

(+) (*R*)- and (–) (*S*)- α -Ethyl[3-oxo-1,2-benzisothiazole-2(3*H*)]-acetamide 1,1-Dioxide. Synthesis and Acid Hydrolysis

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The title compounds have been prepared from enantiomeric α -ethyl[3-oxo-1,2-benzisothiazole-2(3*H*)]acetic acid 1,1-dioxides. These acids were obtained by resolution of the racemic acid. The absolute configurations of the enantiomeric amides and acids were determined by acid hydrolysis to chiral 2-aminobutyric acids. A scheme for the acid hydrolysis is proposed.

Racemic α -ethyl[3-oxo-1,2-benzisothiazole-2(3*H*)]acetamide 1,1-dioxide, *1*, is an experimental drug with potent sedative-hypnotic and anticonvulsant activity.¹ It was therefore of considerable interest to investigate the individual enantiomers. The present paper describes the synthesis of these enantiomers, the results of the pharmacological testing being reported elsewhere.

Racemic *1* has been prepared by alkylation of the sodium salt of saccharine with 2-bromobutyramide, by ammonolysis of α -ethyl[3-oxo-1,2-benzisothiazole-2(3*H*)]acetyl chloride 1,1-dioxide, and by ammonolysis of ethyl α -ethyl[3-oxo-1,2-benzisothiazole-2(3*H*)]acetate 1,1-dioxide *3*.¹ None of these methods were considered suitable for the synthesis of the enantiomers, mainly due to possible racemization. Instead the enantiomeric α -ethyl[3-oxo-1,2-benzisothiazole-2(3*H*)]acetamide 1,1-dioxides (+*1*) and (–*1*) were synthesized from the corresponding acids (+*2*) and (–*2*) using the mixed anhydride coupling reaction² with isobutyl chloroformate, *N*-methylmorpholine and anhydrous ammonia in chloroform.

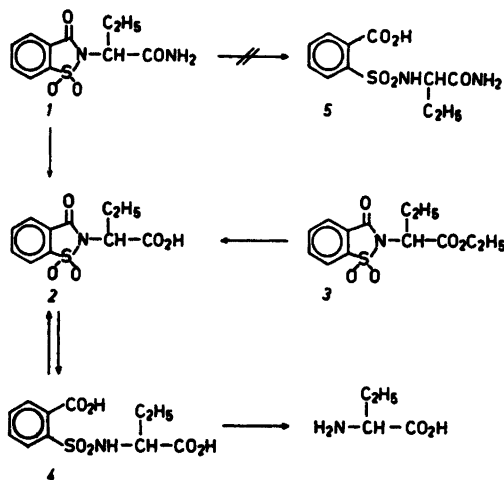
Racemic *2* was prepared in 71 % yield from its ethyl ester *3* by controlled hydrolysis in 6 N hydrochloric acid. It is essential that a small

volume of hydrochloric acid and a short reaction time are used, otherwise complete hydrolysis takes place. Resolution of *2* was accomplished with cinchonine to yield the (–)-acid and with brucine to yield the (+)-acid. Attempted resolution with cinchonidine, (–)-1-phenylethylamine or dehydroabietylamine was unsuccessful.

In order to assign the absolute configuration to the enantiomeric amides and acids, the amides (+*1*, –*1*) and the (–)-acid (–*2*) were completely hydrolyzed in a large volume of 6 N hydrochloric acid to the optically active 2-aminobutyric acids which were isolated in almost quantitative yields by ion exchange chromatography. –*2* and –*3* yielded (+) (*S*)-2-aminobutyric acid and +*1* yielded (–) (*R*)-2-aminobutyric acid. Thus +*2* and +*1* have the *R*-configuration, while –*2* and –*1* have the *S*-configuration.

The 2-aminobutyric acid preparations isolated after the hydrolysis of the –*2*, +*1* and –*1* were only about 70 % optically pure.^{3,4} As the starting materials were apparently optically pure, this was believed to be the result of partial racemization during the hydrolysis. To confirm this, the reaction was performed in 20 % deuterium chloride. It was found that incorporation of deuterium at the asymmetric carbon took place to the same extent as racemization. No racemization took place when (–)-2-aminobutyric acid was refluxed in 6 N hydrochloric acid, and no incorporation of the deuterium at the asymmetric center occurred when the acid *2* was stirred for 6 days in 20 % deuterium chloride at room temperature.

When *1* was hydrolyzed the reaction



Scheme 1. Suggested route for the acid hydrolysis of 1.

required 9–10 h of reflux for completion. Thin layer chromatographic monitoring of the reaction revealed that after 15 min only traces of 1 remained and that large amounts of 2 were present, which gradually disappeared on continued refluxing. Traces of 2-(*o*-carboxybenzenesulfonamido)butyric acid 4, which is also produced by alkaline hydrolysis of the ester 3,⁵ were detected during almost the whole time of the reaction. 2-(*o*-Carboxybenzenesulfonamido)butyramide 5, which has been isolated after mild alkaline hydrolysis of 1,⁵ could not be detected. Experiments with 4 revealed that this diacid was easily hydrolyzed under the conditions used for 1 but that partial ring closure to 2 took place, which delayed the complete hydrolysis.

Based on the above hydrolysis experiments it is suggested that the acid hydrolysis takes place in the following sequence: $1 \rightarrow 2 \rightleftharpoons 4 \rightarrow 2$.

Table 1. Fractional crystallization of the cinchonine salt of 2 to produce the (-)-form.

Crystallization No.	1	2	3	4	5	6
Acetone/ml	16000	8500	5000	3000	2000	1010
Water/ml	3200	2200	3000	1600	1500	550
Salt/g	858	502	297	210	106	70
$[\alpha]_D^{24}$ of salt (c 1, methanol)/deg.	-108					+105
$[\alpha]_D^{24}$ of acid (c 1, acetone)/deg.	-20.7	-40.5	-53.0	-58.0	-59.8	-61.5

aminobutyric acid (see Scheme 1). Because the total hydrolysis of 1 requires the same reaction time as that of 2 it seems that the cleavage of the isothiazoline ring is the rate determining step in the total hydrolysis of 1 to 2-aminobutyric acid. The selective acid hydrolysis of 3 to 2 with very little accompanying cleavage of the isothiazoline ring may also be seen as an indication for this hypothesis. It should also be possible to hydrolyze 1 to 2 under mild conditions.

The alternative route $1 \rightarrow 5 \rightarrow 4$ which has been proposed for the alkaline hydrolysis⁵ is less likely in the acid hydrolysis, also because no 5 could be detected during the hydrolysis.

EXPERIMENTAL

Optical rotations were measured with a Perkin-Elmer 141 Polarimeter, ¹H NMR spectra with a Perkin-Elmer R12 60 MHz instrument and melting points with a Fus-0-mat apparatus (Heraeus). Elemental analyses were carried out by Prof. K. J. Karrman, University of Lund, Lund, Sweden.

Racemic α -ethyl[3-oxo-1,2-benzisothiazole-2(3H)]acetic acid 1,1-dioxide (2). Ethyl α -ethyl[3-oxo-1,2-benzisothiazole-2(3H)]acetate 1,1-dioxide (3)¹ (1380 g; 4.64 mol) was refluxed for 6 h with 6 N hydrochloric acid (4.6 l; 27.6 mol). After cooling, the crystalline precipitate was collected, washed with water and then partitioned between saturated aqueous NaHCO₃ (3.0 l) and methyl isobutyl ketone (3.0 l). The NaHCO₃ solution was acidified with conc. hydrochloric acid, the precipitate was washed with water and dried. Yield 886 g (71%), m.p. 167–168°C (transition point 162–164°C). No traces of the ester 3 or the diacid 4 could be detected by TLC on silica gel with chloroform–acetic acid (9:1) as eluent. Anal. C₁₁H₁₁NO₅S: C, H, N, S.

(-)- α -Ethyl[3-oxo-1,2-benzisothiazole-2(3H)]acetic acid 1,1-dioxide (-2). Racemic acid (1077 g; 4 mol) and cinchonine (1178 g; 4 mol) were dissolved with heating in a mixture

of acetone (16 l) and water (3.2 l). The salt which precipitated on cooling was recrystallized from acetone-water as shown in Table 1. The purification was followed by measurement of the optical rotation of the acid, liberated from 1 g samples of the salt by stirring with 2 N HCl (25 ml), filtering off the solid, washing with much cold water and drying *in vacuo*. The salt was considered optically pure after the sixth crystallization, as three additional crystallizations of a small sample of the salt did not change the optical rotation. The acid was liberated from this preparation and crystallized from methanol. M.p. 139°C (with a transition point at 134.0–134.5°C). $[\alpha]_D^{24} - 61.9 \pm 0.1^\circ$ (c 2, acetone).

(+)- α -Ethyl[3-oxo-1,2-benzisothiazole-2(3H)]-acetamide 1,1-dioxide (+2). The mother liquor from the first crystallization of the cinchonine salt was evaporated to dryness and the residue was crystallized from 9 l of acetone-water (8:1) to give 409 g salt. The acid liberated from this salt had $[\alpha]_D^{24} - 6^\circ$ (c 1, acetone). The mother liquor from this second crop of cinchonine salt was evaporated and the acid was liberated from the residue yielding 340 g of product with $[\alpha]_D^{24} + 29.5^\circ$ (c 1, acetone). This acid (340 g; 1.2 mol) and brucine (500 g; 1.2 mol) were dissolved in hot methanol (95%; 10 l). On cooling, 465 g of crystalline salt was obtained, which was further recrystallized as shown in Table 2. The purification was followed as described above for the (-)-acid. A small sample of the salt $[\alpha]_D^{24} + 22.5^\circ$ was recrystallized four more times from 95% methanol to a rotation of $[\alpha]_D^{24} + 25.0^\circ$. This rotation remained unchanged after two further crystallizations. The +2 liberated from this final salt had $[\alpha]_D^{24} + 61.4^\circ$ (c 2, acetone) m.p. 139.5°C (with a transition point at 133.5–135.0°C). An attempt to carry out a "triangular" fractional crystallization⁶ was unsuccessful, probably because too much decomposition products had accumulated in the mother liquor.

(-)- α -Ethyl[3-oxo-1,2-benzisothiazole-2(3H)]-acetamide 1,1-dioxide (-1). To a suspension of -2 (13.47 g; 0.05 mol; $[\alpha]_D^{24} - 61.5^\circ$) in chloroform (dried over aluminium oxide) was added *N*-methylmorpholine (5.05 g; 0.05 mol) at -30°C, immediately followed at -29°C by isobutyl chloroformate (7.87 g; 0.05 mol). After 10 min at -25 to -15°C an excess of

ammonia in dry chloroform was added. The temperature rose to -2°C and a thick precipitate was at once obtained. The mixture was acidified with dilute hydrochloric acid, the solid was filtered off and recrystallized from 25% aqueous acetic acid without prior drying. Yield of 1 was 9.8 g (72%), $[\alpha]_D^{24} - 36.5^\circ$ (c 2, acetone), m.p. 180°C (transition point 167–169°C). The optical rotation could not be increased by recrystallization from water-acetic acid or water-acetone mixtures. A DSC thermogram showed m.p. 180°C (racemic amide 170°C). Anal. C₁₁H₁₃N₂O₄S: C, H, N, S.

(+)- α -Ethyl[3-oxo-1,2-benzisothiazole-2(3H)]-acetamide 1,1-dioxide (+1). The amide (5.1 g; 76%) was obtained when +2 (6.74 g; 0.025 mol; $[\alpha]_D^{24} + 56.4^\circ$) was treated as described above for the preparation of 1. The product had $[\alpha]_D^{24} + 33.1^\circ$ (c 2, acetone), m.p. 177–180°C (transition point 157–162°C). A DSC thermogram showed m.p. 178°C (racemic amide 170°C). Anal. C₁₁H₁₃N₂O₄S: C, H, N, S.

Hydrolysis of (-)- α -ethyl[3-oxo-1,2-benzisothiazole-2(3H)]-acetamide 1,1-dioxide (-2). The (-)-acid (1.35 g; 0.005 mol; $[\alpha]_D^{24} - 61.5^\circ$) was refluxed with 6 N hydrochloric acid (75 ml; 0.45 mol). After 15 min, all the substance had dissolved. Heating was continued for 9 h, the solvent was evaporated and the residue (1.8 g) was dried *in vacuo*, dissolved in water (5 ml) and placed on a column (diam. 15 mm) containing a cation exchange resin (Dowex 50X-8, 12 g, about 30 mequiv.) in hydrogen form. Elution with water (150 ml) and evaporation afforded an oil (1.2 g) which was discarded. Further elution with 2 N hydrochloric acid (190 ml) yielded after evaporation and drying *in vacuo* (+)-(*S*)-2-aminobutyric acid hydrochloride [0.64 g; 92%; $[\alpha]_D^{20} + 11.0^\circ$ (c 5, water)]. Anal. C₄H₁₀ClNO₂: C, H, Cl, N, O.

The pure compound has $[\alpha]_D^{20} - 14.9^\circ$ (c 5, water),³ thus the product had an optical purity of 74%. The IR spectrum was identical with that of the reference compound. The progress of the hydrolysis was followed by TLC analysis of aliquots using silica gel plates (Merck). For acids 2 and 4, ethyl acetate-formic acid (20:1) was used as eluent, and for 2-aminobutyric acid, butanol-acetic acid-water (80:20:20) was used. The amino acid was developed with ninhydrine.

Table 2. Fractional crystallization of the brucine salt of 2 to produce the (+)-form.

Crystallization No.	1	2	3	4	5	9	10–11
95% Methanol/ml	10000	5700	3700	2050	1200		
Salt/g	465	300	174	99.5	65.5		
$[\alpha]_D^{24}$ of salt (c 2, acetone)/deg.	+13.3	+16.7	+19.5	+21.1	+22.5	+25.5	+25.0
$[\alpha]_D^{24}$ of acid (c 1, acetone)/deg.	+37.3	+42.1	+51.2	+54.5	+56.4		+61.4

Hydrolysis of (-)- α -ethyl[3-oxo-1,2-benzisothiazole-2(3H)]acetamide 1,1-dioxide (-1) with hydrochloric acid. The (-)-amide (-1) (2.7 g; 0.01 mol; $[\alpha]_D^{24} - 35.5^\circ$) was refluxed with 6 N hydrochloric acid (100 ml; 0.60 mol) for 10 h, a clear solution being obtained after a few minutes. After evaporation of the hydrochloric acid, the dried residue (3.8 g) was applied to a cationic exchange resin (Dowex 50X-8, hydrogen form, 24 g; about 60 mekviv., column diam. 15 mm). Elution with water (275 ml) and evaporation of the solvent yielded an oil (2.1 g) which was discarded. Further elution with an approximately 0.2 N ammonium acetate solution of pH 6.0 (375 ml) yielded a ninhydrine positive fraction (125 ml), which on evaporation of water and removal of ammonium acetate by vacuum sublimation at 55°C yielded (-)-2-aminobutyric acid [1.03 g; 100%, $[\alpha]_D^{24} + 6.0^\circ$ (c 5, water)]. IR and ^1H NMR spectra were identical with those of a reference sample. Crystallization from ethanol-water (80:20) yielded a compound with $[\alpha]_D^{24} + 6.5^\circ$ (c 5, water) $M_D + 6.7^\circ$. The reported $M_D^{25} + 9.6^\circ$ value indicates an optical purity of 70%. Anal. $\text{C}_8\text{H}_{11}\text{NO}_2$: C, H, N, O.

The hydrolysis was monitored by TLC. Aliquots were withdrawn after 5, 15 and 30 min, 1, 3 and 9 h of reflux and analyzed on silica gel (Merck) with ethyl acetate-formic acid (20:1) as eluent.

Hydrolysis of (-)- α -ethyl[3-oxo-1,2-benzisothiazole-2(3H)]acetamide 1,1-dioxide (-1) with deuteriochloric acid. Hydrolysis was performed as described above using deuteriochloric acid yielding an amino acid which, after crystallization, had $[\alpha]_D^{24} + 6.5^\circ$ (c 3, water). In the ^1H NMR (D_2O) the relative reduction of the intensity of the signals δ 3.72, due to the H at the chiral centre, and δ 0.99, compared to a reference compound, indicates 27% incorporation of D, corresponding to an optical purity of 70%.^{3,4}

Hydrolysis of (+)- α -ethyl[3-oxo-1,2-benzisothiazole-2(3H)]acetamide 1,1-dioxide (+1). The (+)-amide (+1) (2.7 g; 0.01 mol; $[\alpha]_D^{24} - 33.1^\circ$) was hydrolyzed as described above for -1. The yield of (-) (*R*)-2-aminobutyric acid was 0.92 g (80%). $[\alpha]_D^{24} - 6.0^\circ$ (c 5, water). After crystallization as above it had $[\alpha]_D^{24} - 6.5^\circ$ (c 5, water), $M_D^{24} - 6.7$, equivalent to an optical purity of about 70%.^{3,4} Anal. $\text{C}_8\text{H}_{11}\text{NO}_2$: C, H, N, O.

*Investigation of the stability of the optical activity of (-)-(*R*)-2-aminobutyric acid under the conditions of the hydrolysis experiments.* Commercial (Sigma) (-)-(*R*)-2-aminobutyric acid [1 g; $[\alpha]_D^{24} - 8.1^\circ$, $M_D^{24} - 8.2$ (c 5, water)] was refluxed in 6 N hydrochloric acid (40 ml) for 10 h. Removal of water yielded (-)-(*R*)-2-aminobutyric acid hydrochloride (1.35 g; $[\alpha]_D^{24} - 14.3^\circ$ (c 5, water)). (-)-(*R*)-2-Aminobutyric acid had an optical purity of 86% before reflux, whereas the hydrochloride had an optical purity of 90% after refluxing based on

the specific rotations of the acid and its hydrochloride previously reported.^{3,4}

*Hydrolysis of 2-(*o*-Carboxybenzenesulfonamido)butyric acid (4).* The starting compound 4, m.p. 141.5–143.5°C, was obtained by alkaline hydrolysis of 3 using 2 N sodium hydroxide at 40°C for 18 h and recrystallization from ether.⁵ The diacid 4 (2.9 g; 0.01 mol) was refluxed in 6 N hydrochloric acid (100 ml) for 1.5 h. The solution was concentrated to a volume of about 15 ml and extracted with ether (2 × 20 ml). The ether extracts were washed with water (5 ml) and dried (Na_2SO_4). Evaporation of the ether yielded 0.50 g of a crystalline product which according to TLC consisted mainly of 2 plus some 4. Recrystallization from water-acetic acid (6:2) and chloroform yielded 0.34 g (13%) of pure 2, m.p. 168–169°C. Anal. $\text{C}_{11}\text{H}_{11}\text{NO}_5\text{S}$: C, H, N, S.

The aqueous raffinate and washings were evaporated and the residue (2.6 g) subjected to ion exchange chromatography as described in the hydrolysis procedure of -2, affording 0.80 g (57%) of 2-aminobutyric acid. Anal. $\text{C}_4\text{H}_9\text{ClNO}_2$: C, H, Cl, N, O.

The hydrolysis was monitored by TLC as described for -2. Samples were analyzed after refluxing for 10, 30, 60 and 90 min. The acid 2 was present in the sample taken after 10 min. Diacid 4 content decreased rapidly and only traces could be detected after 90 min.

Investigation of possible deuterium incorporation in α -ethyl[3-oxo-1,2-benzisothiazole-2(3H)]acetic acid 1,1-dioxide (2) without concomitant hydrolysis. The acid 2 (75 mg) was stirred for 7 days at room temperature with 20% deuterium chloride-deuterium oxide (100 ml). Undissolved material (10 mg; m.p. 168°C) was filtered off. The filtrate was concentrated to 2 ml, filtered and cooled to give 48 mg of crystals, m.p. 168°C. Further evaporation to dryness afforded a wax (9 mg). ^1H NMR analyses of the recovered crystalline products showed that deuterium incorporation at the asymmetric centre had not taken place.

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