2,1-Benzisothiazoline 2,2-Dioxide. III. Several 1-(Aminoalkyl)-Substituted Derivatives.

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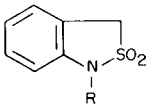
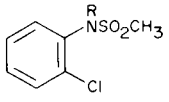
Received August 20, 1973

All of the 2,1-benzisothiazoline 2,2-dioxide derivatives described thus far (1) have had a methyl substituent in position 1. Since our objective was a general evaluation of this heterocyclic system for potential pharmacological activity, other substituents on the ring nitrogen, particularly aminoalkyl groups, were required.

Aminoalkylation of 2,1-benzisothiazoline 2,2-dioxide (Ia) appeared to be the best approach to the desired compounds. However, although the 1-methyl derivative



Ia R = H
b R = CH_3
c R = $CH_2C_6H_5$



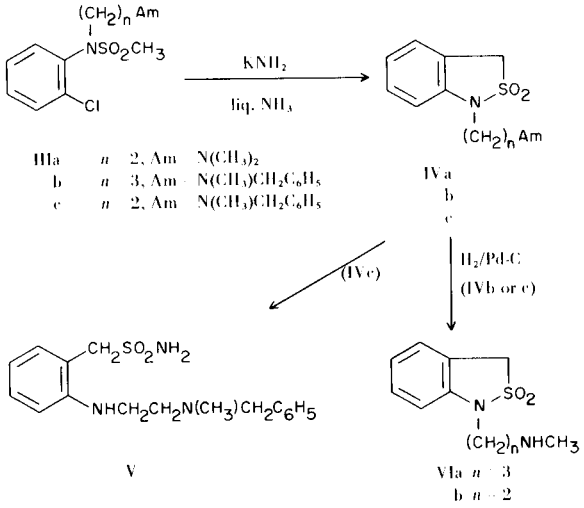
IIa R = H
b R = CH_3
c R = $CH_2C_6H_5$
d R = COC_6H_5

Ib is readily formed *via* a benzyne-carbanion intermediate from 2′-chloro-*N*-methylmethanesulfonanilide (IIb), the identical reaction of 2′-chloromethanesulfonanilide (IIa) with potassium amide in liquid ammonia afforded the starting material in 23% yield as the only neutral product (2). Attempts to ring close methanesulfonanilides having easily removable nitrogen substituents also failed. The *N*-benzyl compound IIc did undergo reaction, but none of the anticipated benzosultam I could be isolated from the predominantly basic product mixture. In comparison, amide ion converted the *N*-benzoyl derivative IId to 2′-chlorobenzanilide in 90% yield, possibly by elimination of sulfene (3) from an intermediate methyl carbanion.

In view of these difficulties, the alternate sequence of aminoalkylation followed by cyclization was tried and found to be successful. Sulfonanilide IIa was treated with sodamide and the appropriate aminoalkyl chloride in DMF to give the intermediate compounds IIIa-c, isolated as the hydrochloride salts. Ring closure of the corresponding free bases with potassium amide in liquid ammonia provided the 1-substituted benzisothiazolines IVa-c in yields of 47 to 69%.

One of the ring closure reactions, that of the (benzylmethylamino)ethyl derivative IIIc, gave the α-toluenesulfonamide V in addition to the expected product IVc. Compound V, isolated in approximately 20% yield, presumably is formed by amide ion attack on the sulfur of IVc. A similar ring cleavage was experienced by Bunnett and co-workers (2) when the reaction time for the formation of Ib was extended from 15 minutes to one hour.

Catalytic debenzylation of benzosultams IVb and c, as hydrochloride salts, afforded the additional 1-(aminoalkyl)-2,1-benzisothiazoline 2,2-dioxides, VIa and b, respectively.



EXPERIMENTAL

Melting points, taken with a Thomas-Hoover capillary apparatus, are uncorrected. Ultraviolet spectra were obtained with a Beckman spectrophotometer, DK 2A.

N-Benzyl-2′-chloromethanesulfonanilide (IIc).

To a cooled and stirred solution of 2′-chloromethanesulfonanilide (IIa) (205.7 g., 1.0 mole) in 250 ml. of DMF was added 43 g. (1.1 moles) of sodamide under nitrogen. After the mixture was stirred overnight at room temperature and heated on a steam bath for 5 hours, benzyl chloride (126.6 g., 1.0 mole) was added dropwise. Heating was continued for 16 hours; the reaction mixture was then diluted with water and extracted with ether.

The ether solution was washed with 2*N* sodium hydroxide, dried and concentrated. Crystallization of the residue from chloroform-Skellysolve B provided 184 g. (62%) of off-white rods, m.p. 68-71°.

Anal. Calcd. for $C_{14}H_{14}ClNO_2S$: C, 56.85; H, 4.77; N, 4.73; S, 10.84. Found: C, 57.00; H, 4.92; N, 4.89; S, 10.86.

2′-Chloro-*N*-(methanesulfonyl)benzanilide (IId).

To a cooled and stirred solution of IIa (20.5 g., 0.1 mole) and triethylamine (10.1 g., 0.1 mole) in 200 ml. of dry benzene was added dropwise a solution of benzoyl chloride (15.4 g., 0.11 mole) in 100 ml. of benzene. The mixture was refluxed overnight, washed with water, dried and concentrated. Two recrystallizations of the residue from benzene-Skellysolve B afforded 16.1 g. (53%) of a pale yellow powder, m.p. 120-122°. An analytical sample from chloroform-Skellysolve B melted at 120-121°.

Anal. Calcd. for $C_{14}H_{12}ClNO_3S$: C, 54.28; H, 3.90; N, 4.52. Found: C, 54.05; H, 3.86; N, 4.55.

Reaction of IId with Potassium Amide in Liquid Ammonia.

To a stirred solution of potassium amide (0.09 mole) in 500 ml. of liquid ammonia was added portionwise 9.3 g. (0.03 mole) of IId. After 15 minutes, the reaction was quenched by adding excess solid ammonium chloride and the ammonia was allowed to evaporate. Chloroform (100 ml.) and 2% hydrochloric acid (50 ml.) were added to the residue. Concentration of the chloroform layer afforded a gummy material which was eluted from 200 g. of silica with benzene-ether (4:1). The resulting tan powder amounted to 6.3 g. (90%), m.p. 95-98°; recrystallization from cyclohexane afforded white needles, m.p. 96-98°.

Anal. Calcd. for $C_{13}H_{10}ClNO$: C, 67.39; H, 4.35. Found: C, 67.22; H, 4.20.

A mixture melting point with authentic 2′-chlorobenzanilide, made from benzoyl chloride and *o*-chloroaniline in aqueous sodium hydroxide, was 95.5-98°. The infrared spectra of the two samples were identical.

Preparation of the Aminoalkylmethanesulfonanilides III.

The general procedure involved the reaction of equimolar amounts of IIa and sodamide in DMF at 100° for 8 hours. The mixture was cooled and treated with a dry ether solution of a 10% excess of the appropriate aminoalkyl chloride. After the ether was removed by distillation, the mixture was heated at 100° overnight, cooled and diluted with water. The crude product was taken up in ether and extracted portionwise with 5% hydrochloric acid. The acid solution was made alkaline and extracted with ether, which was concentrated to a residual oil. Treatment of this material with ethereal hydrogen chloride provided the aminoalkylmethanesulfonanilide hydrochloride, which then was recrystallized.

2′-Chloro-*N*-[2-(dimethylamino)ethyl]methanesulfonanilide Hydrochloride (IIIa).

This compound was obtained in 48% yield from 2-propanol as white rods, m.p. 214-216°.

Anal. Calcd. for $C_{11}H_{18}Cl_2N_2O_2S$: C, 42.18; H, 5.79; Cl, 22.64; N, 8.94; S, 10.23. Found: C, 42.43; H, 5.66; Cl, 22.67; N, 9.00; S, 10.36.

2′-Chloro-*N*-[3-(benzylmethylamino)propyl]methanesulfonanilide Hydrochloride (IIIb).

This material was isolated from methanol-ether as a white powder in 59% yield, m.p. 183-185°.

Anal. Calcd. for $C_{18}H_{24}Cl_2N_2O_2S$: C, 53.59; H, 5.99; Cl, 17.57; N, 6.94; S, 7.93. Found: C, 53.62; H, 5.97; Cl, 17.58; N, 6.73; S, 8.18.

2′-Chloro-*N*-[2-(benzylmethylamino)ethyl]methanesulfonanilide Hydrochloride (IIIc).

This compound was obtained in 78% yield as a white powder from methanol-ether, m.p. 193-196°.

Anal. Calcd. for $C_{17}H_{22}Cl_2N_2O_2S$: C, 52.44; H, 5.69; Cl, 18.21; N, 7.19; S, 8.23. Found: C, 52.46; H, 5.80; Cl, 18.21; N, 6.96; S, 8.14.

Preparation of the Aminoalkylbenzisothiazolines IV.

In a typical experiment, 0.025 mole of the sulfonanilide III, as the free base, in 100 ml. of anhydrous ether was added dropwise to a stirred solution of potassium amide (0.1 mole) in liquid ammonia (600 ml.) under a nitrogen atmosphere. After 30 minutes, the reaction was quenched with solid ammonium chloride and the ammonia was allowed to evaporate. Equal amounts of benzene and water were added to the residue, and the benzene layer was extracted with 10% hydrochloric acid. The acid solution was made alkaline with sodium hydroxide and the crude product taken up in benzene, which was concentrated to a residual oil.

1-[2-(Dimethylamino)ethyl]-2,1-benzisothiazoline 2,2-Dioxide (IVa).

The residual oil solidified on standing, and recrystallization from chloroform-Skellysolve B afforded a yellow powder, m.p. 44-46.5°, in 64% yield; λ max (ethanol) 286 mμ (ε, 1,580) and 236 (8,590).

Anal. Calcd. for $C_{11}H_{16}N_2O_2S$: C, 54.98; H, 6.71; S, 13.34. Found: C, 55.15; H, 6.98; S, 13.40.

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

Elution of the residual oil from silica gel with benzene-ether (1:2) gave the product in 69% yield as an oil, which was converted to a hydrochloride salt and recrystallized from 2-propanol-ether as white granules, m.p. 121-123°; λ max (ethanol) 285 mμ (ε, 1,520), 269 (881), 264 (668), 257 (545), and 235 (8,360).

Anal. Calcd. for $C_{18}H_{23}ClN_2O_2S$: C, 58.92; H, 6.32; N, 7.63. Found: C, 59.06; H, 6.46; N, 7.63.

1-[2-(Benzylmethylamino)ethyl]-2,1-benzisothiazoline 2,2-Dioxide (IVc).

Elution of the residual oil from silica gel with benzene-ether (2:1) provided an oil (47%) which solidified on standing. Recrystallization from cyclohexane-benzene gave white needles, m.p. 91-93°; λ max 287 mμ (ε, 1,603) and 237 (ε, 8,881).

Anal. Calcd. for $C_{17}H_{20}N_2O_2S$: C, 64.53; H, 6.37; N, 8.86. Found: C, 64.83; H, 6.40; N, 8.84.

The corresponding hydrochloride salt melted at 183-185° after recrystallization from ethanol-ether.

Anal. Calcd. for $C_{17}H_{21}ClN_2O_2S$: C, 57.86; H, 6.00; N, 7.94. Found: C, 58.25; H, 6.28; N, 8.01.

Continued elution of the above column with benzene-ether (1:3) gave a second oil (17%) which was converted to a hydrochloride salt, m.p. 224-226° after recrystallization from aqueous methanol-ether, and identified as *o*-[2-(benzylmethylamino)ethyl]-amino-α-toluenesulfonamide monohydrochloride (V). The uv spectrum in 50% ethanol-0.1*N* sodium hydroxide showed λ max 297 mμ (ε, 2,680) and 247 (9,910) (4).

Anal. Calcd. for $C_{17}H_{24}ClN_3O_2S$: C, 55.19; H, 6.54; N, 11.35. Found: C, 55.34; H, 6.72; N, 11.34.

1-[3-(Methylamino)propyl]-2,1-benzisothiazoline 2,2-Dioxide Hydrochloride (VIa).

A solution of the hydrochloride IVb (5.1 g., 0.014 mole) in 220 ml. of ethanol was treated with hydrogen at 24° and 174 psi

in the presence of 10% palladium-on-carbon. After 3 hours, the mixture was filtered and concentrated to a gummy residue, which was treated with dilute sodium hydroxide. The resulting oil was taken up in ether, dried and treated with hydrogen chloride gas. Recrystallization of the crude salt from ethanol gave 2.95 g. (76%) of white needles, m.p. 149-150°.

Anal. Calcd. for $C_{11}H_{17}ClN_2O_2S$: C, 47.73; H, 6.19; N, 10.12. Found: C, 47.98; H, 6.35; N, 10.06.

1-[2-(Methylamino)ethyl]-2,1-benzisothiazoline 2,2-Dioxide Hydrochloride (VIb).

The hydrochloride of IVc (5.6 g., 0.016 mole) was catalytically debenzylated as described for VIa. Concentration of the reduction mixture provided a solid which was recrystallized from methanol-ethanol as white plates (3.55 g., 87%), m.p. 194-195°.

Anal. Calcd. for $C_{10}H_{15}ClN_2O_2S$: C, 45.71; H, 5.75; N, 10.66. Found: C, 45.92; H, 5.68; N, 10.62.

REFERENCES

(1) Part II: J. A. Skorcz, J. T. Suh, and R. L. Germershausen, *J. Heterocyclic Chem.*, 10, 249 (1973).

(2) The reaction was run for 10 minutes with three equivalents of amide ion. J. F. Bunnett, T. Kato, R. R. Flynn, and J. A. Skorcz, *J. Org. Chem.*, **28**, 1 (1963), isolated only intractable basic oils from the exposure of IIa to four equivalents of potassium amide for one hour.

(3) J. F. King and T. Durst, *J. Am. Chem. Soc.*, **86**, 288 (1964).

(4) The uv spectrum of *o*-methylamino-α-toluenesulfonamide, the amide ion cleavage product of Ib, showed λ max in 50% ethanol-0.1*N* sodium hydroxide at 294 mμ (ε, 2,580) and 244 (8,130).