

1,2-Benzothiazines V. (1)
The Preparation of 3,4,5,6-Tetrahydro-2,6-methano-2*H*-1,2,5-benzothiadiazocine 1,1-Dioxide

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As part of a program directed toward the synthesis of 1,2-benzothiazine derivatives, we have prepared bridged compounds having structures V and VI. These are representative of the previously unreported 3,4,5,6-tetrahydro-2,6-methano-2*H*-1,2,5-benzothiadiazocine ring system.

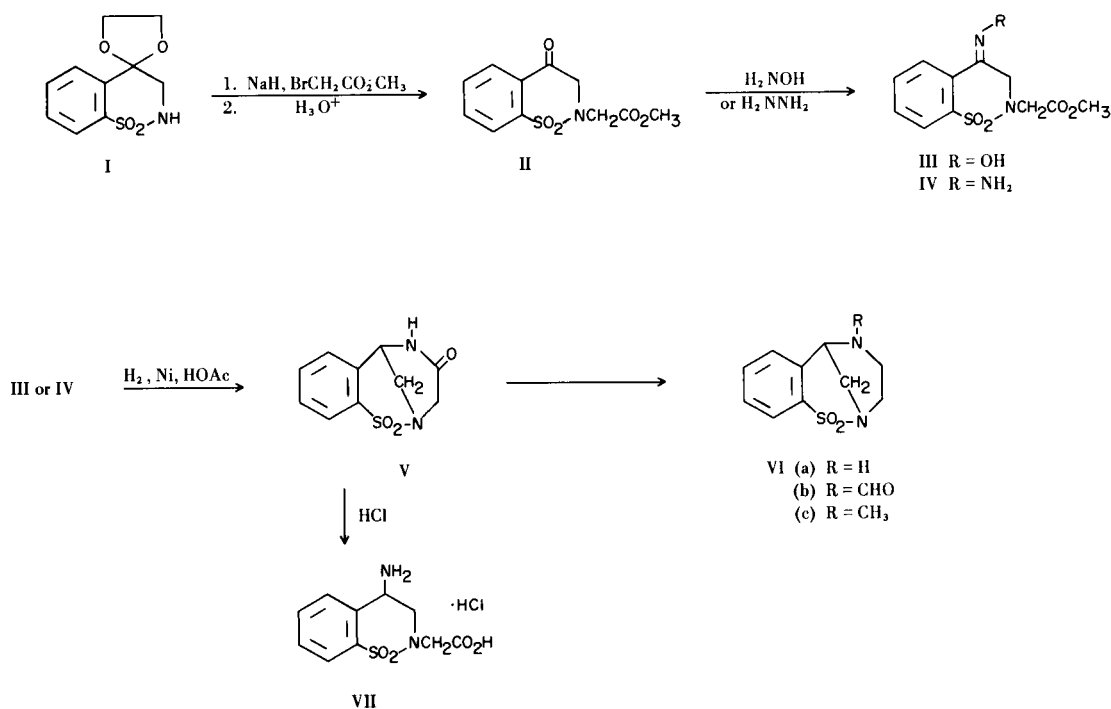
The starting material for this synthesis was the ketal I (3) which was alkylated by refluxing with sodium hydride and methyl bromoacetate in 1,2-dimethoxyethane. Acid hydrolysis of the resulting ester ketal gave the corresponding ketone II which was converted to the oxime III and the hydrazone IV.

When either III or IV was hydrogenated in glacial acetic acid at 55° and 1500 psi, using Raney nickel as catalyst (4), the resulting amino ester cyclized spontaneously to give the lactam V. In the case of the hydrazone, it

was thus apparent that N-N cleavage had occurred (5,6).

Compound V is characterized by strong NH and carbonyl bands at 3270 and 1680 cm^{-1} , respectively, as well as by weak ultraviolet maxima at 268 and 275 ($\epsilon = 800$ and 720, respectively) $\text{m}\mu$. The nmr spectrum (7) shows the NH as a doublet at δ 8.82, the aromatic protons as a multiplet at δ 7.2-8.0, and the remaining five non-aromatic protons as a series of overlapping signals at δ 3.8-4.6 ppm. Included among the latter is a sharp singlet at δ 4.15 ppm which probably represents the protons α to the carbonyl.

Acid hydrolysis of V gave the expected amino acid which was isolated as the hydrochloride salt, VII. Reduction of V to VIa was conveniently achieved in 80% yield by the use of diborane in refluxing tetrahydrofuran (8). This procedure was also used for the preparation of the



N-methyl derivative VIc from VIb. The latter was obtained in near quantitative yield by refluxing VIa with ethyl formate.

Our attempts to reduce V by prolonged refluxing with lithium aluminum hydride in ether resulted in the isolation of VIa in only 26% yield together with unreacted starting material; there was also evidence that concomitant reduction of the sulfonamide group had taken place. Little or no reaction took place in ether or tetrahydrofuran at room temperature, whereas in refluxing tetrahydrofuran, decomposition was so extensive that no clean products could be isolated.

EXPERIMENTAL (9)

2-Carbomethoxymethyl-2*H*-1,2-benzothiazin-4-3*H*-one 1,1-Dioxide (II).

To a slurry of 69.8 g. (1.6 mole) of a 53.4% mineral oil dispersion of sodium hydride in 2400 ml. of 1,2-dimethoxyethane was added a solution of 193.2 g. (0.8 mole) of 2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-dioxide ethylene ketal (I) (3) in 2400 ml. of 1,2-dimethoxyethane and the mixture was refluxed with stirring for 1 hour. It was cooled to room temperature, a solution of 256 g. (1.6 mole) of methyl bromoacetate in 800 ml. of 1,2-dimethoxyethane was added, and refluxing was continued for 19 hours. The mixture was filtered and the filtrate was distilled *in vacuo* to give an oil which was converted to a gummy solid on trituration with petroleum ether (b.p. 40-60°); the infrared spectrum showed the absence of NH absorption. It was refluxed for 15 minutes with a mixture of 2000 ml. of methanol and 2000 ml. of 10% aqueous hydrochloric acid and the methanol was distilled off. The resulting gummy precipitate was trituated with several portions of water and then with 150 ml. of methanol to give 104 g. (48%) of crystalline product, m.p. 108-109°. Recrystallization from methanol gave an analytical sample, m.p. 109-110°; ν max 1740 (s, ester), 1710 (s, ketone) cm^{-1} ; λ max 241 μm (ϵ , 9,600), 287 (1600), 296 (1500).

Anal. Calcd. for $\text{C}_{11}\text{H}_{11}\text{NO}_5\text{S}$: C, 49.07; H, 4.12; N, 5.20; S, 11.91. Found: C, 49.37; H, 4.13; N, 5.04; S, 11.98.

2-Carbomethoxymethyl-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-Dioxide-Oxime (III).

A mixture of 32.3 g. (0.12 mole) of II, 9.2 g. (0.132 mole) of hydroxylamine hydrochloride, 26.4 g. of potassium acetate, and 600 ml. of methanol was refluxed for 3 hours, filtered, and the solvent was evaporated from the filtrate. The oily residue was partitioned between water and ether and the dried ether solution was evaporated to give 30.8 g. (90%) of product, m.p. 123-126°. Recrystallization from isopropyl ether gave 22.2 g. (65%) of material, m.p. 127-128°; γ max 3470 (s, OH) and 1750 cm^{-1} , (s, C=O); λ max 257 μm (ϵ , 11,900).

Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_5\text{S}$: C, 46.47; H, 4.25; N, 9.85; S, 11.28. Found: C, 46.76; H, 4.36; N, 9.69; S, 11.22.

2-Carbomethoxymethyl-2*H*-1,2-benzothiazin-4(3*H*)-one 1,1-Dioxide Hydrazone (IV).

A mixture of 2.7 g. (0.01 mole) of II, 1.18 g. (0.011 mole) of hydrazine dihydrochloride, 4.2 g. of potassium acetate, and 100 ml. of methanol was refluxed for 18 hours, cooled to room temperature, and filtered. The filtrate was concentrated to an

oily residue which was trituated with several portions of water and then dissolved in dichloromethane. The dried solution was evaporated and the gummy residue was trituated with petroleum ether and then crystallized from methanol to give 1.3 g. (46%) of product, m.p. 134-135°; γ max 3400, 3300, 3230 (m, NH), 1740 cm^{-1} (s, C=O); λ max 233 μm (ϵ , 8,500), 292 (12,100).

Anal. Calcd. for $\text{C}_{11}\text{H}_{13}\text{N}_3\text{O}_4\text{S}$: C, 46.64; H, 4.63; N, 14.83; S, 11.32. Found: C, 46.73; H, 4.61; N, 14.65; S, 11.43.

3,4,5,6-Tetrahydro-4-oxo-2,6-methano-2*H*-1,2,5-benzothiadiazocine 1,1-Dioxide (V).

A. Preparation from III.

A solution of 14.5 g. (0.051 mole) of III in 250 ml. of glacial acetic acid was hydrogenated for 17 hours at 55° and 1500 psi using Raney nickel as the catalyst. The catalyst was filtered off, the solvent was removed, and the residue was trituated with water. The resulting solid was collected, washed with water, and dried by azeotropic distillation with benzene to give 8.8 g. (73%) of material, m.p. 250-257° dec. This was stirred with 50 ml. of refluxing chloroform, filtered while hot, and washed with chloroform to give 7.6 g. (63%) of crystalline product, m.p. 261-263° dec. Recrystallization from acetonitrile gave an analytical sample, m.p. 265-266° dec.

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{N}_2\text{O}_3\text{S}$: C, 50.41; H, 4.23; N, 11.76; S, 13.46. Found: C, 50.38; H, 4.19; N, 11.56; S, 13.60.

B. Preparation from IV.

A solution of 1.6 g. (0.0056 mole) of IV in 30 ml. of glacial acetic acid was hydrogenated as in Method A. After removal of the catalyst and solvent, the oily residue was solidified by trituration with water. The solid was dissolved in dichloromethane and the dried solution was evaporated to give 0.5 g. (38%) of material, m.p. 257-260° dec., which was shown by mixture melting point and comparison of infrared spectra to be identical with the product obtained by Method A. Extraction of the aqueous solution with dichloromethane and evaporation of the dried organic solution gave 0.4 g. (31%) of less pure product, m.p. 228-245° dec., which was identified by its infrared spectrum.

3,4,5,6-Tetrahydro-2,6-methano-2*H*-1,2,5-benzothiadiazocine 1,1-Dioxide (VIa).

A. Preparation by Diborane Reduction.

A slurry of 12.0 g. (0.05 mole) of V in 125 ml. of tetrahydrofuran was slowly added to 150 ml. of a 1*M* tetrahydrofuran solution of borane, the materials being kept at 0° and under a nitrogen atmosphere during the addition. Stirring was continued at room temperature for 1 hour and at reflux temperature for 3 hours. The mixture was then treated with 125 ml. of 9% hydrochloric acid, refluxed for 30 minutes and the tetrahydrofuran was distilled off. The aqueous solution was diluted with water to a volume of 1300 ml., washed with dichloromethane, made basic by the addition of 1*N* sodium hydroxide, and extracted with dichloromethane. Evaporation of the solvent gave 8.9 g. (80%) of product, m.p. 159-161° which was devoid of carbonyl absorption. Recrystallization by dissolving in a 2:1 mixture of isopropyl ether and dichloromethane and distilling off some of the latter gave 6.0 g. of material, m.p. 161.5-162.5°; γ max 3320 cm^{-1} (s, NH); λ max 268 μm (ϵ , 1,060), 276 (940).

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{N}_2\text{O}_2\text{S}$: C, 53.55; H, 5.39; N, 12.46; S, 14.30; M. W., 224.3. Found: C, 53.83; H, 5.67; N, 12.36; S, 14.33; M. W., 238.3 (Rast in camphor), 261 (vapor pressure osmometer in dibromomethane).

B. Preparation by Lithium Aluminum Hydride Reduction.

A mixture of 12.0 g. (0.05 mole) of V and 5.7 g. (0.15 mole) of lithium aluminum hydride in 500 ml. of ether was refluxed with stirring for 9 days. Hydrolysis, filtration, and evaporation of the filtrate gave 2.9 g. (26%) of product, m.p. 159-161°, which was shown by mixture melting point and comparison of infrared spectra to be identical to the product of Method A. Extraction of the insoluble residue by boiling with several portions of tetrahydrofuran, and evaporation of the solvent gave 2.6 g. of solid, m.p. 103-190° which showed a strong carbonyl band at 1680 cm^{-1} , indicating that unreacted starting material was still present. When the tetrahydrofuran insoluble residue was dissolved in dilute hydrochloric acid, there was observed the characteristic sulfide odor.

3,4,5,6-Tetrahydro-5-formyl-2,6-methano-2H-1,2,5-benzothiazocine 1,1-Dioxide (VIb).

A mixture of 10.0 g. (0.045 mole) of VIa and 250 ml. of ethyl formate was refluxed for 18 hours. The ethyl formate was removed by distillation and the residue was dissolved in dichloromethane. The solution was washed successively with several portions of 1N hydrochloric acid and water. The dried dichloromethane solution was evaporated to a residue which was triturated with petroleum ether (b.p. 40-60°) to give 10.5 g. (93%) of product, m.p. 142-143°. Recrystallization from isopropyl alcohol gave an analytical sample, m.p. 143.5-145°; γ max 1664 (s, N-CHO) cm^{-1} ; λ max 265 μ (ϵ , 880), 275 (700).

Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}_3\text{S}$: C, 52.37; H, 4.79; N, 11.10; S, 12.71. Found: C, 52.51; H, 4.74; N, 11.27; S, 12.54.

3,4,5,6-Tetrahydro-5-methyl-2,6-methano-2H-1,2,5-benzothiazocine 1,1-Dioxide (VIc).

A solution of 10.5 g. (0.042 mole) of VIb in 250 ml. of tetrahydrofuran was slowly added to 120 ml. of a 1M tetrahydrofuran solution of borane, the materials being kept at 0° and under a nitrogen atmosphere during the addition. Stirring was continued at room temperature for 1 hour and at reflux temperature for 3 hours. The mixture was then treated with 150 ml. of 9% hydrochloric acid, refluxed for 30 minutes and the tetrahydrofuran was distilled off. The resulting aqueous solution was diluted with water to a volume of 1000 ml., washed with dichloromethane, made basic by the addition of 1N sodium hydroxide, and extracted with dichloromethane. Evaporation of the solvent gave 8.0 g. (80%) of product, m.p. 155-156°, which was free of both NH and carbonyl absorption. Recrystallization from isopropyl ether gave an analytical sample, m.p. 156-157°.

Anal. Calcd. for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2\text{S}$: C, 55.44; H, 5.96; N, 11.75; S, 13.45. Found: C, 55.40; H, 6.13; N, 11.47; S, 13.68.

The methobromide, recrystallized from 95% ethanol, had m.p. 245-247° dec.

Anal. Calcd. for $\text{C}_{12}\text{H}_{17}\text{BrN}_2\text{O}_2\text{S}$: C, 43.25; H, 5.14; Br, 23.98; N, 8.40; S, 9.62. Found: C, 43.08; N, 5.16; Br, 23.78; S, 9.45.

The methiodide, recrystallized from methanol, had m.p. 248-249° dec.

Anal. Calcd. for $\text{C}_{12}\text{H}_{17}\text{IN}_2\text{O}_2\text{S}$: C, 37.91; H, 4.51; I, 33.37; N, 7.37; S, 8.43. Found: C, 38.11; H, 4.64; I, 33.23; N, 7.26; S, 8.50.

3,4-Dihydro-4-amino-2-carboxymethyl-2H-1,2-benzothiazine 1,1-Dioxide Hydrochloride (VII).

A mixture of 8.4 g. (0.035 mole) of V, 100 ml. of methanol, and 50 ml. of concentrated hydrochloric acid was refluxed for 1 hour, concentrated to a volume of about 30 ml., and allowed to stand at room temperature. The crystals which separated were collected, and washed successively with a small amount of concentrated hydrochloric acid and then with two 25 ml. portions of ethanol to give 7.7 g. (75%) of product, m.p. 216-217° dec. Recrystallization from ethanol gave an analytical sample, m.p. 217-218° dec.; γ max 3200 (s, NH), 1735 (s, C=O) cm^{-1} ; λ max 266 μ (ϵ , 500), 273 (450).

Anal. Calcd. for $\text{C}_{10}\text{H}_{13}\text{ClN}_2\text{O}_4\text{S}$: C, 41.03; H, 4.48; Cl, 12.11; N, 9.57; S, 10.95. Found: C, 40.86; H, 4.35; Cl, 11.89; N, 9.40; S, 10.74.

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