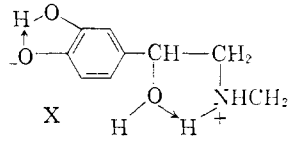
on the benzylic carbon atom in the resonating zwitterion IX.

It would appear that both a *p*-hydroxyl group and an N-methyl group are prerequisite to the formation of this kind of hydrogen bond. This is the second example in this series when a secondary amine is less basic than the corresponding primary amine—in this case by reason of a unique hydrogen bond in the secondary amine.

In comparing the corresponding *m*-hydroxy secondary and primary amines it is seen that the normal order exists—the secondary amine having a pK_a of 8.89 and the primary, 8.67.

Finally, in the case of epinephrine (X), zwitterion formation is further enhanced by additional hydrogen bonding as before, the pK_a being 8.55.



It will be seen therefore that two different types of hydrogen bonding have been proposed for arterenol and epinephrine—each one imposing a different configuration upon the respective molecules.

Discussion

The fact that the pK_a values of the pair, arterenol and epinephrine, are identical would preclude that the ratio of ionic and non-ionic species of each in a buffer system such as blood could be affected in favor of one or the other catechol amine. Hence the body has no mechanism to sort out the two amines on the basis of their electrochemical properties since the pK_a values are delicately balanced by the mutual interaction of the five above-mentioned effects. Yet in certain stress conditions (*e.g.*, hemorrhagic shock) the output and subsequently the concentration of epinephrine may increase 400 to 500% with a lesser increase of the desmethyl analog.[3] The identity of base strength in this pair re-emphasizes that physiological action must be based primarily on morphological differences[4] and not on physicochemical properties. It further strengthens the receptor mechanism concept based on the marked difference in physiological action[5] of each of the optical isomers, where no gross physico-chemical differences can be postulated.

If the relative ratio of the two catecholamines in the body is coupled by an enzymatic methylation reaction and their relative production is a function of biological age,[6] one can further speculate that no marked activation energy can be associated with the methylation or de-methylation reactions.

Experimental

The pK_a values listed in Table I were determined in a manner similar to that given by Parke and Davis[7] in an approximately 5×10^{-6} *M* aqueous solution. The essentials of this method are: (1) obtaining a correction curve by titrating standard alkali potentiometrically into a measured volume of solvent; (2) dissolving the sample in the same quantity of solvent as in (1) and titrating potentiometrically with the standard alkali; (3) subtracting the correction curve from the compound curve; (4) determining the maximum for Δ ml. titrant/Δ *p*H by use of the second derivative of the corrected curve and interpolating between measured values in a manner analogous to the potentiometric determination of end-points as given by Lingane.[8]

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(4) Interestingly, the isopropyl arterenol has a pK_a of 8.64 indicating a slightly higher value than arterenol or epinephrine. This can be explained as a somewhat lesser contribution of the hydrogen bond owing to crowding by the isopropyl group.

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[CONTRIBUTION FROM THE ILLINOIS STATE GEOLOGICAL SURVEY]

Aromatic Fluorine Compounds. VIII. Plant Growth Regulators and Intermediates[1,2]

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The preparation and properties of 41 fluorophenoxyacetic acids, 4 fluorophenoxypropionic acids, 2 fluorobenzoic acids, several indole derivatives, and a number of miscellaneous compounds are described. Data are given for many intermediates such as new fluorinated phenols, anisoles, anilines and nitrobenzenes. Most of the subject compounds are related to a number of well-known herbicides or plant growth regulators such as 2,4-D, 2,4,5-T and others.

Chlorinated plant growth regulators have been studied extensively, whereas very little information is available on the fluoro[4-10] or mixed fluoro-halogen[11-13] analogs. A large number of fluorinated derivatives were synthesized for testing for

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(2) Published by permission of the Chief of the Illinois State Geological Survey.

(3) Formerly Special Research Assistant.

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plant regulating activity by the Army Chemical Corps. Some preliminary activity data have been published by the testing agency.[14-15]

The fluorinated aryloxyalkanoic acids were usually prepared from the corresponding phenols by alkaline condensation[16] with the desired chloroacetic or propionic acids. As expected, the fluorophenoxyacetic acids undergo halogenation[17] and nitration in the 2-, 4- and 6-positions, thus affording some very desirable alternate syntheses. Almost all of the phenoxyacetic acid derivatives have melting points within the range of 100-165° as indicated in Table I, and as such are desirable derivatives of fluorinated phenols.

Most of the phenols were prepared from the corresponding arylamines, Table III, *via* a catalytic hydrolysis[18] of the diazonium sulfates at superheated steam temperatures, 130-195°. By adjusting the water content of the copper sulfate–sulfuric acid hydrolyzing medium, suitable temperatures for the hydrolyses could be maintained. The nitro forbears of many of the new amines are listed in Table V. Some phenols were prepared by demethylation of the anisoles (Table IV), and by direct halogenation or nitration of less substituted phenols. The fluorinated phenols are characterized by their intense phenolic odor, and ease of sublimation or volatilization.

In the class of benzoic acid regulators, the 2-chloro-5-fluoro and 2,3,5-trifluoro derivatives were prepared by strong acid hydrolysis of the $-CF_3$ group in the corresponding benzotrifluorides. As indole compounds have long been associated with plant growth regulating activity, preliminary interest in placing fluorine in the benzene moiety of the indole structure resulted in the synthesis of a couple of 5-fluoroindole derivatives .

Owing to the nature of this study, it was necessary to prepare many new fluoro intermediates. So that they may serve as tools or building blocks for future research, data on them are summarized in the tables.

Experimental[19]

The experimental results are summarized under general procedures, tabular data and special preparations.

A. Nitration.—After nitration, the reaction products were poured into an ice–water mixture. The separated products were collected by filtration or steam distillation, dried, and vacuum distilled or recrystallized. (a) To a mixture of the parent compound and concd. sulfuric acid (molar ratio 1:5), was added a 10% molar excess of concd. nitric acid (70%) in concd. sulfuric acid (1:1 by volume). The temperature was maintained at 15° and, after addition, stirring was continued for 90 minutes on a steam-bath. Phenoxyacetic acids were nitrated at 0–5°, and the final heating period was eliminated. (b) The parent compound dissolved in glacial acetic acid and acetic anhydride (molar ratio, 1:3:1.3) was nitrated at 5–20° with a slight excess of fuming nitric acid (90%) in glacial acetic acid (1:1 by volume). The reaction was allowed to continue at room temperature for one hour. (c) To a solution of the phenoxyacetic acid dissolved in excess acetic anhydride (molar ratio, *ca.* 1:20) at 25°, a 5% excess of fuming nitric acid (90%) in an equal volume of glacial acetic acid was added slowly. Stirring was continued for about 3 hours.

B. Hydrolysis of Acetanilides.—(a) The acetyl derivative was hydrolyzed by heating in concd. sulfuric acid on a steam-bath for about two hours, and poured over ice.

C. Reduction of Nitro Compounds.—(a) An iron reduction[20] followed by steam distillation gave the corresponding amine. 2-Nitro-4-fluorophenoxyacetic acid gave the benzisoxyazine. (b) The usual stannous chloride–hydrochloric acid method was used.

D. Fluorination with Potassium Fluoride.—The aryl fluorides were prepared in (a) dimethylformamide (DMF) or (b) dimethyl sulfoxide (DMSO) *via* the halogen exchange method[21] using anhydrous potassium fluoride. Molar ratio of aryl chloride to KF was 2:1. Approximately 2 ml. of solvent per gram of aryl chloride was used. Unless specified otherwise, the mixtures were heated at 150° for 14 hours.

E. Ether Cleavage of Anisoles: (a) aluminum chloride[22] and benzene under reflux for 6 hours; (b) hydrobromic acid (48%) at 180–190° (10–14 hours) for bromoanisoles or hydriodic acid (sp. gr. 1.5) at 150° (5 hours) for iodoanisoles in sealed tubes; (c) concd. hydrochloric acid at 200° (13 hours) in sealed tube; (d) hydriodic acid (sp. gr. 1.5) and acetic anhydride under reflux for 3 hours.

F. Diazotizations.—(a) The nitrosylsulfuric–phosphoric acid diazotization process[23] was used with slight modification. The sirupy phosphoric acid was added at 35° instead of 0–10° for completion of the diazotization. The phosphoric acid was omitted with #66. (b) Concd. sulfuric acid was used to prepare the amine salts. If the amine hydrosulfate mixture is cooled to 0°, a solid crystalline mass is obtained. Therefore, 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 0–5° by the concurrent addition of powdered sodium nitrite (slight excess) and the amine salt crystals to the hydrosulfate liquor. (c) The sulfuric acid (66°Be. or 93%) indicated in the tables was divided into two parts percentagewise. For the preparation of the amine hydrosulfate (A), as indicated below, is the fraction of the total acid volume. The remaining acid portion was diluted with ice to a lower percentage acid concentration (B) to serve as a medium for the diazotization. The amine was added to the undiluted

SULFURIC ACID DISTRIBUTION FOR DIAZOTIZATION (c)

Cmpd. no.	(A)	(B)	Cmpd. no.	(A)	(B)
46	57	80	81	60	65
52[a]	76	50	82	70	65
54	75	50	110	70	65
58	60	65	111	50	60
59	60	65	112	70	65
60	70	65	113	50	60
63	76	57	114	70	65
64	82	50	115	50	60
68	78	75	120	85	50
69	75	57			
71	75	50			
72	60	65			
75	82	50			
77	75	50			
79	76	57			

[a] Dry powdered sodium nitrite was used in place of an aqueous solution.

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TABLE I

FLUOROPHENOXYACETIC ACIDS

Ring subst.	Empirical formula	M.p., °C.	Analyses, % found (calcd.) C	H	F	N or Br, Cl	Lit. ref.	Compd. no.	Syntheses Parent compd.	Proc.	Re-cryst.	Yield, %
F	$C_8H_7FO_3$		(56.47)	(4.15)	(11.17)							
2	$C_8H_7FO_3$	139	...	..	...		16	1	..	Ja	[a]	93
3	$C_8H_7FO_3$	114	...	..	...		16	2	46	Ja	[a]	73
4	$C_8H_7FO_3$	105	...	..	...		16	3	47	Ja	[a]	63
F–Br	$C_8H_6BrFO_3$		(38.58)	(2.43)	(7.63)	(32.09)						
2–4	$C_8H_6BrFO_3$	113	38.62	2.35	7.46	32.25	14	4	48	Ja	[a]	90
4–2	$C_8H_6BrFO_3$	138	38.52	2.34	7.92	31.78		5	49	Ja	[a]	69
F–Cl	$C_8H_6ClFO_3$		(46.96)	(2.93)	(9.29)	(17.33)						
2–3	$C_8H_6ClFO_3$	152	46.99	2.96	9.47	17.24		6	50	Ja	[a]	38
2–4	$C_8H_6ClFO_3$	125	46.81	2.88	9.24	17.60	14	7	51	Ja	[b]	85
3–4	$C_8H_6ClFO_3$	132	46.96	3.16	9.45	17.12		8	52	Ja	[c]	35
4–2	$C_8H_6ClFO_3$	136	46.99	2.90	9.05	17.47	15	9	3	Ib	[a]	87
4–3	$C_8H_6ClFO_3$	105	47.22	2.96	9.54	17.18		10	54	Ja	[a]	76
5–2	$C_8H_6ClFO_3$	161	46.83	3.04	9.05	17.50		11	55	Ja	[b]	53
F–I	$C_8H_6FIO_3$		(32.43)	(2.04)	(6.42)	(42.87)						
2–4	$C_8H_6FIO_3$	121	32.53	1.93	6.20	43.10	14	12	56	Ja	[c]	65
4–2	$C_8H_6FIO_3$	132	32.43	1.96	6.53	42.63	14	13	57	Ja	[b]	78
F–CH_3	$C_9H_9FO_3$		(58.69)	(4.92)	(10.32)							
2–4	$C_9H_9FO_3$	127	58.89	4.69	10.16		14	14	58	Ja	[c]	85
4–3	$C_9H_9FO_3$	139	58.77	4.72	10.15		14	15	60	Ja	[c]	93
F–NO_2	$C_8H_6FNO_5$		(44.66)	(2.81)	(8.83)	(6.51)						
2–4	$C_8H_6FNO_5$	140	44.73	3.04	...	6.53		16	1	Aa	[a]	63
4–2	$C_8H_6FNO_5$	125	44.82	2.74	...	6.54		17	3	Aa	[a]	67
5–2	$C_8H_6FNO_5$	156	44.82	2.92	...	6.44		18	2	Ac	[c]	36
F–Br_2	$C_8H_5Br_2FO_3$		(29.30)	(1.54)	(5.79)	(48.74)						
2–4,6	$C_8H_5Br_2FO_3$	153	29.14	1.65	5.86	48.80	[f]	19	61	Ja	[a]	54
4–2,6	$C_8H_5Br_2FO_3$	187	29.44	1.64	5.98	48.51		20	62	Ja	[a]	56
F–Cl_2	$C_8H_5Cl_2FO_3$		(40.20)	(2.11)	(7.95)	(29.67)						
2–4,5	$C_8H_5Cl_2FO_3$	138	40.05	2.19	8.03	29.72		21	63	Ja	[a]	89
4–2,5	$C_8H_5Cl_2FO_3$	138	40.07	2.33	8.21	29.78		22	64	Ja	[d]	96
4–2,6	$C_8H_5Cl_2FO_3$	160	40.01	2.17	8.21	29.44		23	65	Ja	[a]	30
4–3,5	$C_8H_5Cl_2FO_3$	131	40.17	2.17	7.88	29.47		24	66	Ja	[a]	76
F–$(NO_2)_2$	$C_8H_5FN_2O_7$		(36.93)	(1.94)	(7.30)	(10.77)						
2–4,6	$C_8H_5FN_2O_7$	121	37.02	2.09	...	10.82		25	1	Aa	[b]	74
4–2,6	$C_8H_5FN_2O_7$	161	36.95	1.86	...	10.55		26	3	Aa	[a]	83
5–2,4	$C_8H_5FN_2O_7$	144	37.16	2.04	...	10.79		27	2	Aa	[c]	30
F–Br–Cl_2	$C_8H_4BrCl_2FO_3$		(30.22)	(1.27)	(5.98)							
4–2–3,5	$C_8H_4BrCl_2FO_3$	144	30.37	1.34	6.10			28	24	Hc	[e]	90
F–Cl_4	$C_8H_3Cl_4FO_3$		(31.20)	(0.98)	(6.17)	(46.06)						
4–2,3,5,6	$C_8H_3Cl_4FO_3$	188	31.43	1.13	6.38	45.92		29	24	Ib	[e]	23
F_2	$C_8H_6F_2O_3$		(51.07)	(3.22)	(20.20)							
2,4	$C_8H_6F_2O_3$	125	50.82	2.95	20.46		4, 15	30	68	Ja	[a]	54
2,5	$C_8H_6F_2O_3$	150	51.08	2.99	19.98		14	31	69	Ja	[a]	38
2,6	$C_8H_6F_2O_3$	89	51.08	3.02	20.47		14	32	70	Ja	[c]	70
3,4	$C_8H_6F_2O_3$	99	51.19	3.33	20.28			33	71	Ja	[a]	81
3,5	$C_8H_6F_2O_3$	127	50.94	3.14	20.32		14	34	72	Ja	[a]	84
F_2–Br	$C_8H_5BrF_2O_3$		(35.98)	(1.89)	(14.23)	(29.93)						
2,4–6	$C_8H_5BrF_2O_3$	121	36.04	1.86	14.48	30.08		35	73	Ja	[a]	61
F_2–Cl	$C_8H_5ClF_2O_3$		(43.17)	(2.26)	(17.07)	(15.93)						
2,4–3	$C_8H_5ClF_2O_3$	135	43.41	2.29	16.94	15.87		36	74	Ja	[a]	75
2,4–5	$C_8H_5ClF_2O_3$	109	42.97	2.44	17.15	15.79		37	75	Ja	[a]	87
2,4–6	$C_8H_5ClF_2O_3$	128	43.05	2.38	16.92	15.99	15	38	76	Ja	[a]	83
2,5–4	$C_8H_5ClF_2O_3$	162	43.26	2.26	17.28	16.06	15	39	31	Ib	[a]	70
3,5–4	$C_8H_5ClF_2O_3$	117	43.20	2.31	...	...		40	78	Ja	[a]	37
4,5–2	$C_8H_5ClF_2O_3$	144	43.27	2.41	17.05	15.86		41	33	Ib	[e]	46

F_3	$C_8H_5F_3O_3$		(46.61)	(2.45)	(27.65)						
2,3,4	$C_8H_5F_3O_3$	132	46.74	2.46	27.88		42	80	Ja	[a]	53
2,3,5	$C_8H_5F_3O_3$	152	46.49	2.59	27.40		43	81	Ja	[c]	53
2,4,5	$C_8H_5F_3O_3$	123	46.89	2.38	27.59	14, 15	44	82	Ja	[c]	85
2,4,6	$C_8H_5F_3O_3$	108	...	...	...	14, 15	45	83	Ja	[a]	35

[a] Benzene. [b] Aqueous ethanol. [c] 3-Fluorobenzotrifluoride. [d] Benzene and low boiling petroleum ether. [e] *m*-Xylene. [f] J. Toothill, R. L. Wain and F. Wightmann, *Ann. Appl. Biol.*, **44**, 547 (1956); no data given for compound 19.

TABLE II

FLUOROPHENOLS

Ring subst.	Empirical formula	M.p., °C.	B.p., °C.	Mm.	Analyses, % found (calcd.) C	H	F	N, Cl or Br, I	Lit. ref.	Cmpd. no.	Syntheses: Parent cmpd. no.	Proc.	Mol. ratio H_2SO_4 to amine	Mol. ratio H_2SO_4 to $NaNO_2$	Temp., °C.[a]	Re-cryst.	Yield, %
F	C_6H_5FO				(64.28)	(4.50)	(16.95)	...									
3	C_6H_5FO	13	178		...	..	...	...	30	46	..	Fc	10:1	....	190	..	55
4	C_6H_5FO	48[b]	185		...	..	...	...	30	47	84	Fa[c]	6:1	6.5:1	140	..	66
F–Br	C_6H_4BrFO				(37.73)	(2.11)	(9.94)	(41.84)									
2–4	C_6H_4BrFO	..	79	7	37.50	1.99	9.69	42.12		48	110	Eb	....	....	..	..	96
4–2	C_6H_4BrFO	43	89	1	37.96	2.29	9.67	41.67		49	47	Hb	....	....	..	..	50
F–Cl	C_6H_4ClFO				(49.17)	(2.75)	(12.96)	(24.20)									
2–3	C_6H_4ClFO	38	96	31	49.15	2.78	12.71	24.14		50	85	Fb	12:1	....	170	..	36
2–4	C_6H_4ClFO	20[d]	64	7	49.14	2.72	12.70	24.20	[o]	51	112	Ea	....	....	..	..	70
3–4	C_6H_4ClFO	..	84	4.4	49.02	2.73	13.12	24.01	[p]	52	87	Fc	11:1	....	160	..	56
4–2	C_6H_4ClFO	23[d]	88	40	48.93	2.66	13.15	23.98		53	113	Ea	....	....	..	..	70
4–3	C_6H_4ClFO	..	104	11	49.27	2.80	12.76	23.99		54	89	Fc	12:1	....	180	..	59
5–2	C_6H_4ClFO	..	185[e]		49.15	2.88	13.10	24.41		55	46	Ia	....	....	..	..	70
F–I	C_6H_4FIO				(30.28)	(1.69)	(7.98)	(53.33)									
2–4	C_6H_4FIO	38	..		29.99	1.70	8.03	53.42		56	114	Eb	....	....	..	[f]	70
4–2	C_6H_4FIO	62	..		30.23	1.78	8.08	53.75		57	115	Ed	....	....	..	[f]	72
F–CH_3	C_7H_7FO				(66.65)	(5.60)	(15.06)										
2–4	C_7H_7FO	..	65	11	66.81	5.37	15.29			58	94	Fc	5:1	....	160	..	40
4–2	C_7H_7FO	35[h]	87	14	66.81	5.40	15.12			59	95	Fc	5:1	....	160	..	53
4–3	C_7H_7FO	32	76	5	66.75	5.55	15.31			60	96	Fc	4:1	....	160	..	53
F–Br_2	$C_6H_3Br_2FO$				(26.69)	(1.12)	(7.04)	(59.20)									
2–4,6	$C_6H_3Br_2FO$	31[g]	..		26.41	1.23	7.17	59.21	[q]	61	..	Ha	....	....	..	[h]	28
4–2,6	$C_6H_3Br_2FO$	56	..		...	...	...	...	[q]	62	47	Ha	....	....	..	[h]	45
F–Cl_2	$C_6H_3Cl_2FO$				(39.81)	(1.67)	(10.49)	(39.18)									
2–4,5	$C_6H_3Cl_2FO$	85	..		39.59	1.70	10.66	39.28		63	91	Fc	12:1	....	195	[i]	88
4–2,5	$C_6H_3Cl_2FO$	55	..		39.84	1.77	10.40	39.04		64	92	Fc	12:1	....	180	[i]	32
4–2,6	$C_6H_3Cl_2FO$	50[j]	..		39.67	1.73	10.32	39.10	[r]	65	47	Ia	....	....	..	[h]	73
4–3,5	$C_6H_3Cl_2FO$	87	..		40.04	1.70	10.47	38.95		66	93	Fa	11:1	11:1	140	[k]	59
5–2,4	$C_6H_3Cl_2FO$	34	..		40.08	1.73	10.41	39.00		67	46	Ia	....	....	..	..	62
F_2	$C_6H_4F_2O$				(55.39)	(3.10)	(29.21)										
2,4	$C_6H_4F_2O$	22.4	74	50	55.33	2.95	28.95			68	..	Fc	10:1	3:1	180	..	55
2,5	$C_6H_4F_2O$	42	..		55.33	2.95	29.22			69	96	Fc	5:1	....	180	..	42
2,6	$C_6H_4F_2O$	46	..		55.66	2.95	29.22			70	117	Ec	....	....	..	[i]	62
3,4	$C_6H_4F_2O$	..	85	20	55.41	3.03	29.30			71	98	Fc	12:1	....	180	..	32
3,5	$C_6H_4F_2O$	55	..		55.50	2.95	29.40			72	99	Fc	5:1	....	180	..	61
F_2–Br	$C_6H_3BrF_2O$				(34.48)	(1.44)	(18.18)	(38.24)									
2,4–6	$C_6H_3BrF_2O$	..	53	1	34.23	1.38	18.43	38.33		73	68	Ha	....	....	..	..	57
F_2–Cl	$C_6H_3ClF_2O$				(43.79)	(1.84)	(23.09)	(21.55)									
2,4–3	$C_6H_3ClF_2O$	44	73.5	9	43.97	1.94	22.86	21.62		74	100	Fb	11:1	....	160	..	38
2,4–5	$C_6H_3ClF_2O$	38	74	18	43.62	2.08	22.90	21.50		75	101	Fc	10:1	....	175	..	40
2,4–6	$C_6H_3ClF_2O$	..	49	1.5	43.99	1.96	23.21	21.58		76	68	Ia	....	....	..	..	57
2,5–4	$C_6H_3ClF_2O$	59	..		43.76	1.91	23.30	21.80		77	102	Fc	10:1	....	170	[f]	41
3,5–4	$C_6H_3ClF_2O$	64.5	..		43.75	1.84	23.06	21.32		78	103	Fa[l]	13:1	10:1	140	[k]	16
4,5–2	$C_6H_3ClF_2O$	..	93	52	44.14	2.15	...	...		79	104	Fc	9.5:1	....	195	..	23
F_3	$C_6H_3F_3O$				(48.66)	(2.04)	(38.49)										
2,3,4	$C_6H_3F_3O$	..	69	43	48.89	2.31	38.23			80	105	Fa	0:1	15:1	140	..	45
2,3,5	$C_6H_3F_3O$	29	57	29	48.60	2.19	38.45			81	106	Fc	7.5:1	....	175	..	57
2,4,5	$C_6H_3F_3O$	42	..		48.69	2.02	38.58			82	107	Fc	5:1	....	180	..	54
2,4,6	$C_6H_3F_3O$	50	..		...	...	...		[t]	83	..	Ed	....	....	..	[m]	79

[a] Procedure Ga used for hydrolysis. [b] Two forms, unstable form m.p. 28.5°. [c] Molar ratio, phosphoric acid:amine, 5:1. [d] Freezing points. [e] Microcapillary boiling point. [f] 3-Fluorobenzotrifluoride (solvent). [g] Literature m.p. 35°. [h] Low boiling petroleum ether and benzene. [i] Low boiling petroleum ether. [j] Literature m.p. 42°. [k] Methylcyclohexane. [l] Molar ratio, phosphoric acid:amine, 4.5:1. [m] 3-Fluorobenzotrifluoride and low boiling petroleum ether. [n] S. Hünig and W. Daum, *Ann.*, **595**, 131 (1955), m.p. 33–34°, b.p. 83° (9 mm.). [o] E. C. Britton and J. D. Head (to Dow Chem. Co.), U. S. Patent 2,576,064–2,576,065 (1951); no data reported. [p] H. H. Hodgson and J. Nixon, *J. Chem. Soc.*, 3437 (1949); no data given. [q] L. C. Raiford and A. Le Rosen, THIS JOURNAL, **66**, 2080 (1944). [r] H. H. Hodgson and J. Nixon, *J. Chem. Soc.*, 1868 (1930). [s] G. Schiemann and M. Seyhan, *Ber.*, **70B**, 2396 (1937). [t] J. E. Dunbar, M.S. Thesis, University of Illinois, 1952.

TABLE III
FLUOROANILINES

Ring subst.	Empirical formula	M.p., °C.	B.p., °C.	Mm.	Analyses, % found (calcd.) C	H	Cl	N	Lit. ref.	Cmpd. no.	Syntheses: Parent cmpd. no.	Proc.	Recryst.	Yield, %	Acetyl m.p., °C.	N, %	Lit. ref.
F	C_6H_6FN				(64.84)	(5.44)	...	(12.61)									
4	C_6H_6FN	...	188		64.88	5.44	...	...	30	84	..	Ca	..	90	152	...	6
F-Cl	C_6H_5ClFN				(49.50)	(3.46)	(24.36)	(9.67)								(7.47)	
2-3	C_6H_5ClFN	[a]	99	14	49.63	3.44	24.60	9.68		85	121	Ca	..	70	100	7.52	
2-5	C_6H_5ClFN	...	89	10	49.49	3.46	24.31	9.63		86	123	Ca	..	32	111	7.43	
3-4	C_6H_5ClFN	61	..		...	..	...	...	[t]	87	..	Ca	..	99	140	...	15
4-2	C_6H_5ClFN		192[b]		49.40	3.53	...	9.84		88	122	Ca	..	91	117	7.36	
4-3	C_6H_5ClFN	44	..		...	..	...	...	[l]	89	..	Ca	[c]	..	..	....	
F-Cl-NO_2	$C_6H_4ClFN_2O_2$				(37.82)	(2.11)	(18.61)	(14.70)								(12.05)	
2-5-4	$C_6H_4ClFN_2O_2$	127	..		38.00	2.03	18.49	14.53		90	86	B	[c]	80	167[d]	11.86	
F-Cl_2	$C_6H_4Cl_2FN$				(40.03)	(2.24)	(39.39)	(7.78)								(6.31)	
2-4,5	$C_6H_4Cl_2FN$	68	..		39.92	2.33	...	7.96		91	128	Ca	[c]	95	159	6.61	
4-2,5	$C_6H_4Cl_2FN$	76	..		39.80	2.43	...	7.92		92	125	Ca	[c]	72	141	6.23	
4-3,5	$C_6H_4Cl_2FN$	102	..		40.04	2.27	39.16	7.79		93	126	Cb	[e]	97	189	6.34	
F-CH_3	C_7H_6FN				(67.21)	(6.41)	...	(11.20)								(8.38)	
2-4	C_7H_6FN	...	190[b]		67.16	6.40	...	11.47	[m]	94	..	Cb	..	82	124[f]	8.47	[m]
4-2	C_7H_6FN	...	94	16	...	..	...	...	34	95	129	Ca	..	90	113	8.56	34
4-3	C_7H_6FN	36[g]	..		67.29	6.27	...	11.38	34	96	..	Ca	..	95	77[h]	8.37	[n]
F_2	$C_6H_5F_2N$				(55.82)	(3.90)	...	(10.84)								(8.18)	
2,5	$C_6H_5F_2N$	13.4	84	30	...	..	...	...	[o]	97	..	Ca	[i]	96	123	...	[o]
3,4	$C_6H_5F_2N$	...	77	7	...	..	...	...	[p]	98	..	Ca		87	124	8.16	21
3,5	$C_6H_5F_2N$	40	80	20	55.89	4.05	...	11.11	[q]	99	..	Ca	[j]	75	130	8.40	[p]
F_2-Cl	$C_6H_4ClF_2N$				(44.06)	(2.46)	(21.68)	(8.56)								(6.81)	
2,4-3	$C_6H_3ClF_2N$	62	..		44.29	2.51	21.72	8.74	[r]	100	..	Ca	[e]	74	131	(6.62)	[r]
2,4-5	$C_6H_4ClF_2N$	51	210		43.95	2.54	...	8.67	[s]	101	..	Ca	..	95	142	6.73	[s]
2,5-4	$C_6H_4ClF_2N$	80	..		44.27	2.61	...	8.58	[s]	102	..	Ca	..	60	157	6.59	[s]
3,5-4	$C_6H_4ClF_2N$	79	..		44.12	2.50	21.85	8.60		103	132	Cb	[e]	99	167	6.74	
4,5-2	$C_6H_4ClF_2N$	57	..		43.85	2.50	21.73	8.73		104	131	Cb	[c]	97	106	6.61	
F_3	$C_6H_4F_3N$				(48.99)	(2.74)	...	(9.52)								(7.41)	
2,3,4	$C_6H_4F_3N$	...	92	48	48.99	2.67	...	9.67		105	133	Ca	..	68	96	7.43	
2,3,5	$C_6H_4F_3N$	...	76	20[b]	49.08	2.49	...	9.69	23	106	..	Ca	..	87	121	7.69	23
2,4,5	$C_6H_4F_3N$	60	..		...	..	...	...	[t]	107	..	Ca	..	90	130	...	[t]

[a] $n^{20}D$ 1.5625. [b] Microcapillary boiling point. [c] Benzene and low boiling petroleum ether (solvent). [d] Procedure Ab, 52% yield. [e] Ethanol. [f] Literature m.p. 128°. [g] Described in the literature as a brown oil, b.p. 85–86° (9 mm.). [h] Literature m.p. 74°. [i] Benzene. [j] Low boiling petroleum ether. [k] $n^{20}D$ 1.4899. [l] C. K. Ingold and C. C. N. Vass, *J. Chem. Soc.*, 417 (1928). [m] A. Ostoszynski, *Bull. soc. sci. lettres Lodz, Classe III*, **3**, no. 15, 10 (1952). [n] Ng. Ph. Buu-Hoi and P. Jacquignon, *J. Chem. Soc.*, 4173 (1952). [o] F. Swarts, *Bull. classe sci. Akad. roy. Belg.*, 176 (1914). [p] A. F. Helin and C. A. VanderWerf, THIS JOURNAL, **73**, 5884 (1951). [q] G. C. Finger, F. H. Reed and J. L. Finnerty, *ibid.*, **73**, 153 (1951). [r] G. C. Finger, R. E. Oesterling and R. H. White, Abstracts of the 130th A.C.S. Meeting, Sept., 1956, Atlantic City, N. J., p. 26-O, and unpublished results. [s] G. C. Finger and R. E. Oesterling, THIS JOURNAL, **78**, 2593 (1956). [t] G. C. Finger, F. H. Reed, D. M. Burness, D. M. Fort and R. R. Blough, *ibid.*, **73**, 145 (1951).

acid to form the amine salt, and cooled. A strong aqueous sodium nitrite (slight excess) solution was prepared. The diazotization was effected at −5° by the concurrent addition of amine salt and nitrite solutions to the ice–acid mixture. Stirring was continued about one hour without further cooling. (d) After addition of the amine to concd. hydrochloric acid, the mixture was heated at 75° for 30 minutes, cooled to 10°, and the amine salt crystals were removed on a glass cloth filter. Diazotization was effected at 0–10° by the concurrent addition of the amine salt crystals and a slight excess of powdered sodium nitrite to the amine hydrochloride liquor. (e) The concd. hydrochloric acid indicated in the tables was divided into two parts percentage-wise. For the preparation of the amine hydrochloride, (X) is the fraction of the total acid which was diluted with water to a lower percentage acid strength (Y). The remaining acid portion was diluted to the acid strength indicated in (Z). The amine was added to the dilute acid (Y), the mixture was heated and cooled as in the previous experiment (d) without the final filtration. The diazotization was effected at 0–10° by the concurrent addition of the amine salt solution and a strong water solution of sodium nitrite (slight excess) to the other dilute acid solution (Z).

HYDROCHLORIC ACID DISTRIBUTION FOR DIAZOTIZATION (e)

Cmpd. no.	(X)	(Y)	(Z)
117	42	37	37
118	70	37	37
119	70	37	37

G. Diazonium Group Replacements.—(a) By –OH: Phenols were prepared by the catalytic hydrolysis[18] of the corresponding diazonium salts in the usual superheated steam distillation apparatus. The temperature of the hydrolyzing medium ($H_2SO_4/H_2O/CuSO_4 \cdot 5H_2O$) is an important factor, and the following temperature-composition formulation was found to be useful. At the temperature specified in Table II, the diazonium salt solution was hydrolyzed by slow addition to the hot hydrolyzing medium.

TEMPERATURE–FORMULATION CHART FOR HYDROLYSIS (a)

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

During hydrolysis a slow current of steam was passed through the system to remove the phenol as formed. The temperature was controlled by the addition rates of the steam and diazonium salt solutions plus external heating when necessary. The phenols were isolated by triple ether extraction of the distillate. They were purified by vacuum distillation or by recrystallization followed by vacuum sublimation. (b) By –H: The diazonium salts were reduced by the hypophosphorous acid–cuprous oxide method.[23] The molar ratio of sodium hypophosphite to diazonium salt was 3:1. After removal of the resulting nitro compound by steam distillation, the residue was neutralized and further steam distillation removed the by-product amine. In general,

TABLE IV

FLUOROANISOLES

Ring subst.	Empirical formula	M.p., °C.	B.p. °C.	Mm.	$n^{20}D$	Analyses, % found (calcd.) C	H	F	N, Cl or Br, I	Lit. ref.	Cmpd. no.	Syntheses: Parent cmpd. no.	Proc.	Yield, %
F-NH_2	C_7H_8FNO					(59.56)	(5.71)	...	(9.93)					
2–4	C_7H_8FNO	83	..		[a]	59.11	5.79	...	9.80	[i]	108	..	Ca	90
4–2	C_7H_8FNO	3[b]	117	20	[c]	59.55	5.53	...	9.84		109	116	Ca	95
F-Br	C_7H_6BrFO					(41.00)	(2.95)	(9.27)	(38.98)					
2–4	C_7H_6BrFO	16	84	7	1.5448	...	..	...	...	22	110	108	Fc,Gc[d]	55
4–2	C_7H_6BrFO	−27[b]	79	5	1.5447	41.19	2.83	9.07	39.29		111	109	Fc,Gc[d]	89
F-Cl	C_7H_6ClFO					(52.35)	(3.77)	(11.83)	(22.08)					
2–4	C_7H_6ClFO	− 6[b]	72	7	1.5173	52.42	3.61	11.96	21.89	[g]	112	108	Fc,Gc[d]	57
4–2	C_7H_6ClFO	−17[b]	67	5	1.5173	52.55	3.75	12.12	21.87	28	113	109	Fc,Gc[d]	88
F-I	C_7H_6FIO					(33.36)	(2.40)	(7.54)	(50.36)					
2–4	C_7H_6FIO	34	86	3	....	33.48	2.30	...	...		114	108	Fc,Gc[d]	78
4–2	C_7H_6FIO	−21[b]	92	3	1.5924	33.41	2.41	7.68	50.69		115	109	Fc,Gc[d]	78
F-NO_2	$C_7H_6FNO_3$					(49.13)	(3.54)	...	(8.19)					
4–2	$C_7H_6FNO_3$	60	..		....	49.35	3.38	...	8.08	[h]	116	..	Ab	80
F_2	$C_7H_6F_2O$					(58.33)	(4.20)	(26.37)	...					
2,6	$C_7H_6F_2O$	...	71	56[e]	....	...	..	...	...	28	117	..	Fe,Gd[f]	38

[a] Acetyl m.p. 112–112.5°. [b] Freezing point. [c] Acetyl m.p. 101–102°. [d] Molar ratio, amine:concd. sulfuric acid, 1:3. [e] Literature b.p. 62° (40 mm.). [f] Molar ratio, amine:hydrochloric acid, 1:3. [g] E. Pendl and G. Radinger, *Monatsh.*, **72**, 378 (1939). [h] F. Swarts, *Rec. trav. chim.*, **35**, 131 (1915). [i] Table II, ref. *s*.

TABLE V

BENZENE DERIVATIVES

Ring subst.	Emprical formula	M.p., °C.	B.p. °C.	Mm.	Analyses, % found (calcd.) C	H	F	Cl	N	Lit. ref.	Cmpd. no.	Syntheses: Parent cmpd.	Proc.	%
F-Cl_2	$C_6H_3Cl_2F$				(43.67)	(1.83)	(11.52)	(42.98)	..					
1-2,4	$C_6H_3Cl_2F$	...	174		...	..	...	...	..	[o]	118	..	Fe,Gd[a]	62
1-2,5	$C_6H_3Cl_2F$	...	168		...	..	...	...	..	[p]	119	..	Fe,Gd[b]	64
1-3,4	$C_6H_3Cl_2F$	−1[c]	172[d]		43.76	1.83	11.84	43.02	..	[q]	120	88	Fc,Gc[e]	85
F-Cl-NO_2	$C_6H_3ClFNO_2$				(41.05)	(1.72)	...	(20.20)	(7.98)					
1-2-6	$C_6H_3ClFNO_2$	[f]	106	5	41.04	1.74	...	20.45	8.01		121	..	Da[g]	53
1-3-4	$C_6H_3ClFNO_2$	37			41.13	1.57	...	...	8.01	[r]	122	..	Fa,Gc[h]	41
1-4-2	$C_6H_3ClFNO_2$	8.3	237		...	..	...	...	..	[r]	123	..	Db[i]	58
F-Cl_2-NO_2	$C_6H_2Cl_2FNO_2$				(34.31)	(0.96)	(9.05)	(33.77)	(6.67)					
1-2,4-5	$C_6H_2Cl_2FNO_2$	...	77	1	34.46	0.73	...	...	6.66		124	118	Aa	93
1-2,5-4	$C_6H_2Cl_2FNO_2$	37			34.39	0.82	...	33.58	6.68		125	119	Aa	90
1-2,6-4	$C_6H_2Cl_2FNO_2$	44	..		34.44	0.94	...	33.95	6.65		126	..	Da	83
1-2,6-5	$C_6H_2Cl_2FNO_2$	...	88	1	34.50	1.06	...	33.55	6.79	17	127	..	Aa[j]	82
1-4,5-2	$C_6H_2Cl_2FNO_2$	17[c]	247[k]		34.35	0.85	...	...	6.90		128	120	Aa	97
F-CH_3-NO_2	$C_7H_6FNO_2$				(54.20)	(3.90)	(12.25)	...	(9.03)					
1-3-4	$C_7H_6FNO_2$	...	98	10	...	..	...	...	..	34	129	..	Aa	88
F_2-Cl	$C_6H_3ClF_2$				(48.51)	(2.03)	(25.58)	(23.87)	..					
1,2-4	$C_6H_3ClF_2$	...	127		48.44	2.16	25.63	24.10	..		130	98	Fd,Gc[l]	70
F_2-Cl-NO_2	$C_6H_2ClF_2NO_2$				(37.23)	(1.04)	...	(18.32)	(7.24)					
1,2-4-5	$C_6H_2ClF_2NO_2$	...	118	31	37.46	1.09	...	18.26	7.41		131	130	Aa	84
1,3-2-5	$C_6H_2ClF_2NO_2$	42	..		37.52	1.14	...	18.18	7.27	[s]	132	..	Fa,Gb[m]	24
F_3-NO_2	$C_6H_2F_3NO_2$				(40.69)	(1.14)	...	...	(7.91)					
1,2,3-4	$C_6H_2F_3NO_2$	..	92	20	40.51	1.10	...	...	8.02		133	127	Da[n]	34

[a] Molar ratio, amine:concd. hydrochloric acid, 1:3. [b] Molar ratio, amine:concd. hydrochloric acid, 1:5. [c] Freezing point. [d] Microcapillary boiling point, $n^{20}D$ 1.5235, literature b.p. 171°. [e] Molar ratio, amine:concd. sulfuric acid 1:6.5. [f] $n^{20}D$ 1.5524. [g] Reaction time, 4 days. [h] Molar ratio, amine:concd. sulfuric acid:phosphoric acid, 1:6:11.5; sodium nitrite:concd. sulfuric acid, 1:6. [i] Reaction time and temperature, 4 hours at 166°. [j] Reaction temperature 35–40°; no data given in literature. [k] Microcapillary boiling point, $n^{20}D$ 1.5741. [l] Molar ratio, amine:concd. hydrochloric acid:water, 1:10:4. [m] Molar ratio, amine:concd. sulfuric acid:phosphoric acid, 1:14:10; concd. sulfuric acid:sodium nitrite, 14:1. [n] Reaction time, 8 hours. [o] L. M. F. Van de Lande, *Rec. trav. chim.*, **51**, 98 (1932). [p] T. de Crauw, *ibid.*, **48**, 1061 (1929). [q] G. M. Kraay, *Diss. Amsterdam*, 68 (1926); *C. A.*, **20**, 2152 (1926). [r] Table IV, ref. *h*. [s] Table III, ref. *r*.

TABLE VI

MISCELLANEOUS FLUORO COMPOUNDS

Ring subst.	Empirical formula	M.p., °C.	Analyses, % found (calcd.) C	H	F	Cl or N, P	Cmpd. no.	Syntheses: Parent cmpd. no.	Procedure	Yield, %
			(β-Fluorophenoxy)-propionic acids							
F	$C_9H_9FO_3$		(58.69)	(4.92)	(10.32)	...				
4	$C_9H_9FO_3$	86	58.47	4.92	10.22	...	134	47	Jb	17
F-Cl_2	$C_9H_7Cl_2FO_3$		(42.71)	(2.79)	(7.51)	(28.02)				
5-2,4	$C_9H_7Cl_2FO_3$	110	42.70	2.72	7.34	28.15	135	67	Jb	80
F_2	$C_9H_8F_2O_3$		(53.47)	(3.99)	(18.80)	...				
2,4	$C_9H_8F_2O_3$	76	53.24	3.94	18.95	...	136	68	Jb	60
F_3	$C_9H_7F_3O_3$		(49.10)	(3.21)	(25.89)	...				
2,4,5	$C_9H_7F_3O_3$	82	49.25	3.21	25.90	...	137	82	Jb	85
			Fluorobenzoic acids							
F-Cl	$C_7H_4ClFO_2$		(48.16)	(2.31)	(10.88)	(20.31)				
5-2	$C_7H_4ClFO_2$	148	48.11	2.30	10.65	20.17	138	..	K	61
F_3	$C_7H_3F_3O_2$		(47.74)	(1.73)	(32.37)	...				
2,3,5	$C_7H_3F_3O_2$	106	47.69	1.86	32.22	...	139	..	K	96
			Bis-(3-fluorophenyl)-phosphinic acid							
	$C_{12}H_9F_2O_2P$		(56.70)	(3.57)	...	(12.19)				
	$C_{12}H_9F_2O_2P$	167	56.74	3.55	...	12.10	140	..	O	50
			2-Hydro-3-keto-6-fluoro-1,4-benzisoxyazine							
	$C_8H_6FNO_2$		(57.48)	(3.62)	...	(8.38)				
	$C_8H_6FNO_2$	204	57.37	3.60	...	8.33	141	17	Ca	41
			2-Nitro-5-fluorophenylpyruvic acid							
	$C_9H_6FNO_5$		(47.59)	(2.66)	...	(6.17)				
	$C_9H_6FNO_5$	147	47.88	2.84	...	6.01	142	129	M	31
			5-Fluoro-2-indolecarboxylic acid							
	$C_9H_6FNO_2$		(60.33)	(3.38)	...	(7.82)				
	$C_9H_6FNO_2$		60.45	3.09	...	7.69	143	142	N	92
			Ethyl 2-carboethoxy-5-fluoro-3-indoleacetate							
	$C_{15}H_{16}NO_4$		(61.42)	(5.50)	...	(4.78)				
	$C_{15}H_{16}NO_4$	124	61.38	5.60	...	4.84	144	84	L	30

[a] Vacuum sublimation, 140°.

equal weights of the nitro and amine compounds were obtained. (c) By -Cl, -Br, -I: To a cuprous chloride–concd. hydrochloric acid mixture (molar ratio 4.5:1) at 10–15°, was added slowly, with shaking, the diazonium salt solution. After dilution with an equal volume of water, steam distillation removed the chloro compound. In case of replacement by -Br, cuprous bromide–concd. hydrobromic acid (48%) was used. For replacement by -I, the potassium iodide method was used. (d) By -F: The replacement of the diazonium group by -F was effected by the Schiemann transformation.[24] To the diazonium chloride solution cooled to −30°, sodium fluoroborate (twice calcd.) was added as a slurry in an equal weight of water. The precipitated diazonium fluoroborate salt was isolated, dried, and thermally decomposed to the desired fluoro compound in the usual manner.[25]

H. Brominations.—(a) A slight excess of bromine was added slowly to an aqueous suspension of the phenol with stirring. (b) To a dilute solution of the phenol in carbon disulfide, a slight excess of bromine was added slowly with stirring. (c) Bromine was added dropwise to a 3:1 mixture (by weight) of trichloroacetic acid and the phenoxyacetic acid at 140° with a trace of iron as catalyst. Stirring was continued until the evolution of hydrogen bromide stopped. After cooling below 100°, the reaction mixture was poured over an ice–water mixture, filtered and recrystallized.

I. Chlorinations.—(a) Dry chlorine gas was passed slowly into the phenol until a gain in weight of one or two mole equivalents of chlorine was obtained. (b) Dry chlorine gas was passed slowly into a solution of the phenoxyacetic acid[17] in acetic acid at room temperature over an iron catalyst. Highly substituted rings may require the use of trichloroacetic acid as a solvent at temperatures greater than 100°.

J. Aryloxyalkanoic Acid Preparation.—(a) The phenoxyacetic acids were prepared by the alkaline condensation of chloroacetic acid and the phenol.[16] The phenol and an appreciable excess of chloroacetic acid were melted, and 30% aqueous sodium hydroxide was added to strong alkalinity. The mixture was evaporated to sensible dryness. The residue was dissolved in hot water, cooled, and acidification with dilute hydrochloric acid gave the phenoxyacetic acid as a white solid. (b) In the synthesis of the phenoxypropionic acids, the above procedure was followed using β-chloropropionic acid.

K. Hydrolysis of Benzotrifluorides.—Compound 138 was hydrolyzed by heating with 90% sulfuric acid, and compound 139 was heated with a mixture of fuming sulfuric acid and a small amount of aluminum chloride. These methods are modifications of procedures given in the literature.[26,27]

2-Fluoro-6-nitroanisole[28] was prepared as described in the literature except that a concd. nitric–sulfuric acid mixture was used for nitration in place of fuming nitric acid. The resulting 2-fluoro-6-nitrophenol, m.p. 91–92°, was methylated by the dimethyl sulfate–potassium carbonate procedure[29] in xylene; boiling point of the anisole, 81–83° (3 mm.) (lit. 93° (3 mm.)).

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L. Ethyl 2-Carboethoxy-5-fluoro-3-indoleacetate.—A mixture of 4-fluoroaniline,[30] 67 ml. of concd. hydrochloric acid and 100 ml. of water was diazotized in the usual manner with 14 g. of sodium nitrite in 25 ml. of water. The condensation and cyclization process was accomplished by the King and L'Ecuyer[31] procedure. The diazonium solution was added slowly to a mixture of 48 g. of ethyl α-acetoglutarate,[32] 200 ml. of ethanol and 150 ml. of 20% sodium hydroxide at 0–5° 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, dried and the ether was evaporated. The dried residue was dissolved in 100 ml. of absolute ethanol, dry hydrogen chloride gas was passed in to saturation, and the mixture was then refluxed for one hour. Upon pouring into ice, a brown semisolid separated which upon recrystallization from aqueous ethanol gave yellow needles. Vacuum sublimation gave pure ethyl 2-carboethoxy-5-fluoro-3-indoleacetate as white needles, m.p. 123–124°, yield 15 g. (30%).

M. 2-Nitro-5-fluorophenylpyruvic Acid.—The procedure of Meyer and Balle[33] was adapted to the synthesis of this compound. To 150 m . of absolute ethanol, 14 g. of clean sodium chips was added slowly and allowed to react completely. With stirring and cooling, 88 g. of diethyl oxalate was added slowly and followed by a solution of 78 g. of 2-nitro-5-fluorotoluene[34] 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 a ice–hydrochloric acid mixture, whereupon a red oil separated. The oil was collected in ether, and two extractions with 200-ml. portions of sodium hydroxide (*N*) 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, m.p. 146–147°, yield 38 g. (31%).

N. 5-Fluoro-2-indolecarboxylic Acid.—The preceding pyruvic acid was converted to an indole derivative by the Cornforth and Robinson[35] procedure. Ten grams of 2-nitro-5-fluorophenylpyruvic acid was added to 2.2 g. of sodium hydroxide in 85 ml. of water. With stirring, 30 g. of sodium hydrosulfite dihydrate was added slowly and the reaction was slightly exothermic. Stirring was continued until a test sample gave no red color in excess alkali solution. The mixture was acidified with hydrochloric acid, heated on a steam-bath to expel sulfur dioxide, cooled, and extracted with ether. The yield of crude product from ether evaporation was 8 g. Recrystallization from aqueous ethanol followed by vacuum sublimation (140° (1 mm.)) gave white granular crystals as pure 5-fluoro-2-indolecarboxylic acid. The compound does not melt, but at 245° it appears to decarboxylate to the fluoroindole.

O. Bis-(3-fluorophenyl)-phosphinic acid was prepared by the general procedure described by Doak and Freedman.[36] To 14 g. of phosphorus trichloride and 29 g. of cuprous bromide in 200 ml. of dry ethyl acetate, 42 g. of 3-fluorobenzenediazonium fluoroborate[24] was added gradually at 50°. The reaction mixture was refluxed two hours and steam distilled. The residue was evaporated to about 50 ml. and, on cooling, the diarylphosphinic acid crystallized. Recrystallization from low boiling petroleum ether with a few drops of benzene gave white needles, m.p. 166–167°.

Tabulation of Experimental Data.—The tables contain information on the physical constants and notes on the experimental work on the compounds studied. Known compounds are listed in cases where they were required to operate a given synthesis or where the literature data are inadequate.

The syntheses notes indicate the parent compound required in the synthesis, the procedure or general method of preparation, the recrystallization solvents for final purification, and the yield data based on the parent compound. In some cases molar ratios of reactants and reaction temperatures are given. The tables are interrelated through compound numbers, thus making it possible to trace the ancestry of a given compound back to a known starting material. The previous information can be illustrated as follows: compound no. 21 (2-fluoro-4,5-dichlorophenoxyacetic acid) was prepared from parent compound no. 63 (2-fluoro-4,5-dichlorophenol) by procedure Ja, recrystallized from benzene (footnote *a*), yield 89%. Likewise, the ancestry of parent compound no. 63 can be traced back through its intermediates, 91 and 128, to a known starting material, compound no. 120 (3,4-dichlorofluorobenzene).

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Multiple Variation in Structure–Reactivity Correlations[1]

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As a natural extension of linear correlations of structure with reactivity, it is proposed that the four-parameter equation $y = px + qxz + rz + s$ be used for dual variations where these are characterized by the structural constants x and z. The theoretical implications of this equation and its capacity to store, predict and evaluate data is indicated. For the rapid review of data in which two structural variations separately give linear correlations, an approximate but convenient graphical method, the "generating procedure," is developed.

Quantitative correlations of chemical data have often been cast in the form of two- or three-parameter equations.[2–4] What are the consequences of introducing multiple structural variations in systems to which these equations apply?

The discussion begins with the straight line

$$y = Ax + B \qquad (1)$$

Consider a specific example in which the Hammett[3] and Swain–Scott[5] equations apply.

Hammett	$\log k = \rho\sigma + \log k_0$	(1a)
Swain-Scott	$\log k = sn + \log k_0$	(1b)

The rate constants, k, for a series of reactions

$$R_iC_6H_4E + N_j \longrightarrow \text{Products} \qquad (2)$$

are to be correlated. R_i, the substituent of an

(1) Supported by the Office of Ordnance Research, U. S. Army.
(2) L. P. Hammett, "Physical Organic Chemistry," McGraw–Hill Book Co., Inc., New York, N. Y., 1940, Chap. 7; J. Hine, "Physical Organic Chemistry," McGraw–Hill Book Co., Inc., New York, N. Y., 1956, Chaps. 2, 6, 8, 12.
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