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The Preparation of α-Amino-α-benzylmercaptopropionic Acid Derivatives

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The preparation of *N*-acyl derivatives of α-amino-α-benzylmercaptopropionic acid was investigated. It is described that pyruvic acid was treated with amides to afford *N*-acyl-α-amino-α-hydroxypropionic acids, which were then substituted into *N*-acyl-α-amino-α-benzylmercaptopropionic acids. In another experiment, Steglich's method was improved in order to afford three *N*-acyl derivatives of α-amino-α-benzylmercaptopropionic acid in a better yield.

α-Amino-α-mercaptocarboxylic acid has not been isolated in a pure form, and only two methods for the preparation of its derivatives have been reported by Steglich[1] and by Shemiyakin.[2] This paper will report a simple method for the preparation of α-amino-α-benzylmercaptopropionic acid derivatives from pyruvic acid and also an improvement of Steglich's method to give a better yield.

It has been described[3] that pyruvic acid (**1**) was heated with acetamide to give α-acetamidoacrylic acid (**2**) and α,α-diacetamidopropionic acid (**3**), which were produced through the intermediate, a complex of α-acetamido-α-hydroxypropionic acid acetamide.

$$CH_3COCOOH + 3CH_3CONH_2 \longrightarrow$$
(**1**)

$$\left[\begin{array}{l} OH \\ CH_3-C-COOH \\ NHCOCH_3 \end{array}\right] 2CH_3CONH_2$$

$$\begin{array}{l} NHCOCH_3 \\ CH_3-C-COOH \\ NHCOCH_3 \\ (\mathbf{3}) \end{array} \rightleftharpoons \begin{array}{l} CH_2=C-COOH \\ NHCOCH_3 \\ (\mathbf{2}) \end{array}$$

On the other hand, Shieve[4] reported that adding formamide to pyruvic acid (**1**) yielded α-formamido-α-hydroxypropionic acid (**4**), which was then isolated in a pure form.

When the acid **4** was refluxed with benzyl mercaptan in a benzene solution by means of the use of a water separator for 3 hr, 1 mol of water was separated and α-formamido-α-benzylmercaptopropionic acid (**5**) was obtained in a good yield.

$$CH_3COCOOH + HCONH_2 \longrightarrow \begin{array}{l} OH \\ CH_3-C-COOH \\ NHCHO \\ (\mathbf{4}) \end{array}$$

$$\xrightarrow{C_6H_5CH_2SH} \begin{array}{l} SCH_2C_6H_5 \\ CH_3-C-COOH \\ NHCHO \\ (\mathbf{5}) \end{array} \xrightarrow{CH_2N_2} \begin{array}{l} SCH_2C_6H_5 \\ CH_3-C-COOCH_3 \\ NHCHO \\ (\mathbf{8}) \end{array}$$

The structure of Compound **5** was characterized by elementary analysis and by a study of its IR and NMR spectrum. This reaction process was supported by the fact that carbinolamine (**6**) was replaced by mercaptan to give aminomethyl thioether (**7**).[5]

$$\underset{(\mathbf{6})}{RCONHCH_2OH} + RSH \rightarrow \underset{(\mathbf{7})}{RCONHCH_2SR}$$

After the α-formamido-α-benzylmercaptopropionic acid (**5**) had been neutralized with a sodium bicarbonate solution, it was converted to its methyl ester with diazomethane.

On the other hand, pyruvic acid (**1**) did not react with urethane at room temperature, unlike the case of formamide. However, when pyruvic acid was refluxed with urethane in a benzene solution, it gave α-ethoxycarbonylaminoacrylic acid (**9**). Thus, pyruvic acid, urethane, and benzyl mercaptan were heated together under 60°C for 3 hr; α-ethoxycarbonylamino-α-benzylmercaptopropionic acid (**10**) was thus obtained.

$$\begin{array}{l} CH_2=C-COOH \\ NHCOOC_2H_5 \\ (\mathbf{9}) \end{array} \qquad \begin{array}{l} SCH_2C_6H_5 \\ CH_3-C-COOH \\ NHCOOC_2H_5 \\ (\mathbf{10}) \end{array}$$

1) W. Steglich, H. Tanner and R. Hurnaus, *Chem. Ber.*, **100**, 1824 (1967).

2) M. M. Shemyakin, E. S. Chaman and L. I. Denisova, *Doklady Akad. Nauk SSSR*, **106**, 675 (1965); *Chem. Abstr.*, **50**, 13809 (1956).

3) J. P. Greestein and M. Winits, "Chemistry of Amino Acids," Vol. 1, John Wiley & Sons, Inc., New York (1961), p. 846.

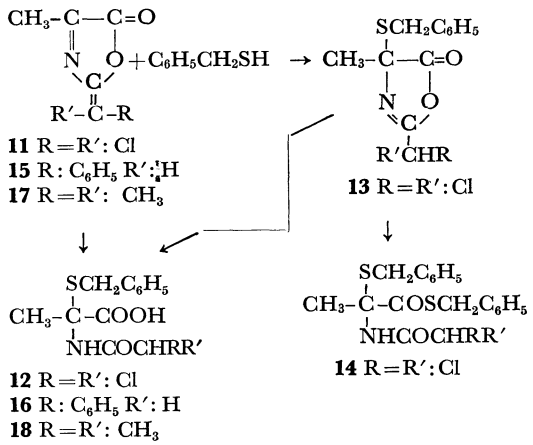
4) W. Shieve, *J. Amer. Chem. Soc.*, **68**, 118 (1946).

5) H. E. Zaugg, "Organic Reactions," Vol. **14**, (1965), p. 113.

Similarly, acetamide and chloroacetamide did not give α-amino-α-mercaptocarboxylic derivative, but α-acetamidoacrylic acid and α,α-diacetamidopropionic acid derivatives were formed.

Moreover, another method was investigated. Steglich[1] has described how the mercaptolysis of 2-dichloromethylene-4-methy-3-oxazolin-5-one (**11**) with ethyl mercaptan in an acetic acid solution containing hydrogen bromide gave α-dichloroacetamido-α-ethylmercaptopropionic acid and its ethyl thioester at the same time.

In our study, however, when **11** was treated with benzyl mercaptan in a solvent such as methylene-dichloride or tetrahydrofuran (THF) under neutral conditions and at room temperature, it gave only 2-dichloromethylene-4-methyl-4-benzylmercapto-2-oxazolin-5-one (**13**) and no further addition of mercaptan was observed. In an acetic acid solution however, Compound **13** reacted with another molecule of mercaptan to give α-dichloroacetamido-α-benzylmercaptopropionic acid benzyl thioester (**14**). Compound **13** was hydrolyzed, in an acetic acid solution, into α-dichloroacetamido-α-benzylmercaptopropionic acid (**12**), which was also obtained directly in low yields by the reaction of **11** with benzyl mercaptan in an acetic acid solution containing a small amount of water. Similarly, 2-benzylidene-4-methyl-3-oxazolin-5-one (**15**) also reacted with benzyl mercaptan in a THF solution; subsequent hydrolysis gave α-phenylacetamido-α-benzylacetamido-α-benzylmercaptopropionic acid (**16**), and in the case of 2-isopropylidene-4-methyl-3-oxazolin-5-one (**17**) it did not react with benzyl mercaptan in an acetic acid or THF solution, but in an acetic acid solution containing hydrogen bromide, α-isobutyrylamido-α-benzylmercaptopropionic acid (**18**) was obtained.



Experimental

α-Formamido-α-hydroxypropionic Acid (4). This was prepared by the method of Shieve;[4] mp 53°C, yield 98%.

α-Formamido-α-benzylmercaptopropionic Acid (5). A benzene solution (50 m*l*) of **4** (6.6 g, 1/20 mol) was heated with benzyl mercaptan (6.2 g, 1/20 mol) under refluxing for 3 hr. After cooling, the solvent was removed and the residue was treated with a sodium bicarbonate solution. The water layer was washed with ether and acidified with dilute hydrochloric acid under cooling. An oily substance was thus separated and crystallized. Recrystallization from ethanol gave white needles with a mp of 148—149°C; yield 18 g (75%). IR bands (KBr), 3290 cm^{-1} (NH), 1685, 1705 cm^{-1} (COOH), 720 cm^{-1} (C_6H_5). NMR spectrum (DMSO, TMS as internal reference), τ 8.26 (3H, singlet) for CH_3, τ 6.12 (2H, doublet) for S-$CH_2C_6H_5$, τ 2.61 (5H, singlet) for C_6H_5, τ 1.90 (1H, singlet) for NH. This compound was hydrolyzed to pyruvic acid and benzyl mercaptan under refluxing for 1 hr in water. In an attempted debenzylation and deacylation, it was unsuccessful in isolating α-mercapto-α-amino acid itself in a pure form.

Methyl α-Formamido-α-benzylmercaptopropionate (8). To a solution of 2.39 g (1/100 mol) of **5** in ether, was added, drop by drop, a solution of diazomethane in ether until nitrogen-gas ceased to be evolved. The mixture was stirred at room temperature for 0.5 hr, and the excess diazomethane was treated with a small quantity of acetic acid. The mixture was then concentrated under reduced pressure. The residue was washed with a saturated sodium bicarbonate solution, extracted with ethyl acetate, and dried over anhydrous sodium sulfate. The evaporation of the organic layer afforded 2.40 g (95%) of a methyl ester of **5**. Recrystallization from dibutyl ether gave colorless crystals; mp 57—58°C. IR (KBr) 3290 cm^{-1} (NH), 1730 cm^{-1} ($COOCH_3$), 1665 cm^{-1} (CONHR), 700, 720 cm^{-1} (C_6H_5).

Found: C, 57.05; H, 6.25; N, 5.74%. Calcd for $C_{12}H_{15}NO_3S$: C, 56.91; H, 5.97; N, 5.53%.

α-Ethoxycarbonylamino-α-benzylmercaptopropionic Acid (10). Pyruvic acid (4.4 g, 1/20 mol) and ethyl carbamate (4.4 g, 1/20 mol) were dissolved in 50 m*l* of benzene. The solution was heated at 40°C for 1 hr, and then benzyl mercaptan (6.2 g, 1/20 mol) was added to this solution. The mixture was heated for 2 hr at 60°C. After the removal of the benzene, the residue was treated with a sodium bicarbonate solution. The water layer was washed with ether and then acidified with dilute hydrochloric acid under cooling. An oily substance which separated gradually crystallized on cooling. Recrystallization from ethylene dichloride-cyclohexane gave colorless prisms with a mp of 90—91°C; yield 8.2 g (58%). IR bands (KBr), 3300 cm^{-1} (NH), 1939 cm^{-1} ($COOC_2H_5$), 1660 cm^{-1} (COOH), 715 cm^{-1} (C_6H_5). NMR spectrum ($CDCl_3$, TMS as internal reference), τ 8.78 (3H, triplet) for CH_2CH_3, τ 8.06 (3H, singlet) for CH_3, τ 6.10 (2H, singlet) for S-CH_2-C_6H_5, τ 5.88 (2H, quartet) for CH_2CH_3, τ 2.15 (5H, singlet) for C_6H_5, τ 2.15 (1H, singlet) for COOH.

2-Dichloromethylene-4-methyl-3-oxazolin-5-one (11). This was prepared by the method of Steglich;[1] mp 77°C, yield 78%.

2-Benzylidene-4-methyl-3-oxazolin-5-one (15). This was prepared by the method of Filler;[6] mp 110—

6) R. Filler and E. J. Piasek, *J. Org. Chem.*, **28**, 221 (1963).

115°C, yield 85%.

2-Isopropylidene-4-methyl-3-oxazolin-5-one (17). This was prepared by the method of Bergmann;[7] bp 56°C/1.5 mmHg, yield 62%.

2-Dichloromethylene-4-methyl-4-benzylmercapto-2-oxazolin-5-one (13). In 50 m*l* of ethylene dichloride **11** (9.0 g, 1/20 mol) was dissolved, and to this solution was added benzyl mercaptan (12.4 g, 1.0 mol). The resulting solution was kept at room temperature for 24 hr. After the evaporation of the solvent, the residual benzyl mercaptan was removed by distillation under reduced pressure. The residue was chromatographed on an alumina column in benzene to afford a syrup. This syrup could not be distilled and crystallized; yield, 11.0 g (62%). IR bands (liquid film), 1805 (C=O) and 1650 cm^{-1} (C=N). NMR bands ($CDCl_3$, TMS was used as the internal reference), τ 7.84 (3H, singlet) for CH_3, τ 6.18 (2H, singlet) for $C_6H_5CH_2$, τ 4.01 (1H, singlet) for $CHCl_2$, and τ 2.72 (5H, singlet) for $C_6H_5CH_2$.

Found: C, 47.66; H, 3.74; N, 4.36%. Calcd for $C_{12}H_{11}O_2SNCl_2$: C, 47.37; H, 3.62; N, 4.61%.

α-Dichloroacetamido-α-benzylmercaptopropionic Acid-*S*-Benzylester (14). To a solution of **13** (6.1 g, 1/50 mol) in 50 ml of acetic acid was added 2.5 g (1/50 mol) of benzyl mercaptan. The resulting mixture was kept at room temperature for 48 hr. After the evaporation of the solvent, the residue was chromatographed on an alumina column in benzene to afford a crude product, which was recrystallized from isopropyl alcohol to give colorless prisms; mp 94—95°C, yield 4.2 g (50%). IR bands (KBr), 1690 cm^{-1} ($COSCH_2C_6H_5$), 1680 and 1560 cm^{-1} (CONH).

Found: C, 53.48; H, 4.54; N, 3.42%. Calcd for $C_{19}H_{19}O_2NS_2Cl_2$: C, 53.25; H, 4.44; N, 3.27%.

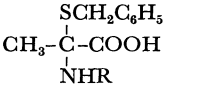
α-Dichloroacetamido-α-benzylmercaptopropionic Acid (12). a) In 50 m*l* of acetic acid containing a small amount of water was dissolved 6.1 g (1/50 mol) of **13**. The resulting mixture was kept at room temperature for 48 hr. After the evaporation of the solvent, the oily residue was dissolved in a sodium bicarbonate solution and washed with ether. The aqueous solution was acidified with dilute hydrochloric acid under cooling. An oily substance which separated crystallized standing. The crystals were recrystallized from acetic acid to give colorless prisms; mp 166—167°C, yield 4.2 g (65%). IR bands (KBr), 3300 cm^{-1} (NH), 1713 cm^{-1} (COOH), 1685 and 1542 cm^{-1} (CONH).

b) To a solution of **11** (9.0 g, 1/20 mol) in 50 m*l* of acetic acid was added 6.2 g (1/20 mol) of benzyl mercaptan and a small amount of water. The resulting mixture was kept at room temperature for 2 days and they treated by a procedure similar to a) above to yield compound **12**.

α-Phenylacetamido-α-benzylmercaptopropionic Acid (16). To a solution of **15** (9.5 g 1/20 mol) in 50 m*l* of THF was added 6.2 g (1/20 mol) of benzyl mercaptan. The resulting mixture was kept at room temperature for 24 hr. After the removal of the solvent, the residue was dissolved in a mixture of 30 m*l* of acetic acid and 10 m*l* of water, and the resulting mixture was heated for 5 hr. After the removal of the acetic acid, the residue was neutralized with a sodium bicarbonate solution. This solution was acidified with dilute hydrochloric acid to give crystals. Recrystallization from ethyl acetate gave colorless crystals; mp 157—158°C, yield 11 g (66.7%). IR bands (KBr), 3300 cm^{-1} (NH), 1710 cm^{-1} (COOH), 1628 and 1516 cm^{-1} (NHCO).

α-Isobutyrylamido-α-benzylmercaptopropionic Acid (18). In an acetic acid solution containing 20% hydrogen bromide **17** was treated by a procedure similar to **16**. The recrystallization of a crude product from ethylene dichloride gave colorless prisms; mp 114—115°C, yield 40%. IR bands (KBr), 3330 cm^{-1} (NH), 1730 cm^{-1} (COOH) and 1615 cm^{-1} (NHCO).

Table 1. Elementary analysis of α-amino-α-benzylmercaptopropionic acid derivatives



Compound number	R	Anal. % Calcd C	H	N	Found C	H	N
5	CHO	55.23	5.48	5.86	55.00	5.00	5.57
10	$COOC_2H_5$	55.12	6.05	4.95	54.91	6.02	4.87
12	$COCHCl_2$	44.75	4.04	4.35	44.99	3.97	4.38
16	$COCH_2C_6H_5$	65.64	5.82	4.25	65.71	5.71	4.23
18	$COCH(CH_3)_2$	59.77	6.81	4.98	59.86	6.55	5.09

7) M. Bergmann and S. Stern, *Ann.*, **448**, 20 (1926).