
	1-2,3,6	—

[a] microcap
[b] crude

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
—	123	-45	1.4553/20	—	—	20,23	—
—	125	-26	—	—	—	15	—
—	124	-3	1.4550/20	1.463	28.59	6,23	*
—	138/7	—	—	—	—	23	*
—	77/1	—	1.5650/20	—	—	22	*
37	—	—	—	—	—	22	*
—	88/1	—	1.5685/20	—	—	12,22	*
44	—	—	—	—	—	22	*
—	247[a]	17	1.5741/20	—	—	22	*
—	170	—	—	—	—	23	*
—	—	—	—	—	—	23	—
—	171	—	—	—	—	23	—
34	165[a]	—	—	—	—	—	—
—	172	—	—	—	—	23	*
—	65/14	—	—	—	—	23	—
—	160	12	1.5028/20	—	—	23	—
—	164	—	1.5034/20	1.505	33.04	—	—
35	—	—	—	—	—	—	*
45	164	—	—	—	—	15,25	*
—	165	—	1.5041/20	—	—	15,23,25	*
—	oil[b]	—	—	—	—	—	—
85	—	—	—	—	—	—	—
104	—	—	—	—	—	—	—
154	—	—	—	—	—	—	—
43	—	—	—	—	—	23	*
—	80/8	—	1.5480/20	—	—	23	*
—	105/30	—	1.5509/25	—	—	23	*

next page)

Empirical formula	Ring substitution	Compound type or derivative
	1-2,4,5	—
	1-2,4,6	—
$C_6H_2Cl_3FO$	$\frac{F\text{-}Cl_3\text{-}OH}{1\text{-}2,4,6\text{-}3}$	—
$C_6H_2Cl_3F_2N$	$\frac{NH_2\text{-}F_2\text{-}Cl_3}{1\text{-}2,5\text{-}3,4,6}$	—
	—	acetyl
$C_6H_2Cl_6F_4$	$\frac{F_4\text{-}Cl_6}{1,2,4,5\text{-}1,2,3,4,5,6}$	cyclohexane
$C_6H_2FIN_2O_4$	$\frac{F\text{-}(NO_2)_2\text{-}I}{1\text{-}2,4\text{-}5}$	—
$C_6H_2FI_3O$	$\frac{OH\text{-}F\text{-}I_3}{1\text{-}3\text{-}2,4,6}$	—
$C_6H_2F_2INO_3$	$\frac{OH\text{-}F_2\text{-}I\text{-}NO_2}{1\text{-}3,4\text{-}6\text{-}5}$	benzoate
$C_6H_2F_2N_2$	$\frac{CN\text{-}F_2}{2\text{-}3,5}$	pyridine
$C_6H_2F_2N_2O_4$	$\frac{F_2\text{-}(NO_2)_2}{1,2\text{-}4,5}$	—
	1,3-4,6	—
$C_6H_2F_2O_2$	$\frac{F_2}{2,5}$	1,4-quinone
$C_6H_2F_3I$	$\frac{F_3\text{-}I}{1,2,4\text{-}5}$	—
	1,3,5-2	—
$C_6H_2F_3NO_2$	$\frac{F_3\text{-}NO_2}{1,2,3\text{-}4}$	—
	1,2,3-5	—
	1,2,4-5	—
	1,3,4-5	—
	1,3,5-2	—
$C_6H_2F_4$	$\frac{F_4}{1,2,3,4}$	—
	1,2,3,5	—
	1,2,4,5	—

[a] Bp 192° C
[b] microcap

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
62	—	—	—	—	—	—	*
—	208	11	1.5429/27	—	—	—	*
55	—	—	—	—	—	—	*
113	—	—	—	—	—	—	—
187	—	—	—	—	—	—	*
80	—	—	—	—	—	15	—
99	—	—	—	—	—	7	*
139	—	—	—	—	—	—	—
136	—	—	—	—	—	15	—
—	—	—	—	—	—	—	*
85	—	—	—	—	—	—	*
74	—	—	—	—	—	9,10,12	—
173	—	—	—	—	—	9,10,17,19, 25	*
—	72/20	24	1.5371/20	—	—	—	—
—	165-167	28	—	—	—	—	*
—	92/20	—	1.4928/20	—	—	12,22	*
—	76/24	—	—	—	—	21	—
—	94/20[a]	-11	1.4938/20	—	—	13,24	—
—	187[b]	-20	1.4873/20	—	—	26	*
—	81/20	—	1.4783/20	—	—	6,13,27	*
—	94	—	1.4069/20	—	—	12,23,24	*
—	83	—	1.4038/20	1.393	23.99	23,26	*
—	88	—	1.4074/20	—	—	25	*

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TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
$C_6H_2F_5N$	$\frac{F_5\text{-}NH_2}{1,2,3,4,5\text{-}6}$	—
C_6H_3BrClF	$\frac{F\text{-}Br\text{-}Cl}{1\text{-}2\text{-}6}$	—
$C_6H_3BrClF_2N$	$\frac{NH_2\text{-}Br\text{-}Cl\text{-}F_2}{1\text{-}2\text{-}4\text{-}3,6}$	—
$C_6H_3BrFNO_2$	$\frac{F\text{-}NO_2\text{-}Br}{1\text{-}2\text{-}4}$	—
	1-2-5	—
	1-3-4	—
	1-4-2	—
	1-4-3	—
$C_6H_3BrF_2$	$\frac{F_2\text{-}Br}{1,2\text{-}4}$	—
	1,3-4	—
	1,4-2	—
$C_6H_3BrF_2N_2O_2$	$\frac{NH_2\text{-}NO_2\text{-}F_2\text{-}Br}{1\text{-}2\text{-}3,4\text{-}6}$	—
	—	acetyl
$C_6H_3BrF_2O$	$\frac{OH\text{-}F_2\text{-}Br}{1\text{-}2,4\text{-}6}$	—
$C_6H_3Br_2F$	$\frac{F\text{-}Br_2}{1\text{-}2,4}$	—
$C_6H_3Br_2FO$	$\frac{OH\text{-}F\text{-}Br_2}{1\text{-}2\text{-}4,6}$	—
	1-4-2,6	—
C_6H_3ClFI	$\frac{Cl\text{-}I\text{-}F}{2\text{-}6\text{-}1}$	—
$C_6H_3ClFNO_2$	$\frac{F\text{-}Cl\text{-}NO_2}{1\text{-}2\text{-}3}$	—
	1-2-4	—
	1-2-5	—
	1-2-6	—
	1-3-4	—

[a] Bp 65° C/45 mm
[b] Bp 58° C/20 mm

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
—	—	—	—	—	—	—	*
44	—	—	—	—	—	—	*
—	—	—	—	—	—	—	*
—	—	—	—	—	—	—	*
88	—	—	—	—	—	13	*
—	—	—	—	—	—	—	—
—	—	19	—	—	—	—	—
44	—	—	—	—	—	—	*
—	147[a]	—	1.5082/20	—	—	21	*
—	146-148	—	1.5059/20	—	—	20	*
—	152[b]	—	1.5086/20	—	—	15	*
96	—	—	—	—	—	—	*
171	—	—	—	—	—	—	*
—	53/1	—	—	—	—	22	*
—	104/32	—	—	—	—	—	*
—	—	31	—	—	—	22	—
56	—	—	—	—	—	22	*
—	—	—	—	—	—	—	*
—	80/2.5	—	1.5450/20	—	—	—	*
42	237	—	—	—	—	—	—
64	114-116/24	—	—	—	—	12	—
46-50	106/4	—	—	—	—	12,22	*
37	—	—	—	—	—	22	*

next page)

TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
	1-3-6	—
	1-4-2	—
	1-4-3	—
$C_6H_3ClF_2$	$\frac{F_2\text{-}Cl}{1,2\text{-}3}$	—
	1,2-4	—
	1,3-2	—
	1,3-4	—
	1,3-5	—
	1,4-2	—
$C_6H_3ClF_2N_2O_2$	$\frac{NH_2\text{-}NO_2\text{-}F_2\text{-}Cl}{1\text{-}2\text{-}3,5\text{-}6}$	—
	1-2-3,6-4	—
	—	acetyl
	—	quinoxaline
	1-2-4,6-3	—
	—	acetyl
	—	quinoxaline
	1-2-4,6-5	—
	—	acetyl
	1-4-2,5-3	—
	—	acetyl
	1-4-3,5-2	—
	—	acetyl

[a] Bp 237° C

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
49	—	—	—	—	—	28	—
—	138/29[a]	8	—	—	—	12,22	—
38	239	—	—	—	—	—	—
—	138	—	—	—	—	23,29	—
—	127	—	—	—	—	12,29	*
—	132	—	—	—	—	29	*
—	127	-26	1.4751/20	1.353	30.41	20,29	*
—	119	—	1.4683/20	—	—	27,29	*
—	129	-25	1.4772/20	—	—	15,20	*
80	—	—	—	—	—	—	*
82	—	—	—	—	—	—	*
180	—	—	—	—	—	—	*
170	—	—	—	—	—	—	—
83	—	—	—	—	—	14	*
184	—	—	—	—	—	14	—
180	—	—	—	—	—	14	—
97	—	—	—	—	—	21	—
158	—	—	—	—	—	—	*
116	—	—	—	—	—	—	*
116	—	—	—	—	—	—	*
102	—	—	—	—	—	—	—
105	—	—	—	—	—	—	—

next page)

TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
$C_6H_3ClF_2O$	$\frac{OH\text{-}F_2\text{-}Cl}{1\text{-}2,4\text{-}3}$	—
	1-2,4-5	—
	1-2,4-6	—
	1-2,5-4	—
	1-3,5-2	—
	1-3,5-4	—
	1-4,5-2	—
$C_6H_3ClF_3N$	$\frac{NH_2\text{-}F_3\text{-}Cl}{1\text{-}2,4,6\text{-}3}$	—
	—	acetyl
$C_6H_3Cl_2F$	$\frac{F\text{-}Cl_2}{1\text{-}2,3}$	—
	1-2,4	—
	1-2,5	—
	1-2,6	—
	1-3,4	—
	1-3,5	—
$C_6H_3Cl_2FN_2O_2$	$\frac{NH_2\text{-}NO_2\text{-}F\text{-}Cl_2}{1\text{-}2\text{-}6\text{-}3,4}$	—
	—	acetyl
$C_6H_3Cl_2FO$	$\frac{OH\text{-}F\text{-}Cl_2}{1\text{-}2\text{-}4,5}$	—
	1-2-4,6	—
	1-3-2,4	—
	1-3-4,6	—
	1-4-2,5	—

[a] microcap

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	$n_D/^oC$	D_4^{20}	δ^{20}	Reference	Sample available
44	74/9	—	—	—	—	22	*
38	74/18	—	—	—	—	22	—
—	49/1.5	—	—	—	—	22	*
59	—	—	—	—	—	22	*
44	—	—	—	—	—	—	—
65	—	—	—	—	—	22	*
—	93/52	—	—	—	—	22	*
43	—	—	—	—	—	20	*
186	—	—	—	—	—	20	*
—	174-176	—	—	—	—	12,23,29	*
—	174	—	—	—	—	22,29	*
—	166	—	1.5195	—	—	12,22,29	*
38	73/24	—	—	—	—	12,29	*
—	172[a]	-1	1.5235	—	—	22,29	*
—	162	—	—	—	—	29	*
102	—	—	—	—	—	—	—
174	—	—	—	—	—	—	—
85	—	—	—	—	—	22	*
35	98/10	—	—	—	—	—	*
64	—	—	—	—	—	—	—
35	—	—	—	—	—	22	*
55	—	—	—	—	—	22	*

next page)

TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
	1-4-2,6	—
	1-4-3,5	—
$C_6H_3Cl_2F_2N$	$\frac{NH_2\text{-}F_2\text{-}Cl_2}{1\text{-}2,3\text{-}5,6}$	—
	—	acetyl
	1-3,5-2,4	—
	—	acetyl
	1-3,5-2,6	—
	—	acetyl
$C_6H_3Cl_3FN$	$\frac{NH_2\text{-}F\text{-}Cl_3}{1\text{-}3\text{-}2,4,6}$	—
	—	acetyl
	1-3-2,5,6	—
	—	acetyl
$C_6H_3FINO_2$	$\frac{F\text{-}NO_2\text{-}I}{1\text{-}3\text{-}4}$	—
	1-4-2	—
	1-4-3	—
$C_6H_3FN_2$	$\frac{F\text{-}CN}{2\text{-}3}$	pyridine
	2-4	pyridine
	2-5	pyridine
	2-6	pyridine
$C_6H_3FN_2O_4$	$\frac{F\text{-}(NO_2)_2}{1\text{-}2,4}$	—
	1-3,5	—

[a] Bp 149° C/8 mm

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	$n_{D}/^{o}C$	D_4^{20}	δ^{20}	Reference	Sample available
50	—	—	—	—	—	22	*
87	—	—	—	—	—	22	*
79	—	—	—	—	—	—	—
142	—	—	—	—	—	—	*
67	—	—	—	—	—	14	*
119	—	—	—	—	—	14	*
78	114/20	—	—	—	—	14	*
183	—	—	—	—	—	14	*
70	—	—	—	—	—	14	*
194	—	—	—	—	—	14	*
64	—	—	—	—	—	—	—
146	—	—	—	—	—	—	—
—	163/35	—	—	—	—	—	—
—	174-176/45	—	—	—	—	—	—
—	148/20	28	—	—	—	—	—
31	90/6	—	—	—	—	30	—
34	76/3	—	—	—	—	30	*
52	—	—	—	—	—	30	*
36	—	—	—	—	—	30	*
—	133/2[a]	14	—	—	—	9,10	*
43	—	—	—	—	—	—	—

next page)

TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
$C_6H_3FN_2O_5$	$\frac{OH\text{-}F\text{-}(NO_2)_2}{1\text{-}2\text{-}4,6}$	—
	1-3-4,6	—
	1-4-2,6	—
$C_6H_3FO_2$	$\frac{F}{2}$	1,4-quinone
$C_6H_3F_2Cl$	$\frac{Cl\text{-}F_2}{1\text{-}2,4}$	—
$C_6H_3F_2I$	$\frac{F_2\text{-}I}{1,3\text{-}4}$	—
	1,3-5	—
	1,4-2	—
$C_6H_3F_2NO_2$	$\frac{F_2\text{-}NO_2}{1,2\text{-}4}$	—
	1,3-5	—
	1,3-4	—
	1,4-2	—
$C_6H_3F_2NO_3$	$\frac{OH\text{-}NO_2\text{-}F_2}{1\text{-}2\text{-}4,5}$	—
	1-2-4,6	—
	1-3-4,5	—
	—	benzoate
	1-4-2,5	—
$C_6H_3F_3$	$\frac{F_3}{1,2,3}$	—
	1,2,4	—
	1,3,5	—
$C_6H_3F_3N_2O_2$	$\frac{NH_2\text{-}NO_2\text{-}F_3}{1\text{-}2\text{-}3,4,6}$	—
	—	acetyl
	—	ethyl carbamate
	1-2-3,5,6	—
	—	acetyl
	1-3-2,4,6	—
	—	acetyl
	—	ethyl carbamate

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
102	—	—	—	—	—	—	*
80	—	—	—	—	—	9,10	*
51	—	—	—	—	—	9,10	*
80	—	—	—	—	—	19	*
—	127	-26	1.4751/20	1.353	—	20	—
—	176	4	1.5581/20	—	—	—	—
—	168	-15	1.5535/20	—	—	—	—
—	75/20	—	—	—	—	—	—
—	85/15	—	—	—	—	12,16	—
—	177	—	1.4981/20	—	—	6,27	—
—	96/20	—	1.5060/20	—	—	9,10,28	*
—	103/25	-12	1.5112/17.2	—	—	9,10	*
60	—	—	—	—	—	7	—
50	—	—	—	—	—	8	*
105	—	—	—	—	—	15	—
89	—	—	--	—	—	15	—
90	—	—	—	—	—	—	*
—	95	-13	1.4230/20	1.302	26.1	21,29	*
—	91	-35	1.4226/20	—	—	29	*
—	76	-6	1.4140/20	1.2775	23.9	6,27,29,31	*
59	—	—	—	—	—	15,18	*
125	—	—	—	—	—	15	*
90	—	—	—	—	—	—	*
66	—	—	—	—	—	—	*
135	—	—	—	—	—	—	*
62	—	—	—	—	—	—	—
174	—	—	—	—	—	—	*
80	—	—	—	—	—	—	*

next page)

Empirical formula	Ring substitution	Compound type or derivative
	1-4-2,3,5	—
$C_6H_3F_3O$	OH-F_3 / 1-2,3,4	—
	1-2,3,5	—
	1-2,4,5	—
	1-2,4,6	—
$C_6H_3F_4N$	NH_2-F_4 / 1-2,3,4,6	—
	—	acetyl
$C_6H_4BF_5N_2$	N_2BF_4-F / 1-3	—
C_6H_4BrF	F-Br / 1-2	—
	1-3	—
	1-4	—
$C_6H_4BrFN_2O_2$	NH_2-F-Br-NO_2 / 1-2-4-6	—
	—	acetyl
C_6H_4BrFO	OH-F-Br / 1-2-4	—
	1-4-2	—
$C_6H_4BrFO_2$	$(OH)_2$-F-Br / 1,4-2-5	—
	—	acetate
$C_6H_4BrF_2N$	NH_2-F_2-Br / 1-2,3-5	—
	—	acetyl
	1-2,4-5	—
	—	acetyl
	1-3,4-6	—
	—	acetyl
C_6H_4ClF	F-Cl / 1-2	—
	1-3	—
	1-4	—
$C_6H_4ClFN_2O_2$	NH_2-F-Cl-NO_2 / 1-2-5-4	—

[a] microcap [b] Bp 61° C/57 mm

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
126	—	—	—	—	—	—	*
—	69/43	—	—	—	—	22	*
29	57/29	—	—	—	—	22	—
41	70/43	—	—	—	—	22	*
50	—	—	—	—	—	22,31	—
—	64/20	—	1.4623/20	—	—	26	*
141	—	—	—	—	—	26	*
150d	—	—	—	—	—	—	—
—	157-159	—	1.5317/21	—	—	—	*
—	149-151	—	1.5279/20	—	—	—	*
—	152	—	1.5286/21	—	—	—	*
122	—	—	—	—	—	—	*
169	—	—	—	—	—	—	*
—	79/7	—	—	—	—	22	—
43	89/1	—	—	—	—	9,10,22	*
111	—	—	—	—	—	19	*
90	—	—	—	—	—	19	—
—	223[a]	—	—	—	—	—	—
126	—	—	—	—	—	—	*
26	—	—	—	—	—	20	—
141	—	—	—	—	—	20	*
48	—	—	—	—	—	—	*
108	—	—	—	—	—	—	*
—	135[b]	—	1.5010/20	—	—	29	*
—	128	—	1.4911/27	—	—	29	—
—	130	—	1.4949/20	1.2318	—	29	*
127	—	—	—	—	—	22	*

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TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
	—	acetyl
C_6H_4ClFO	OH-F-Cl / 1-2-3	—
	1-2-4	—
	1-3-4	—
	1-3-6	—
	1-4-2	—
	1-4-3	—
$C_6H_4ClFO_2$	$(OH)_2$-F-Cl / 1,4-2-5	—
	—	acetate
$C_6H_4ClF_2N$	NH_2-F_2-Cl / 1-2,4-3	—
	—	acetyl
	1-2,4-5	—
	—	acetyl
	1-2,4-6	—
	—	acetyl
	1-2,5-3	—
	—	acetyl
	1-2,5-4	—
	—	acetyl
	1-3,4-2	—
	—	acetyl
	1-3,4-6	—
	—	acetyl
	1-3,5-2	—
	—	acetyl
	1-3,5-4	—
	—	acetyl
$C_6H_4Cl_2FN$	NH_2-F-Cl_2 / 1-2-4,5	—
	—	acetyl
	1-3-2,4	—
	—	acetyl

[a] microcap [b] Bp 180-182° C [c] 202° C microcap

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
167	—	—	—	—	—	22	*
38	96/31	—	—	—	—	22	*
—	64/7	20	—	—	—	22	—
—	107/19	—	—	—	—	22	—
—	185[a]	—	—	—	—	22	—
—	88/40	23	—	—	—	9,22	*
—	104/11	—	—	—	—	22	*
105-107	—	—	—	—	—	8,19	*
113	—	—	—	—	—	8,19	—
62	—	—	—	—	—	22	*
131	—	—	—	—	—	22	*
51	210	—	—	—	—	20,22	—
142	—	—	—	—	—	20,22	*
—	101/20[b]	19	—	—	—	23	—
147	—	—	—	—	—	23	*
—	210[a]	—	1.5375/20	—	—	—	—
117	—	—	—	—	—	—	*
80	—	—	—	—	—	20,22	*
157	—	—	—	—	—	20,22	—
43	—	—	—	—	—	—	—
127	—	—	—	—	—	—	*
57	—	—	—	—	—	22	*
106	—	—	—	—	—	22	—
—	101/20[c]	25	1.5333/20	—	—	23	—
87	—	—	—	—	—	23	*
79	—	—	—	—	—	22,32	*
167	—	—	—	—	—	22,32	*
68	—	—	—	—	—	22	*
159	—	—	—	—	—	22	*
87	—	—	—	—	—	—	*
126	—	—	—	—	—	—	*

next page)

Empirical formula	Ring substitution	Compound type or derivative
	1-3-4,6	—
	—	acetyl
	1-4-2,3	—
	—	acetyl
	1-4-2,5	—
	—	acetyl
	1-4-3,5	—
	—	acetyl
C_6H_4FI	F-I / 1-2	—
	1-3	—
	1-4	—
C_6H_4FIO	OH-F-I / 1-2-4	—
	1-4-2	—
$C_6H_4FNO_2$	F-NO_2 / 1-2	—
	1-3	—
	1-4	—
	F-COOH / 2-3	pyridine
	—	methyl ester
	2-4	pyridine
	2-5	pyridine
	—	methyl ester
	2-6	pyridine
	—	amide
	—	azide
	—	hydrazide
	—	methyl ester
$C_6H_4FNO_3$	OH-F-NO_2 / 1-2-4	—

[a] Bp 28° C/4 mm
[b] Bp 215° C
[c] 22 (unstable form)
[d] Bp 97° C/28 mm

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
68	—	—	—	—	—	—	*
126	—	—	—	—	—	—	—
65	—	—	—	—	—	23	*
162	—	—	—	—	—	23	—
76	—	—	—	—	—	22	*
141	—	—	—	—	—	22	*
102	—	—	—	—	—	22	*
189	—	—	—	—	—	22	*
—	189[a]	—	—	—	—	—	*
—	—	—	—	—	—	—	*
—	184	—	—	—	—	—	—
38	—	—	—	—	—	22	—
62	—	—	—	—	—	22	*
—	87/11[b]	-6	1.5488/17	—	—	—	—
—	86/19	—	1.5362/19	—	—	—	*
27[c]	205[d]	—	—	—	—	28	*
166	—	—	—	—	—	—	*
—	101/10	—	1.4978/25	—	—	4,5	*
197	—	—	—	—	—	—	—
144	—	—	—	—	—	—	*
51	—	—	—	—	—	—	*
143	—	—	—	—	—	5	*
—	—	—	—	—	—	—	*
60-63	—	—	—	—	—	5	*
122	—	—	—	—	—	4,5	*
51-54	—	—	—	—	—	4,5	*
118	—	—	—	—	—	—	*

next page)

Empirical formula	Ring substitution	Compound type or derivative
	1-2-6	—
	1-3-6	—
	1-4-2	—
$C_6H_4FNO_4S$	$\frac{SO_2\text{-}F\text{-}NO_2}{1\text{-}3}$	—
$C_6H_4F_2$	$\frac{F_2}{1,2}$	—
	1,3	—
	1,4	—
$C_6H_4F_2N_2O_2$	$\frac{NH_2\text{-}NO_2\text{-}F_2}{1\text{-}2\text{-}3,5}$	—
	—	acetyl
	1-2-3,6	—
	—	acetyl
	1-2-4,6	—
	—	acetyl
	—	ethyl carbamate
	1-4-2,5	—
	—	acetyl
	1-4-3,5	—
	—	acetyl
$C_6H_4F_2O$	$\frac{OH\text{-}F_2}{1\text{-}2,4}$	—
	1-2,5	—
	1-2,6	—
	1-3,4	—
	1-3,5	—
$C_6H_4F_2O_2$	$\frac{(OH)_2\text{-}F_2}{1,4\text{-}2,5}$	—
	—	acetate
$C_6H_4F_3N$	$\frac{NH_2\text{-}F_3}{1\text{-}2,3,4}$	—
	—	acetyl
	1-2,3,5	—
	—	acetyl

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
95	—	—	—	—	—	9,10	*
32	—	—	—	—	—	—	*
75	—	—	—	—	—	9,10	*
49	—	—	—	—	—	—	—
—	92	—	1.4451/18	—	—	29	*
—	83	-59	1.4404/18	—	—	29	*
—	89	—	1.4423/20	—	—	—	*
108	—	—	—	—	—	6,9,10,27	*
138	—	—	—	—	—	6,9	—
81	—	—	—	—	—	15	*
161	—	—	—	—	—	15	*
87	—	—	—	—	—	6	*
143	—	—	—	—	—	6	—
111	—	—	—	—	—	—	*
154	—	—	—	—	—	15,20,25	*
190	—	—	—	—	—	15,20	—
180	—	—	—	—	—	—	*
135	—	—	—	—	—	—	—
22	74/50	—	—	—	—	9,10,22	*
42	—	—	—	—	—	22	*
46	—	—	—	—	—	22	—
—	85/20	—	—	—	—	22	—
55	—	—	—	—	—	22	*
130	—	—	—	—	—	8,9,10,19	*
152	—	—	—	—	—	8,9,10,19	*
—	92/48	—	—	—	—	12,22	*
96	—	—	—	—	—	12,22	*
—	76/20	—	1.4899/20	—	—	18,22,26	—
121	—	—	—	—	—	22	*

next page)

TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
	1-2,4,5	—
	—	acetyl
	—	ethyl carbamate
	—	isopropyl carbamate
	1-2,4,6	—
	—	acetyl
	—	ethyl carbamate
	—	isopropyl carbamate
	1-3,4,5	—
	—	acetyl
C_6H_5BrFN	$\frac{NH_2\text{-}F\text{-}Br}{1\text{-}2\text{-}4}$	—
	—	acetyl
	—	glycine ethyl ester
	—	glycine hydrazide
	1-4-2	—
	—	acetyl
	—	glycine ethyl ester
	—	glycine hydrazide
C_6H_5ClFN	$\frac{NH_2\text{-}F\text{-}Cl}{1\text{-}2\text{-}3}$	—
	—	acetyl
	—	ethyl carbamate
	—	glycine ethyl ester
	—	glycine hydrazide
	—	isopropyl carbamate
	1-2-4	—
	—	acetyl
	1-2-5	—
	—	acetyl
	1-3-4	—
	—	acetyl
	1-3-6	—
	—	acetyl

[a] Bp 92° C/2.5 mm

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
60	—	—	—	—	—	13,15,18,22	*
130	—	—	—	—	—	13,15,18,22	*
30	112/8[a]	—	—	—	—	33	*
54	—	—	—	—	—	33	*
34	147	—	—	—	—	6,27	*
153	—	—	—	—	—	6	*
90	—	—	—	—	—	—	*
92	—	—	—	—	—	7	*
62	92/23	—	—	—	—	—	*
116	—	—	—	—	—	—	*
40	—	—	—	—	—	—	*
153	—	—	—	—	—	—	*
—	141/2	—	—	—	—	34	*
117	—	—	—	—	—	34	*
—	64/2	—	—	—	—	—	*
118	—	—	—	—	—	—	*
46	—	—	—	—	—	34	*
130	—	—	—	—	—	34	*
—	97-99/14	—	1.5625/20	—	—	12,22	*
100	—	—	—	—	—	12,22	*
—	132/4	—	1.5294/25	—	—	33	*
—	101/1.5	—	—	—	—	34	*
112	—	—	—	—	—	34	*
—	139/10	—	1.5190/25	—	—	33	*
—	76/5.5	—	1.5558/25	—	—	—	—
155	—	—	—	—	—	—	—
—	89/10	—	—	—	—	22	*
111	—	—	—	—	—	22	*
61	—	—	—	—	—	22	—
146	—	—	—	—	—	22	—
26	—	—	—	—	--	—	—
91	—	—	—	—	—	—	—

next page)

TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
	1-4-2	—
	—	acetyl
	—	ethyl carbamate
	—	glycine ethyl ester
	—	glycine hydrazide
	—	β-Naphthol derivative
	1-4-3	—
	—	glycine ethyl ester
	—	glycine hydrazide
	—	hydrochloride salt
$C_6H_5ClF_2N_2$	$\frac{(NH_2)_2\text{-}F_2\text{-}Cl}{1,2\text{-}3,5\text{-}4}$	—
	—	quinoxaline
	1,2-3,5-6	quinoxaline
	1,2-3,6-4	—
	—	quinoxaline
	1,4-2,5-3	—
	1,4-2,6-3	—
C_6H_5F	$\frac{F}{1}$	—
$C_6H_5FN_2O_2$	$\frac{NH_2\text{-}NO_2\text{-}F}{1\text{-}2\text{-}3}$	—
	1-2-4	—
	1-2-5	—
	—	acetyl
	1-2-6	—
	—	acetyl
	1-3-4	—
	—	acetyl
	1-4-2	—
	—	acetyl
	1-4-3	—
	—	acetyl

[a] microcap
[b] Bp 85° C/9mm

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
—	192[a]	—	—	—	—	22	*
117	—	—	—	—	—	22	*
—	84/9	—	—	—	—	34	—
42	140/2[b]	—	—	—	—	—	*
129	—	—	—	—	—	34	*
165	—	—	—	—	—	—	—
45	—	—	—	—	—	22	*
108	—	—	—	—	—	34	*
101	—	—	—	—	—	34	*
—	—	—	—	—	—	—	*
85-90d	—	—	—	—	—	—	—
145	—	—	—	—	—	—	*
180	—	—	—	—	—	—	*
98	—	—	—	—	—	—	*
170	—	—	—	—	—	—	*
103	—	—	—	—	—	—	*
108	—	—	—	—	—	—	—
—	85	—	1.4658/20	—	—	29,35	*
—	—	—	—	—	—	—	*
93	—	—	—	—	—	9,10	—
97	—	—	—	—	—	9,10	*
85	—	—	—	—	—	—	—
76	—	—	—	—	—	—	—
183	—	—	—	—	—	—	—
91-93	—	—	—	—	—	9,10	*
139	—	—	—	—	—	—	—
131	—	—	—	—	—	—	*
205	—	—	—	—	—	—	*
162	—	—	—	—	—	—	*
174	—	—	—	—	—	—	—

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TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
	—	hydrochloride salt
C_6H_5FO	OH-F / 1-2	—
	—	chloroacetate ester
	1-3	—
	1-4	—
$C_6H_5FO_2$	$(OH)_2$-F / 1,4-2	—
	—	acetate
$C_6H_5FO_2S$	SO_2F / 1	—
$C_6H_5F_2N$	NH_2-F_2 / 1-2,4	—
	—	acetyl
	—	ethyl carbamate
	—	glycine ethyl ester
	—	glycine hydrazide
	—	isopropyl carbamate
	1-2,5	—
	—	acetyl
	—	ethyl carbamate
	—	isopropyl carbamate
	1-2,6	acetyl
	1-3,5	—
	—	acetyl
	1-3,4	—
	—	acetyl
	—	ethyl carbamate
	—	glycine ethyl ester
	—	glycine hydrazide
	—	isopropyl carbamate

[a] Bp 66-68° C/20 mm
[b] 29 (unstable mp)

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
—	—	—	—	—	—	—	*
16	152[a]	—	1.5160/16	—	—	9,10	*
36-38	90-94/4	—	—	—	—	—	—
13	178	—	—	—	—	9,10,22	*
48[b]	185	—	—	—	—	9,10,22	*
123	—	—	—	—	—	19	—
118	—	—	—	—	—	19	*
—	207	—	—	—	—	—	—
—	170	—	—	—	—	—	*
121	—	—	—	—	—	—	*
55	—	—	—	—	—	33	*
94	—	—	—	—	—	34	—
106	—	—	—	—	—	34	*
76	—	—	—	—	—	33	*
13	85/30	—	—	—	—	22	*
123	—	—	—	—	—	22	*
—	121/14	—	1.4989/20	—	—	33	*
—	114/5	—	1.4910/20	—	—	33	*
145	—	—	—	—	—	—	*
40	82/20	—	—	—	—	6,23,27	—
130	—	—	—	—	—	6,27	—
—	77/7	—	—	—	—	—	*
124	—	—	—	—	—	—	*
46	—	—	—	—	—	33	*
71	—	—	—	—	—	34	*
96	—	—	—	—	—	34	*
57	—	—	—	—	—	33	—

next page)

Empirical formula	Ring substitution	Compound type or derivative
	1-3,5	—
	—	acetyl
	—	ethyl carbamate
$C_6H_5F_3N_2$	$\frac{(NH_2)_2\text{-}F_3}{1,2\text{-}3,4,6}$	—
	—	quinoxaline
	1,4-2,3,5	—
$C_6H_6BrFN_2$	$\frac{(NH_2)_2\text{-}F\text{-}Br}{1,2\text{-}3\text{-}5}$	—
	—	quinoxaline
	1,4-2-5	—
$C_6H_6ClFN_2$	$\frac{(NH_2)_2\text{-}F\text{-}Cl}{1,2\text{-}4\text{-}5}$	—
	—	quinoxaline
	1,4-2-5	—
C_6H_6FN	$\frac{NH_2\text{-}F}{1\text{-}2}$	—
	—	acetyl
	—	ethyl carbamate
	—	glycine ethyl ester
	—	glycine hydrazide
	—	isopropyl carbamate
	1-3	—
	—	acetyl
	—	ethyl carbamate
	—	glycine ethyl ester
	—	glycine hydrazide
	—	isopropyl carbamate
	1-4	—
	—	acetyl
	—	diazonium fluoborate
	—	ethyl carbamate
	—	glycine ethyl ester
	—	glycine hydrazide
	—	isopropyl carbamate

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
40	80/20	—	—	—	—	—	*
130	—	—	—	—	—	—	*
74	—	—	—	—	—	—	*
76	—	—	—	—	—	15	—
170	—	—	—	—	—	15	*
109	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—
142	—	—	—	—	—	—	*
107	—	—	—	—	—	—	—
112	—	—	—	—	—	—	*
132	—	—	—	—	—	—	*
121	—	—	—	—	—	—	—
—	176	1.5467/18	—	—	—	—	*
80	—	—	—	—	—	—	*
—	122/14	—	1.5125/25	—	—	33	*
—	121/5	—	—	—	—	34	*
91	—	—	—	—	—	34	*
—	119/10	—	1.5031/25	—	—	33	*
—	186	—	1.5453/20	—	—	—	*
85	—	—	—	—	—	—	—
39	—	—	—	—	—	33	*
80	—	—	—	—	—	34	*
114	—	—	—	—	—	34	*
36	—	—	—	—	—	33	*
—	188	-0.82	1.5395/20	—	—	22	*
152	—	—	—	—	—	22	*
155-160	—	—	—	—	—	—	*
56	—	—	—	—	—	33	*
74	—	—	—	—	—	34	*
115	—	—	—	—	—	34	*
88	—	—	—	—	—	33	*

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TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
	$\frac{F\text{-}CH_3}{2\text{-}3}$	pyridine
	2-5	pyridine
	2-6	pyridine
$C_6H_6F_2N_2$	$\frac{(NH_2)_2\text{-}F_2}{1,2\text{-}3,5}$	—
	—	quinoxaline
	1,2-3,6	—
	—	quinoxaline
	1,3-4,6	—
	—	diacetyl
	1,4-2,5	—
	—	diacetyl
$C_6H_7FN_2$	$\frac{(NH_2)_2\text{-}F}{1,2\text{-}4}$	—
	—	quinoxaline
	1,4-2	—
	$\frac{F\text{-}NHNH_2}{1\text{-}3}$	—
	1-4	—
$C_7HClF_5NO_2$	$\frac{F_2\text{-}NO_2\text{-}CF_3\text{-}Cl}{1,3\text{-}6\text{-}5\text{-}4}$	—
$C_7HCl_2F_4NO_2$	$\frac{CF_3\text{-}NO_2\text{-}F\text{-}Cl_2}{1\text{-}2\text{-}3\text{-}5,6}$	—
$C_7HCl_2F_5$	$\frac{F_2\text{-}CF_3\text{-}Cl_2}{1,3\text{-}5\text{-}4,6}$	—
$C_7HCl_3F_4$	$\frac{F\text{-}CF_3\text{-}Cl_3}{1\text{-}3\text{-}2,4,5}$	—
$C_7HF_6NO_2$	$\frac{F_3\text{-}NO_2\text{-}CF_3}{1,2,5\text{-}4\text{-}3}$	—
	1,3,5-2-4	—
$C_7H_2BrClF_3I$	$\frac{CF_3\text{-}Cl\text{-}I\text{-}Br}{1\text{-}2\text{-}3\text{-}5}$	—
$C_7H_2ClF_4NO_2$	$\frac{F\text{-}NO_2\text{-}CF_3\text{-}Cl}{1\text{-}2\text{-}6\text{-}4^d}$	—

[a] Bp 126° C/19 mm
[b] 178° C microcap
[c] microcap
[d] from GLC

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
—	150	—	—	—	—	—	*
—	156-158	—	—	—	—	—	*
—	141	—	1.4678/25	—	—	—	*
48	—	—	—	—	—	6,27	—
138	—	—	—	—	—	6,27	—
80	—	—	—	—	—	15	*
192	—	—	—	—	—	15	*
111	—	—	—	—	—	—	—
222	—	—	—	—	—	—	*
129	—	—	—	—	—	15	*
306	—	—	—	—	—	15	*
98	—	—	—	—	—	—	*
136	—	—	—	—	—	—	*
81	—	—	—	—	—	—	—
—	130/20	—	1.5700/20	—	—	—	—
—	104/8[a]	—	—	—	—	—	—
—	105/20	—	—	—	—	—	—
—	122/20	—	—	—	—	—	*
—	83/20[b]	—	1.4659/20	—	—	—	*
—	102/20	—	1.4997/20	—	—	—	—
—	90/20	—	1.4269/20	—	—	—	—
—	185[c]	—	1.4347/20	—	—	—	—
53	—	—	—	—	—	—	*
—	—	—	—	—	—	—	*

next page)

Empirical formula	Ring substitution	Compound type or derivative
	1-3-5-4	—
$C_7H_2ClF_5$	$\frac{F_3\text{-}CClF_2}{1,3,5\text{-}2}$	—
	$\frac{F_2\text{-}CF_3\text{-}Cl}{1,3\text{-}5\text{-}4}$	—
	1,4-3-2	—
	1,4-3-5	—
$C_7H_2Cl_2F_3NO_2$	$\frac{CF_3\text{-}Cl_2\text{-}NO_2}{1\text{-}2,5\text{-}3}$	—
$C_7H_2Cl_2F_4$	$\frac{F\text{-}CF_3\text{-}Cl_2}{1\text{-}3\text{-}2,4}$	—
	1-3-4,5	—
$C_7H_2Cl_3F_3$	$\frac{F_3\text{-}CCl_3}{1,3,5\text{-}2}$	—
$C_7H_2F_2INO_4$	$\frac{COOH\text{-}F_2\text{-}I\text{-}NO_2}{1\text{-}3,4\text{-}6\text{-}5}$	—
	—	phenyl ester
$C_7H_2F_3N$	$\frac{F_3\text{-}CN}{1,3,5\text{-}2}$	—
$C_7H_2F_4N_2O_4$	$\frac{F\text{-}(NO_2)_2\text{-}CF_3}{1\text{-}4,5\text{-}3}$	—
$C_7H_2F_5NO_2$	$\frac{F_2\text{-}NO_2\text{-}CF_3}{1,3\text{-}4\text{-}5}$	—
	1,4-5-3	—
$C_7H_2F_6$	$\frac{F_3\text{-}CF_3}{1,3,4\text{-}5}$	—
	1,3,5-2	—
$C_7H_3BrClF_3$	$\frac{CF_3\text{-}Br\text{-}Cl}{1\text{-}3\text{-}4}$	—
$C_7H_3Br_2F_3$	$\frac{CF_3\text{-}Br_2}{1\text{-}2,5}$	—
$C_7H_3BrF_4$	$\frac{CF_3\text{-}F\text{-}Br}{1\text{-}2\text{-}5}$	—

[a] Bp 148° C
[b] Bp 91° C/20 mm
[c] Bp 205° C
[d] Bp 89° C/20 mm

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
—	110/20	—	1.4769/20	—	—	—	—
—	137	—	1.4287/20	—	—	—	—
—	137	-24	1.4281/20	—	—	—	—
—	70/25[a]	—	1.4389/20	—	—	—	—
—	137	-55	1.4264/20	—	—	—	—
54-57	—	—	—	—	—	—	*
—	186 microcap[b]	-22	1.4797/20	—	—	—	—
—	167	4	1.4669/20	—	—	—	—
—	56/3[c]	—	1.5070/20	—	—	31	—
—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	*
59	—	—	—	—	—	31	—
102	—	—	—	—	—	—	*
—	182	—	1.4353/20	—	—	36	—
—	192[d]	—	1.4883/20	1.6058	—	33,36	—
—	103	—	1.3830/20	1.495	21.6	36	*
—	106	—	1.3844/20	—	—	—	—
—	100/37	—	—	—	—	—	*
48-50	—	—	—	—	—	—	*
—	67/23	—	—	—	—	—	—

next page)

TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
	1-3-6	—
$C_7H_3ClF_3NO_2$	$\frac{CF_3\text{-}NO_2\text{-}Cl}{1\text{-}2\text{-}5}$	—
	1-3-5	—
$C_7H_3ClF_4$	$\frac{CF_3\text{-}F\text{-}Cl}{1\text{-}2\text{-}5}$	—
	1-3-4	—
	1-3-6	—
	1-4-3	—
$C_7H_3ClF_4N_2O_2$	$\frac{NH_2\text{-}NO_2\text{-}CF_3\text{-}F\text{-}Cl}{1\text{-}4\text{-}3\text{-}5\text{-}2}$	—
	—	acetyl
$C_7H_3ClF_5N$	$\frac{NH_2\text{-}CF_3\text{-}F_2\text{-}Cl}{1\text{-}2\text{-}4,6\text{-}3}$	—
	—	acetyl
$C_7H_3Cl_2FO$	$\frac{CHO\text{-}Cl_2\text{-}F}{1\text{-}2,6\text{-}3}$	—
	—	acetyl
$C_7H_3Cl_2FO_2$	$\frac{COOH\text{-}Cl_2\text{-}F}{1\text{-}2,5\text{-}3}$	—
	1-2,6-3	—
$C_7H_3Cl_2F_3$	$\frac{CF_3\text{-}Cl_2}{1\text{-}2,5}$	—
	$\frac{F_3\text{-}CHCl_2}{1,3,5\text{-}2}$	—
$C_7H_3Cl_2F_4N$	$\frac{NH_2\text{-}CF_3\text{-}F\text{-}Cl_2}{1\text{-}2\text{-}6\text{-}3,4}$	—
	—	acetyl
$C_7H_3FN_2O_6$	$\frac{COOH\text{-}(NO_2)_2\text{-}F}{1\text{-}3,5\text{-}4}$	—
$C_7H_3F_2N$	$\frac{CN\text{-}F_2}{1\text{-}2,4}$	—
	1-2,6	—
$C_7H_3F_2NO_4$	$\frac{COOH\text{-}F_2\text{-}NO_2}{1\text{-}2,6\text{-}3}$	—
$C_7H_3F_3N_2O_4$	$\frac{CF_3\text{-}(NO_2)_2}{1\text{-}3,5}$	—

[a] 179° C microcap

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
—	—	—	—	—	—	—	*
—	84/53	—	—	—	—	—	—
—	—	—	—	—	—	—	*
—	142	-5	1.4369/20	—	—	—	*
—	136-138	—	—	—	—	—	—
—	136	-20	1.4388/20	1.4601	—	—	*
—	136-138	—	1.4359/20	—	—	—	—
97	—	—	—	—	—	—	—
179	—	—	—	—	—	—	*
—	94/20	—	—	—	—	—	—
147	—	—	—	—	—	—	*
—	—	—	—	—	—	—	*
91	—	—	—	—	—	—	*
143	—	—	—	—	—	—	*
138	—	—	—	—	—	—	*
—	172	—	—	—	—	—	*
—	103/6[a]	—	1.4898/20	—	—	—	—
—	110/20	—	—	—	—	—	*
175	—	—	—	—	—	—	*
—	—	—	—	—	—	—	*
47	—	—	—	—	—	—	—
—	99/20	—	—	—	—	—	—
103	—	—	—	—	—	—	*
50	—	—	—	--	—	9,10,37	*

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TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
$C_7H_3F_3O$	CHO-F_3 / 1-2,4,6	—
	—	oxime
$C_7H_3F_3O_2$	COOH-F_3 / 1-2,3,4	—
	1-2,3,5	—
	1-2,4,5	—
	1-2,4,6	—
	CF_3 / 2	1,4-quinone
$C_7H_3F_4I$	F-CF_3-I / 1-3-4	—
$C_7H_3F_4NO_2$	F-NO_2-CF_3 / 1-2-4	—
	1-3-5	—
	1-4-2	—
	1-4-3	—
$C_7H_3F_5$	F_2-CF_3 / 1,2-4	—
	1,3-5	—
	1,4-2	—
	F_3-CHF_2 / 1,3,5-2	—
$C_7H_3F_5N_2O_2$	NH_2-NO_2-CF_3-F_2 / 1-4-3-2,5	—
	—	acetyl
$C_7H_3F_6N$	NH_2-F_3-CF_3 / 1-2,4,5-6	—
	—	acetyl
$C_7H_4BrCl_2F$	CH_2Br-Cl_2-F / 1-2,6-3	strong lachrymator
	1-2,6-4	strong lachrymator
$C_7H_4BrFO_2$	COOH-Br-F / 1-2-3	—
	1-2-6	—

[a] 200° C microcap

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
66	—	—	—	—	—	—	—
176	—	—	—	—	—	—	*
138	—	—	—	—	—	—	*
106	—	—	—	—	—	22	*
98	—	—	—	—	—	9,10	*
142	—	—	—	—	—	31	*
47	—	—	—	—	—	—	—
—	83-85/25	—	—	—	—	—	*
—	92/15	—	1.4618/20	—	—	13	*
—	181	—	—	—	—	—	—
—	95/23	—	—	—	—	13	*
—	98/21[a]	—	1.4610/20	—	—	38	*
—	103 microcap	—	1.3948/20	—	—	—	—
—	95	—	1.3873/20	—	—	36,38	—
—	109	-14	1.3942/20	—	—	36,38	*
—	125 microcap	—	—	—	—	—	—
75	—	—	—	—	—	—	*
136	—	—	—	—	—	—	*
—	44/6.4	-13	1.4390/20	—	—	—	—
120	—	—	—	—	—	—	*
—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	—
159	—	—	—	—	—	—	*
154	—	—	—	—	—	—	*

next page)

TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
	1-4-2	—
	1-4-3	—
$C_7H_4BrF_3$	$\frac{CF_3\text{-}Br}{1\text{-}2}$	—
	1-3	—
$C_7H_4ClFN_2O_4$	$\frac{CH_3\text{-}F\text{-}Cl\text{-}(NO_2)_2}{1\text{-}2\text{-}6\text{-}3,5}$	—
$C_7H_4ClFO_2$	$\frac{COOH\text{-}F\text{-}Cl}{1\text{-}2\text{-}3}$	—
	1-2-4	—
	1-2-6	—
	1-3-2	—
	1-3-6	—
$C_7H_4ClF_3$	$\frac{F_3\text{-}CH_2Cl}{1,3,5\text{-}2}$	—
	$\frac{CF_3\text{-}Cl}{1\text{-}2}$	—
	1-3	—
	1-4	—
$C_7H_4ClF_3O$	$\frac{OCF_3\text{-}Cl}{1\text{-}4}$	—
$C_7H_4ClF_4N$	$\frac{NH_2\text{-}CF_3\text{-}F\text{-}Cl}{1\text{-}3\text{-}5\text{-}2}$	—
	—	acetyl
$C_7H_4Cl_2F_3N$	$\frac{NH_2\text{-}Cl_2\text{-}CF_3}{1\text{-}2,5\text{-}3}$	—
	—	acetyl
C_7H_4FN	$\frac{F\text{-}CN}{1\text{-}2}$	—
	1-4	—
$C_7H_4FNO_4$	$\frac{COOH\text{-}F\text{-}NO_2}{1\text{-}2\text{-}4}$	—
	1-2-5	—
	1-4-3	—
$C_7H_4F_2O_2$	$\frac{COOH\text{-}F_2}{1\text{-}2,4}$	—

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
210-212	—	—	—	—	—	—	*
145-148	--	—	—	—	—	—	*
—	—	—	—	—	—	—	*
—	156	—	—	—	—	39	*
84	--	—	—	—	—	7	*
175	—	—	—	—	—	—	*
206	—	—	—	—	—	—	*
157	—	—	—	—	—	—	*
170	—	—	—	—	—	—	*
148	—	—	—	—	—	22	*
—	156-160	—	—	—	—	9,10,31	*
—	153	—	—	—	—	—	*
—	138 microcap	-55	1.4466/21	—	—	—	*
—	—	—	-	—	—	—	*
—	144	—	—	—	—	—	*
—	109/20	—	—	—	—	—	—
139	—	—	—	—	—	—	*
—	—	—	—	—	—	—	*
141	—	—	—	—	—	—	*
—	103/35	—	—	—	—	12,30	—
38	—	—	—	—	—	30	*
—	—	—	—	—	—	—	*
137	—	—	—	—	—	—	*
121	—	—	—	—	—	—	*
184	—	—	—	—	—	9,10	*

next page)

Empirical formula	Ring substitution	Compound type or derivative
	—	sodium salt
	1-2,5	—
	1-2,6	—
	—	amide
	—	ethyl ester
	—	methyl ester
	1-3,4	—
	1-3,5	—
$C_7H_4F_3I$	$\frac{CF_3\text{-}I}{1\text{-}3}$	—
	$\frac{F_3\text{-}CH_2I}{1,3,5\text{-}2}$	—
$C_7H_4F_3NO_2$	$\frac{CF_3\text{-}NO_2}{1\text{-}2}$	—
	1-3	—
	1-4	—
$C_7H_4F_3NO_3$	$\frac{OH\text{-}NO_2\text{-}CF_3}{1\text{-}2\text{-}3}$	—
	1-4-3	—
	—	benzoate
$C_7H_4F_3N_3$	$\frac{CF_3}{5}$	benzotriazole
$C_7H_4F_4$	$\frac{F\text{-}CF_3}{1\text{-}2}$	—
	1-3	—
	1-4	—
	$\frac{F_3\text{-}CH_2F}{1,3,5\text{-}2}$	—
$C_7H_4F_4N_2O_2$	$\frac{NH_2\text{-}NO_2\text{-}CF_3\text{-}F}{1\text{-}2\text{-}3\text{-}5}$	—
	—	acetyl
	1-2-6-4	—
	—	acetyl
	1-4-3-5	—
	—	acetyl
	1-4-5-2	—

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
—	—	—	—	—	—	—	—
131	—	—	—	—	—	—	*
156	—	—	—	—	—	—	*
142	—	—	—	—	—	—	*
—	112/20	—	—	—	—	—	—
—	102/20	—	—	—	—	—	*
120	—	—	—	—	—	—	*
122	—	—	—	—	—	—	*
—	83/25	—	—	—	—	39	*
—	60/.4	—	1.5531/20	—	—	—	—
33	217-219	—	—	—	—	—	—
2	94-99/20	—	—	—	—	40	*
—	197	—	—	—	—	—	*
74	—	—	—	—	—	—	*
78-80	—	—	—	—	—	—	*
109	—	—	—	—	—	—	—
132-134	—	—	—	—	—	—	*
—	114	—	1.4071/20	—	—	—	*
—	101	-49	1.4005/20	—	—	—	*
—	102	—	—	—	—	—	*
—	63/68	—	1.4295/20	—	—	—	—
121	—	—	—	—	—	—	*
140	—	—	—	—	—	—	*
69	—	—	—	—	—	41	*
180	—	—	—	—	—	41	*
122	—	—	—	—	—	—	*
133	—	—	—	—	—	—	*
98	—	—	—	—	—	—	*

next page)

TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
	—	acetyl
$C_7H_4F_5N$	$\frac{NH_2\text{-}CF_3\text{-}F_2}{1\text{-}2\text{-}4,6}$	—
	—	acetyl
	1-3-2,5	—
	—	acetyl
	—	ethyl carbamate
	—	hydrochloride salt
	—	isopropyl carbamate
$C_7H_5BrF_3N$	$\frac{NH_2\text{-}CF_3\text{-}Br}{1\text{-}3\text{-}4}$	—
	—	glycine ethyl ester
	—	glycine hydrazide[a]
	1-3-6	—
	—	acetyl
	—	glycine ethyl ester
$C_7H_5ClF_2O$	$\frac{OCH_3\text{-}F_2\text{-}Cl}{1\text{-}3,5\text{-}2}$	—
$C_7H_5ClF_3N$	$\frac{NH_2\text{-}CF_3\text{-}Cl}{1\text{-}2\text{-}4}$	—
	1-3-4	—
	—	glycine ethyl ester
	—	glycine hydrazide[c]
$C_7H_5ClF_4N_2$	$\frac{(NH_2)_2\text{-}CF_3\text{-}F\text{-}Cl}{1,4\text{-}2\text{-}6\text{-}3}$	—
	1,4-3-2-5	—
$C_7H_5Cl_2F$	$\frac{CH_3\text{-}Cl_2\text{-}F}{1\text{-}2,6\text{-}3}$	—
$C_7H_5Cl_2FO$	$\frac{CH_2OH\text{-}Cl_2\text{-}F}{1\text{-}2,6\text{-}3}$	—
	—	acetate
$C_7H_5FN_2O_4$	$\frac{F\text{-}(NO_2)_2\text{-}CH_3}{1\text{-}2,4\text{-}5}$	—

[a] Bp 181° C
[b] acetone derivative
[c] acetone derivative

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
152-154	—	—	—	—	—	—	*
—	150	—	1.4441/20	—	—	36	*
149	—	—	—	—	—	—	*
—	78/20[a]	-12	1.4519/25	1.5096	—	33,36	*
105	—	—	—	—	—	33	*
—	116/8	—	1.4552/25	—	—	33	*
—	—	—	—	—	—	—	*
—	120/8	—	1.4500/25	—	—	33	*
—	—	—	—	—	—	—	—
111	—	—	—	—	—	34	*
154	—	—	—	—	—	34	*
—	—	—	—	—	—	—	—
138	—	—	—	—	—	—	*
50-51	—	—	—	—	—	—	—
60	—	—	—	—	—	—	*
—	77/7.4	—	—	—	—	—	*
—	90/.6	—	—	—	—	—	*
103	—	—	—	—	—	34	*
156	—	—	—	—	—	34	*
70	—	—	—	—	—	—	*
71	—	—	—	—	—	—	*
35-37	—	—	—	—	—	—	*
—	108/4	—	—	—	—	—	—
54	—	—	—	—	—	—	*
79	—	—	—	—	—	8,9,10	*

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Empirical formula	Ring substitution	Compound type or derivative
$C_7H_5FO_2$	CHO-F-OH / 1-2-4	—
	F-CH_3 / 2-5	1,4-quinone
	COOH-F / 1-2	—
	—	hydrazide
	—	methyl ester
	—	sodium salt
	1-3	—
	1-4	—
$C_7H_5FO_3$	COOH-OH-F / 1-2-3	—
	1-2-5	—
	—	acetoxy
	1-2-6	—
	—	methyl ester
	1-4-2	—
	1-4-3	—
	—	acetoxy
$C_7H_5F_2IO$	OCH_3-F_2-I / 1-2,4-6	—
$C_7H_5F_2NO_2$	CH_3-F_2-NO_2 / 1-2,6-3	—
$C_7H_5F_2NO_3$	OCH_3-F_2-NO_2 / 1-2,4-5	—
	1-2,4-6	—
	1-3,5-2	—
$C_7H_5F_3$	F_3-CH_3 / 1,2,4-3	—
	1,3,5-2	—
	CF_3 / 1	—
$C_7H_5F_3N_2O_2$	NH_2-NO_2-CF_3 / 1-2-3	—

[a] Bp 107° C

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
—	—	—	—	—	—	—	*
78	—	—	—	—	—	9,10,19	—
123	—	—	—	—	—	12	*
73	—	—	—	—	—	—	*
—	110/30	—	1.4999/25	—	—	—	*
—	—	—	—	—	—	42	*
124	—	—	—	—	—	—	*
184	—	—	—	—	—	—	*
141-144	—	—	—	—	—	—	*
178	—	—	—	—	—	—	*
137	—	—	—	—	—	—	*
160	—	—	—	—	—	—	*
157	—	—	—	—	—	—	*
183	—	—	—	—	—	—	—
162	—	—	—	—	—	—	*
207	—	—	—	—	—	—	*
—	73/5	—	1.5493/20	—	—	—	*
—	96/8	—	—	—	—	—	*
95	—	—	—	—	—	—	*
33	—	—	—	—	—	9,10	*
60	—	—	—	—	—	—	*
119	—	—	—	—	—	—	*
—	49/98[a]	—	1.4292/20	—	—	31	*
—	99	—	1.4141/20	1.1869	—	—	*
61	—	—	—	—	—	—	*

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TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
	—	acetyl
	—	ethyl carbamate
	1-2-4	—
	1-2-5	—
	—	acetyl
	—	benzene sulfonamide
	1-3-5	—
	—	acetyl
	1-4-2	—
	1-4-3	—
	—	acetyl
	—	benzamide
	—	benzene sulfonamide
	—	ethyl carbamate
$C_7H_5F_3O$	$\frac{CF_3\text{-}OH}{1\text{-}3}$	—
	—	p-nitrobenzoate
	$\frac{F_3\text{-}CH_2OH}{1,3,5\text{-}2}$	—
	$\frac{OCH_3\text{-}F_3}{1\text{-}2,4,6}$	—
$C_7H_5F_3O_2$	$\frac{(OH)_2\text{-}CF_3}{1,4\text{-}2}$	—
$C_7H_5F_4N$	$\frac{NH_2\text{-}CF_3\text{-}F}{1\text{-}2\text{-}4}$	—
	—	acetyl
	—	benzamide
	—	benzene sulfonamide
	—	p-nitrobenzamide
	1-3-2	—
	1-3-4	—
	—	acetyl
	—	ethyl carbamate
	—	glycine ethyl ester

[a] BP 176° C

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
171	—	—	—	—	—	—	*
115	—	—	—	—	—	—	*
107	—	—	—	—	—	—	*
103	—	—	—	—	—	—	*
68	—	—	—	—	—	—	*
183	—	—	—	—	—	—	—
81	—	—	—	—	—	—	*
135	—	—	—	—	—	—	*
96	—	—	—	—	—	—	*
129	—	—	—	—	—	—	*
122	—	—	—	—	—	—	—
131	—	—	—	—	—	—	—
174-176	—	—	—	—	—	—	—
134	—	—	—	—	—	—	*
—	79-83/22[a]	—	—	—	—	—	*
90	—	—	—	—	—	—	*
45	—	—	—	—	—	—	*
—	134	—	—	—	—	—	—
109	—	—	—	—	—	—	—
—	63/14.8	—	1.4638/20	—	—	38	*
123	—	—	—	—	—	38	*
135	—	—	—	—	—	—	—
101	—	—	—	—	—	—	—
143	—	—	—	—	—	—	—
—	—	—	—	—	—	—	*
—	96/20	—	—	—	—	33	*
61	—	—	—	—	—	33	*
—	125/3	—	—	—	—	33	*
82	—	—	—	—	—	34	*

next page)

Empirical formula	Ring substitution	Compound type or derivative
	—	glycine hydrazide
	—	isopropyl carbamate
	1-3-5	acetyl
	1-3-6	—
	—	acetyl
	—	ethyl carbamate
	—	glycine ethyl ester
	—	glycine hydrazide
	—	isopropyl carbamate
$C_7H_5F_5N_2$	$\underline{(NH_2)_2\text{-}CF_3\text{-}F_2}$ 1,4-2-3,6	—
	—	acetyl
	—	diacetyl
C_7H_6BrF	$\underline{CH_3\text{-}Br\text{-}F}$ 1-2-3	—
	1-2-6	—
	1-4-2	—
C_7H_6BrFO	$\underline{OCH_3\text{-}F\text{-}Br}$ 1-2-4	—
	1-2-6	—
	1-4-2	—
C_7H_6ClF	$\underline{CH_3\text{-}Cl\text{-}F}$ 1-2-3	—
	1-2-6	—
	1-3-6	—
	1-4-2	—
C_7H_6ClFO	$\underline{CH_2OH\text{-}Cl\text{-}F}$ 1-2-6	—
	$\underline{OCH_3\text{-}F\text{-}Cl}$ 1-2-4	—
	1-4-2	—
C_7H_6FI	$\underline{CH_3\text{-}F\text{-}I}$ 1-2-6	—
	$\underline{CH_2Cl\text{-}F}$ 1-4	—

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
114	—	—	—	—	—	—	*
79	—	—	—	—	—	33	*
101	—	—	—	—	—	—	*
—	81/20	—	1.4608/20	—	—	13	*
122	—	—	—	—	—	13	*
—	127/6	—	1.4620/25	—	—	33	*
—	110/2	—	—	—	—	34	*
151	—	—	—	—	—	34	*
46	116/7	—	—	—	—	33	*
58	—	—	—	—	—	—	—
105	—	—	—	—	—	—	*
157	—	—	—	—	—	—	*
—	87/30	—	1.5315/25	—	—	—	*
—	86.5/40	—	1.5318/20	—	—	—	*
—	72/17	—	1.5258/25	—	—	—	*
16	84/7	—	1.5448/20	—	—	22	*
104-108	—	—	—	—	—	—	*
—	79/5	-27	1.5447/20	—	—	22	*
—	161	—	—	—	—	—	*
—	—	—	—	—	—	—	—
151-154	—	—	—	—	—	—	*
—	158	—	—	—	—	—	—
—	112-114/7	—	—	—	—	—	—
—	72/7	-6	—	—	—	22	*
—	67/5	-17	1.5173/20	—	—	22	*
—	102/30	—	1.5793/25	—	—	—	*
—	—	—	—	—	—	—	*

next page)

TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
C_7H_6FIO	$\frac{OCH_3\text{-}F\text{-}I}{1\text{-}2\text{-}4}$	—
	1-4-2	—
$C_7H_6FNO_2$	$\frac{F\text{-}CH_3\text{-}NO_2}{1\text{-}2\text{-}3}$	—
	1-2-4	—
	1-2-6	—
	1-3-2	—
	1-3-4	—
	1-3-6	—
	1-4-2	—
	1-4-3	—
	$\frac{COOH\text{-}F\text{-}NH_2}{1\text{-}2\text{-}4}$	—
	—	acetyl
$C_7H_6FNO_3$	$\frac{OCH_3\text{-}F\text{-}NO_2}{1\text{-}2\text{-}4}$	—
	1-2-6	—
	1-4-2	—
$C_7H_6F_2$	$\frac{CH_3\text{-}F_2}{1\text{-}2,4}$	—
$C_7H_6F_2O$	$\frac{OCH_3\text{-}F_2}{1\text{-}2,4}$	—
	1-2,6	—
$C_7H_6F_2O_2$	$\frac{OH\text{-}CH_2OH\text{-}F_2}{1\text{-}2\text{-}4,6}$	—
$C_7H_6F_3N$	$\frac{NH_2\text{-}CF_3}{1\text{-}2}$	—
	—	acetyl
	—	hydrochloride salt
	1-3	—
	—	acetyl
	—	benzamide
	—	ethyl carbamate
	—	glycine ethyl ester

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
34	86/3	—	—	—	—	22	*
—	92/3	-21	1.5924/20	—	—	22	*
—	218	—	—	—	—	—	*
40	100/13	—	—	—	—	—	—
—	—	—	—	—	—	—	*
—	92/11	—	—	—	—	—	—
28	98/10	—	—	—	—	9,10,22	*
54	—	—	—	—	—	9,10	*
—	132-135/21.5	—	—	—	—	—	—
—	102/20	—	—	—	—	—	—
216	—	—	—	—	—	—	*
260	—	—	—	—	—	—	*
104	—	—	—	—	—	—	*
—	93/3	—	—	—	—	—	—
62	—	—	—	—	—	22	*
—	114	—	—	—	—	—	*
—	151	-16	1.4705/20	—	—	9,10	*
—	71/56	—	—	—	—	22	*
62	—	—	—	—	—	9,10	*
—	72/21	—	—	—	—	—	*
95	—	—	—	—	—	—	—
—	—	—	—	—	—	—	*
—	188	—	—	—	—	—	*
104	—	—	—	—	—	—	—
206	—	—	—	—	—	—	—
47	135/7	—	—	—	—	33	*
85	—	—	—	—	—	34	*

next page)

TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
	—	glycine hydrazide
	—	glycine hydrazide[a]
	—	isopropyl carbamate
	1-4	—
	—	acetyl
	—	ethyl carbamate
	—	glycine ethyl ester
$C_7H_6F_4N_2$	$\underline{(NH_2)_2\text{-}CF_3\text{-}F}$ 1,2-3-5	—
	—	quinoxaline
	1,3-5-2	—
C_7H_7F	$\underline{F\text{-}CH_3}$ 1-2	—
	1-3	—
	1-4	—
$C_7H_7FN_2O_2$	$\underline{NH_2\text{-}NO_2\text{-}CH_3\text{-}F}$ 1-4-5-2	—
	—	acetyl
C_7H_7FO	$\underline{OCH_3\text{-}F}$ 1-2	—
	1-3	—
	1-4	—
	$\underline{OH\text{-}CH_3\text{-}F}$ 1-2-3	—
	—	acetate
	1-2-4	—
	1-3-4	—
	1-4-2	—
$C_7H_7FO_2$	$\underline{(OH)_2\text{-}CH_3\text{-}F}$ 1,4-2-5	—
	—	acetate
$C_7H_7FO_2S$	$\underline{SO_2F\text{-}CH_3}$ 1-4	—

[a] acetone derivative

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
—	—	—	—	—	—	—	*
134	—	—	—	—	—	34	*
63	—	—	—	—	—	33	*
—	65-68/2	—	—	—	—	—	*
151	—	—	—	—	—	—	*
105	—	—	—	—	—	—	*
85	—	—	—	—	—	34	*
—	—	—	—	—	—	41	—
134	—	—	—	—	—	41	*
—	—	—	—	—	—	—	*
—	115	—	1.4735/20	—	—	—	*
—	115	—	1.4652/27	—	—	—	*
—	117	—	1.4688/20	—	—	—	—
107	—	—	—	—	—	—	—
180	—	—	—	—	—	—	*
—	74/30	—	1.4952/20	—	—	—	*
—	47/12	—	1.4888/20	—	—	—	*
—	64/20	—	1.4873/20	—	—	—	*
56	96/36	—	—	—	—	—	*
56	—	—	—	—	—	—	*
35	87/14	—	—	—	—	9,10,22	*
32	76/5	—	—	—	—	22	—
—	64/11	—	—	—	—	22	*
120	—	—	—	—	—	8,19	*
66	—	—	—	—	—	8,19	*
42	97-100/11.5	—	—	—	—	—	—

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TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
$C_7H_7F_2N$	$\frac{CH_3\text{-}F_2\text{-}NH_2}{1\text{-}2,6\text{-}3}$	—
	—	acetyl
$C_7H_7F_2NO$	$\frac{OCH_3\text{-}F_2\text{-}NH_2}{1\text{-}2,4\text{-}5}$	—
	—	acetyl
	1-2,4-6	—
	—	acetyl
	1-3,5-2	—
	—	acetyl
$C_7H_7F_3N_2$	$\frac{(NH_2)_2\text{-}CF_3}{1,2\text{-}3}$	—
	—	acetyl
	1,2-4	—
	—	acetyl
	1,3-5	—
	—	acetyl
	1,4-2	—
	—	acetyl
	$\frac{CF_3\text{-}NHNH_2}{1\text{-}3}$	—
C_7H_8FN	$\frac{NH_2\text{-}CH_3\text{-}F}{1\text{-}2\text{-}3}$	—
	—	acetyl
	—	ethyl carbamate
	—	glycine ethyl ester
	—	glycine hydrazide
	—	isopropyl carbamate
	1-2-4	—
	—	acetyl
	—	benzamide
	—	ethyl carbamate
	—	isopropyl carbamate
	1-3-4	—

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
—	94/28	—	—	—	—	—	*
115	—	—	—	—	—	—	*
70	—	—	—	—	—	—	—
128	—	—	—	—	—	—	*
—	104/22	—	—	—	—	—	*
79	—	—	—	—	—	—	*
48	—	—	—	—	—	—	—
143	—	—	—	—	—	—	*
—	—	—	—	—	—	—	—
231	—	—	—	—	—	—	*
63	—	—	—	—	—	—	—
—	—	—	—	—	—	—	*
88	—	—	—	—	—	—	*
295	—	—	—	—	—	—	*
58	—	—	—	—	—	—	—
189	—	—	—	—	—	—	*
—	124/17	—	—	—	—	—	—
80	—	—	—	—	—	—	—
129-131	—	—	—	—	—	—	*
80	—	—	—	—	—	—	*
52.5	123/2.75	—	—	—	—	34	*
121	—	—	—	—	—	34	*
106	—	—	—	—	—	—	*
—	94/16	—	—	—	—	22	*
113	—	—	—	—	—	22	*
164	—	—	—	—	—	—	—
69	—	—	—	—	—	33	*
114	—	—	—	—	—	33	*
36	—	—	—	—	—	22	*

next page)

TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
	—	acetyl
	1-3-6	—
	—	acetyl
	1-4-2	—
	—	acetyl
	1-4-3	—
	—	acetyl
	—	glycine ethyl ester
	—	glycine hydrazide
C_7H_8FNO	$\frac{OCH_3\text{-}NH_2\text{-}F}{1\text{-}2\text{-}4}$	—
	—	acetyl
	—	ethyl carbamate
	—	isopropyl carbamate
	1-2-6	—
	1-4-2	—
	—	acetyl
$C_7H_9FN_2$	$\frac{(NH_2)_2\text{-}CH_3\text{-}F}{1,4\text{-}2\text{-}5}$	—
	—	acetyl
$C_8H_3ClF_3N$	$\frac{CF_3\text{-}CN\text{-}Cl}{1\text{-}3\text{-}4}$	—
$C_8H_3ClF_6$	$\frac{(CF_3)_2\text{-}Cl}{1,3\text{-}5}$	—
$C_8H_3Cl_4FO_3$	$\frac{OCH_2COOH\text{-}F\text{-}Cl_4}{1\text{-}4\text{-}2,3,5,6}$	—
$C_8H_3F_4N$	$\frac{CF_3\text{-}CN\text{-}F}{1\text{-}3\text{-}4}$	—
$C_8H_3F_7$	$\frac{(CF_3)_2\text{-}F}{1,3\text{-}5}$	—
$C_8H_4BrCl_2FO_3$	$\frac{OCH_2COOH\text{-}F\text{-}Br\text{-}Cl_2}{1\text{-}4\text{-}2\text{-}3,5}$	—
$C_8H_4ClF_3O_2$	$\frac{ClCHCOOH\text{-}F_3}{1\text{-}2,4,6}$	—
	—	amide

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
77	—	—	—	—	—	22	*
—	—	—	—	—	—	—	—
77	—	—	—	—	—	—	*
—	190 microcap	—	—	—	—	22	*
124	—	—	—	—	—	22	*
—	200-205	—	—	—	—	—	—
134	—	—	—	—	—	—	*
79	—	—	—	—	—	34	*
152	—	—	—	—	—	34	*
—	117/20	3	—	—	—	22	*
102	—	—	—	—	—	—	*
52	—	—	—	—	—	33	*
—	138/4	—	1.5080/20	—	—	33	*
—	88/8.5	—	—	—	—	—	—
83	—	—	—	—	—	22	*
113	—	—	—	—	—	—	—
107	—	—	—	—	—	—	—
274	—	—	—	—	—	—	*
—	—	—	—	—	—	—	*
—	135	—	1.4031/25	—	—	—	*
188	—	—	—	—	—	22	*
—	99/27	—	—	—	—	30	*
—	105/739	—	—	—	—	—	*
144	—	—	—	—	—	22	*
97	—	—	—	—	—	—	*
94	—	—	—	—	—	—	*

next page)

Empirical formula	Ring substitution	Compound type or derivative
$C_8H_4Cl_3F_3O$	$\frac{CHOHCCl_3\text{-}F_3}{1\text{-}2,4,6}$	—
$C_8H_4F_3N$	$\frac{F_3\text{-}CH_2CN}{1,3,5\text{-}2}$	—
	$\frac{CF_3\text{-}CN}{1\text{-}4}$	—
$C_8H_4F_3NO_4$	$\frac{COOH\text{-}NO_2\text{-}CF_3}{1\text{-}3\text{-}4}$	—
$C_8H_4F_4O_2$	$\frac{COOH\text{-}CF_3\text{-}F}{1\text{-}3\text{-}6}$	—
$C_8H_5BrF_2O_3$	$\frac{OCH_2COOH\text{-}F_2\text{-}Br}{1\text{-}2,4\text{-}6}$	—
$C_8H_5Br_2FO_3$	$\frac{OCH_2COOH\text{-}F\text{-}Br_2}{1\text{-}2\text{-}4,6}$	—
	1-4-2,6	—
$C_8H_5ClF_2O_3$	$\frac{OCH_2COOH\text{-}F_2\text{-}Cl}{1\text{-}2,4\text{-}3}$	—
	1-2,4-5	—
	1-2,4-6	—
	1-2,5-4	—
	1-3,4-6	—
	1-3,5-2	—
	1-3,5-4	—
$C_8H_5Cl_2FO_3$	$\frac{OCH_2COOH\text{-}F\text{-}Cl_2}{1\text{-}2\text{-}4,5}$	—
	1-2-4,6	—
	1-3-2,4	—
	1-3-4,6	—
	1-4-2,5	—
	1-4-2,6	—
	1-4-3,5	—
$C_8H_5Cl_2F_3$	$\frac{F_3\text{-}(CH_2Cl)_2}{1,3,5\text{-}2,4}$	—
$C_8H_5FN_2O_7$	$\frac{OCH_2COOH\text{-}F\text{-}(NO_2)_2}{1\text{-}2\text{-}4,6}$	—

[a] 226° C microcap

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
—	106/4	—	—	—	—	—	*
—	125/40	—	1.4633/20	—	—	—	—
38	86/20	—	—	—	—	—	—
156-158	—	—	—	—	—	—	—
98	—	—	—	—	—	—	*
121	—	—	—	—	—	22	*
153	—	—	—	—	—	22	*
187	—	—	—	—	—	22	*
135	—	—	—	—	—	22	*
109	—	—	—	—	—	22	*
128	—	—	—	—	—	22	*
162	—	—	—	—	—	22	*
144	—	—	—	—	—	22	*
163	—	—	—	—	—	—	*
117	—	—	—	—	—	22	*
138	—	—	—	—	—	22	*
135	—	—	—	—	—	—	*
150	—	—	—	—	—	—	*
147	—	—	—	—	—	—	*
138	—	—	—	—	—	22	*
160	—	—	—	—	—	22	*
131	—	—	—	—	—	22	*
—	76/2[a]	—	1.5072/20	—	—	—	*
121	—	—	—	—	—	22	*

next page)

Empirical formula	Ring substitution	Compound type or derivative
	1-3-4,6	—
	1-4-2,6	—
$C_8H_5F_3O$	$\frac{CH_3CO\text{-}F_3}{1\text{-}2,4,5}$	—
	1-2,4,6	—
	—	oxime
$C_8H_5F_3O_2$	$\frac{COOH\text{-}CF_3}{1\text{-}2}$	—
	1-3	—
	—	ethyl ester
	—	methyl ester
	1-4	—
	$\frac{CH_2COOH\text{-}F_3}{1\text{-}2,4,6}$	—
	—	amide
$C_8H_5F_3O_3$	$\frac{OCH_2COOH\text{-}F_3}{1\text{-}2,3,4}$	—
	1-2,3,5	—
	1-2,4,5	—
	1-2,4,6	—
$C_8H_5F_6N$	$\frac{NH_2\text{-}(CF_3)_2}{1\text{-}3,5}$	—
	—	ethyl carbamate
	—	isopropyl carbamate
$C_8H_6BrFO_3$	$\frac{OCH_2COOH\text{-}F\text{-}Br}{1\text{-}2\text{-}4}$	—
	1-4-2	—
$C_8H_6ClFO_3$	$\frac{OCH_2COOH\text{-}F\text{-}Cl}{1\text{-}2\text{-}3}$	—
	1-2-4	—
	1-3-4	—
	1-3-6	—
	1-4-2	—
	1-4-3	—

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
144	—	—	—	—	—	22	*
161	—	—	—	—	—	22	*
—	99/20	7	1.4718/20	—	—	—	—
—	81/19	—	1.4659/20	—	—	—	—
100	—	—	—	—	—	31	*
108	—	—	—	—	—	—	—
105	—	—	—	—	—	—	*
—	216-219	—	—	—	—	—	—
—	194	—	—	—	—	—	—
216	—	—	—	—	—	—	*
110	—	—	—	—	—	31	*
160	—	—	—	—	—	—	*
132	—	—	—	—	—	22	*
152	—	—	—	—	—	22	*
123	—	—	—	—	—	22	*
108	—	—	—	—	—	22	*
—	—	—	—	—	—	—	—
93-95	—	—	—	—	—	33	*
124	—	—	—	—	—	33	*
113	—	—	—	—	—	22	*
138	—	—	—	—	—	22	*
152	—	—	—	—	—	22	—
125	—	—	—	—	—	22	*
132	—	—	—	—	—	22	*
161	—	—	—	—	—	22	*
136	—	—	—	—	—	22	*
105	—	—	—	—	—	22	*

next page)

Empirical formula	Ring substitution	Compound type or derivative
$C_8H_6ClF_3$	$\frac{CF_3\text{-}CH_2Cl}{1\text{-}3}$	—
$C_8H_6FIO_3$	$\frac{OCH_2COOH\text{-}F\text{-}I}{1\text{-}2\text{-}4}$	—
	1-4-2	—
C_8H_6FN	$\frac{F}{5}$	indole
$C_8H_6FNO_2$	—	2-Hydro-3-keto-6-fluoro-1,4-benzisoxazine
$C_8H_6FNO_4$	$\frac{CO_2CH_3\text{-}F\text{-}NO_2}{1\text{-}4\text{-}3}$	—
$C_8H_6FNO_5$	$\frac{OCH_2COOH\text{-}F\text{-}NO_2}{1\text{-}2\text{-}4}$	—
	1-3-6	—
	1-4-2	—
$C_8H_6F_2O$	$\frac{CH_3CO\text{-}F_2}{1\text{-}2,4}$	—
	1-2,5	—
	1-3,4	—
$C_8H_6F_2O_3$	$\frac{OCH_2COOH\text{-}F_2}{1\text{-}2,4}$	—
	1-2,5	—
	1-2,6	—
	1-3,4	—
	1-3,5	—
$C_8H_6F_3NO_2$	$\frac{COOH\text{-}NH_2\text{-}CF_3}{1\text{-}3\text{-}4}$	—
C_8H_7FO	$\frac{CH_3CO\text{-}F}{1\text{-}4}$	—
$C_8H_7FO_2$	$\frac{COOH\text{-}CH_3\text{-}F}{1\text{-}2\text{-}3}$	—
$C_8H_7FO_3$	$\frac{CHOHCOOH\text{-}F}{1\text{-}4}$	—
	$\frac{OCH_2COOH\text{-}F}{1\text{-}2}$	—
	1-3	—
	1-4	—

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
—	—	—	—	—	—	—	*
121	—	—	—	—	—	22	*
132	—	—	—	—	—	22	*
47	—	—	—	—	—	—	*
204	—	—	—	—	—	22	*
61	—	—	—	—	—	—	—
140	—	—	—	—	—	22	*
156	—	—	—	—	—	22	*
125	—	—	—	—	—	22	*
—	89/14	—	1.4881/20	—	—	—	—
—	91/25	—	1.4895/20	—	—	—	—
—	96/22	—	1.4920/20	—	—	—	*
125	—	—	—	—	—	22	*
150	—	—	—	—	—	22	*
89	—	—	—	—	—	22	*
99	—	—	—	—	—	22	*
127	—	—	—	—	—	22	*
176	—	—	—	—	—	—	—
—	91/20	—	—	—	—	—	—
158	—	—	—	—	—	—	*
137	—	—	—	—	—	—	*
139	—	—	—	—	—	22	*
114	—	—	—	—	—	22	*
105	—	—	—	—	—	22	*

next page

TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
	COOH-OCH_3-F 1-2-3	—
	1-2-4	—
	1-2-5	—
	1-2-6	—
	1-4-3	—
$C_8H_7F_3O$	OCH_3-CF_3 1-3	—
C_8H_8ClFO	CH_2Cl-F-OCH_3 1-3-4	—
	1-3-6	—
$C_8H_8FNO_4$	NO_2-$(OCH_3)_2$-F 1-2,6-4	—
C_8H_9FO	OCH_3-F-CH_3 1-3-4	—
$C_9Cl_9F_3$	F_3-$(CCl_3)_3$ 1,3,5-2,4,6	—
$C_9H_3Cl_6F_3$	F_3-$(CHCl_2)_3$ 1,3,5-2,4,6	—
$C_9H_4F_9N$	NH_2-$(CF_3)_3$ 1-3,4,5	—
	—	ethyl carbamate
$C_9H_5FOS_2$	—	5-(4-fluorophenyl)-1,2-dithiole-3-one
$C_9H_6FNO_2$	F-COOH 5-2	indole
$C_9H_6FNO_5$	$CH_2COCOOH$-F-NO_2 1-3-6	—
$C_9H_7FO_4$	$(COOH)_2$-CH_3-F 1,3-5-6	—
$C_9H_7Cl_2FO_3$	OCH_2CH_2COOH-F-Cl_2 1-3-4,6	—
$C_9H_7FO_2$	F-(CH=CHCOOH) 1-2	—
	—	ethyl ester
	1-4	—

[a] sublimes

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
105-108	—	—	—	—	—	—	*
132	—	—	—	—	—	—	*
88	—	—	—	—	—	—	*
88-90	—	—	—	—	—	—	*
212	—	—	—	—	—	—	*
—	158-160	—	—	—	—	—	—
37	—	—	—	—	—	—	—
53	—	—	—	—	—	—	—
145	—	—	—	—	—	—	*
—	—	—	—	—	—	—	*
126	—	—	—	—	—	11	*
117	—	—	—	—	—	11	*
—	—	—	—	—	—	—	—
124	—	—	—	—	—	—	*
—	—	—	—	—	—	—	*
—	140/1[a]	—	—	—	—	22	*
147	—	—	—	—	—	22	*
289-291	—	—	—	—	—	—	—
110	—	—	—	—	—	22	*
—	—	—	—	—	—	—	—
—	—	—	—	—	—	—	*
—	—	—	—	—	—	—	—

next page)

Empirical formula	Ring substitution	Compound type or derivative
	—	ethyl ester
$C_9H_7FO_5$	$\frac{OCH_2COOH\text{-}COOH\text{-}F}{1\text{-}2\text{-}4}$	—
$C_9H_7F_3O_3$	$\frac{OCH_2COOH\text{-}CF_3}{1\text{-}3}$	—
	$\frac{OCH_2CH_2COOH\text{-}F_3}{1\text{-}2,4,5}$	—
C_9H_8FNO	$\frac{CH_2CN\text{-}F\text{-}OCH_3}{1\text{-}2\text{-}4}$	—
	1-3-4	—
	1-3-6	—
$C_9H_8F_2O_3$	$\frac{OCH_2CH_2COOH\text{-}F_2}{1\text{-}2,4}$	—
$C_9H_9FN_2O_4$	$\frac{F\text{-}(CH_3)_3\text{-}(NO_2)_2}{1\text{-}2,4,6\text{-}3,5}$	—
$C_9H_9FO_2$	$\frac{COOH\text{-}(CH_3)_2\text{-}F}{1\text{-}3,5\text{-}4}$	—
$C_9H_9FO_3$	$\frac{OCH_2CH_2COOH\text{-}F}{1\text{-}4}$	—
	$\frac{OCH_2COOH\text{-}F\text{-}CH_3}{1\text{-}2\text{-}4}$	—
	1-3-2	—
	1-4-2	—
	1-4-3	—
	$\frac{CH_2COOH\text{-}OCH_3\text{-}F}{1\text{-}2\text{-}5}$	—
	—	amide
	—	isopropyl ester
$C_9H_9F_2I$	$\frac{F_2\text{-}(CH_3)_3\text{-}I}{1,3\text{-}2,4,6\text{-}5}$	—
$C_9H_9F_2NO_2$	$\frac{F_2\text{-}NO_2\text{-}(CH_3)_3}{1,3\text{-}5\text{-}2,4,6}$	—
$C_9H_9F_3$	$\frac{CH(CH_3)_2\text{-}F_3}{1\text{-}2,4,6}$	—
	$\frac{F_3\text{-}(CH_3)_3}{1,3,5\text{-}2,4,6}$	—

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
—	—	—	—	—	—	—	*
156-158	—	—	—	—	—	—	*
94	—	—	—	—	—	—	—
82	—	—	—	—	—	22	*
43	—	—	—	—	—	—	—
—	—	—	—	—	—	—	*
54	—	—	—	—	—	—	*
76	—	—	—	—	—	22	*
97	—	—	—	—	—	11	*
171-173	—	—	—	—	—	—	*
86	—	—	—	—	—	22	*
127	—	—	—	—	—	22	*
173	—	—	—	—	—	—	*
148	—	—	—	—	—	—	*
139	—	—	—	—	—	22	*
111	—	—	—	—	—	—	*
125	—	—	—	—	—	—	*
—	120/0.5	—	—	—	—	—	*
65	—	—	—	—	—	—	*
54	—	—	—	—	—	11	*
—	73/78	—	1.4364/20	—	—	—	—
67	92/60	—	—	—	—	11	*

next page)

TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
$C_9H_9F_3O$	$\frac{CH_2OCH_2CH_3\text{-}F_3}{1\text{-}2,4,6}$	—
	$\frac{OCH_2CH_3\text{-}CF_3}{1\text{-}3}$	—
$C_9H_{10}ClF$	$\frac{F\text{-}Cl\text{-}(CH_3)_3}{1\text{-}3\text{-}2,4,6}$	—
$C_9H_{10}FI$	$\frac{F\text{-}I\text{-}(CH_3)_3}{1\text{-}3\text{-}2,4,6}$	—
$C_9H_{10}FNO_2$	$\frac{F\text{-}NO_2\text{-}(CH_3)_3}{1\text{-}3\text{-}2,4,6}$	—
$C_9H_{10}F_2$	$\frac{F_2\text{-}(CH_3)_3}{1,3\text{-}2,4,6}$	—
$C_9H_{11}F$	$\frac{F\text{-}(CH_3)_3}{1\text{-}2,4,6}$	—
$C_9H_{11}F_2N$	$\frac{NH_2\text{-}F_2\text{-}(CH_3)_3}{1\text{-}3,5\text{-}2,4,6}$	—
	—	acetyl
$C_9H_{11}FN_2O_2$	$\frac{NH_2\text{-}NO_2\text{-}(CH_3)_3\text{-}F}{1\text{-}5\text{-}2,4,6\text{-}3}$	—
	—	acetyl
$C_9H_{11}F_2N$	$\frac{NH_2\text{-}(CH_3)_3\text{-}F_2}{1\text{-}2,4,6\text{-}3,5}$	—
	—	acetyl
$C_9H_{12}FN$	$\frac{NH_2\text{-}(CH_3)_3\text{-}F}{1\text{-}2,4,6\text{-}3}$	—
	—	acetyl
$C_9H_{13}FN_2$	$\frac{(NH_2)_2\text{-}(CH_3)_3\text{-}F}{1,3\text{-}2,4,6\text{-}5}$	—
	—	diacetyl
$C_{10}H_7F$	$\frac{F}{2}$	naphthalene
$C_{10}H_8FS_3I$	—	3-Methylthio-5-(4-fluorophenyl)-1,2-dithiolium iodide
$C_{10}H_9FN_2O$	$\frac{mFC_6H_4\text{-}CH_3}{1\text{-}3}$	5 pyrazolone
	$\frac{pFC_6H_4\text{-}CH_3}{1\text{-}3}$	5 pyrazolone

[a] microcap

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
—	171[a]	—	1.4445/20	—	—	—	—
—	174	—	—	—	—	—	—
—	204	—	—	—	—	11	*
—	248	—	—	—	—	—	—
44	—	—	—	—	—	11	*
—	70/20	—	—	1.183	30.94	11	*
—	172	—	1.4844/20	.981	29.19	—	*
52	—	—	—	—	—	—	*
—	—	—	—	—	—	—	*
79	—	—	—	—	—	11	*
207	—	—	—	—	—	11	*
52	—	—	—	—	—	11	*
186	—	—	—	—	—	11	*
40	—	—	—	—	—	11	*
182	—	—	—	—	—	11	*
135	—	—	—	—	—	11	*
>285	—	—	—	—	—	—	—
61	211-213	—	—	—	—	—	*
153d	—	—	—	—	—	7	*
117	—	—	—	—	—	—	*
148	—	—	—	—	—	—	*

next page)

Empirical formula	Ring substitution	Compound type or derivative
$C_{10}H_{10}F_2O_2$	$\frac{COOH\text{-}(CH_3)_3\text{-}F_2}{1\text{-}2,4,6\text{-}3,5}$	—
	—	amide
$C_{11}H_8FNO_4$	$\frac{COOH\text{-}CH_2COOH\text{-}F}{2\text{-}3\text{-}5}$	indole
$C_{11}H_8F_2N_4O$	—	N,N'-Bis-6-fluoro-2-pyridylurea
$C_{11}H_9Br_3F_2O$	$\frac{CBr_3CO\text{-}(CH_3)_3\text{-}F_2}{1\text{-}2,4,6\text{-}3,5}$	—
$C_{11}H_9Cl_3F_2O$	$\frac{CCl_3CO\text{-}(CH_3)_3\text{-}F_2}{1\text{-}2,4,6\text{-}3,5}$	—
$C_{11}H_9F_3N_2O$	$\frac{CF_3C_6H_4\text{-}CH_3}{1\text{-}3}$	5 pyrazolone
$C_{11}H_9F_3N_2O_5$	$\frac{COCF_3\text{-}(CH_3)_3\text{-}(NO_2)_2}{1\text{-}2,4,6\text{-}3,5}$	—
$C_{11}H_{11}FN_2O$	$\frac{mFC_6H_4\text{-}(CH_3)_2}{1\text{-}2,3}$	5 pyrazolone
	$\frac{pFC_6H_4\text{-}(CH_3)_2}{1\text{-}2,3}$	5 pyrazolone
	—	acetone
$C_{11}H_{11}F_3O$	$\frac{COCF_3\text{-}(CH_3)_3}{1\text{-}2,4,6}$	—
$C_{11}H_{12}F_2O$	$\frac{CH_3CO\text{-}(CH_3)_3\text{-}F_2}{1\text{-}2,4,6\text{-}3,5}$	—
$C_{11}H_{14}F_2$	$\frac{F_2\text{-}(CH_3)_3\text{-}CH_2CH_3}{1,3\text{-}2,4,6\text{-}5}$	—
$C_{12}H_3F_7$	$\frac{F_7}{2,2',3,4',5,5',6}$	biphenyl
$C_{12}H_4F_4N_2O_4$	$\frac{F_4\text{-}(NO_2)_2}{2,2',4,4'\text{-}6,6'}$	biphenyl
$C_{12}H_4F_6$	$\frac{F_6}{2,2',4,4',5,5'}$	biphenyl
	2,2',4,4',6,6'	biphenyl
$C_{12}H_5F_5$	$\frac{F_5}{2,2',4,5,5'}$	biphenyl
	2,3',4,5',6	biphenyl
$C_{12}H_6F_2N_2O_4$	$\frac{F_2\text{-}(NO_2)_2}{3,3'\text{-}6,6'}$	biphenyl

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
157	—	—	—	—	—	11	*
197	—	—	—	—	—	—	*
229	—	—	—	—	—	—	—
—	—	—	—	—	—	—	*
82	—	—	—	—	—	11	*
—	123/5	—	—	—	—	11	*
120	—	—	—	—	—	—	*
82	—	—	—	—	—	11	*
87	—	—	—	—	—	7	*
128	—	—	—	—	—	—	*
130	—	—	—	—	—	—	—
—	97/25	—	—	—	—	11	*
—	120/20	—	—	—	—	11	*
—	110-112/25	—	—	—	—	—	—
124	—	—	—	—	—	43	*
81	—	—	—	—	—	—	*
121	—	—	—	—	—	43	*
132	—	—	—	—	—	43	*
100	—	—	—	—	—	43	*
97	—	—	—	—	—	43	*
122	—	—	—	—	—	43	*

next page)

Empirical formula	Ring substitution	Compound type or derivative
$C_{12}H_6F_4$	$\frac{F_4}{2,2',4,4'}$	biphenyl
	2,2',5,5'	biphenyl
	3,3',5,5'	biphenyl
$C_{12}H_6F_4N_2$	$\frac{F_4}{2,2',4,4'}$	azobenzene
	2,2',5,5'	azobenzene
	3,3',5,5'	azobenzene
$C_{12}H_6F_4O_2$	$\frac{F_4\text{-}(OH)_2}{3,3',5,5'\text{-}2,2'}$	biphenyl
$C_{12}H_7F_3$	$\frac{F_3}{2,2',3}$	biphenyl
	2,3',4	biphenyl
	3,4',5	biphenyl
$C_{12}H_8F_2$	$\frac{F_2}{2,2'}$	biphenyl
	2,4'	biphenyl
	3,3'	biphenyl
	4,4'	biphenyl
$C_{12}H_8F_2O$	$\frac{F_2}{3,3'}$	diphenyl ether
	4,4'	diphenyl ether
$C_{12}H_8F_2O_2$	$\frac{F_2\text{-}(OH)_2}{3,3'\text{-}4,4'}$	biphenyl
	3,3'-6,6'	biphenyl
$C_{12}H_8F_2O_2S$	$\frac{F_2\text{-}(OH)_2}{3,3'\text{-}6,6'}$	diphenyl sulfide
$C_{12}H_9F$	$\frac{F}{2}$	biphenyl
	4	biphenyl
$C_{12}H_9F_2O_2P$	—	Bis(3-fluorophenyl)phosphinic acid
$C_{12}H_{11}F_3N_2O$	$\frac{mCF_3C_6H_4\text{-}(CH_3)_2}{1\text{-}2,3}$	5 pyrazolone

[a] Bp 78/2° C/mm

(Continued on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
138	—	—	—	—	—	43	*
78	—	—	—	—	—	43	*
87	—	—	—	—	—	43	*
147	—	—	—	—	—	8,9,10	*
129	—	—	—	—	—	—	*
94	—	—	—	—	—	—	*
173	—	—	—	—	—	9,10	*
81	—	—	—	—	—	43	*
41	102/5	—	—	—	—	43	*
52	87/0.5	—	—	—	—	43	*
116	—	—	—	—	—	—	—
50	—	—	—	—	—	43	*
—	240	7	—	—	—	—	*
89	—	—	—	—	—	—	*
—	102/5	—	1.5448/20	—	—	—	—
54	—	—	—	—	—	—	*
189	—	—	—	—	—	9,10	*
139	—	—	—	—	—	9,10	*
119	—	—	—	—	—	9,10	*
72	248	—	—	—	—	—	*
74	253[a]	—	—	—	—	—	*
167	—	—	—	—	—	22	*
102	—	—	—	—	—	7	*

next page)

Empirical formula	Ring substitution	Compound type or derivative
$C_{14}H_4Cl_4F_6$	—	1,2-Bis-(2,4,6-trifluorophenyl)-tetrachloroethane
$C_{14}H_6F_6N_2O_5$	$\frac{(CF_3)_2\text{-}(NO_2)_2}{2,2'\text{-}4,4'}$	diphenyl ether
	4,4'-2,2'	diphenyl ether
$C_{14}H_6F_6N_4O_4$	$\frac{(CF_3)_2\text{-}(NO_2)_2}{3,3'\text{-}5,5'}$	azobenzene
$C_{14}H_6F_6N_4O_5$	$\frac{(CF_3)_2\text{-}(NO_2)_2}{3,3'\text{-}5,5'}$	azoxybenzene
$C_{14}H_6F_8$	$\frac{(CF_3)_2\text{-}F_2}{2,2'\text{-}4,4'}$	biphenyl
$C_{14}H_8F_6$	$\frac{F_6\text{-}(CH_3)_2}{2,2',4,4',6,6'\text{-}3,3'}$	biphenyl
$C_{14}H_8F_6N_2$	$\frac{(CF_3)_2}{3,3'}$	azobenzene
$C_{14}H_9F$	$\frac{F}{9}$	anthacene
$C_{14}H_{10}F_2O_4S$	$\frac{OH\text{-}OCH_2COOH\text{-}F_2}{2\text{-}2'\text{-}5,5'}$	diphenyl sulfide
$C_{14}H_{10}F_4N_2O_2$	$\frac{F_4\text{-}(OCH_3)_2}{3,3',5,5'\text{-}2,2'}$	azobenzene
$C_{14}H_{10}F_4O_2$	$\frac{F_4\text{-}(OCH_3)_2}{3,3',5,5'\text{-}2,2'}$	biphenyl
$C_{14}H_{10}F_5N_3$	$\frac{F_5\text{-}N(CH_3)_2}{2,2',4',6,6'\text{-}4}$	azobenzene
$C_{14}H_{10}F_6N_2O$	$\frac{(CF_3)_2\text{-}(NH_2)_2}{2,2'\text{-}4,4'}$	diphenyl ether
	4,4'-2,2'	diphenyl ether
$C_{14}H_{11}F_4N_3$	$\frac{F_4\text{-}N(CH_3)_2}{2,2',5,5'\text{-}4}$	azobenzene
	2,3',5',6-4	azobenzene
$C_{14}H_{12}F_2O_2$	$\frac{F_2\text{-}(OCH_3)_2}{3,3'\text{-}4,4'}$	biphenyl
	3,3'-6,6'	biphenyl
$C_{14}H_{12}F_2O_2S$	$\frac{F_2\text{-}(OCH_3)_2}{3,3'\text{-}4,4'}$	diphenyl sulfide
$C_{14}H_{12}F_2O_3S$	$\frac{F_2\text{-}(OCH_3)_2}{3,3'\text{-}4,4'}$	diphenyl sulfoxide

(Concluded on

Continued

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
178	—	—	—	—	—	—	—
116	—	—	—	—	—	13	*
108	—	—	—	—	—	13	*
187-189	—	—	—	—	—	—	—
136	—	—	—	—	—	—	*
62	—	—	—	—	—	43	*
63	—	—	—	—	—	—	*
84	—	—	—	—	—	—	—
110	—	—	—	—	—	—	—
117-119	—	—	—	—	—	7	*
160	—	—	—	—	—	—	*
50	—	—	—	—	—	43	*
152	—	—	—	—	—	44	—
124	—	—	—	—	—	13	*
80	—	—	—	—	—	13	*
148	—	—	—	—	—	44	*
157	—	—	—	—	—	44	*
154	—	—	—	—	—	43	*
122	—	—	—	—	—	43	*
38	—	—	—	—	—	—	*
104	—	—	—	—	—	7	*

next page)

TABLE 1—

Empirical formula	Ring substitution	Compound type or derivative
$C_{14}H_{12}F_3N_3$	$\frac{F_3\text{-}N(CH_3)_2}{2,4,6\text{-}4'}$	azobenzene
$C_{14}H_{13}F_2N_3$	$\frac{F_2\text{-}N(CH_3)_2}{2,4\text{-}4'}$	azobenzene
	2,5-4'	azobenzene
	3,5-4'	azobenzene
	2,6-4	azobenzene
	3',4'-4	azobenzene
$C_{14}H_{14}FN_3$	$\frac{F\text{-}N(CH_3)_2}{2\text{-}4'}$	azobenzene
	3-4	azobenzene
$C_{15}H_8F_6N_2O_5$	$\frac{(CF_3)_2\text{-}(NO_2)_2}{4,4'\text{-}2,2'}$	N,N-diphenylurea
$C_{15}H_8F_6N_4O_5$	—	N,N'-Bis(2-nitro-4-trifluoro-methylphenyl)urea
$C_{15}H_8F_8N_2O$	—	N,N'-Bis(4-fluoro-3-trifluoro-methylphenyl)urea
$C_{15}H_{16}FNO_4$	$\frac{F\text{-}CH_2CO_2C_2H_5\text{-}CO_2C_2H_5}{5\text{-}3\text{-}2}$	indole
$C_{16}H_6F_6N_2O$	$\frac{(CN)_2\text{-}(CF_3)_2}{2,2'\text{-}4,4'}$	diphenyl ether
$C_{16}H_{12}F_2O_6S$	$\frac{(OCH_2COOH)_2\text{-}F_2}{2,2'\text{-}5,5'}$	diphenyl sulfide
$C_{16}H_{21}FN_2O_3$	—	2,6-Dimorpholino-4-fluoro acetophenone
$C_{18}H_{12}F_2$	$\frac{F_2}{4,4''}$	terphenyl
$C_{18}H_{13}F$	$\frac{F}{2}$	terphenyl
	3	terphenyl
	4	terphenyl
$C_{18}H_{18}F_4$	$\frac{F_4\text{-}(CH_3)_6}{3,3',5,5'\text{-}2,2',4,4',6,6'}$	biphenyl
$C_{18}H_{20}F_2$	$\frac{F_2\text{-}(CH_3)_6}{3,3'\text{-}2,2'4,4'6,6'}$	biphenyl
$C_{19}H_{10}F_6$	$\frac{F_6}{2,2',2'',5,5',5''}$	triphenyl methane

Concluded

Mp °C	Bp °C/mm	Fp °C	n_D/°C	D_4^{20}	δ^{20}	Reference	Sample available
112	—	—	—	—	—	45	*
133	—	—	—	—	—	45	*
136	—	—	—	—	—	45	*
111	—	—	—	—	—	45	*
129	—	—	—	—	—	44	*
141	—	—	—	—	—	44	*
108	—	—	—	—	—	45	*
54	—	—	—	—	—	44	*
—	—	—	—	—	—	—	—
197	—	—	—	—	—	—	*
224	—	—	—	—	—	33	*
124	—	—	—	—	—	22	*
147	—	—	—	—	—	—	*
195-197	—	—	—	—	—	7	*
148	—	—	—	—	—	31	*
90-92	—	—	—	—	—	—	—
174	—	—	—	—	—	43	*
175	—	—	—	—	—	43	*
161	—	—	—	—	—	43	*
162	—	—	—	—	—	43	*
132	—	—	—	—	—	—	*
99	—	—	—	—	—	—	*

SUMMARY OF GENERAL SYNTHETIC METHODS

A brief outline of the general synthetic procedures used in preparing the aromatic fluorine compounds listed in the tabular survey follows. The quantities of reactants and the conditions used in these procedures have been optimized for most cases, but for others further research and development may be necessary.

The usual procedure for synthesizing aromatic fluorine compounds involved the introduction of fluorine into the molecule at an early stage, followed by other functional group syntheses and reactions. This procedure is ordinarily possible because fluorine substituted on the aromatic nucleus is stable and does not interfere in most functional group operations.

Fluorine can be conveniently introduced into the aromatic nucleus by two methods: (1) the Schiemann synthesis, and (2) the aryl chloride-potassium fluoride exchange reaction. In the Schiemann synthesis, an aryl amine is converted to an insoluble diazonium fluoborate salt, followed by a thermal decomposition to the desired fluoride, as illustrated by the conversion of aniline to fluorobenzene. This method is quite versatile but somewhat time consuming. Yields may vary from 40 to 80 percent depending upon the reaction conditions and the purity of the starting aniline. In the recently developed exchange method, chlorine is replaced with fluorine in an aryl chloride with yields up to 80 percent using anhydrous potassium and/or cesium fluoride in a suitable solvent such as DMF, DMSO, or $DMSO_2$. The method is simple and economical.

GENERAL SYNTHETIC METHODS USED IN PREPARING AROMATIC FLUORINE COMPOUNDS

1. NITRATIONS

- 1.A. Halobenzenes (mononitrations)
- 1.B. Phenoxyacetic acids
  - *1.B.1. Concentrated nitric acid (sp gr 1.42)*
  - *1.B.2. Fuming nitric acid (sp gr 1.49)*
- 1.C. Anisoles
- 1.D. Phenols
  - *1.D.1. Concentrated nitric acid (sp gr 1.42)*
  - *1.D.2. Nitric acid (35 percent) in benzene*
- 1.E. Acetanilides
  - *1.E.1. Fuming nitric acid (sp gr 1.59)*
  - *1.E.2. Fuming nitric acid (sp gr 1.59) in glacial acetic acid and concentrated sulfuric acid (sp gr 1.84)*
- 1.F. Urethanes
- 1.G. Benzotrifluoride (mononitration)
  - *1.G.1. Concentrated nitric acid (sp gr 1.42) and concentrated sulfuric acid (sp gr 1.84)*
  - *1.G.2. Sodium nitrate*
- 1.H. Halobenzenes (dinitrations)
  - *1.H.1. Concentrated nitric acid (sp gr 1.49)*
  - *1.H.2. Fuming nitric acid (sp gr 1.59)*
  - *1.H.3. Concentrated nitric acid (sp gr 1.49) and fuming sulfuric acid (sp gr 1.915)*
- 1.J. Large-scale nitrations
- 1.K. Nitration of difluoromesitylenes in anhydrous hydrofluoric acid

2. HYDROLYSIS OF ACETANILIDES

- 2.A. Concentrated sulfuric acid (sp gr 1.84)
- 2.B. Hydrochloric acid (18.5 percent)

3. REDUCTION OF NITROCOMPOUNDS

- 3.A. Iron reduction
- 3.B. Large-scale iron reductions
- 3.C. Stannous chloride method

4. FLUORINATIONS USING KF OR KF AND CsF MIXTURES

- 4.A. Nitrohalobenzenes
  - *4.A.1. Replacement of halogen*
  - *4.A.2. Replacement of the nitro group*
- 4.B. Nitrohalopyridine
- 4.C. Halopyridine
- 4.D. Cyanobenzenes and pyridines

4.E. Nonactivated aromatic compounds
4.E.1. Tri- and tetrahalobenzenes
4.E.1.a. Method A--Glass apparatus
4.E.1.b. Method B--Parr reactor
4.E.2. Pentachlorobenzene

5. DIAZOTIZATIONS AND DIAZONIUM GROUP REPLACEMENTS

5.A. Schiemann transformations
5.A.1. With hydrochloric acid--laboratory scale
5.A.2. With hydrochloric acid--large scale
5.A.3. With 50 percent fluoboric acid
5.A.4. With ammonium fluoborate
5.A.5. Pyridine derivatives
5.A.5.a. Diazotization with sodium nitrite
5.A.5.b. Diazotization with ethyl nitrite
5.B. Replacement with chlorine
5.B.1. In hydrochloric acid
5.B.2. In sulfuric acid
5.B.2.a. Nitrosyl sulfuric acid
5.B.2.b. Aqueous sodium nitrite
5.C. Replacement with bromine
5.C.1. In 48 percent hydrobromic acid
5.C.2. In sulfuric acid
5.D. Replacement with iodine
5.E. Replacement with hydrogen
5.E.1. Deamination
5.E.2. Combined deamination and nitro reduction
5.F. Replacement with hydroxyl
5.F.1. Sulfuric-phosphoric acid, large scale
5.F.2. Sulfuric acid
5.F.2.a. Soluble salt
5.F.2.b. Insoluble salt
5.F.3. Sulfuric acid--insoluble hydrosulfate salt

6. BY-PRODUCTS FROM THE SCHIEMANN TRANSFORMATION

6.A. Displacement of arylfluorine in diazonium salts
6.B. Biphenyl formation
6.C. Diphenyl ether formation
6.D. Azobenzene formation

7. ETHER CLEAVAGE OF ANISOLES

7.A. Aluminum chloride
7.B. Aluminum bromide
7.C. Sealed tube reactions
7.C.1. 48 percent hydrobromic acid
7.C.2. 57 percent hydriodic acid
7.C.3. 37 percent hydrochloric acid
7.D. 57 percent hydriodic acid and acetic anhydride

8. BROMINATIONS

8.A. Aqueous suspensions (phenols)
8.B. Carbon disulfide solution (phenols)
8.C. Trichloroacetic acid (phenoxyacetic acids)
8.D. Carbon tetrachloride (benzenes)
8.E. No solvent (benzenes)

9. CHLORINATIONS

9.A. No solvent
9.A.1. Phenols
9.A.2. Benzenes
9.B. Acetic acid (phenoxyacetic acids)

10. ARYLOXYALKANOIC ACID PREPARATIONS

11. SYNTHESIS OF DI- AND POLYPHENYL COMPOUNDS

11.A. Ullmann reaction
11.A.1. Symmetrical Ullmann
11.A.2. Mixed Ullmann
11.B. Gomberg-Bachmann-Hey reaction

12. QUINONE FORMATION

12.A. Oxidation of 1,4-diamines
12.B. Fluorine expulsion in fluorinated benzenes

13. HYDROQUINONE FORMATION

14. SYNTHESIS OF BENZOIC ACIDS

14.A. Via Grignard reagents
14.B. Oxidation of toluene derivatives
14.C. Oxidation of benzyl alcohols
14.D. Oxidation of acetophenones
14.E. Hydrolysis of nitriles
14.F. Hydrolysis of benzotrifluorides
14.F.1. Sulfuric acid
14.F.2. Potassium hydroxide

15. HYDROLYSIS OF ANILINES

16. N-PHENYLGLYCINE ETHYL ESTER

17. N-PHENYLGLYCINEHYDRAZIDES

18. N-(FLUOROPHENYL) CARBAMATES

19. BENZYL CHLORIDE SYNTHESIS

20. BENZYL CYANIDE SYNTHESIS

21. PHENYLACETIC ACID SYNTHESIS

22. PHENYLACETAMIDE

23. SPECIAL PREPARATIONS

- 23.A. Fluoroindole derivatives
  - *23.A.1. Ethyl-2-carbethoxy-5-fluoroindoleacetate*
  - *23.A.2. 2-Nitro-5-fluorophenylpyruvic acid*
  - *23.A.3. 5-Fluoro-2-indolecarboxylic acid*
- 23.B. Bis-(3-fluorophenyl) phosphinic acid
- 23.C. 1-(3-Trifluoromethylphenyl)-2,3-dimethyl-5-pyrazalone
  - *23.C.1. 3-Trifluoromethylphenyl hydrazine*
  - *23.C.2. Condensation with ethyl acetoacetate*
  - *23.C.3. Methylation*
- 23.D. 2,2'-Dihydroxy-5,5'-difluorodiphenyl sulfide
- 23.E. 3,3'-Difluoro-4,4'-dimethoxydiphenyl sulfoxide

DESCRIPTIONS OF GENERAL SYNTHETIC METHODS

1. NITRATIONS

After nitration, the reaction mixtures were poured into ice and water. The separated products were collected by filtration or steam distillation, dried, and purified by recrystallization, sublimation, or vacuum distillation with caution.

1.A. Halobenzenes (mononitrations)

To a mixture (molar ratio 1:5) of 1-fluoro-3,4-dichlorobenzene and concd sulfuric acid (sp gr 1.84) was added a 10 percent molar excess of concd nitric acid (sp gr 1.42) in concd sulfuric acid (1:1 v:v) while a temperature of 15° C was maintained. After the addition, the mixture was stirred for 1.5 hr at steam bath temperature. A 97 percent yield of 2-fluoro-4,5-dichloronitrobenzene was obtained.

1.B. Nitration of phenoxyacetic acids (22)

1.B.1. Concentrated nitric acid (sp gr 1.42). 4-Fluorophenoxyacetic acid was nitrated as in A but in a temperature range of 0 to 5° C and with the final heating period eliminated. 2-Nitro-4-fluorophenoxyacetic acid was obtained in a 67 percent yield.

1.B.2. Fuming nitric acid (sp gr 1.49). A 5 percent molar excess of fuming nitric acid (sp gr 1.49) mixed with an equal volume of glacial acetic acid was slowly added to a solution of 3-fluorophenoxyacetic acid dissolved in acetic anhydride (molar ratio 1:20) at 25° C. After the addition was complete, stirring was continued for 3 hr. 3-Fluoro-6-nitrophenoxyacetic acid was obtained in a 36 percent yield.

1.C. Nitration of anisoles (22)

4-Fluoroanisole dissolved in glacial acetic acid, and acetic anhydride (molar ratio 1:3:1.3) was nitrated in a temperature range of 5 to 20° C with a slight excess of fuming nitric acid (sp gr 1.49) in glacial acetic acid (1:1 v:v). The reaction mixture was stirred at room temperature for 1 hr. An 80 percent yield of 4-fluoro-2-nitroanisole was obtained.

1.D. Nitration of phenols

1.D.1. Concentrated nitric acid (sp gr 1.42) (22). A solution of 2-fluorophenol in glacial acetic acid (molar ratio 1:11) was nitrated at 20° C with the theoretical amount of concd nitric acid (sp gr 1.42). The nitric acid was previously diluted with an equal volume of glacial acetic acid. The reaction mixture was stirred for 2 hr. Purification gave an 80 percent yield of 2-fluoro-4-nitrophenol.

If 2-fluoro-4,6-dinitrophenol (23) was desired, two equivalents of nitric acid were used. The second equivalent of nitric acid was added in a temperature range of 40 to 50° C and resulted in a 79 percent yield.

1.D.2. Nitric acid (35 percent) in benzene. With thorough stirring, a 10 percent molar excess of dilute nitric acid (35 percent) was added slowly at 15° to 3-fluorophenol dissolved in excess benzene. The mixture was stirred for 2 hr. The resulting 3-fluoro-6-nitrophenol was isolated in a yield of 44 percent.

1.E. Nitration of acetanilides

1.E.1. Fuming nitric acid (sp gr 1.59). One gram of 2,4-difluoro-3-chloroacetanilide was added to 5 ml of fuming nitric acid (sp gr 1.59) at 20° C. The mixture was stirred at this temperature for 2 hr. Purification gave a 75 percent yield of 2,4-difluoro-3-chloro-6-nitroacetanilide.

1.E.2. Fuming nitric acid (sp gr 1.59) in glacial acetic acid and concentrated sulfuric acid (sp gr 1.84). 2,4,5-Trifluoroacetanilide in glacial acetic- concd sulfuric acid solution (molar ratio 1:4:10) was nitrated at 10° C with a 10 percent molar excess of fuming nitric

acid (sp gr 1.59) dissolved in an equal volume of concd sulfuric acid. The reaction mixture was allowed to come to room temperature while being stirred for 1 hr. Purification gave an 81 percent yield of 2,4,5-trifluoro-6-nitroacetanilide.

1.F. Nitration of urethanes (46)

A mixture of 7.6 g (0.035 mole) of 2,4,6-trifluorophenylurethane and 50 ml of concd sulfuric acid (sp gr 1.84) was nitrated at 38° C for 20 min with a solution of 2 ml of fuming nitric acid (sp gr 1.59) and 4 ml of concd sulfuric acid. After the addition of the nitrating mixture, the temperature was increased to 55° C for 25 min. The yield of crude 3-nitro-2,4,6-trifluorophenylurethane was 83 percent.

1.G. Mononitration of benzotrifluoride (40)

1.G.1. Nitric acid (sp gr 1.42) and concentrated sulfuric acid (sp gr 1.84). One half mole of benzotrifluoride was added dropwise to 0.55 mole of nitric acid (sp gr 1.42) in 1.55 moles of concd sulfuric acid (sp gr 1.84) at a rate which maintained a temperature range of 30 to 35° C. After the addition was complete, the mixture was warmed to 60° C and stirred for 1 hr. Purification gave a 90 percent yield of 3-nitrobenzotrifluoride. The optimum conditions for this reaction involve a 10 percent excess of concd nitric acid, a sufficient amount of concd sulfuric acid to form a monohydrate with the total water content, a temperature range of 30 to 35° C for nitration, and a finishing-off temperature of 60° C.

1.G.2. Sodium nitrate. A 20 percent excess of finely ground sodium nitrate was added in small portions to a 1:5.5 (v:v) mixture of benzotrifluoride and concd sulfuric acid (sp gr 1.84) over a temperature range of 25 to 30° C. After the addition of the sodium nitrate, the reaction was finished by increasing the temperature to 60° C. The maximum yield of pure product by this method was 89 percent.

1.H. Halobenzenes (dinitrations)

In general, the nitration mixture consisted of 5 volume equivalents of sulfuric acid and a 10 percent molar excess of nitric acid.

1.H.1. Nitric acid (sp gr 1.49). 1-3-Difluoro-2,5-dichlorobenzene was dinitrated with a mixture of concd sulfuric acid (sp gr 1.84) and fuming nitric acid (sp gr 1.49) in a temperature range of 50 to 98° C over an 0.5 hr period, to give 1,3-difluoro-2,5-dichloro-4,6-dinitrobenzene (7).

1.H.2. Nitric acid (sp gr 1.59). 1,2-Difluoro-3-chlorobenzene was dinitrated with a mixture of concd sulfuric acid (sp gr 1.84) and red fuming nitric acid (sp gr 1.59) to give 1,2-difluoro-3-chloro-4,6-dinitrobenzene.

1.H.3. Nitric acid (sp gr 1.49), sulfuric acid (sp gr 1.92). 1,3-Difluoro-2-chlorobenzene or 1-fluoro-2-chlorobenzene can be dinitrated with a mixture of fuming sulfuric acid (sp gr 1.92) and fuming nitric acid (sp gr 1.49) to give 1,3-difluoro-3-chloro-4,6-dinitrobenzene and 1-fluoro-2-chloro-4,5-dinitrobenzene, respectively.

1.J. Large-scale nitrations

Large-scale nitrations have been done in the laboratory on compounds such as fluorobenzene and 1,3-difluorobenzene. To a mixture of 21 moles of 1,3-difluorobenzene in 2245 ml of concd sulfuric acid in a 22-l flask was slowly added a solution of 1342 ml of concd nitric acid (sp gr 1.42) in 1342 ml of concd sulfuric acid (sp gr 1.84) while a temperature range of 20 to 30° C. was maintained by the internal addition of powdered Dry Ice. The mixture was stirred for 3 hr at this temperature to give a 90 percent yield of 2,4-difluoronitrobenzene. Yields in excess of 90 percent of 4-fluoronitrobenzene can be obtained by this method.

1.K. Nitration of difluoromesitylenes (11) in anhydrous hydrofluoric acid

The reaction vessel for nitrations in liquid anhydrous hydrofluoric acid was either an iron retort or a copper beaker. An anchor-shaped stirrer was used to ensure thorough agitation at all times. A thermometer well was located close to the stirrer and extended into the center of the reaction vessel. The reaction temperature was controlled by an external Dry Ice-acetone cooling bath.

To a cooled, well stirred mixture of 1 kg (50 moles) of liquid anhydrous hydrofluoric acid and 0.77 mole of difluoromesitylene, 0.8 mole of powered sodium nitrate was added at such a rate that the reaction temperature was held below 5° C. The reaction mixture was then stirred for 20 min at this temperature. The resulting 2,4-difluoro-6-nitromesitylene precipitated as a yellow solid.

After the mixture was poured over 2.5 kg of ice, the 2,4-difluoro-6-nitromesitylene was collected on a filter, washed with water, and air-dried to give a 92 percent yield.

2. HYDROLYSIS OF ACETANILIDES

2.A. Concentrated sulfuric acid

One gram of 2,4-difluoro-3-chloro-6-nitroacetanilide was added to 2 ml of concd sulfuric acid (sp gr 1.84). The

resulting solution was heated at steam bath temperature for 2 hr and then poured over ice. The product was collected on a filter, dried, and recystallized from 3-fluorobenzotrifluoride to give an 80 percent yield of 2,4-difluoro-3-chloro-6-nitroaniline.

2.B. Hydrochloric acid

2,4,5-Trifluoro-6-nitroacetanilide was added to 10 times its own volume of 18.5 percent hydrochloric acid. The mixture was heated at reflux temperature for 1 hr and poured into an ice-water mixture. The mixture was neutralized with a 20 percent aqueous sodium hydroxide solution and filtered to give an 80 percent yield of 2,4,5-trifluoro-6-nitroaniline.

3. REDUCTION OF NITRO COMPOUNDS

3.A. Iron reduction

One mole (193.5 g) of 3-chloro-2,4-difluoronitrobenzene was added dropwise with stirring at reflux temperature to 2.5 liters of 0.78 N ammonium chloride solution containing 6 moles of iron filings. The reaction was completed by stirring at reflux temperature for an additional 4 hr. Steam distillation gave an 80 percent yield of 3-chloro-2,4-difluoroaniline.

3.B. Large-scale iron reductions

The apparatus used for iron reductions was a shop-built, 50-liter, steam-jacketed steel reaction vessel with a variable-speed motor and an anchor-type stirrer. It was further equipped with an addition inlet, a steam inlet, a cold water nozzle with a quick trip valve, and two upright condensers. A large drain plug was located in the bottom. The dual condensers consisted of 2-ft sections of 2-in. Pyrex pipe containing stainless steel cooling coils. The bottoms of the condensers were fitted with collecting traps and drain cocks. The condensers were connected by suitable valving so that the assembly could be used for both the refluxing and the steam distillation procedure.

Fifty moles of 2,4-difluoronitrobenzene were added over a period of 3.5 hr to a stirred, refluxing mixture containing 8 liters of 0.78 N ammonium chloride solution and 135 moles of iron filings. The mixture was then stirred at reflux temperature for an additional 1 hr. Steam distillation gave a 94.5 percent yield of crude 2,4-difluoroaniline.

Frothing of the reaction mixture, which generally occurs near the end of the steam distillation procedure, can be broken up by a periodic short burst of cold water through the quick trip valve.

3.C. Stannous chloride method

When an iron reduction was impractical or when highly halogenated nonvolatile anilines were involved, the usual stannous chloride method was used.

2-Fluoro-6-nitroanisole (35.5 g, or 0.2 mole) was added to a mixture of 129 g (0.63 mole) of stannous chloride and 2 moles of hydrochloric acid at room temperature. The mixture was stirred for 1.5 hr and poured over a mixture of ice and dil aqueous sodium hydroxide solution (2.1 moles). Steam distillation gave a 68 percent yield of 2-fluoro-6-aminoanisole.

4. FLUORINATIONS USING KF AND CsF MIXTURES

Potassium fluoride and cesium fluoride can be used in either dimethylformamide (DMF) or dimethylsulfoxide (DMSO) to replace chlorine with fluorine in aryl chlorides. However, certain difficulties arise with the use of these two solvents. In DMF, the less reactive aromatic halides are sluggish and the overall reaction is usually incomplete. In DMSO, severe decomposition of the reaction medium and malodorous sulfur-containing by-products are often encountered. Furthermore, both solvents frequently give products that are contaminated with chlorine-containing materials which make the purification difficult. These difficulties can be alleviated by using dimethylsulfone (29) ($DMSO_2$), mp 109° C, bp 238° C, as the reaction solvent.

The potassium fluoride used in these experiments was dried in an oven at 120° C for 24 hr and then quickly powdered in a warm mortar. Alternatively, the potassium fluoride can be dried by using a benzene azeotrope. The cesium fluoride (99 percent) was dried in an oven at 120° for 24 hr prior to use.

4.A. Nitrohalobenzenes

4.A.1. Replacement of halogen (13). A mixture of 78.5 g (0.5 mole) of 4-chloronitrobenzene, 58 g (1 mole) of dried potassium fluoride and 80 ml of dimethylsulfoxide was stirred and heated at 190° C for a period of 14 hr. The reaction mixture was poured into water and steam-distilled to give 51 g or a 72 percent yield of 4-fluoronitrobenzene. This compound was also prepared in a 73 percent yield in a similar reaction using the same quantities of reactants, but with 100 g of dimethylsulfone as the solvent. The reaction was heated at 225° C and stirred for only 7 hr. Nonreacted starting materials can be recovered easily.

4.A.2. Replacement of the nitro group (13, 14). A mixture of 34.9 g (0.13 mole) of 2,3,5,6-tetrachlo-

TABLE 2—SYNTHESIS OF FLUOROCYANO-BENZENES ANO -PYRIOINES WITH KF IN $OMSO_2$[a]

Reaction conditions			Reaction products			
Reactant	Time	Temp (°C)	Compound	Mp (°C)	Bp (°C/mm)	Yield (%)
(A) Cyano benzenes						
2-Chloro-	40 hr	200	2-Fluoro-	—	103/35	66·5
4-Chloro-	96 hr	200	4-Fluoro-	38	—	59
2,4-Oichloro-	30 hr	160	2,4-Oifluoro-	47	—	48
2,6-Oichloro-	7 hr	200	2,6-Oifluoro-	—	99/20	77
2-Chloro-5-tri-fluoromethyl-	3 hr	160	2-Fluoro-5-tri-fluoromethyl-	—	99/27	83
(B) Cyano pyridines						
2-Chloro-3-cyano-	120 min	140	2-Fluoro-3-cyano-	31	90/6	88[b]
2-Chloro-4-cyano-	90 min	180	2-Fluoro-4-cyano-	34	76/3	56
2-Chloro-5-cyano-	10 min	180	2-Fluoro-5-cyano-	52	—	78
2-Chloro-6-cyano-	80 min	180	2-Fluoro-6-cyano-	34	—	54

[a] Source: (30).
[b] DMF as solvent.

ronitrobenzene, 62 g (1.05 moles) of potassium fluoride, and 75 ml of DMF was stirred and heated at 147° C for a period of 4.5 hr. After steam distillation and recrystallization, 2,3,5,6-tetrachlorofluorobenzene was obtained in a 37 percent yield.

In a similar manner, 3-fluoro-2,4,6-trichloronitrobenzene (14) can be converted to 1,3-difluoro-2,4,6-trichlorobenzene in a 15 percent yield using dimethyl sulfoxide as the solvent, a temperature of 170° C, and a reaction time of 2 hr.

4.B. Nitrohalopyridines

To a solution of 12.3 g (0.075 mole) of 2-chloro-3-nitropyridine (2) and 30 ml of DMF at 120° C was added 9 g (0.15 mole) of anhydrous potassium fluoride. After 6 hr the mixture was poured into ice and water. Saturation of the mixture with salt followed by steam distillation gave 8.4 g (76 percent) of 2-fluoro-3-nitropyridine.

4.C. Halopyridine (1)

A mixture of 14.8 g (0.1 mole) of 2,3-dichloropyridine, 11.6 (0.2 mole) of potassium fluoride, and 30 g of dimethylsulfone was stirred and heated at 200° C for 48 hr. The mixture was cooled to below 100° C and carefully diluted with water. A subsequent steam distillation gave 8.6 g or a 65 percent yield of 3-chloro-2-fluoropyridine.

4.D. Cyanobenzenes and pyridines (30)

The chlorocyano-benzene or pyridine compound was reacted with anhydrous potassium fluoride by heating and stirring in dimethylsulfone in the usual manner (table 2). In some cases, dimethylformamide can also be used.

4.E. Nonactivated aromatic compounds

4.E.1. Tri- and tetrahalobenzenes. The syntheses and reactions of the polyhalobenzenes can be found in tables 3, 4, and 5.

Yields were determined from gas chromatographic data by using a Model 500 F & M gas chromatograph fitted with a 3 percent silicone rubber (SE-30) column that measured 3 m × 6 mm and a Beckman GC-4 gas chromatograph fitted with a 3 percent PO-1 (Pierce Chemical Co., Rockford, Illinois) column measuring 1.8 m × 3 mm. Peak areas were determined by use of an Infotronics Integrator. The identity of all of the individual products was established by elemental analysis and by analysis of the ^{19}F NMR spectra in conjunction with gas chromatographic retention times. Infrared spectral analysis also aided in structure confirmation.

The halogen-exchange reactions were run in a glass apparatus at low temperatures and mild reaction conditions and in a Parr 4501 stainless steel pressure reactor at higher temperatures and under more servere conditions.

4.E.1.a. Method A--Glass apparatus (tables 3, 4, 5). The polychlorobenzene was added to a slurry of the potassium fluoride and melted dimethylsulfone (mp 109° C) in a glass reaction flask. The mixture was stirred and heated for the times and at the temperatures indicated in the tables. After the mixture was diluted with water, the fluorinated reaction products were collected by steam distillation.

The crude products were washed successively with concd sulfuric acid (sp gr

TABLE 3—FLUORINATION OF TRIHALOBENZENES[a]

Trihalobenzene Cl-F	Moles	KF (moles)	CsF (moles)	$DMSO_2$ (g)	Temp (°C)	Time (hr)	Method	Products (mole%yield) $Cl_2C_5H_3F$	$ClC_6H_3F_2$	$C_6H_3F_3$	ClC_6H_4F	$C_6H_4F_2$
I. 1,2,3-Trihalobenzenes												
1,2,3-	0.75	3.37	—	480	200	720	A	1,2-3(9.8)[b] 1,3-2(5.3)	trace —	—		
	0.75	2.37	1.0	480	200	168	B-1	1,2-3(29.0) 1,3-2(19.2)	1-2,6(13.2) 1-2,3(11.0)	—	1-2(0.8)	
	0.75	3.0	0.35	950	243	168	B-1	1,2-3(10.0) 1,3-2(6.6)	1-2,6(14.0) 1-2,3(11.7)	12.8	1-2(0.8)	1,2(1.8)[c] 1,3(2.3)
1,2-3	0.48	2.16	0.72	960	265	5.5	B-2	1,2-3(20.0)	48.0	2.9	1.1[d]	1.2[d]
1,3-2	0.5	1.25	0.5	600	250	26	B-1	1,3-2(17.8)	1-2,3(20.9)	8.6		
1-2,3	0.5	1.0	0.5	1000	265	6	B-2	—	1-2,3(21.2)	23.9		
1-2,6	0.4	1.0	0.2	800	265	6	B-2	—	1-2,6(32.5)	9.0		
II. 1,2,4-Trihalobenzenes												
1,2,4-	0.75	3.37	—	480	200	504	A	1,4-2(17.3) 1,2-4(4.7) 1,3-4(3.4)	—	—		
	0.5	4.0	—	320	263	192	B-1	1,4-2(17.5) 1,2-4(4.6) 1,3-4(3.4)	1-2,4(26.7) 1-3,4(8.9)	2.5	1-4(1.8)	
	0.5	4.0	—	544	273	240	B-1	1,4-2(2.0) 1,2-4(0.6) 1,3-4(0.4)	1-2,4(12.4) 1-3,4(4.3)	8.3	1-4(0.7)	
	0.4	1.02	0.18	500	243	168	B-1	1,4-2(7.0) 1,2-4(1.9) 1,3-4(1.3)	1-2,4(17.6) 1-3,4(5.9)	4.2	1-4(1.0)	
1,2-4	0.25	1.25	0.12	500	265	6	B-2	1,2-4(6.1)	50.2	4.2		
1,3-4	0.48	2.16	0.72	960	265	6	B-2	1,3-6(32.4)	39.6	1.8		
1,4-2	0.5	2.5	0.5	1000	265	6	B-2	1,4-2(8.8)	32.0	3.2		
1-2,4	0.5	1.5	—	1000	265	6	B-2	—	1-2,4(58.8)	2.1		
	0.5	1.25	0.25	1000	265	5	B-2	—	1-2,4(45.0)	7.1		
1-2,5	0.5	—	0.5	1000	265	6	B-2	—	1-2,5(34.1)	34.0		1,4(2.5)
	0.5	1.25	0.25	1000	265	6	B-2	—	1-2,5(34.7)	33.2		1,4(2.1)
1-3,4	0.5	1.25	0.25	1000	265	6	B-2	—	1-3,4(41.0)	7.0		
III. 1,3,5-Trihalobenzene												
1,3,5-	1.5	1.65	—	813	225	240	B-1	1,3-5(54.5)	1-3,5(22.4)	—		
	2.0	8.0	—	670	280	48	B-1	1,3-5(6.6)	1-3,5(47.7)	27.8		1.3(1.7)
	2.0	9.0	1.0	865	275	6	B-1	1,3-5(8.8)	1-3,5(40.5)	31.4		
	2.0	8.0	—	865	265	168	B-1	—	1-3,5(17.4)	56.2		1,3(4.4)
	2.0	9.0	1.0	1100	290	5	B-1	1,3-5(0.1)	1-3,5(22.2)	43.5		1,3(4.0)

[a] For descriptions of Methods A and B, see p. 95. Data taken from reference 29.
[b] Numbers preceding hyphen refer to Cl; those after the hyphen refer to F.
[c] Trace of fluorobenzene.
[d] Structure not proven.

1.84), water, 5 percent aqueous sodium hydroxide solution (1.25 N) and again with water. After the products were dried over anhydrous magnesium sulfate, they were fractionally distilled in an annular Teflon Spinning-band column.

4.E.1.b. Method B--Parr reactor (tables 3, 4, 5). The polyhalobenzene was added to a heated mixture (ca 200° C) of dimethylsulfone and metal fluoride in the autoclave. If the halobenzene was solid (method B-1 in the tables), it was added directly; but if liquid (method B-2 in the tables), it was injected into the closed autoclave with a slight nitrogen pressure. The reaction mixtures were allowed to react under autogenous pressure and were stirred at the temperatures and time intervals indicated in the tables. The reaction products were removed from the reactor by distillation and were purified as described above in Method A.

4.E.2. Pentachlorobenzene (14). A mixture of 33.5 g (0.137 mole) of pentachlorobenzene, 58 g (1 mole) of potassium fluoride, and 100 ml of DMSO in a glass reaction vessel were stirred and heated at 180° C for

TABLE 4—FLUORINATION OF TETRAHALOBENZENES[a]

$C_6H_2X_4$ (moles)	KF (moles)	CsF (moles)	Solvent (g)	Temp (°C)	Time (hr)	Method	Product (mole%yield) $Cl_3C_6H_2F$	$Cl_2C_6H_2F_2$	$ClC_6H_2F_3$	$C_6H_2F_4$	$C_6H_3F_3$
I. 1,2,3,4-Tetrachlorobenzene											
0.2	1.8	—	128	200	168	A	1,2,4-3(46.7)[b] 1,2,3-4(8.3)	1,3-2,4(10.7) 1,4-2,3(7.5) 1,2-3,4(1.4)	—	—	—
0.2	1.8	—	430	225	168	A	1,2,4-3(8.1) 1,2,3-4(1.4)	1,3-2,4(22.8) 1,4-2,3(15.6) 1,2-3,4(2.8)	1-2,3,4(11.7)	0.7	—
0.1	—	0.4	215	170	168	A	1,2,4-3(1.2) 1,2,3-4(0.3)	1,3-2,4(3.0) 1,4-2,3(2.1) 1,2-3,4(0.4)	1-2,3,4(1.5)	—	—
0.1	0.76	0.09[c]	430	200	168	A	1,2,4-3(0.1) 1,2,3-4(0.0)	1,3-2,4(14.1) 1,4-2,3(9.8) 1,2-3,4(1.9)	1-2,3,4(24.4)	0.7	—
1.0	9.0	—	645	245	240	B-1	—	1,3-2,4(8.1) 1,4-2,3(5.6) 1,2-3,4(1.1)	1-2,3,4(19.5)	—	—
1.0	8.9	0.1	645	245	96	B-1	—	1,3-2,4(15.0) 1,4-2,3(10.3) 1,2-3,4(1.7)	1-2,3,4(15.6)	0.1	—
II. 1,2,3,5-Tetrachlorobenzene											
1.05	1.6	—	300[d]	183	72	A	1,3,4-5(7.2)	1,4-3,5(0.4) 1,3-4,5(0.4)	—	—	—
0.2	2.4	—	200[d]	195	168	A	1,3,4-5(32.1)	1,4-3,5(31.8) 1,3-4,5(8.5)	—	—	—
0.25	2.25	—	500	265	6	B-1	—	1,4-3,5(2.9) 1,3-4,5(0.8)	1-2,4,6(47.0) 1-3,4,5(6.6)	3.7	3.7[e]
0.25	2.0	0.25	500	265	5	B-1	—	1,4-3,5(0.8) 1,3-4,5(0.2)	1-2,4,6(8.6) 1-3,4,5(1.2)	1.4	3.5[e]
III. 2,4,6-Trichlorofluorobenzene											
0.1	1.0	—	250	240	6	B-2	—	1,3-4,5(17.4) 1,3-2,5(10.0)	1-2,3,5(27.6) 1-3,4,5(11.8)	3.0	0.5[f]
0.1	1.0	0.5	225	250	5.5	B-2	—	1,3-4,5(5.5) 1,3-2,5(3.2)	1-2,3,5(25.9) 1-3,4,5(11.1)	4.7	0.75[f]
IV. 2,6-Dichloro-1,4-difluorobenzene											
0.41	1.63	—	900	265	6	B-2	—	—	1-2,3,5(28.6)	39.8	3.1[g]
0.5	2.9	0.1	1240	265	6	B-2	—	—	1-2,3,5(5.5)	44.8	3.7[g]

[a] Reference (23).
[b] Numbers preceding hyphen refer to Cl; those after the hyphen refer to F.
[c] 0.05 mole BaF_2 added.
[d] DMSO.
[e] Mixture of 1,3,5-trifluoro- and 1,2,3-trifluorobenzene.
[f] Mixture of 1,2,4-trifluoro- and 1,2,3-trifluorobenzene.
[g] 1,2,4-trifluorobenzene.

24 hr. The reaction mixture was diluted with water and steam distilled. Distillation at reduced pressure gave three fractions (A, B, and C) based on boiling point. The products within each fraction along with their physical properties are listed in table 6.

5. DIAZOTIZATIONS AND DIAZONIUM GROUP REPLACEMENTS

5.A. Schiemann transformations

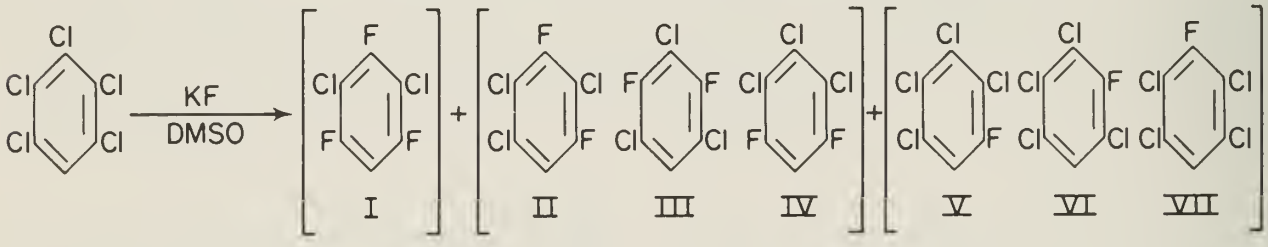
5.A.1. With hydrochloric acid–laboratory scale. To a solution of 2500 ml of concd hydrochloric acid in 1300 ml of water were added concurrently, a mixture of 546 g (3.0 moles) of 2-fluoro-3-chloroaniline in 1000 ml of water and 350 ml of concd hydrochloric acid and a solution of 227.7 g of sodium nitrite in 300 ml of water. The sodium nitrite solution was added subsurface in a temperature of 0 to -10° C and was always in slight excess until all of the aniline had been added. The mixture was stirred for 1.5 hr and then cooled internally with Dry Ice to -30° C. A slurry of 660 g (6 moles) of sodium fluoborate in 600 ml of water was added and the diazonium fluoborate salt was filtered to give 746 g or an 88.5 percent yield. The diazonium fluoborate was thermally decomposed. Steam distillation gave 303 g or a 68 percent yield of 1,2-difluoro-3-chlorobenzene. This synthesis can be further illustrated for a number of compounds by the following general procedure (see table 7).

TABLE 5—TETRAFLUOROBENZENE BY KF FLUORINATION[a]

$C_6H_2X_4$ (moles)	KF (moles)	CsF (moles)	$DMSO_2$ (g)	Temp (°C)	Time (hr)	Method	Product (mole%yield) $Cl_2C_6H_2F_2$	$ClC_6H_2F_3$	$C_6H_2F_4$
I. 2,3-Dichloro-1,4-difluorobenzene									
0.33	1.32	—	600	265	3.5	B-1	18.4	47.5	6.0
0.33	0.99	0.11	600	265	3.0	B-1	—	30.2	22.6
0.25	0.75	0.25	455	265	2.3	B-1	—	39.0	18.2
II. 3,4-Dichloro-1,2-difluorobenzene									
0.15	0.45	0.1	300	265	3.5	B-2	3.8	25.9	1.8
III. 2,4-Dichloro-1,3-difluorobenzene									
0.15	0.45	0.1	300	265	3.5	B-2	18.0	20.7	1.3
IV. 2,3,4-Trifluorochlorobenzene									
0.08	0.31	—	200	265	5.5	B-2	—	29.0	1.9
0.08	0.31	—	100	225	5.5	B-2	—	76.0	1.0
0.08	—	0.1	100	225	5.5	B-2	—	51.5	2.5
V. 2,3,6-Trifluorochlorobenzene									
0.08	0.31	—	200	265	5.5	B-2	—	27.6	16.4
0.33	0.89	0.1	600	265	2.0	B-2	—	37.1	25.5
0.33	0.89	0.19	650	270	1.5	B-2	—	18.5	26.3
0.17	—	0.25	300	225	3.5	B-2	—	29.0	11.5

[a] Reference (24).

TABLE 6—FLUORINATION OF PENTACHLOROBENZENE[a]



Distillation fraction	A		B			C	
Fraction bp (°C/mm)	79-82/42		89/15			114/8.5	
Components bp (°C/mm)	160/atm	91/45	104/18	200/atm	75/0.7	—	—
Fraction n_D^{20}	1.4870		1.5298			1.5738	
Components n_D^{20}	1.4865	1.5310	1.5290	—	—	—	—
Components mp (°C)	—	—	—	50	66	17	73
Yield of fraction (%)	7.3		30.3			17.1	
Distribution (%)	100	50.0	25.0	25.0	33.3	33.3	33.3

[a] Reference (14).

The concd hydrochloric acid was divided into two parts by percentage, as indicated in table 7. For the preparation of the aniline hydrochloride, (A) is the fraction of the total acid which was diluted with water to a lower percentage acid strength (B). The remaining acid portion was diluted to the acid strength indicated in (C). The appropriate aniline was added to the dilute acid (B). The diazotization was effected in a temperature range of 0 to 10° C by the concurrent addition of the aniline salt solution (B) and a strong water solution of sodium nitrite (slight excess) to the other dilute acid solution (C).

The diazonium fluoborate was prepared and treated in the manner described for the preparation of 1,2-difluoro-3-chlorobenzene.

5.A.2. With hydrochloric acid--large scale. Sixty moles or 5580 g of aniline was added rather rapidly to 17.3 liters of commercial hydrochloric acid (18° Bé) in a 30-gal crock jar. The warm mixture was stirred and allowed to cool to almost room temperature. After the mixture was cooled with the internal addition of Dry Ice to -5° C, the diazotization was effected by the subsurface addition of a solution of 4180 g (60.5 moles) of sodium nitrite in 6300 ml of water. This procedure was performed over a 45 min period while the temperature was maintained between 0 and -5° C. The resulting clear red solution was cooled to -30° C and a slurry of 11,000 g (100 moles) of sodium fluoborate in 9000 ml of water was added. The resulting diazonium fluoborate salt was collected on a filter and dried. The salt was decomposed thermally in 5-liter flasks connected to a series of six 4-ft condensers. Steam distillation of the crude condensate gave 4065 g or a 71 percent yield of fluorobenzene.

5.A.3. With 50 percent fluoboric acid. To 800 ml of 50 percent fluoboric acid in a stainless steel beaker, 163.5 g (1.0 mole) of 2-chloro-3,4-difluoroaniline was added. The temperature was reduced to -10° C by the use of an acetone-Dry Ice external cooling bath. The mixture was diazotized by carefully adding a solution of 76 g (1.1 moles) of sodium nitrite in 120 ml of water. After the addition was complete, the mixture was cooled to -35° C and the precipitated diazonium fluoborate salt was collected on a filter, dried, and washed with ethyl ether. After removal of the ether, the salt was thermally decomposed to give 112 g or a 67 percent yield of 2-chloro-1,3,4-trifluorobenzene.

5.A.4. With ammonium fluoborate (35). Ammonium fluoborate gives yields of benzene diazonium fluoborate, similar to that obtained when sodium fluoborate is used. However, in the case of aniline itself lower yields are obtained. The solubility of the benzene diazonium fluoborate is an important factor. Decreased yields may be due in part to the larger volume of water which is necessary to slurry the more insoluble ammonium fluoborate.

5.A.5. Pyridine derivatives (4).

5.A.5.a. Diazotization with sodium nitrite. Sodium nitrite (10.2 g, or 0.15 mole) was added in small portions to a stirred mixture of 2-amino-6-fluoropyridine (10.0 g, or 0.089 mole) and 50 percent fluoboric acid (65 ml) at -8 to -10° C. The mixture was then stirred for 30 min at 0° C, heated to 50° C, cooled to room temperature,

TABLE 7—SCHIEMANN TYPE SYNTHESIS OF FLUOROBENZENES

Ring substitution	Starting aniline	Mole ratio HCl to aniline	Percentage of acid for hydrochloride (A)	Final concentration of diluted A (B)	Final concentration of remaining acid (C)	Yield (%)
1F-2Cl	2Cl	5:1	78	28	18.5	74
1F-2,4Cl_2	2,4Cl_2	3:1	70	37	37	62
1F-2,5Cl_2	2,5Cl_2	5:1	70	37	37	64
1F-3(CH_3)	3(CH_3)	2.5:1	50	37	37	65
1(OCH_3)-2F	2(OCH_3)	3:1	50	13	13	51
1(OCH_3)-4F	4(OCH_3)	3:1	50	13	13	73
1(OCH_3)-2,6F_2	3F-2(OCH_3)	3:1	42	37	37	38
1(OCH_3)-2,4,6F_3	3,5F_2-2(OCH_3)	4:1	63	23.5	23.5	19

poured onto ice, neutralized with sodium carbonate, and steam distilled. A yield of 27 percent or 2.8 g of 2,6-difluoropyridine was obtained.

5.A.5.b. Diazotization with ethyl nitrite (4). 2-Fluoro-3-aminopyridine (4.8 g, or 0.043 mole) was dissolved in a mixture of 40 percent fluoboric acid (20.1 moles) and absolute ethanol (40 ml). The mixture was stirred and cooled to -5° C by an external Dry Ice-acetone bath; diazotization was effected over a 30 min period with ethyl nitrite. Upon addition of absolute ethanol (30 ml) and anhydrous ether (40 ml) and subsequent cooling to Dry Ice-acetone bath temperature, precipitation occurred. The solid was collected on a filter and was twice washed with cold absolute ethanol and twice with anhydrous ether. The salt was immediately thermally decomposed in a round bottom flask equipped with a condenser. Steam distillation, followed by a micro-distillation, gave 1 g or a 20 percent yield of 2,3-difluoropyridine.

5.B. Replacement with chlorine

5.B.1. In hydrochloric acid. 2-Chloro-3,4-difluoroaniline (177 g, or 1.08 moles) was melted and poured slowly into 1776 ml of concd hydrochloric acid. After the mixture was stirred for 30 min, it was cooled to 8° C and then diazotized by the subsurface addition of a solution of 83 g (1.2 moles) of sodium nitrite in 83 ml of water. The 2-chloro-3,4-difluorobenzene diazonium chloride solution was poured with rapid stirring into a mixture of 225 g of cuprous chloride in 1000 ml of concd hydrochloric acid at 0° C. Steam distillation gave 130 g or a 66 percent yield of 1,2-difluoro-3,4-dichlorobenzene.

5.B.2. In sulfuric acid

5.B.2.a. Nitrosyl sulfuric acid. A mixture of 390 g (or 2.5 moles) of 3-fluoro-6-nitroaniline and 800 ml of concd sulfuric acid was heated at 70° C for 80 min and then cooled to 0° C. Diazotization was started by the slow addition of a solution of 183 g (2.7 moles) of sodium nitrite in 800 ml of concd sulfuric acid in a temperature range of 0 to -10° C. Diazotization was then effected by the addition of 1600 ml of 85 percent phosphoric acid at the same temperature. The 3-fluoro-6-nitrobenzenediazonium hydrosulfate solution was added slowly with rapid stirring to a mixture of 453 g of cuprous chloride in 3000 ml of concd hydrochloric acid. After the evolution of nitrogen had ceased, the slurry was steam distilled to give 179.5 g or a 41 percent yield of 2-chloro-4-fluoronitrobenzene.

5.B.2.b. Aqueous sodium nitrite. The volume of sulfuric acid (66° Bé or 93 percent) to be used in the reaction was divided into two parts by percentage as indicated in table 8. The percent volume of concd sulfuric acid (A) was used to prepare the aniline hydrosulfate. The remaining volume of concd sulfuric acid was diluted to the percent concentration (B) and used as the diazotization medium. The aniline was added to the undiluted acid (A) to form the amine salt, and cooled. A concentrated aqueous sodium nitrite (slight molar excess) solution was prepared. The diazotization was effected

TABLE 8—CHLOROFLUOROBENZENE SYNTHESES

Ring substitution	Starting aniline	Mole ratio H_2SO_4 to aniline	Percentage of acid for hydrosulfate (A)	Concentration of diluted acid (B)	Yield (%)
$1(OCH_3)$-2F-4Cl	3F-4(OCH_3)	3:1	70	65	57
$1(OCH_3)$-4F-2Cl	3F-6(OCH_3)	3:1	50	60	88
$1,3F_2$-4Cl	$2,4F_2$	6:1	82	50	70
1F-$3,4Cl_2$	4F-2Cl	6.5:1	85	50	85

at -5° C by the concurrent addition of aniline salt and nitrite solutions to the ice-acid mixture (B). Stirring was continued approximately 1 hr without further cooling. Decomposition of the diazonium salt was effected as described above using cuprous chloride.

5.C. Replacement with bromine

5.C.1. In 48 percent hydrobromic acid. 2-Amino-3-nitrotoluene (30.4 g, or 0.2 mole) was added rapidly to 200 ml of 48 percent hydrobromic acid while being stirred and heated to 70° C. The mixture was cooled to room temperature for 45 min and then cooled to 0° C with the internal addition of Dry Ice. The hydrobromide salt was diazotized over a 15 min period and over a temperature range of -5 to 0° C by the subsurface addition of a solution of 15 g (0.22 mole) of sodium nitrite in 25 ml of water. After the mixture was sitrred for 40 min, 4 drops of an antifoaming agent and 0.3 g of copper bronze powder were added. Since the evolution of nitrogen was slow, the mixture was heated to 65° C and stirred for 45 min. Dilution with an equal volume of water followed by steam distillation gave 40 g or a 92 percent yield of 2-bromo-3-nitrotoluene.

5.C.2. In sulfuric acid. A mixture of 234 g (1.5 moles) of 2-amino-4-fluoronitrobenzene and 507 ml of concd sulfuric acid was prepared and heated to 80° C for 15 min and then cooled to 0° C. Diazotization was effected over a 1.5 hr period by the concurrent addition of the aniline hydrosulfate solution and a solution of 114 g (1.65 moles) of sodium nitrite in 204 ml of water, to 450 ml of concd sulfuric acid at 0° C. After the addition was complete, 750 ml of 85 percent phosphoric acid was added. The mixture was then heated to 50° C to insure complete diazotization and after 1 hr was cooled to 15° C. The diazonium solution was added with thorough stirring to a mixture of 300 g of cuprous bromide in 1200 ml of 48 percent hydrobromic acid. Steam distillation gave 232 g or a 70.3 percent yield of 2-bromo-4-fluoronitrobenzene.

5.D. Replacement with iodine

2-Amino-4-fluoroanisole (283 g, or 2.0 moles) was added slowly to 370 ml of commercial sulfuric acid (66° Bé) in 370 ml of water while the temperature was controlled at or below 55° C. The aniline hydrosulfate solution was diazotized by the subsurface addition of 152 g (2.2 moles) of sodium nitrite in 216 ml of water at 0° C. The diazonium solution was then added slowly with thorough stirring to a solution of 500 g (3 moles) of potasisum iodide in 750 ml of water. Steam distillation followed by washing with a dilute sodium thiosulfate solution gave 433 g or an 85 percent yield of 2-iodo-4-fluoroanisole.

5.E. Replacement with hydrogen

5.E.1. Deamination (6). A solution of 67 g (0.38 mole) of 4-amino-5-nitro-1,3-difluorobenzene in 150 ml of concd sulfuric acid was prepared and stirred for 3 hr at room temperature. Sodium nitrite (0.41 mole) in 150 ml of concd sulfuric acid was added slowly to the above aniline hydrosulfate solution, in a temperature range of 0 to 10° C. In order to effect the diazotization, 300 ml of 85 percent phosphoric acid was added slowly while the temperature was maintained between 10 and 15° C.

To the rapidly stirring diazonium solution at 0° C, a slurry of 250 g of sodium hypophosphite, 35 g cuprous oxide, and 150 ml of water was slowly added. The resulting exothermic reaction was controlled below 35° C with the internal addition of Dry Ice. The reaction mixture was then diluted with an equal volume of water in a 12-liter flask and cautiously steam distilled. The use of a large flask is essential because near the end of the steam distillation, the hypophosphorous acid reduces the copper salts with an almost uncontrollable exothermic reaction, causing the entire mixture to suddenly superheat and foam. The yield of pure distilled 5-nitro-1,3-difluorobenzene was 37 g or 60 percent.

5.E.2. Combined deamination and nitro reduction (32). A mixture of 119 g (0.57 mole) of 4,6-difluoro-5-chloro-2-nitroaniline and 84 ml of glacial acetic acid was dissolved in 640 ml of concd sulfuric acid. Nitrosyl sulfuric acid was prepared by adding 46 g (0.66 mole) of sodium nitrite to 424 ml of concd sulfuric acid in a temperature range of 20 to 25° C. The aniline salt was added to the nitrosyl sulfuric acid solution at room temperature and the mixture was stirred for 2 hr. The diazotization was completed at 0 to 10° C by the addition of 272 ml of 85 percent phosphoric acid and subsequent warming to 60 to 70° C. The diazonium solution was cooled and added slowly with thorough stirring to a slurry of 301 g of sodium hypophosphite, 326 g of cuprous oxide, and 500 ml of water in a 12-liter flask. Considerable foaming took place as the temperature increased to 50° C. The mixture was then heated at steam bath temperature for 4 hr. Steam distillation gave 60 g or a 64 percent yield of 3,5-difluoro-4-chloroaniline.

5.F. Replacement with hydroxyl

5.F.1. Sulfuric-phosphoric acid, large-scale. 4-Fluoroaniline (832 g, or 7.5 moles) was added to 3000 ml of concd sulfuric acid without external cooling. The aniline hydrosulfate solution was heated at steam bath temperature for 2.5 hr and allowed to cool.

A nitrosyl sulfuric acid solution was prepared by slowly adding 569 g (8.25 moles) of powdered sodium nitrite to 3750 ml of concd sulfuric acid in a 5-liter Morton-type flask over a temperature range of 30 to 40° C and with vigorous stirring. After heating for 2.5 hr on a steam bath, the nitrosyl sulfuric acid solution was allowed to cool to room temperature and then was further cooled to 0° C by the internal addition of powdered Dry Ice. The aniline hydrosulfate was added to the nitrosyl sulfuric acid solution at a moderate-to-rapid rate over a temperature range of 0 to 10° C. Stirring was continued for 20 min followed by the addition at 35° C of 2250 ml of 85 percent phosphoric acid. The mixture was then stirred for 1 hr.

Hydrolysis of the diazonium sulfate solution was effected in a flask equipped with a dropping funnel, a thermometer, and a steam inlet suitable for steam distillation. One kg of copper sulfate, 1250 ml of commercial sulfuric acid (66° Bé), and 1000 ml of water were added to the hydrolysis flask. During the mixing, the temperature rose to 120° C. The diazonium salt solution was added in a small stream concurrently with steam from the steam leg while the temperature was maintained in the range of 140 to 150° C with external heat from a ring burner. About 5 to 6 hr were required for the hydrolysis and a total of 8 to 24 liters of steam distillate were collected. Salt was added to the distillate to 10 percent concentration. The distillate was neutralized with sodium carbonate to destroy any hydrofluoric acid present and then acidified to congo red with hydrochloric acid. Ether extraction followed by vacuum distillation gave 1154 g or a 63 percent yield of 4-fluorophenol.

5.F.2. Sulfuric acid. 2,4-Difluoroaniline (64.5 g, or 0.5 mole) was added to 323 ml of concd sulfuric acid, and the warm mixture was stirred for 0.5 hr.

Nitrosyl sulfuric acid was formed by the addition of 38 g of sodium nitrite to 270 ml of concd sulfuric acid with stirring. The mixture was heated at steam bath temperature until a complete solution was obtained. At room temperature, the aniline hydrosulfate was added to the nitrosyl sulfuric acid solution rather rapidly and then stirred at 35° C for 0.5 hr. After the solution was cooled to 0° C, 200 ml of 85 percent phosphoric acid was added at a rate which allowed the temperature to increase to 45° C.

The diazonium solution was hydrolyzed by adding it to 250 g of copper sulfate, 200 ml of water, and 400 ml of concd sulfuric acid while a current of steam was passed through the mixture. The temperature was maintained in a range of 138 to 143° C. The steam distillate was saturated with salt (10 percent), extracted with ether, and flash distilled to give 32.5 g or a 50 percent yield of 2,4-difluorophenol.

It may be advantageous to change the hydrolysis vessel often because of excessive tar formation. If this is done, a 100 ml sample of the spent hydrolysis mixture should be added to the new mixture to aid in the initial decomposition of the diazonium salt.

This method can be further illustrated with the following general procedure for a number of compounds (table 9). In the diazotization, the sulfuric acid (66° Bé) indicated in the table was divided into two parts by percentage. (A) is the percentage of the sulfuric acid used for the preparation of the aniline hydrosulfate. The remaining fraction was diluted with ice to an acid concentration (B) to serve as a medium for the diazotization. The aniline was added to the undiluted acid to form the aniline hydrosulfate salt and cooled. A concentrated aqueous sodium nitrite (slight excess) solution was prepared. The diazotization was effected at -5° C by the concurrent addition of the aniline hydrosulfate salt and nitrite solutions to the ice-acid mixture. Stirring was continued approximately 1 hr without further cooling.

As an aid to achieving the desired temperature listed in table 9, the temperature composition formulation in table 10 was found to be useful.

5.F.3. Sulfuric acid--insoluable hydrosulfate salt. In some cases, where the aniline hydrosulfate mixture was cooled to 0° C, a solid crystalline mass was obtained. In these cases, the mixture was cooled in several stages, and at each stage the crystal crop was removed by filtration on a glass fiber cloth. Diazotization was effected at 0 to 5° C by the concurrent addition of powdered sodium nitrite (slight excess) and aniline salt crystals to the hydrosulfate salt liquor. Examples of this method are illustrated in table 11.

6. BY-PRODUCTS FROM THE SCHIEMANN TRANSFORMATION

6.A. Displacement of arylfluorine in diazonium salts (20)

Diazotization for the Schiemann synthesis is usually effected in hydrochloric acid, and sodium fluoborate is the most convenient source of the fluoborate ion. If the diazonium fluoborate is not purified, it contains varying

TABLE 9—PHENOL SYNTHESIS

Ring substitution	Mole ratio H_2SO_4 to aniline	Percentage of acid for hydrosulfate (A)	Final concentration of diluted acid (B)	Hydrolysis (°C)	Yield (%)
3F	10:1	57	80	190	55
3F-4Cl	11:1	76	50	160	56
4F-3Cl	12:1	75	50	180	59
2F-4(CH_3)	5:1	60	65	160	40
4F-2(CH_3)	5:1	60	65	160	53
4F-3(CH_3)	4:1	70	65	160	53
2F-4,5Cl_2	12:1	76	57	195	47
4F-2,5Cl_2	12:1	82	50	180	32
2,5F_2	5:1	75	57	180	42
3,4F_2	12:1	75	50	180	32
3,5F_2	5:1	60	65	180	61
2,4F_2-5Cl	10:1	82	50	175	40
2,5F_2-4Cl	10:1	75	50	170	41
4,5F_2-2Cl	9.5:1	76	57	195	23
2,3,4F_3	7.5:1	60	65	175	57
2,3,5F_3	5:1	70	65	180	54

TABLE 10—HYDROLYSIS TEMPERATURES

Temp (°C)	H_2SO_4 (66° Be)	H_2O	$CuSO_4 \cdot 5H_2O$
140-160	1250 ml	1000 ml	450 g
170-190	1200 ml	400 ml	500 g

TABLE 11—PHENOL SYNTHESIS

Synthesized phenol	Mole ratio H_2SO_4 to aniline	Hydrolysis (°C)	Yield (%)
2F-3Cl	12:1	170	36
2,4F_2-3Cl	11:1	160	38

amounts of coprecipitated sodium chloride, which may affect the final thermal decomposition reaction. Recrystallization of the benzenediazonium fluoborate is impractical for large-scale syntheses, and organic solvents are ineffective in removing sodium chloride. As a result, appreciable amounts of chlorobenzenes may be formed in the preparation of some fluorobenzenes. The chloro mixtures from three such preparations have been isolated and identified.

A 10 percent yield of 2,5-difluorochlorobenzene (fig. 1, IV) and a 1 percent yield of 2,4-difluorochlorobenzene (fig. 1, V) were obtained in the synthesis of 1,2,4-trifluorobenzene (fig. 1, II) from 2,4-difluoroaniline. This was the first observed instance of the formation of chloro isomers. The identical isomers were also obtained from 2,5-difluoroaniline with 2,4-difluorochlorobenzene (fig. 1, V) as the major component. 2,4,6-Trifluorochlorobenzene with a trace of 2,3,5-trifluorochlorobenzene was obtained in the synthesis of 1,2,3,5-tetrafluorobenzene from 2,3,5-trifluoroaniline. These compounds gave evidence of two independent reactions forming monochloro isomers: (1) displacement of a fluorine ortho to the diazonium group with chlorine, and (2) replacement of the diazonium group with chlorine. The second reaction, a Griess type, is more or less expected; however, the very small yield of chloro compounds produced by this reaction shifted attention to the importance of the first reaction. In other words, the predominating reaction is an aromatic nucleophilic substitution of a fluorine atom strongly activated by an ortho diazonium group.

The question arises as to whether the displacement reaction occurs in solution during the diazotization process or during thermal decomposition in the presence of

sodium chloride. It was established that displacement occurs during thermal decomposition of the dry diazonium fluoborate salt and that the amount of sodium chloride present determines the yield of chloro product. A series of thermal decompositions of pure, recrystallized 2,4-difluorobenzenediazonium fluoborate (fig. 1, I) mixed with increasing amounts of sodium chloride gave increasing yields of difluorochlorobenzene and decreasing yields of trifluorobenzene. With a large excess of sodium chloride, the difluorochloro- and trifluoro- compounds were obtained in 30 percent and 10 percent yields, respectively.

The displacement reaction did not occur during the diazotization process in hydrochloric acid. Solutions of either the diazonium chloride or the diazonium fluoborate in hydrochloric acid heated at 60° C for 1 hr did not result in displacement of the o-fluorine by chlorine.

To demonstrate that the displacement reaction is independent of the thermal decomposition reaction, recrystallized 2,4-difluorobenzenediazonium fluoborate (fig. 1, I) was converted to 2-chloro-4-fluorobenzenediazonium fluoborate (fig. 1, III) by mixing the first with dry lithium chloride and heating carefully for a short period above the melting point but below the decomposition point. In this instance, the differential between the two points is about 35° C. The melt was chilled rapidly to a solid and recrystallized from water to give the pure displacement product with only slight loss due to decomposition of the diazonium group.

An experiment with 2-fluorobenzenediazonium fluoborate, where the melting and decomposition points are almost identical, gave a considerable yield of 2-chlorofluorobenzene. Here also, of major significance is o-fluorine displacement rather than diazonium displacement with chlorine, which in this case produces the same chloro compound.

Examination of residues from many large-scale Schiemann syntheses of fluorobenzene, 1,3-difluorobenzene, 1,3,5-trifluorobenzene, and 1,4-difluorobenzene usually gave a chloro by-product yield of 2 percent or less. From this it can be inferred that chloro compound formation does not result from m- or p-fluorine displacement. It is interesting to point out that heating a mixture of 4-fluorobenzenediazonium fluoborate with lithium chloride does not cause p-fluorine displacement. No formation of dichloro compounds was detected in any preparations.

The foregoing mechanism of isomeric chloro formation adequately explains the chloro products from 2,5-difluoroaniline and 2,3,5-trifluoroaniline; no detailed study was made of the second except to establish the predominance of the chloro isomers from the displacement reaction. The major components were identified by comparison of derivatives with compounds of known structure; in addition, both the major and minor components

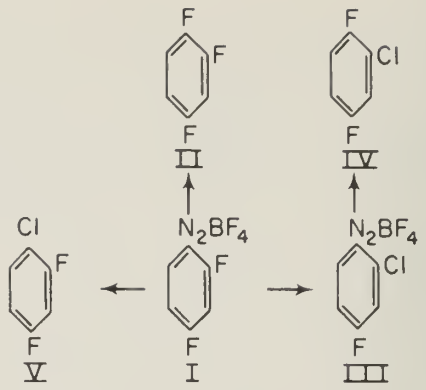


Figure 1. Displacement of arylfluorine

were identified and estimated by infrared spectra and ^{19}F nuclear magnetic resonance (NMR).

The effect of other alkali metal salts on the thermal decomposition of 2,4-difluorobenzenediazonium fluoborate was investigated. Lithium chloride appears to appreciably lower the melting point of this diazonium fluoborate, thus favoring completion of the displacement reaction before decomposition. A 2:1 mole ratio of lithium chloride to diazonium fluoborate gave a 37 percent yield of the chloro fraction. By NMR analysis the chloro mixture contained approximately 95 percent 2,5-difluorochlorobenzene (fig. 1, IV) with less than 5 percent 2,4-difluorochlorobenzene (fig. 1, V). This suggests a possible use of the displacement reaction in special preparative problems and identification studies. In contrast, heating the diazonium fluoborate with potassium chloride or sodium cyanide caused vigorous decomposition to tar and coke. From this it can be inferred that reagents providing alkaline media reduce the stability of the diazonium group and catalyze the decomposition to coupled products or tars of undetermined structure. Sodium bromide gave a low yield of 2,4-difluorobromobenzene, with no evidence of fluorine displacement by bromine. The aniline hydrochloride salt, a possible contaminant in diazotization reactions, also causes difficulty in the thermal decomposition. Heating a mixture of one part of initial aniline hydrochloride salt with ten parts of recrystallized diazonium fluoborate gave very little evidence of chloro formation, and the yield of 1,2,4-trifluorobenzene was reduced to less than 10 percent.

6.B. Biphenyl formation

The diazonium group replacement by fluorine also yields varying amounts of biphenyl by-products.

The vacuum distillation of the crude steam-distilled product from a series of large-scale syntheses of fluorobenzene via the Schiemann transformation left a

TABLE 12—SCHIEMANN TRANSFORMATION BY-PRODUCTS

Ring substitution biphenyl	Parent aniline
$2,2',4,5,5'F_5$	$2,5F_2$
$2,3',4,5',6F_5$	$3,5F_2$
$2,3',4F_3$	3F
$2,2',3F_3$	2F
$2,4',5F_3$	4F

TABLE 13—DIPHENYL ETHER FORMATION

Ring substitution diphenyl ether	Parent aniline
$3,3'F_2$	3F
$4,4'F_2$	4F
$2,2',5,5'F_4$	$2,5F_2$

residue containing biphenyls. This residue was vacuum distilled (bp 78° C/2 mm) to give a mixture of three products. The compounds were identified by ^{19}F NMR spectrum and consisted of 2-fluoro-, 3-fluoro-, and 4-fluorobiphenyl in concentrations of 22 percent, 69 percent, and 9 percent, respectively. Other examples of biphenyl formation are illustrated in table 12.

6.C. Diphenyl ether formation

Distillation of the crude aromatic fluorides obtained from the Schiemann transformation yields residues which contain diphenyl ethers of various structure or composition depending upon the diazotization conditions and the character of the aniline.

Three of the ethers and the anilines from which they were derived are listed in table 13.

6.D. Azobenzene formation

Synthesis of 1,2,4-trifluorobenzene from the corresponding 2,4-difluoroaniline via the Schiemann transformation yielded a small amount of 2,2',4,4'-tetrafluoroazobenzene. Similarly, 2,2',5,5'-tetrafluoroazobenzene was obtained when 2,5-difluoroaniline was used.

7. ETHER CLEAVAGE OF ANISOLES

7. A. Aluminum chloride

2-Fluoroanisole (755 g, or 6 moles) was added to 1369 g of anhydrous aluminum chloride in 2000 ml of benzene and heated at reflux temperature for 3.5 hr. The mixture was poured over an ice-water mixture and steam distilled. The steam distillate was treated with excess aqueous sodium hydroxide (20 percent) and steam distilled to remove the benzene. Acidification of the residue with dil hydrochloric acid followed by steam distillation and vacuum distillation gave 442 g or a 66 percent yield of 2-fluorophenol.

7.B. Aluminum bromide

The procedure is the same as described in the preceding section except that aluminum bromide is used in place of the aluminum chloride.

7.C. Sealed tube reactions

7.C.1. 48 percent Hydrobromic acid. 2-Fluoro-4-bromoanisole (2.5 g, or 0.012 mole) and 3.5 ml of 48 percent hydrobromic acid were mixed and added to a 12 mm by 225 mm tube. The tube was sealed and heated in a tube furnace at 180 to 190° C for 10 hr. After being cooled, the tube was opened and the contents steam distilled to give 2.2 g or a 96 percent crude yield of 2-fluoro-4-bromophenol.

7.C.2. 57 percent Hydriodic acid. 2-Fluoro-4-iodoanisole was reacted as in part 1 above, except that 57 percent hydriodic acid was used at 150° C for 5 hr. The yield of 2-fluoro-4-iodophenol was 70 percent.

7.C.3. 37 percent Hydrochloric acid. 2,6-Difluoroanisole was reacted as in part 1 above, except that 37 percent hydrochloric acid was used at 200° C for 13 hr. A yield of 62 percent 2,6-difluorophenol was obtained.

7.D. 57 percent Hydriodic acid and acetic anhydride

4-Fluoro-2-iodoanisole (15 g, or 0.06 mole), acetic anhydride (20 ml), and 30 ml of 57 percent hydriodic acid were heated at reflux temperature for 3 hr. The mixture was poured into an ice-water mixture and neutralized with sodium hydroxide. Steam distillation removed the unreacted anisole. Acidification of the residue with sulfuric acid followed by steam distillation gave 13.8 g or a 72 percent yield of 4-fluoro-2-iodophenol.

8. BROMINATIONS

8.A. Aqueous suspension (phenols)

Bromine (51.5 g, or 0.323 mole) was added to a stirred mixture of 42 g (0.322 mole) of 2,3-difluorophenol and 200 ml of water. The mixture was neutralized with sodium carbonate, steam distilled, and then vacuum distilled to give 38 g or a 57 percent yield of 2,4-difluoro-6-bromophenol.

8.B. Carbon disulfide solution (phenols)

Bromine (36 g, or 0.224 mole) was added dropwise, with good ventilation, to a solution of 25 g (0.223 mole) of 4-fluorophenol in 500 ml of carbon disulfide for 1.5 hr at 0° C. The mixture was stirred for 6.5 hr and then warmed gently and cautiously on a steam bath to remove the carbon disulfide. Vacuum distillation gave 20 g or a 50 percent yield of 4-fluoro-2-bromophenol.

8.C. Trichloroacetic acid (phenoxyacetic acids)

A mixture of 10 g (0.042 mole) of 4-fluoro-3,5-dichlorophenoxyacetic acid, 32 g of trichloroacetic acid, and a small amount of iron was heated to 140° C. Bromine (16.1 g, or 0.1 mole) was added dropwise, and the temperature was increased to 165° C. After being cooled to below 100° C, the mixture was poured into water. The resulting solid was filtered, washed with water, and recrystallized to give 12 g or a 60 percent yield of 4-fluoro-3,5-dichloro-2-bromophenoxyacetic acid.

8.D. Carbon tetrachloride (benzenes)

1,4-Difluorobenzene (171 g, or 1.5 moles) was brominated in the presence of 10 g of iron filings with a solution of 240 g (1.5 moles) of bromine in 75 ml of carbon tetrachloride at room temperature. A small amount of heat was required to start the reaction. After the addition was complete, the mixture was warmed to 80° C and stirred for 3 hr. The mixture was cooled, treated to excess with sodium bisulfite, and steam distilled. Purification gave 131 g or a 45 percent yield of 2-bromo-1,4-difluorobenzene and 73 g or an 18 percent yield of 2,5-dibromo-1,4-difluorobenzene.

8.E. No solvent (benzenes)

1,2-Difluorobenzene was brominated essentially as described in part D above, except that no solvent was used. A yield of 67 percent 4-bromo-1,2-difluorobenzene and 8.5 percent 4,5-dibromo-1,2-difluorobenzene was obtained.

9. CHLORINATIONS

9.A. No solvent

9.A.1. Phenols. Dry chlorine gas was bubbled through 45 g (0.4 mole) of 3-fluorophenol in the presence of a small amount of iron filings until a weight gain of 16.1 g (0.448 mole) was realized. A temperature range of 40 to 50° C was maintained during the addition. The reaction mixture was poured into ice-water and the excess acid was neutralized with sodium carbonate. Steam distillation gave 41 g or a 70 percent yield of crude 3-fluoro-6-chlorophenol.

In a similar manner, the following phénols were prepared: name, (% yield); 2-fluoro-4,6-dichloro-, (47); 4-fluoro-2,6-dichloro-, (73); 3-fluoro-4,6-dichloro-, (62); 2,4-difluoro-6-chloro-, (57).

9.A.2. Benzenes. Dry chlorine gas was added through a sintered glass gas dispersion tube into a refluxing mixture of 570 g (5.0 moles) of 1,4-difluorobenzene and a small amount of iron filings until a weight gain of 165 g (4.6 moles) was realized. The internal temperature increased from an initial 86° C to a final 119° C during the reaction. After being cooled, the mixture was poured into water, neutralized with sodium carbonate, and steam distilled. Distillation of the crude product gave 96 g of unreacted 1,4-difluorobenzene and 391 g or a 53 percent yield of 2-chloro-1,4-difluorobenzene.

9.B. Acetic acid (phenoxyacetic acids)

3-Fluorophenoxyacetic acid (39 g, or 0.23 mole) in 450 ml of glacial acetic acid at 25° C was chlorinated with dry chlorine gas until 15.8 g (0.445 mole) had been adsorbed. The product was poured into an ice-water mixture, and the solid was collected on a filter to give 49 g or a 90 percent yield of crude 3-fluoro-4,6-dichlorophenoxyacetic acid.

Similarly, 2,5-difluoro-4-chloro- and 3,4-difluoro-6-chlorophenoxyacetic acid were prepared in yields of 70 percent and 46 percent, respectively.

10. ARYLOXYALKANOIC ACID PREPARATIONS

Phenoxyacetic acids were prepared by the alkaline condensation of chloroacetic acid with the appropriate phenol. The phenol and an appreciable excess of chloroacetic acid were melted, and 30 percent aqueous sodium hydroxide was added to strong alkalinity. The mixture was evaporated to sensible dryness. The residue was dissolved in hot water and cooled, and acidification with dilute hydrochloric acid gave the phenoxyacetic acid as a white solid.

TABLE 14—POLYPHENYL FLUORIDE SYNTHESIS

Ring substitution	Mp (°C)	Synthesis		Aryl intermediate
		Method[a]	Time/temp (hr/°C)	Benzene derivative
Biphenyl				
$2,2',4,4',5,5'F_6$	120.5	A	3/210-250	$2,4,5F_3$-I
$2,2',4,4',6,6'F_6$	130.0	A	2/200	$2,4,6F_3$-I
$2,2',4,5,5'F_5$	102.0	B	—	$2,4,5F_3$-NH_2
	—			$1,4,F_2$
$2,2'(NO_2)_2$-$5,5'F_2$	121.0	A	2/170-200	$2(NO_2)$-5F-I
$2,2',4,4'F_4$	137.0	A	4/150-230	$2,4F_2$-I
$2,2',5,5'F_4$	78.5	A	0.25/180	$2,5F_2$-I
$3,3',5,5'F_4$	85.5	A	4/150-250	$3,5F_2$-I
$4,4'(OCH_3)_2$-$3,3'F_2$	153.5	A	6/190-215	$4(OCH_3)$-3F-I
$2,2'(CF_3)_2$-$4,4'F_2$	61.5	A	1.5/250	$2(CF_3)$-4F-I
$2,2'(OCH_3)_2$-$3,3',5,5'F_4$	49.5	A	3/200-210	$2(OCH_3)$-$3,5F_2$-I
$2,2',4,4',6,6'(CH_3)_6$-$3,3',5,5'F_4$	161	A	4/170-220	$2,4,6(CH_3)_3$-$3,5F_2$-I
p-Terphenyl				
2F	173.5	A	2/220-270	2F-I
				4-Iodobiphenyl
3F	174.0	A	3/210-275	3F-I
				4-Iodobiphenyl
4F	160.0	A	3.5/200-230	4F-I
				4-Iodobiphenyl

[a] Methods: A = Ullmann reaction; B = Gomberg-Bachmann-Hey reaction.

Phenoxypropionic acids were prepared by the above procedure using β-chloropropionic acid.

11. SYNTHESIS OF DI- AND POLYPHENYL COMPOUNDS

11.A. Ullmann reaction

11.A.1. Symmetrical Ullmann. 4-Fluoro-2-iodoanisole (316 g, or 1.25 moles) was stirred and heated to 238° C. Copper powder (300 g) was added in five or six portions through a powder funnel over 1.5 hr. After approximately 75 percent of the copper was added, the reaction became exothermic but was maintained at 240° C with a hot water bath. The mixture was heated at reflux temperature for 12 hr and allowed to cool to room temperature. The flask and its contents were pulverized and extracted for 6 hr in a soxhlet extractor using acetone as solvent. (Ether can also be used.) After distillation of the acetone, the residue was washed with water, filtered, and recrystallized from ethanol to give 95 g or a 60 percent yield of 2,2'-dimethoxy-5,5'-difluorobiphenyl. Further examples of this synthesis are illustrated in table 14.

11.A.2. Mixed Ullmann. A 3:1 ratio of 4-fluoroiodo- to 2-fluoroiodobenzene was used in the synthesis of 2,4'-difluorobiphenyl. After evaporation of the ether, the crude product was partially solidified, and the solid was removed by filtration. The solid was probably an enriched mixture of the 2,2'- and 4,4'-difluorobiphenyl (mp 118° C and 95° C, respectively). The liquid phase was distilled into three fractions: A, bp <194° C; B, bp 194 to 220° C; and C, bp 220 to 245° C. Distillation of fraction B gave a middle cut, bp 188 to 190° C. Upon distillation this cut gave an end fraction which solidified on cooling. Recrystallization of this solid from ethanol gave pure 2,4'-difluorobiphenyl, mp 50° C.

11.B. Gomberg-Bachmann-Hey reaction

To 100 ml of concd hydrochloric acid was added 56 g (0.5 mole) of 4-fluoroaniline to form the hydrochloride salt. Diazotization was effected in a temperature range of 0 to 5° C by adding a solution of 38 g (0.55 mole) of sodium nitrite in 60 ml of water. The clear diazonium was added to 180 g (1.57 moles) of 1,4-difluorobenzene with stirring. After cooling to -10° C, a solution of 34 g of sodium hydroxide in 150 ml of water was added dropwise over a period of 1 hr. Stirring was continued for 1 hr at 0 to -5° C, and then for an additional hour while the mixture came to room temperature. A flash steam distillation gave 15.5 g of unreacted 1,4-difluorobenzene, bp 89° C. Continued steam distillation of the residue gave 67 g of a crude product, which was washed with cold concd sulfuric acid, water, and dil sodium carbonate solution and then dried. Vacuum distillation (bp 87° C/5 mm) followed by recrystallization from ethanol gave 8 g of 2,4',5-trifluorobiphenyl (mp 51° C). An additional example of this method can be found in table 14.

12. QUINONE FORMATION

12.A. Oxidation of 1,4-diamines (19)

1,4-Difluoro-2,5-diaminobenzene (10 g, or 0.07 mole) was added to 400 ml of 20 percent sulfuric acid and allowed to stand for a short period. After the sulfuric acid solution was cooled internally with ice to 10° C, 20 g of sodium dichromate was slowly added as a saturated aqueous solution. After the mixture turned black, it was stirred an additional 2 hr. Filtration followed by vacuum sublimation gave 5.5 g or a 55 percent yield of 2,5-difluoro-1,4-benzoquinone.

Recrystallization of 2,5-difluoro-1,4-benzoquinone from hot ethanol was unsuccessful because the fluorine atoms are readily exchanged for ethoxy groups to give 2,5-diethoxy-1,4-benzoquinone.

12.B. Fluorine expulsion in fluorinated benzenes (15)

A mixture of 20 ml of fuming sulfuric acid (sp gr 1.915) and 30 g (0.2 mole) of 1,2,4,5-tetrafluorobenzene was prepared and cooled to 25° C. Fourteen grams of fuming nitric acid (sp gr 1.52) was added over a temperature range of 25 to 30° C. After the addition was complete, the reaction mixture was poured over ice and filtered to give 10 g of crude 2,5-difluoro-1,4-benzoquinone.

Similarly, 2,5-dichloro-1,4-benzoquinone was prepared by fluorine expulsion from 2,5-dichloro-1,4-difluorobenzene.

13. HYDROQUINONE FORMATION (19)

Sulfur dioxide gas was bubbled through a water suspension of 5 g (0.035 mole) of 2,5-difluoro-1,4-benzoquinone until an almost colorless solution was obtained. The water solution was extracted several times with ether. Evaporation of the ether extract gave 3 g or an 80 percent yield of crude 2,5-difluoro-1,4-hydroquinone.

14. SYNTHESIS OF BENZOIC ACIDS

14.A. Via Grignard reagents

Aryl bromide (0.27 mole) was dissolved in anhydrous ether and added slowly to a stirred mixture of magnesium turnings (6.38 g, or 0.27 mole) and approximately 250 ml of anhydrous ether.

After the Grignard reagent had formed, carbon dioxide gas was passed through the reaction mixture for 1 hr. A 10 percent hydrochloric acid solution was added carefully, and the ether layer containing the benzoic acid derivative was separated. The benzoic acid was extracted from the ether by washing either with saturated sodium carbonate or, preferably, with sodium bicarbonate solution. Acidification of the aqueous carbonate solution with dil hydrochloric acid gave a white precipitate of the crude benzoic acid. The pure acids were obtained by a combination of vacuum sublimation and recrystallization from water or carbon tetrachloride. Examples of benzoic acids prepared by this method can be found in table 15.

14.B. Oxidation of toluene derivatives

2-Chloro-3-fluorotoluene (14.5 g, or 0.1 mole) was added dropwise with stirring to a solution of 68 g of potassium permanganate and 1 g of sodium hydroxide in 500 ml of water at refluxing temperature. An excess of potassium permanganate was maintained by adding small increments of the reagent as required. The total oxidation time was 24 hr. Steam distillation removed about 2 g of unoxidized material. The reaction mixture was filtered hot to remove the manganese dioxide precipitate. The filtrate was evaporated to one-fourth of the original volume,

TABLE 15—SYNTHESIS OF BENZOIC ACIDS VIA GRIGNARD REAGENT

Benzoic acid	Yield (%)
2-Fluoro-3-chloro-	60
3,5-Difluoro-	38
2-Methyl-3-fluoro-	38
2,3,4-Trifluoro-	50

and the concentrate was acidified to pH 1 with concd hydrochloric acid to precipitate the benzoic acid. The product was collected on a filter, dried, and vacuum sublimed to give a yield of 7 g or 47 percent. Recrystallization from a large volume of water (40 ml of water, 1 g of acid) gave pure 2-chloro-3-fluorobenzoic acid.

14.C. Oxidation of benzyl alcohols

Bromine (22 ml) was added over a 50 min period to 67 g (0.38 mole) of 2,6-dichloro-3-fluorotoluene at reflux temperature. The resulting 2,6-dichloro-3-fluorobenzyl bromide (98 g) was not purified.

The crude benzyl bromide was added to a stirred, refluxing mixture of 200 g of potassium acetate in 1200 ml of ethanol. After 2 hr, the reaction mixture was poured into 3 liters of water, and the 2,6-dichloro-3-fluorobenzyl acetate precipitate was collected on a filter and dried, yielding 77 g of crude product.

The 2,6-dichloro-3-fluorobenzyl acetate was hydrolyzed and oxidized by addition to a dilute aqueous solution of sodium hydroxide containing a large excess of potassium permanganate. The mixture was heated at reflux temperature and stirred for 6 hr. After removal of the unoxidized material by steam distillation, the reaction mixture was filtered, and the filtrate was reduced by evaporation to a smaller volume. Excess concd hydrochloric acid was added, and the precipitate was collected on a filter. The dried, crude product was vacuum sublimed and recrystallized from water (25 ml water/g product) to give a 47 percent yield of 2,6-dichloro-3-fluorobenzoic acid.

14.D. Oxidation of acetophenones (46)

Eighty grams (0.6 mole) of powdered anhydrous aluminum chloride was added to 80 g (0.61 mole) of 1,3,5-trifluorobenzene with vigorous stirring. This was followed by the dropwise addition of 26.4 g (0.26 mole) of acetic anhydride over a period of 15 min. During the addition of the anhydride, heat was produced and the evolution of hydrogen chloride was obvious.

After the reaction mixture was stirred at reflux temperature for 3 hr, it was chilled in an ice bath, poured into an ice-water mixture, and steam distilled. The organic layer of the distillate was separated and the aqueous layer was extracted several times with ether. The crude product was washed with 25 ml of 10 percent sodium hydroxide solution and then with 15 ml of water. Vacuum distillation gave 30.3 g or a 67 percent yield (based on the acetic anhydride) of 2,4,6-trifluoroacetophenone.

One-half gram of 2,4,6-trifluoroacetophenone was heated at reflux temperature for 5 hr with 4 g of potassium permanganate in 30 ml of water to which 0.5 ml of sodium hydroxide solution had been added. The reaction mixture was cooled and filtered to remove the precipitated manganese dioxide. After the filter cake (manganese dioxide) had been washed with 10 ml of water, the filtrate was acidified, chilled, and extracted with ether. The ether extract was dried and evaporated. Recrystallization from carbon tetrachloride followed by vacuum sublimation gave pure 2,4,6-trifluorobenzoic acid.

14.E. Hydrolysis of nitriles

2,6-Difluorobenzonitrile (27.8 g, or 0.2 mole) and 100 ml of 10 percent sodium hydroxide were heated at reflux temperature for 4 hr. The mixture was cooled and acidified with 18.5 percent hydrochloric acid. Filtration and drying gave 28 g or an 87 percent crude yield of 2,6-difluorobenzoic acid.

14.F. Hydrolysis of benzotrifluorides

14.F.1. Sulfuric acid. A mixture of 2 g (0.01 mole) of 2,3,5-trifluorobenzotrifluoride, 2.5 ml of concd sulfuric acid (sp gr 1.84), 2.5 ml of fuming sulfuric acid (sp gr 1.915), and a catalytic amount of aluminum chloride was heated at refluxing temperature for 4 hr. The mixture was poured into water, dissolved in dil (10 percent) sodium hydroxide, filtered, and acidified with 18.5 percent hydrochloric acid. Filtration gave 1.6 g or a 96 percent crude yield of 2,3,5-trifluorobenzoic acid.

When this reaction was carried out under the same conditions but without the aluminum chloride, a 74 percent yield of the benzoic acid was obtained.

14.F.2. Potassium hydroxide. 2-Fluoro-5-nitrobenzotrifluoride (48.3 g, or 0.231 mole) was added to 900 ml of 1 N potassium hydroxide solution. The mixture was heated on a steam bath for 24 hr and then at reflux temperature for 7 hr. Steam distillation of the reaction mixture removed the unreacted benzotrifluoride. The residue was acidified with 18.5 percent hydrochloric acid and filtered to give 27 g or a 64 percent yield of the unfluorinated 2-hydroxy-5-nitrobenzoic acid.

15. HYDROLYSIS OF ANILINES

2-Nitro-3-aminobenzotrifluoride (30 g, or 1.49 moles) was added to 150 ml of 6 N potassium hydroxide, and the mixture was heated to reflux temperature for 27 hr.

Steam distillation removed the unreacted starting material. The residue was acidified with concd hydrochloric acid and the resulting solid was extracted into ether.

The ether extract was washed with 5 percent sodium bicarbonate, dried, and evaporated to dryness. Vacuum sublimation of the residue gave 23 g or a 77 percent yield of 2-nitro-3-trifluoromethylphenol.

16. N-PHENYLGLYCINE ETHYL ESTER (34)

To a well stirred mixture of 114 g (0.75 mole) of sodium acetate trihydrate and 50 to 75 ml of ethanol were added 0.5 mole of the appropriate aniline and 62 g (0.5 mole) of ethyl chloroacetate. The reaction mixture was stirred with gentle refluxing for 24 to 48 hr. Anilines with an ortho substituent usually required a longer reaction time. The reaction mixtures were cooled and poured into 1500 ml of cold water to give crude yields of 25 to 50 percent of the N-phenylglycine ethyl ester.

17. N-PHENYLGLYCINEHYDRAZIDES (34)

To a solution of 0.5 mole of the N-phenylglycine ethyl ester in 1200 ml of ethanol was added 24 g (0.75 mole) of 95 percent hydrazine. The mixture was gently heated at reflux temperature for 22 hr but was stirred during the first hour only. Evaporation of the solvent in a rotary vacuum evaporator gave the crude hydrazides in yields of approximately 95 percent.

Hydrazides with trifluoromethyl substitution on the phenyl group readily form solid hydrazone derivations upon heating in acetone.

18. N-(FLUOROPHENYL) CARBAMATES

Ethyl or isopropyl chlorocarbonate was added dropwise to a stirred mixture of 25 g of sodium carbonate, 0.5 mole of fluoroaniline, and 250 ml of water. The temperature was controlled in a range of 0 to 5° C. After the addition was complete, the mixture was stirred for 1.5 hr and then allowed to come to room temperature. Solid products were vacuum filtered and air dried. The dry products were extracted repeatedly with hot petroleum ether (bp 30 to 60° C) to separate the soluble fluorophenyl carbamate from the insoluble aniline hydrochloride and diphenylurea. The hot extracts were decolorized with activated charcoal and, upon cooling, the products usually crystallized.

Liquid carbamates were purified by distillation. Although there were considerable variations in yields, 60 percent appeared to be about average.

19. BENZYL CHLORIDE SYNTHESIS (46)

1,3,5-Trifluorobenzene (39.6 g, or 0.3 mole), paraformaldehyde (8.6 g), and freshly ground fused zinc chloride (27.2 g) were mixed in a 100-ml three-necked flask and connected to a hydrogen chloride generator.

A steady stream of hydrogen chloride was passed through the vigorously stirred reaction mixture at 65° C for 4 hr. The mixture was cooled, poured into 200 ml of cold water containing enough sodium carbonate to make the resulting mixture alkaline to litmus, and then steam distilled. The organic layer of the steam distillate was separated, dried, and distilled to give 28 g or a 54 percent yield of 2,4,6-trifluorobenzyl chloride.

20. BENZYL CYANIDE SYNTHESIS (46)

Three and one half grams of sodium cyanide and 5 ml of water were placed in a 50-ml two-necked flask equipped with a reflux condenser and a dropping funnel. The flask was warmed at steam bath temperature until nearly all the cyanide went into solution. A solution of 10 g (0.055 mole) of 2,4,6-trifluorobenzyl chloride and 10 ml of ethanol was added dropwise to the cyanide solution over a period of 10 min. The resulting mixture was refluxed for 2 hr, cooled, and filtered to remove the sodium chloride. The sodium chloride filter cake was washed with a few ml of ethanol and the washings were combined with the filtrate. As much ethanol as possible was evaporated at steam bath temperature. The crude 2,4,6-trifluorobenzyl cyanide was separated from the aqueous layer of the residue and was vacuum distilled to give 8.4 g or an 88.5 percent yield of 2,4,6-trifluorobenzyl cyanide.

21. PHENYLACETIC ACID SYNTHESIS (46)

Two grams of 2,4,6-trifluorobenzyl cyanide and 13 ml of concd hydrochloric acid were mixed and refluxed for 1.5 hr. The reaction mixture was poured into ice, and the precipitated solid was removed by filtration. Since some 2,4,6-trifluorobenzyl cyanide was still present, the product was heated at reflux temperature for 1.25 hr with 12 ml of concd hydrochloric acid to complete the hydrolysis. The flask was cooled in an ice bath, and the resulting crystalline precipitate was filtered to give 2.1 g of crude 2,4,6,-trifluorophenylacetic acid.

22. PHENYLACETAMIDE (46)

One gram of 2,4,6-trifluorobenzyl cyanide dissolved in 5 ml of concd sulfuric acid was allowed to stand at room temperature for 11 hr and then was poured into an ice-water mixture. The white precipitate was filtered and washed with sodium carbonate solution and then with water. One gram of crude 2,4,6-trifluorophenylacetamide was obtained.

23. SPECIAL PREPARATIONS

23.A. Fluoroindole derivatives

23.A.1. Ethyl 2-carbethoxy-5-fluoro-indole-acetate. A mixture of 22 g (0.2 mole) of 4-fluoroaniline, 67 ml of concd hydrochloric acid, and 100 ml of water was diazotized by the subsurface addition of 14 g (0.203 mole) of sodium nitrite dissolved in 25 ml of water.

The diazonium solution was added slowly to a mixture of 48 g of ethyl α-acetoglutarate, 200 ml of ethanol, and 150 ml of aqueous 20 percent sodium hydroxide at 0 to -5° C with stirring. Thirty minutes after the addition, the mixture was acidified with hydrochloric acid, and a dark red oil separated which partially solidified on standing. The precipitate was dissolved in ether and dried with anhydrous magnesium sulfate. After evaporation of the ether, the residue was dissolved in 100 ml of absolute ethanol, and the resulting solution was saturated with dry hydrogen chloride gas. The mixture was heated to reflux temperature for 1 hr and then poured into ice and water. The brown semisolid which separated was collected on a filter and vacuum sublimed to give pure ethyl-2-carbethoxy-5-fluoro-3-indoleacetate as white needles, mp 124° C, yield 15 g (30 percent).

23.A.2. 2-Nitro-5-fluorophenylpyruvic acid. Sodium ethoxide was prepared by the addition of 14 g (0.61 mole) of sodium chips to 150 ml of absolute ethanol. Diethyl oxalate (88 g, or 0.6 mole) was added slowly to this solution, with stirring and cooling. This was followed by the addition of a solution of 78 g (0.53 mole) of 2-nitro-5-fluorotoluene in 150 ml of anhydrous ether. No evidence of sodium enolate precipitation was observed, and the ether was evaporated to reduce the volume. The concentrate was acidified by pouring into an ice-hydrochloric acid mixture, whereupon a red oil separated. The oil was collected in ether. Two extractions of the ethereal solution with 200-ml portions of 1 N sodium hydroxide solution removed the alkali-soluble material. Acidification of the alkaline extract precipitated the crude pyruvic acid. Recrystallization from benzene gave the pure compound as white needles, mp 147° C, yield 38 g (31 percent).

23.A.3. 5-Fluoro-2-indolecarboxylic acid. Ten grams (0.045 mole) of 2-nitro-5-fluorophenylpyruvic acid were added to 2.2 g of sodium hydroxide in 85 ml of water. Sodium hydrosulfite dihydrate (30 g) was added slowly with stirring. The reaction was slightly exothermic. Stirring was continued until a test sample gave no red color in excess alkali solution. The mixture was then acidified with hydrochloric acid, heated on a steam bath to expel the sulfur dioxide, cooled to room temperature, and extracted with ether. After evaporation of the ether, the resulting 8 g of crude product was recrystallized from aqueous ethanol. Vacuum sublimation (140° C/1 mm) gave white granular crystals of pure 5-fluoro-2-indolecarboxylic acid. The compound does not melt, but at 245° C it appears to decarboxylate to the fluoroindole.

23.B. Bis-(3-fluorophenyl) phosphinic acid

3-Fluorobenzenediazonium fluoborate (42 g, or 0.2 mole) was added gradually at 50° C to 14 g of phosphorous trichloride and 29 g of cuprous bromide in 200 ml of dry ethyl acetate.

The reaction mixture was heated at reflux temperature for 2 hr and steam distilled to remove the ethyl acetate. The residue was evaporated to about 50 ml and upon cooling, the diaryl phosphinic acid crystallized. Recrystallization from low boiling petroleum ether (30 to 60° C) containing a few drops of benzene gave white needles, mp 167° C.

23.C. 1-(3-Trifluoromethylphenyl)-2,3-dimethyl-5-pyrazalone

23.C.1. 3-Trifluoromethylphenyl hydrazine. 3-Trifluoromethylaniline (40.0 g, or 0.25 mole) was added to 800 ml of concd hydrochloric acid and cooled to between -5 and -10° C. Diazotization was effected by the subsurface addition of 19 g (0.27 mole) of sodium nitrite in 100 ml of water. After the sodium nitrite had been added, the reaction mixture was stirred for 20 min and filtered. Stannous chloride (150 g, or 0.79 mole) in 125 ml of hydrochloric acid was added to the clear diazonium filtrate. The resulting salt precipitated and was collected on a filter. It was made basic to give 33 g or a 50 percent yield of 3-trifluoromethylphenyl hydrazine.

23.C.2. Condensation with ethyl acetoacetate. 3-Trifluoromethylphenyl hydrazine (40.2 g, or 0.23 mole) was mixed with 29.6 g (0.23 mole) of ethyl acetoacetate and after 10 min the mixture solidified. The reaction mixture was heated at steam bath temperature for 2 hr. Upon cooling to room temperature, the mixture resolidified. A small amount of ether was mixed with the solid to form a slurry which was filtered to give 44 g or a 79.5 percent yield of 1-(3-trifluoromethylphenyl)-3-methyl-5-pyrazalone.

23.C.3. Methylation. A mixture of 10 g (0.41 mole) of 1-(3-trifluoromethylphenyl)-3-methyl-5-pyrazalone and 9.5 g (0.067 mole) of methyl iodide in

10 g of methanol was heated for 3 hr in a sealed tube. The tube was cooled and opened, and the contents were poured into a beaker. A small amount of a solution of sulfur dioxide and water was added. The mixture was then boiled to expel the methanol. After the mixture was cooled, a slight excess of 10 percent sodium hydroxide solution was added. The resulting mixture was extracted several times with small portions of chloroform. Distillation of the chloroform extract followed by several recrystallizations from toluene gave 8 g or a 75.5 percent yield of 1-(3-trifluoromethylphenyl)-2,3-dimethyl-5-pyrazalone.

23.D. 2,2'-Dihydroxy-5,5'-difluorodiphenyl sulfide

A solution of 618 g (6 moles) of sulfur dichloride in 1200 ml of dry chloroform was added to 1344 g (12 moles) of 4-fluorophenol at 52° C under anhydrous conditions (system protected with calcium chloride drying tubes). The mixture was stirred for 0.5 hr while a stream of hydrogen chloride slowly evolved. The reaction mixture was poured into a beaker and cooled to -20° C. The gum-like solid was transferred to a Büchner funnel where it was allowed to stand overnight under vacuum. Recrystallization from 2000 ml of chloroform gave 693 g or a 45 percent yield of 2-2'-dihydroxy-5,5'-difluorodiphenyl sulfide.

23.E. 3,3'-Difluoro-4,4'-dimethoxydiphenylsulfoxide

2-Fluoroanisole (20 g, or 0.16 mole), anhydrous aluminum choride (13.3 g, or 0.1 mole), and 50 ml of carbon disulfide were mixed and cooled to 10° C. Thionyl chloride (18.8 g, or 0.16 mole) was added over a 15 min period. Stirring was continued for 1 hr while the temperature was allowed to rise to 32° C. The reaction mixture was poured into water. To remove the residual chlorine, the aqueous mixture was warmed on a steam bath, cooled, and then filtered. Recrystallization from ethanol gave 11 g or a 46 percent yield of 3,3'-difluoro-4,4'-dimethoxydiphenyl sulfoxide.

NUCLEAR MAGNETIC RESONANCE (^{19}F)

Several polyhalobenzenes were prepared during the course of studying the potassium fluoride halogen-exchange reaction (see Chapter 2, Section IV). Most of these compounds were prepared by unequivocal methods while a few were halogen-exchange reaction products. These compounds were submitted for ^{19}F NMR analysis (47) using a Varian DP-60 instrument. From this data, delta (δ) values, the corresponding predicted shifts were calculated. Table 16 illustrates these results.

TABLE 16—VALUES FOR POLYHALOBENZENES

Compound	Shift observed	Shift predicted	Calculated δ values
Tetrasubstituted			
1,2,3,5F$_4$			
1[a]	7566	7488	-1.97
2	9511	9659	-5.82
5	6527	6388	-0.02
1,2,4,5F$_4$			
1	7998	7883	-2.67
1,2,3F$_3$-4Cl			
1	7567	7798	-2.52
2	8887	9180	-4.97
3	7645	7815	-2.55
1,2,3F$_3$-5Cl			
1	7527	7544	-2.07
2	9203	9334	-5.42
1,2,4F$_3$-6Cl			
1	8159	8351	-3.50
2	7447	7544	-2.07
4	6497	6450	-0.13
1,3,5F$_3$-2Cl			
1	6247	6191	+0.33
5	6205	6163	+0.38
1,2F$_2$-3,4Cl$_2$			
1	7667	7855	-2.62
2	7689	7872	-2.65
1,2F$_2$-3,5Cl$_2$			
1	7449	7601	-2.17
2	7964	8125	-3.10
1,2F$_2$-3,6Cl$_2$			
1	7614	7872	-2.65
1,3F$_2$-2,4Cl$_2$			
1	6315	6490	-0.20
3	6420	6507	-0.23
1,3F$_2$-2,5Cl$_2$			
1	6551	6236	+0.25
1,4F$_2$-2,3Cl$_2$			
1	6444	6772	-0.70
1,4F$_2$-2,6Cl$_2$			
1	6815	7026	-1.15
4	6505	6501	-0.22
1F-2,3,4Cl$_3$			
1	6173	6546	-0.30
1F-2,3,6Cl$_3$			
1	6130	6563	-0.33
Trisubstituted			
1,2,3F$_3$			
1	7675	7663	-2.28
2	9166	9299	-5.18
1,2F$_2$-3Cl			
1	7642	7719	-2.38
2	7869	7990	-2.86
1,2F$_2$-4Cl			
1	7899	7973	-2.83
2	7598	7719	-2.38
1,3F$_2$-2Cl			
1	6396	6354	+0.04
1,3F$_2$-5Cl			
1	6097	6084	+0.52
1F-2,3Cl$_2$			
1	6189	6411	-0.06
1F-2,4Cl$_2$			
1	6626	6665	-0.51
1F-2,5Cl$_2$			
1	6305	6411	-0.06
1F-2,6Cl$_2$			
1	6544	6682	-0.54
1F-3,4Cl$_2$			
1	6367	6394	-0.03
1F-3,5Cl$_2$			
1	6143	6140	+0.42
Disubstituted			
1,2F$_2$			
1	7862	7838	-2.59
1F-2Cl			
1	6526	6529	-0.27

[a] Position of the fluorines.

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