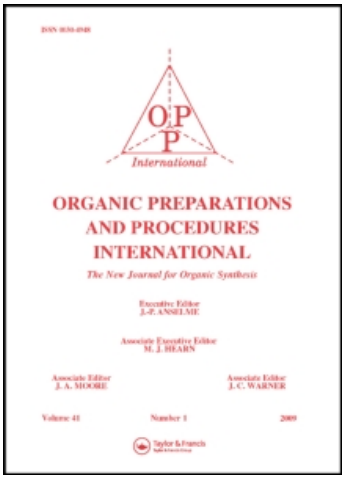

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FACILE PREPARATION OF L-2-OXOTHLUOLIDINE-4-CARBOXYLIC ACID (OTC)

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30 min, and then filtered. The filtrate was poured into ice water (100 ml), and neutralized with sodium bicarbonate. The precipitate was collected by suction, washed with water and dried. The product was recrystallized from benzene as light beige crystals (1.6 g, 67%, mp 120-124°). IR (KBr): 3430 and 3320 (NH_2), 1690 (C = O) cm^{-1}; ^{1}H-NMR ($CDCl_3$), δ: 3.95 (3H, s, CH_3) 4.6 (2H, broad s, NH_2); MS m/z: 209 (M^+), 211 (M^++2), 213 (M^++4).

Anal. Calcd for $C_6H_5Cl_2NO_3$: C, 34.45; H, 2.34; N, 6.7. Found: C, 34.51; H, 2.28; N, 6.81

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FACILE PREPARATION OF

L-2-OXOTHIAZOLIDINE-4-CARBOXYLIC ACID (OTC)

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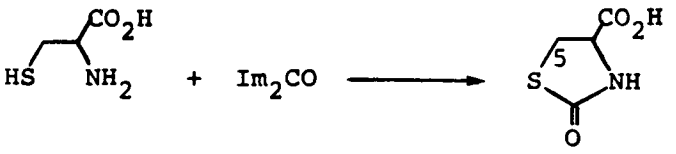
The title compound (OTC) has recently been identified as a non-toxic precursor for the introduction of L-cysteine into living cells and as a stimulant of the biosynthesis of glutathione (g-L-glutamyl-L-cysteinyl-glycine).[1] The preparation of OTC normally involves the use of dangerous phosgene;[2,3] in addition, we encountered inordinate difficulties in purifing OTC prepared this way. Attempted recrystallizations from hot water[2] resulted in a gum, while the laborious modification of Shah et al.[3] (repeated extractions of OTC with ethyl acetate from acidified water) gave pure OTC albeit in only 5% yield.

We report a simple method to prepare OTC from L-cysteine that may be carried out even in



a biochemical/pharmacological laboratory. It is based on the attractive replacement of phosgene with carbonyldiimidazole.[4] This change allows a homogenous reaction in water with a high yield and an efficient removal of contaminants and by-products with acidic ion-exchange resin.

EXPERIMENTAL SECTION

L-Cysteine and carbonydiimidazole were commerical samples (Fluka AG, Buchs, Switzerland) and were used without further purification. Dowex 50W-X8 (16-40 mesh, Fluka AG) was washed with 1N HCl then to neutral with distilled water before use. Raman, IR, and NMR spectra were recorded on Cary 82, Nicolet 170SX, and Varian XL-400 spectrometers, respectively.

Preparation of L-2-Oxothiazolidine-4-carboxylic acid (OTC).- L-Cysteine (1.21 g, 10 mmol) in 15 ml of distilled water was stirred at 1-5°. Carbonyldiimidazole (2.82 g, 11 mmol) was added at once and stirring was continued until it dissolved (ca. 5 min). The clear solution was kept in the refrigerator overnight at 2-4°, then its pH adjusted to 3 by batchwise addition of Dowex 50W-X8 and the resin removed by filtration. The filtrate was concentrated to dryness on a rotarty evaporator at 50° to yield 0.89 g (71%) of OTC as white crystals, mp. 173-174°, lit.[2] mp. 173-174°.

Anal. Calcd for $C_4H_5NO_3S$: C, 32.68; H, 3.51; N, 9.52; S, 21.79

Found: C, 32.86; H, 3.53; N, 9.57; S, 21.33

NMR (DMSO-d_6): δ 4.35 (dd, 1H, J = 5.8 Hz, J = 7.7 Hz), 3.58 (dd, 1H, J = 7.7 Hz, J = 7.72, bs, 1H), Raman: 3280 (NH), 3012, 2953 and 2924 (aliphatic CH), 1737 (CO carboxylic acid) and 1625 (CO cyclic thiolcarbamate) cm^{-1}; IR (KBr): 3280 (NH), 1738 (CO carboxylic acid), and 1623 (CO cyclic thiolcarbamate) cm^{-1}; thin layer chromatography (Kieselgel 60, 0.125 mm) eluent 1-butanol-acetic acid pyridine-water (4:1:1:2): RF, OTC = 0.52, imidazole = 0.68 and L-cysteine = 0.33.

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A CONVENIENT PREPARATION OF ETHYL 7-BROMOHEPTANOATE

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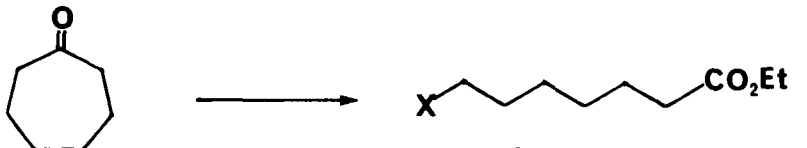
As part of a program[1] aimed at the synthesis of prostaglandins[2] and their analogues,[3] we needed ethyl 7-bromohepanoate (2). Compound 2 has been obtained from tetrahydropyran by conversion to 5-chloropentyl acetate and treatment with diethyl sodium malonate followed by hydrolysis and decarboxylation[4] or by reaction of monoethyl suberate with red mercury (II) oxide and bromine.[5] The first method gives acceptable overall yield (about 40% in our hands) but suffers from time-consuming and tedious manipulations, while the second gives poor yields (25%) and utilizes toxic materials.



1 X = OH
2 X = Br

We now report that the reaction of cycloheptanone with three equiv. of potassium persulfate in the presence of sulfuric acid and ethanol was complete in 8 hrs at 15° affording ethyl 7-hydroxyheptanoate 1 in 85% yield (pure by GLC).[6] Higher temperatures or different ratios between the oxidizing agent and cycloheptanone had a deleterious effect on the yield of 1. Subsequent treatment of ethyl 7-hydroxyheptanoate with phosphorus tribromide in toluene gave the title compound 2 in 60% yield after distillation. This method is simple, short and proceeds in good yield, from inexpensive starting materials and may be run on a preparative useful scale.The oxidative procedure gives better yields than the methods using trifluoroperacetic acid[7] or sodium perborate.[8]