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Studies on 3-Substituted 1,2-Benzisoxazole Derivatives. VII.[1] Catalytic Reduction of 3-Sulfamoylmethyl-1,2-benzisoxazole and Reactions of the Resulting Products

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Hydrogenation of 3-sulfamoylmethyl-1,2-benzisoxazole (**1**) gave ω-sulfamoyl-2-hydroxyacetophenone (**3**) and its imide (**2**). Treatment of **3** with acid afforded a new route to 1,2-benzoxathiin-4(3*H*)-one-2,2-dioxide (**5**). The oxime of **3** (**4**) was recyclized to provide 1,2-benzisoxazole derivatives by treatment with acid or base. On pyrolysis **4** gave benzoxazole derivatives.

Keywords——1,2-benzisoxazole; benzoxazole; 1,2-benzoxathiin-4(3*H*)-one-2,2-dioxide; hydrogenation; rearrangement; hydrolysis; pyrolysis

In the course of studies on 3-substituted 1,2-benzisoxazole derivatives, 3-sulfamoylmethyl-1,2-benzisoxazole (**1**) was found to show a strong anticonvulsant activity in animals.[1] In this paper, the catalytic hydrogenation of **1** and some reactions of the resulting compounds are described.

Casini *et al.*[2] reported that the N–O bond of the 1,2-benzisoxazole ring was cleaved when 1,2-benzisoxazole-3-acetate was reduced in the presence of palladium-carbon (Pd-C). In our early experiments on some other 1,2-benzisoxazole derivatives,[3] fission of the N–O bond was also observed.

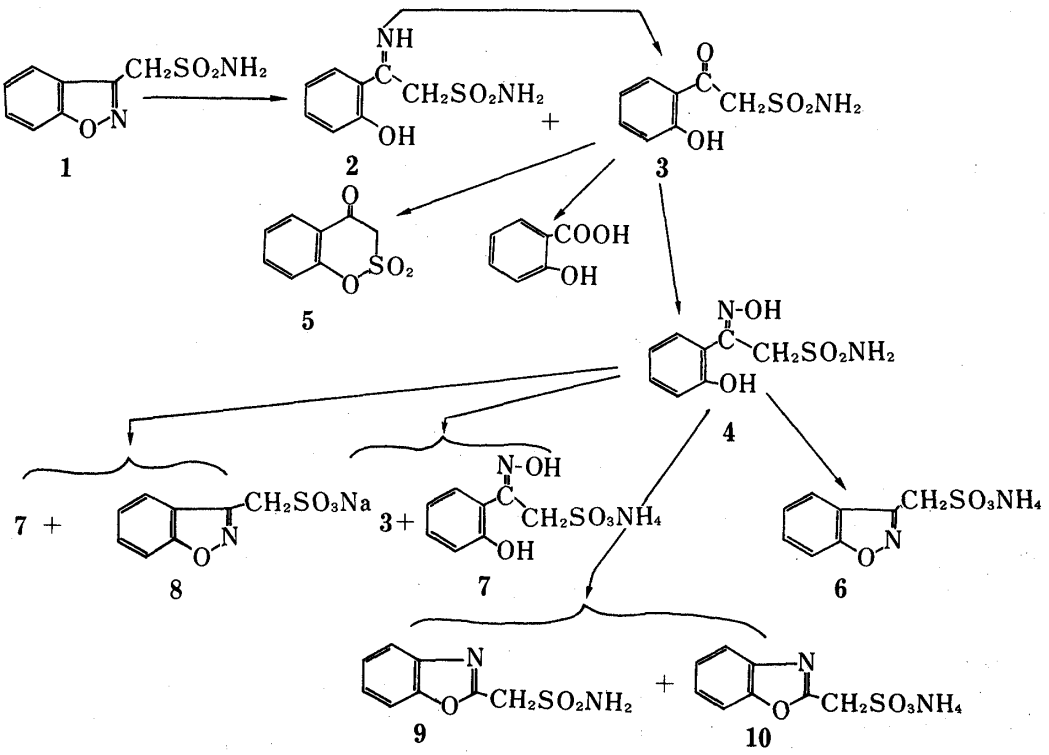


Chart 1

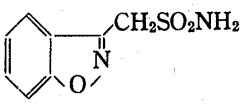
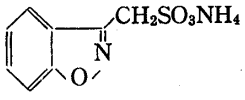
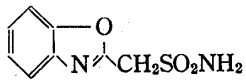
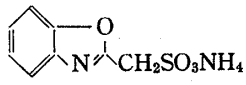
The reduction of **1** was carried out in the presence of 5% Pd-C and hydrogen at atmospheric pressure in ethanol. A mixture of two compounds was obtained and separated by chromatography on a column of silica gel. Thus, ω-sulfamoyl-2-hydroxyacetophenone imide (**2**), which was the product of fission of the N–O bond of **1**, and ω-sulfamoyl-2-hydroxyacetophenone (**3**) were obtained. The latter (**3**) was also obtained by the treatment of **2** with 5% hydrochloric acid (HCl). Upon reaction with hydroxylamine, the oxime of **3** (**4**) was obtained.

An attempt to hydrolyze **3** with 5% HCl gave an unexpected product, 1,2-benzoxathiin-4(3*H*)-one-2,2-dioxide (**5**).[4] Elemental analysis and the mass spectrum of **5** showed its formula to be $C_8H_6O_4S$. The infrared (IR) spectrum of **5** showed no absorption band due to an amino group. The proton magnetic resonance (PMR) spectrum of **5** showed the signal of two methylenic protons at δ 4.46 ppm. Hydrolysis of **3** with 5% sodium carbonate (Na_2CO_3) gave salicylic acid.

Compound **4** was refluxed in water and gave the ammonium salt of 1,2-benzisoxazole-3-methanesulfonic acid (**6**), which was identical with a sample obtained from 1,2-benzisoxazole-3-methanesulfonic acid.[1] When heated with 5% HCl at 95°C for 1 hour, **4** gave a mixture of **3** and the ammonium salt of 2-(*o*-hydroxyphenyl)-2-hydroxyiminoethanesulfonic acid (**7**). The treatment of **4** with 5% Na_2CO_3 gave a mixture of **7** and the sodium salt of 1,2-benzisoxazole-3-methanesulfonic acid (**8**).

When **4** was heated without any solvent, rearrangement took place and a mixture of 2-sulfamoylmethylbenzoxazole (**9**) and the ammonium salt of benzoxazole-2-methanesulfonic acid (**10**) was obtained. The PMR data for **9** and **10** are listed in Table I and compared with those of the 1,2-benzisoxazole analogs, **1** and **6**. Aldous *et al.*[5] have reported that on flash vacuum pyrolysis, 3-phenyl-1,2-benzisoxazole was transformed in 80% yield into a benzoxazole derivative *via* an aziridine intermediate. A similar mechanism might be involved in this rearrangement of **4**.

Table I. PMR Data, ppm (in DMSO-d_6)

1		$-NH_2$ 7.23 (2H, s) $-CH_2-$ 4.84 (2H, s) –H (4) 7.82—8.02 (1H, m) –H (5, 6 and 7) 7.35—7.80 (3H, m)
6		$-NH_4$ 7.13 (4H, broad) $-CH_2$ 4.25 (2H, s) –H (4) 7.96—8.15 (1H, m) –H (5,6 and 7) 7.20—7.70 (3H, m)
9		$-NH_2$ 7.36 (2H, s) $-CH_2-$ 4.86 (2H, s) –H (4 and 7) 7.68—7.85 (2H, m) –H (5 and 6) 7.35—7.50 (2H, m)
10		$-NH_4$ 7.15 (4H, s) $-CH_2-$ 4.17 (2H, s) –H (4 and 7) 7.60—7.80 (2H, m) –H (5 and 6) 7.26—7.42 (2H, m)

Experimental

All melting points are uncorrected. PMR spectra were taken with a Varian A-60 spectrometer using TMS as an internal standard, and mass spectra with a Hitachi RMU-6L mass spectrometer.

ω-Sulfamoyl-2-hydroxyacetophenone Imide (2) and ω-Sulfamoyl-2-hydroxyacetophenone (3)——Pd-C (5%, 2.5 g) was added to a solution of 3-sulfamoylmethyl-1,2-benzisoxazole (**1**) (5.0 g) in EtOH (150 ml), and the mixture was shaken under a hydrogen atmosphere. The catalyst was filtered off, and the filtrate was evaporated to dryness *in vacuo*. The residue was chromatographed on a column of silica gel. The

fraction eluted with 2% MeOH–CH_2Cl_2 was evaporated to dryness and the residue was crystallized from EtOH to give **3**, mp 138—141°C, 1.5 g (30%). *Anal.* Calcd for $C_8H_9NO_4S$: C, 44.64; H, 4.21; N, 6.50; S, 14.90. Found: C, 44.63; H, 4.11; N, 6.29; S, 14.64.

The fraction eluted with 5% MeOH–CH_2Cl_2 was evaporated to dryness and the residue was recrystallized from AcOEt to give **2**, mp 165—167°C, 1.8 g (36%). *Anal.* Calcd for $C_8H_{10}N_2O_3S$: C, 44.84; H, 4.70; N, 13.70; S, 14.96. Found: C, 44.95; H, 4.74; N, 13.21; S, 14.43.

Oxime of 3 (4)——Compound **3** (10 g) was added to a solution of hydroxylamine (prepared from $NH_2OH \cdot HCl$ 9.7 g, EtOH 300 ml and Na 3.2 g) and the mixture was refluxed for 3 h, then filtered. The solvent was removed and the residue was dissolved in AcOEt (400 ml). The solution was treated with charcoal. The solvent was removed and the residue was recrystallized from AcOEt to give **4**, mp 196—197°C, 9.5 g (89%). *Anal.* Calcd for $C_8H_{10}N_2O_4S$: C, 41.73; H, 4.38; N, 12.17; S, 13.93. Found: C, 41.92; H, 4.30; N, 12.26; S, 14.10.

Treatment of 3 with 5% HCl——A solution of **3** (0.5 g) in 5% HCl (50 ml) was heated at 110°C for 16 h. The solution was extracted with AcOEt, then extract was washed with H_2O and dried over Na_2SO_4. After the solvent had been removed, the oily residue was chromatographed on a column of silica gel. The fraction eluted with $CHCl_3$ was evaporated to dryness and the residue was recrystallized from MeOH to give **5**, mp 90—92°C, 0.45 g (98%). *Anal.* Calcd for $C_8H_6O_4S$: C, 48.48; H, 3.05; S, 16.18. Found: C, 48.30; H, 2.92; S, 16.05.

Treatment of 3 with 5% Na_2CO_3——A solution of **3** (0.6 g) in 5% Na_2CO_3 (50 ml) was refluxed for 5 h. After being cooled, the solution was neutralized with dil. HCl and extracted with AcOEt. The extract was washed with saturated NaCl sol. and dried over Na_2SO_4. The solvent was removed and the residue was recrystallized from $CHCl_3$ to give salicylic acid, 0.4 g (100%), mp 159—161°C.

Treatment of 4 with H_2O——An aq. solution of **4** (0.13 g in 50 ml H_2O) was refluxed for 17 h then evaporated to dryness *in vacuo*. The residue was recrystallized from MeOH to give **6**, mp 268—272°C, 0.1 g (92%).

Treatment of 4 with 5% HCl——A solution of **4** (1.0 g) in 5% HCl (50 ml) was heated at 95°C for 1 h and allowed to stand at room temperature overnight, then extracted with AcOEt. The extract was washed with saturated NaCl sol. and dried over Na_2SO_4. The solvent was removed and crude **3** (0.2 g, 21%) was obtained as the residue.

The aq. layer was concentrated and the residue was recrystallized from MeOH to give **7**, mp 250—290°C, 0.3 g (28%). *Anal.* Calcd for $C_8H_{12}N_2O_5S$: C, 38.70; H, 4.87; N, 11.29; S, 12.92. Found: C, 38.44; H, 4.72; N, 11.57; S, 13.12.

Treatment of 4 with 5% Na_2CO_3——A solution of **4** (1.0 g) in 5% Na_2CO_3 (50 ml) was heated at 95°C for 3 h. The solution was neutralized with 5% HCl and extracted with AcOEt. The extract was washed with saturated NaCl sol. and dried over Na_2SO_4. After removal of the solvent by evaporation, **4** (0.5 g) was recovered. NH_4OH was added to the aq. layer and the solution was evaporated to dryness. The residue was dissolved in EtOH and treated with charcoal. The solvent was removed and the residue was recrystallized from MeOH to give **7**, 0.1 g (10%). From the mother liquor of recrystallization, a small amount of **8** was obtained by preparative thin-layer chromatography.

Pyrolysis of 4——Compound **4** (1.0 g) was heated at 170°C under slightly reduced pressure for 10 min. MeOH was added to the cooled material and the whole was evaporated to dryness. AcOEt was added to the residue, and insoluble material was collected and recrystallized from EtOH to give **10**, mp 275—285°C, 0.1 g (10%). *Anal.* Calcd for $C_8H_{10}N_2O_4S$: C, 41.73; H, 4.38; N, 12.17; S, 13.93. Found: C, 41.89; H, 4.44; N, 12.43; S, 14.02.

The AcOEt solution was concentrated to give an oily residue, which was subjected to chromatography on a silica gel column. The fraction eluted with 5% MeOH–$CHCl_3$ was collected and concentrated, and the residue was recrystallized from AcOEt to give **9**, mp 167—169°C, 30 mg (3%). *Anal.* Calcd for $C_8H_8N_2O_3S$: C, 45.27; H, 3.80; N, 13.20; S, 15.11. Found: C, 45.50; H, 3.86; N, 13.48; S, 14.94.

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References and Notes

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