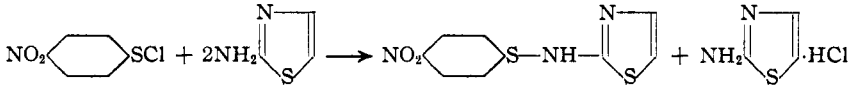
[CONTRIBUTION FROM RESEARCH LABORATORIES OF PARKE, DAVIS AND COMPANY]

Some Chemotherapeutically Active Sulfones. II. 4-Aminophenyl-2′-aminothiazolyl-5′ Sulfone and Analogs[1]

BY L. L. BAMBAS

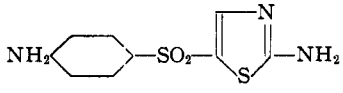
In the previous paper[2] of this series a number of 4-aminophenylamino heterocycle sulfones were described, some of which possessed considerable antistreptococcal activity. This chemotherapeutic activity led to further investigation of other members of the series. 4-Aminophenyl-2′-aminothiazolyl-5′ sulfone (trademarked Promizole) was prepared. Feldman, Hinshaw and Mann[3] have shown that this compound possessed tuberculotherapeutic activity for a human strain of the tubercle bacillus in the guinea pig. Furthermore, a low degree of human toxicity was noted.[4]

The preparation of 4-aminophenyl-2′-aminothiazolyl-5′ sulfone was accomplished in several steps, one of which involves the rearrangement of



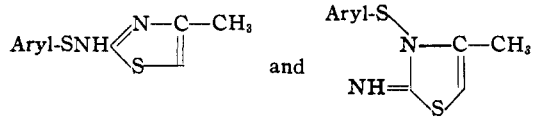
2-(4′-nitrophenyl-sulfen)-aminothiazole in the presence of acetic anhydride to 4-nitrophenyl-2′-acetylaminothiazolyl-5′ sulfide.

The 4-nitrophenyl-2′-acetylaminothiazolyl-5′ sulfide was oxidized to the sulfone with hydrogen peroxide. The acetyl group was removed by hydrolysis and the nitro group was reduced to the amine to give 4-aminophenyl-2′-aminothiazolyl-5′ sulfone.

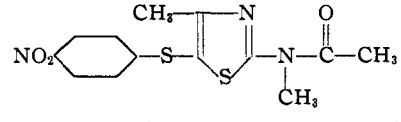


In this synthesis, 4-nitrophenylsulfenyl chloride and two equivalents of 2-aminothiazole yielded 2-(4′-nitrophenyl-sulfen)-aminothiazole. This intermediate was heated at 85° in the presence of acetic anhydride to give 4-nitrophenyl-2′-acetylaminothiazolyl-5′ sulfide. Zincke and Linhardt[5] described the reaction of 4-nitrophenylsulfenyl chloride with α-naphthylamine to give the 4-nitrophenyl-1′-amino-4′-naphthyl sulfide. Dimethylaniline and 4-nitrophenylsulfenyl chloride gave a similar reaction. No indication was given as to whether any source of energy was required for this reaction. Moore and Johnson[6] isolated the 4-nitrophenylsulfen-*o*-chloroanilide and found it necessary to heat in an excess of *o*-chloroaniline at 180–190° for four hours to rearrange to 4-nitrophenyl-3′-chloro-4′-aminophenyl sulfide. Bann, *et al.*,[7] found that the reaction between sulfenyl chloride and 2-aminothiazole resulted in a product which had a melting point of 166°. A mixed melting point of this compound and 4-nitrophenyl-2′-aminothiazolyl-5′ sulfide (m. p. 170–172°) was considerably lower (140–142°) than either compound. Bann, *et al.*,[7,8] show that 4-nitrophenyl sulfenyl chloride reacts with 2-amino-4-methylthiazole. This compound may be isomerized by heating at 80–90° in the presence of acetic anhydride to give a compound having the melting point of 181°. These conditions are identical with those utilized in this Laboratory to obtain 4-nitrophenyl-2′-acetylamino-4′-methylthiazolyl-5′sulfide for which compound their melting point (181°) is in agreement.

Bann, *et al.*,[7,8] postulate the following formulas for their compounds



An analogous reaction was carried out using 2-methylamino-4-methylthiazole[9,10] and 4-nitrophenyl sulfenyl chloride and heating the resulting intermediate in the presence of acetic anhydride to give 4-nitrophenyl-2′-acetylmethylamino-4′-methylthiazolyl-5′ sulfide.



The 5-position on the thiazolyl ring is the only position available for the 4-nitrophenyl sulfenyl group.

The 4-aminophenyl-2′-imino-4′-methylthiazol-

(1) Presented in part before the Division of Medicinal Chemistry at the Memphis, April 20, 1942, and at the New York, September 11, 1944, meetings of the American Chemical Society.

(2) L. L. Bambas, THIS JOURNAL, **67**, 668 (1945).

(3) Feldman, Hinshaw and Mann, *Proc. Staff Meet., Mayo Clinic*, **19**, 25 (1944).

(4) Hinshaw, Feldman and Pfuetze, *ibid.*, **19**, 33 (1944).

(5) Zincke and Linhardt, *Ann.*, **400**, 2 (1913).

(6) Moore and Johnson, THIS JOURNAL, **58**, 1091 (1936).

(7) Bann, Krug, Wheeler, Taylor and Gladding, British Patent 551,681 (1943).

(8) Bann, Krug, Wheeler, Taylor and Gladding, British Patent 559,384 (1944).

(9) Traumann, *Ann.*, **249**, 43 (1888).

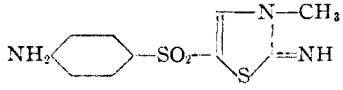
(10) Young and Crookes, *J. Chem. Soc.*, **89**, 68 (1906).

TABLE I

4-Aminophenyl sulfones	M. p., °C. (uncor.)	Anti-streptococcal[a] activity	Formula	Analyses,[b] % Calculated C	H	N	Found C	H	N
2′-Aminothiazolyl-5′ (Promizole)[c]	219–221 dec.	Active	$C_9H_9O_2N_3S_2$	42.4	3.6	16.5	42.6	3.7	16.1
2′-Amino-4′-methylthiazolyl-5′[c]	175–178	Active	$C_{10}H_{11}O_2N_3S_2$	44.6	4.08		44.5	4.2	
2′-Methylamino-4′-methylthiazolyl-5′[c]	220–222	Active	$C_{11}H_{13}O_2N_3S_2$	46.7	4.6		46.8	4.7	
2′-Imino-3′-methylthiazolonyl-5′[c]	Blackens 160–170, m. p. 209–210	Active	$C_{10}H_{11}O_2N_3S_2$			15.6			15.6
2′-Methylimino-3′,4′-dimethylthiazolonyl-5′	165–167		$C_{12}H_{15}O_2N_3S_2$	48.5	5.05		48.7	5.3	
2′-Allylamino-4′-methylthiazolyl-5′[c]	168–170		$C_{13}H_{16}O_2N_3S_2$	50.5	4.85		50.9	4.9	
2′-Acetylaminothiazolyl-5′[c]	267–269	Active	$C_{11}H_{11}O_3N_3S_2$	44.4	3.7		44.7	3.75	
2′-Crotonylaminothiazolyl-5′	268–270		$C_{13}H_{13}O_3N_3S_2$	48.3	4.05		48.9	4.2	
2′-Succinylaminothiazolyl-5′	225–229	Active	$C_{13}H_{13}O_5N_3S_2$			11.8			12.0
2′-Nicotinylaminothiazolyl-5′[c]	246–248		$C_{15}H_{11}O_3N_4S_2$	50.0	3.33		49.5	3.1	
4-Nitrophenyl-2′-acetylmethylamino-4′-methylthiazolyl-5′ sulfide	192–194		$C_{13}H_{13}O_4N_3S_2$	48.3	4.02		48.2	4.0	

[a] Data supplied by O. M. Gruhzit of these Laboratories. [b] Microanalyses by A. W. Spang, M. McCarthy Ledyard and F. Cope Hummel. [c] Tuberculotherapeutic activity of these compounds will be reported by W. H. Feldman and H. C. Hinshaw, Mayo Foundation and Mayo Clinic.

onyl-5′ sulfone was prepared by heating 4-nitrophenyl-2′-aminothiazolyl-5′ sulfone with an excess of dimethyl sulfate, followed by the reduction of the nitro group.



The position of the methyl group in the 3-position on the thiazole ring was deduced from the work of Näff[11] with 2-aminothiazole and methyl iodide to obtain 2-imino-3-methylthiazolone. The 4-amino phenyl-2′-imino-3′-methylthiazolonyl-5′ sulfone is relatively unstable; it darkens on heating and aqueous suspensions of this compound become colored on standing. Higher homologs such as the ethyl- and α-acetic acid derivatives were so unstable that they decomposed into tars before they could be isolated.

The 4-aminophenyl-2′-acylaminothiazolyl-5′ sulfones are soluble in dilute alkali. The resultant solutions are fairly stable. 4-Aminophenyl-2′-acetylaminothiazolyl-5′ sulfone forms a salt at *p*H 10. 4-Aminophenyl-2′-aminothiazolyl-5′ sulfone is a very weak acid since it dissolves only in 10% alkali. Some decomposition takes place as evidenced by color formation and a positive nitroprusside test for mercaptans. However, some of this compound may be recovered on acidification of the solution with acetic acid. The identity of this material was confirmed by means of melting and mixed melting points. The salt formation must involve one of the hydrogens of the amine on the thiazole ring since 4-aminophenyl-2′-acetylmethylaminothiazolyl-5′ sulfone is not soluble in alkali.

Method

4-Nitrophenyl-2′-acetylaminothiazolyl-5′ Sulfide.—4-Nitrophenyl sulfenyl chloride[5] from 125 g. of pure 4,4′-dinitrodiphenyl disulfide was added to a cool (20°) solution of 2-aminothiazole (143 g.) in 750 cc. of glacial acetic acid. Acetic anhydride (150 cc.) was added and the solution was allowed to stand sixteen to twenty-four hours at 85–90°. Crystals of 4-nitrophenyl-2′-acetylaminothiazolyl-5′ sulfide began to appear in about three-quarters of an hour. After a twenty-four-hour period, the crystals were filtered from the warm solution. The product was recrystallized from hot dioxane; m. p. 258–260° (a few samples having a melting point of 273–275° were obtained. This is probably an instance of dimorphism); yield, 80–100 g. (33–42%). *Anal.* Calcd. for $C_{11}H_9O_3N_3S_2$: N, 14.2. Found: N, 14.2.

Ethylene dichloride, chloroform, carbon tetrachloride or benzene may be used instead of glacial acetic acid as the solvent in the above reaction.

4-Nitrophenyl-2′-acetylaminothiazolyl-5′ sulfone was prepared by suspending 4-nitrophenyl-2′-acetylaminothiazolyl-5′ sulfide (70 g.) in glacial acetic acid (600 cc.). Seventy cc. of 30% hydrogen peroxide was added portionwise to the warm (70°) suspension. Care was taken that the temperature did not rise above 85–90° since some destruction of the compound may occur at higher temperatures. The suspension gradually went into solution and the product then recrystallized out of solution as it formed. After the reaction appeared to be complete, the reaction mixture was heated at 80–90° for two hours on the steam-bath. The mixture was then cooled and the crystalline precipitate was filtered off, m. p. 274–276°; yield, 62 g. (80%). *Anal.* Calcd. for $C_{11}H_9O_5N_3S_2$: N, 12.8. Found: N, 12.8.

4-Nitrophenyl-2′-aminothiazolyl-5′ sulfone was prepared by suspending the 4-nitrophenyl-2′-acetylaminothiazolyl-5′ sulfone (62 g.) in a solution consisting of 375 cc. of glacial acetic acid and 100 cc. of 6 *N* hydrochloric acid. The suspension was heated at reflux temperature until solution occurred and for an additional thirty minutes. The solution was cooled, neutralized to congo red with dilute alkali and diluted to 2 volumes. The crystalline precipitate was filtered off; m. p. 230–232°; yield, 46 g. (85%). *Anal.* Calcd. for $C_9H_7O_4S_2N_3$: N, 14.8. Found: N, 14.6.

4-Aminophenyl-2′-aminothiazolyl-5′ Sulfone.—Ammonium chloride (10 g.) was dissolved in one liter of water at 70°. Reduced iron (60 g.) was suspended in this solution by vigorous stirring. 4-Nitrophenyl-2′-aminothiazolyl-5′ sulfone (46 g.) was added portionwise, care being taken that the temperature did not rise above 85°. After all the sulfone was added, the temperature of the reaction was maintained at 80° for two hours. The reaction mix-

(11) Näff, *Ann.*, **265**, 112 (1892).

ture was cooled. The liquor was decanted and the residual iron mud was extracted with acetone. The acetone was distilled off *in vacuo*. The residue was dissolved in hot absolute ethanol and charcoaled. On cooling the alcoholic solution, fine white needles of the 4-aminophenyl-2′-aminothiazolyl-5′ sulfone formed and were filtered off; m. p. 219–221°, with decomposition; yield, 35 g. (85%).

Summary

The preparation and some of the chemical characteristics of 4-aminophenyl-2′-aminothiazolyl-5′ sulfone (Promizole) and its derivatives have been described.

Evidence is presented in support of the conclusion that under the influence of heat and acetic anhydride the 4-nitrophenyl sulfenyl group migrates from the amine of 2-aminothiazole to the 5-position on the thiazole ring.

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[CONTRIBUTION FROM THE DEPARTMENTS OF PHYSIOLOGICAL CHEMISTRY AND PHYSICS OF THE UNIVERSITY OF MINNESOTA]

Extreme Ultraviolet Absorption Spectra of the Fatty Acids[1,2]

BY I. I. RUSOFF, J. R. PLATT,[3] H. B. KLEVENS[4] AND G. O. BURR

The fatty acids offer one of the best series of compounds available for study of the effects of double bonds upon light absorption. Well-known members of the series range from zero to four unconjugated double bonds. There are also several distinct conjugated systems and by elaidinization the *trans*-configuration can be compared with the *cis*.

In several recent reviews[5,6,7] absorption data for numerous simple aliphatic compounds have been assembled and the effects of unsaturation, conjugation and geometric configuration discussed. However, only recently a fairly complete study of the far ultraviolet absorption by purified fatty acids has been made.[8] The work of Barnes *et al.*, extends the curves of the saturated acids, oleic, linoleic, linolenic and arachidonic, to 2100 Å. where the effect of additional double bonds is so marked that extinction coefficients of oils may be used in the calculation of composition.

However, at the limit of the above work (2100 Å.) none of the curves of the unsaturated fatty acids has reached a peak. A compilation of the spectral data for the unconjugated fatty acids and oils shows that in most of the work done to date the curves stop at or above 2200 Å.[9] It was thought desirable to extend these measurements into the Schumann region in order to get a complete picture of light absorption by these biologically important natural products. In the present paper the absorption curves of the unconjugated fatty acids have been extended to 1700 Å.; in addition a number of conjugated systems and geometric isomers have been included.

Experimental

Description of Instruments.—The fluorite vacuum spectrograph system employed in the studies presented in this paper was similar to that described by Scheibe.[10] A diagram of the essential parts of the apparatus is shown in Fig. 1. The light source (L) is a modified Urey type hydrogen discharge tube operating at approximately 0.8 ampere from the secondary of a 4000 v., 5 K. V. A. transformer. Light from the discharge tube (L) passes through the absorption cell (C) which is formed by the gap between two lithium fluoride windows which are permanently sealed to the hydrogen tube and the spectrograph, respectively. The window on the spectrograph is sealed with wax to a collar which, in turn, is sealed to an end-plate and attached to the spectrograph by a flexible bellows which permits easy adjustment and alignment of the cell. Three springs are connected to the end-plate of the spectrograph and the water jacket of the Urey tube. By adjusting the tension of the springs, the two windows are pressed uniformly against a copper spacer which separates them by a distance of 0.026 cm. During a test exposure the solution was continuously admitted into the cell through a capillary

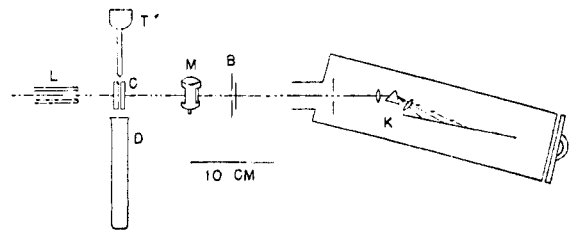

Fig. 1.—Vacuum spectrograph and accessories used in photographing the absorption spectra.

(1) The experimental data are taken from a thesis submitted to the faculty of the Graduate School of the University of Minnesota by I. I. Rusoff in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

(2) This work was supported by grants from the Rockefeller Foundation, the National Live Stock and Meat Board, and the Graduate School of the University of Minnesota. The authors are indebted to Professors Joseph Valasek and Elmer S. Miller (deceased) for their advice and criticisms; to J. B. Brown for a sample of methyl arachidonate and recrystallized linolenic acid; to J. Nichols for the preparation of debrominated linolenic and linoleic acid; to J. P. Kass for samples of elaidic acid, elaidolinolenic acid, the conjugated isomers of linoleic acid, and pseudoeleostearic acid; to W. M. Lauer for 2-heptadecenoic acid. They also express their thanks to F. Thurston for assistance with the laboratory work.

(3) Present address: Northwestern University, Evanston, Illinois.

(4) Present address: University of Chicago, Chicago, Illinois.

(5) E. P. Carr and H. Stücklen, "Proc. of the Seventh Summer Conference on Spectroscopy and its Applications," John Wiley and Sons, Inc., New York, N. Y., 1940, p. 128.

(6) K. Dimroth, *Angew. Chem.*, **52**, 545 (1939).

(7) G. O. Burr and E. S. Miller, *Chem. Rev.*, **29**, 419 (1941).

(8) R. H. Barnes, I. I. Rusoff, E. S. Miller and G. O. Burr, *Ind. Eng. Chem., Anal. Ed.*, **16**, 385 (1944).

(9) I. I. Rusoff, "Spectral Absorption Characteristics of Lipids," Thesis, University of Minnesota, 1943.

(10) G. Scheibe, *Z. physik. Chem.*, **B5**, 355 (1929).