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A Synthetic Approach to DL-α-(2-Thiazolyl)glycines

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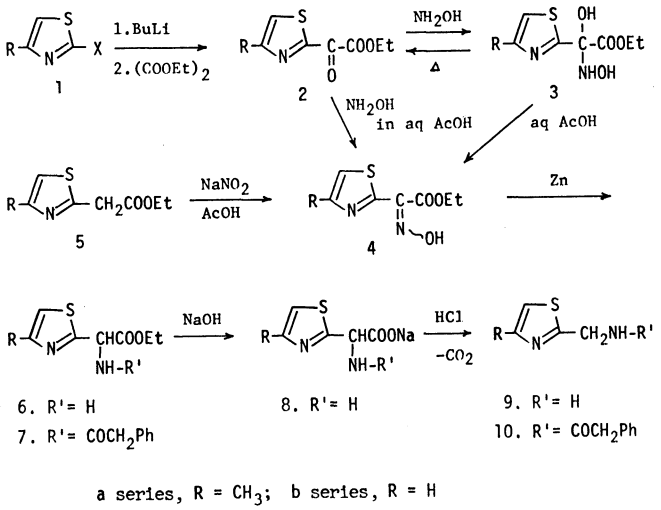
As a part of the investigation of the synthesis of the α-substituted glycine derivatives with heterocyclic rings,[1] the synthesis of 2-thiazolylglycine was studied. Since 2-thiazolylacetic acid has been reported to show a remarkable ease of decarboxylation,[2] we adopted a synthetic route *via* the amino acid esters, **6**. The unusual behavior of the 2-thiazolylglycines, which were decarboxylated too rapidly to be isolated, is the subject of this note.

The starting materials, ethyl 4-methylthiazole-2-glyoxalate (**2a**) and ethyl thiazole-2-glyoxalate (**2b**), were prepared from 4-methylthiazole (**1a**, R=CH_3, X=H) and 2-bromothiazole (**1b**, R=H, X=Br) respectively by lithiation, followed by the addition of the 2-lithio compounds to an excess of ethyl oxalate. The subsequent treatment of **2a** with hydroxylamine in aqueous methanol at 0 °C gave a crystalline product, **3a**, in a high yield; its empirical formula, $C_8H_{12}N_2O_4S$, corresponded to that of a monohydrate of the expected oxime. The IR spectrum, in addition to one carbonyl band at 1720 cm^{-1}, exhibited a very broad and strong band at 3150 cm^{-1}. Under the same conditions, **2b** yielded **3b** as a sirup; the IR spectrum of **3b** was similar to that of **3a**. Compounds **3a** and **3b**, when heated in refluxing benzene, regenerated the starting glyoxalates, **2a** and **2b** respectively, while upon treatment with aqueous acetic acid they gave the desired oximes, **4a** and **4b** respectively, which were mixtures of geometrical isomers, separable by column chromatography. These oximes were also formed when the reaction of **2a** and **2b** with hydroxylamine was carried out in aqueous acetic acid. From these results, it is evident that **3a** and **3b** are carbinolamine intermediates. Their having stability enough to permit isolation can be ascribed to the strong electron-withdrawing influence of both the carboxyl and the 2-thiazolyl moieties.[3]

The oxime, **4a**, was more conveniently prepared from ethyl 4-methylthiazole-2-acetate (**5a**) by isonitrosation with sodium nitrite in aqueous acetic acid at 0 °C. This reaction gave, stereoselectively, a single isomer in a high yield.

The reduction of **4a** with zinc dust in aqueous formic acid produced the amino acid ester, **6a** (*N*-phenylacetyl derivative **7a**; mp 80—81 °C). However, attempts to isolate the free amino acid after the alkaline



hydrolysis of **6a** failed. When the sodium salts, **8a**, were neutralized with hydrochloric acid at 0 °C, a vigorous evolution of CO_2 gas occurred to give the amine, **9a** (*N*-phenylacetyl derivative **10a**; mp 112—114 °C). Upon a similar treatment, the amino acid ester, **6b**, prepared by the reduction of **4b** with zinc dust, also furnished the amine, **9b** (*N*-phenylacetyl derivative **10b**; mp 102—104 °C). Figure 1 illustrates

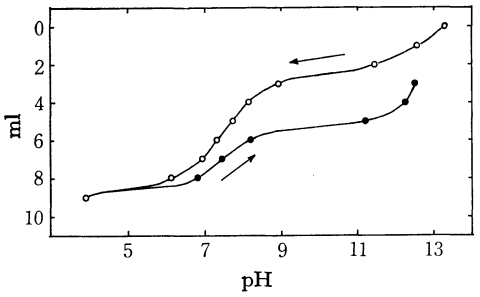


Fig. 1. Potentiometric titration of the sodium salt (**8a**) with 0.1 M hydrochloric acid (open circles) followed by a back titration with 0.1 M sodium hydroxide (filled circles).

the titration of **8a** with 0.1 M hydrochloric acid, followed by back titration with 0.1 M sodium hydroxide. The back-titration curve delineates the neutralization of the conjugate acid of the amine, **9a**. The amount of alkali required to neutralize the conjugate acid was almost equal to a half of that of acid needed for the initial titration, indicating that the decarboxylation takes place simultaneously with the transformation of the sodium salt to the free amino acid. The unusual instability of 2-thiazolylglycines is of interest in comparison with the 4- and 5-thiazolylglycines previously prepared by us;[1] the latter substances are stable and can be recrystallized from boiling water.

Similar differences have been found among thiazolylacetic acids; the activation energy of the decarboxyla-

1) M. Hatanaka and T. Ishimaru, *J. Med. Chem.*, **16**, 978 (1973).

2) H. Schenkel and R. Mory, *Helv. Chim. Acta*, **33**, 16 (1950).

3) In particular, the strong electron-withdrawing effect of the 2-thiazolyl moiety should be noted, for ethyl 3-methylisothiazole-5-glyoxalate was directly converted to the oxime by treatment with hydroxylamine under the same conditions as described for **3a** (see Ref. 1). Isolation of an analogous carbinolamine intermediate in the formation of 2-formyl-1-methylpyridinium iodide oxime has also been reported [E. J. Poziomek, D. N. Kramer, B. W. Fromm, and W. A. Mosher, *J. Org. Chem.*, **26**, 423 (1961)].

tion of 2-thiazolylacetic acid is much smaller than those for the 4- and 5-acetic acids.[2] Our finding indicates that the substitution of the amino group at the α-position of 2-thiazolylacetic acid makes the decarboxylation easier.

Experimental

Ethyl 4-Methylthiazole-2-glyoxalate (2a). A stirred solution of 4-methylthiazole (25.6 g, 0.259 mol) in dry ether (150 ml) was cooled at −70 °C in a Dry Ice–acetone bath, and then a 15% ethereal *n*-butyllithium solution (150 ml) was added at such a rate that the temperature was maintained below −65 °C. The cold mixture was then added through a glass tube to a stirred and cooled (−65 °C) solution of diethyl oxalate (58 g, 0.39 mol) in dry ether (200 ml). After an additional hour at −60 °C, 10% hydrochloric acid (260 ml) was added and the aqueous layer was neutralized with K_2CO_3 and extracted with ether. The evaporation of the ether, and distillation of the residue gave a yellow liquid (27.4 g, 53%); bp 106—107 °C/0.4 mmHg; IR (liquid film) 1740 (C=O) and 1700 (C=O) cm^{-1}; NMR ($CDCl_3$, TMS) δ 1.40 (*t*, 3H), 4.50 (*q*, 2H), 2.59 (*s*, 3H), and 7.38 (*s*, 1H).

Ethyl Thiazole-2-glyoxalate (2b). By a similar procedure, this was prepared from 2-bromothiazole (30 g, 0.183 mol); yield, 15.8 g (46.6%); bp 102—108 °C/0.6 mmHg; IR (liquid film) 1740 (C=O) and 1690 (C=O) cm^{-1}; NMR ($CDCl_3$, TMS) δ 1.42 (*t*, 3H), 4.44 (*q*, 2H), 7.92 (*d*, J=2.8 Hz, 1H), and 8.08 (*d*, J=2.8 Hz, 1H).

Ethyl α-Hydroxy-α-hydroxamino-4-methylthiazole-2-acetate (3a). A mixture of **2a** (6 g, 0.03 mol) and hydroxylamine hydrochloride (3.15 g, 0.045 mol) in methanol (15 ml) was cooled in an ice bath, and then a 2 M sodium hydroxide soluuion (17 ml) was slowly stirred in. After stirring for 6 h at 0 °C, the precipitate was collected by filtration; it yielded white crystals (5.2 g). An additional crop was obtained by the extraction of the filtrate with chloroform; total yield, 5.4 g (77.7%); mp 120—121 °C (from chloroform); IR (Nujol) 3150 (NH, OH) and 1720 (C=O) cm^{-1}. Found: C, 41.56; H, 5.22; N, 12.38%. Calcd for $C_8H_{12}N_2O_4S$: C, 41.37; H, 5.21; N, 12.06%.

Ethyl α-Oximino-4-methylthiazole-2-acetate (4a). A. From the Glyoxalate, 2a. A mixture of **2a** (2.6 g, 0.013 mol) and hydroxylamine hydrochloride (1.5 g, 0.0216 mol) in acetic acid (4 ml) was cooled in an ice bath, and then a 1 M sodium hydroxide solution (14 ml) was stirred in, drop by drop. After stirring overnight, the precipitate was collected by filtration. The pale yellow solid (2.43 g, 87%) thus obtained was chromatographed on silica gel. Elution with chloroform gave pale yellow prisms (1.5 g); mp 111—112 °C (from ether–petroleum ether); IR (KBr) 1709 (C=O)cm^{-1}. Found: C, 44.79; H, 4.74; N, 13.16%. Calcd for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.71; N, 13.08%.

Further elution with chloroform–methanol gave white needles (820 mg); mp 140—141 °C (from benzene–petroleum ether); IR (KBr) 1734 (C=O) cm^{-1}. Found: C, 44.99; H, 4.96; N, 13.04%. Calcd for $C_8H_{10}N_2O_3S$: C, 44.85; H, 4.71; N, 13.08%.

B. Isonitrosation of Ethyl 4-Methylthiazole-2-acetate (5a). Into an ice-cooled solution of **5a** (2.8 g, 0.015 mol) in acetic acid (4 ml), a solution of sodium nitrile (1.2 g, 0.0174 mol) in water (3 ml) was slowly stirred over a period of 30 min. After an additional 30 min, the mixture was diluted with water (10 ml) and then stirred for 2 h at 0 °C. The yellow precipitate was collected by filtration, washed with cold water, and dried *in vacuo*; yield, 2.3 g (71.2%). Recrystallization from ether–petroleum ether gave yellow prisms, which were identical with crystals (mp 111—112 °C) obtained by means of Method A (IR and NMR).

Ethyl α-Oximino-thiazole-2-acetate (4b). This was prepared from **2b** (1.85 g, 0.01 mol) according to the procedure (Method A) described for **4a**. The crude product was chromatographed on silica gel. Elution with chloroform gave pale yellow needles (537 mg); mp 58—59 °C (from ether–petroleum ether); IR (KBr) 1709 (C=O) cm^{-1}. Found: C, 42.33; H, 3.99; N, 14.19%. Calcd for $C_7H_8N_2O_3S$: C, 41.99; H, 4.02; N, 13.99%.

Further elution with chloroform–methanol gave white needles (139 mg); mp 121—122.5 °C (from ether–petroleum ether); IR (KBr) 1735 (C=O) cm^{-1}. Found: C, 42.07; H, 4.02; N, 14.20%. Calcd for $C_7H_8N_2O_3S$: C, 41.99; H, 4.02; N, 13.99%.

Ethyl α-Amino-4-methylthiazole-2-acetate (6a). Into an ice-cooled solution of **4a** (1.0 g, 4.66 mmol) in methanol (5 ml) and 40% formic acid (9 ml), zinc dust (1.0 g, 15.3 mmol) was stirred, portion by portion. The mixture was stirred at 5 °C for an additional 5 h, and then filtered. After the addition of 2 M hydrochloric acid (5 ml), the filtrate was evaporated *in vacuo*. The oily residue was dissolved in water (10 ml), neutralized with K_2CO_3, and extracted with chloroform. Drying (K_2CO_3) and evaporation of the chloroform *in vacuo* left 0.9 g of a pale-brown oil, pK_a 5.55 (in 50% ethanol), which showed one spot on tlc.

N-Phenylacetyl Derivative (7a). A solution of the crude **6a** (0.9 g) in chloroform (10 ml) was shaken with a 1 M sodium bicarbonate solution (20 ml), and then phenylacetyl chloride (900 mg, 5.8 mmol) was added gradually. After stirring for 24 h, the aqueous layer was extracted with chloroform. The combined organic layers were dried ($MgSO_4$) and evaporated *in vacuo*. The remaining sirup (1.5 g) was chromatographed on silica gel with chloroform to give **7a** as pale-brown crystals (1.2 g); mp 80—81 °C (from benzene); IR (Nujol) 3320 (NH), 1750 (C=O), and 1650 (CONH) cm^{-1}. Found: C, 60.59; H, 5.91; N, 8.66%. Calcd for $C_{16}H_{18}N_2O_3S$: C, 60.35; H, 5.70; N, 8.80%.

Hydrolysis of Ethyl α-Amino-4-methylthiazole-2-acetate (6a). Into an ice-cooled solution of the crude **6a** [prepared from **4a** (1.0 g, 4.66 mmol)] in methanol (20 ml), a 1 M sodium hydroxide solution (5.7 ml) was stirred, drop by drop. The mixture was stirred overnight at room temperature, and then evaporated *in vacuo*. The residue was dissolved in water (15 ml). The solution was washed with chloroform and cooled in an ice bath, and then 2 M hydrochloric acid was gradually added. When the pH of the solution reached 7, a vigorous gas evolution took place; stirring was continued at pH 6 for 30 min until the gas evolution ceased. The cold mixture was then washed with chloroform, saturated with K_2CO_3, and extracted with chloroform. The evaporation of the chloroform left the amine, **9a**, as a brown liquid.

This material was converted to the *N*-phenylacetyl derivative **10a** according to the procedure described for **7a**; yield, 0.6 g; mp 112—114 °C (from ether–petroleum ether); IR (Nujol) 3300 (NH) and 1650 (C=O) cm^{-1}. Found: C, 63.18; H, 5.61; N, 11.55%. Calcd or $C_{13}H_{14}N_2OS$: C, 63.38; H, 5.73; N, 11.37%.

Hydrolysis of Ethyl α-Amino-thiazole-2-acetate (6b). **6b**, prepared from **4b** (1.0 g, 5 mmol), was hydrolyzed in a manner similar to that described for **6a**. The resulting amine, **9b**, was converted to the *N*-phenylacetyl derivative, **10b** (yield, 540 mg); mp 102—104 °C (from benzene–petroleum ether); IR (Nujol) 3300 (NH) and 1640 (C=O) cm^{-1}. Found: C, 61.90; H, 5.06; N, 12.19%. Calcd for $C_{12}H_{12}N_2OS$: C, 62.04; H, 5.20; N, 12.05%.