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# Characterization of the Ultraviolet Absorption Spectra of Some Substituted Benzenesulfonamides

BY J. M. VANDENBELT AND LEONARD DOUB

Several publications have described the ultraviolet absorption spectra of sulfanilamide derivatives,[1,2,3,4] but very little has been done toward identification and characterization of the individual absorption bands occurring in these spectra.[5,6,7]

Following an extensive study of the ultraviolet absorption of sulfanilamide derivatives with the Beckman spectrophotometer, such a characterization has now been made. The procedure consisted first in the determination of the absorption bands of the simple derivatives over a wide *p*H range. By means of the wave length and reaction to *p*H of these bands, the corresponding maxima were located in the more complicated derivatives. Where necessary, identity was confirmed by observation of suitably constructed analogous compounds.

**I. Simple Sulfanilamide Derivatives.**—The simple sulfanilamide derivatives have one single band of strong absorption ($\epsilon$ about $17 \times 10^3$) in the accessible ultraviolet region.[8] This maximum occurs in the region of 260 m$\mu$ in neutral solution. In derivatives capable of acidic and basic dissociation, the behavior at different *p*H values is exemplified by the curves for sulfanilamide (Fig. 1, top).[7] Acidic ionization (in alkaline solution) results in a shift toward shorter wave length with little change in intensity, while basic dissociation (in acid solution) decreases the absorption almost to disappearance of the band.

The wave length of the band may shift to some extent with substitution. For example, acetylation of the sulfonamide nitrogen in sulfanilamide (Fig. 1, bottom) results in a band of wave length 269 m$\mu$ in weakly acid solution.[7,8] In alkaline solution, the peak is at 257 m$\mu$, showing the same ionization shift as sulfanilamide. This compound behaves similarly to sulfanilamide in strong acid also. $N^1$-Ethylsulfanilamide and $N^1$,$N^1$-dimethylsulfanilamide (curves not shown) have maximum absorption in neutral solution at 260 and 263 m$\mu$, respectively. Simple substitution of the sulfonamide nitrogen therefore causes but slight change in the wave length of the absorption maximum.

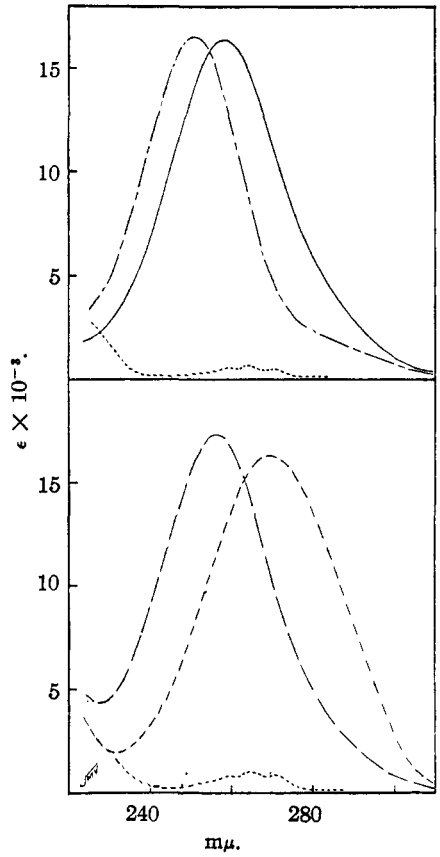


Fig. 1.—Top—sulfanilamide: — - — -, in 1 *N* NaOH; ————, *p*H 7; -------, in 2 *N* HCl. Bottom—$N^1$-acetylsulfanilamide: —— ——, *p*H 11; - - - - -, *p*H 2.5; ----------, in 2 *N* HCl.

Sulfanilylguanidine (sulfaguanidine) ($\epsilon$ = $18.2 \times 10^3$ at 259 m$\mu$ in neutral solution), in line with its very weak acidic properties, shows no shift with alkali, but has the characteristic decrease in acid. $N^4$-Acetylsulfanilamide ($\epsilon$ = $19.8 \times 10^3$ at 257 m$\mu$ in neutral solution), while showing the shift to shorter wave length with acidic ionization, is incapable of forming an amine salt and shows relatively little decrease in acid ($\epsilon$ = $18.4 \times 10^3$ at 257 m$\mu$ in 2 *N* hydrochloric acid).

From these observations, it can be stated that the principal features of sulfanilamido absorption consist of a single band of high intensity in the neighborhood of 260 m$\mu$ in neutral solution, which

(1) F. H. Bergeim, N. H. Coy and W. A. Lott, THIS JOURNAL, **62**, 1873 (1940).

(2) J. V. Scudi, *Science*, **91**, 486 (1940).

(3) W. F. Elvidge, *Quart. J. Pharm. Pharmacol.*, **14**, 134 (1941).

(4) J. L. Ciminera and P. W. Wilcox, *J. Am. Pharm. Assoc.*, **33**, 85 (1944).

(5) R. G. Shepherd, A. C. Bratton and K. C. Blanchard, THIS JOURNAL, **64**, 2532 (1942).

(6) H. Bohme and J. Wagner, *Arch. Pharm.*, **280**, 255 (1942), from *C. A.*, **37**, 2517 (1943).

(7) W. D. Kumler and L. A. Strait, THIS JOURNAL, **65**, 2349 (1943).

(8) At this acidity the absorption is essentially that of the unionized molecule. However, some is undoubtedly present as the basic ion and the absorption intensity is correspondingly lower.

shifts to shorter wave length with alkalinity and decreases in intensity with acidity. Simple substitution has but little effect on the wave length of the band, and very little on the intensity, except in cases where the substitution causes changes in the basic ionization properties of the molecule.

**II. Sulfanilamido Heterocycles: 1. Sulfathiazole.**—Figure 2 (top) gives the absorption curves at various *p*H values of 2-sulfanilamidothiazole (sulfathiazole). The band at 257–259 mμ has characteristics of the absorption band of sulfanilamide; *i. e.*, it shifts slightly to shorter wave length in alkali and decreases markedly in acid. Meanwhile, the band at 280–283 mμ shifts to shorter wave length in alkali and is not destroyed in 2 *N* hydrochloric acid. Its apparent decrease in acid is due to reduction in the 258 mμ band absorption at 280 mμ. Because of the sensitivity to acid, it is concluded that the band at 257–259 mμ is due to the sulfanilamide portion of the molecule. The absorption at 280–283 mμ is then caused by the thiazole portion. This, however, is in disagreement with the conclusions of Shepherd, *et al.*,[5] who identify the 258 mμ absorption with a thiazolone structure.

In $N^4$-acetylsulfathiazole, the absorption bands are very similar to those occurring in the spectra of the parent unacetylated compound. In view of the fact that $N^4$-acetylation of sulfanilamide causes but slight change in absorption, it is reasonable to assume that in this compound the bands observed correspond to those of sulfathiazole and are due to the same portions of the molecule. Since the acetylated amino group is no longer capable of forming a salt in dilute acid solution, the absorption due to the sulfanilamide portion should be unaffected. That this is the case is shown in Fig. 2 (bottom). The 257 mμ peak identified above with the sulfanilamide portion of the molecule is now unaffected in 2 *N* hydrochloric acid.

The persistence of the 282 mμ peak in acid is in line with behavior of a thiazole structure. Figure 2 (bottom) gives curves of 2-aminothiazole. This compound shows an increase in absorption rather than a decrease in strongly acid solution. Substitution with the strongly electronegative sulfonyl group would be expected to lower the basic strength of 2-aminothiazole and render it relatively insensitive to acid.

Shepherd, *et al.*,[5] base their identification of the 260 mμ absorption of sulfathiazole (in alcohol) with a thiazolone structure partly on the fact that 3-methyl-2-thiazolone imine shows an absorption peak at 258 mμ. This is very nearly the same region at which 2-aminothiazole absorbs and the absorption is probably due to the same resonance structure in each case. However, it seems unlikely that the position of the maximum would remain unaltered by substitution with the strongly electronegative sulfanilyl group. The fact that a maximum does occur at the same point in this substituted compound could be as easily interpreted as evidence for non-identity as the contrary.

Obviously a derivative which approximates the polar character of the sulfanilyl group but without appreciable absorption in the same region would be useful in identification of the absorption characteristics of the thiazole structure in this type of compound. 2-Benzenesulfonamidothiazole[9] is

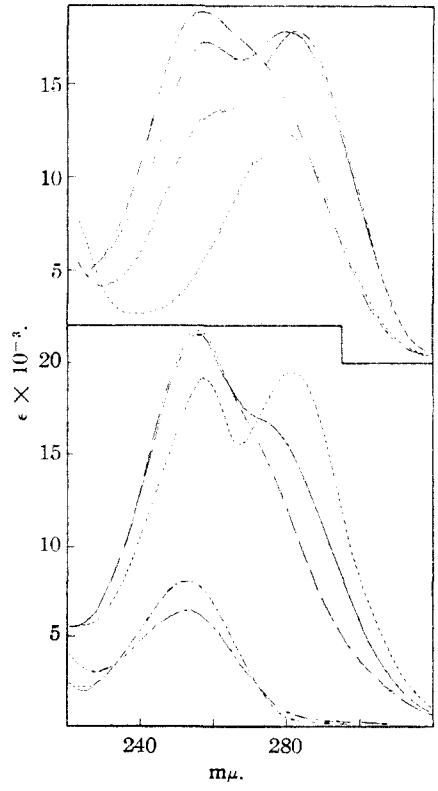


Fig. 2.—Top—sulfathiazole: —— ——, *p*H 11; ———, *p*H 7; – – – – –, *p*H 2.5; - - - - - - - -, in 2 *N* HCl. Bottom —$N^4$-acetylsulfathiazole: —— ——, *p*H 11; ————, *p*H 7; - - - - - - - -, in 2 *N* HCl; 2-aminothiazole: — - — -, *p*H 11; – – – – –, *p*H 0.3.

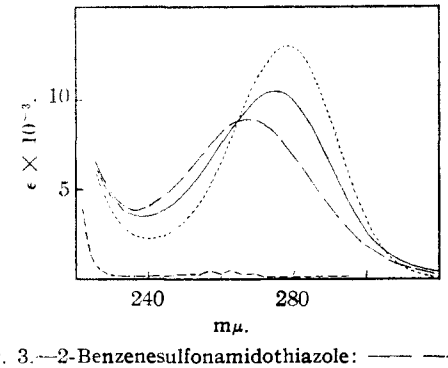


Fig. 3.—2-Benzenesulfonamidothiazole: —— ——, *p*H 11; ————, *p*H 7; - - - - - - - -, in 2 *N* HCl; sodium benzenesulfonate: – – – –.

(9) J. P. English, D. Chappell, P. H. Bell and R. O. Roblin, THIS JOURNAL, 64, 2516 (1942).

such a compound (Fig. 3). The benzenesulfonyl group has insignificant absorption in the range of wave length under consideration as is shown by the curve for sodium benzenesulfonate (Fig. 3). The 259 mμ band identified above with the absorption of the sulfanilyl group is not present in 2-benzenesulfonamidothiazole, and the remaining peak exhibits the properties of the 282 mμ band of sulfathiazole with respect to wave length and change in *p*H.

A final test of the validity of this last comparison is found in the absorption curve of sulfathiazole in strongly acid solution. Here the effect of the amino group on the benzene resonance has been destroyed by formation of the cation.[7] Its resonance effect on the thiazole portion more nearly approaches that of the unsubstituted benzene group. Consequently, the absorption spectra of sulfathiazole and 2-benzenesulfonamidothiazole, both in 2 *N* acid, should be, and are, almost exactly identical (Figs. 2 and 3).

**2. Sulfapyridine.**—Figure 4 (top) gives the ultraviolet absorption for 2-sulfanilamidopyridine (sulfapyridine), possessing maxima in neutral and slightly acid solution at 242, 261 and 311 mμ. We are in agreement with Shepherd, *et al.*,[5] that the peak at 311 mμ is due to the pyridine portion of the molecule. They locate the longer wave length band from 1-(β-hydroxyethyl)-2-pyridone imine, although in sulfapyridine a considerable shift has taken place.[10]

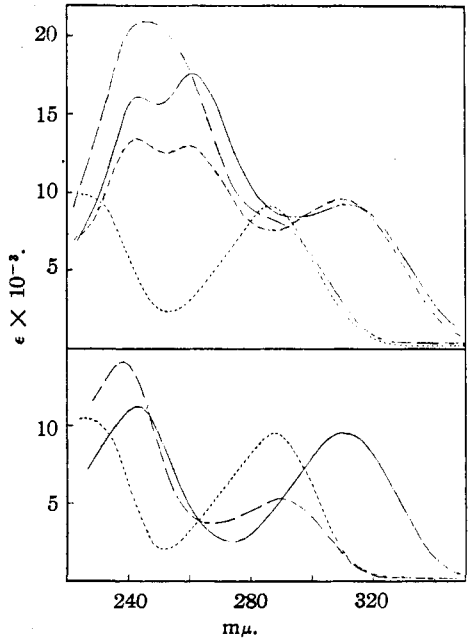


Fig. 4.—Top—sulfapyridine: ——— ———, *p*H 11; ———, *p*H 7; – – – – –, *p*H 2.5; – – – – – – –, in 2 *N* HCl. Bottom—2-benzenesulfonamidopyridine: ——— ———, *p*H 11; ———, *p*H 7; ---------, in 2 *N* HCl.

(10) A similar shift in the thiazole absorption of sulfathiazole might reasonably be expected as was pointed out earlier in this paper. The evidence is unambiguous with sulfapyridine because there is no other band in the vicinity.

With 2-benzenesulfonamidopyridine[9] (Fig. 4, bottom), two peaks at 242 and 311 mμ are present in neutral solution, corresponding to similar bands in sulfapyridine. Since the benzenesulfonamido structure absorbs insignificantly, these bands are due to the pyridine portion of the molecule. The 261 mμ band of sulfapyridine is again due to sulfanilyl absorption. In 2 *N* hydrochloric acid, there is an exact agreement in position and intensity of the bands for sulfapyridine and 2-benzenesulfonamidopyridine.

The case of sulfapyridine is complicated somewhat by the curves in alkaline solution. Here the maximum at 311 mμ shifts toward the shorter wave length, giving an inflection at 290 mμ. The peaks at 261 and 242 mμ have apparently fused to form a single broad band of increased intensity at 245 mμ. This interpretation is supported by the spectrum of the benzenesulfonamide derivative in alkaline solution. The peak at 311 mμ has disappeared and one at 290 mμ has replaced it. The peak at 243 mμ has shifted to shorter wave length, but has increased markedly in intensity If the 261 mμ band in sulfapyridine shifts toward the shorter wave length in alkali one might expect fusion with the 242 mμ band to a single broad maximum. That this is the case is shown in Fig. 5, where the area under the absorption curve of sulfanilamide at *p*H 11 has been subtracted from that of sulfapyridine at *p*H 11. Since the absorption peak of sulfanilamide in neutral solution at 258 mμ has shifted to 261 mμ in the sulfapyridine molecule, a difference of 3 mμ, the curve area of sulfanilamide was shifted 3 mμ to longer wave length before subtraction. Figure 5 compares the difference curve with that of 2-benzenesulfonamidopyridine at *p*H 11. The similarity in position and intensity of the two bands is apparent.

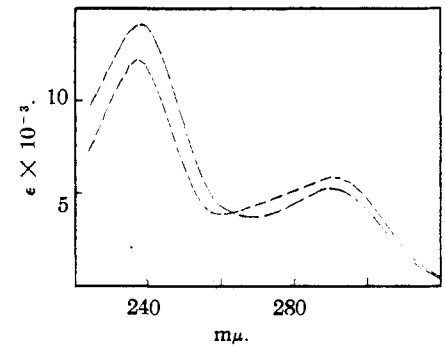


Fig. 5.—2-Benzenesulfonamidopyridine: – – – ———, *p*H 11; sulfapyridine (*p*H 11) less sulfanilamide (*p*H 11): – – – – –. The sulfanilamide curve was moved 3 mμ to the longer wave length before subtraction.

**3. Sulfadiazine.**—Figure 6 (top) gives curves of 2-sulfanilamidopyrimidine (sulfadiazine) at various *p*H values. By reference to the analogous compound 2-benzenesulfonamidopyrimidine[9] (Fig.

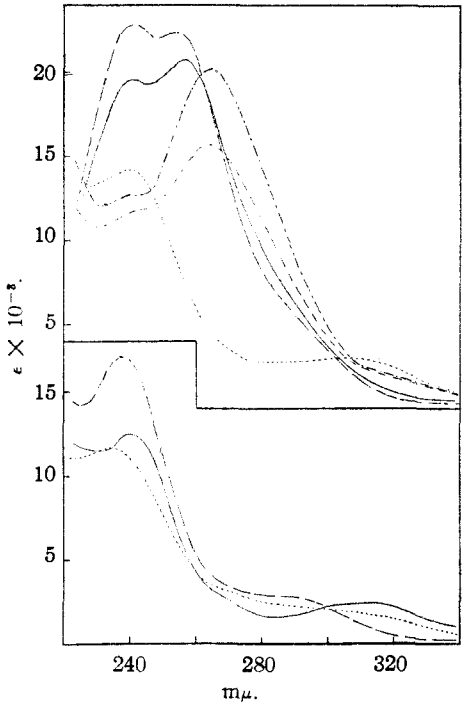


Fig. 6.—Top—sulfadiazine: ——— ———, *p*H 11; ———, *p*H 7; ——— · ——— ·, *p*H 5.0; - - - -, *p*H 2.5; · · · · · · · · ·, in 2 *N* HCl. Bottom—2-benzenesulfonamidopyrimidine: ——— ———, *p*H 11; ———, *p*H 5; - - - - - - -, in 2 *N* HCl.

6, bottom), it is evident that the 257 mμ band is again due to the *p*-aminobenzenesulfonamido absorption, while the 241 mμ band and the longer wave length weak absorption is due to the pyrimidine ring. There is a shift in wave length from 265 to 254 mμ of the sulfanilyl peak with change from acid to base coincident with acidic ionization. In strong acid, *i. e.*, with greatly decreased *p*-aminobenzenesulfonamido absorption, the curves for sulfadiazine and 2-benzenesulfonamidopyrimidine are almost identical.

As would be expected, 2-sulfanilamido-4-methylpyrimidine (sulfamerazine) and 2-sulfanilamido-4,6-dimethylpyrimidine (sulfamethazine) have absorption very similar to that of sulfadiazine.[4] There is a sulfanilyl peak near 260 mμ in neutral solution, a pyrimidyl peak at 241 mμ, and in strongly acid solution, also at 311 mμ.

## Summary

1. The ultraviolet absorption spectra of several substituted benzenesulfonamide derivatives have been examined and characterized with respect to changes in *p*H.

2. By examination of the band changes with variation in *p*H, and by comparison with the action of the bands in simpler analogous compounds, the bands of the more complicated derivatives have been associated with the absorbing groups in the molecule.

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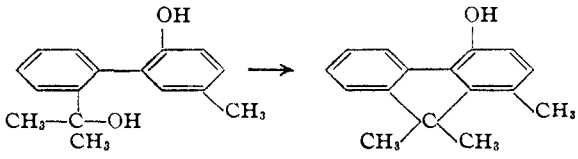
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF ROCHESTER]

# Syntheses Leading to Substituted Tetrahydrofluorenols

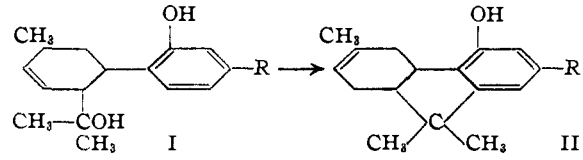
BY WARREN D. MCPHEE[1] AND FRANK J. BALL[2]

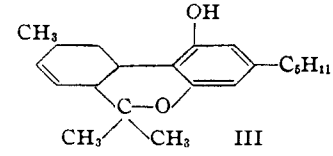
The interesting reaction reported by Anchel and Blatt[3] whereby dialkyl-*o*-xenylcarbinols may be dehydrated to 9,9-dialkylfluorenols by heating with acids, as shown in the example

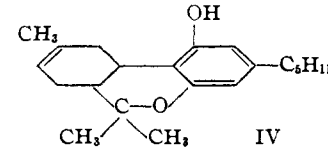



seemed to offer a new approach to the synthesis of tetrahydrofluorenols of type (II). A carbinol of structure (I) might be expected to cyclize to (II) under conditions similar to those used by Anchel and Blatt.

It was thought that these tetrahydrofluorenols might possess marihuana activity because of their structural relationship to the tetrahydrocannabinols (III and IV), differing only in the absence of the oxygen bridge of the pyran ring.




The tetrahydrocannabinols were demonstrated to have high physiological activity by Adams and

(1) Present address: Winthrop Chemical Company, Rensselaer, N. Y.

(2) Present address: West Virginia Pulp and Paper Company, Charleston, S. C.

(3) Anchel and Blatt, THIS JOURNAL, 63, 1948 (1941).