

## 2-Mercaptolevulinic Acid

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In connection with other work on levulinic acid and its derivatives in progress in this department a sample of 2-mercaptolevulinic acid was desired. It seemed most conveniently prepared by the addition of thiolacetic acid to 4-oxo-2-pentenoic acid with the subsequent removal of the S-acetyl group.

The addition of one mole of thiolacetic acid was performed without any solvent or catalyst, the reaction was exothermic and a high yield of a thiolacetate was obtained.

Thiolacetic acid has been studied as an additive agent by a number of workers. Recently Larsson studied the literature on this subject, concluding that in additions to  $\alpha,\beta$ -unsaturated carbonyl compounds the thiolacetate group invariably appeared at the  $\beta$ -carbon atom.<sup>1</sup>

4-Oxo-2-pentenoic acid is both an  $\alpha,\beta$ -unsaturated ketone and an  $\alpha,\beta$ -unsaturated acid and in this compound the -M effects oppose each other.

Addition to the double bond in 4-oxo-2-pentenoic acid has been studied recently by Rappe. He obtained 2-(carboxymethylthio)levulinic acid by addition of mercaptoacetic acid.<sup>2</sup> The addition of hydrogen bromide gave the very unstable 2-bromolevulinic acid.<sup>3</sup>

In order to determine whether the thiolacetate group appeared at the  $\alpha$  or  $\beta$ -carbon atom in the levulinic acid, the addition product was first hydrolyzed and the mercaptolevulinic acid isolated. Attempts were made to hydrolyze the thiolester with aqueous sodium hydroxide solution, but the subsequent acidification

caused a brisk evolution of hydrogen sulfide, thus characterizing bis(2,4-dinitrophenyl)sulfide. Rapid base-catalyzed cleavage of the carbon-sulfur bond when an unsaturated group is attached to the  $\beta$ -carbon is a general reaction.<sup>4</sup>

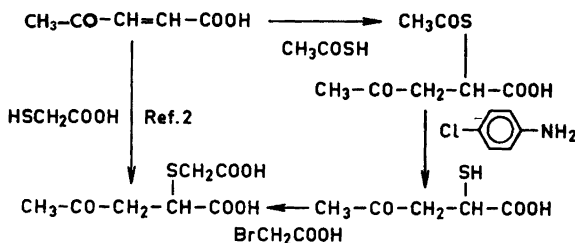
The aminolysis was, therefore, carried out with the very weak base, 4-chloroaniline, in benzene solution at room temperature. A mercaptolevulinic acid with a melting point of 65–67°C was obtained. The di-sodium salt of this mercaptan in aqueous solution was treated with bromoacetic acid and a compound with a melting point of 121–123°C was obtained. When the synthesis was performed without base in aqueous solution the melting point of the resulting product was 120–122°C. These two compounds were proved to be identical with a sample of 2-(carboxymethylthio)levulinic acid prepared according to Rappe,<sup>2</sup> by their infrared spectra and mixed melting points. Therefore, the addition of thiolacetic acid and related reactions can be written as shown in the scheme.

*Experimental.* The melting point measurements were performed using the Kofler microscopic method. The infrared spectra were obtained with a Perkin Elmer Model 337 Grating Spectrophotometer.

*Thiolacetic acid.* Commercial sample, distilled. B.p. 87–90°C.

*4-Oxo-2-pentenoic acid,* prepared according to Wolff,<sup>5</sup> recrystallized from chloroform and sublimed, m.p. 121–125°C.

*2-(Acetylthio)levulinic acid.* 11.4 g 4-oxo-2-pentenoic acid and 7.6 g thiolacetic acid were mixed in an Erlenmeyer flask with a glass rod. After the reaction has started it proceeds vigorously and cooling with water is then necessary in order to avoid loss of thiolacetic acid. The resulting oily liquid solidified to a compact cake after one day at room temperature. This cake was dissolved in 40 ml boiling benzene, 10 ml petroleum ether was added and the solution chilled in a refrigerator. 18 g (representing a 95 %



yield) of white crystals, m.p. 63–65°C, were collected. Repeated recrystallisations did not raise the melting point. (Found: C 44.21; H 5.33; S 16.83. Calc. for  $C_7H_{10}O_4S$  (190.2): C 44.19; H 5.29; S 16.85). The IR-spectrum (in KBr): 3375 w, 3300~2800 s(br), 2780 w, 2650 w, 2560 w, 2500 sh, 1725~1675 s, 1420 s, 1390 m, 1360 m, 1345 w, 1320 m, 1275 w, 1250 s, 1190 sh, 1180 s, 1160 m, 1135 m, 1106 m, 1045 m, 995 w, 965 m, 920 m, 855 w, 808 w, 687 m, 628 s, 610 sh, 520 m, 492 w, 462  $cm^{-1}$  w.

*2-Mercaptolevulinic acid.* 71.2 g 2-(acetylthio)levulinic acid, 52.5 g 4-chloroaniline and 400 ml benzene were mixed and allowed to stand at room temperature for 24 h. The yellow crystalline precipitate was filtered with suction, washed with 50 ml benzene and dried. Its melting point was 172–175°C, while that of 4-chloroacetanilide is 179°C.<sup>6</sup> A yield of 58.2 g was obtained, corresponding to 92%. The benzene solution was shaken with 200 + 150 + 100 ml 1 M sulfuric acid. The water phase was extracted with methylene chloride (7 × 100 ml). After drying over anhydrous magnesium sulfate, the solvent was removed *in vacuo* leaving a yellow oil. The oil was taken up in 150 ml chloroform-carbon tetrachloride (1:1) and was left at –25°C. 22.9 g (41%) of white crystals, m.p. 60–65°C, were collected. Repeated recrystallizations from the same solvent raised the m.p. to 65–67°C. (Found: Equiv.wt. 148.9 iodine titr. C 40.79; H 5.46; S 21.48. Calc. for  $C_6H_8O_3S$  (148.1): C 40.52; H 5.44; S 21.63). The IR-spectrum (in KBr): 3400~2600 s(br), 2569 m, 2534 w, 1729~1684 s, 1424 m, 1394 m, 1364 m, 1344 w, 1324 m, 1304 sh, 1284 w, 1253 s, 1205 m, 1187 m, 1167 m, 1087 w, 1045 sh, 1035 m, 930 s, 906 sh, 825 w, 806 w, 783 w, 688 m, 626 m, 600 m, 523 s, 467  $cm^{-1}$  w.

*2-Mercaptolevulinic acid semicarbazone.* The semicarbazone was prepared according to Shriner *et al.*<sup>7</sup> and recrystallized from 50% ethanol, m.p. 175°C (decomp.). (Found: N 20.34. Calc. for  $C_6H_{11}N_3O_3S$  (205.2): N 20.47).

*2-(Carboxymethylthio)levulinic acid.* (A) 7.0 g bromoacetic acid was neutralized with 2.7 g sodium carbonate in 15 ml water. A solution of 7.4 g 2-mercaptolevulinic acid and 4.1 g sodium hydroxide in 30 ml water was added dropwise to this solution. After five days at room temperature, the solution was acidified with 3 M sulfuric acid. The solution was extracted continuously with 250 ml ether for 18 h. The ether phase was dried over magnesium sulfate and the solvent was removed *in vacuo* leaving a yellow-colored solid cake. This cake (m.p. 90–100°C) was dissolved in

40 ml hot ethyl acetate, whereafter 10 ml petroleum ether was added. After one day at –25°C, 2.7 g (26%) white crystals (m.p. 118–120°C) were filtered off. Repeated recrystallization from the same solvent raised the m.p. to 121–123°C. (Ref. 2: 123.5–124.5°C). The IR-spectrum (in KBr): 3400~2500 s(br), 1798 sh, 1743~1698 s, 1428 m, 1408 sh, 1373 m, 1363 sh, 1338 w, 1318 m, 1258 m, 1212 s, 1205 sh, 1160 m, 1085 w, 1043 m, 930 m, 893 w, 848 w, 808 w, 781 w, 689 w, 661 m, 635 w, 610 w, 535 sh, 513 m, 465 sh, 445  $cm^{-1}$  m.

(B) 3.7 g 2-mercaptolevulinic acid, 3.5 g bromoacetic acid and 10 ml water were mixed. The mixture was allowed to stand at room temperature for five days. The solution was worked up as described above. Yield 1.0 g (19%), m.p. 120–122°C.

*2-(Acetylthio)levulinic acid and sodium hydroxide solution.* 1.0 g 2-(acetylthio)levulinic acid was dissolved in 5 ml methanol. 2.5 ml 6 M sodium hydroxide was added and the solution was allowed to stand at room temperature for one hour. A solution of 1.1 g 1-chloro-2,4-dinitrobenzene in 5 ml methanol was added. After 15 min the yellow crystalline precipitate was collected, washed with water and dried. Yield 0.5 g, m.p. 190–192°C. Recrystallization from 1-butanol raised the m.p. to 193–194°C. Bis(2,4-dinitrophenyl)sulfide has m.p. 195°C.<sup>8</sup> 0.75 g 2-mercaptolevulinic acid yielded, with a similar procedure, 0.6 g crystalline precipitate, m.p. 189–191°C.

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