^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.

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Synthesis and Properties of Substituted α-Phenylcinnamonitrilesulfonamides

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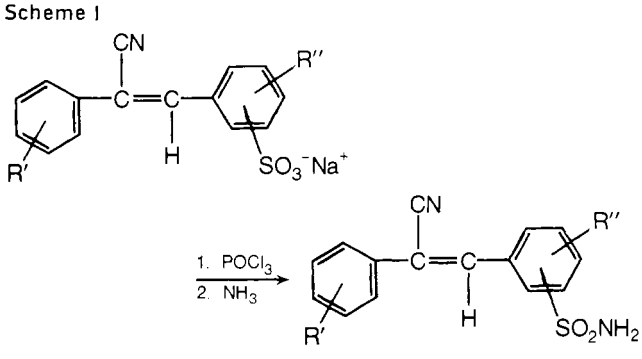
Some substituted α-phenylcinnamonitrilesulfonamides are synthesized from the corresponding sulfonates via reaction with phosphorus oxychloride and ammonia. A summary of the physical properties of the new compounds is presented.

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)

Table I. Summary of Physical Properties of Substituted α-Phenylcinnamonitrilesulfonamides[a]

Compd	R_1	R_2	R_3	R_4	R_5	R_6	Mp, °C	Yield,[b] %	UV (EtOH) λ_{max}, nm	Solid[c]	Fluorescence: Soln[d] excit max	Soln[d] emiss max	Rel fluores QRU[e]
1	H	H	H	SO_2NH_2	H	H	162–165	73	305 (ε 12600)	Yellow	311	403	0.006
2	H	H	H	H	SO_2NH_2	OCH_3	195–199	77	325 (ε 17800)	Yellowish green	312	403	0.004
3	H	OCH_3	H	SO_2NH_2	H	H	255–259	43	312 (ε 1250)	Blue	398	410	0.017
4	H	OCH_3	H	H	SO_2NH_2	OCH_3	215–218	68	335 (ε 15000)	*f*	310	407	0.013
5	OCH_3	OCH_3	H	SO_2NH_2	H	H	208–212	74	330 (ε 5480)	Bluish white	345	493	0.288
6	OCH_3	OCH_3	H	H	SO_2NH_2	OCH_3	229–231	91	345 (ε 11600)	Yellowish green	355	436	0.016
7	OCH_3	OCH_3	OCH_3	SO_2NH_2	H	H	171–174	84	315 (ε 2540)	Bluish white	322	510	0.103
8	OCH_3	OCH_3	OCH_3	H	SO_2NH_2	OCH_3	220–222	54	340 (ε 10300)	Yellowish green	312	404	0.014
9	H	Br	H	SO_2NH_2	H	H	189–192	77	308 (ε 3350)	Yellow	311	404	0.001
10	H	Br	H	H	SO_2NH_2	OCH_3	248–251	53	330 (ε 20400)	Yellowish green	310	405	0.004
11	H	C_6H_5	H	SO_2NH_2	H	H	219–225	85	252 (ε 21100)	Blue	311	406	0.005

[a] Elemental analyses were determined for each compound and agreed with calculated values within ± 0.4%. IR assignments also agreed with the indicated structures. [b] No attempt was made to optimize yield. Yields are based on starting sulfonate. [c] Ascertained by visual observation of the dry powder when exposed to UV light from a long wavelength UV lamp. [d] Measurements were recorded on a Perkin-Elmer MPF-4 spectrophotofluorometer using ethanol as solvent. [e] Quinine reference unit, see ref 1. [f] Denotes that no fluorescence was observed in the solid state.

was performed (*1*). It was concluded that most of the compounds possessed only moderate to weak fluorescence compared to quinine sulfate. Compounds **5** and **7** were the most fluorescent of the sulfonamides in that they showed QRU values of 0.288 and 0.103, respectively.

The sulfonamides were also tested for potential antimalarial activity against mice infected with *Plasmodium berghei*. At single doses of 40, 160, and 640 mg kg^{-1} administered subcutaneously, the compounds showed no cures and were nontoxic.

Experimental Section

Melting points were taken in open capillary tubes with a Thomas-Hoover apparatus; they are uncorrected. UV spectra were determined in ethanol solution by means of a Perkin-Elmer Model 450 spectrophotometer. IR spectra were obtained with a Perkin-Elmer Model 467 spectrophotometer. Fluorescence spectra were determined with a Perkin-Elmer Model MPF-4 spectrophotofluorometer equipped with a corrected spectra accessory. Microanalyses were performed by Atlantic Microlab, Inc., Atlanta, Ga.

Preparation of Substituted Sodium α-Phenylcinnamonitrilesulfonates. The compounds were synthesized via base-catalyzed condensations of substituted phenylacetonitriles and benzaldehyde sulfonic acid sodium salts as reported previously (*2*). The sulfonates usually precipitated from solution and were collected and dried. In those cases where no precipitation occurred, the solvent was evaporated on a rotary evaporator to near dryness, and the residue collected and dried.

Preparation of Sulfonamide Derivatives. The general procedure as reported by Vogel (*3*) was utilized to convert the respective sulfonates to their sulfonamide derivatives. The sulfonamides were recrystallized using benzene, ethanol, and/or ethanol–water mixture.

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