disulfide solution is heated to 100° and the spectrum recorded within 10 minutes. Using the rate constants from Table II and a time of 600 seconds for reaction 8, the maximum concentration of radicals III from MBTS is 6×10^{-7} molar. If radical III is responsible for the increase in optical density (Fig. 1), the extinction coefficient of the radical must be at least 3×10^5 at 300 mμ. Such a value is unusually high and would require a very narrow absorption band with an oscillator strength or effective f_i number of one (fully allowed transition).[22] Such an interpretation cannot explain the time independence of the absorption values as more radicals are being produced and equilibrium established. Besides, the extinction value of radical III must be tremendous over the entire spectral range of 230 to 400 mμ.

For dissociation of TMTD the maximum amount of radicals produced by the time of measurements would be 1.4×10^{-7} molar. Once again the extinction coefficients are calculated to be abnormally high over the entire spectral range. It would be predicted that as more radicals are produced the spectrum would continue to change. However, the spectrum is nearly time independent at 100° with a change of less than 1% per hour.

The change in spectrum with increasing temperature must then be a ground state phenomenon, a property of the molecule itself rather than its dissociation products. This can be best described as thermal broadening of the absorption band. As a consequence of the Franck–Condon principle, a change in distribution of molecules over the various vibrational levels of the ground state leads to flattening and broadening of the absorption bands with rise in temperature. At low temperatures the vibrational quantum numbers of the absorbing molecules will be preponderally zero. As the temperature is raised, the absorbing molecules are raised into higher vibrational quantum states in accordance with the Boltzmann exponential distribution law. The most probable electronic transitions for these molecules would then involve different changes of the vibrational quantum numbers from those of the molecules in the lowest level. The superposition of all these transitions must result in broadening and flattening of the absorption curve. Both compounds I and II have heavy atoms and skeletal vibrations of low frequency. Therefore, the vibrational spacings of the ground states are quite close together. Compounds I and II have rather strong absorption bands tailing well toward the visible. The extra thermal perturbation extends this tail just enough such that the solution becomes perceptionally yellow.

The authors wish to thank Prof. P. D. Bartlett for helpful encouragement. We are indebted to Mr. R. Wall and T. Kaiser for their thermochemical measurements.

CAMBRIDGE, MASS.

(22) The absorption bands of most organic compounds in solution have half-widths of the order of 5000 cm.$^{-1}$. Since oscillator strengths of greater than unity are very unusual, E_{max} values are generally not greater than 5×10^4.

[CONTRIBUTION FROM THE ORGANIC CHEMICAL RESEARCH LABORATORIES, LEPETIT S.P.A. MILANO]

Synthesis of a New Heterocyclic Ring—2,5-Dihydro-1,2,4-benzothiadiazepine 1,1-Dioxide and its Intermediates

BY GIORGIO CIGNARELLA AND UBERTO TEOTINO

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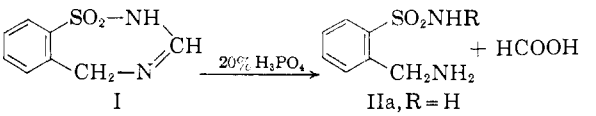
A new heterocyclic derivative, 2,5-dihydro-1,2,4-benzothiadiazepine 1,1-dioxide (I), has been synthesized by the condensation of *o*-aminomethylbenzenesulfonamide (IIa) with ethyl orthoformate. The starting material IIa was obtained by chlorine oxidation of dithiosalicylamide (III) to *o*-cyanobenzenesulfonic acid (IV), and conversion to IV to the acid chloride V which was converted to the amide VIa. Upon catalytic reduction with palladium, VIa afforded the desired IIa. Two N′-substituted derivatives of IIa were also prepared.

In a previous paper[1] we described the synthesis of a new seven-membered heterocyclic compound, 1,3 - dihydro - 2,3,5 - benzothiadiazepine 2,2-dioxide, by the condensation of *o*-aminobenzylsulfonamide with ethyl orthoformate. We now report the preparation of a new isomeric benzothiadiazepine dioxide. The condensation of ethyl orthoformate with *o*-aminomethylbenzenesulfonamide (IIa) gave a compound, $C_8H_8N_2O_2S$ (I), which upon hydrolysis with phosphoric acid yielded *o*-aminomethylbenzenesulfonamide (IIa) and formic acid. The infrared spectrum of I was very similar to that reported for 1,3-dihydro-2,3,5-benzothiadiazepine 2,2-dioxide.[1] On the basis of these findings, the structure 2,5-dihydro-1,2,4-benzothiadiazepine 1,1-dioxide was assigned to I as shown.



I IIa, R = H

When the N^1-substituted sulfonamides IIb and IIc (b, R = CH_3; c, R = C_6H_5) were condensed with ethyl orthoformate no product could be isolated. In our previous work,[1] however, the N^1-substituted *o*-aminobenzylsulfonamides yielded not the desired benzothiadiazepines but N,N′-disubstituted formamidines; yields were about 50%.

A few *o*-aminomethylbenzenesulfonamides II have been reported. Only the unsubstituted derivative IIa was isolated by Angyal and Foukin[2] in 9% yield as a by-product of the synthesis of the isomeric homosulfanylamide by chlorosulfonation of N-benzylacetamide followed by treatment with

(1) U. M. Teotino and G. Cignarella, THIS JOURNAL, **81**, 4935 (1959).

(2) S. J. Angyal and S. R. Foukin, *Australian J. Sci. Research*, **3A**, 461 (1950).

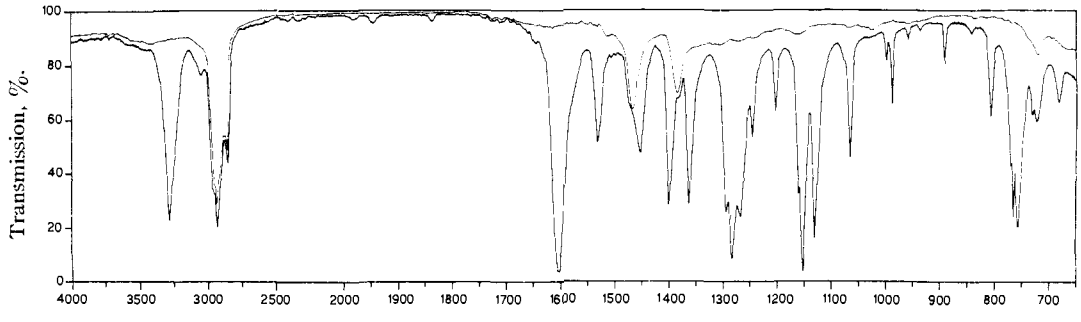
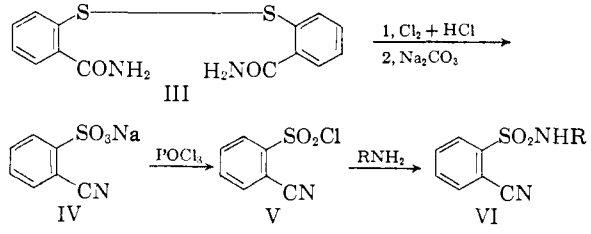


Fig. 1.

ammonia and deacetylation. However, the melting point of the free base (83–84°), of the hydrochloride (238–239°) and of the acetyl derivative (137–138°) reported by these authors differ considerably from those observed by us (114–115°, 210–212° and 157–158°, respectively). The synthesis of IIa by oxidation of *o*-toluenesulfonamide to the corresponding aldehyde followed by reduction of the aldehyde oxime[3] is also briefly mentioned in a Japanese report.[4] We have synthesized *o*-aminomethylbenzenesulfonamide (IIa) and its N^1-methyl IIb and N^1-phenyl IIc derivatives starting with *o*-cyanobenzenesulfonylchloride (V). As the preparation of V from saccharin and phosphorus pentachloride[5,6] is inconvenient owing to poor yields and difficulties encountered in the purification of the product, we have developed a new procedure starting with dithiosalicylamide (III).[7,8]

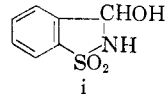
The oxidation of III with chlorine surprisingly afforded *o*-cyanobenzenesulfonic acid, isolated as the sodium salt (IV) instead of the expected *o*-carbamylbenzenesulfonic acid. The reaction of IV with phosphorus oxychloride yielded *o*-cyanobenzenesulfonyl chloride (V). Upon treatment with ammonia or a



a, R = H; b, R = CH_3; c, R = C_6H_5

primary amine V gave the corresponding *o*-cyanobenzenesulfamides (VIa, b and c) which are stable in neutral media but easily isomerize in alkali to the pseudosaccharinimides (VII).

(3) However, J. and P. Koetschet [*Helv. Chim. Acta*, **12**, 669 (1929)] show that *o*-sulfamidobenzaldehyde cannot exist because it isomerizes readily to i.



i

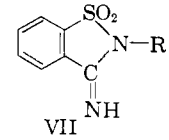
(4) T. Momose and T. Shoji, *J. Pharm. Soc. Japan*, **70**, 71 (1950); *C.A.*, **44**, 5324f (1950).

(5) J. A. Jesurun, *Ber.*, **26**, 2286 (1893).

(6) A. J. Walker and E. Smith, *J. Chem. Soc.*, **89**, 350 (1906).

(7) R. List and M. Stein, *Ber.*, **31**, 1648 (1898).

(8) E. W. McClelland and J. Longwell, *J. Chem. Soc.*, **123**, 3310 (1923).



VII

The reaction of V with ammonia and aniline has been already reported. Care must be taken to avoid an excess of the amine because of this isomerization. However, we have noted that while this is necessary in the case of VIb because of the high basicity of methylamine, in the case of VIa it is unnecessary to prepare a titrated solution of ammonia; it is sufficient to isolate the precipitate of VIa as soon as it is formed. The *o*-aminomethylbenzenesulfonamides (IIa, b and c) were obtained in good yield by catalytic hydrogenation of the corresponding *o*-cyanosulfonamides VI.

Acknowledgment.—We are indebted to Prof. Fusco for a valuable discussion of this subject and to Dr. Wittgens for the assistance in the preparation of the manuscript.

Experimental

***o*-Cyanobenzenesulfonic Acid (Na Salt) (IV).**—A stream of chlorine was bubbled into a suspension of 30 g. of dithiosalicylamide in 900 ml. of hydrochloric acid (1:1) with stirring at room temperature. In 1–1.5 hours solution was complete and the evolution of heat had subsided. After air had been bubbled through to remove the excess chlorine, the solution was neutralized with a saturated sodium carbonate solution and evaporated to dryness *in vacuo* at 45–50°.

The residue, dried *in vacuo* at 100°, was extracted in a Soxhlet with two 250-ml. portions of absolute ethanol. Sodium *o*-cyanobenzenesulfonate (IV) separated as white needles. Additional product separated upon concentration and cooling of the mother liquor. The total yield of IV was 28.6 g. The infrared spectrum shows the absorption bands of the —C≡N and $—SO_3^-$ groups, while the band of the $—CONH_2$ group is absent.

Anal. Calcd. for $C_7H_4NNaO_3S$: N, 6.83; S, 15.6. Found: N 6.78; S, 15.32.

***o*-Cyanobenzenesulfonyl Chloride (V).**—Sodium *o*-cyanobenzenesulfonate (10 g.) was refluxed with 25 ml. of phosphorus oxychloride for 2 hours in an oil-bath at 95–100°. When the reaction mixture (cooled to room temperature) was poured into 50 ml. of ice-water with vigorous stirring, *o*-cyanobenzenesulfonyl chloride separated as colorless oil which crystallized rapidly on rubbing. The product was washed on the filter first with cold dilute sodium bicarbonate solution and then with water, and dried in a desiccator over potassium hydroxide; yield 8.5 g. (86.5%). After recrystallization from ether the melting point was 69–69.5°.

Anal. Calcd. for $C_7H_4ClNO_2S$: N, 6.97; Cl, 17.61. Found: N, 6.97; Cl, 17.45.

o-**Cyanobenzenesulfonamide** (**VIa**).—A slow stream of gaseous ammonia was passed into a solution of 8 g. of *o*-cyanobenzenesulfonyl chloride in 50 ml. of anhydrous ether, which was cooled with water. Care was taken to avoid saturation of the ether solution with ammonia. The resulting white precipitate was collected immediately and treated with 10 ml. of water to remove the ammonium chloride. The residual *o*-cyanobenzenesulfonamide which was dried *in vacuo*, is sufficiently pure for the next step; yield 5.4 g., m.p. 163–165°. From absolute ethyl alcohol it crystallized in the form of white plates, m.p. 165–167°.

Anal. Calcd. for $C_7H_6N_2O_2S$: N, 15.38. Found: N, 15.45.

o-**Cyano-N-methylbenzenesulfonamide** (**VIb**).—A 4% ethereal solution of methylamine (51 ml.) was added dropwise with stirring to an ice-cold solution of 7 g. of *o*-cyanobenzenesulfonyl chloride in 70 ml. of anhydrous ether; this amount of methylamine is 95% of the theoretical quantity. The resulting white precipitate was suspended in 15 ml. of water. The insoluble *o*-cyano-N-methylbenzenesulfonamide (VIb) was collected and dried *in vacuo;* yield 3.2 g., m.p. 82–84°. Upon evaporation to dryness the mother liquor yielded additional VIb which was crystallized from benzene; yield 1.5 g., m.p. 81–83°. The infrared spectrum shows the —C≡N band.

Anal. Calcd. for $C_8H_8N_2O_2S$: N, 14.28. Found: N, 14.12.

o-**Cyanobenzenesulfonanilide** (**VIc**).—To a solution of 5 g. of *o*-cyanobenzenesulfonyl chloride in 30 ml. of ether was slowly added 4.55 g. of aniline with stirring at room temperature. Stirring was continued for 15 minutes to remove the ether. Then the reaction mixture was treated with 30 ml. of water and stirred for several minutes. The *o*-cyanobenzenesulfonanilide was collected (yield 6 g.) and crystallized from benzene; m.p. 151–153°.

Anal. Calcd. for $C_{13}H_{10}N_2O_2S$: N, 10.85. Found: N, 11.00.

N¹-Methyl-pseudosaccharinimide (VII, R = CH_3).—The procedure described for the preparation of VIb was followed except that an excess of methylamine was used; VII was crystallized from water; m.p. 165–166°. The infrared spectrum shows the absence of the —C≡N band and the presence of the =C=N— band. Upon hydrolysis with hot water containing a few drops of sulfuric acid and subsequent cooling, a microcrystalline product precipitated (m.p. 134–136°) which was identified as N-methylsaccharin.[9]

o-**Aminomethylbenzenesulfonamide** (**IIa**).—A solution containing 6 g. (0.033 mole) of VIa (m.p. 163–165°) in 300 ml. of absolute alcohol was shaken for several hours with 1 g. of palladium-on-charcoal. After filtration, 500 ml. of 4% hydrochloric acid in absolute alcohol was added to the filtrate and the solution hydrogenated at room pressure and temperature in the presence of 2 g. of 10% palladium-on-charcoal. The reduction was complete in 5–6 hours. Then the catalyst was filtered and the solution evaporated to a small volume from which the amine hydrochloride separated as white needles; yield 3.6 g., m.p. 210–212°. Additional product was obtained from the mother liquor which was evaporated to dryness. The residue was treated with water, the insoluble material removed, and the filtrate evaporated to dryness *in vacuo*. The residue was recrystallized from absolute alcohol to yield 0.5 g. of the hydrochloride.

Anal. Calcd. for $C_7H_{10}N_2O_2S \cdot HCl$: C, 37.75; H, 4.98; N, 12.58; Cl, 15.82. Found: C, 37.51; H, 5.11; N, 12.65; Cl, 16.20.

To prepare the free base IIa a suspension of the hydrochloride in alcohol was treated with the theoretical amount of a 2% alcoholic solution of sodium ethoxide. The separated sodium chloride was filtered and the solution evaporated to dryness *in vacuo*. The residue was crystallized from water to yield IIa, m.p. 114–115°.

Anal. Calcd. for $C_7H_{10}N_2O_2S$: N, 15.05. Found: N, 14.95.

N-Acetamidomethylbenzenesulfonamide.—A mixture of 0.9 g. of IIa, suspended in 5 ml. of glacial acetic acid, and 0.7 g. of acetic anhydride was heated on a water-bath for 30 minutes; upon cooling the acetyl derivative separated; it was recrystallized from water and dried *in vacuo;* m.p. 157–158°.

Anal. Calcd. for $C_9H_{12}N_2O_3S$: C, 47.35; H, 5.79; N, 12.27. Found: C, 47.16; H, 5.90; N, 12.36.

o-**Aminomethylbenzenesulfonmethylamide** (IIb) was prepared from 3.3 g. of VIb by the method described for IIa; yield 2.6 g. of the hydrochloride, m.p. 200–202°.

Anal. Calcd. for $C_8H_{13}ClN_2O_2S$: Cl, 14.95; N, 11.84. Found: Cl, 15.20; N, 11.95.

The free base (yield 2 g.) was crystallized from 90% ethanol; m.p. 120–122°.

Anal. Calcd. for $C_8H_{12}N_2O_2S$: N, 14.0. Found: N, 14.0.

o-**Aminomethylbenzenesulfonphenylamide** (**IIc**) was obtained as described for IIa from 3 g. of VIc; yield 2.2 g. of IIc hydrochloride, m.p. 176–178°.

Anal. Calcd. for $C_{13}H_{15}ClN_2O_2S$: Cl, 11.87; N, 9.36. Found: Cl, 11.99; N, 9.33.

The free base (yield 1.6 g.) melted at 164–165°.

Anal. Calcd. for $C_{13}H_{14}N_2O_2S$: N, 10.69. Found: N, 10.79.

2,5-Dihydro-1,2,4-benzothiadiazepine-1,1-dioxide (I).—In a 50-ml. flask fitted with a thermometer and connected to a distillation apparatus, 2.4 g. of IIa was dissolved in 8 ml. of propylene glycol with mild heating. Then 8 ml. of ethyl orthoformate (excess 4:1) was added and the solution heated for 6 hours in an oil-bath at 120–130°. The ethanol formed in the reaction distilled over. The 2,5-dihydro-1,2,4-benzothiadiazepine 1,1-dioxide, which crystallized when the solution was cooled with ice, was filtered *in vacuo* and recrystallized from 60 ml. of methanol; yield 1.3 g. (51.5%), m.p. 240–241°.

Anal. Calcd. for $C_8H_8N_2O_2S$: C, 48.96; H, 4.10; N, 14.27; S, 16.34. Found: C, 48.74; H, 4.00; N, 14.36; S, 16.52.

Compound I is insoluble in most organic solvents and in acids; it dissolves in hot methanol, and at ordinary temperatures in dilute ethanol and alkali from which it is precipitated by the addition of mineral acid. The benzothiadiazepine is slightly acid (pK 11.2).

When Compound I was allowed to stand for some hours in alkaline solution, it hydrolyzed to aminomethylbenzenesulfonamide.

The acid hydrolysis of I, which was carried out as follows, leads to the formation of IIa and formic acid.

Compound I (0.8 g.) was refluxed for 1 hour with 10 ml. of 20% phosphoric acid and then steam distilled. The formic acid which distilled was identified by the reduction of ammoniacal silver nitrate solution.

The distillation residue was neutralized with sodium hydroxide and exhaustively extracted with ether. The extract was dried (Na_2SO_4) and the solvent removed by distillation. The residue (0.51 g.) was dissolved in ether and a stream of gaseous HCl bubbled through the solution. The resulting white precipitate (0.53 g.) was crystallized from absolute alcohol; m.p. 209–211°. From a mixed melting point determination with an authentic sample and from the infrared spectrum, this product was identified as the hydrochloride of IIa.

MILAN, ITALY

(9) I. Remsen and F. B. Clark, *Am. Chem. J.*, **30**, 278 (1903).