2-(*p*-Aminobenzenesulfonamido)-4-ethylthiazole

By Frank H. Bergeim, N. H. Coy and W. A. Lott

In a previous communication[1] we mentioned that 2-(*p*-aminobenzenesulfonamido)-4-ethylthiazole, had the low melting point of 149.5–150.5° (uncor.) as against 237–238° (uncor.) for the methyl derivative. Although this phenomenon is fairly common, we felt it essential to assure ourselves that this lower melting point was not due to impurities, since the compound was to be subjected to biological evaluation for use as a chemotherapeutic agent.

We have now prepared this compound by two different synthetic routes with similar results.

The toxicity of the 4-ethyl derivative is much greater than that of the 4-methyl homolog or sulfathiazole itself.

Experimental Part

2-Amino-4-ethylthiazole.—This substance was prepared by the procedure given in "Organic Syntheses"[2] for the analogous methyl derivative. From 1-chloro-2-butanone a 72% yield of a white hydrochloride was obtained which after recrystallization from alcohol and acetone melted at 185.5–187.5° (uncor.). The free base was liberated with concentrated aqueous ammonia, taken up in ether, and on evaporation obtained in crystalline form (m. p. 35°; b. p. 118–120°, 7 mm.). Calcd. for $C_5H_8N_2S$: N, 21.87; S, 25.01. Found: N, 21.49; S, 25.27. It had a faint "burnt amine" odor, was readily soluble in carbon tetrachloride, ether and absolute alcohol, and only slightly soluble in water. Acetic anhydride gave the mono acetyl derivative (m. p. 117.5 (uncor.)). Calcd. for $C_7H_{10}N_2OS$: N, 16.46. Found: N, 16.70.

2-(*p*-Acetaminobenzenesulfonamido)-4-ethylthiazole.—2-Amino-4-ethylthiazole, dissolved in pyridine, was treated with one mole of *p*-acetaminobenzene sulfone chloride, heated for one hour on a steam-bath and diluted with water. The crystalline product separated almost quantitatively. After recrystallization from alcohol it melted at 230.5–231° (uncor.). Calcd. for $C_{13}H_{15}N_3O_3S_2$: N, 12.92; S, 19.69. Found: N, 12.87; S, 19.66

2-(*p*-Aminobenzenesulfonamido)-4-ethylthiazole.—By refluxing the above acetyl derivative with ten times its weight of 10% hydrochloric acid, cooling and alkalinizing to congo red there was obtained an 80% yield of crude product which after recrystallization from water had a m. p. of 151–151.5° (uncor.). Calcd. for $C_{11}H_{13}N_3O_2S_2$: N, 14.83; S, 22.62. Found: N, 14.74; S, 22.53.

The hydrochloride salt (m. p. 226–228° (uncor.) with foaming) was obtained by treating the base with 10% hydrochloric acid.

The sodium salt was prepared by adding the base to an alcoholic solution of sodium hydroxide, m. p. 277.5–278° (uncor.). Calcd. for $C_{11}H_{12}N_3O_2S_2Na$: Na, 7.53. Found: Na, 7.30. The *p*H of a 2% aqueous solution was 10.1.

The copper salt, prepared by mixing an aqueous solution of one-half mole of copper sulfate with one mole of sodium 2-(*p*-aminobenzenesulfonamido)-4-ethylthiazole, has a characteristic greenish-gray color.

2-(*p*-Nitrobenzenesulfonamido)-4-ethylthiazole.—This compound was prepared by dissolving 2-amino-4-ethylthiazole in pyridine and adding one mole of *p*-nitrobenzenesulfone chloride. Upon diluting with water the crystalline product separated in 83% yield. Recrystallized from acetone it melted at 193–195° (uncor.). Calcd. for $C_{11}H_{11}N_3O_4S_2$: S, 20.45. Found: S, 20.51.

Catalytic reduction (PtO_2 catalyst) of 2-(*p*-nitrobenzenesulfonamido)-4-ethylthiazole gave a product which was found by melting point and mixed m. p. to be identical with that obtained by deacylating 2-(*p*-acetaminobenzenesulfonamido)-4-ethylthiazole.

The ultraviolet absorption spectra of 2-(*p*-aminobenzenesulfonamido)-thiazole, 2-(*p*-aminobenzenesulfonamido)-4-ethylthiazole and 2-(*p*-aminobenzenesulfonamido)-4-methylthiazole were measured with the aid of a remodeled Judd Lewis spectrophotometer and a medium Bausch and Lomb spectrograph, using tungsten-steel spark discharge as the light source. Absolute alcohol was used as a solvent for all three compounds.

The absorption curves are given in Fig. 1. The curves of 2-(*p*-aminobenzenesulfonamido)-4-methylthiazole and 2-(*p*-aminobenzenesulfonamido)-4-ethylthiazole are identical. They have distinct maxima at 262 mμ ($\log \epsilon = 4.18$) and 292 mμ ($\log \epsilon = 4.30$) and a minimum at 263 mμ ($\log \epsilon = 4.1$). These curves are coincident within the experimental error of the instruments, but are shifted two

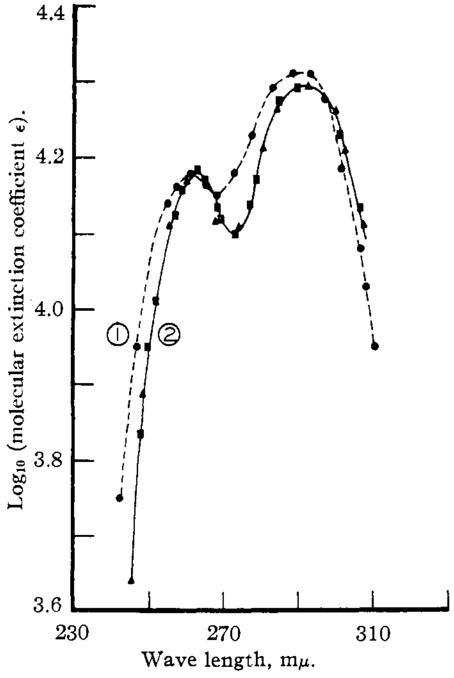

Fig. 1.—① ●, 2-(*p*-Aminobenzenesulfonamido)-thiazole; ② ■, 2-(*p*-aminobenzenesulfonamido)-4-methylthiazole; ② ▲, 2-(*p*-aminobenzenesulfonamido)-4-ethylthiazole.

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[1] This Journal, **61**, 3593 (1939).

[2] "Organic Syntheses," John Wiley and Sons, Inc., New York, N. Y., Vol. XIX, 1939, p. 10.

or three millimicrons toward longer wave lengths with respect to that of 2-(*p*-aminobenzenesulfonamido)-thiazole. This shift is compatible with the substitution of a hydrogen by an alkyl radical.

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RECEIVED APRIL 29, 1940

A Continuous Source for the Spekker Photometer

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The principles of the hydrogen discharge tube are so well known that the description of another model would be superfluous, were it not that the tube to be described here has certain practical advantages over other types. Its form is such that it can be used satisfactorily as a source in connection with a Hilger Spekker photometer, where a continuous spectrum is highly desirable. It also requires very little attention. One of these tubes has been in use for three years without having to be refilled.

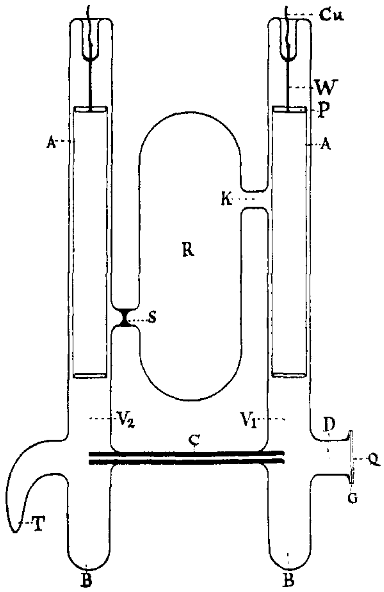

Fig. 1.—Hydrogen discharge tube for ultraviolet spectrograph.

A scale diagram of the tube[1] is shown in Fig. 1. With the exception of the quartz window Q, it is made of Pyrex glass which, besides cheapness, has the advantage of absorbing ultraviolet light so that goggles are unnecessary. The reservoir R is open to the rest of the tube on one side K, but is sealed off on the other S to prevent any short circuit through it. The horizontal tube C is a thick-walled capillary of 1-mm. bore, which connects the two vertical cylinders V, and in which the light is generated. This capillary extends almost, but not quite, to the centers of the cylinders on both sides, as shown in the diagram. It is essential that the capillary be straight and horizontal. Its protrusion to the center of the vertical cylinder V_1 causes a cone of light to come to a point at its end and thus to form the point source necessary for a Spekker. If the capillary tube terminates at the wall, a diffuse source results.

Opposite the end of the capillary, the cylinder V_1 is provided with a collar D with a flange to which the quartz window is affixed. For use with the Spekker photometer, the distance from the end of the capillary to the outside surface of the window Q must not exceed 4 cm., to permit correct focusing of the point of light onto the prism of the Spekker. To cylinder V_2, opposite the other end of the capillary, is attached a side tube bent down in the form of a cornucopia T. This serves to trap reflections, and is also used for outgassing the tube.

Below the ends of the capillary tube, the cylinders V are prolonged for 8 cm. As the tube is set up in a vertical plane, with the electrodes pointing down, these prolongations B act as traps for any sputtered aluminum or impurities from the electrodes. After a year or so of operation, the traps become coated with material, some of which would otherwise find its way to the inner surface of the quartz window. If the traps are made shallower, after some time the inside of the window becomes coated with enough material to weaken markedly the output of the tube in the short ultraviolet. The over-all length of the cylinders V is 42 cm., and their outside diameter is 3.2 cm. The hydrogen reservoir is 21.5 cm. high by 7.5 cm. in diameter.

The quartz window, which must be exactly perpendicular to the axis of the capillary tube C, is 3.8 cm. in diameter and 1 mm. thick. It is sealed to the flange of collar D with glyptal G, which should be allowed to dry for forty-eight hours before evacuating the tube.

The electrodes A are of rolled aluminum, and are long enough (20 cm.) to permit considerable cooling. Their external diameter is 2.2 cm., and the aluminum is 0.5 mm. thick. Care must be taken in the rolling of the aluminum that no impurities such as mercury are on the bench, as it is impossible to get them out of the tube afterward. The plug P connecting each electrode with a tungsten rod W which supports it through the glass must be carefully fastened to the electrode, preferably by a set of aluminum rivets. This contact must be perfect, lest it offer enough resistance to become a source of heat. The tungsten rods are fused into depressions in the tops of the cylinders, and outside of the tube are welded to heavy flexible copper wires Cu.

The apparatus is evacuated by means of a mercury pump, and after twenty-four hours is washed out with hydrogen. This process is repeated three or four times, and the tube is finally filled with hydrogen at a pressure of 1.0 to 1.5 mm.

The tube can be operated for periods up to ten to fifteen minutes on 15,000 volts, 100 milliamperes, without special air cooling. For longer periods it has been found satisfactory to blow a current of air over the capillary with an ordinary fan. It can be used with much higher amperages,

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(1) This is the tube referred to by R. N. Jones, in THIS JOURNAL, 62, 148 (1940).