2,1-Benzisothiazoline 2,2-Dioxide. II. Some 5-Substituted Derivatives

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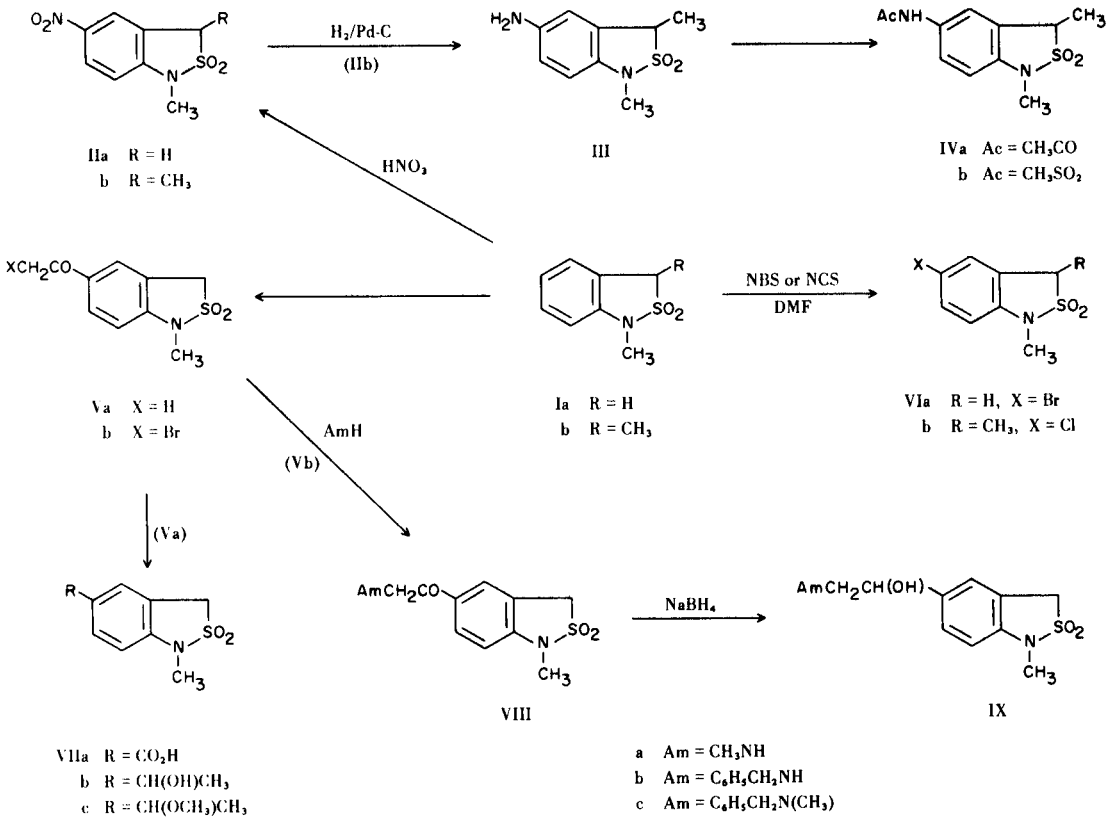
The first publication (1) from this laboratory regarding the chemistry of 2,1-benzisothiazoline 2,2-dioxide described several reactions at position 3 of the 1-methyl (Ia) and 1,3-dimethyl (Ib) derivatives. This report deals with the aromatic nitration, halogenation, and acylation of these two materials. Also included are subsequent conversions of the initially formed 5-substituted products to materials of possible pharmacological interest.

Treatment of Ia with nitric acid in glacial acetic acid afforded a mononitro derivative in 51% yield. The substituent was assigned to the 5-position (IIa) in view of the reported conversion of oxindole, the carbonyl analog of 2,1-benzisothiazoline 2,2-dioxide, to a 5-nitro derivative under similar conditions (2). The structure of IIa was confirmed by nmr which displayed doublets centered at 7.17 and 8.35 ppm (J = 9 cps) for the coupled protons at positions 7 and 6 and a singlet with hyperfine structure at 8.33 ppm for the proton at position 4.

Benzosultam Ib also was used to prepare a 5-nitro compound (IIb). Reduction of IIb provided the amine III, which was converted to the *N*-acetyl and *N*-methanesulfonyl derivatives, IVa and b. Several attempts to obtain the corresponding 5-hydroxy compound from a diazonium salt of III were unsuccessful.

The reaction of *N*-bromosuccinimide (NBS) with benzolactams and benzosultams is known to lead to aromatic substitution at the position *para* to the nitrogen of the hetero ring (3). In the present case, benzosultam Ia and



NBS afforded the 5-bromo compound VIa and the reaction of Ib with *N*-chlorosuccinimide gave the 5-chloro product VIb, both halogenations occurring in dimethylformamide.

Friedel-Crafts acylation of Ia with acetic anhydride in phosphoric acid provided the ketone Va in moderate yield. The aromatic proton portion of the nmr spectrum of Va was similar to those of the nitration and halogenation products.

Oxidation of Va with sodium hypobromite gave a mixture of products from which the carboxylic acid VIIa was isolated in 50% yield. Reduction of Va with sodium borohydride in methanol afforded the carbinol VIIb. If the *p*H was not carefully controlled during the acid hydrolysis of the intermediate boron complex, reaction with the solvent occurred to give the methyl ether VIIc as a co-product.

Since ketone Va could not be α-brominated cleanly, bromoketone Vb was prepared directly from Ia with bromoacetyl bromide and aluminum chloride. Compound Vb readily reacted with amines to give the aminoketones VIIIa-c, which were reduced to the corresponding amino alcohols IXa-c.

One of the latter, the benzylamino alcohol IXb, was used to prepare several additional amines for a somewhat broader screen of 5-substituted 2,1-benzisothiazolines in animals. Reduction of the hydroxyl group with diborane in tetrahydrofuran (4) afforded Xa, which was methylated to the *t*-amine Xb. Compound IXb was also allowed to react with ethylene oxide to give the diol XI.

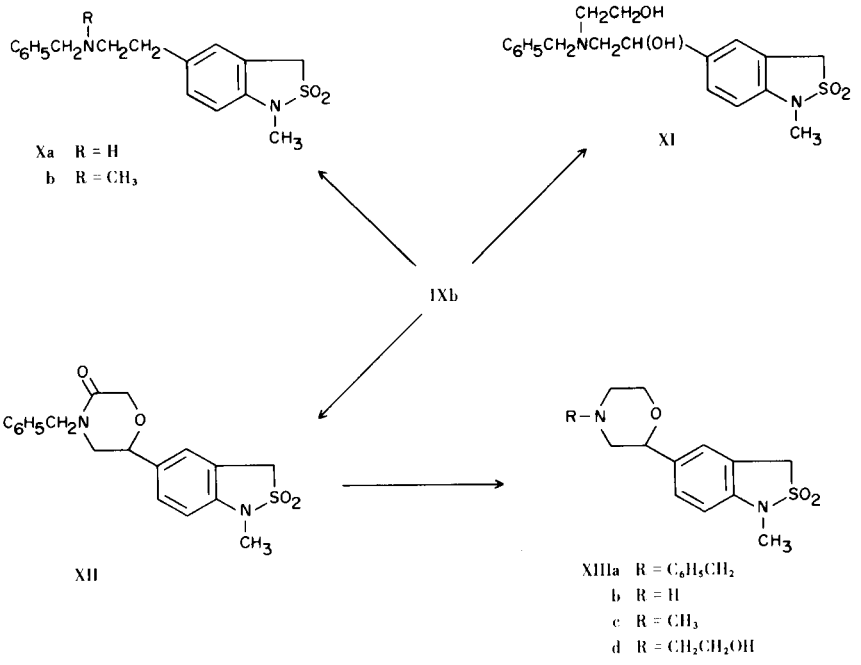
By the procedure of Surrey and co-workers (5), IXb reacted with chloroacetyl chloride to give a product presumed to be 5-[2-benzyl(chloracetyl)amino-1-hydroxy]-ethyl-1-methyl-2,1-benzisothiazoline 2,2-dioxide. Exposure of this material to ethanolic potassium hydroxide provided the morpholinone XII. Diborane reduction then led to the disubstituted morpholine XIIIa, isolated as the hydrochloride salt in an overall yield of 76%. Debenzylation of XIIIa afforded XIIIb, which was converted to the *N*-methyl compound XIIIc and the hydroxyethyl derivative XIIId.

EXPERIMENTAL

Melting points, taken with a Thomas-Hoover capillary apparatus, are uncorrected. Analyses were performed in our laboratories and by Drs. G. Weiler and F. B. Strauss, Oxford, England. Infrared spectra were obtained with a Beckman spectrophotometer, Model IR 8, and ultraviolet spectra with a Beckman spectrophotometer, DK 2A. Nuclear magnetic resonance spectra were obtained on a Varian A-60 Spectrometer with TMS as the internal standard.

1-Methyl-5-nitro-2,1-benzisothiazoline 2,2-Dioxide (IIa).

A well stirred solution of Ia (2.7 g., 0.015 mole) in 20 ml. of glacial acetic acid was cooled to 15° and treated dropwise with concentrated nitric acid. After the addition of 7 ml. of acid, the temperature rose to 35° and a precipitate formed. The mixture was stirred for 30 minutes and poured into ice water. The precipitate was filtered, washed with water, and dried. Recrystallization from chloroform, including treatment with decolorizing carbon, afforded a pale tan, crystalline powder (1.75 g., 51%), m.p. 214-216°; λ max (ethanol) 324 mμ (ε 11,800) and 228 (6,170); nmr (DMSO-d_6): δ 3.24 (s, 3H, CH_3), 4.90 (s, 2H,



CH_2), 7.17 (d, 1H, J = 9 cps, 7-ArH), 8.33 (s with hyperfine structure, 1H, 4-ArH), and 8.35 (d of doublets, 1H, J = 9 cps, 6-ArH).

Anal. Calcd. for $C_8H_8N_2O_4S$: C, 42.10; H, 3.54; N, 12.28; S, 14.05. Found: C, 42.05; H, 3.67; N, 12.50; S, 14.16.

1,3-Dimethyl-5-nitro-2,1-benzisothiazoline 2,2-Dioxide (IIb).

A solution of Ib (19.7 g., 0.1 mole) in 100 ml. of glacial acetic acid was treated with 65 ml. of concentrated nitric acid as described for IIa. The crude product was taken up in chloroform, which was washed with sodium bicarbonate solution, concentrated, treated with activated carbon, and diluted with Skellysolve B. The resulting solid amounted to 11.3 g. (47%), m.p. 146-149°. An analytical sample melted at 148.5-150°; λ max (ethanol) 322 mμ (ε 11,590) and 229 (6,200); nmr (deuteriochloroform): δ 1.77 (d, 3H, J = 7 cps, 3-CH_3), 3.24 (s, 3H, 1-CH_3), 4.43 (q, 1H, J = 7 cps), 6.83 (d, 1H, J = 8 cps, 7-ArH), 8.18 (m, 1H, 4-ArH), and 8.30 (d of doublets, 1H, 6-ArH).

Anal. Calcd. for $C_9H_{10}N_2O_4S$: C, 44.62; H, 4.16; N, 11.58. Found: C, 44.80; H, 4.38; N, 11.25.

5-Amino-1,3-dimethyl-2,1-benzisothiazoline 2,2-Dioxide (III).

A suspension of the nitro compound IIb (11.3 g., 0.047 mole) and 2.2 g. of 10% palladium-on-carbon in 200 ml. of ethyl acetate was treated with hydrogen at 400 psi and 25°. The reduction was completed within 3 minutes; the reaction mixture was cooled, filtered, and concentrated. The residual oil solidified on standing, and recrystallization from benzene-chloroform-Skellysolve B provided 7.0 g. (70%) of tan crystals, m.p. 103-104.5°; nmr (deuteriochloroform): δ 1.63 (d, 3H, J = 7 cps, 3-CH_3), 3.07 (s, 3H, 1-CH_3), 3.62 (s, 2H, NH_2), 4.20 (q, 1H, J = 7 cps) and 6.58 (s, 3H, ArH).

Anal. Calcd. for $C_9H_{12}N_2O_2S$: C, 50.92; H, 5.71; N, 13.20. Found: C, 51.11; H, 5.70; N, 13.38.

The corresponding hydrochloride salt melted at 204.5-206° dec., after recrystallization from ethanol-ether.

Anal. Calcd. for $C_9H_{13}ClN_2O_2S$: C, 43.47; H, 5.27; N, 11.26. Found: C, 43.50; H, 5.46; N, 11.32.

5-Acetamido-1,3-dimethyl-2,1-benzisothiazoline 2,2-Dioxide (IVa).

A solution of the amine III (2.1 g., 0.01 mole) and triethylamine (1 g., 0.01 mole) in 125 ml. of dry benzene was treated dropwise under nitrogen with 0.94 g. (0.012 mole) of acetyl chloride. The solution was stirred at room temperature for 4 hours, refluxed for 8 hours, and concentrated. A chloroform solution of the residue was washed with 5% hydrochloric acid, dried, and concentrated. Crystallization of the residual gum from chloroform-Skellysolve B provided 1.8 g. (72%) of off-white granules, m.p. 141.5-143°; λ max (ethanol) 298 mμ (ε 2,040) and 260 (17,700); ν max (Nujol) 1655, 1610 cm^{-1} (C=O).

Anal. Calcd. for $C_{11}H_{14}N_2O_3S$: C, 51.98; H, 5.55; N, 11.02. Found: C, 51.87; H, 5.81; N, 10.95.

5-Methanesulfonamido-1,3-dimethyl-2,1-benzisothiazoline 2,2-Dioxide (IVb).

Compound III (2.1 g., 0.01 mole), triethylamine (1 g., 0.01 mole) and methanesulfonyl chloride (1.26 g., 0.011 mole) in benzene (120 ml.) were allowed to react as described for IVa. Crystallization from chloroform-Skellysolve B gave 1.45 g. (50%) of off-white rhombs, m.p. 139-141°. An analytical sample melted at 139-140°; λ max (ethanol) 298 mμ (ε 1,710) and 247 (14,900).

Anal. Calcd. for $C_{10}H_{14}N_2O_4S_2$: C, 41.36; H, 4.86; N, 9.65. Found: C, 41.31; H, 4.80; N, 9.53.

5-Acetyl-1-methyl-2,1-benzisothiazoline 2,2-Dioxide (Va).

A solution of Ia (27 g., 0.15 mole) and 5 ml. of 85% phosphoric acid in 125 ml. of acetic anhydride was heated in an oil bath at 100° for 1 hour. The solution was poured into ice water and the excess anhydride was decomposed with solid sodium carbonate. The insoluble gum was taken up in chloroform, which was washed with saturated sodium bicarbonate solution, dried, and concentrated. Elution of the residue from silica gel with benzene-ether (4:1) afforded 15% of unreacted Ia, followed by the ketone, which was recrystallized from chloroform-Skellysolve B as pale amber needles (14.5 g., 43%), m.p. 139.5-143°. An analytical sample melted at 142-144°; λ max (ethanol) 288 mμ (ε 23,900) and 228 (14,500); ν max (Nujol) 1670 cm^{-1} (CO); nmr (deuteriochloroform): δ 2.57 (s, 3H, CH_3CO), 3.20 (s, 3H, CH_3), 4.39 (s, 2H, CH_2), 6.76 (d, 1H, J = 8 cps, 7-ArH), 7.89 (s, 1H, 4-ArH), and 7.97 (d, 1H, J = 10 cps, 6-ArH).

Anal. Calcd. for $C_{10}H_{11}NO_3S$: C, 53.32; H, 4.92; N, 6.22; S, 14.23. Found: C, 53.09; H, 4.89; N, 6.37; S, 14.33.

5-Bromoacetyl-1-methyl-2,1-benzisothiazoline 2,2-Dioxide (Vb).

To a stirred, cooled mixture of Ia (36.6 g., 0.2 mole) and 72.6 g. (0.36 mole) of bromoacetyl bromide in 200 ml. of carbon disulfide was added portionwise 85.3 g. (0.6 mole) of aluminum chloride. After an additional 30 minutes of stirring, the reddish-brown mass was poured into 1 l. of ice water containing 15 ml. of concentrated hydrochloric acid. The resulting solid was filtered, washed with water, dried, and recrystallized from chloroform-Skellysolve B. The bromoketone amounted to 53.3 g. (88%), m.p. 146-148.5°. An analytical sample of pale yellow needles melted at 146-147.5°; ν max (Nujol) 1665 cm^{-1} (CO).

Anal. Calcd. for $C_{10}H_{10}BrNO_3S$: C, 39.49; H, 3.31; N, 4.61. Found: C, 39.83; H, 3.40; N, 4.84.

5-Bromo-1-methyl-2,1-benzisothiazoline 2,2-Dioxide (VIa).

A solution of Ia (7.4 g., 0.04 mole) and *N*-bromosuccinimide (7.1 g., 0.04 mole) in 60 ml. of dimethylformamide was heated in an oil bath at 105° for 18 hours, cooled, and poured into 500 ml. of water. The insoluble oil was taken up in chloroform, which was washed with water, dried, and concentrated. Treatment of the residual oil with benzene induced crystallization; the resulting solid was triturated with Skellysolve B, filtered, and dried. Recrystallization from benzene-cyclohexane afforded 7.05 g. (68%) of material melting at 107-109°. An analytical sample of white flakes melted at 109-110.5°; λ max (ethanol) 298 mμ (ε 1,520) and 242 (12,970).

Anal. Calcd. for $C_8H_8BrNO_2S$: C, 36.65; H, 3.08; N, 5.35. Found: C, 36.66; H, 2.99; N, 5.60.

5-Chloro-1,3-dimethyl-2,1-benzisothiazoline 2,2-Dioxide (VIb).

Compound Ib (9.85 g., 0.05 mole) and *N*-chlorosuccinimide (6.5 g., 0.05 mole) were allowed to react in 60 ml. of dimethylformamide as described for VIa. Elution of the crude product from silica gel with benzene-ether (8:1) afforded a solid, which was recrystallized from benzene-cyclohexane, 6.05 g. (52%), m.p. 74-76°; λ max (ethanol) 296 mμ (ε 1,730) and 243 (12,200); nmr (deuteriochloroform): δ 1.67 (d, 3H, J = 7 cps, 3-CH_3), 3.11 (s, 3H, 1-CH_3), 4.27 (q, 1H, J = 7 cps), 6.64 (d of doublets, 1H, 7-ArH), 7.18 (s, 1H, 4-ArH), 7.28 (d of doublets, 1H, 6-ArH).

Anal. Calcd. for $C_9H_{10}ClNO_2S$: C, 46.65; H, 4.35; N, 6.05. Found: C, 46.46; H, 4.17; N, 5.95.

1-Methyl-2,1-benzisothiazoline-5-carboxylic Acid 2,2-Dioxide (VIIa).

To a solution of sodium hydroxide (9.6 g., 0.24 mole) and bromine (7.2 g., 0.045 mole) in 50 ml. of water at 0° was added a suspension of the ketone Va (6.8 g., 0.03 mole) in 110 ml. of dioxane over a 1-hour period. The resulting solution was stirred for 2 hours, during which time the temperature was allowed to increase to 20°. The solution was extracted with chloroform and acidified with concentrated sulfuric acid to give a light brown precipitate. This material (4.5 g.) was fractionally crystallized from a solution of 200 ml. of chloroform-ethanol (2:1) by the addition of Skellysolve B in portions increasing from 30 to 200 ml. A total of 760 ml. of Skellysolve B was used and ten crops of tan powder were collected. The acid was present in the last four fractions and amounted to 3.4 g. (50%), m.p. 246-250° dec. An analytical sample melted at 246-248° (dec.); λ max (ethanol) 268 mμ (ε 14,960); ν max (Nujol) 1690 cm^{-1} (CO).

Anal. Calcd. for $C_9H_9NO_4S$: C, 47.57; H, 4.00; N, 6.16. Found: C, 47.39; H, 3.84; N, 5.94.

5-(1-Hydroxyethyl)-1-methyl-2,1-benzisothiazoline 2,2-Dioxide (VIIb).

To a cooled and stirred suspension of the ketone Va (11.3 g., 0.05 mole) in 150 ml. of methanol was added 1.9 g. (0.05 mole) of sodium borohydride over a 20-minute period. The resulting solution was stirred at room temperature for 16 hours, refluxed for 1 hour, and acidified to *p*H 6.95 with 2 *N* sulfuric acid. Water was added and the insoluble oil was taken up in chloroform, which was dried and concentrated. The residue crystallized from benzene-Skellysolve B, 9.75 g. (86%), m.p. 82-84.5°. An analytical sample melted at 83-84°; λ max (ethanol) 289 mμ (ε 1,618) and 238 (11,000); ν max (Nujol) 3540 cm^{-1} (OH).

Anal. Calcd. for $C_{10}H_{13}NO_3S$: C, 52.84; H, 5.77; N, 6.16. Found: C, 53.05; H, 5.69; N, 6.27.

Acidification to a *p*H of 6.5 or lower during hydrolysis afforded a secondary product which was identified as 5-(1-methoxyethyl)-1-methyl-2,1-benzisothiazoline 2,2-dioxide (VIIc). This material was eluted, prior to the alcohol VIIb, from silica gel with benzene-ether (1:1). Several recrystallizations from benzene-Skellysolve B provided a white, crystalline powder, m.p. 173-174.5°; λ max (ethanol) 289 mμ (ε 1,741) and 241 (13,650); ν max (Nujol) 1077 cm^{-1} (OCH_3).

Anal. Calcd. for $C_{11}H_{15}NO_3S$: C, 54.75; H, 6.27; N, 5.81. Found: C, 55.00; H, 5.81; N, 5.92.

Preparation of the Aminoketones VIII.

The general procedure involved adding the bromoketone Vb to a cooled and stirred solution of 2 to 4 equivalents of the appropriate amine in tetrahydrofuran. The mixture was stirred at room temperature for 30 minutes, and the solvent was removed under vacuum. Acetone was added to the solid residue and the mixture was filtered. With methylamine and benzylamine, the solid isolated at this point was the desired aminoketone, as the hydrobromide salt. With benzylmethylamine, the free aminoketone was isolated from the acetone filtrate.

5-(Methylamino)acetyl-1-methyl-2,1-benzisothiazoline 2,2-Dioxide Hydrobromide (VIIIa).

This compound was obtained in 65% yield as pale golden flakes, m.p. 232-233° dec.; ν max (Nujol) 1680 cm^{-1} (CO).

Anal. Calcd. for $C_{11}H_{15}BrN_2O_3S$: C, 39.41; H, 4.51; N, 8.36. Found: C, 39.03; H, 4.98; N, 8.25.

5-(Benzylamino)acetyl-1-methyl-2,1-benzisothiazoline 2,2-Dioxide Hydrobromide (VIIIb).

This compound was obtained in 83% yield, m.p. > 360°. An analytical sample was prepared by recrystallization from a large excess of water.

Anal. Calcd. for $C_{17}H_{19}BrN_2O_3S$: C, 49.64; H, 4.66; N, 6.81. Found: C, 49.40; H, 4.58; N, 6.95.

5-(Benzylmethylamino)acetyl-1-methyl-2,1-benzisothiazoline 2,2-Dioxide Hydrochloride (VIIIc).

This compound was prepared from the corresponding free base, which was isolated in 67% yield by concentration of the acetone filtrate. The pale tan powder melted at 120-123° after recrystallization from ethanol-ether.

Anal. Calcd. for $C_{18}H_{21}ClN_2O_3S$: C, 56.75; H, 5.56; N, 7.35. Found: C, 56.42; H, 5.44; N, 7.17.

Preparation of the Aminoalcohols IX.

The general procedure involved treating the aminoketone salt VIII in methanol with an equimolar amount of sodium borohydride. The resulting solution was stirred at room temperature for 2 hours, acidified with 4 *N* hydrochloric acid and concentrated to dryness. Ether and dilute sodium hydroxide were added to the residue and the mixture stirred for 2 hours. The insoluble amino alcohol then was filtered and recrystallized.

5-(2-Methylamino-1-hydroxy)ethyl-1-methyl-2,1-benzisothiazoline 2,2-Dioxide (IXa).

This compound was isolated in 79% yield, m.p. 124-127°. An analytical sample from chloroform-Skellysolve B melted at 126-128°; ν max (Nujol) 3310 cm^{-1} (OH).

Anal. Calcd. for $C_{11}H_{16}N_2O_3S$: C, 51.55; H, 6.29; N, 10.93; S, 12.51. Found: C, 51.26; H, 6.16; N, 10.69; S, 12.24.

5-(2-Benzylamino-1-hydroxy)ethyl-1-methyl-2,1-benzisothiazoline 2,2-Dioxide (IXb).

This compound was obtained in 99% yield after recrystallization from chloroform-Skellysolve B, m.p. 127-129°.

Anal. Calcd. for $C_{17}H_{20}N_2O_3S$: C, 61.42; H, 6.06; N, 8.43. Found: C, 61.10; H, 5.90; N, 8.20.

5-(2-Benzylmethylamino-1-hydroxy)ethyl-1-methyl-2,1-benzisothiazoline 2,2-Dioxide (IXc).

This compound was prepared in 78% yield. An analytical sample from benzene-Skellysolve B melted at 112-114.5°.

Anal. Calcd. for $C_{18}H_{22}N_2O_3S$: C, 62.39; H, 6.40; N, 8.09; S, 9.26. Found: C, 62.64; H, 6.51; N, 7.93; S, 9.15.

5-[2-(Benzylamino)ethyl]-1-methyl-2,1-benzisothiazoline 2,2-Dioxide Hydrochloride (Xa).

To a cooled, stirred solution of the amino alcohol IXb (4.65 g., 0.014 mole) and 3.8 g. (0.1 mole) of sodium borohydride in 75 ml. of tetrahydrofuran was added under nitrogen a solution of boron trifluoride etherate (34 ml.) in 40 ml. of tetrahydrofuran. The mixture was stirred at room temperature for 2 hours and concentrated. Methanol (150 ml.) was added to the residue and the solution was refluxed for 2 hours, stirred at room temperature for an additional 12 hours and concentrated. Water was added to the residue and the insoluble material was filtered and heated at reflux in a solution of methanol containing 4 *N* hydrochloric acid for 12 hours. Cooling and dilution with ether provided 4.4 g. (90%) of white needles, m.p. 246-247° dec. Recrystallization from aqueous methanol-ether raised the melting point to 249-250° dec.; λ max (ethanol) 290 mμ (ε 1,670), 268 (650), 263 (570), 261 (570) and 239 (12,510).

Anal. Calcd. for $C_{17}H_{21}ClN_2O_2S$: C, 57.86; H, 6.00; N, 7.94. Found: C, 57.75; H, 6.14; N, 7.88.

5-[2-(Benzylmethylamino)ethyl]-1-methyl-2,1-benzisothiazoline 2,2-Dioxide Hydrochloride (Xb).

A 3.3 g. (0.01 mole) sample of the amine isolated from the hydrochloride Xa was heated with 20 ml. of 37% formaldehyde solution and 10 ml. of formic acid on a steam bath for 4 hours. The solution was diluted with water, extracted with ether and made alkaline with solid sodium hydroxide. The deposited oil was taken up in ether, which was dried and then treated with hydrogen chloride. Recrystallization of the resulting precipitate from ethanol-ether provided 2.6 g. (70%) of white granules, m.p. 176-178°.

Anal. Calcd. for $C_{18}H_{23}ClN_2O_2S$: C, 58.92; H, 6.32; N, 7.63. Found: C, 59.18; H, 6.68; N, 7.60.

5-[2-Benzyl(2-hydroxyethyl)amino-1-hydroxy]ethyl-1-methyl-2,1-benzisothiazoline 2,2-Dioxide Hexamate (XI).

To a stirred solution of IXb (13.3 g., 0.04 mole) in 80 ml. of methanol containing a drop of dilute hydrochloric acid was added 2.1 g. (0.048 mole) of ethylene oxide in 40 ml. of methanol. The solution was stirred at room temperature for a day, made alkaline with dilute sodium hydroxide and concentrated. Elution of the residual oil from alumina with chloroform-methanol (9:1) provided 10.4 g. (70%) of the dicarbinol as a pale yellow oil, which was treated with an equivalent amount of hexamic acid. The hexamate salt was isolated as pale yellow crystals, m.p. 145-148°.

Anal. Calcd. for $C_{25}H_{37}N_3O_7S_2$: C, 54.03; H, 6.71; N, 7.56. Found: C, 53.78; H, 6.68; N, 7.64.

5-(4-Benzyl-5-oxomorpholin-2-yl)-1-methyl-2,1-benzisothiazoline 2,2-Dioxide (XII).

A cooled and stirred mixture of IXb (16.8 g., 0.05 mole) and sodium hydroxide (2.8 g., 0.07 mole) in dichloromethane (125 ml.)-water (50 ml.) was treated dropwise with a solution of chloroacetyl chloride (7.9 g., 0.07 mole) in 10 ml. of dichloromethane over a 20-minute period. After 30 minutes, the ice bath was removed, and stirring was continued at room temperature for 4 hours. The dichloromethane layer was separated, washed with 5% sodium hydroxide, dried and concentrated. Elution of the residue from silica gel with chloroform-methanol (3:1) provided 5-[2-benzyl(chloracetyl)amino-1-hydroxy]ethyl-1-methyl-2,1-benzisothiazoline 2,2-dioxide (19 g., 93%) as a gummy foam; ν max (chloroform) 3390 cm^{-1} (OH) and 1635 cm^{-1} (CO).

To a stirred solution of this amide (18.8 g., 0.046 mole) in 100 ml. of absolute ethanol at room temperature was added a solution of potassium hydroxide (3.1 g., 0.055 mole) in 50 ml. of ethanol over a 30-minute period. The mixture was stirred for 22 hours, concentrated to near dryness and treated with water (150 ml.). The insoluble pale yellow powder was filtered and dried, 15.1 g. (88%), m.p. 143-145°. An analytical sample from chloroform-Skellysolve B melted at 143-144.5°; ν max (Nujol) 1660 cm^{-1} (CO).

Anal. Calcd. for $C_{19}H_{20}N_2O_4S$: C, 61.27; H, 5.41; N, 7.52. Found: C, 61.33; H, 5.47; N, 7.51.

5-(4-Benzylmorpholin-2-yl)-1-methyl-2,1-benzisothiazoline 2,2-Dioxide Hydrochloride (XIIIa).

A mixture of XII (22.3 g., 0.06 mole), sodium borohydride (3.4 g., 0.09 mole) and boron trifluoride etherate (15.2 ml., 0.12 mole) in 230 ml. of tetrahydrofuran was allowed to react as described for Xa. After stirring for a day, the mixture was treated with 40 ml. of 4 *N* hydrochloric acid and concentrated under vacuum. To the residue was added 150 ml. of methanol and the mixture was refluxed for several hours and concentrated. Chloroform and 10% sodium hydroxide were added to the residue with stirring; the chloroform was separated, dried and concentrated. The resulting gum in chloroform was treated with ethereal hydrogen chloride to afford 22 g. (93%) of cream-colored granules, m.p. 227-228.5° dec. An analytical sample from ethanol-methanol-ether melted at 229.5-230° dec.

Anal. Calcd. for $C_{19}H_{23}ClN_2O_3S$: C, 57.78; H, 5.87; N, 7.09. Found: C, 58.04; H, 5.97; N, 6.95.

1-Methyl-5-(morpholin-2-yl)-2,1-benzisothiazoline 2,2-Dioxide Hydrochloride (XIIIb).

A mixture of XIIIa (3.95 g., 0.01 mole) and 0.4 g. of 10% palladium on carbon in ethanol (100 ml.)-water (40 ml.) was treated with hydrogen at 3 atm in a Parr apparatus. After 17 hours the mixture was filtered and the filtrate concentrated. Recrystallization of the residue from ethanol-methanol-ether afforded 2.8 g. (92%) of a white powder, m.p. 211-212° dec.

Anal. Calcd. for $C_{12}H_{17}ClN_2O_3S$: C, 47.28; H, 5.62; N, 9.20. Found : C, 47.54; H, 5.50; N, 9.21.

1-Methyl-5-(4-methylmorpholin-2-yl)-2,1-benzisothiazoline 2,2-Dioxide Hydrochloride (XIIIc).

A 4.4 g. (0.016 mole) sample of the amine isolated from the hydrochloride XIIIb was allowed to react with formaldehyde and formic acid as described for Xb. The resulting *t*-amine was treated with hydrogen chloride in chloroform-ether and the salt was recrystallized from ethanol-methanol (1:1). The yield of small white flakes was 3 g. (59%), m.p. 229-230° dec.

Anal. Calcd. for $C_{13}H_{19}ClN_2O_3S$: C, 48.97; H, 6.00; N, 8.79. Found : C, 49.27; H, 5.71; N, 8.61.

5-[4-(2-Hydroxyethyl)morpholin-2-yl]-1-methyl-2,1-benzisothiazoline 2,2-Dioxide Hydrochloride (XIIId).

To a stirred solution of the amine (4 g., 0.015 mole) from XIIIb in methanol (80 ml.)-tetrahydrofuran (20 ml.) containing one drop of 1% hydrochloric acid was added dropwise a solution of ethylene oxide (0.7 g., 0.016 mole) in 20 ml. of methanol. After a day, the solution was concentrated; the residual oil was eluted from alumina with chloroform-methanol (15:1) and converted to a hydrochloride salt. Recrystallization from methanol-ether provided 3.3 g. (63%) of a white powder, m.p. 171-173°. An analytical sample melted at 176-178°.

Anal. Calcd. for $C_{14}H_{21}ClN_2O_4S$: C, 48.20; H, 6.07; N, 8.03. Found: C, 48.18; H, 5.78; N, 7.95.

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