

Resolution and Absolute Configuration of α -(Benzimidazolyl-2-thio)-propionic Acid

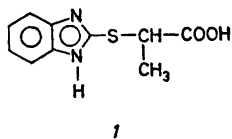
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Dedicated to Professor K. A. Jensen on his 70th birthday

The title compound (*1*) has been prepared and resolved using quinine and quinidine. The enantiomers have $[\alpha]_D^{25} \pm 124^\circ$ (in 96 % ethanol). (*S*)-(-)- α -Bromopropionic acid gave the (+)-form of the title compound. Postulating an S_N2 mechanism, the (+)-form of the title compound should then possess the (*R*)-configuration. The growth-regulating activity is being investigated and some preliminary data are given. The acetic acid derivative has been prepared for comparison.

In the course of current investigations on optically active compounds having growth-regulating effects in higher plants, the title compound (*1*) has been prepared and resolved. It is known that various phenoxy and naphthoxy acids have strong auxin effects while the corresponding arylthio and arylseleno acids are very weak auxins or even anti-auxins. In gen-



eral there is a great difference between optical isomers.¹⁻⁵ It was therefore of interest to study a bicyclic aromatic system containing nitrogen. While the mechanism of the auxin activity is still obscure, it is obvious that an acceptable theory must explain both positive and antagonistic effects and their dependence on structural and sterical factors. The problems connected with the auxin mechanism have also some interest with regard to current discussions

on possible deleterious effects of phenoxy acids used as herbicides in agriculture and forestry.

The title compound is easily prepared from 2-mercaptobenzimidazole and α -bromopropionic acid in slightly alkaline solution. The corresponding acetic acid has also been prepared for comparison. The acids gave no reaction for the mercapto group, showing that the reaction had proceeded as expected.

The propionic acid derivative could be resolved using quinine and quinidine, giving the enantiomers with $[\alpha]_D^{25} \pm 124^\circ$ in 96 % ethanol. The synthesis was also carried out with partially resolved (*S*)-(-)- α -bromopropionic acid giving a dextrorotatory product. No significant racemisation had taken place. In all probability the reaction follows an S_N2 mechanism with inversion. The (+)-form of the title compound should therefore possess the (*R*)-configuration.

The growth-regulating activity is being investigated by Professor B. Åberg (Agricultural University of Sweden), who has kindly submitted some preliminary results.⁶ The (*S*)-(-)- α -(benzimidazolyl-2-thio)-propionic acid is a rather strong anti-auxin. The (*R*)-(+)-form has a much weaker anti-auxin effect; possibly it can be classified as an "intermediate" with a very weak auxin component. This is in full agreement with the configurational assignment.

EXPERIMENTAL (in collaboration with Kerstin Stadell)

The rotations have been measured in 96 % ethanol. The analyses were carried out by the Analytical Division of the Institute.

(±)- α -(Benzimidazolyl-2-thio)-propionic acid. 2-Mercaptobenzimidazole (12.0 g, 0.08 mol)⁷ was dissolved with sodium hydroxide (3.2 g, 0.08 mol) in 500 ml of water and α -bromopropionic acid (12.2 g, 0.08 mol) neutralised with sodium hydrogen carbonate in 50 ml of water was added. After 1 h the solution was acidified with hydrochloric acid to pH 3. The separated acid was filtered off after standing for 2–3 h and washed with water. Yield, 15.5 g (87 %), after recrystallisation from 320 ml of 35 % ethanol, 13.1 g (73 %). Colourless needles with m.p. 166–167 °C. Anal. C₁₀H₁₀N₂O₂S: C, H, N, S. Equiv.wt. Found: 222.0. Calc. 222.3.

Preliminary experiments on resolution. Salts of common alkaloids were prepared on a 0.001 mol scale in dilute ethanol. The quinine salt gave the acid with $[\alpha]_D^{25} - 115^\circ$ while the acid from the quinidine salt had $[\alpha]_D^{25} + 107^\circ$. Strychnine and cinchonine gave acid with very low rotation. The cinchonine salt was obtained in a very low yield and the brucine salt failed to crystallise.

(-)- α -(Benzimidazolyl-2-thio)-propionic acid. Racemic acid (26.6 g, 0.12 mol) was dissolved in 350 ml of 96 % ethanol and quinine (38.9 g, 0.12 mol) in 100 ml of the same solvent was added. After standing overnight, the salt (34.9 g) was filtered off: $[\alpha]_D^{25}$ of the acid -112° . Since the salt was only sparingly soluble, it was divided into two portions of 17 g each. The first portion was recrystallised as shown in Table 1.

The second portion of the salt was treated in the same way. Systematic fractionation of the salt from the mother liquors gave a third crop. The total yield of salt containing acid of maximum activity was 21.5 g. It was decomposed with excess aqueous ammonia, the quinine extracted with chloroform and the remaining solution acidified with hydrochloric acid to pH 3. The crude product (7.4 g) was recrystallised from 96 % ethanol, yielding 6.7 g of colourless needles with m.p. 176–177 °C; Equiv.wt. Found: 222.2. Calc. for C₁₀H₁₀N₂O₂S, 222.3. $[\alpha]_D^{25} - 124^\circ$; $[M]_D^{25} - 276^\circ$ (c 0.522, 96 % ethanol).

(+)- α -(Benzimidazolyl-2-thio)-propionic acid. The various mother liquors from the quinine salt yielded 11.2 g of acid having $[\alpha]_D^{25} + 119^\circ$. This acid (0.05 mol) was dissolved with quinidine (16.2 g, 0.05 mol) in 350 ml of ethanol

and 50 ml of water were added. After evaporation to half the volume, the solution yielded 9.7 g of salt containing acid with $[\alpha]_D^{25} + 123^\circ$. Recrystallisation from 80 ml of 75 % ethanol gave 6.9 g salt with acid of $[\alpha]_D^{25} + 124^\circ$. Systematic fractionation of the salt from the mother liquors gave a further 13.8 g salt with acid of maximum activity. The acid was isolated and recrystallised as described for the enantiomer. The salt (19.0 g) gave 6.5 g of pure acid, m.p. 176–177 °C. Equiv.wt. Found: 222.1. Calc. for C₁₀H₁₀N₂O₂S: 222.3. $[\alpha]_D^{25} + 124^\circ$; $[M]_D^{25} + 276^\circ$ (c 0.488, 96 % ethanol).

Synthesis from (-)- α -bromopropionic acid. Since the preparation of optically pure acid is a very tedious process, a partially resolved acid was used. It was prepared as described by Ramberg⁸ and had $\alpha_D^{25} - 19.3^\circ$ (homogeneous, 1 dm) which means 40 % of active acid. The reaction was carried out as described above. The crude product had $[\alpha]_D^{25} + 54^\circ$, which increased on recrystallisation from 60 % ethanol. Equiv.wt. Found: 221.9. Calc. for C₁₀H₁₀N₂O₂S: 222.3. $[\alpha]_D^{25} + 64^\circ$ (c 0.863, 96 % ethanol).

The crude product thus contained 44 % and the recrystallised compound 52 % of active acid. The results show that no significant racemisation had taken place and that the proportion of the less soluble active acid had increased during the operations.

Benzimidazolyl-2-thio-acetic acid. 2-Mercaptobenzimidazole (4.5 g, 0.03 mol) was dissolved with sodium hydroxide (1.3 g, 0.033 mol) in 100 ml of water and chloroacetic acid (3.1 g, 0.032 mol) neutralised with potassium hydrogen carbonate in 30 ml of water was added. After 2 days the solution was acidified with hydrochloric acid to pH 3. Yield of crude product, 6.2 g (92 %). 2.0 g recrystallised from 200 ml of 60 % ethanol gave 1.5 g of colourless needles, m.p. 202 °C (dec.). Anal. C₈H₈N₂O₂S: C, H, N, S. Equiv.wt. Found: 208.3. Calc.: 208.2.

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Table 1. Recrystallisation of the quinine salt from dilute ethanol to constant activity of the acid.

Re-cryst.	Ethanol/ ml	Water/ ml	Salt ob- tained/g	$[\alpha]_D^{25}/^\circ$
1	380	190	11.8	-119
2	330	170	8.7	-123
3	230	120	6.6	-124
4	190	90	5.2	-124