2,1-Benzisothiazoline 2,2-Dioxide. I. Some 3-Substituted Derivatives.

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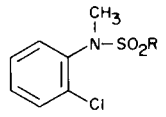
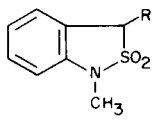
A number of 3-mono- and 3,3-disubstituted derivatives of 1-methyl 2,1-benzisothiazoline 2,2-dioxide (IIa), a unique benzosultam, were synthesized. Starting materials for the condensation and aminoalkylation reactions utilized were IIa and the 3-methyl compound IIb, which were prepared by cyclization of the 2′-chloro-*N*-methylalkylsulfonanilides, Ia and b, respectively.

The 2,1-benzisothiazoline ring system was first described in 1963 by Bunnett and co-workers (1), who obtained the 1-methyl 2,2-dioxide derivative IIa from the reaction of 2′-chloro-*N*-methylmethanesulfonanilide (Ia) with potassium amide in liquid ammonia. The synthesis was one of a number of successful ring closures uncovered during a study of the intramolecular addition of side chain anions to an aryne bond (2). Because of the uniqueness of this aromatic sultam, we prepared, shortly thereafter, various derivatives of IIa for pharmacological evaluation. This paper describes some 3-substituted compounds; subsequent publications will cover the chemistry of positions 5 and 1.



Ia) R = CH_3
b) R = CH_2CH_3

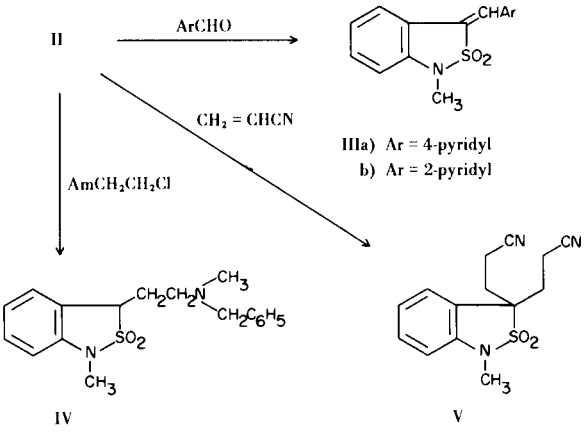


IIa) R = H
b) R = CH_3

Initial reactions were carried out with IIa itself, which was prepared from the sulfonanilide Ia in liquid ammonia with either potassium amide or commercial sodium amide. Although the similar conversion of *o*-chlorohydrocinnamonitrile to 1-cyanobenzocyclobutene proceeds equally well with both bases (3), potassium amide, in this case, was decidedly superior in regard to the amount and quality of the cyclized product.

With the well documented reactions of the carbonyl analog of 2,1-benzisothiazoline 2,2-dioxide, 2-indolinone (oxindole), as reference, the behaviour of IIa was investigated in regard to aldol condensation, aminoalkylation, and cyanoethylation at the methylene carbon atom.

Oxindole readily condenses with pyridine aldehydes in the presence of piperidine (4,5) or pyrrolidine (6). In contrast, the reaction of IIa and pyridine-4-carboxaldehyde required potassium hydroxide in refluxing ethanol for an acceptable yield of the pyridylmethylene derivative IIIa. Chromatographic separation of the crude product provided two isomers in a ratio of 8 to 1 with the *trans* structure of IIIa tentatively assigned to the more abundant isomer. A similar reaction with pyridine-2-carboxaldehyde also gave a mixture of products, but only a small amount of one of the isomers (IIIb) could be isolated. Several experiments using 1-benzyl-4-piperidone instead of an aldehyde provided unreacted IIa as the sole identifiable product.



Attempts to alkylate IIa with several *t*-aminoethyl and propyl chlorides, under various conditions, resulted in complex mixtures of basic materials from which only small amounts of the desired products could be isolated. In one of the more successful reactions, the use of potassium amide and 2-(benzylmethylamino)ethyl chloride in liquid ammonia gave the amine IV in 20% yield. Since IIa is known to react with amide ion to form *o*-(methylamino)-α-toluenesulfonamide (1), opening of the hetero-

cyclic ring of both the starting benzosultam and the aminoalkyl product undoubtedly were significant competing reactions. Similar derivatives of 1-alkyl- and 1,3-dialkyloxindole have been prepared in good yield by direct aminoalkylation (6 and references cited therein).

The base-catalyzed reaction of IIa with three equivalents of acrylonitrile afforded, along with a 20% recovery of unreacted starting material, the anticipated bis-cyanoethyl compound V in moderate yield. Although this type of reaction apparently has not been reported for a 1-alkyl oxindole, Michael condensations of 1,3-dialkyloxindoles with acrylonitrile (7) and ethyl acrylate (8) have been described.

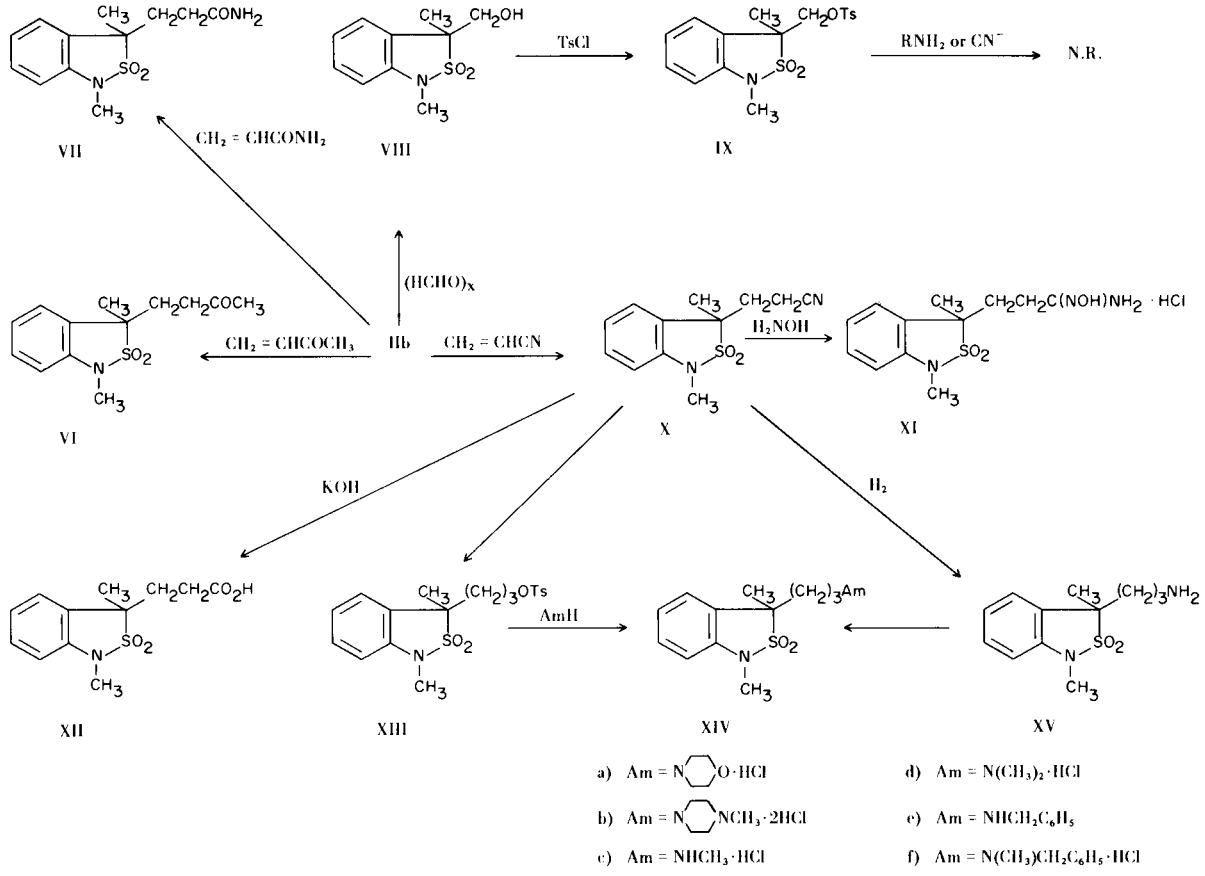
In order to pursue the latter approach with the heterocyclic system under investigation, a 3-alkyl derivative of IIa was required. Since direct alkylation did not appear promising, 1,3-dimethyl-2,1-benzisothiazoline 2,2-dioxide (IIb) was synthesized, instead, from 2′-chloro-*N*-methylethanesulfonanilide (Ib) under the usual cyclization conditions of potassium amide in liquid ammonia. Yields were comparable to those realized in the preparation of IIa and indicate that the methylene carbanion of Ib adds intramolecularly to the aryne bond as readily as the methyl anion of Ia. The precursor, Ib, was prepared by methylation of the product from the reaction of ethanesulfonyl chloride and *o*-chloroaniline.

Condensation of IIb with methyl vinyl ketone, acrylamide, and acrylonitrile afforded the 3,3-disubstituted compounds VI, VII, and X, respectively. Yields ranged from 21% for the ketone VI to 74% for the nitrile X, but only the amide VII could be isolated cleanly without chromatography.

A hydroxymethyl substituent was introduced at position 3 of benzosultam IIb by condensation with paraformaldehyde; and the product, VIII, was converted to the tosylate IX. Displacement of the hindered tosyl group by amines or cyanide ion, however, could not be accomplished even under vigorous conditions.

As an alternate approach to a 3-aminomethyl derivative, IIb was subjected to the Mannich reaction with dimethylamine hydrochloride. No reaction occurred in refluxing ethanol, whereas in refluxing dimethylformamide an intractable basic material was formed. Again emphasizing the difference in behaviour of the two analogous ring systems, 1,3-dialkyloxindoles provide normal Mannich products (7,8) under similar conditions.

The nitrile X was used to prepare a number of related compounds. Reaction with hydroxylamine provided (1,3-dimethyl-2,1-benzisothiazolin-3-yl)propionamidoxime, isolated as the hydrochloride XI in good yield. Alkaline



hydrolysis of X gave the acid XII. A sequence involving ethanolysis, reduction, and esterification converted X to the tolsylate XIII. Treatment of this material with morpholine, methylpiperazine, and methylamine readily afforded compounds XIVa-XIVc, respectively. Catalytic reduction of X gave the amine XV, which was converted to the *N,N*-dimethyl compound XIVd and the *N*-benzyl derivative XIVe. Finally, the tertiary amine XIVf was obtained from XIVe under Eschweiler-Clarke conditions.

Each of the 2,1-benzisothiazoline 2,2-dioxides derivatives exhibited typical sulfonamide absorption (9) in the infrared with strong bands near 1315 and 1150 cm^{-1}. For the non-conjugated compounds, ultraviolet maxima appeared at 285 and 235 mμ.

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, Model DK 2A.

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

In a typical experiment, 2′-chloro-*N*-methyl-methanesulfonanilide (Ia) (87.6 g., 0.4 mole) was allowed to react with 3 equivalents of potassium amide in 2.5 l. of liquid ammonia for 8 minutes as described in the literature (1). Recrystallization of the crude product from chloroform-Skellysolve B provided 54.6 g. (75%) of cyclized material, m.p. 88-91° (lit. (1) m.p. 91-92°); λ max (ethanol) 285 mμ (ϵ, 1,649) and 234 (8,126); ν max (Nujol) 1313 and 1151 cm^{-1} (O=S-O).

1-Methyl-3-[(4-pyridyl)methylene]-2,1-benzisothiazoline 2,2-Dioxide (IIIa).

A solution of IIa (18.5 g., 0.1 mole), 16.1 g. (0.15 mole) of freshly distilled pyridine-4-carboxaldehyde, and 0.2 g. of potassium hydroxide in 250 ml. of absolute ethanol was refluxed for 20 hours. The solvent was removed under vacuum, water was added, and the mixture was extracted portionwise with 500 ml. of ether. The ether solution was concentrated until a precipitate began to form. Cooling and filtration afforded 8.6 g. (31%) of yellow rods, m.p. 125-126°.

Evaporation of the filtrate gave 23 g. of a viscous liquid which was put on a column of alumina (500 g.). Elution with benzene-ether (1:2) afforded 5.1 g. of an amber oil, followed by a semi-solid. Recrystallization of the latter from chloroform-Skellysolve B provided an additional 7.6 g. (59% overall for one isomer) of material melting at 125-126°; λ max (ethanol) 385 mμ (ϵ, 5,360), 303 (11,870), 260 (10,890).

Anal. Calcd. for $C_{14}H_{12}N_2O_2S$: C, 61.75; H, 4.45; S, 11.77. Found: C, 61.53; H, 4.73; S, 12.01.

Rechromatography of the initially eluted oil on alumina with benzene-ether (4:1) and two recrystallizations of the resulting solid from benzene-Skellysolve B provided 2.2 g. (67% overall for both isomers) of yellow rods. This isomer melted at 131-132.5°; λ max (ethanol) 373 mμ (ϵ, 4,120), 339 (2,740), 290 (9,540).

Found: C, 61.36; H, 4.76; S, 11.87.

1-Methyl-3-[(2-pyridyl)methylene]-2,1-benzisothiazoline 2,2-Dioxide (IIIb).

Compound IIa (0.1 mole) and a 50% excess of pyridine-2-carboxaldehyde were allowed to react as described for IIIa. Elution of the crude product (30 g.) from alumina with varying ratios of benzene and ether provided viscous oils, which appeared to be mixtures of the two possible isomers on the basis of infrared and analytical data. One of the fractions solidified, and recrystallization from chloroform-Skellysolve B gave yellow needles (2.5 g., 9%), m.p. 167-169°; λ max (ethanol) 376 mμ (ϵ, 5,964), 315 (14,900), 255 (8,870).

Found: C, 61.69; H, 4.63; S, 11.89.

3-[2-(Benzylmethylamino)ethyl]-1-methyl-2,1-benzisothiazoline 2,2-Dioxide Maleate (IV).

To a stirred solution of 0.066 mole of potassium amide in 500 ml. of liquid ammonia was added 11 g. (0.06 mole) of IIa. After 20 minutes, a solution of 2-(benzylmethylamino)ethyl chloride (44.1 g., 0.24 mole) in 100 ml. of dry benzene was added dropwise. Stirring was continued for 6 hours, then the ammonia was allowed to evaporate. Water was added, and the mixture was extracted with three 100-ml. portions of ether. The combined ether solution was washed portionwise with 300 ml. of 10% hydrochloric acid, which then was made alkaline with solid sodium hydroxide. An oil separated which was taken up in ether. Evaporation of the ether and removal of the excess aminoalkyl halide by distillation provided 6.3 g. of an oil. Elution of this material from 250 g. of alumina with benzene-ether (4:1) gave 3.9 g. (20%) of product as a yellow oil. The maleate salt melted at 98-101° after recrystallization from 2-propanol-ether.

Anal. Calcd. for $C_{22}H_{26}N_2O_6S$: C, 59.17; H, 5.87; N, 6.27. Found: C, 59.27; H, 5.84; N, 6.16.

3,3-Bis(2-cyanoethyl)-1-methyl-2,1-benzisothiazoline 2,2-Dioxide (V).

A solution of IIa (16.5 g., 0.09 mole) and 1 ml. of Triton B in 75 ml. of dioxane was cooled and treated dropwise with 14.7 g. (0.27 mole) of acrylonitrile. The solution was stirred overnight at 25°, acidified with 1 *N* sulfuric acid, and evaporated under vacuum. The residue was taken up in chloroform, which was washed with water, dried, and evaporated. Elution of the residual oil from alumina with benzene-ether (2:1) provided 21% of unreacted IIa, followed by 13.4 g. (51%) of the dinitrile as an orange-yellow oil which solidified on standing. Recrystallization from chloroform-Skellysolve B yielded cream-colored granules, m.p. 100-101.5°; ν max (Nujol) 2250 cm^{-1} (C≡N).

Anal. Calcd. for $C_{14}H_{15}N_3O_2S$: C, 58.11; H, 5.22; N, 14.52; S, 11.08. Found: C, 58.00; H, 5.08; N, 14.21; S, 11.39.

2′-Chloroethanesulfonanilide.

To a solution of *o*-chloroaniline (986 g., 7.8 moles) in 1.1 l. of toluene was added a solution of ethanesulfonyl chloride (498 g., 3.9 moles) in 550 ml. of toluene over a 2-hour period. The mixture was refluxed for 16 hours, cooled, and filtered. The filtrate was washed thoroughly with 10% hydrochloric acid and with saturated brine, dried, and concentrated. The residue was stirred with 5 l. of 10% sodium hydroxide solution for 3 hours. The mixture was filtered, and the filtrate was acidified with concentrated hydrochloric acid and cooled. Filtration and drying afforded 458 g. (54%) of product, m.p. 47-50°. An analytical sample melted at 48-50.5°.

Anal. Calcd. for $C_8H_{10}ClNO_2S$: C, 43.74; H, 4.59; Cl, 16.14; S, 14.59. Found: C, 43.81; H, 4.72; Cl, 16.16; S, 14.69.

2′-Chloro-*N*-methyl-ethanesulfonanilide (Ib).

To a solution of 2′-chloroethanesulfonanilide (458 g., 2.1 moles) and potassium hydroxide (295 g., 5.25 moles) in 2.5 l. of

water was added 530 g. (4.2 moles) of dimethyl sulfate. The mixture was stirred at 70° for 6 hours and then cooled. The crude product was taken up in chloroform, and the solution was dried and concentrated. Distillation of the residue afforded the sulfonanilide as a colorless liquid (387 g., 79%), b.p. 120-122° (0.05 mm.).

Anal. Calcd. for $C_9H_{12}ClNO_2S$: C, 46.25; H, 5.18; Cl, 15.17; S, 13.72. Found: C, 46.36; H, 5.30; Cl, 15.22; S, 13.98.

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

A solution of Ib (23.4 g., 0.1 mole) in 40 ml. of anhydrous ether was added dropwise to 0.35 mole of potassium amide in 1 l. of liquid ammonia. After 15 minutes, the reaction was quenched with 0.25 mole of ammonium chloride and the ammonia was allowed to evaporate. The residue was stirred with equal volumes of 10% hydrochloric acid and chloroform. Concentration of the dried chloroform solution and distillation of the residual liquid provided 14.3 g. (73%) of a straw-colored oil, b.p. 130-132° (0.06 mm.); λ max (ethanol) 285 mμ ($\epsilon_{\pm}$ 1,740) and 235 (7,821); ν max (neat) 1318 and 1145 cm^{-1} (O=S-O).

Anal. Calcd. for $C_9H_{11}NO_2S$: C, 54.80; H, 5.58; N, 7.13; S, 16.25. Found: C, 55.05; H, 5.87; N, 7.15; S, 16.21.

4-(1,3-Dimethyl-2,1-benzisothiazolin-3-yl)-2-butanone 2,2-Dioxide (VI).

A solution of IIb (5.9 g., 0.03 mole), 3 g. (0.043 mole) of methyl vinyl ketone, and 0.6 ml. of Triton B in 30 ml. of *t*-butyl alcohol was stirred for 2 days at room temperature. Following the work-up procedure outlined for V and chromatography on silica gel, the product was isolated as a white powder (1.7 g., 21%), m.p. 76-78.5°; ν max (Nujol) 1710 cm^{-1} (C=O).

Anal. Calcd. for $C_{13}H_{17}NO_3S$: C, 58.40; H, 6.41; N, 5.25. Found: C, 58.38; H, 6.47; N, 5.48.

(1,3-Dimethyl-2,1-benzisothiazolin-3-yl)propionamide 2,2-Dioxide (VII).

A solution of IIb (19.7 g., 0.1 mole) and 2 ml. of 30% methanolic potassium hydroxide in 100 ml. of *t*-butyl alcohol was treated portionwise with 7.8 g. (0.11 mole) of acrylamide and then was stirred at room temperature for 34 hours. The usual isolation procedure gave a solid which was recrystallized from chloroform-Skellysolve B (14.5 g., 54%), m.p. 115-117°; ν max (Nujol) 1675, 1605 cm^{-1} (C=O).

Anal. Calcd. for $C_{12}H_{16}N_2O_3S$: C, 53.73; H, 6.01; N, 10.44; S, 11.94. Found: C, 53.39; H, 5.89; N, 10.52; S, 11.54.

(1,3-Dimethyl-2,1-benzisothiazolin-3-yl)propionitrile 2,2-Dioxide (X).

A solution of IIb (19.7 g., 0.1 mole), 5.8 g. (0.11 mole) of acrylonitrile, and 1 ml. of 30% methanolic potassium hydroxide in 100 ml. of *t*-butyl alcohol was stirred at room temperature for 20 hours. Chromatography of the crude product on alumina afforded 18.4 g. (74%) of the nitrile as a straw-colored oil, ν max (neat) 2250 cm^{-1} (C≡N).

Anal. Calcd. for $C_{12}H_{14}N_2O_2S$: C, 57.58; H, 5.63; N, 11.19; S, 12.81. Found: C, 57.81; H, 5.79; N, 10.92; S, 12.64.

3-Hydroxymethyl-1,3-dimethyl-2,1-benzisothiazoline 2,2-Dioxide (VIII).

To a solution of 40 g. (0.21 mole) of IIb and 10.5 g. (0.35 mole) of paraformaldehyde in 200 ml. of pyridine was added 1.2 ml. of Triton B, and the solution was stirred at room temperature for 4.5 hours. The solution was diluted with 1.3 l. of water and extracted with four 300-ml. portions of ether, which were combined, dried, and concentrated. The residue was recrystallized from chloroform-Skellysolve B to yield the carbinol as white flakes (29.5 g., 62%), m.p. 93-96°. An analytical sample melted at 94-96°; ν max (Nujol) 3530 cm^{-1} (OH).

Anal. Calcd. for $C_{10}H_{13}NO_3S$: C, 52.85; H, 5.77; S, 14.11. Found: C, 52.95; H, 5.86; S, 13.96.

Treatment of the carbinol (9.1 g., 0.04 mole) with equimolar amounts of sodium hydride dispersion and *p*-toluenesulfonyl chloride in 150 ml. of benzene at room temperature provided, after recrystallization from chloroform-Skellysolve B, 12.3 g. (81%) of the tosylate IX as pale tan crystals, m.p. 148-152°. An analytical sample melted at 151-154°.

Anal. Calcd. for $C_{17}H_{19}NO_5S_2$: C, 53.53; H, 5.02; N, 3.68; S, 16.81. Found: C, 53.52; H, 4.82; N, 3.72; S, 16.91.

(1,3-Dimethyl-2,1-benzisothiazolin-3-yl)propionamidoxime 2,2-Dioxde Hydrochloride (XI).

To a solution of 0.46 g. (0.02 g.-atom) of sodium in 40 ml. of absolute ethanol was added under nitrogen 1.4 g. (0.02 mole) of hydroxylamine hydrochloride. The mixture was stirred for several minutes at room temperature, and then a suspension of 5.0 g. (0.02 mole) of the nitrile X in 60 ml. of ethanol was added. The reaction mixture was refluxed for 6 hours, stirred overnight at 25°, and then filtered. The filtrate was diluted with approximately 300 ml. of ether and was saturated with hydrogen chloride gas. The deposited solid (4.4 g., 69%) melted at 199-200° with decomposition. Recrystallization from ethanol-ether afforded a tan powder, m.p. 200-201° (dec.); ν max (Nujol) 1657 cm^{-1} (C=N).

Anal. Calcd. for $C_{12}H_{18}ClN_3O_3S$: C, 45.07; H, 5.67; S, 10.03. Found: C, 44.92; H, 5.77; S, 9.78.

(1,3-Dimethyl-2,1-benzisothiazolin-3-yl)propionic Acid 2,2-Dioxide (XII).

To 15 g. (0.06 mole) of X was added 100 ml. of potassium hydroxide-saturated ethanol, and the solution was stirred at 25° overnight. Water (40 ml.) was added, and the solution was refluxed for 7 hours. The solvent was removed under vacuum, and the residue was dissolved in 300 ml. of water. After two extractions with ether and acidification with concentrated hydrochloric acid, the separated organic layer was taken up in ether, which was dried and concentrated. Recrystallization of the residual solid from chloroform-Skellysolve B provided the acid as light tan flakes (14.8 g., 91%), m.p. 126-128°; ν max (Nujol) 1700 cm^{-1} (C=O).

Anal. Calcd. for $C_{12}H_{15}NO_4S$: C, 53.53; H, 5.62; S, 11.91. Found: C, 53.35; H, 5.51; S, 11.96.

3-(3-Hydroxypropyl)-1,3-dimethyl-2,1-benzisothiazoline 2,2-Dioxide Tosylate (XIII).

A solution of X (35 g., 0.14 mole) and an equimolar amount of water in 500 ml. of absolute ethanol was stirred and treated with a stream of hydrogen chloride gas for 1 hour. The mixture was filtered and the filtrate concentrated. Elution of the residue from silica gel with benzene-ether (4:1) afforded 30.8 g. (74%) of the ethyl ester as a straw-colored oil; ν max (neat) 1730 cm^{-1} (C=O).

Addition of 0.033 mole of lithium aluminum hydride in ether to 17.4 g. (0.06 mole) of the ester in 150 ml. of ether gave, after chromatography on silica gel with ether-chloroform (4:1), 9.5 g. (62%) of the alcohol as a colorless oil; ν max (neat) 3540 and 3370 cm^{-1} (OH).

The alcohol (10.7 g., 0.042 mole) was allowed to react successively with equivalent amounts of sodium hydride dispersion and tosyl chloride in 110 ml. of refluxing benzene. Elution of the

crude product from silica gel with benzene-ether (3:1) provided 8.9 g. (52%) of the tosylate as an oil, which crystallized when refrigerated under Skellysolve B, m.p. 88-90°.

Anal. Calcd. for $C_{19}H_{23}NO_5S_2$: C, 55.72; H, 5.66; N, 3.42. Found: C, 56.14; H, 5.55; N, 3.34.

1,3-Dimethyl-3-(3-morpholinopropyl)-2,1-benzisothiazoline 2,2-Dioxide Hydrochloride (XIVa).

A solution of the tosylate XIII (4.1 g., 0.01 mole) and 1.92 g. (0.022 mole) of morpholine in 50 ml. of dry toluene was refluxed for 20 hours, cooled, and poured into a mixture of benzene (40 ml.) and 5% aqueous sodium hydroxide (40 ml.). The organic phase was washed several times with water, dried, and concentrated. The residual oil was treated with ethereal hydrogen chloride to afford a light tan powder, which was recrystallized from ethanol-methanol-ether to give 2.3 g. (64%) of product, m.p. 202-203°.

Anal. Calcd. for $C_{16}H_{25}ClN_2O_3S$: C, 53.24; H, 6.98; N, 7.76. Found: C, 53.55; H, 7.08; N, 7.87.

1,3-Dimethyl-3-[3-(4-methylpiperazinyl)propyl]-2,1-benzisothiazoline 2,2-Dioxide Dihydrochloride (XIVb).

Reaction of XIII with 1-methylpiperazine, as described for XIVa, provided a white powder in 51% yield, m.p. 221-224° dec.

Anal. Calcd. for $C_{17}H_{29}Cl_2N_3O_2S$: C, 49.75; H, 7.13; N, 10.24. Found: C, 49.51; H, 7.17; N, 10.18.

1,3-Dimethyl-3-[3-(methylamino)propyl]-2,1-benzisothiazoline 2,2-Dioxide Hydrochloride (XIVc).

A solution of XIII (8.5 g., 0.02 mole) in 200 ml. of benzene saturated with methylamine at 25° was heated in an autoclave at 100° for 24 hours. The cooled mixture was washed with saturated sodium bicarbonate and brine solution, dried over sodium sulfate, and concentrated. The residual oil, in dry ether, was treated with hydrogen chloride gas; and the precipitate was recrystallized from ethanol-ether to give white granules (2.6 g., 43%), m.p. 164-166°. An analytical sample melted at 166-167°.

Anal. Calcd. for $C_{13}H_{21}ClN_2O_2S$: C, 51.22; H, 6.94; N, 9.19. Found: C, 51.23; H, 6.98; N, 9.06.

3-(3-Aminopropyl)-1,3-dimethyl-2,1-benzisothiazoline 2,2-Dioxide (XV).

A solution of 22 g. (0.088 mole) of the nitrile X in 200 ml. of ethanol was treated at room temperature with hydrogen at 1000 psi in the presence of Raney nickel; the theoretical uptake was realized after 6 hours. The reaction mixture was filtered, concentrated, and diluted with chloroform. This solution was extracted with three 100-ml. portions of hydrochloric acid, which were combined and made alkaline with solid sodium hydroxide. The separated oil was taken up in chloroform, which was dried and concentrated. The residual oil was eluted from 150 g. of silica gel with chloroform-methanol (1:3) to give the amine (14.4 g., 64%) as a light amber gum.

Conversion of a portion of this material to the hydrochloride salt, followed by recrystallization from ethanol-ether, afforded an off-white powder, m.p. 173-175°.

Anal. Calcd. for $C_{12}H_{19}ClN_2O_2S$: C, 49.56; H, 6.58; Cl, 12.19; S, 11.03. Found: C, 49.74; H, 6.41; Cl, 12.38; S, 11.20.

1,3-Dimethyl-3-[3-(dimethylamino)propyl]-2,1-benzisothiazoline 2,2-Dioxide Hydrochloride (XIVd).

Reaction of XV (2.5 g., 0.01 mole) with 4 g. of 90% formic acid and 2 g. of 37% aqueous formaldehyde afforded, after treatment of the crude product with hydrogen chloride gas, 2.15 g. (67%) of white granules, m.p. 180-182°.

Anal. Calcd. for $C_{14}H_{23}ClN_2O_2S$: C, 52.73; H, 7.27; N, 8.78. Found: C, 52.63; H, 7.46; N, 8.94.

3-[3-(Benzylamino)propyl]-1,3-dimethyl-2,1-benzisothiazoline 2,2-Dioxide (XIVe).

A solution of XV (4.4 g., 0.017 mole) and 1.8 g. (0.017 mole) of freshly distilled benzaldehyde in 75 ml. of dry benzene was refluxed in a water-separator apparatus for 15 hours. The benzene was dried and concentrated; and the residual oil in ethanol was reduced with hydrogen at 50 psi in the presence of Raney nickel. The catalyst was filtered, the filtrate was concentrated, and the remaining oil was eluted from 200 g. of alumina with benzene-ether (2:1). The product (2.3 g., 42%) was isolated as an oil which slowly solidified while refrigerated under Skellysolve B, m.p. 89.5-91°.

Anal. Calcd. for $C_{19}H_{24}N_2O_2S$: C, 66.24; H, 7.02; N, 8.13. Found: C, 66.05; H, 7.21; N, 7.90.

3-[3-(Benzylmethylamino)propyl]-1,3-dimethyl-2,1-benzisothiazoline 2,2-Dioxide Hydrochloride (XIVf).

Reaction of XIVe with formic acid-formaldehyde gave, after chromatography on silica gel, 1.65 g. (31%) of the tertiary amine as an oil. The corresponding hydrochloride salt melted at 202-203° after recrystallization from ethanol-ether.

Anal. Calcd. for $C_{20}H_{27}ClN_2O_2S$: C, 60.81; H, 6.89; N, 7.09. Found: C, 60.90; H, 6.93; N, 7.18.

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