Identification of Sulfonamides by NMR Spectroscopy

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Abstract □ A classification scheme based on the NMR spectra of 21 sulfonamides was developed. This scheme permits the rapid and simple identification of these drugs when they are encountered as unknowns.

Keyphrases □ Sulfonamides—NMR identification, classification scheme □ NMR spectroscopy—identification, classification scheme, sulfonamides

The use of NMR spectroscopy for identifying organic compounds is well established. This technique is both specific and rapid. If a suitable solvent is available and a reasonable concentration of the unknown can be achieved, identification is conveniently accomplished.

A number of therapeutically useful sulfonamides are often analyzed in this laboratory. NMR spectroscopy seems ideally suited to the identification of these drugs since their solubility in suitable solvents makes attainment of desired solution concentrations possible. This work represents a study of 21 pure sulfa drugs. In Table I the NMR spectra are classified into four main groups, after which the identification of a specific compound follows. These spectra and accompanying data (Figs. 1–21) are published to permit the use of this identification scheme. Although it was not done in this study, the identification of sulfas in pharmaceutical preparations is a logical next step, particularly since their dosage is high enough to permit isolation of a sufficient quantity of drug.

EXPERIMENTAL

NMR spectra were recorded with a spectrometer[1] (ambient probe temperature of 41°) using a sweep time of 500 sec. and a sweep width of 1000 Hz.; the delta (δ) scale was used throughout. Solutions (approximately 50–60 mg. of solute in 0.5 ml. solvent) were prepared with dimethyl sulfoxide-d_6[2] and were studied in sample tubes[3]. The small multiplet signal seen in each spectrum and centered at about 2.5 p.p.m. is due to dimethyl sulfoxide-d_6 in the solvent. Tetramethylsilane[4] was used as the internal reference in the dimethyl sulfoxide-d_6 solutions.

The compounds studied are working standards in this laboratory and gave assay results within compendial rubric standards as well as melting-point ranges in agreement with reported values. No special precautions were taken to dry the sulfonamides studied; in some cases, proton absorption ascribable to water may be seen in the 3.3–3.5-p.p.m. range.

RESULTS AND DISCUSSION

The individual spectra of the sulfas listed in Table I permit classification of these drugs into four major groups, depending upon the nature of the 6–8-p.p.m. region. Generally, the absorptions forming the basis for this approach to identification are due to protons bonded to aromatic or heterocyclic nuclei, but some exceptions can be found. The N'-hydrogen, acidic by virtue of being part of the sulfonamide group, is found in the 10–12-p.p.m. region. In many instances, the peak is very broad and not immediately apparent. Assignments for these peaks may simply be designated as "too broad." Furthermore, the presence of a characteristic broad singlet arising from the N^4-protons, although extending into the region as far as about 6.5 p.p.m., does not complicate the proposed identification scheme. This situation will be discussed subsequently.

The classification into groups is made according to the following spectral patterns:

Group I—an $AA'BB'$ pattern only
Group II—an $AA'BB'$ pattern and a sharp singlet, ascribable to one proton
Group III—an $AA'BB'$ and an AB pattern
Group IV—an $AA'BB'$ and an overlapping multiplet arising from three or more protons

Since the sulfanilic acid portion is common to all structures, the major peaks ascribable to the four phenyl protons resemble an AB pattern with small peaks at the base of each main peak. This arrangement is an $AA'BB'$ system, where exact values for neither the coupling constants nor the chemical shifts are available by simple inspections (1). However, for the sake of completeness, approximate values for the AA' and BB' chemical shifts ($\Delta\nu$) are noted on each spectrum. The coupling constant $J_{AB} = J_{A'B'}$ is about 9 Hz. in all of the compounds studied.

The differential assignment of the four phenyl protons is based on the spectrum of succinylsulfathiazole (Compound 11). The inductive effect of the succinyl substituent is assumed to deshield the 3,5-protons more effectively than the 2,6-protons, a reasonable assumption based on proximity. Since in the succinylsulfathiazole spectrum all four phenyl protons produce a singlet somewhat downfield from the $AA'BB'$ pattern due to the protons in the unsubstituted sulfathiazole, it seems clear that the protons most affected by the succinyl group should have the greatest chemical shift. On this basis, the 3,5-protons are assigned the AA' designation, leaving the 2,6-protons as the BB' pair. In all spectra, except for succinylsulfathiazole, the four phenyl protons produce an $AA'BB'$ pattern. It is noted that succinylsulfathiazole is included in Group II, even though its four phenyl protons, being accidentally equivalent as is evident from the foregoing discussion, are manifest as a singlet.

A discussion of the spectra of these compounds must include some consideration of the proton absorption of the sulfonamide —NH— and the —NH_2 group in the 4-position. For each compound the specific field positions of these protons is noted on the spectrum. The —NH— absorptions for these compounds appear as broad peaks in the region from 10.1 to 11.67 p.p.m. and, in each instance, are not involved with, and pose no complication to, the proposed identification scheme. On the other hand, the —NH_2 absorptions in the region from 5.83 to 6.5 p.p.m. do overlap the range (6.0–8.0 p.p.m.) chosen for the identification scheme. However, the broadness of these peaks permits easy differentiation from the absorption peaks needed for identity classification.

After initial classification into one of the four groups, the identification of specific sulfonamides may be accomplished by means of the spectral features of the 0–5.0 p.p.m. region, except for Group IV. The Group I compounds show heterocyclic alkyl (Compounds 1–3, 5, and 6), methylene (Compound 3), or methyl (Compound 4) proton absorptions at the field positions indicated on each figure. The Group II sulfas all exhibit one or two singlets assignable to methyl or methoxyl protons. In the case of Group III, the region either contains singlets arising from methoxyl, methyl, or methylene proton resonance or is blank. The last-named situation is noted

[1] Varian A-60.
[2] Minimum 99.5% deuterium, Mallinckrodt.
[3] Varian.
[4] Mallinckrodt.

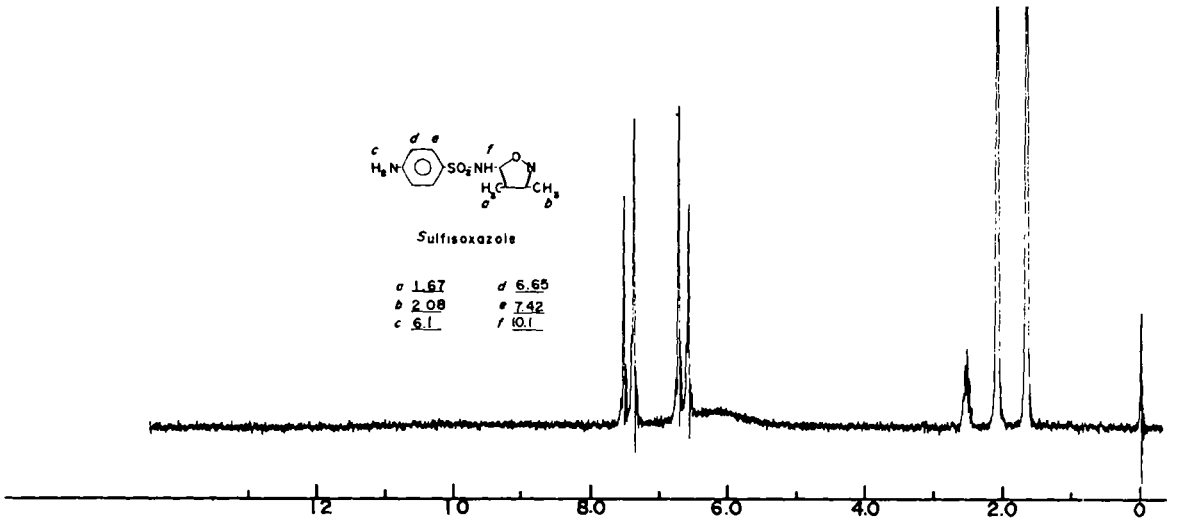


Figure 1—*Sulfisoxazole.*

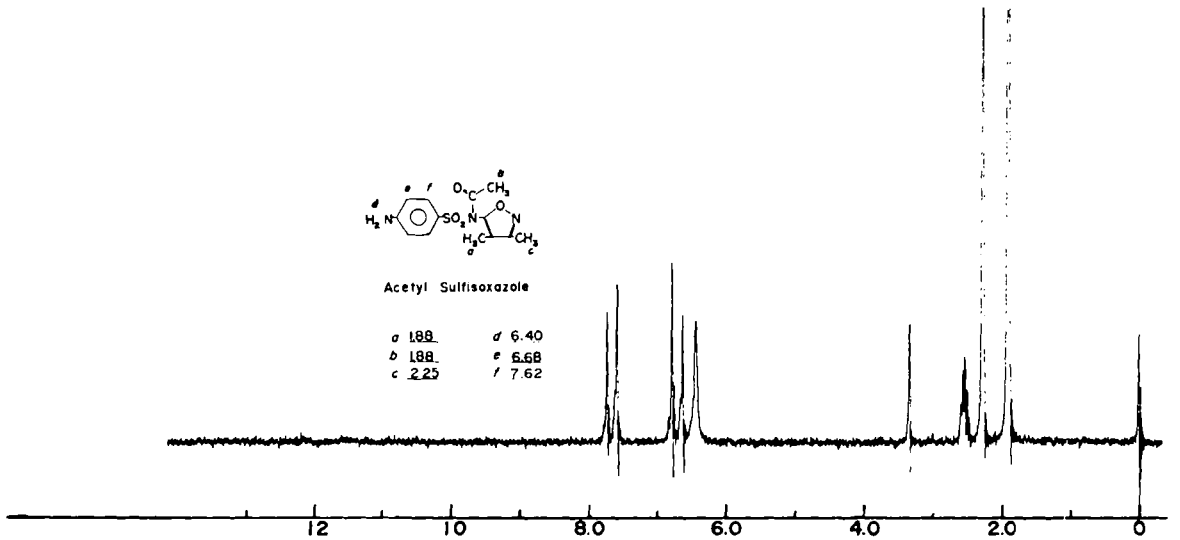


Figure 2—*Acetyl sulfisoxazole.*

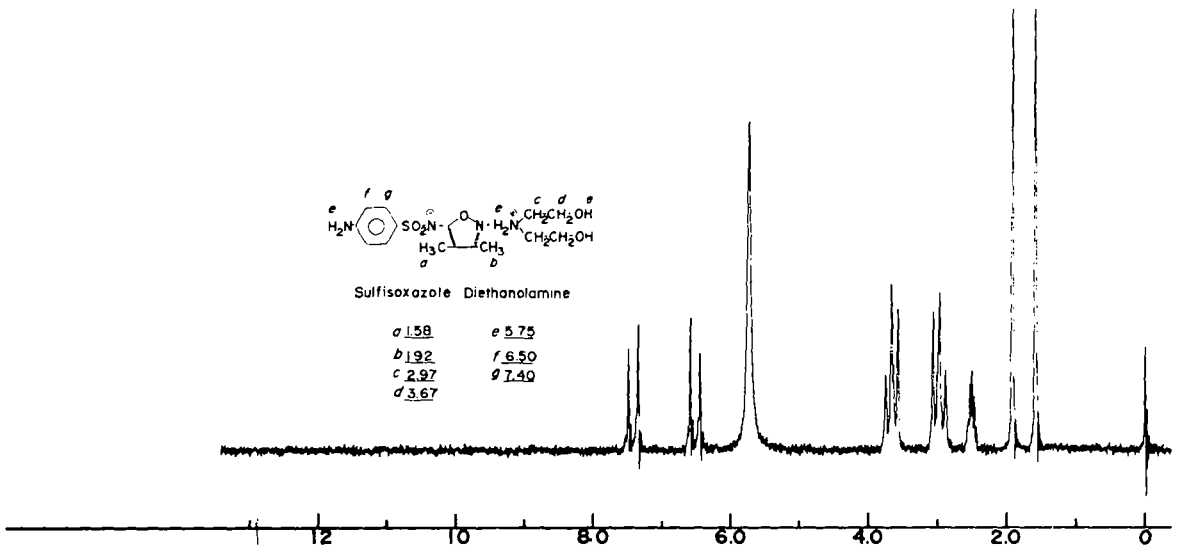
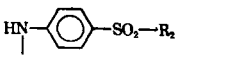


Figure 3—*Sulfisoxazole diolamine [diethanolamine].*

Table I—Structures and Some Significant NMR Spectral Features of the Sulfonamides Studied



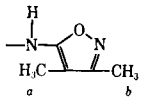
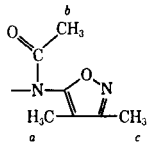
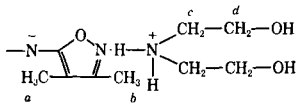
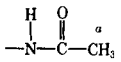
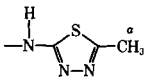
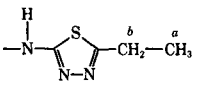
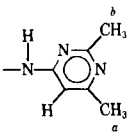
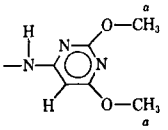
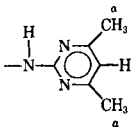
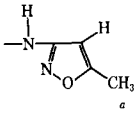
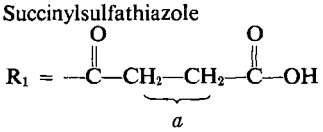
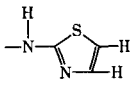
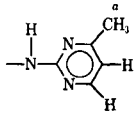
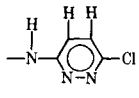
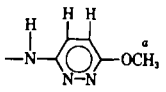
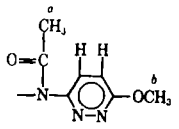
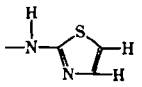
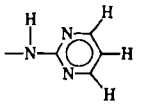
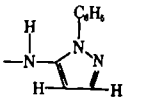
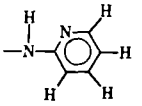
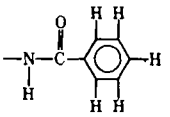
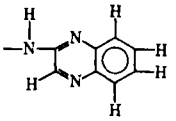
Compound and Figure	R_2	Significant Features in 0–5-p.p.m. (δ) Region — Signal Pattern	δ
	Group I		
1 Sulfisoxazole		(*a*) Singlet (*b*) Singlet	1.67 2.08
2 Acetyl sulfisoxazole		(*a*) Singlet (*b*) Singlet (*c*) Singlet	1.88 1.88 2.25
3 Sulfisoxazole diolamine [diethanolamine]		(*a*) Singlet (*b*) Singlet (*c*) A_2 portion of A_2B_2 pattern (*d*) B_2 portion of A_2B_2 pattern	1.58 1.92 2.97 3.67
4 Sulfacetamide		(*a*) Singlet	1.92
5 Sulfamethizole		(*a*) Singlet	2.47
6 Sulfaethidole		(*a*) Triplet (*b*) Quartet	1.21 2.83
	Group II		
7 Sulfisomidine		(*a*) Singlet (*b*) Singlet	2.25 2.35
8 Sulfadimethoxine		(*a*) Singlet	3.83
9 Sulfamethazine		(*a*) Singlet	2.25
10 Sulfamethoxazole		(*a*) Singlet	2.30
11 Succinylsulfathiazole R_1 = 		(*a*) Singlet	2.60
	Group III		
12 Sulfamerazine		(*a*) Singlet	2.33
13 Sulfachlorpyridazine			

Table I—*Continued*

Compound and Figure	R_1	—Significant Features in 0–5-p.p.m. (δ) Region— Signal Pattern	δ
14 Sulfamethoxypyridazine		(*a*) Singlet	3.90
15 Acetyl sulfamethoxypyridazine		(*a*) Singlet (*b*) Singlet	1.88 4.13
16 Sulfathiazole			
	Group IV		
17 Sulfadiazine			
18 Sulfaphenazole			
19 Sulfapyridine			
20 Sulfabenzamide			
21 Sulfaquinoxaline			

in Compounds 13 and 16, but in these cases the aromatic region is distinctive and permits identification. Since the members of Group IV do not show any activity in the upfield region, their characterization is based strictly on the aromatic region patterns.

The most difficult group of sulfa drugs to identify is Group IV. This is understandable since in each case there are two or three rings, aromatic or heterocyclic, with hydrogen substituents that exhibit resonance in the same spectral region. Fortunately, two compounds of this group are most easily identified. One is sulfadiazine (Compound 17) whose pyrimidine group's three protons exhibit an AX_2 system and are manifest in the same vicinity as the phenyl protons' $AA'BB'$ pattern. The other compound, sulfaphenazole (Compound 18), has an AB pattern arising from the 3,4-protons of pyrazole (5.85 and 7.55 p.p.m., respectively, having J_{AB} = 1.5 Hz.) and a less obvious $AA'BB'$ phenyl system. The broad singlet at 7.47 p.p.m. partially overlapping the BB' part of the $AA'BB'$ system is ascribable to the protons of the phenyl group bonded to the 1-position of pyrazole. The remaining three members present complex spectra not amenable to interpretation by simple means but still permitting identification by comparison with authentic spectra.

Although specific interpretation of the spectra is not presented here, except for that which is felt to be necessary for the identification of these compounds, some added comment about specific spectral features of certain sulfas seems warranted. Two compounds in Group I are interesting. Compound 3, sulfisoxazole diolamine [diethanolamine], has two pairs of methylene groups, part of the diethanolammonium cation, whose protons display an A_2B_2 system easily recognizable and convenient for identification. Compound 2, acetyl sulfisoxazole, is of interest since the methyl protons of the acetyl group produce a singlet overlapping the singlet ascribable to the protons of the methyl group at the 4-position of the isoxazole ring. The rationale for the proton assignments for this compound will appear in a subsequent publication.

Three compounds in Group III deserve some comment. The spectrum of sulfamerazine indicates that the coupling of the 4- and 5-protons of the pyrimidine ring results in a pair of doublets. The reduced intensity of the five-proton doublet is a manifestation of unresolved coupling with the adjacent methyl protons. The assignments for the protons of Compounds 13 and 14 are made from the work of Tori and Ogata (2) and reaffirm the predicted ring effects of the chloro and methoxy substituents.

An observation relating to compounds from three different groups involves the field position of the acidic —NH— portion of the sulfonamide. The chemical shift of this acidic proton is difficult to predict since it depends on structural properties and the acid-base nature of the solution environment. Properties of a compound determined in one solvent may not be a valid measure of another solvent, although it is convenient to use available data in solvents such as water when other measurements are not in hand. Thus, it is not surprising that no overall relationship exists when a plot of pKa (in water or alcohol-water) is made against $\Delta\nu$ for sulfamethazine (Compound 9, pKa 7.37, $\Delta\nu$ 11.0), sulfamerazine (Compound 12, pKa 7.06, $\Delta\nu$ 11.15), and sulfadiazine (Compound 17, pKa 6.48, $\Delta\nu$ 11.30), three pyrimidine-containing sulfonamides (3).

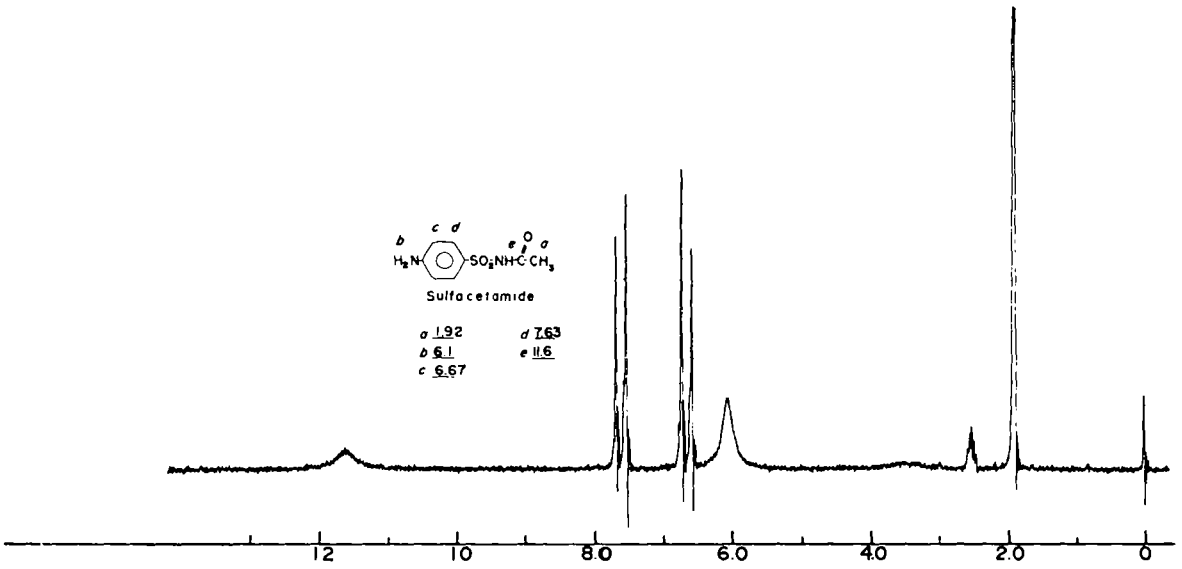


Figure 4—*Sulfacetamide.*

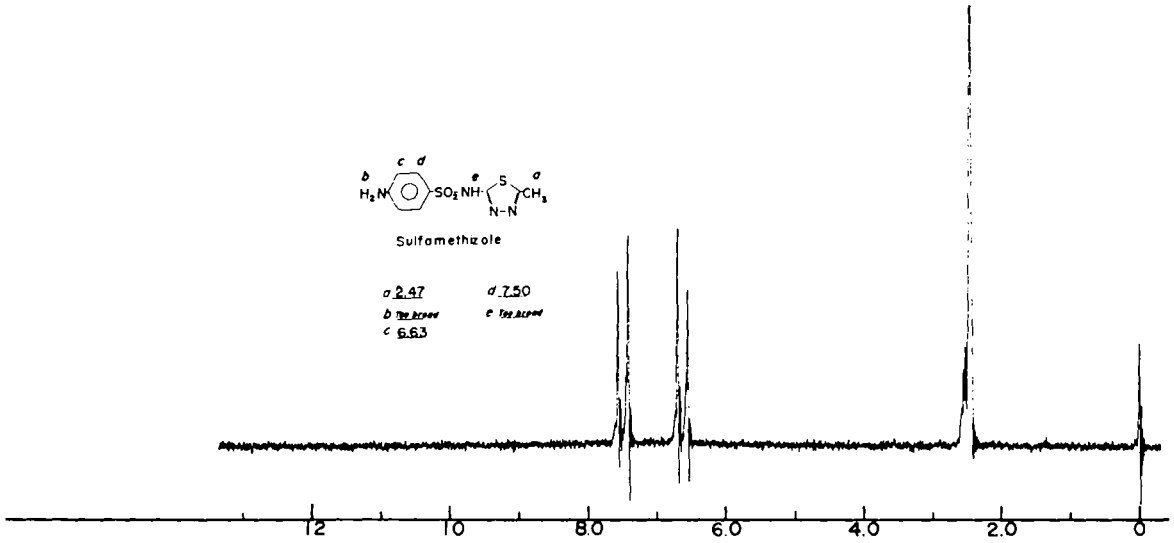


Figure 5—*Sulfamethizole.*

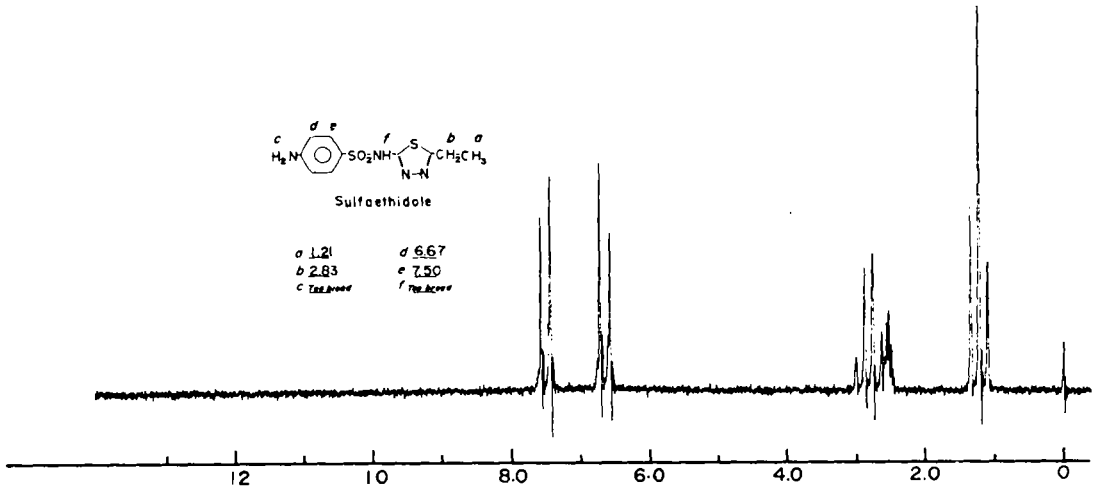


Figure 6—*Sulfaethidole.*

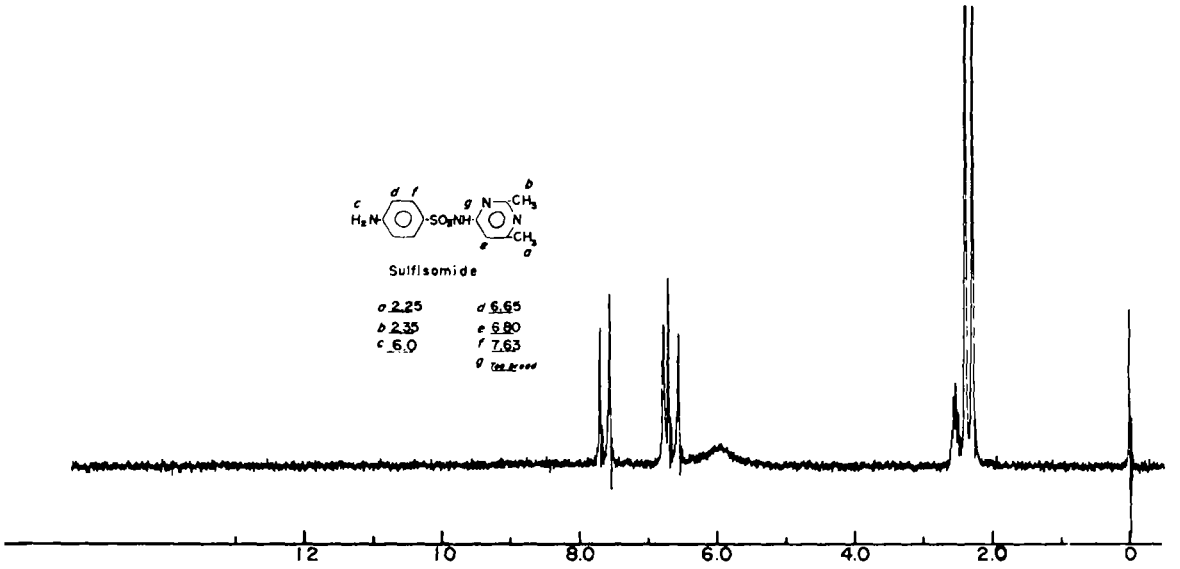


Figure 7—*Sulfisomidine.*

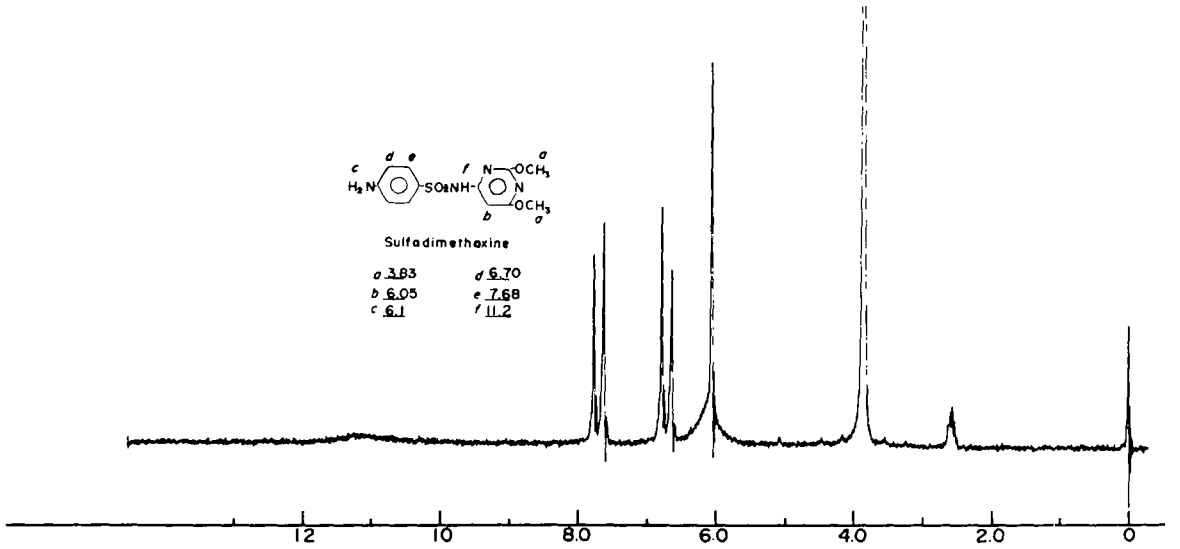


Figure 8—*Sulfadimethoxine.*

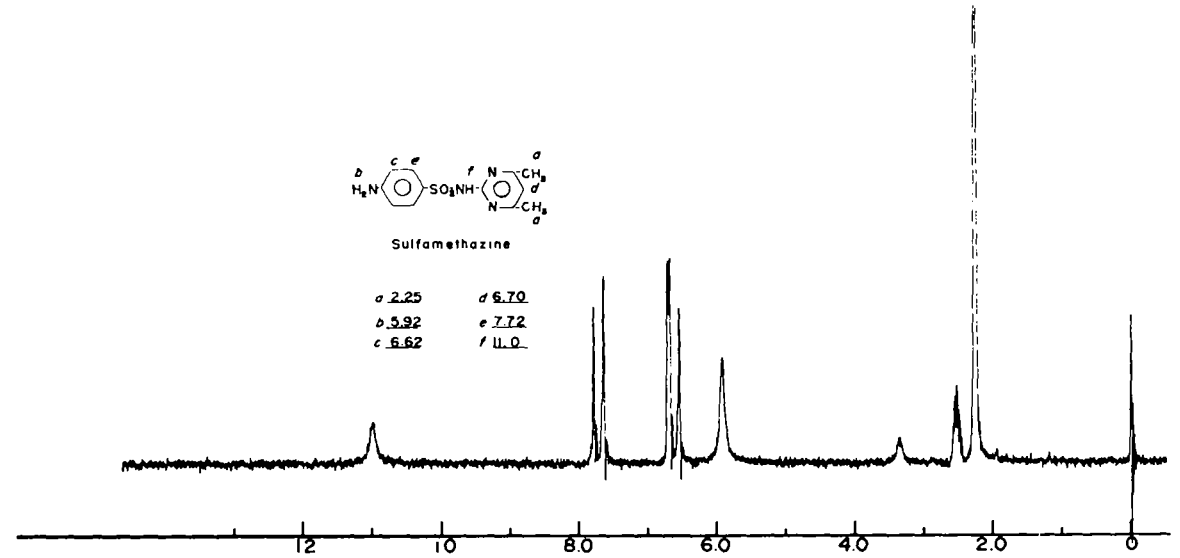


Figure 9—*Sulfamethazine.*

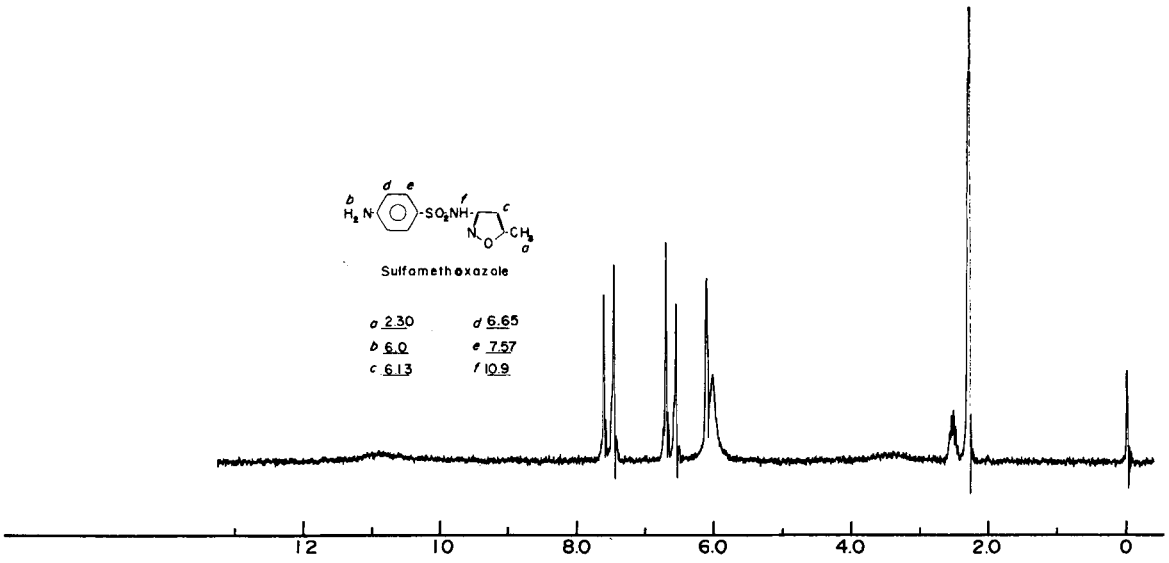


Figure 10—*Sulfamethoxazole.*

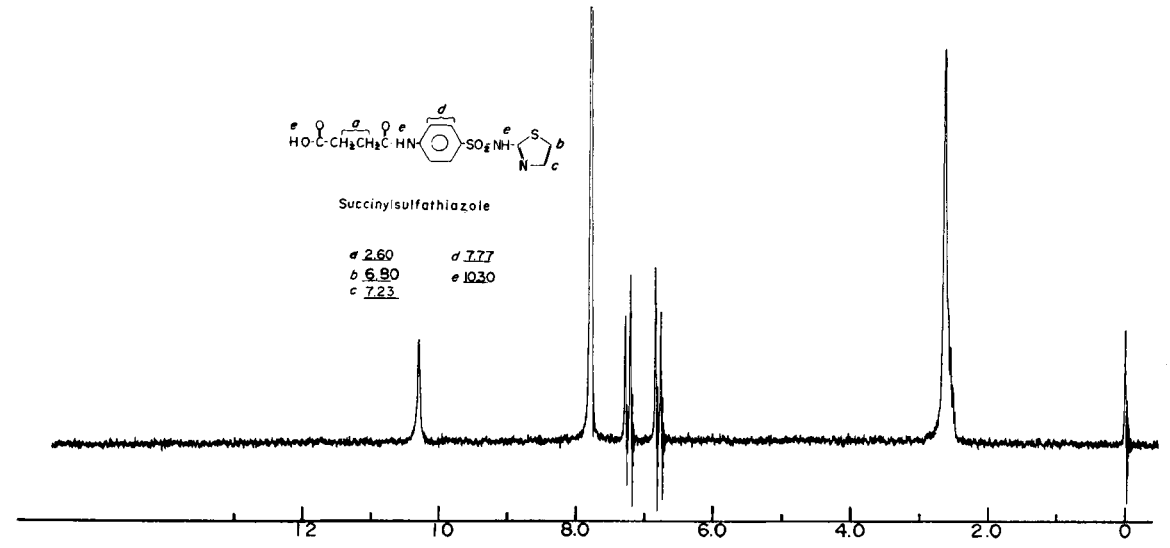


Figure 11—*Succinylsulfathiazole.*

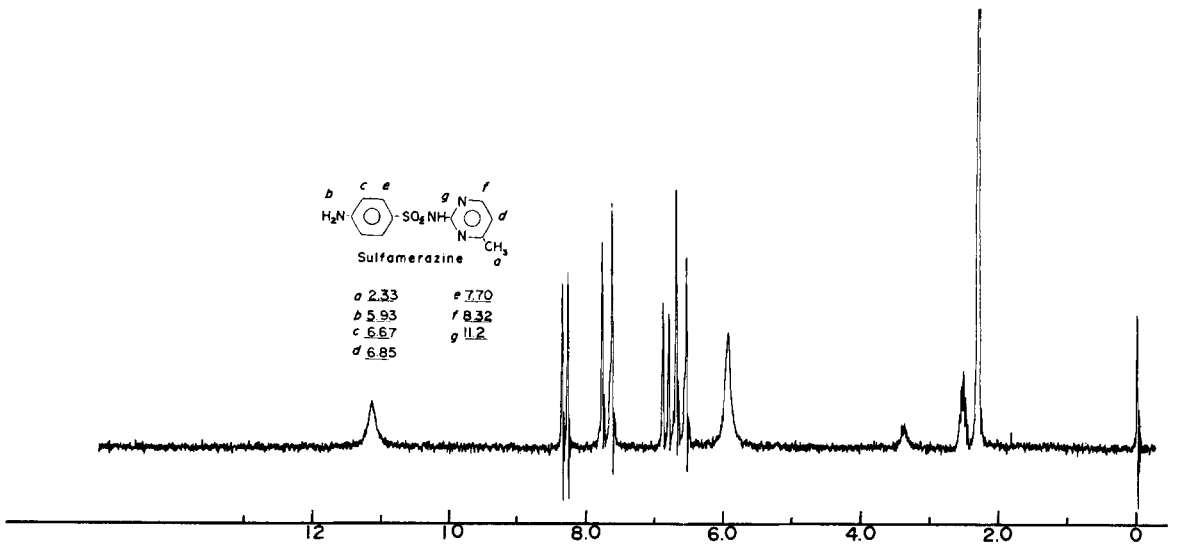


Figure 12—*Sulfamerazine.*

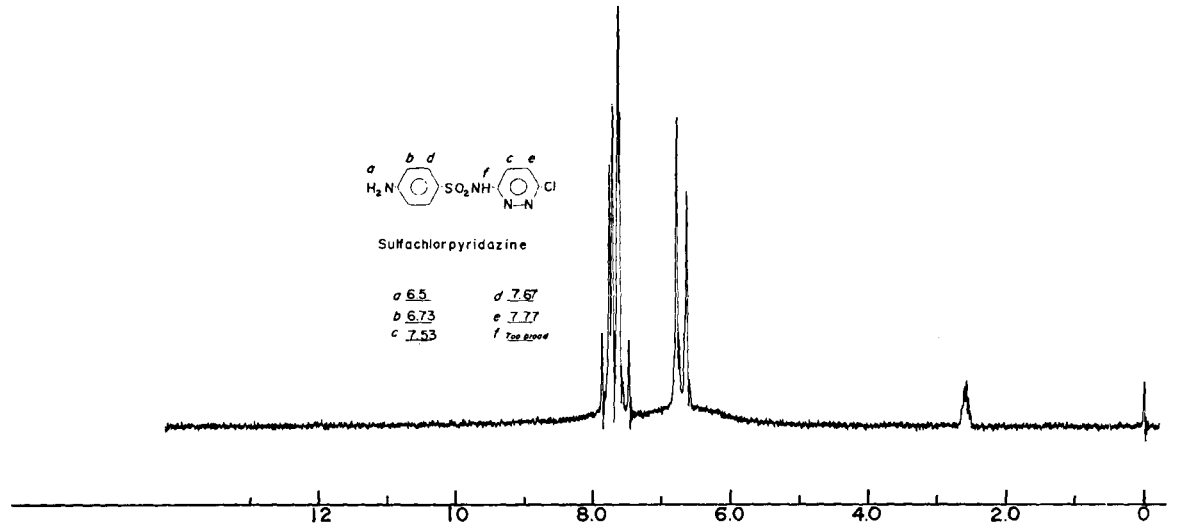


Figure 13—*Sulfachlorpyridazine.*

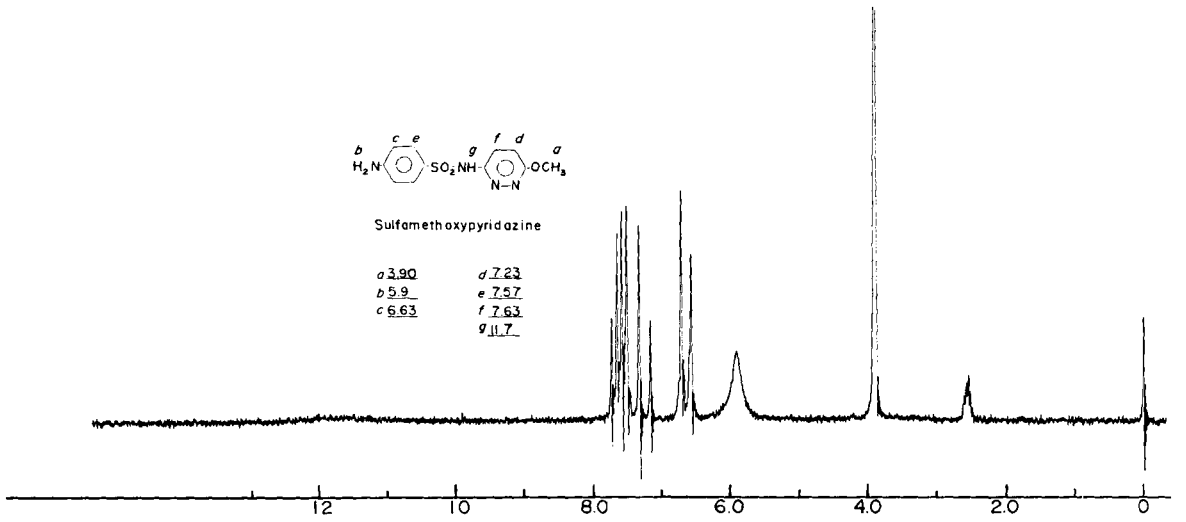


Figure 14—*Sulfamethoxypyridazine.*

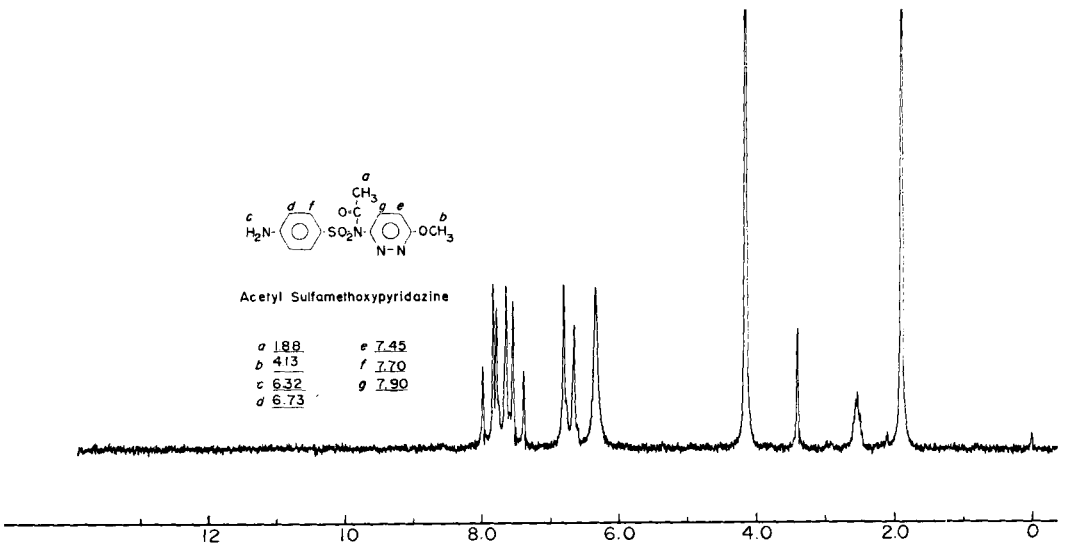


Figure 15—*Acetyl sulfamethoxypyridazine.*

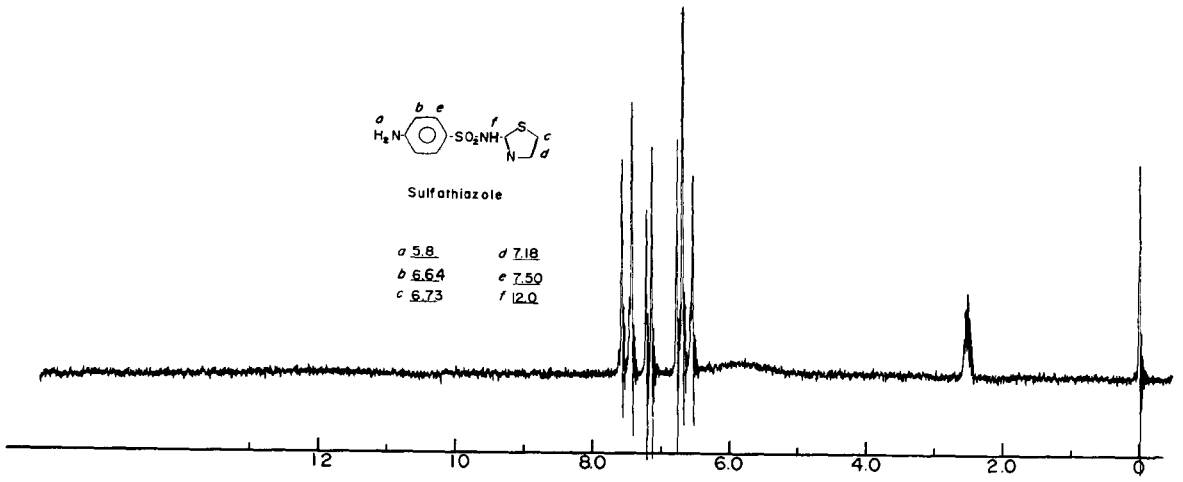


Figure 16—*Sulfathiazole.*

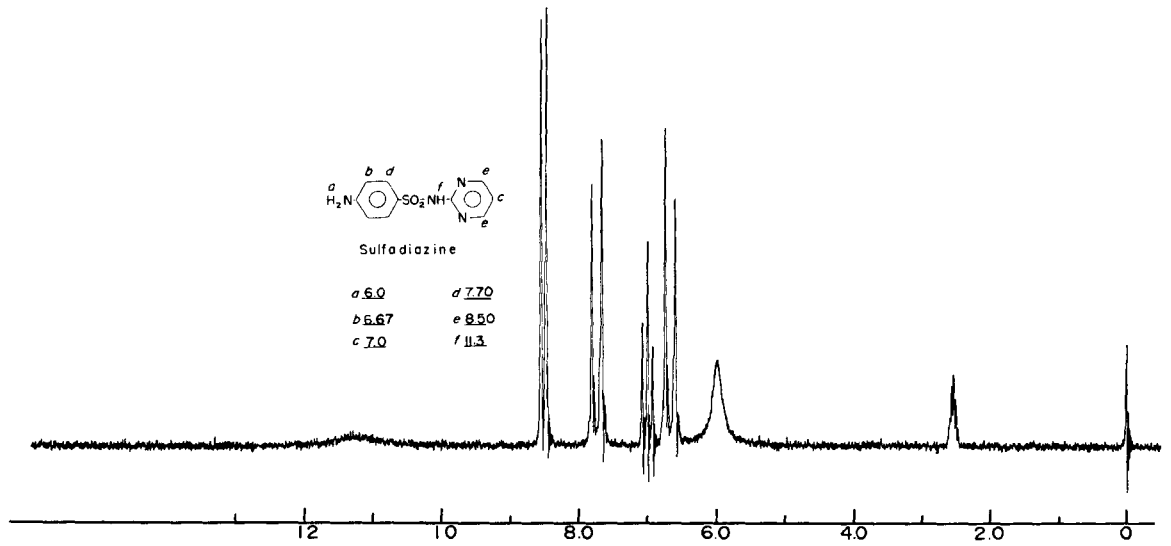


Figure 17—*Sulfadiazine.*

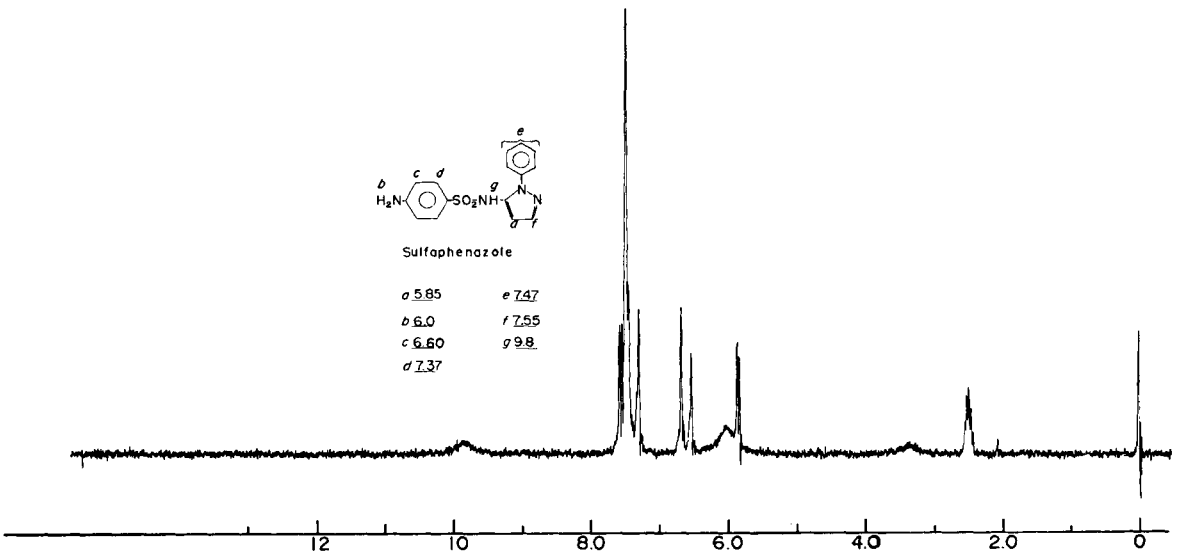


Figure 18—*Sulfaphenazole.*

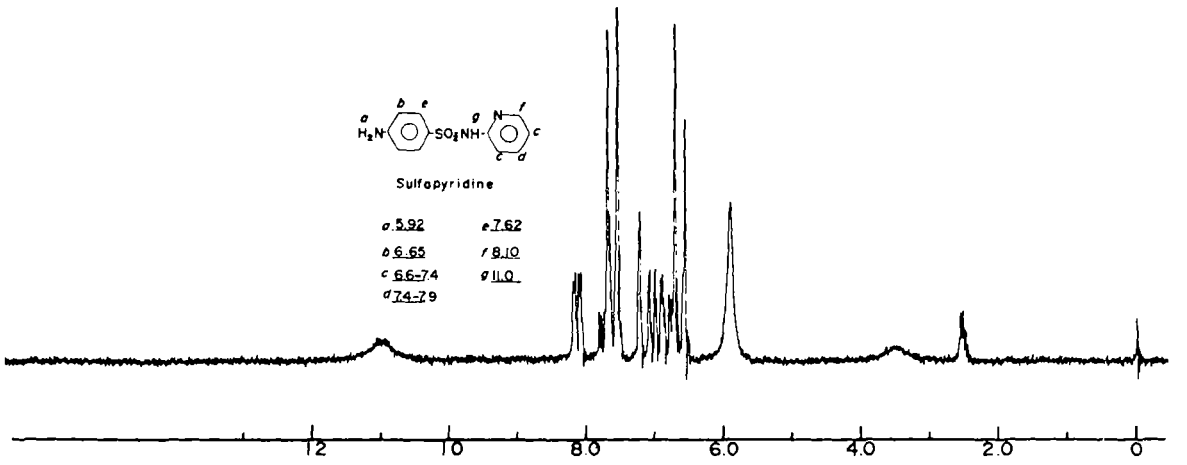


Figure 19—*Sulfapyridine.*

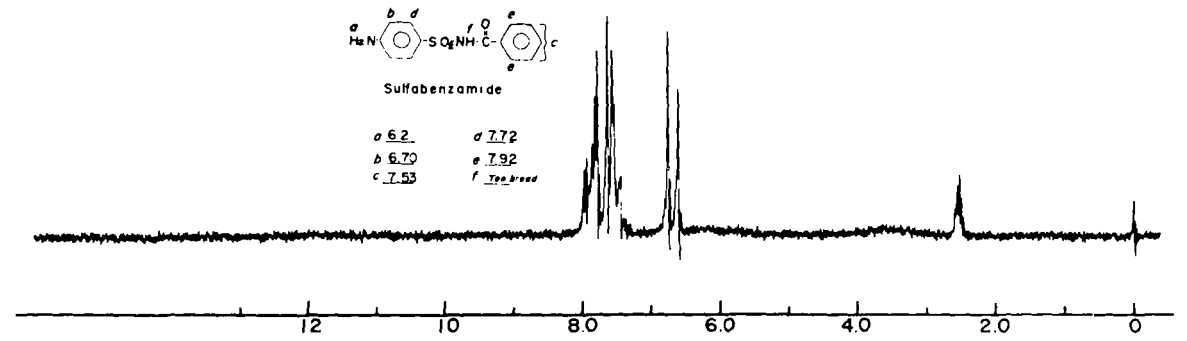


Figure 20—*Sulfabenzamide.*

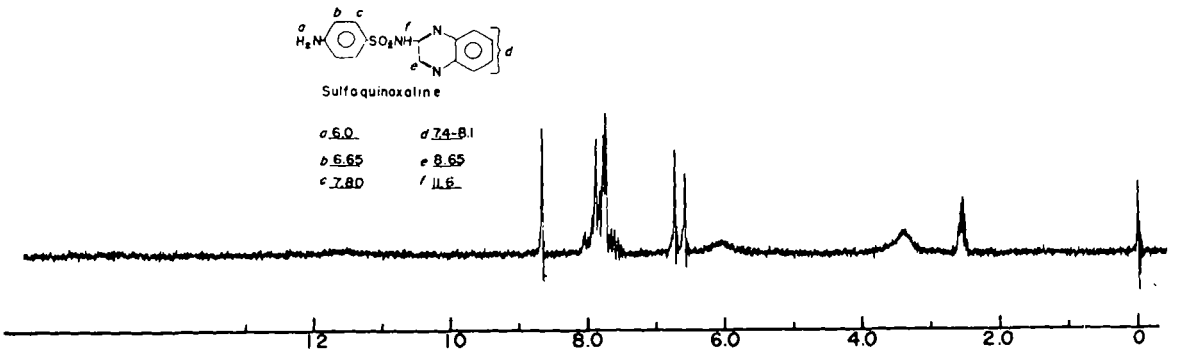


Figure 21—*Sulfaquinoxaline.*

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