Experimental Section

The details of the procedures and pertinent properties of the products are summarized in Table III.

Literature Cited

(1) Bergmann, M., Michalis, M., *Chem. Ber.*, **63,** 987 (1930).
(2) Cleland, G. H., Nieman, C., *J. Am. Chem. Soc.*, **71,** 841 (1949).
(3) Dakin, H. D., West, R., *J. Biol. Chem.*, **78,** 745, 757 (1928).
(4) Hiskey, R. G., Adams, J. B., Jr., *J. Org. Chem.*, **30,** 1340 (1965).
(5) King, J. A., McMillan, F. H., *J. Am. Chem. Soc.*, **74,** 2859 (1952).
(6) Smissman, E. E., Inloes, R. L., El-Antably, S., Shaffer, P. J., *J. Med. Chem.*, **19,** 161 (1976).
(7) Smissman, E. E., Warner, V. D., *J. Med. Chem.*, **15,** 681 (1972).
(8) Smissman, E. E., Weis, J. A., *J. Med. Chem.*, **14,** 945 (1971).
(9) Taylor, R. J., Jr., Leinweber, F. J., Braun, G. A., *Biochem. Pharmacol.*, **22,** 2299 (1973).
(10) Weygand, F., Klinke, P., Eigen, I., *Chem. Ber.*, **90,** 1896 (1957).
(11) Weygand, F., Ropsch, A., *Chem. Ber.*, **92,** 2095 (1959).
(12) Wiley, R. H., Borum, O. H., "Organic Syntheses", Collect Vol. 4, Wiley, New York, N.Y., 1963, p 5.
(13) Zervas, L., Photaki, I., *J. Am. Chem. Soc.*, **84,** 3887 (1962).

Received for review September 13, 1976. Accepted January 6, 1977. This work was supported in part by the National Institutes of Health Grants GM 9254 and GM 14270. This paper is dedicated to the memory of Professor Edward E. Smissman and Mr. S. H. Israili.

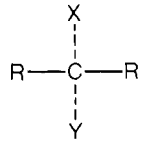
Chemical Shift Nonequivalence of Prochiral Groups in the ^{1}H Nuclear Magnetic Resonance Spectra of Some 3-Alkyl Derivatives of Phthalic Anhydride and Tetrachlorophthalic Anhydride

Norman F. Bray,* Reuben L. Baumgarten,* and Edward Edelson

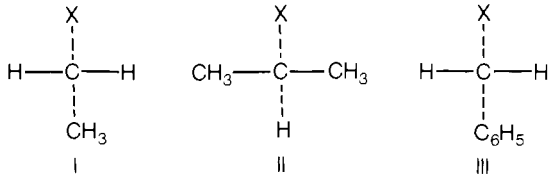
Department of Chemistry, Herbert H. Lehman College of the City University of New York, Bronx, New York 10468

^{1}H NMR spectra of molecules containing prochiral centers such as various 3-alkyl derivatives of phthalic anhydride and tetrachlorophthalic anhydride have been examined and interpreted. This investigation has found the ^{1}H NMR data to be consistent with the concept of prochirality in relation to the chemical shift nonequivalence of geminal groups.

Some reported ^{1}H NMR spectra have been misinterpreted (*16*) because of the unawareness of the effect of the chemical shift nonequivalence of geminal groups and the concept of prochirality. The prochirality concept of Hanson (*15*) and the nomenclature of Mislow and Raban (*19*) are applicable to a prochiral center represented as

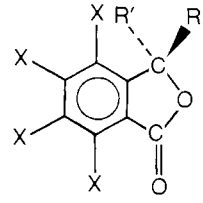


In the ^{1}H NMR spectrum of such a prochiral assembly, the ligands (R) can be equivalent (isochronous) or nonequivalent (anisochronous) in their chemical shift depending on the other substituents, X and Y. This investigation concerns itself primarily with the effect of the ethyl, I, isopropyl, II, and benzyl, III, moieties on the ^{1}H NMR spectra of some 3-alkylphthalides and 3-alkyltetrachlorophthalides.



I II III

There has been considerable interest in various alkylphthalides and their applicability to food flavorings, since some 3-alkylphthalides (**1**, R′, X = H) are known constituents of oil of celery and believed to be responsible for celery flavor (*10, 11*).



1

In a prior investigation (*5*), the ^{1}H NMR splitting of some 3,3-dialkylphthalides (**1**, X = H) and 3-alkyltetrachlorophthalides (**1**, R′ = H; X = Cl) have been attributed to molecular asymmetry and the effect of the magnetic anisotropy of the aromatic ring current. Our studies on these and related compounds indicate that the splitting is more accurately attributed to the presence of a prochiral center in the molecule.

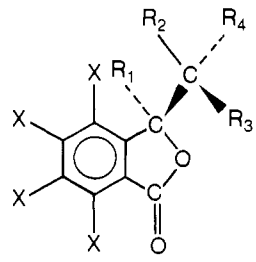
Discussion and Results

Chemical shift nonequivalence of chemically equivalent protons has been known for some time (*14*). Usually, phenomena of this type were attributed to different conformer populations which are temperature dependent. Experimentally, systems of this type are detected by running the spectra over a broad temperature range. Several years ago, some phthalic anhydride derivatives were synthesized and their ^{1}H NMR spectra showed several interesting results (*5*). For example, in 3-isopropyltetrachlorophthalide (**1**, R = $(CH_3)_2CH$–; R′ = H; X = Cl), the two geminal methyl groups of the isopropyl moiety were found to be magnetically nonequivalent with a separation of 44 Hz at 60 MHz (0.73 ppm) and were independent of temperature in the range of 25 to 160 °C.

Other compounds such as 3-ethyltetrachlorophthalide (**1**, R = CH_3CH_2–; R′ = H; X = Cl) and 3,3-dibenzylphthalide (**1**, R, R′ = $C_6H_5CH_2$–; X = H) also showed similar spectral features (*5*).

From these spectral data, the earlier investigators assumed that some other effect was operating in this system, postulating that the aromatic ring current in these compounds behaved as an asymmetric or chiral center producing the observed anomalous splitting pattern.

In order to reinvestigate the spectral data in terms of the concept of prochirality, new phthalic anhydride derivatives were synthesized and their ^1H NMR spectra recorded. From the data reported in this paper, it is now evident that the aromatic ring current is not the significant factor responsible for the multiple splitting patterns observed in the ^1H NMR spectra, but it is the existence of a prochiral center on the carbon atom adjacent to the 3-position, in which R_2 and R_3, **2**, are diastereotopic.



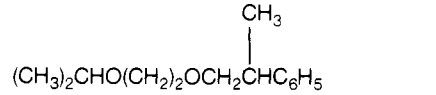
2

In order to test this hypothesis, 3-isopropyltetrachlorophthalide (**2**, R_1, R_4 = H; R_2, R_3 = CH_3; X = Cl) and 3-ethyltetrachlorophthalide (**2**, R_1, R_2, R_3 = H; R_4 = CH_3; X = Cl) were prepared and their ^1H NMR spectra recorded.

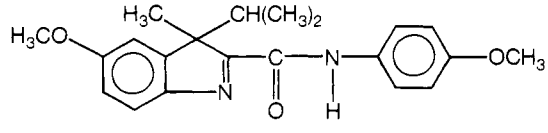
The spectrum of 3-isopropyltetrachlorophthalide shows two methyl doublets separated by 44 Hz, a complex multiplet in the methine region, and a doublet for the 3-hydrogen (**2**, R_1 = H) further downfield. The spectrum was further elucidated through spin–spin decoupling experiments. When 3-isopropyltetrachlorophthalide was irradiated at the position of the methinyl hydrogen of the isopropyl moiety (R_4), it was found that the 3-hydrogen doublet and the geminal methyl doublets reduced to singlets. The chemical shift of the methyl groups was not affected, the 44 Hz separation remaining constant. When the same compound was irradiated at the position of the 3-hydrogen, the methyl peaks were again unaffected, but the methinyl multiplet of the isopropyl group was simplified.

Decoupling experiments (frequency sweep mode) were also run on 3-ethyltetrachlorophthalide. On irradiating the position of the methyl group, the methylene absorption was observed to simplify but did not reduce to any recognizable pattern. The corresponding 3-alkylphthalides were synthesized; their ^1H NMR spectra were run and decoupled. Similar spectral features were observed for these compounds.

These decoupling experiments show that the geminal methyl protons in 3-isopropyltetrachlorophthalide and the methylene protons in 3-ethyltetrachlorophthalide are anisochronous and that their spectral features can be attributed to the presence of a prochiral center in these molecules. Similar effects have been observed in other molecules (*21*). Reported geminal methyl separations in molecules containing prochiral centers range from zero in **3** (*23*) to 0.91 ppm in **4** (*17*). The separation of the methyl



3



4

groups appears to increase with the size and complexity of the molecule. The separation of 0.73 ppm in 3-isopropyltetrachlorophthalide agrees favorably with these data.

In contrast to these observed complex splitting patterns, the 3-methyl- (**2**, R_1, R_2, R_3, R_4, X = H) and 3-*tert*-butylphthalides (**2**, R_1, X = H; R_2, R_3, R_4 = CH_3) do not have a prochiral center, and their ^1H NMR spectra exhibit spectral features which can be interpreted by first-order methods.

In the case of 3-benzylphthalide (**2**, R_1, R_2, R_3, X = H; R_4 = C_6H_5) the benzyl methylene carbon represents a prochiral center. However, the ^1H NMR spectrum of this compound shows no apparent difference in the methylene protons. This is not unusual as many prochiral systems do not necessarily exhibit complex splitting patterns, especially in achiral media.

The 3-alkyltetrachlorophthalides were prepared and used by Brumlik et al. (*5*) in preference to the 3-alkylphthalides because the chloro compounds are solids, and can be prepared and isolated readily, whereas the nonchloro compounds are liquids and are not easily synthesized and isolated. In order to study the possibility that the chloro substituents caused a preferred conformation of the 3-alkyl group which could cause the observed splitting pattern, the nonchlorinated derivatives were synthesized also. On investigating the 3-alkylphthalides, we found their ^1H NMR spectra to be very similar to the chloro analogues, except for the presence of an aromatic absorption.

All ^1H NMR spectral parameters are reported in Table I.

Experimental Section

Preparation of 3-Alkyltetrachlorophthalides and 3,3-Dialkylphthalides. The 3-alkyltetrachlorophthalides and 3,3-dialkylphthalides have been synthesized by several methods, which are described vaguely, with poor purification procedures in the literature. A series of 3-alkyltetrachlorophthalides (or 3,3-dialkylphthalides) was prepared by modification of the methods of Bauer (*1–3*). Grignard reagents were prepared by reacting the corresponding alkyl iodide or bromide with magnesium metal in anhydrous ether. Equal volumes (250 mL) of the 3.50 M Grignard reagent and of toluene are placed in a 1-L three-necked round-bottom flask, fitted with a mechanical stirrer, reflux condenser, and polyethylene bag or other suitable device for adding the anhydride.

Small quantities of finely powdered tetrachlorophthalic anhydride (or phthalic anhydride) are added from the polyethylene bag, allowing each portion to react completely with the Grignard reagent before adding more anhydride (till foaming ceases and the material goes into solution). It is best to keep the reaction temperature slightly below the reflux temperature of ether. When all the anhydride (the same number of moles as the moles of Grignard reagent used) has been added, the reaction mixture is poured onto 100 g of ice containing dilute hydrochloric acid in a fourfold molar concentration with respect to the starting materials. The organic layer is separated and washed with dilute sodium bicarbonate solution until the aqueous layer is colorless. The ether and toluene are removed from the reaction mixture, and the remaining solid residue is dissolved in chloroform. The insoluble material is filtered off. The excess chloroform is evaporated, and the product is recrystallized from ethyl alcohol (using decolorizng carbon if necessary) or from chloroform and petroleum ether, the latter being preferable to ethyl alcohol. Several recrystallizations are necessary to obtain a pure product with a sharp melting point. The yield of 3-alkyltetrachlorophthalide or 3,3-dialkylphthalide is obtained in about 15–25%. The data are reported in Table II.

Preparation of 3-Alkylphthalides. Various 3-alkylphthalides have been synthesized and reported in the chemical literature (*8, 9, 12, 13, 18, 22*). *o*-Pthalaldehydic acid (*o*-carboxybenzaldehyde) is prepared by the method of Fuson (*7*) or purchased directly from the Aldrich Chemical Co. and reacted with the corresponding Grignard reagents to produce the 3-alkyl-

Table I. NMR Data

Compound[e]						Chemical shift, Hz[a]				Coupling constants, Hz[a]					
No.	X	R_1	R_2	R_3	R_4	δ_1	δ_2	δ_3	δ_4	J_{12}	J_{13}	J_{14}	J_{23}	J_{24}	J_{34}
I[b]	H	CH_3	H	H	H	500.4s (-)	500.4s (-)	500.4s (-)	500.4s (-)						
II[b]	Cl	CH_3	H	H	H	496.8s (-)	496.8s (-)	496.8s (-)	496.8s (-)						
III	H	H	H	H	H	269.239q	501.854d	501.854d	501.854d	6.596	6.596	6.596			
						†0.023	†0.016	†0.016	†0.016	†0.023	†0.023	†0.023			
IV	H	H	H	H	CH_3	271.595q	471.694m	487.749m	541.106t	6.842	4.437		−12.337	7.036	6.051
						†0.046	†0.121	†0.122	†0.071	†0.097	†0.098		†0.134	†0.092	†0.108
V	Cl	H	H	H	CH_3	267.863q	449.142m	491.629m	541.800t	7.000	3.758		−10.665	6.747	7.292
						†0.057	†0.120	†0.065	†0.076	†0.099	†0.087		†0.121	†0.089	†0.070
VI[c]	H	H	CH_3	H	CH_3	275.4d (-)	532.8d (-)	460.8m (-)	553.0d (-)		|5.41| (-)		|6.72| (-)		|6.58| (-)
VII[c]	Cl	H	CH_3	H	CH_3	251.4d (-)	532.422d	409.376m	553.101d		|2.40|		−7.073		−6.795
							†0.051	†0.080	†0.068		(-)		†0.073		†0.063
VIII[b]	H	H	CH_3	CH_3	CH_3	289.8s (-)	539.4s (-)	539.4s (-)	539.4s (-)						
IX	H	H	H	H	C_6H_5	255.126t	407.037d	407.037d		6.197	6.197				
						†0.081	†0.081	†0.081		†0.094	†0.094				

[a] Shifts relative to δ_{Me_4Si} = 600 Hz. The value preceded by the symbol † indicates the probable error for the parameters as calculated by LAOCN3 (*6*). Multiplicity of line indicated by s, singlet; d, doublet; t, triplet; q, quartet; m, complex multiplet. Unreported coupling constants are assumed to be zero. [b] Spectrum, except for aromatic region (where present), composed of one or more singlets; all values read directly from spectrum. [c] Too large for LAOCN3; compound lost before double irradiated spectrum was obtained. Values reported are read directly from the spectrum; position of δ_3 is center of multiplet. Coupling constants are assigned on the basis of the analysis of VII. [d] Analysis carried out on the spectrum irradiated at the 3-H position; since the 3-H line in the nonirradiated spectrum is a doublet, J_{12} and J_{13} are assumed equal, and these parameters are taken directly from the nonirradiated spectrum. [e] See compound **2**.

Table II. 3-Alkyltetrachlorophthalides and 3,3-Dialkylphthalides

Compound[b]	MP, °C
R = CH_3; R′ = CH_3 (3,3-Me_2);[a] X = Cl	165–166
R = C_2H_5; R′ = H; X = Cl	132–133
R = $(CH_3)_2CH$–; R′ = H; X = Cl	154–156
R, R′ = CH_3; X = H	70–71
R, R′ = $C_6H_5CH_2$–; X = H	202–204

[a] The dimethyl compound is obtained (rather than the monomethyl) because of the small size of the methyl groups; no steric factors are present. [b] See compound **1**.

Table III. 3-Alkylphthalides (See Compound 1, R′ = H)

R	Mp, °C	Bp, °C		% C	% H
CH_3		275[a]			
C_2H_5–	12[c]	289[b], 291,[c]	Calcd	74.04	6.22
		24 at 10 mmHg[e]	Found	73.88[f]	6.50[f]
$(CH_3)_2CH$	32–34[d]	225–229,[c]	Calcd	74.97	6.86
		131–135 at	Found	74.89[f]	6.82[f]
		1 mmHg[e]			
		55–60 at			
		0.7 mmHg[e]			
$(CH_3)_3C$		140–143 at			
		10 mmHg[e]			
$C_6H_5CH_2$	60–61[e]				

[a] Reported in ref 22. [b] Reported in ref 18. [c] Reported in ref 12. [d] Reported in ref 8. [e] Reported in this paper. [f] Carbon and hydrogen analyses performed by Schwartzkopf Microanalytical Laboratory, Woodside, N.Y.

phthalides as reaction products. The preparative and purification procedures were modifications of those devised by Mermod and Simonis (*18, 22*).

The 3-methyl-, 3-ethyl-, and 3-isopropylphthalides were prepared by adding 5 g of phthaldehydic acid very slowly (over a period of 2 h) from a polyethylene bag to 250 mL of 1 M Grignard reagent while stirring the reaction mixture. The solution turned green in color and, after addition of the phthalaldehydic acid, was poured onto 100 g of ice containing 25 mL of concentrated hydrochloric acid. The ether layer was separated in a separatory funnel. The aqueous layer was extracted with two 25-mL portions of ether, and the ether extracts were combined. The acidic ether layer was neutralized with 600 mL of saturated sodium bicarbonate solution, separated, and dried over anhydrous sodium sulfate. The yellowish ether layer was concentrated by warming, and the yellow oil transferred to a 25-mL microdistilling flask, and distilled under reduced pressure. Several vacuum distillations were required to produce a clear, colorless, viscous liquid. All the 3-alkylphthalides had the characteristic celery-like odor (*10, 11*). The yields obtained were about 1–2 g. Although some of the compounds are known compounds, several were sent out for carbon–hydrogen analysis. The data are reported in Table III.

Attempts to prepare 3-benzylphthalide by reacting benzylmagnesium bromide with phthaldehydic acid resulted in the formation of 1,2-diphenylethane (identified by a comparison of IR spectra and melting point data), free the coupling reaction characteristic of benzyl Grignard reagents. The 3-benzylphthalide was prepared by the reduction of 3-benzalphthalide (*4*) over a Pd/C catalyst or using Raney nickel, which proved to be more successful, giving a higher yield (8.1 g of 3-benzylphthalide from 10 g of 3-benzalphthalide) of product. The 3-benzalphthalide was prepared by reacting phthalic anhydride with phenylacetic acid in the presence of freshly fused sodium acetate as described in "Organic Synthesis" (*20*).

^1H NMR Spectra. All spectra were recorded using a Perkin-Elmer R-12 60 MHz spectrometer equipped with a Perkin-Elmer Model R-12 double resonance accessory having a probe temperature of ca. 35 °C. Each spectrum was run as a saturated solution in deuteriochloroform (Merck) with 1% (v/v) tetramethylsilane used as an internal standard and recorded at 2.2 Hz/s. All measurements are accurate to ±1 Hz. Except for those compounds exhibiting a single-line spectrum and/or exceeding seven nuclei of spin ½, analysis of the spectra of the groups attached at the 3-position was carried out using a version of the 2 to 7 spin-½ program LAOCN3 (*6*) of Bothner-By and Castellano run on the CUNY/UCC IBM 370/168 computer.

The analysis of the 3-isopropylphthalide, which is too large for this program, was carried out on spectra irradiated at the 3-H position. In this spectrum the methine proton of the isopropyl moiety is simplified while the methyl proton is unaffected. Since no long range coupling is observed, the doublet at ca. 5.5 ppm can be attributed to the interaction between the ring 3H and the methine proton of the isopropyl moiety.

The 3-isopropyltetrachlorophthalide was not analyzed, as the compound was too large for LAOCN3 and the sample was lost before the double resonance experiments could be completed. The values reported are read from the unirradiated spectrum using the nonchloro analogue as a guide. The chemical shift of the complex multiplet of the isopropyl methine proton is reported as the position of the center of the multiplet.

Acknowledgment

The authors wish to thank Mr. John Klonowski who assisted in the maintenance of the NMR spectrometer and Professor Donald Clark of Fordham University, Bronx, N.Y., for his assistance.

Literature Cited

(1) Bauer, H., *Arch. Pharm. Ber. Dtsch. Pharm.*, **247**, 220–225 (1909).
(2) Bauer, H., *Ber.*, **37**, 735–737 (1904).
(3) Bauer, H., *Ber.*, **38**, 240–241 (1905).
(4) Berti, G., *Gazz. Chim. Ital.*, **86**, 655–666 (1956).
(5) Brumlik, G. C., Baumgarten, R. L., Kosak, A. I., *Nature (London)*, **201**, 388–389 (1964).
(6) DeTar, D. F., Ed., "Computer Programs for Chemistry," Vol. I, W.A. Benjamin, New York, N.Y., 1968, pp 10–53. The program was modified to use scratch disk rather than scratch tape; output was checked using sample data from this reference.
(7) Fuson, R. C., *J. Am. Chem. Soc.*, **48**, 1093–1096 (1926).
(8) Gabriel, S., *Ber.*, **18**, 3480 (1885).
(9) Gabriel, S., Posner, T., *Ber.*, **27**, 2505 (1894).
(10) Gold, H. J., Wilson III, C. W., *Florida State Horticultural Society*, **74**, 291–296 (1961).
(11) Gold, H. J., Wilson III, C. W., *J. Food Sci.*, **28**, 484–488 (1963).
(12) Gottlieb, J., *Ber.*, **32**, 960 (1899).
(13) Gucci, P., *Gazz. Chim. Ital.*, **28**, I, 297, and **28**, II, 504 (1898).
(14) Gutowsky, H. S., *J. Chem. Phys.*, **37**, 2196 (1962).
(15) Hanson, K. R., *J. Am. Chem. Soc.*, **88**, 2731 (1966).
(16) Jennings, W. B., *Chem. Rev.*, **75**, 307–322 (1975).
(17) Kessler, H., Zeeh, B., *Tetrahedron*, **24**, 6825 (1968).
(18) Mermod, E., Simonis, H., *Ber.*, **41**, 982 (1908).
(19) Mislow, K., Raban, M., *Top. Stereochem.*, **1**, 1 (1967).
(20) "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 61.
(21) Reference 1, especially p 313.
(22) Simonis, H., Marben, E., Mermod, E., *Ber.*, **38**, 3982 (1905).
(23) Whitesides, G. M., Holtz, D., Roberts, J. D., *J. Am. Chem. Soc.*, **86**, 2628 (1964).

Received for review November 24, 1976. Accepted April 8, 1977.

Synthesis and Properties of Substituted α-Phenylcinnamonitrilesulfonamides

James T. Stewart,* Richard D. Dowling, and Otis J. Bouwsma
Department of Medicinal Chemistry, School of Pharmacy, University of Georgia, Athens, Georgia 30602

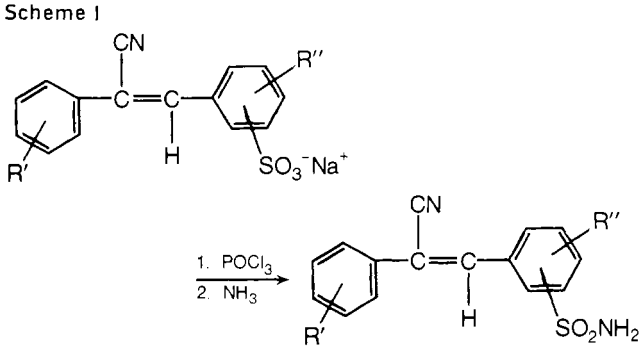
Some substituted α-phenylcinnamonitrilesulfonamides are synthesized from the corresponding sulfonates via reaction with phosphorus oxychloride and ammonia. A summary of the physical properties of the new compounds is presented.

Interest in this laboratory in the medicinal activity of α-phenylcinnamonitrilesulfonamides as potential antimalarial agents resulted in the synthesis of some model compounds (Table I). A literature search revealed that little if any information was available concerning the synthesis and physical properties of these substances.

The compounds were synthesized from the corresponding sodium α-phenylcinnamonitrilesulfonates (*2*) by reaction with phosphorus oxychloride to yield the sulfonyl chloride followed by conversion to the sulfonamide with ammonia (Scheme I). The resulting products usually precipitated from solution upon evaporation of the organic phase. Many of the sulfonamides were hygroscopic and had to be well dried in a vacuum oven before satisfactory elemental analyses and resulting crystalline products could be obtained.

Table I presents a summary of the physical properties of the sulfonamides. There was special interest in the fluorescence of these compounds since previous experience with other types

Scheme I



of α-phenylcinnamonitriles had shown that such substances possessed good fluorescent intensity in solution (*1*). Fluorescent measurements were performed by visual examination of the dry powder using long wavelength ultraviolet light (Ultra-violet Products, Inc., San Gabriel, Calif) and by determination of the excitation and emission maxima of the compounds in ethanol using a spectrophotofluorometer. The compounds all possessed varied fluorescent intensities in the solid state and in ethanol solution. Comparison of the fluorescent intensity of the sulfonamides to quinine sulfate via the quinine reference unit (QRU)