five-membered rings should be viewed with caution. Therefore, the τ values calculated for both the 1,3-dioxolanes and the 1,3-dithiolanes are presented only to establish general differences between the two ring systems and not to establish accurate values for the respective torsional angles. Nevertheless, it is interesting to note that the values obtained from the vicinal coupling constants are in good agreement with the maximum torsional angles obtained by X-ray analysis of 2,2′-bis-1,3-dioxolane (±31°) and 2,2′-bis-1,3-dithiolane (±45°).[3]

These results do not, however, give unambiguous evidence of the conformational form, C_2 or C_s, since the maximum torsional angles of both forms are nearly identical.

The ring protons have been shown to be significantly more staggered in the sulfur isosteres than in their oxygen analogs, and therefore the 1,3-dithiolane ring is more puckered than the 1,3-dioxolane.

The increased size of the sulfur atom and the increased C–S bond lengths result in a smaller 1,3-transannular alkyl proton interaction between C-2 substituents and the ethylene bridge protons in the case of 1,3-dithiolanes than with the corresponding 1,3-dioxolanes.[5,34] As indicated by Dreiding models, it can be anticipated that the tendency of the ring to flatten in order to decrease syn-axial repulsion is less for the 1,3-dithiolanes than their oxygen counterpart, thus contributing to the observed differences in coupling values and corresponding conformational changes.

Experimental Section

Nmr spectra were determined with Varian Associates HA-100 and HR-220 spectrometers with approximately 5% solutions in CCl_4. Chemical shifts of all compounds are reported in parts per million (δ) and were measured from internal TMS. The coupling constants, expressed in hertz, were determined under standard conditions except for those of 1,3-dithiolane and 2,2-dimethyl-1,3-dithiolane which were determined from neat samples.

The AA′BB′ spectra were calculated using LAOCN3[35] and were simulated with a Calcomp plotter using NMRPL.[36] Initial parameters were chosen from those previously reported for 2-alkyl-1,3-dioxolanes[16] and 2-alkoxy-1,3-dioxolanes.[12] Iterations were performed using several different starting parameters and always minimized to the same solution which, when plotted, was indistinguishable from the experimental spectra. Analysis of AA′BB′ spectra yields four sets of mathematically correct solutions,[37] and since not physically meaningful solutions have been encountered in the analysis of the spectra of 1,3-oxathiolanes,[15,16] the spectrum of 2-methyl-2-phenyl-1,3-dithiolane was obtained at both 100 and 220 MHz.[38] The coupling constants determined at both field strengths are identical as are the field-dependent expressions of the chemical shift differences when changed by the proper factor. This clearly indicates that the minimized solution is physically significant.[39]

The 1,3-dithiolanes were prepared by the method of Coffin, *et al.*,[40] and their physical properties were in satisfactory agreement with literature values.[41,42] All compounds were homogeneous by the criterion of thin-layer chromatography.

Acknowledgments. The assistance and helpful advice of Dr. M. I. Levenberg and Mr. W. C. Bass (Abbott Laboratories) and Dr. C. L. Bell (University of Illinois at the Medical Center) is thankfully acknowledged. Stimulating discussions with Dr. Peter Beak (University of Illinois), Dr. J. Tadanier (Abbott Laboratories), Dr. A. J. Perkins (University of Illinois at the Medical Center), and Dr. M. M. Mertes (University of Kansas) were appreciated. The facilities at the University of Kansas were generously made available (to L. A. S.) for the completion of part of the synthetic work.

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Long-Range Hydrogen–Fluorine Spin–Spin Coupling. Further Support for the "Through-Space" (Direct) Mechanism

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Contribution from the Medical Research Laboratories,
Pfizer Inc., Groton, Connecticut 06340. Received September 3, 1970

Abstract: Hydrogen–fluorine long-range coupling is studied in a novel class of 2-substituted-3-trifluoromethylquinoxalines, their 1-oxides, and 1,4-dioxides. It is shown that J_{H-F} is susceptible to changes in hydrogen–fluorine internuclear distances. This effect is explained by the through-space mechanism.

The nature of long-range fluorine–flourine and fluorine–hydrogen spin–spin couplings has been a controversial issue for some time. Early investigators found that the coupling constant increased with decreasing internuclear distance[2a] and suggested that coupling occurred through space. However, systems with long-range couplings were soon found in which the

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(2) (a) L. Petrakis and C. H. Sederholm, *J. Chem. Phys.*, **35**, 1243 (1961); (b) D. R. Davis, R. P. Lutz, and J. D. Roberts, *J. Amer. Chem. Soc.*, **83**, 246 (1961); (c) M. Takahashi and J. D. Roberts, *ibid.*, **84**, 2935 (1962); (d) S. Ng and C. H. Sederholm, *J. Chem. Phys.*, 40, 2090 (1964); (e) A. H. Lewin, *J. Amer. Chem. Soc.*, **86**, 2203 (1964); (f) J. Burdon, *Tetrahedron*, **21**, 1101 (1965).

nuclei were too far apart for nonbonded interactions to occur. Thereafter, such results were explained by involving coupling through bonds rather than "through-space" mechanism.[3] Cross and Landis, working exclusively with fluorinated steroids, advanced the empirical "conversion vector rule" which expressed the spatial requirements for hydrogen-fluorine coupling.[4] Nonetheless, they were unable to determine whether a "through-space" or "through-bond" coupling had occurred.[5]

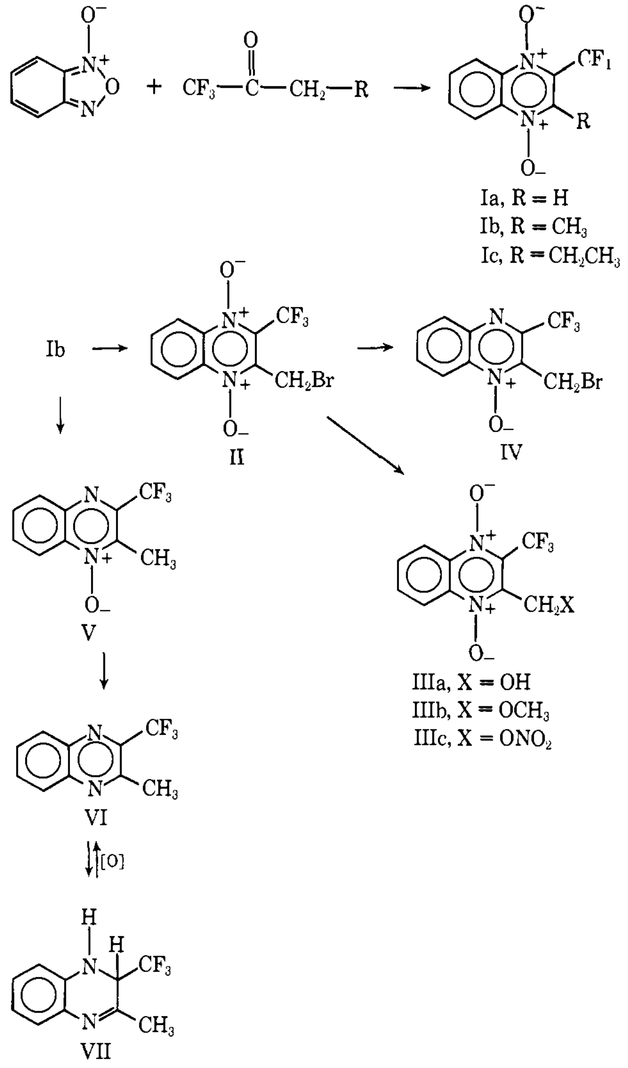
Although early data of Gutowsky and coworkers on long-range fluorine-fluorine coupling were interpreted in terms of bond-mediated spin-spin interactions,[6a,b] later findings led them to conclude that nonbonded interactions make a major "through-space" contribution to coupling of the fluorines.[6c] Myhre and coworkers, studying long-range hydrogen-fluorine coupling in alkylfluorobenzenes, furnished convincing data to support the through-space mechanism. From their data and that published on fluorinated steroids, they developed the relationship between the coupling constant and internuclear distance shown in Figure 2.[7] Other examples showing the dominant effect of through-space coupling have since followed.[8]

In the present work further support for through-space hydrogen-fluorine long-range coupling is furnished by a study of a novel class of 2-substituted-3-trifluoromethylquinoxalines, their 1-oxides, and 1,4-dioxides. These compounds are models in which reasonable changes and estimates of the internuclear distances between the coupling nuclei may be made. Our results also provide convincing evidence that electronic disturbances are not involved in determining the magnitude of coupling.

Chemistry. The quinoxaline 1,4-dioxides were all prepared according to published procedures.[9] The quinoxalines and their 1-oxides were obtained by reduction of the parent 1,4-dioxides as outlined in Scheme I.

The position of the oxygen in compounds IV and V was assigned on the basis of their nmr spectra. The chemical shifts of the methylene and methyl groups in the monoxides IV and V are not greatly different from those of the parent dioxides; however, an upfield shift of 4.1 ppm was noted for the trifluoromethyl group quartet when the dioxide Ib was reduced to the monoxide V showing clearly the deshielding effect of the 4-oxygen on the trifluoromethyl group. That reduction occurred at the 4 position is not surprising since it represents the most electrophilic center of the molecule. This also explains the selective reduction of quinoxaline VI to the dihydro derivative VII. The assignment of this structure was made on the basis of its nmr spectrum. After deuterium exchange the resonance of the C_3-methine proton (δ 4.4 ppm) appeared as a quartet (J_{H-F} = 8 Hz) showing clearly its vicinal coupling to the trifluoromethyl group. The singlet resonance of the methyl group (δ 2.38 ppm) provided further support for the structure.

Scheme I



Discussion

A summary of pertinent nmr data is presented in Table I. The most important features are the variations in the coupling constants about which the following generalizations may be drawn: (1) a decrease in J_{H-F} was found (a) when the 2-methyl groups of both the quinoxaline 1,4-dioxides (Ib) and the 1-oxide (V) were substituted, and (b) upon reduction of the 4-oxide; (2) no detectable hydrogen-fluorine coupling was observed in the hydroxymethyl IIIa, the dihydroquinoxaline VII, and 2-trifluoromethylquinoxaline 1,4-dioxide (Ia).

The observed reduction of J_{H-F} upon substitution of one of the hydrogens in the methyl group of Ib and V is best explained by through-space coupling. The magnitude of coupling does not appear to be related to the electronegativities of the substituents which, when contact terms are involved, play a significant role in the determination of J.[10] In quinoxaline 1,4-dioxides, there are two important conformational isomers of the

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[3] (a) N. Boden, J. Feeny, and L. H. Sutcliffe, *J. Chem. Soc.*, 3482 1965); (b) K. L. Servis and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 1339 (1965).

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[9] (a) M. J. Haddadin and C. H. Issidorides, *Tetrahedron Lett.*, 3253 (1965); (b) M. J. Haddadin and C. H. Issidorides, *J. Org. Chem.*, **31**, 4076 (1966).

[10] R. J. Abraham and G. Gatti, *J. Chem. Soc. B*, 961 (1969).

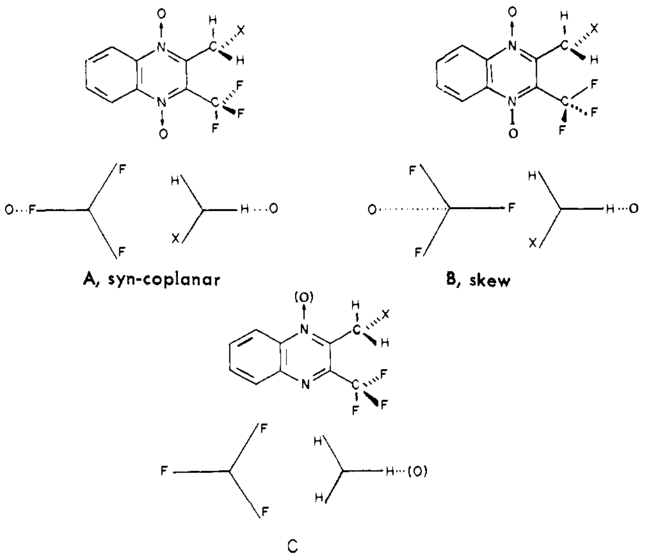
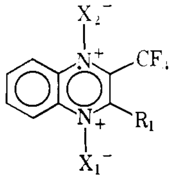


Figure 1.

trifluoromethyl group where a fluorine is either syn coplanar or skew with the 4-oxide oxygen (Figure 1A and B). Inspection of molecular models strongly suggested the skew rotamer (B) to be more stable than the syn coplanar rotamer (A), due to steric repulsion between the fluorine and oxygen in the latter rotamer.

Table I



Compd	R_1	X_1	X_2	J_{H-F}, Hz	δ, ppm
Ia	H	O	O		8.57
Ib	CH_3	O	O	3.0	2.82
Ic	CH_2CH_3	O	O	2.1	3.33
II[a]	CH_2Br	O	O	1.3	4.98
IIIa	CH_2OH	O	O		5.13
IIIb	CH_2OCH_3	O	O	2.0	5.05
IIIc	CH_2ONO_2	O	O	2.0	6.08
IV	CH_2Br	O			4.90
V	CH_3	O		1.2	2.77
VI	CH_3			1.6	2.90

[a] The reported coupling constant is that measured in tetrachloroethylene at 100°. The chemical shift, on the other hand, was determined in deuteriochloroform at room temperature.

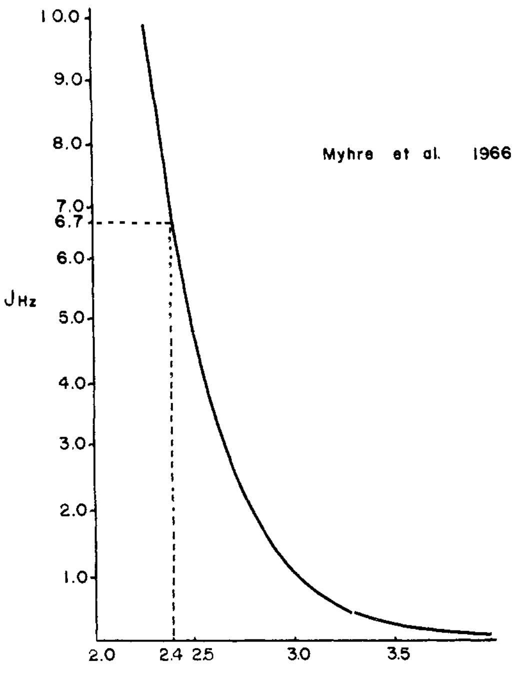


Figure 2.

Measurements of fluorine–oxygen internuclear distances further substantiate this conclusion. It is known that two nonbonded atoms experience steric repulsion when their internuclear distance is smaller than the sum of their van der Waals radii.[11] Such a distance was found to be 0.6 Å shorter, in rotamer A, and 0.2 Å longer, in rotamer B, than the sum of the oxygen–fluorine van der Waals radii. Further evidence is also furnished by rotational isomerism studies on XCH_2CH_2Y systems where X and Y are oxygen and fluorine. There was an observed, but yet unexplained, attraction between these two atoms, which favors the gauche over the trans isomer by 1 kcal/mole.[11] An analogous situation was found in 5-fluoro-2-isopropyl-1,3-dioxans, where the cis isomer is favored at equilibrium, presumably due to the same type of F–O gauche attractions.[12,13] If across-space interactions are operative here, there are only two out of a possible nine that contribute to the observed coupling constant.[2d] Thus J_{obsd} can be expressed as (when X = H)

$$J_{\text{obsd}} = \frac{2}{9}J' \qquad (1)$$

where J' is the coupling constant for the closest fluorine and hydrogen nuclei. Substituting the value of J_{obsd} in eq 1 we find $3 = (2/9)J'$; then $J' = 13.5$ Hz. However, when X is not a proton $J_{\text{obsd}} = (1/6)J'$; using the above value of J' we find the calculated J to be $J_{\text{calcd}} = 13.5/6 = 2.2$ Hz, which is in close agreement with the observed values.

Examination of molecular models suggested the preferred conformation of the trifluoromethyl group in quinoxalines and their 1-oxides to be that depicted in Figure 1C, where no fluorine–oxygen repulsion exists. A literature analogy for this conformational relationship of the two substituents at C_2 and C_3 was found for the two adjacent groups in *o*-xylene[14] and *o*-perfluoroxylene.[15] Following similar arguments to those applied in the quinoxaline 1,4-dioxides we find (when X = H) $J_{\text{obsd}} = (2/9)J'$, $1.22 = (2/9)J'$, then $J' = 5.49$ Hz; (when X = Br) $J_{\text{calcd}} = (1/6)J'$, $J_{\text{calcd}} = 0.91$ Hz; this explains the broadened singlet for the methylene group resonance in IV. In the most stable forms mentioned earlier (Figure 1B and C), the shortest fluorine–hydrogen internuclear distance in the quinoxaline 1,4-dioxides, on one hand, and the corresponding

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[11] R. J. Abraham and K. Parry, *J. Chem. Soc. B*, 539 (1970).

[12] E. L. Eliel and M. Kaloustian, *Chem. Commun.*, 290 (1970).

[13] The author thanks a referee for pointing out this information.

[14] (a) K. S. Pitzer and D. W. Scott, *J. Amer. Chem. Soc.*, **65**, 803 (1943); (b) W. R. Wolfenden and D. M. Grant, *ibid.*, **88**, 1496 (1966).

[15] J. Jonáš, *J. Chem. Phys.*, **47**, 4884 (1967).

quinoxalines and their 1-oxides, on the other, is 2.0 Å and 2.4 Å, respectively. Myhre's curve (Figure 2) which relates H–F internuclear distance to $J_{\text{H-F}}$ predicts the respective values of greater than 12 Hz and 6.7 Hz. These are in good agreement with those calculated above. Thus the through-space mechanism provides a good explanation for the decrease in $J_{\text{H-F}}$ upon methyl substitution and reduction of the 1,4-dioxides to the 1-oxides. Reduction in $J_{\text{H-F}}$ was not observed when the quinoxaline 1-oxide (V) was further reduced to the corresponding quinoxaline. Thus electronic disturbances should not be responsible for the 60% decrease in $J_{\text{H-F}}$ upon reduction of the dioxide to the monoxide.

The nmr spectrum of 2-bromomethyl-3-trifluoromethylquinoxaline 1,4-dioxide at room temperature showed the methylene protons as a broad signal. This is probably due to restricted rotation of the bromomethyl group, rendering its protons magnetically nonequivalent as molecular models suggested. The broad signal was resolved into the expected quartet by raising the temperature to 100° using tetrachloroethylene as the solvent. The observed coupling constant is 1.3 Hz which is less than the predicted value of 2.2 Hz. However variations in J due to temperature and solvent changes have been reported.[16,17]

Further support for coupling through space in these systems was provided by other compounds where no detectable H–F coupling was observed. One such compound is 3-trifluoromethylquinoxaline 1,4-dioxide (Ia) whose 2-hydrogen resonance appeared as a singlet, even though the number of connecting bonds was reduced from five to four. The effective H–F internuclear distance, as measured in molecular models, is larger in this component. Another one is the dihydro compound VII, where the methyl group appeared as a singlet instead of the expected quartet. Reduction of the double bond could result in increased hydrogen–fluorine distances since the trifluoromethyl group is no more in the plane of the aromatic ring.

The appearance of methylene singlet in the hydroxymethyl IIIa can be rationalized with arguments similar to those presented above. Hydrogen bonding between the hydroxyl proton and the *N*-oxide can be responsible for altering the averaged hydrogen–fluorine internuclear distances. That hydrogen bonding existed was proven by infrared studies where no shifts for its resonance were observed upon dilution.[18] In compounds IIIb and IIIc where hydrogen bonding is eliminated the expected methylene quartets were restored.

It is conceivable that the above results could be rationalized by bond-mediated interactions, especially since coupling is known to be sensitive to the dihedral angles of the bonds involved.[19] However, it is felt that the through-space mechanism provides a more plausible explanation.

Experimental Section

Melting points were not corrected and were taken on a 6406H Thomas-Hoover apparatus. Nuclear magnetic resonance experiments were performed using either Varian A-60 or Perkin-Elmer HR-20 spectrometers. Infrared spectra were determined on a Perkin-Elmer 21 spectrophotometer. Ultraviolet data were obtained on a Cary Model 14 spectrophotometer. Mass spectral analyses were performed on a Perkin-Elmer RMV-6E mass spectrometer.

2-Trifluoromethylquinoxaline 1,4-Dioxide (Ia). To a solution of sodium (1.15 g, 0.05 g-atom) in ethanol (100 ml) trifluoroacetone (21.8 g, 0.2 mole) and benzofuroxan (17.2 g, 0.2 mole) were added, and the reaction mixture was refluxed for 0.5 hr. It was then allowed to stand at room temperature overnight. The product crystallized (7.7 g, 17% yield). The analytical sample was obtained from acetone–hexane, mp 190–192°. The mass spectrum showed a molecular ion at *m/e* 230; ir (KBr) 7.2, 8.5, 9.1, 11.2, and 11.85 μ; $\lambda_{\max}^{\text{MeOH}}$ 388 (10,100), 257 (12,400), and 232 mμ (ϵ 23,600). *Anal.* Calcd for $C_9H_5O_2N_2F_3$: C, 46.95; H, 2.17; N, 12.60. Found: C, 46.63; H, 2.14; N, 12.17.

2-Methyl-3-trifluoromethylquinoxaline 1,4-Dioxide (Ib). Sodium metal pellets (0.187 g, 0.0085 g-atom) were dissolved in ethanol (35 ml), and the resulting solution was cooled to room temperature. Benzofuroxan (4.5 g, 0.034 mole) and 1,1,1-trifluoro-2-butanone (4.3 g, 0.034 mole) were added, and the mixture was refluxed for 2 hr and then allowed to stand overnight at room temperature. The reaction mixture was evaporated to dryness, and the residue was taken up in benzene and chromatographed on an acid-washed Florisil column (250 g).

The column was eluted first with benzene (which permitted recovery of 3.19 g of unreacted benzofuroxan) and then with chloroform. Evaporation of the chloroform eluate yielded a gum (1.28 g, 48% yield) which crystallized from ether, mp 126–128°. Further recrystallization raised the melting point to 135–135.5°. The mass spectrum showed a molecular ion at *m/e* 244; ir (KBr) 6.65, 7.4, 8.7, 12.85, and 13.75 μ; $\lambda_{\max}^{\text{MeOH}}$ 400 (9200), 264 (20,100), and 233 mμ (ϵ 23,100). *Anal.* Calcd for $C_{10}H_7O_2N_2F_3$: C, 49.18; H, 2.87; N, 11.47. Found: C, 48.99; H, 2.99; N, 11.52.

2-Ethyl-3-trifluoromethylquinoxaline 1,4-Dioxide (Ic). Following the procedure of Ib, benzofuroxan (1.36 g, 0.01 mole) and 1,1,1-trifluoro-2-pentanone (1.4 g, 0.01 mole) were added to a solution of sodium (0.057 g, 0.0025 g-atom) in ethanol (10 ml). After work-up the product was obtained (0.4 g). Crystallization from hexane–ether provided the analytical sample, mp 107–108°. The mass spectrum showed a molecular ion at *m/e* 258; ir (KBr) 6.65, 7.4, 8.65, 12.9, and 13.85 μ; $\lambda_{\max}^{\text{MeOH}}$ 400 (8900), 264 (20,600), and 232 mμ (ϵ 23,700). *Anal.* Calcd for $C_{11}H_9O_2N_2F_3$: C, 51.16; H, 3.49; N, 10.89. Found: C, 51.02; H, 3.49; N, 10.79.

2-Bromomethyl-3-trifluoromethylquinoxaline 1,4-Dioxide (II). 2-Trifluoromethyl-3-methylquinoxaline 1,4-dioxide (0.6 g, 0.0025 mole) was dissolved in ethyl acetate (10 ml), and heated to reflux. Bromine (0.62 g, 0.005 mole) in ethyl acetate (5 ml) was added to the hot solution. Refluxing continued for 10 min, then the solvent was evaporated to dryness. The residue was crystallized from methanol to yield the product (0.48 g, 60% yield), mp 140–141°. Further crystallization gave the analytical sample, mp 153–154°. The mass spectrum showed two molecular ions at *m/e* 324 and 322; ir (KBr) 6.7, 7.35, 7.45, 10.02, 12.75, and 13.85 μ; $\lambda_{\max}^{\text{MeOH}}$ 390 (10,500), 272 (17,200), and 242 mμ (ϵ 30,500). *Anal.* Calcd for $C_{10}H_6O_2N_2BrF_3$: C, 37.15; H, 1.86; N, 8.67. Found: C, 37.65; H, 1.90; N, 8.72.

3-Trifluoromethyl-2-quinoxalinylmethanol 1,4-Dioxide (IIIa), 3-Trifluoromethyl-2-quinoxalinylmethanol Methyl Ether (IIIb), and 3-Trifluoromethyl-2-quinoxalinylmethanol Nitrate (IIIc). A mixture of 2-bromomethyl-3-trifluoromethylquinoxaline 1,4-dioxide (0.085 g, 0.0026 mole), silver nitrate (1.7 g, 0.01 mole), methanol (25 ml), and water (25 ml) was refluxed on a steam bath for 6 hr. Silver nitrate (1.7 g) was added, and the mixture was refluxed overnight. The reaction mixture was filtered and the methanol removed from the filtrate by evaporation. Extraction of the aqueous solution with chloroform, drying the extract with anhydrous sodium sulfate, and evaporation of the extract to dryness gave an oil.

A benzene solution of the oil was chromatographed on a Florisil column (30 g) packed with benzene. Fractions (50 ml) were collected as follows: fractions 1–6, benzene; fractions 7–16, 3% chloroform–benzene; fractions 17–21, chloroform; fractions 22–29, 3% methanol–chloroform. Fractions 9–11 yielded crude IIIc (70 mg). The analytical sample was obtained from ether, mp 125–127°. The mass spectrum showed a molecular ion at *m/e* 305; ir (KBr) 6.07, 7.45, 7.75, 12.85, and 13.82 μ; $\lambda_{\max}^{\text{MeOH}}$ 390 (10,300), 265 (13,300), 260 (13,300), and 238 mμ (ϵ 30,500). *Anal.* Calcd for $C_{10}H_6O_5N_3F_3$: C, 39.34; H, 1.97; N, 13.77. Found: C, 39.60; H, 2.02; N, 13.70.

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(16) W. S. Brey, Jr., and K. C. Ramey, *J. Chem. Phys.*, **39**, 844 (1963).

(17) S. Ng, J. Tane, and C. H. Sederholm, *ibid.*, **42**, 79 (1965).

(18) Hydrogen bonding has also been observed in similar systems. See, for example, L. P. Kuhn, R. A. Wises, W. Ruoff, and H. Kuart, *J. Amer. Chem. Soc.*, **91**, 4790 (1969).

(19) M. Barkfield and B. Chakrabarti, *Chem. Rev.*, **69** 757 (1969).

Fractions 12–21 (0.155 g) when worked up in the same manner yielded the analytical sample of IIIb, mp 121–123°. The mass spectrum showed a molecular ion at *m/e* 274; ir (KBr) 6.65, 7.4, 8.6, 12.85, and 13.8 μ; λ_{max}^{MeOH} 388 (11,000), 262 (13,400), and 235 mμ (ϵ 27,700). *Anal.* Calcd for $C_{11}H_9O_3N_2F_3$: C, 48.17; H, 3.28; N, 10.21. Found: C, 48.13; H, 3.18; N, 10.04.

Fractions 22–29 yielded crude IIIa (85 mg). The analytical sample was obtained from ether, mp 130–131°. The mass spectrum showed a molecular ion at *m/e* 260; ir (KBr) 2.95, 6.75, 7.35, 8.7, 12.95, and 13.75 μ; λ_{max}^{MeOH} 386 (10,200), 267 (16,100), and 236 mμ (ϵ 25,700). *Anal.* Calcd for $C_{10}H_7O_3N_2F_3$: C, 46.15; H, 2.70; N, 10.77. Found: C, 46.09; H, 2.73; N, 10.71.

2-Methyl-3-trifluoromethylquinoxaline 1-Oxide (V). 2-Methyl-3-trifluoromethylquinoxaline 1,4-dioxide (0.73 g, 0.003 mole) was suspended in water (3 ml). To this suspension a solution of sodium dithionite (1.56 g, 0.009 mole) in water (2 ml) was added dropwise while stirring. The product (0.21 g, 30% yield) precipitated out of the resulting solution. Ether–hexane crystallization gave the analytical sample, mp 142–144°. The mass spectrum showed a molecular ion at *m/e* 228; ir (KBr) 6.3, 6.65, 7.35, 8.0, 8.90, 9.70, 13.00, and 13.80 μ; λ_{max}^{MeOH} 322 (8100) and 240 mμ (ϵ 35,200). *Anal.* Calcd for $C_{10}H_7ON_2F_3$: C, 52.36; H, 3.07; N, 12.28. Found: C, 52.38; N, 3.18; N, 12.00.

2-Bromomethyl-3-trifluoromethylquinoxaline 1-Oxide (IV). Bromine (0.8 g, 0.005 mole) was dissolved in methylene chloride (5 ml) and was added dropwise to a refluxing solution of 2-methyl-3-trifluoromethylquinoxaline 1,4-dioxide (1.2 g, 0.005 mole) in the same solvent (15 ml). The reaction was refluxed overnight. The dried residue was crystallized several times from methanol to yield the analytical sample (0.125 g, 8% yield), mp 130–131°. The mass spectrum showed two molecular ions at *m/e* 308 and 306; ir (KBr) 6.30, 6.65, 7.30, 8.50, 9.90, 10.70, 12.85, and 13.82 μ; λ_{max}^{MeOH} 330 (2400) and 245 mμ (ϵ 11,000). *Anal.* Calcd for $C_{10}H_6ON_2BrF_3$: C, 39.08; H, 1.95; N, 9.11. Found: C, 38.78; H, 1.93; N, 9.01.

2-Methyl-3-trifluoromethylquinoxaline (VI). 2-Methyl-3-trifluoromethylquinoxaline 1,4-dioxide (0.19 g, 0.0008 mole) was suspended in water (2 ml). To this suspension a solution of sodium dithionite (0.630 g, 0.0036 mole), in water (2 ml), was added dropwise while stirring. After a few hours the reaction was extracted with chloroform, which was dried, filtered, and evaporated to dryness. The residue (0.10 g) was sublimed at room temperature to yield the pure sample, mp 80–82° (lit. 83–84°).[20] The mass spectrum showed a molecular ion at *m/e* 212.

3,4-Dihydro-2-methyl-3-trifluoromethylquinoxaline (VII). 2-Methyl-3-trifluoromethylquinoxaline 1,4-dioxide (0.63 g, 0.00026 mole) was dissolved in 50% aqueous methanol (5 ml). A solution of sodium dithionite (0.21 g, 0.0012 mole) in water (1 ml) was added. An immediate precipitate was formed which redissolved upon stirring. The reaction was further stirred for 1.5 hr at room temperature. Evaporation of the methanol under reduced pressure was followed by ether extraction of the aqueous solution. The organic phase was dried, filtered, and evaporated to dryness to yield a gum which crystallized from ether–hexane (0.015 g), mp 122–127°. The mass spectrum showed a molecular ion at *m/e* 214. No further purification by crystallization was possible since the compound was air oxidized to VI.

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Nitrogen-15 Nuclear Magnetic Resonance Spectroscopy. Substituent Effects on ^{15}N–H Coupling Constants and Nitrogen Chemical Shifts in Aniline Derivatives

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Abstract: Substituent effects on one-bond ^{15}N–H couplings and nitrogen chemical shifts in a series of aniline-^{15}N derivatives have been examined. Electron-withdrawing substituents are found to cause an increase in the magnitude of $^1J(^{15}\text{N–H})$ and a downfield shift of the nitrogen resonance. These observations are interpreted in terms of a change in hybridization and a concomitant decrease in π electron density at nitrogen.

It has long been recognized that, among other properties, the basicity of aniline is significantly altered by the presence of a ring substituent. Since anilinium ion formation requires the donation of the nitrogen lone pair to a proton, any structural feature which tends to reduce the electron density at nitrogen will decrease its proton affinity, whereas any factor which enhances this density will have the opposite effect. These same considerations should be reflected in the nuclear magnetic resonance parameters of aniline and its ring-substituted derivatives. This paper is concerned with the effect of substituents on the one-bond ^{15}N–H coupling constants and nitrogen-15 chemical shifts in aniline derivatives.[1]

In the absence of overriding anisotropic effects, the chemical shifts of the carbon atoms in a benzene ring and of any atom attached to it should reflect the electron density at the position in question. It is generally considered that a substituent alters the π electron density of the aromatic ring by both resonance and inductive interactions and that the latter effects are transmitted to ring protons or side chain atoms by successive and diminishing polarization of the intervening σ bonds or by a through-space field effect.[2] The

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