SYNTHESIS OF 4-AZA-2-OXA-6-THIABICYCLO[3.3.0]OCTANE

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Starting from cysteine, 4-aza-2-oxa-6-thiabicyclo-[3.3.0]octane has been synthesized in a four step synthesis; the over all yield is 40 %.

During our research about cytostatic effective heterocycles derived from cysteine a simple method was found for preparing 4-aza-2-oxa-6-thiabicyclo[3.3.0]octane (5). After the condensation[1] of formaldehyde with cysteine hydrochloride (1) thiazolidine-4-carboxylic acid was obtained which in turn was converted into the ethyl carboxylate (3) with diethyl sulfite, prepared from absolute ethanol and thionyl chloride.

The ring system of 4-substituted thiazolidines was cleaved when attempting reduction of the ester (3) with lithium aluminium hydride.[2] However, using calcium borohydride the reduction took place without concomitant side reactions and 4-(2-hydroxymethyl)-

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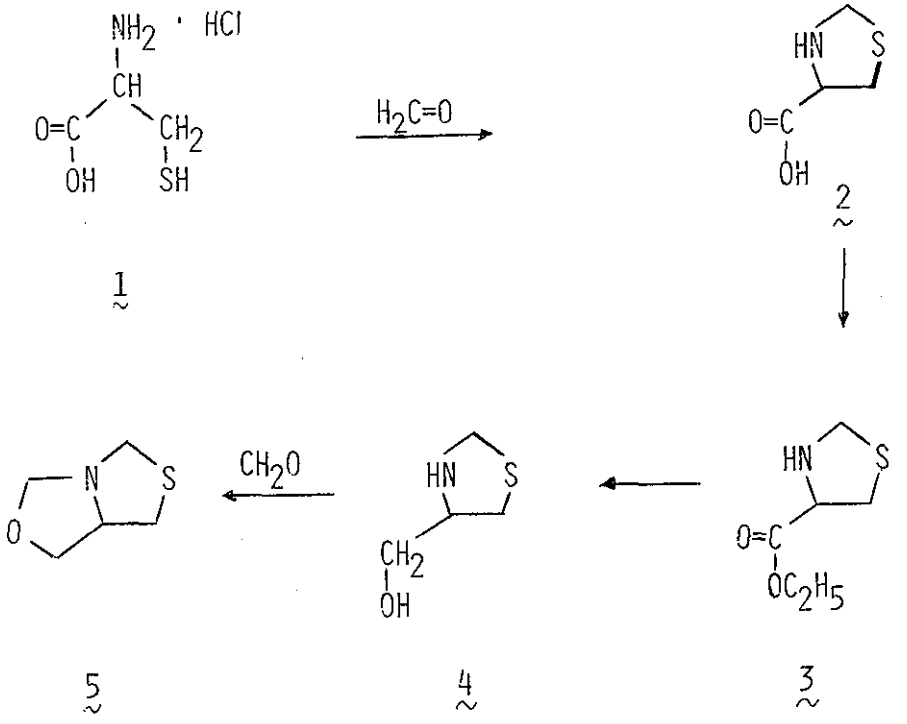
Dedicated to Prof. Dr. R. B. Woodward on his sixtieth birthday.

thiazolidine (4) was obtained in 80 % yield.

The second ring was formed in the reaction of the amino alcohol (4) with formaldehyde removing the water with a powdered molecular sieve. The 4-aza-2-oxa-6-thiabicyclo[3.3.0]octane (5) was obtained after purification on a silica gel column as an oily colourless compound that was subsequently identified by its mass spectrum and ^{13}C-NMR spectrum. The heterocyclic compound is stable at room temperature; it forms an oxalate, mp 100-101°.



Experimental Part

Thiazolidine-4-carboxylic Acid (2).

Cysteine hydrochloride (1) (17.3 g; 0.1 mole) was dissolved in water (100 ml) and 40 % aqueous solution of formaldehyde (18 ml) was then added. After standing overnight at room temperature pyridine (20 ml) was dropwise added to the clear solution and water (approximately 50 ml) was removed by the rotatory evaporator. The mixture was kept in an ice-bath to give colourless crystals which were filtered by suction and recrystallised from water to afford thiazolidine-4-carboxylic acid (10.5 g; 70 % yield) (mp 199-201°).

$C_4H_7NO_2S$ (133.10)	calc.	C	36.09	H	5.25	N	10.51
	found	C	35.92	H	5.33	N	10.47

4-Ethoxycarbonylthiazolidine hydrochloride (3).

In a 250 ml Erlenmeyer flask absolute ethanol (100 ml) was cooled with an ice/sodium chloride bath to -10°. Under vigorous stirring freshly distilled thionyl chloride (15 ml) was dropwise added and during the addition the temperature has been kept below -5°. To the cooled solution thiazolidine-4-carboxylic acid (13.3 g; 0.1 mole) was added in small portions with stirring. The mixture has been stirred for another 2 hr at 40°. Afterwards the solution became clear, so it was cooled and ethanol and excess thionyl chloride were removed by a rotatory evaporator. The white solid residue was recrystallised twice from ethanol and dried

(P_2O_5). 4-Ethoxycarbonylthiazolidine hydrochloride (12.8 g; 80 % yield) was obtained as colourless crystals, mp 142-144°.

$C_6H_{11}NO_2SCl$ (197.58)	calc.	C	36.47	H	6.07	N 7.08
	found	C	36.48	H	5.98	N 6.94

4-(2-Hydroxymethyl)thiazolidine (4).

In a 500 ml three-necked flask, equipped with a stirrer, thermometer and dropping funnel, calcium chloride dihydrate (3.4 g) was dissolved in absolute ethanol (120 ml) and cooled with dry ice/methanol at -30°. Sodium borohydride (1.58 g) in absolute ethanol (200 ml) was then slowly added to the cooled solution and during the addition the temperature was kept below -20°. After the addition was complete the solution was stirred for 20 min at -20°. A solution of 4-ethoxycarbonylthiazolidine (8.05 g; 0.05 mole) in absolute ethanol (50 ml) was added dropwise to the above cooled mixture, which was subsequently stirred at -20° for 10 hr. The solution was then allowed to warm up to room temperature and ethanolic 25 % hydrogen chloride (10 ml) was added and the solvent was completely removed on a rotatory evaporator. Thereafter the solid residue was dissolved in water (100 ml). The clear solution was made alkaline with concentrated ammonium hydroxide solution (10 ml) and was extracted three times with methylene chloride. The combined organic layers were dried (Na_2SO_4), filtered and the solvent was removed by a rotatory evaporator. A colourless oily residue which was obtained slowly became crystalline. The crude product was recrystallised from methylene chloride to give 4.75 g (80 % yield) of

4-(2-hydroxymethyl)thiazolidine as colourless crystals, mp 79-81°.

C_4H_9NOS (119.10)	calc.	C	40.33	H	7.55	N 11.75
	found	C	40.31	H	7.59	N 11.81

4-Aza-2-oxa-6-thiabicyclo[3.3.0]octane (5).

In a 100 ml flask 4-(2-hydroxymethyl)thiazolidine (4) (2.4 g; 0.02 mole) was dissolved under stirring in dry benzene (60 ml). After the addition of paraformaldehyde (4 g) and powdered molecular sieve (5 Å) (3 g) the mixture was heated for 2 hr at 40°. The solution was thereafter cooled and filtered and the benzene was removed by a rotatory evaporator. The residue was dissolved in methylene chloride, dried and filtered. After removing the solvent an oil was obtained and then purified on a silica gel column (hexane/chloroform 10 : 1) to give 4-aza-2-oxa-6-thiabicyclo-[3.3.0]octane (2.47 g; 80 % yield) as a colourless clear oil, which was decomposed during distillation. Oxalate: mp 100-101°.

C_5H_9NOS (131.11)	calc.	C	45.80	H	6.86	N 10.60
	found	C	45.87	H	6.79	N 10.48

Mass spectrum (70 eV): M^+: 131 (27 %).

^{13}C NMR spectrum (chloroform) 72 ppm (C-1); 87 ppm (C-2); 67 ppm (C-3); 38 ppm (C-4); 59 ppm (C-5).

REFERENCES

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