as these, a whole spectrum of values will be found. Their magnitudes will depend on which part of the Hammett plot is used in estimating rho. Thus the tentative values for electrophilic reactions proposed by Pearson, *et al.*,[13] on the basis of data on the Beckmann rearrangement of acetophenone are not applicable to nitration or brominolysis of areneboronic acids, nor are they entirely satisfactory for the pinacol rearrangement.

Experimental

All melting points are uncorrected.

Analyses were performed by Dr. Carl Tiedcke and by the Galbraith Laboratories.

***p*-Iodobenzeneboronic Acid.**—The preparation of the *p*-iodo acid has not been described in the literature. *p*-Diiodobenzene was prepared by iodination of iodobenzene.[14] This compound was converted to the monomagnesium iodide and added to butyl borate; the product was hydrolyzed to give the acid.

To 5.4 g. (0.22 mole) of magnesium turnings in 50 ml. of dry anisole was added dropwise a solution of 73.2 g. (0.22 mole) of *p*-diiodobenzene in 175 ml. of dry anisole. This solution was kept warm to prevent separation of the diiodobenzene. Ethyl iodide was added to start the reaction. As the reaction proceeded the reaction mixture became dark brown. After the diiodobenzene had all been added and evolution of heat had ceased, stirring was continued for a half hour whence only a small amount of magnesium remained.

This solution was added dropwise to 75 ml. (0.28 mole) of butyl borate in 175 ml. of dry ether cooled in a Dry Ice–acetone bath. After warming to room temperature overnight the reaction mixture was poured on 135 g. of ice and 7 ml. of concd. sulfuric acid. The resulting layers were separated and the water layer extracted with three 50-ml. portions of ether. These were combined with the original extract and extracted with four 50-ml. portions of 10% sodium hydroxide. These latter were combined and acidified with sulfuric acid, yielding a brown resinous material and white solid which were filtered off and extracted with portions of hot dilute sulfuric acid until a precipitate no longer appeared in the extract on cooling. The combined precipitates were tan in color, 9.8 g. Crystallization from benzene and twice from water (treated with Norite) yielded white needles of the acid which after drying at 110° for three hours yielded the anhydride, 3.2 g., 6.3% yield, m.p. 314–318°.

Anal. Calcd. for C_6H_4BIO: C, 31.36; H, 1.75; I, 55.26; neut. equiv., 229.8. Found: C, 31.27, 31.41; H, 1.74, 1.78; I, 55.19, 55.31; neut. equiv., 229.4.

***m*-Iodobenzeneboronic Acid.**—Direct iodination of benzeneboronic acid in sulfuric acid with silver sulfate as a promoter[15] could not be used because of hydrolytic cleavage to yield benzene and boric acid. A procedure involving the reaction of the diazonium salt from *m*-aminobenzeneboronic acid with iodide also proved to be unsuccessful.

The method which was successful[16] started with *m*-phenylenediamine which was tetrazotized and converted to *m*-diiodobenzene in 75% yield. A 40% excess of potassium iodide over that necessary for the formation of *m*-diiodobenzene was used in order to ensure destruction of any excess nitrite. When urea or stannous chloride was used excessive foaming occurred and yields were negligible. Using the same procedure as for *p*-iodobenzeneboronic acid a yield of 5.1% of the *m*-iodo acid was obtained; m.p. 186.5–187.5° (anhydride).

Anal. Calcd. for C_6H_4BOI: neut. equiv., 229.8; I, 55.24. Found: neut. equiv., 227.9; I, 54.84.

The other boronic acids used have been prepared previously and characteristics of the samples in this investigation are listed in Table II.

TABLE II

SUBSTITUTED BENZENEBORONIC ANHYDRIDES[a]

Substituent	M.p., °C. This paper	M.p., °C. Lit.[c]	Neut. equiv. Obsd.	Neut. equiv. Calcd.
p-F	265–266	289–290[d]	121.1	121.9
p-C_6H_5	231–232	232–234[e]	180.6	182.6
m-Br	172.5–175.5	170[d]	182.6	182.6
m-F	211.5–213.5	220–221[d]	121.8	121.9
m-OCH_3	158.5–159.5	147[f]	134.4	134.0

[a] Acids dried to constant weight at 110°. [b] Uncorrected. [c] Corrected. [d] B. Bettman, G. E. K. Branch and D. L. Yabroff, THIS JOURNAL, **56**, 1865 (1934). [e] D. L. Yabroff and G. E. K. Branch, *ibid.*, **56**, 1850 (1934). [f] W. Konig and W. Scharrnbeck, *J. prakt. Chem.*, **128**, 153 (1930); *C. A.*, **25**, 927 (1931).

The kinetic procedure was as previously described.[4]

DURHAM, N. H.

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[13] D. E. Pearson, J. F. Baxter and J. C. Martin, *J. Org. Chem.*, **17**, 1511 (1952).

[14] R. L. Datta and N. R. Chatterjee, THIS JOURNAL, **41**, 293 (1919).

[15] D. H. Derbyshire and W. A. Waters, *J. Chem. Soc.*, 3694 (1950).

[16] K. H. Saunders, "The Aromatic Diazo Compounds and Their Technical Applications," Edward Arnold and Co., London, 1949, p. 25.

[CONTRIBUTION NO. 97 FROM THE CENTRAL RESEARCH DEPARTMENT, MINNESOTA MINING AND MANUFACTURING CO.]

The Chemistry of Perfluoro Ethers. I. Substitution of α-Fluorine by Chlorine: The α,α,α'-Trichloro Perfluoro Ethers[1]

BY GEORGE VAN DYKE TIERS

RECEIVED FEBRUARY 23, 1955

The first chemical reaction of perfluoro ethers is reported. Selective substitution of the α-fluorine atoms by chlorine has been achieved, using aluminum chloride as the exchange agent. Perfluorotetrahydrofurans and tetrahydropyrans bearing a single perfluoroalkyl substituent in the α-position are converted to their α,α,α'-trichloro analogs in good yield. Physical properties are reported for the compounds prepared. Synthesis of a perhalo lactone is described.

Perfluoro ethers are thermally and chemically very stable; indeed, chemical reactions have not hitherto been reported.[2] However, researches carried out in this Laboratory have indicated slight but definite activation of the α-fluorine atoms. This communication describes the reaction of aluminum chloride with members of a class of cyclic perfluoro ethers bearing a single perfluoroalkyl substituent in the α-position.[3,4]

The use of aluminum chloride to replace fluorine

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[1] Presented at the 126th Annual Meeting of the American Chemical Society, New York, 1954; Abstracts, p. 27M.

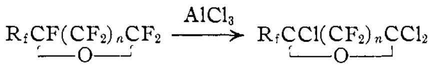
[2] (a) W. H. Pearlson in J. H. Simons, "Fluorine Chemistry," Academic Press, Inc., New York, N. Y., 1950, p. 489; (b) R. N. Haszeldine and A. G. Sharpe. "Fluorine and Its Compounds," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 144.

[3] T. J. Brice and R. I. Coon, THIS JOURNAL, **75**, 2912 (1953).

[4] E. A. Kauck and J. H. Simons, U. S. Patent 2,644,823, July 7, 1953.

by chlorine has been reported previously. Chlorofluorocarbons[5] and even CF_4[6] undergo substitution, the former at 50–80° and the latter at 190–260°.

The perfluoro ethers used in this research undergo selective reaction with aluminum chloride, the three α-fluorine atoms being replaced by chlorine. The corresponding cyclic α,α,α′-trichloro perfluoro ethers are obtained in good yield. The reaction is illustrated by the following equation, in which R_f represents a perfluoroalkyl group and n is 2 or 3.



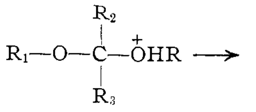
$$R_f\underbrace{CF(CF_2)_nCF_2}_{O} \xrightarrow{AlCl_3} R_f\underbrace{CCl(CF_2)_nCCl_2}_{O}$$

For this reaction pressure equipment is necessary, as temperatures of 150 to 200° are required. Best yields were obtained with a 50% excess of aluminum chloride. The use of excessive quantities of aluminum chloride or too-high temperatures leads to extensive decomposition of the product. Low temperatures and short reaction times lower the conversions but do not improve the yields above 60%. The remaining material has not been accounted for completely: some aluminum fluoride and carbonized tars are formed, and distillation residues amount to 3 to 10%.

One of the more important decomposition products is hexachloroethane. It has been isolated from each of the reaction mixtures, roughly 5 g. being formed per 100 g. of perfluoro ether. In no case has carbon tetrachloride been detected, despite infrared analyses of each fraction from the distillations of the reaction products.

Monochloro or dichloro fluoro ethers, if present, should have been isolated during these distillations. No such materials were detected even when reactions were stopped at low conversion. It follows that these compounds, which probably are actual reaction intermediates, must react appreciably more rapidly than does the perfluoro ether itself. There is no evidence for preferential reaction among isomeric perfluoro ether constituents: unreacted ethers recovered from the reaction mixture were unchanged in refractive index or in infrared spectrum.

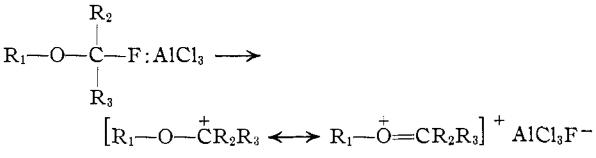
Both the selectivity in fluorine replacement at the α-position and the need for a strong Lewis acid suggest a mechanism analogous to that for the acid-catalyzed hydrolysis of acetals.[7] In the latter case the rate-determining step is considered to be dissociation of the conjugate acid (formed by addition of a proton).



$$R_1\text{—}O\text{—}\overset{R_2}{\underset{R_3}{C}}\text{—}\overset{+}{O}HR \longrightarrow [R_1\text{—}O\text{—}\overset{+}{C}R_2R_3 \longleftrightarrow R_1\text{—}\overset{+}{O}{=}CR_2R_3]^+ + ROH$$

Elimination of the alcohol is facilitated by resonance stabilization of the resulting cation. This mechanism provides an explanation for the tremendous increases in rate of hydrolysis found when R_2 and R_3 are alkyl groups instead of hydrogen.[7]

A formally similar mechanism may be written for fluorine–chlorine interchange in the perfluoro ethers, if the proton is replaced by the Lewis acid $AlCl_3$.

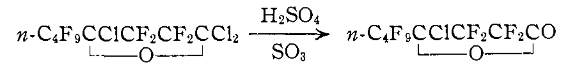


$$R_1\text{—}O\text{—}\overset{R_2}{\underset{R_3}{C}}\text{—}F{:}AlCl_3 \longrightarrow [R_1\text{—}O\text{—}\overset{+}{C}R_2R_3 \longleftrightarrow R_1\text{—}\overset{+}{O}{=}CR_2R_3]^+\ AlCl_3F^-$$

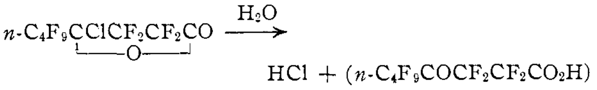
Exchange is completed by capture of chloride ion from the $AlCl_3F^-$ anion.[8] Attack by $AlCl_3$ is considered to be upon the fluorine atom, with carbonium–oxonium resonance of the resulting cation facilitating its removal.[9]

If R_2 and R_3 were powerful electron-attracting perfluoroalkyl groups or fluorine atoms, rather than hydrogen or alkyl groups, a very large decrease in ease of formation of the positive ion (and hence in rate of reaction) would be expected. This provides an attractive explanation for the extremely low reactivity of the perfluoro ethers.

This argument implies that the α,α,α′-trichloro perfluoro ethers should be somewhat more reactive toward strongly acidic reagents than are the perfluoro ethers, since chlorine is less electronegative than fluorine. Such is indeed the case: although without effect upon a perfluoro ether, hot fuming sulfuric acid slowly solvolyzed the corresponding trichloro perfluoro ether. The solvolysis product is shown to be a perfluoro-type lactone by the appearance of a single, sharp, intense infrared band at 5.34 μ.[10] The only other simple carbonyl band found at this extremely short wave length is that due to acyl fluorides.[11] This possibility is excluded at once by the observation that aqueous hydrolysis yields one chloride ion per molecule, but no fluoride at all. By these solvolytic reactions, it is firmly established that the three chlorine atoms are located in the α-positions of the trichloro perfluoro ether.



$$n\text{-}C_4F_9\underbrace{CClCF_2CF_2CCl_2}_{O} \xrightarrow[SO_3]{H_2SO_4} n\text{-}C_4F_9\underbrace{CClCF_2CF_2CO}_{O}$$



$$n\text{-}C_4F_9\underbrace{CClCF_2CF_2CO}_{O} \xrightarrow{H_2O} HCl + (n\text{-}C_4F_9COCF_2CF_2CO_2H)$$

The cyclic α,α,α′-trichloro perfluoro ethers show good chemical and thermal stability. However,

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[5] (a) A. L. Henne and M. S. Newman, THIS JOURNAL, **60**, 1697 (1938); (b) W. T. Miller, Jr., *ibid.*, **62**, 993 (1940); (c) W. T. Miller, Jr., E. W. Fager and P. H. Griswold, *ibid.*, **72**, 705 (1950).

[6] W. C. Schumb and D. W. Breck, *ibid.*, **74**, 1754 (1952).

[7] C. K. Ingold, "Structure and Mechanism in Organic Chemistry," Cornell University Press, Ithaca, N. Y., 1953, pp. 333–335.

[8] Radiochemical evidence has been presented[5c] which suggests the formation of such a reversible, metastable complex between $AlCl_3$ and fluoride ion.

[9] Attack upon the oxygen atom necessarily would exclude the oxonium resonance form for the cation, and would lead to cleavage with ultimate formation of an acyl chloride (or ketone). Only traces of such reactive material, insufficient for identification, were found.

[10] M. Hauptschein and A. V. Grosse, THIS JOURNAL, **74**, 1974 (1952), reported that perfluorobutyrolactone has an intense infrared band (due to carbonyl) at 5.34 μ, rather than 5.5 to 5.7 μ as is found for non-halogenated lactones.

[11] R. N. Haszeldine, *Nature*, **168**, 1028 (1951), and R. E. Kagarise, THIS JOURNAL, **77**, 1377 (1955), listed 5.30 to 5.43 μ as the characteristic wave length range for acyl fluorides. Although acid anhydrides have a strong band at 5.30 to 5.45 μ, an equally intense band invariably appears at 5.50 to 5.70 μ due to vibrational coupling between the two carbonyl groups.

TABLE I

ANALYTICAL DATA, PHYSICAL PROPERTIES, AND YIELDS OF THE α,α,α'-TRICHLORO FLUORO ETHERS

Trichloro fluoro ether	B.p., °C. (760 mm.)	n^{25}D	Carbon, %		Chlorine, %		Fluorine, %		Perfluoro ether used	Amt. not recvd., %	Yield based on unrecvd. ether, %
			Calcd.	Found	Calcd.	Found	Calcd.	Found			
c-$C_5Cl_3F_7O$	114	1.3620	..	..	33.8	33.9	42.2	42.1	c-$C_5F_{10}O$ (2-$CF_3C_4F_7O$)	65	40
c-$C_6Cl_3F_9O$	136	1.3566	..	..	29.1	29.1	46.8	46.9	c-$C_6F_{12}O$	50	45
c-$C_8Cl_3F_{13}O$	171	1.3494	20.6	21.2	22.8	23.1	53.1	54.3	c-$C_8F_{16}O$	87	54
c-$C_{10}Cl_3F_{17}O$	207	1.3455	21.2	21.3	18.8	18.8	57.1	56.0	c-$C_{10}F_{20}O$	81	60

the presence of chlorine results in marked solubility in organic solvents: qualitative data are given in the Experimental section for c-$C_8Cl_3F_{13}O$. The solubility parameter, δ,[12] is estimated as 7.2 for this compound, as compared with 5.7 for the perfluoro ether c-$C_8F_{16}O$. Electrical properties, viscosity and surface tension data also are compared for these two ethers. The differences observed can be attributed exclusively to the chlorine atoms, as the ether structure is unchanged.

Experimental

Perfluoro Ethers.—The perfluoro ethers used in this research were prepared by the Simons electrochemical fluorination process.[4,13] Boiling points and refractive indices agreed with previously reported values,[3,4] and infrared spectra indicated comparable purity. The ethers c-$C_6F_{12}O$, c-$C_8F_{16}O$ and c-$C_{10}F_{20}O$, obtained in the fluorination of the acids n-$C_5H_{11}CO_2H$, n-$C_7H_{15}CO_2H$ and n-$C_9H_{19}CO_2H$, respectively,[4] are known to be mixtures of perfluorinated α-substituted tetrahydrofurans and α-substituted tetrahydropyrans.[3] The ether c-$C_5F_{10}O$ was prepared from α-methyltetrahydrofuran, and was isolated in a state of high purity by fractional distillation. Its physical properties have been described,[3] and its infrared spectrum demonstrated the absence of the isomeric c-$C_5F_{10}O$ which has been prepared from tetrahydropyran.[3,14]

Reactions with Aluminum Chloride.—Similar procedures were used for all of the $AlCl_3$ reactions. The perfluoroether was heated with 1.5 equivalents of $AlCl_3$ for 14 hours at 180° (C_5- and C_6-ethers) or 200–220° (C_8- and C_{10}-ethers). Shorter reaction times may be found satisfactory. An Aminco rocking autoclave of 43-ml. capacity (No. 406-35AX3) or of 180-ml. capacity (No. 406-35CX3)[15] with automatic temperature control was used. The factor of safety provided by this equipment is very large, as pressures usually encountered were only 100 to 200 p.s.i. However, extensive decomposition, attended by much higher pressures, has been observed upon overheating of the reaction mixture to 280–320°. Sealed (Carius) tubes of $^1/_2''$ or $^3/_4''$ o.d. and $^1/_8''$ wall thickness also may, with proper safety precautions, be employed.

Properties and yields of the trichloro perfluoro ethers are presented in Table I.

Preparation of α,α,α'-$C_8Cl_3F_{13}O$ from $C_8F_{16}O$.—The following is an example of the procedure that was found suitable for the preparation of the α,α,α'-trichloro perfluoro ethers.

In a 180-ml. rocking autoclave were placed 88 g. (0.212 mole) of the ether, c-$C_8F_{16}O$, and 45 g. (0.339 mole) of anhydrous aluminum chloride. The autoclave was heated for 14 hours at 200°, then after cooling to room temperature was vented in an efficient hood. Some gases escaped, but the pasty black reaction mixture weighed 121 g. It was mixed with about 60 g. of c-$C_6F_{12}O$ (solvent) and filtered under pressure. (CCl_4 is quite satisfactory as a solvent. The perfluoro ether was used in this experiment as CCl_4 might have been formed in a side reaction. None was found.) The filtered solution was crudely fractionated in a 25-cm. Vigreux column. Only 13 g. of unreacted c-$C_8F_{16}O$ was recovered, and 50 g. of crude c-$C_8Cl_3F_{13}O$, b.p. 167–172°, n^{25}D 1.3550 was obtained.

The intercut, b.p. 105–167°, weighed only 3.2 g. and came over almost entirely between 150 and 167°. It solidified to a slush in the condenser. Its infrared spectrum indicated the presence of hexachloroethane and c-$C_8Cl_3F_{13}O$, but only small amounts of other substances. The solid component was recrystallized from c-$C_8F_{16}O$ and showed no depression of melting point upon admixture with an authentic sample of C_2Cl_6. The lower b.p. found for the intercut appears to result from codistillation of the solid C_2Cl_6 with the liquid c-$C_8Cl_3F_{13}O$.

Some C_2Cl_6 was present in the crude c-$C_8Cl_3F_{13}O$ and was responsible for its high refractive index. The following procedure was adopted for purification. Ammonia gas was bubbled through the crude c-$C_8Cl_3F_{13}O$ to react with all acidic materials, then the mixture was chilled to −40° or lower and filtered centrifugally. The ammonia reaction products and the C_2Cl_6 were removed almost entirely in this step: yield 45 g. (54%), n^{25}D 1.3509.

Further purification was desirable to prepare the sample for analysis and determination of physical properties: adsorption fractionation[16] has been found satisfactory. A column of 100 to 200 mesh silica gel 25 cm. long by 2.5 cm. diameter was used for 50 g. of filtered trichloro ether, with isopropyl alcohol as desorbent. By this procedure there was obtained 30 g. (36%) of purified c-$C_8Cl_3F_{13}O$, each cut of which had n^{25}D 1.3494. Analytical data are furnished in Table I. If desirable, the rest of the material may be recovered from the column and the tail fractions.

Solvolysis and Proof of Structure of c-$C_8Cl_3F_{13}O$.—The cyclic trichloro perfluoro ether, c-$C_8Cl_3F_{13}O$, 46.5 g. (0.10 mole), fuming sulfuric acid (20% SO_3), 26.1 g., and a trace of mercuric sulfate, 0.2 g., contained in a sealed (Carius) tube were heated for 15 hours at 150°. The refractive index of the ether phase had fallen from n^{25}D 1.3494 to 1.3271. This phase was separated and distilled in a short helix-packed fractionating column. In addition to unreacted trichloro perfluoro ether and some high-boiling residue, there was obtained the α-chloroperfluorolactone, c-$C_8ClF_{13}O_2$, b.p. 140°, n^{25}D 1.3192, in 70% yield.

Anal. Calcd. for $C_8ClF_{13}O_2$: Cl, 8.64; F, 60.1; Cl(hydr.), 8.64; F(hydr.), 0.0. Found: Cl, 8.50; F, 59.5; Cl(hydr.), 8.20; F(hydr.), 0.0.

The presence of hydrolyzable chlorine, but not fluorine, served to confirm the proposed structure when taken in conjunction with the observation of an extremely intense, sharp infrared absorption band at 5.34 μ, assignable to the perfluorolactone carbonyl stretching vibration.

Physical Properties of c-$C_8Cl_3F_{13}O$.—Several physical properties not recorded in Table I are listed below, and are compared with those for the parent perfluoro ether, c-$C_8F_{16}O$.[3,4,17]

For c-$C_8Cl_3F_{13}O$: d^{25} 1.813, b.p. 171°, m.p. not obsd. (glass below −100°), dielectric constant 2.25 ± 0.05 (1000 cyc.), loss factor less than 0.0005 (1000 cyc.), dielectric strength about the same as for c-$C_8F_{16}O$, surface tension (dynes/cm., 25°) 23.8; viscosity (centipoises) 8.3 (0°), 3.9 (25°), 1.8 (60°); solubility, miscible with benzene, benzotrifluoride, acetone, heptane, carbon tetrachloride, some-

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(12) J. H. Hildebrand and R. L. Scott, "The Solubility of Non-electrolytes," Reinhold Publishing Corp., N. Y., 3rd. Ed., 1950, p. 253 *et seq.*

(13) J. H. Simons, "Fluorine Chemistry," Academic Press, Inc., New York, N. Y., 1950, p. 414.

(14) E. A. Kauck and J. H. Simons, U. S. Patent 2,594,572, April 29, 1952.

(15) American Instrument Co., Silver Spring, Md.

(16) B. J. Mair, J. Westhaver and F. D. Rossini, *Ind. Eng. Chem.*, **42**, 1279 (1950).

(17) Technical Bulletin "Fluorochemical 0-75," Minnesota Mining and Manufacturing Co., Fluorochemicals Department, St. Paul. Minn., 1952. Other physical properties and extended, quantitative solubility data are given.

what soluble in carbon disulfide and acetonitrile, very slightly soluble in ethanol, insoluble in water, solubility parameter[12] $\delta = 7.2$ (est.).

For $c\text{-}C_8F_{16}O$: d^{25} 1.7602, b.p. 104°, m.p. not obs. (glass below −113°) dielectric constant 1.85 ± 0.05 (1000 cyc.), loss factor less than 0.0001 (100 cyc.), dielectric strength 37 kv. (ASTM-D877), surface tension (dynes/cm., 25°), 15.2; viscosity (centipoises), 2.41 (0°), 1.45 (25°), 0.80 (60°); solubility, miscible with benzotrifluoride, somewhat soluble in heptane and carbon tetrachloride, very slightly soluble in benzene, acetone and ethanol, insoluble in water, soluble parameter[12] $\delta = 5.7$ (est.).

Infrared Spectra of α,α,α'-Trichloro Perfluoro Ethers.—These compounds exhibit complex spectra, difficult to interpret. In each case, however, two fairly strong infrared bands were found in the region 10.70–11.10 and 11.20–11.55 μ, using liquid sample thicknesses of 0.007 mm. These bands possibly may be attributable to the trichloro ether grouping.

Other Lewis Acids.—No reaction was observed between the ether $c\text{-}C_8F_{16}O$ and the less powerful Lewis acids BCl_3 (350°, 24 hours) or $NaCl{\cdot}AlCl_3$ (230°, 15 hours). The ether was recovered quantitatively, with unchanged refractive index and infrared spectrum. Aluminum bromide, however, reacted at 170° with this ether but produced only aluminum fluoride, carbonized tars and bromine; no impurities were detectable in the recovered ether phase.

Acknowledgment.—The author would like to thank Dr. H. E. Freier for the analytical data, Dr. W. E. Keiser and Dr. J. McBrady for the infrared spectra, Mr. G. Filipovich for the electrical measurements, Mr. V. Welschinger for the viscosity data, and Mr. J. D. Keating for assistance with the autoclave reactions.

ST. PAUL 6, MINN.

[CONTRIBUTION FROM THE MEDICINAL CHEMICAL RESEARCH SECTION, RESEARCH DIVISION, LEDERLE LABORATORIES, AMERICAN CYANAMID CO.]

α-Bromoacid Amides and Ureas as Anticonvulsants

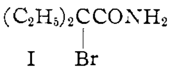
BY S. R. SAFIR, H. DALALIAN, W. FANSHAWE, K. CYR, R. LOPRESTI, R. WILLIAMS, S. UPHAM, L. GOLDMAN AND S. KUSHNER

RECEIVED APRIL 8, 1955

A large number of α-bromoacid amides and ureas related to neuronal and carbromal has been synthesized for anticonvulsant activity. Maximum activity was encountered with compounds in which some branching in the acid chain was coupled with the simpler amide and urea functions.

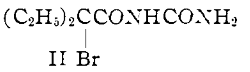
Although α-bromoamides and ureas have for many years been used in medicine as sedatives and hypnotics, no systematic survey of this class of drugs for anticonvulsant potentiality appears to have been made.[1] The finding that neuronal (I) and carbromal (II) exhibited a high degree of protection against metrazole-induced seizures in rats gave impetus to the hope that a drug useful in petit mal epilepsy might be found in the class of α-bromoamides and ureas. A synthetic program with this goal in mind is the subject of this paper.

In the selection of compounds to be synthesized, it was decided to retain the α-bromo atom while varying, on the one hand, the alkyl groups on the α-carbon atom and, on the other, the amide or urea function. These features are represented by formula III in which the nitrogen is incorporated into R_2.



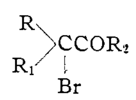
$(C_2H_5)_2C(Br)CONH_2$

I



$(C_2H_5)_2C(Br)CONHCONH_2$

II



$RR_1C(Br)COR_2$

III

The most active group among the compounds listed in Table I is that derived from 2-bromo-2-ethylbutyric acid. The N-methyl (XLI) and N-methylol (XLII) amides of this acid are about as active as neuronal and carbromal. The N_3-methyl analog LVII of carbromal, although active, is somewhat less potent than carbromal. Alterations in the alkyl amide group involving increase in the chain length, unsaturation or branching, all resulted in loss or elimination of anticonvulsant activity. The glycine amide derivatives LII, LIII, LIV, and LV, the amides LI and LVI derived from heterocyclic amines and the isothiuronium derivative LIX also proved to be inactive. Compound LVIII, 1,3-bis-(2-bromo-2-ethylbutyryl)-urea, also was inactive. Thus it appears that anticonvulsant potency is retained within narrow limits of substitution among the derivatives of 2-bromo-2-ethylbutyric acid.

Some branching of the acid chain appears to be necessary for anticonvulsant activity as may be inferred from the high potency shown by compounds XXII, XXV, XXXIII, XXXIV, XXXVIII, LX and LXI and from the virtual absence of anticonvulsant activity among the linear derivatives. Isopropyl groups in particular seem to have a salutary effect.

Comparison of the amide derivatives with the urea derivatives does not permit an unequivocal preference to be made for either group as a structural requirement for anticonvulsant activity.

The amides were prepared by classical procedures, namely, reaction between the requisite acid chlorides or bromides and ammonia or amines. Examples of compounds requiring less conventional treatment are furnished in the Experimental section. 2-Amino-2-ethylbutyramide was prepared readily by hydrolysis of the nitrile. The urea derivatives were prepared in fair yields by reaction of the acid chlorides with urea or methylurea.

Several of the most active compounds are presently undergoing a limited clinical trial.

The pharmacological data were secured by Drs. R. W. Cunningham and W. Gray, assisted by F. Smith and C. Rauh, and will be published in full elsewhere.

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[1] The Merck Index, 5th ed., Merck & Co., Inc., Rahway, N. J., 1940, p. 196, lists epilepsy as one of the uses for neuronal. Stroux, in an early clinical report [*Deut. med. Wochschr.*, **30**, 1497 (1904)] comments on the "extraordinarily favorable effect of neuronal on epilepsy but his work was performed on only a few unclassified epileptic patients without benefit of modern, long-range, controlled methods.