200 ml of hot EtOH, and clarified, H_2O was added, and the cyanoguanidine (1) precipitated.

Using a similar procedure and the same molar quantities of the reactants, 1-*t*-amyl-3-cyanoguanidine (**2**) was prepared from the corresponding amine hydrochloride.

N-Cyano-3-carboxamidino-3-azabicyclo[3.2.2]nonane (8).—To a solution of 1.25 g of the azabicyclononane in 1 ml of concentrated HCl and 4 ml of H_2O was added 0.9 g (0.01 mole) of sodium dicyanamide. The mixture was refluxed for 2 hr; however, within 20 min of refluxing a solid had precipitated. The reaction mixture was cooled and the solid was filtered off and recrystallized from aqueous EtOH.

1-*t*-Butyl-2-cyano-3-methylguanidine (17).—A steel autoclave equipped with a glass liner was charged with 3.2 g (0.025 mole) of 1-cyano-2,3-dimethyl-2-thiopseudourea, 15 ml of *t*-butylamine, and 60 ml of EtOH and was heated at 125° for 6 hr. The vessel was cooled, and the light brown solution was removed and evaporated to a syrup. When this syrup was dissolved in a 50% EtOH–H_2O mixture by warming and the solution was decolorized with charcoal, 0.2 g of an unidentified material melting at 201–211° was obtained. The filtrate from it, on further dilution with 30 ml of H_2O, gave 0.7 g of the desired product. It was recrystallized from dilute EtOH.

1-Cyclohexyl-2-cyano-3-(2-morpholinoethyl)guanidine (18).—A mixture containing 2.61 g (0.009 mole) of 1-cyclohexyl-3-(2-morpholinoethyl)thiourea (Aldrich Chemical Co.), 2.72 g (0.011 mole) of lead cyanamide, and 16 ml of EtOH was stirred and refluxed for 18 hr. The reaction was not complete as observed by the formation of mercuric sulfide when a clarified aliquot of the mixture was heated with yellow mercuric oxide. Another 0.5 g of PbNCN was added to the reaction mixture and refluxing was continued for 7 hr longer. The precipitated sulfide was filtered off and the cyanoguanidine was isolated by cooling the filtrate. It was recrystallized from EtOH.

The physical constants, yields, and other pertinent data for the individual compounds are given in Table I.

7-Chloro-1,3-dihydro-6-methyl-2H-pyrrolo[3,4-*c*]pyridine-2-carboxamidine Dihydrochloride (19).—A mixture containing 6.7 g (0.04 mole) of 7-chloro-6-methylmerimine,[12] 5.6 g (0.02 mole) of S-methylpseudothiourea sulfate, and 30 ml of H_2O was refluxed for 18 hr. The hot mixture was decolorized with charcoal and filtered. A solid which precipitated on cooling was filtered and dried. A satisfactory elemental analysis for the sulfate of the desired compound could not be obtained even after repeated recrystallizations. By neutralizing an aqueous solution of the sulfate with $NaHCO_3$ and then dissolving it in ethanolic HCl 2.5 g (22%) of the dihydrochloride was obtained; recrystallized from 95% EtOH, mp 285–295° dec. *Anal.* ($C_9H_{11}ClN_4 \cdot 2HCl$) C, H, N.

1-[2-(7-Chloro-1,3-dihydro-6-methyl-2H-pyrrolo[3,4-*c*]pyridine-2-yl)ethyl]guanidine Sulfate Hemihydrate (20).—A mixture containing 1.06 g (0.005 mole) of the base of the merimine used in the preparation of **16**, 0.7 g (0.0025 mole) of 2-methylthiopseudourea sulfate, and 5 ml of H_2O was refluxed for 8 hr. The solid which precipitated on cooling was filtered, washed with cold H_2O, and dried to yield 0.93 g (60%), mp 217–221°; recrystallized from MeOH and Et_2O, mp 219–222°. *Anal.* [$(C_{10}H_{16}ClN_5)_2 \cdot H_2SO_4 \cdot H_2O$] C, H, N.

Acknowledgments.—We wish to express our thanks to Mr. L. Brancone and his associates for microanalyses, Dr. P. J. Kohlbrenner and his group and especially to Mr. L. Binovi for certain large-scale preparations, and Mmes. A. M. Kotsen and B. Hoffman for experimental assistance.

The Synthesis and Activity of Some 2,6-Difluorophenyl-Substituted Compounds

A. M. ROE, R. A. BURTON, G. L. WILLEY, M. W. BAINES, AND A. C. RASMUSSEN

Smith Kline and French Research Institute, Welwyn Garden City, Hertfordshire, England

Received December 14, 1967

The preparation of 2,6-difluorophenyllithium, and its conversion into a range of 2,6-difluoroaromatic compounds (see Chart I), has led to the synthesis of several difluoro analogs of known pharmacologically active compounds such as lidocaine and xylocholine. Their local anesthetic activity, adrenergic neurone blocking activity, nicotinic activity, and some of the effects that these compounds have on the behavior of conscious mice are reported and discussed.

A wide variety of pharmacologically active 1,2,3-trisubstituted aromatic compounds in which the 1 and 3 substituents are chlorine or methyl have been described. These include the local anesthetics lidocaine (**28**),[1] 2-(2,6-dichlorophenoxy)ethyldimethylamine (**14**), and xylocholine (**19**), and the adrenergic neurone blocking drugs xylocholine (**19**) and its guanidino analog (**11**).

This paper describes the completion of the series of compounds to which the foregoing belong by the synthesis of the 2,6-difluorophenyl analogs, and we report a study of the comparative pharmacology of the unsubstituted, the difluoro, the dichloro, and the dimethyl compounds (Table I). A series of related ureas has also been prepared and tested for their effect on the behavior of conscious mice.

2,6-Difluorobenzoic acid[2] and 2,6-difluorophenol[3] are both known compounds, but when this investigation started, they were not easily prepared in quantity. We therefore set out to find a convenient and suitably versatile synthesis for these and other 2,6-difluoroaryl compounds. The employment of an aryllithium intermediate seemed feasible,[4] and we found that 1,3-difluorobenzene in tetrahydrofuran, or in mixtures of THF and hexane or heptane (2:1–4:1), formed a stable aryllithium (I) when treated with *n*-butyllithium at below −50°. This was demonstrated by the formation of 2,6-difluorobenzoic acid (II) in 81% yield after

(1) The compounds studied in this work have been assigned the numbers shown in Table I. Pertinent references to the origin of the compound and, if previously described, to its pharmacology are given in the footnotes to Table I.

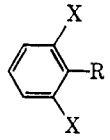
(2) J. Thomas and J. Caney, *J. Pharm. Pharmacol.*, **14**, 587 (1962).

(3) G. C. Finger, M. J. Gortatowski, R. H. Sliley, and R. H. Wilde, *J. Am. Chem. Soc.*, **81**, 94 (1959).

(4) We are grateful to Dr. J. N. Gardner for suggesting this reaction to us. H. Gilman and T. S. Soddy, *J. Org. Chem.*, **22**, 1715 (1957), converted fluorobenzene into 2-fluorophenyllithium, which was stable in THF at −60°, and then into 2-fluorobenzoic acid. G. Wittig and W. Merkle, *Ber.*, **75**, 1491 (1942), demonstrated that 1,3-difluorobenzene was metallated by phenyl- or by methyllithium in ether; the products of their reactions, which were conducted at −15 or 0°, were consistent with the formation of a substituted benzyne from a putative 2,6-difluorophenyllithium. J. Hine and P. B. Langford, *J. Org. Chem.*, **27**, 4149 (1962), demonstrated the acidity of the hydrogen at the 2-carbon in 1,3-difluorobenzene by deuterium exchange studies.

Table I

Serial Number and Structure of Compounds Studied



R	Compd no.—X— H	F[a]	Cl	CH_3
$CH_2NHC(NH_2)=NH$	1[b,c]	2	...	3[b,d]
$CH_2CH_2NHC(NH_2)=NH$	4[b,c]	5	6[b,d]	7[b,d]
$OCH_2CH_2NHC(NH_2)=NH$	8[b,e]	9	10[f]	11[b,e,g]
$OCH_2CH_2N(CH_3)_2$	12[h,i]	13	14[j,k]	15[j,k,l]
$OCH_2CH_2N^+(CH_3)_3\cdot Y^-$	16[m,n]	17	18[m,o]	19[l,m,p]
$OCH_2CH_2N^+(CH_3)_2C_2H_5\cdot Y^-$	...	20	21[q]	22[m,r]
$NHCOCH_2N(CH_3)_2$	...	23	24[h,s]	...
$NHCOCH_2N(C_2H_5)_2$	25[t]	26	27[h,s]	28[h,u]
$CH_2NHCONH_2$	29[v]	30	...	31[d]
$CH_2CH_2NHCONH_2$	32[w]	33	34[d]	35[d]
$OCH_2CH_2NHCONH_2$	36[x]	37	38[f]	39[y]

[a] See Table II. [b] 0.5 H_2SO_4. [c] R. Fielden, A. L. Green, and G. L. Willey, *Brit. J. Pharmacol.*, **24**, 395 (1965). [d] A. L. Green, unpublished. [e] D. I. Barron, P. M. G. Bavin, G. J. Durant, I. L. Natoff, R. G. W. Spickett, and D. K. Vallance, *J. Med. Chem.*, **6**, 705 (1963). [f] Unpublished. [g] A. L. A. Boura, F. C. Copp, A. F. Green, H. F. Hodson, G. R. Ruffell, M. F. Sim, E. Walton, and E. M. Grivsky, *Nature*, **191**, 1312 (1961); D. I. Barron, I. L. Natoff, and D. K. Vallance, *Brit. J. Pharmacol.*, **25**, 534 (1965). [h] HCl. [i] S. Kuroda and S. Koyama, *J. Pharm. Soc. Japan*, **63**, 382 (1943). [j] HBr. [k] Reference 19. [l] Reference 23. [m] Y = Br. [n] Reference 17. [o] R. A. McLean, R. J. Geus, R. J. Mohrbacher, P. A. Mattis, and G. E. Ullyot, *J. Pharmacol. Exptl. Therap.*, **129**, 11 (1960). [p] K. A. Exley, *Brit. J. Pharmacol.*, **12**, 297 (1957). [q] Y = I. Unpublished; *cf.* P. Hey and G. L. Willey, British Patent 765,850 (1957). [r] P. Hey, unpublished; see ref 16. [s] L. S. Fosdick and J. A. Carbon, *J. Am. Chem. Soc.*, **76**, 1296 (1954). [t] H. Erdtman and N. Löfgren, *Svensk Kem. Tidskr.*, **49**, 163 (1937). [u] N. Löfgren, *Arkiv Kemi Mineral. Geol.*, **22A** (18), 1 (1946). [v] E. Paterno and P. Spica, *Gazz. Chim. Ital.*, **5**, 388 (1875); J. S. Buck, A. M. Hjort, and E. J. de Beer, *J. Pharmacol. Exptl. Therap.*, **54**, 188 (1935). [w] J. S. Buck, *J. Am. Chem. Soc.*, **56**, 1607 (1934); E. J. de Beer and A. M. Hjort, *J. Pharmacol. Exptl. Therap.*, **52**, 211 (1934). [x] S. Gabriel, *Ber.*, **47**, 3028 (1914). [y] G. J. Durant and S. H. B. Wright, *J. Med. Chem.*, **9**, 247 (1966).

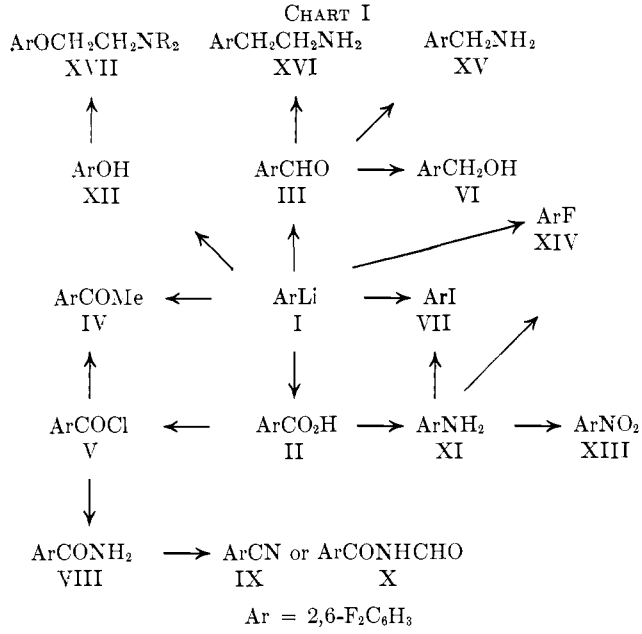
carbonation.[5] Analogous reactions have been carried out on 1,2-difluorobenzene (74% yield of 2,3-difluorobenzoic acid) and 1,3-dichlorobenzene (75% of 2,6-dichlorobenzoic acid); in the latter reaction a careful search did not reveal any 2,4-dichlorobenzoic acid.

2,6-Difluorophenyllithium (I) gave 2,6-difluorobenzaldehyde (III) in good yield by the action of N-methylformanilide, and 2,6-difluoroacetophenone (IV) in poor yield by the action of acetyl chloride (Chart I). The acetophenone was advantageously obtained from 2,6-difluorobenzoyl chloride (V) by reaction with diethyl ethoxymagnesiomalonate,[6] followed by hydrolysis and decarboxylation. Reduction of the aldehyde (III) by

(5) (a) A. M. Roe, R. A. Burton, and D. R. Reavill, *Chem. Commun.*, 582 (1965); A. M. Roe and R. A. Burton, British Patent 1,080,167 (1967). (b) At about the time this work was done, P. L. Coe, R. Stephens, and J. C. Tatlow, *J. Chem. Soc.*, 3227 (1962), reported that pentafluorophenyllithium was stable in ether at 0°; its enhanced stability over other 2-halogenophenyllithium derivatives was ascribed to the inductive effect of the five fluorine atoms; it was also reported that pentafluorobenzoic acid could not be obtained by carbonation of the aryllithium. However, an extensive study by R. J. Harper, Jr., E. J. Soloski, and C. Tamborski, *J. Org. Chem.*, **29**, 2385 (1964), and C. Tamborski and E. J. Soloski, *ibid.*, **31**, 743, 746 (1966), of this and similar reactions has delineated the most satisfactory conditions for metallation and carbonation of fluoroaromatic compounds in general.

(6) H. G. Walker and C. R. Hauser, *J. Am. Chem. Soc.*, **68**, 1386 (1946).

Chart I



$LiAlH_4$ gave 2,6-difluorobenzyl alcohol (VI). 2,6-Difluoroiodobenzene (VII) was prepared from the aryllithium by the addition of iodine in THF.

The preparation of 2,6-difluorobenzonitrile (IX) was of interest;[7] dehydration of 2,6-difluorobenzamide (VIII) by thionyl chloride in DMF produced two compounds, depending on the conditions. Reaction with 2 moles of $SOCl_2$ at 80° for 0.5 hr gave the required nitrile (IX) in 90% yield, whereas reaction with **1** mole at room temperature for several days (a procedure recommended[8] for benzonitrile itself) gave only N-formyl-2,6-difluorobenzamide (X) in 46% yield. Proof of the structure of the latter compound rests on its analysis, ir spectrum, and conversion by reaction with phenylhydrazine into 3-(2,6-difluorophenyl)-2-phenyl-1,2,4-triazole.

Our next synthetic objective was the preparation of the hitherto undescribed 2,6-difluoroaniline (XI) and of the known 2,6-difluorophenol (XII).[3] The aniline was obtained in 86% yield by a Schmidt reaction on the benzoic acid. Unexpectedly, the phenol could not be obtained from this aniline. The diazotized aniline was heated in solution in the presence of various salts, under various different conditions, and the crystalline diazonium fluoroborate was also variously treated, but the phenol could not be isolated. This behavior was paralleled by the analogous 2,6-dichloroaniline, which gave less than 5% of 2,6-dichlorophenol under the usual conditions.

That the diazonium group could be replaced was shown by its conversion into 2,6-difluoroiodobenzene (VII) when treated with KI, by its conversion into 2,6-difluoronitrobenzene (XIII) with $NaNO_2$ in the presence of copper powder, and by the formation of 1,2,3-trifluorobenzene (XIV).[5a] No useful products were obtained from 2,6-difluoro- or 2,6-dichlorobenzenediazonium fluoroborate and acetic acid or acetic anhydride.[9]

(7) 2,6-Dichlorobenzonitrile has been used as a herbicide: H. Koopman and J. Daams, *Nature*, **186**, 89 (1960); G. E. Barnsley, *Proc. British Weed Control Conf. 5th, Brighton, 1960*, 597 (1961).

(8) J. C. Thurman, *Chem. Ind.* (London), 752 (1964).

(9) H. L. Haller and P. S. Schaffer, *J. Am. Chem. Soc.*, **55**, 4954 (1933); L. E. Smith and H. L. Haller, *ibid.*, **61**, 143 (1939).

TABLE II

2,6-F_2C_6H R COMPOUNDS PREPARED FOR PHARMACOLOGICAL STUDY

Compd	R	Mp, °C	Cryson solvent	Formula	Analyses
23	$NHCOCH_2N(CH_3)_2 \cdot HCl$	250.5–251.5	*n*-BuOH	$C_{10}H_{13}ClF_2N_2O$	C, H, Cl, N
26	$NHCOCH_2N(C_2H_5)_2 \cdot HCl$	179–180.5	Me_2CO	$C_{12}H_{17}ClF_2N_2O$	C, H, F, N
	$CH_2NH_2 \cdot HCl$	196–197	*n*-BuOH	$C_7H_5ClF_2N$	C, H, F, N
	$CH_2N(CH_3)_2 \cdot HCl$	200.5–201.5	*n*-BuOH	$C_9H_{12}ClF_2N$	C, H, F, N
30	$CH_2NHCONH_2$	148.5–149	H_2O	$C_8H_8F_2N_2O$	C, H, F, N
2	$CH_2NHC(NH_2)=NH \cdot HNO_3$	180.5–181.5	H_2O	$C_8H_{10}F_2N_4O_3$	C, H, F, N
	$CH_2N^+(CH_3)_3 \cdot I^-$	240–241	EtOH	$C_{10}H_{14}F_2IN$	C, H, F, N
	$CH_2N^+(CH_3)_2C_2H_5 \cdot I^-$	184.5–185.5	*n*-BuOH	$C_{11}H_{16}F_2IN$	C, H, F, N
	$CH_2CH_2NH_2 \cdot HCl$	164–164.5	Me_2CO	$C_8H_{10}ClF_2N$	C, H, Cl, N
33	$CH_2CH_2NHCONH_2$	125.5–126.5	H_2O	$C_9H_{10}F_2N_2O$	C, H, F, N
5	$CH_2CH_2NHC(NH_2)=NH \cdot HNO_3$	188.5–189.5	H_2O	$C_9H_{12}F_2N_4O_3$	C, H, F, N
13	$OCH_2CH_2N(CH_3)_2 \cdot HCl$	155–156	*n*-BuOH	$C_{10}H_{14}ClF_2NO$	C, H, F, N
37	$OCH_2CH_2NHCONH_2$	94.5–95.5	H_2O	$C_9H_{10}F_2N_2O_2$	C, H, F, N
9	$OCH_2CH_2NHC(NH_2)=NH \cdot HNO_3$	130.5–131.5	H_2O	$C_9H_{12}F_2N_4O_4$	C, H, F, N
17	$OCH_2CH_2N^+(CH_3)_3 \cdot I^-$	173.5–174.5	EtOH	$C_{11}H_{16}F_2INO$	C, H, F, N
20	$OCH_2CH_2N^+(CH_3)_2C_2H_5 \cdot I^-$	120	EtOH–Et_2O	$C_{12}H_{18}F_2INO$	C, H, F, N

Several methods for the conversion of an aryllithium or an aryl Grignard reagent into the corresponding phenol were tried before succeeding with the method of Hawthorne.[10] Treatment with trimethyl borate at below −50° gave the arylboronic ester which, without isolation, was hydrolyzed and oxidized to 2,6-difluorophenol (XII) in an over-all yield of 41% from 1,3-difluorobenzene.

With the intermediates now available, we were able to prepare, by routine methods, the compounds listed in Table II for pharmacological examination.

Our earliest attempts to enter this series of 2,6-difluorophenyl compounds were unsuccessful but instructive. 2,4-Dichloronitrobenzene reacts with dry KF in dimethyl sulfone at 170° to give 4-chloro-2-fluoronitrobenzene followed by 2,4-difluoronitrobenzene, with no 2-chloro-4-fluoronitrobenzene being formed.[11] According to Starr and Finger "this shows that in dimethyl sulfone the stronger *ortho* activation predominates over the steric considerations of the nitro group, and that the 2-chlorine atom is the first to be replaced."[11] We considered it possible that 2,6-dichloronitrobenzene would give 2,6-difluoronitrobenzene by this reaction. However, a series of reactions at various temperatures gave very disappointing results, maximum conversion into 2,6-difluoronitrobenzene being only a few per cent. The products of the reaction were analyzed by vapor phase chromatography, and the results (Table VI) show that the presence of a 6 substituent hinders the replacement of the 2 substituent, there being no effective *ortho* activation.

This failure can be explained if the results of Starr and Finger[11] are ascribed not to *ortho* activation, but to steric inhibition of resonance. Maximum activation of groups to nucleophilic displacement by an *o*- or *p*-nitro group requires the nitro group to be coplanar with the ring in the transition state. This is possible in the transition state for the formation of 4-chloro-2-fluoronitrobenzene since the chlorine atom has moved out of the plane of the ring. However, neither 2-chloro-4-fluoronitrobenzene (from 2,4-dichloronitrobenzene) nor 2-chloro-6-fluoronitrobenzene (from 2,6-dichloronitrobenzene) is obtained because the nitro group in both is prevented by a 2-chlorine atom from achieving coplanarity with the ring. This effect[12] explains both Starr and Finger's[11] and our own results more satisfactorily.[13]

Pharmacological Results. Adrenergic Neurone Blocking Activity.—The adrenergic neurone blocking activities of the guanidines and the aryloxyethylammonium salts were estimated[16] on the nictitating membranes of conscious and anesthetized cats. Table III shows the subcutaneous doses that cause 30% relaxation of the nictitating membranes of conscious cats, and the minimum intravenous doses that abolish the response of the cat nictitating membrane to postganglionic stimulation of the cervical sympathetic nerve.

The aralkylguanidines (**1**–**7**) are either inactive at 50 mg/kg or only weakly active on conscious cats, but they are apparently more active on anesthetized cats. This pattern is contrary to what is observed in the aryloxyethylguanidines (**8**–**11**) and aryloxyethylammonium salts (**16**–**22**) and may be due in part to the marked and sustained contraction of the nictitating membranes of anesthetized cats caused by the aralkylguanidines (particularly **1**, **4**, and **7**) completely masking the effect of electrical stimulation.

In the aryloxyethylguanidine series (**8**–**11**), the substituted are all more active than the unsubstituted compound **8**, the difluoro derivative **9** being the most active on conscious cats.

The adrenergic neurone blocking activity of the aryloxyethylammonium salts has been studied extensively, particularly on conscious cats. Compounds **17**–**19** have been tested using a cross-over technique with a group of

(10) (a) M. F. Hawthorne, *J. Org. Chem.*, **22**, 1001 (1957); T. L. Yarboro and C. Karr, *ibid.*, **24**, 1141 (1959); (b) G. M. Brooke, B. S. Furniss, W. K. R. Musgrave, and M.I. A. Quasem, *Tetrahedron Letters*, 2991 (1965), have successfully adapted this method to the preparation of penta- and tetrafluorophenols.

(11) L. D. Starr and G. C. Finger, *Chem. Ind.* (London), 1328 (1962).

(12) J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, **49**, 273 (1951).

(13) Some recent reports on the nucleophilic replacement of activated aromatic chlorine atoms are in agreement with this interpretation. 2,6-Dichloronitrobenzene does not react with azide ion or ammonia, whereas 2,6-dichloronitrosobenzene does react with azide ion[14] and 2,6-dichlorobenzonitrile can be converted into 2,6-difluorobenzonitrile,[15] there being no steric inhibition of resonance in these two examples.

(14) A. J. Boulton, P. B. Ghosh, and A. R. Katritzky, *J. Chem. Soc., B*, 1004 (1966).

(15) (a) G. C. Finger, D. R. Dickerson, T. Adl, and T. Hodgins, *Chem. Commun.*, 430 (1965); (b) R. Battershell, 3rd International Symposium on Fluorine Chemistry, Munich, 1965.

(16) R. Fielden, A. M. Roe, and G. L. Willey, *Brit. J. Pharmacol.*, **23**, 486 (1964).

Table III

Adrenergic Neurone Blocking Activity

Compd	mg/kg[a]	mg/kg[b]
1	*c*	25
2	50	10
3	25	5
4	*c*	10
5	25	5
6	50	10
7	*c*	5
8	*c*	10
9	5	5
10	>10	5
11	10	5
16	*d*	*d*
17	4.5[e]	5
18	2	2
19	3.5	5
20	2.5	10
21	2.5	10
22	10	25

[a] Subcutaneous dose that causes 30% relaxation of the nictitating membranes of conscious cats, measured at time of peak action (5 hr). [b] Minimum intravenous dose that abolishes the response of the cat nictitating membrane to postganglionic stimulation of the cervical sympathetic nerve (50 pulses/sec, 0.5 msec). [c] No relaxation following injection of 50 mg/kg. [d] Nicotine-like stimulant compound. [e] After 24 hr.

six conscious cats. The order of activity is **18** > **19** > **17**. Compound **16** shows marked nicotine-like stimulant activity;[17] very weak blocking activity can, however, be demonstrated in the anesthetized cat when pretreated with hexamethonium bromide.

The time of maximum effect and the duration of effectiveness of equiactive doses in conscious cats show clear differences. Compounds **18** and **19** have a similar onset and duration, peak action occurring at 5 hr and all effects disappearing within 48 hr. On the other hand, **17** exhibits peak action at 24 hr, relaxation being still apparent after 72 hr.

Compounds **20**–**22** are less active than their N-trimethyl analogs (**17**–**19**) on the anesthetized cat. However, **20** and **21** show a similar order of activity to that of the N-trimethyl compounds on conscious cats, an effect which is not accounted for by ganglion blocking activity.

Local Anesthetic Activity.—The local anesthetic activities of the lidocaine analogs (**23**–**28**), the aryloxyethylamines (**12**–**15**), and their quaternary salts (**16**–**22**) were assessed by the Bülbring and Wajda technique.[18] Table IV shows the concentrations that cause a mean anesthetic effect of 50% over a 30-min period and also shows the per cent anesthesia produced by these equieffective concentrations at intervals after injection.

Lidocaine (**28**) is twice as potent as the next most potent analog, the order of activity being **28** >> **26** > **27** > **25**. However, with the dimethylamino compounds, the dichloro (**24**) is more active than the difluoro compound (**23**). All these compounds cause rapid onset of anesthesia, but equieffective doses of **12**–**15** cause more prolonged effects. Compound **14**[19] is the most active; **15** is slightly less potent and its duration of action is shorter. Compounds **12** and **13** are much less potent still and even shorter acting.

Table IV

Local Anesthetic Activity

Compd	Equieffective concn,[a] g/100 ml	% anesthesia: Time after injection of equieffective concn, min 10	30	60	120	180	240	300	360
23	3.2	69	22	0					
24	1.2	64	21	0					
25	1.6	86	19	0					
26	1.0	78	3	0					
27	1.3	88	11	0					
28	0.5	80	6	0					
12	0.59	64	28	7	0				
13	0.53	54	30	6	0				
14	0.06	50	44	35	3	0			
15	0.07	55	36	17	0				
16	*b*	*b*							
17	3.4	40	64	61	36	19	14	7	6
18	0.33	36	64	60	53	35	28	22	11
19	0.76	39	68	69	44	28	11	8	4
20	3.3	39	58	55	44	27	16	4	0
21	0.27	42	69	67	42	35	4	0	
22	0.47	35	67	73	44	35	13	8	0

[a] Estimated by the method of Bülbring and Wajda.[18] [b] See Discussion.

The quaternary salts (**17**–**22**) have the same relative potencies as the related aryloxyethyldimethylamines (**13**–**15**). The concentration of **16** required to cause 50% anesthesia could not be estimated owing to its high nicotinic activity. However, intradermal injection of a 2% solution of **16** causes slight local anesthesia which is less than that produced by a 2% solution of **17**. The maximal anesthetic effects of all the quaternary salts are apparent 30–60 min after injection; the duration of the effect is much more prolonged than with the tertiary bases (**12**–**15** and **23**–**28**), the most prolonged being the trimethylammonium salts (**17**–**19**).

Nicotinic Activity.—The nicotinic activity of the trimethylammonium salts (**16**–**19**) was estimated on atropine-treated (2 mg/kg, ip) spinal cats using a 2 + 1 assay technique. Two doses of the standard (**16**)[17] were followed by a single dose of the test drug, and the activity was estimated by interpolation. Nicotine-like activity was confirmed by the abolition of the response with hexamethonium bromide. Compound **16** is the most active; the activities of the other drugs relative to **16** (activity = 1.0) are **17** = 0.026, **18** = 0.002, and **19** = 0.001.[20]

The Effect of Substituted Ureas on Conscious Mice.—As part of a wider (unpublished) investigation into the behavioral pharmacology of substituted ureas, the compounds shown in Table V were examined. Estimates of the LD_{50} and of the dose that caused depression of motor activity in 50% of the mice (DD_{50}) were made from dose-range studies. All these compounds inhibit polysynaptic reflexes (indicated by the abolition of the pinnal reflex) at doses lower than those that inhibit monosynaptic reflexes (corneal reflex); see Table V.

Benzylurea (**29**) and its substituted derivatives (**30** and **31**) abolish the pinnal reflex only at doses much

(17) (a) P. Hey, *Brit. J. Pharmacol.*, **7**, 117 (1952); (b) M. E. Coleman, A. H. Haine, and W. C. Holland, *J. Pharmacol. Exptl. Therap.*, **148**, 66 (1965).

(18) E. Bülbring and I. Wajda., *ibid.*, **85**, 78 (1945).

(19) P. Hey and G. L. Willey, *Nature*, **198**, 390 (1963).

(20) When pure, **19** does not show the nicotinic pressor activity that was originally reported.[17a] The impurity responsible for that activity has been clearly identified by E. R. Clark and M. deL. S. A. Jana, *Brit. J. Pharmacol.*, **27**, 135 (1966), as 1–2% of the 2-tolyloxy analog.

TABLE V
ED_{50} OF SUBSTITUTED UREAS FROM MOUSE DOSE-RANGE STUDY

		ED_{50}, mg/kg po		
Compd	LD_{50}, mg/kg	Motor depression	Abolition of corneal reflex	Abolition of pinnal reflex
29	570	60	1430	180
30	>1600	110	1800	480
31	>3200	140	>3200	900
32	2260	110	1130	450
33	710	55	280	90
34	110	5	70	20
35	1425	60	570	90
36	>3200	90	2690	565
37	>3200	140	1400	350
38	1800	90	900	280
39	>3200	360	3200	350

higher than those that cause motor depression. The substituted arylethylureas (**33–35**) are more active than the substituted benzylureas and abolish the pinnal reflex at doses of the same order as those that cause motor depression. However, the difluoro compound (**33**) does not show the same degree of selectivity for polysynaptic reflexes as the dimethyl compound (**35**); a similar reduction in selectivity is also seen in the benzyl- (**30** and **31**) and in the aryloxyethylureas (**37** and **39**).

Discussion

The effect that the presence of halogen atoms, and in particular fluorine atoms, has on the pharmacological properties of a molecule has been discussed[21] and broadly categorized into the effects due to the lability of the halogen, primary steric effects, electronic effects, and obstructive steric effects. The unique position of fluorine is due to its size and electronic properties and is well documented.[22]

Although the extent of the present work is not sufficient to define those constitutional factors that are determining maximum activity in the tests studied, some comments may be made.

The activities (but not the duration of action) of the quaternary ammonium compounds lie in the same order for adrenergic neurone blockade as for local anesthesia, that is **18** > **19** > **17** > **16**. This would seem to support the original view[23] that the activity of these adrenergic neurone blocking drugs derives from their anesthetic effect; alternatively, both responses may be the result of a similar physicochemical effect.[23] Whatever the mode of action, the primary steric effect would appear to be predominant in these quaternary compounds and also in the related tertiary amines, since the activities of the methyl and the chloro compounds are of the same order.

Clark and Williams[24] have suggested that nicotine-like stimulant activity of the aryloxyethylammonium salts is observed when the benzene ring, the ether oxygen, and the adjacent methylene group are capable of lying in the same plane. Although this suggestion was mainly based on an examination of certain cyclic ethers, the present work would appear to support this view, since **18** and **19** have very low nicotine-like activity and are the most sterically hindered, whereas **17** has an activity intermediate between **18** or **19** and the most active compound (**16**), which can take up a planar conformation.

We are not suggesting that a steric effect is the only one operating in substituted aryloxyethylammonium salts; the results of Hey[17a] and others[25] demonstrate that the electronic nature of substituents *meta* and *para* to the side chain have a significant effect on the biological activity.

Finally, we must record the nicotine-like stimulant activity of 2,3-dihydrobenzofuran-3-yl trimethylammonium iodide[16] which has the criteria for high activity suggested by Clark and Williams[24] but in fact is only 0.035 times as active as **16**.

Experimental Section[26]

2,6-Difluorobenzoic Acid (II).—A solution of *n*-BuLi in THF (210 ml, 1.25 *M*, 0.262 mole) was added during 0.5 hr to a stirred solution of 1,3-difluorobenzene (30.9 g, 0.27 mole) in dry THF (200 ml) which was maintained at below −50° and protected from moisture by dry N_2. The mixture was kept under these conditions for a further 2–5 hr and then poured into a slurry of dry Et_2O and solid CO_2. The resulting suspension was extracted with 2 *N* KOH and the extract was acidified with 2 *N* HCl. The acid was collected and crystallized from H_2O (34.7 g, 84%), mp 159–160°. Thomas and Cauty[2] record mp 155–156°.

2,6-Difluorobenzoyl chloride (V), bp 76–79° (15 mm), was prepared from the acid with $SOCl_2$ in the usual way. Methanolysis gave **methyl 2,6-difluorobenzoate,** bp 90–91° (15 mm). *Anal.* ($C_8H_6F_2O_2$) C, H, F.

Ethanolysis of the acid chloride gave **ethyl 2,6-difluorobenzoate,** bp 99.5–102° (15 mm). *Anal.* ($C_9H_8F_2O_2$) C, H, F.

Ammonolysis of the acid chloride gave **2,6-difluorobenzamide (VIII),** which crystallized from C_6H_6 in needles, mp 144.5–145.5°. *Anal.* ($C_7H_5F_2NO$) C, H, F, N.

2,6-Difluorobenzaldehyde (III).—*n*-BuLi in heptane (130 ml, 2.8 *M*, 0.364 mole) was added to a stirred solution of 1,3-difluorobenzene (40.0 g, 0.35 mole) in dry THF (300 ml) maintained at −50° and protected from moisture. After 1.5 hr at −50°, *N*-methylformanilide (47.3 g, 0.35 mole) in dry THF (100 ml) was added during 20 min and the mixture was stirred at −50° for 1.5 hr more. The mixture was poured into dilute H_2SO_4 and ice, and the aldehyde was collected in Et_2O and distilled at 85–87° (20 mm) (35.5 g, 71%). Lock, *et al.*,[27] record bp 82–84° (15 mm).

2,6-Difluorobenzaldoxime separated from H_2O in needles, mp 114.5–115°. *Anal.* ($C_7H_5F_2NO$) C, H, F, N.

2,6-Difluoroacetophenone (IV). (**a**) 1,3-Difluorobenzene (25.0 g, 0.22 mole) was converted into a solution of 2,6-difluorophenyllithium in a mixture of THF (275 ml) and heptane (105 ml). This solution was treated at below −50° with AcCl (17.7 g, 0.226 mole) in THF (75 ml). After initial darkening, the clear orange solution was kept below −50° for 1.5 hr and then poured into dilute H_2SO_4 and ice. The organic phase was separated and washed with dilute NaOH and 10% aqueous NaCl. The dried solution was evaporated and the acetophenone was twice distilled to give a colorless liquid, bp 76–79° (15 mm) (2.3 g, 6.7%). *Anal.* ($C_8H_6F_2O$) C, H, F.

(**b**) 2,6-Difluorobenzoyl chloride (8.50 g, 0.048 mole) was treated with diethyl ethoxymagnesiomalonate (0.044 mole); the reaction was carried out as described by Walker and Hauser[6] and 2,6-difluoroacetophenone (5.51 g, 73%) was obtained.

(21) M. B. Chenoweth and L. P. McCarey, *Pharm. Rev.*, **15**, 673 (1963).
(22) *E.g.*, N. P. Buu-Hoi, *Progr. Drug Res.*, **3**, 5 (1961).
(23) P. Hey and G. L. Willey, *Brit. J. Pharmacol.*, **9**, 171 (1954).
(24) E. R. Clark, P. M. Dawes, and S. G. Williams, Communication, British Pharmacological Society Meeting, July 1964; E. R. Clark and S. G. Williams, *J. Chem. Soc., B*, 859 (1967).
(25) A. A. Sokol and W. C. Holland, *J. Pharmacol. Exptl. Therap.*, **133**, 313 (1961).
(26) Melting points (determined in capillary tubes in a gas-heated block) were corrected by use of a calibrated thermometer. *n*-BuLi was prepared in THF [H. Gilman and B. J. Gaj, *J. Org. Chem.*, **22**, 1165 (1957)] or in hexane or heptane (purchased from Pfizer Ltd., Sandwich, Kent). Microanalyses of the elements indicated were within 0.4% of the theoretical values and were carried out by A. Bernhardt (Mülheim). The nmr spectra of many of these compounds have been studied by R. J. Abraham, D. B. Macdonald, and E. S. Pepper, *Chem. Commun.*, 542 (1966); *J. Chem. Soc., B*, 835 (1967).
(27) G. Lock, E. Stoits, and H. Gassner, *Ber.*, **69B**, 2253 (1936).

2,6-Difluoroacetophenone oxime separated from petroleum ether (bp 60–80°) as colorless needles, mp 94.5–95.5°. *Anal.* ($C_8H_7F_2NO$) C, H, F, N.

2,6-Difluorobenzyl alcohol (VI), bp 88° (14 mm), was obtained (70%) from 2,6-difluorobenzaldehyde with $LiAlH_4$ in refluxing Et_2O for 6 hr. The **3,5-dinitrobenzoate** was crystallized from EtOH and had mp 168.5–169°. *Anal.* ($C_{14}H_8F_2N_2O_6$) C, H, F, N.

2,6-Difluoroiodobenzene (VII).—1,3-Difluorobenzene (5.0 g, 0.044 mole) in THF (50 ml) was converted into 2,6-difluorophenyllithium in the usual way. Iodine (5.8 g, 0.023 mole) in THF (75 ml) was added and the mixture was stirred below −50° for 1.5 hr. Isolation of the neutral liquid gave 4.53 g (43%) of VII, bp 70.5–71° (14 mm), mp 22.5–25.5°. *Anal.* ($C_6H_3F_2I$) C, H, F, I.

The same iodo compound was obtained (28%) when KI was added to an aqueous solution of 2,6-difluorophenyldiazonium chloride.

2,6-Difluorobenzonitrile (IX).—$SOCl_2$ (12.0 g, 0.1 mole) in DMF (20 ml) was added dropwise to 2,6-difluorobenzamide (7.06 g, 0.045 mole) in DMF (30 ml). The temperature rose and the mixture was kept at 80° for 0.5 hr. After pouring the mixture onto ice, the solid was collected in Et_2O, washed with 10% aqueous NaCl, dried ($MgSO_4$), and distilled to give the nitrile (5.63 g, 90%), bp 81–83° (13 mm), which solidified and separated from petroleum ether (bp 40–60°) in plates, mp 29–30°.[28] *Anal.* ($C_7H_3F_2N$) C, H, F, N.

N-Formyl-2,6-difluorobenzamide (X).—$SOCl_2$ (5.8 g, 0.049 mole) was slowly added to 2,6-difluorobenzamide (7.57 g, 0.049 mole) in DMF (25 ml) which was stirred at 0°. After 2 hr at 0°, the mixture was kept at room temperature for 8 days, when a portion was withdrawn and shown (ir) not to contain nitrile. The reaction mixture was then heated at 100° for 1 hr, cooled, and poured onto ice. The resulting solid was dissolved in $CHCl_3$, washed with dilute Na_2CO_3, and dried (Na_2SO_4). Evaporation gave X (4.08 g, 46%), mp 109–129°, unchanged after several recrystallizations from petroleum ether (bp 80–100°); ν_{max} (Nujol) 1625, 1656, 1688, and 1732 cm^{-1}. *Anal.* ($C_8H_5F_2NO_2$) C, H, F, N. N-Formylbenzamide itself has ν_{max} (Nujol) 1672, 1692, and 1729 cm^{-1}.

Treatment of the foregoing compound with phenylhydrazine in 30% AcOH gave **3-(2,6-difluorophenyl)-2-phenyl-1,2,4-triazole**, mp 92–93.5° after crystallization from petroleum ether (bp 60–80°). Its ir spectrum was similar to that of 2,3-diphenyl-1,2,4-triazole. *Anal.* ($C_{14}H_9F_2N_3$) C, H, F, N.

2,6-Difluoroaniline (XI).—2,6-Difluorobenzoic acid (19.9 g, 0.125 mole) was stirred in concentrated H_2SO_4 (65 ml) at 60° for 1.5 hr. NaN_3 (10.0 g, 0.154 mole) was added in small portions while the temperature was kept at 65°. The mixture was then stirred at room temperature for 42 hr. After cooling to 0° and basification with concentrated NH_4OH, Et_2O extraction afforded XI (14.0 g, 86%), bp 51–52° (15 mm), $n^{27.5}D$ 1.5040. *Anal.* ($C_6H_5F_2N$) C, H, F, N.

2,6-Difluoroacetanilide separated from 50% aqueous EtOH in needles, mp 144.5–146.5°.[29] *Anal.* ($C_8H_7F_2NO$) C, H, N.

2,6-Difluorophenyldiazonium Fluoroborate.—2,6-Difluoroaniline (12 g, 0.093 mole), dissolved in 42% fluoroboric acid (40 ml), was stirred at about 5°. Finely powdered $NaNO_2$ (10.0 g, 0.145 mole) was added in small portions and the mixture was stirred at 5° for a further hour. The solid was colle ted and washed with cold 5% fluoroboric acid, followed by Me_2CO–Et_2O (2:3). The dried (H_2SO_4 *in vacuo*) solid (19.5 g, 92%) decomposed at about 167°.

A portion was crystallized from Me_2CO–Et_2O and decomposed at about 180°. *Anal.* ($C_6H_3BF_6N_2$) C, H, B, F, N.

2,6-Difluoronitrobenzene (XIII).—The foregoing diazonium salt (7.73 g, 0.034 mole) was slowly added to a stirred mixture of $NaNO_2$ (58.5 g, 0.85 mole) and Cu powder (11.8 g, 0.186 g-atom) in H_2O (125 ml). After a further 0.5 hr at room temperature the mixture was acidified (H_2SO_4) and extracted with Et_2O. Distillation gave the nitrobenzene (1.88 g, 35%), bp 91–92° (11 mm), which solidified on cooling to 0°. *Anal.* ($C_6H_3F_2NO_2$) C, H, F, N.

2,6,2′,6′-Tetrafluoroazoxybenzene was the only compound isolated when 2,6-difluoroaniline was oxidized by the method that converts 2,6-dichloroaniline into 2,6-dichloronitrobenzene (see below). After crystallization from petroleum ether (bp 40–60°) and sublimation at 70° (0.1 mm) it had mp 88.5–90.5°. *Anal.* ($C_{12}H_6F_4N_2O$) C, H, F, N.

Table VI

Vpc Analysis of the Reaction of 2,4-Dichloronitrobenzene with Potassium Fluoride. Retention Times and Estimated Weights of Products[a]

Temp, °C	153–158	153–158	204–212	204–212
Reaction time, hr	6	23	6[b]	23[c]
Retention time, min (wt, g)	4.3 (1.5)	4.3 (1.5)	4.3 (1.0)	4.5 (0.05)
			3.2 (0.09)[d]	
			2.6 (0.07)	2.5 (0.13)

[a] Measured on Autoprep A 700, SE30 column at 272–275°, injection temperature 323–326°, He flow rate 200 cc/min; the retention time of 2,6-dichloronitrobenzene is 4.2 min and the retention time of 2,6-difluoronitrobenzene is 2.4 min. [b] Slight charring occurred. [c] Considerable charring occurred. [d] The identity of this material is not proven, but presumably it is 2-chloro-6-fluoronitrobenzene.

2,6-Difluorophenol (XII).—1,3-Difluorobenzene (25.0 g, 0.22 mole) in THF (200 ml) was converted into 2,6-difluorophenyllithium in the usual way and poured into trimethyl borate (23.0 g, 0.22 mole) in dry THF (200 ml) at −50°. The reaction was kept at −50° for 2 hr and then at room temperature for 48 hr. The gum obtained on evaporation under reduced pressure was dissolved in C_6H_6 (250 ml) and treated with 5 *N* HCl until the aqueous layer remained acidic on shaking. The C_6H_6 layer was separated, washed twice with 10% aqueous NaCl, and concentrated to about 150 ml. While being heated under reflux the solution was treated with 30% H_2O_2 (50 ml) during 30 min, and heating under reflux was continued for 2 hr. The cooled solution was washed successively with H_2O, 10% acidified $FeSO_4$, and H_2O. The phenol was extracted into 5 *N* NaOH, liberated with concentrated HCl at 0°, and extracted into Et_2O. Distillation of the dried ($MgSO_4$) solution gave 11.55 g (41%), bp 59–61° (17 mm), mp 42°. Finger, *et al.*,[3] record mp 46°.

Table II lists the compounds prepared for pharmacological study. **2,6-Difluorobenzylamine** (XV) was obtained from the benzaldoxime (see above), and the **arylethylamine** (XVI) from the β-nitrostyrene (which was not characterized) both by reduction with $LiAlH_4$ in refluxing Et_2O. The **aryloxyethylamine** (XVII, R = H) was obtained from the aryloxyacetonitrile by reduction with $LiAlH_4$ in Et_2O at 0°; **N,N-dimethyl-2-(2,6-difluorophenoxy)ethylamine** (XVII, R = CH_3) was obtained from the phenol and 2-dimethylaminoethyl chloride directly. In addition, the following intermediates were characterized.

N-(2,6-Difluorophenyl)chloroacetamide crystallized from petroleum ether (bp 60–80°), mp 141–142°. *Anal.* ($C_8H_6ClF_2NO$) C, H, F.

2-(2,6-Difluorophenoxy)ethylamine (XVII, R = H) **hydrochloride** crystallized from nitropropane, mp 111.5–112.5°. *Anal.* ($C_8H_{10}ClF_2NO$) C, H, Cl, F N.

2,6-Dichloronitrobenzene.[30]—A solution of 2,6-dichloroaniline (40 g, 0.247 mole), 30% H_2O_2 (300 ml), concentrated H_2SO_4 (20 ml), and glacial AcOH (1 l.) was heated for 3 hr on the steam bath. More 30% H_2O_2 (150 ml) and glacial AcOH (500 ml) were added to the deep amber solution, which was then kept on the steam bath for 20 hr. The cooled solution was poured into H_2O (8 l.) and the yellow solid was collected. Crystallization from cyclohexane gave the nitro compound (20.4 g, 43%), mp 70.5–71.5° (lit.[14] mp 70°).

Reaction of 2,6-Dichloronitrobenzene with Potassium Fluoride.—2,6-Dichloronitrobenzene (2.0 g, 0.0104 mole) and anhydrous KF (2.4 g, 0.0414 mole) were heated with dimethyl sulfone (4.0 g). The resulting mixture was diluted with H_2O (50 ml) and extracted with Et_2O. The dried ($MgSO_4$) solution was evaporated, and the residue was warmed with a measured volume of cyclohexane and filtered. This solution was applied to a vapor phase chromatograph; the amount of each product (see Table VI) was estimated by comparison with standard solutions of 2,6-dichloro- and 2,6-difluoronitrobenzene.

Acknowledgments.—We thank Dr. P. Hey, Dr. A. L. Green, and Dr. G. J. Durant for some of the compounds used in this study.

(28) This nitrile has previously been described as a liquid, bp 99° (20 mm).[15a]

(29) N. Ishikawa, M. J. Namkung, and T. L. Fletcher, *J. Org. Chem.*, **30**, 3878 (1965), prepared this anilide, mp 144.5–145°, by a circuitous route from 2,4-difluoroaniline.

(30) This oxidation has recently been carried out in two stages by isolating 2,6-dichloronitrosobenzene, in an over-all yield of 71%.[14]