

## N-Quaternary Compounds

### Part XI. The Synthesis of Dihydrothiazolo[3,2-a]pyridinium-8-oxide Derivatives from L-Cysteine

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L-(—)-8-Hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate has been synthesized from L-cysteine by acid catalyzed rearrangement of 4-carbomethoxy-2-(5-hydroxymethyl-2-furyl)thiazolidine or by a similar reaction between L-cysteine and 2,5-dimethoxy-2,5-dihydro-5-methylfurfural dimethyl acetal. The desmethyl analogue was optically inactive. An explanation is given.

In previous reports<sup>1,2</sup> we have discussed syntheses of the dihydrothiazolo[3,2-a]pyridinium-8-oxide derivatives. In particular it was shown that 8-hydroxy-5-methyldihydrothiazolo[3,2-a]pyridinium-3-carboxylate thus synthesized was the racemic equivalent of the levorotatory blue fluorescent substance isolated from liver hydrolysates.<sup>3</sup> In this report we describe the synthesis of this compound from L-cysteine.

The important intermediate in our planned synthesis was the highly reactive *cis*-1,4-diketo olefin derivative of thiazolidine (II). *cis* 1,4-Diketo alkenes are best obtained by acid catalysed ring opening of furan derivatives at the right oxidation level, a technique we have used in the syntheses of 6-methylpyridinium-3-oxides from amino acids.<sup>4</sup> The desired oxidation level in our first approach was arrived at by using a furan derivative carrying a hydroxyl group on the  $\alpha$ -carbon in the 5-side-chain. The methyl ester of cysteine and 5-hydroxymethylfurfural were condensed together in cold aqueous ethanol buffered at pH 5 as this was thought to give about optimal conditions for ylidene formation followed by thiol addition.

A new asymmetric center has been introduced at C-2 in the thiazolidine part of the molecule. However, this leads to no synthetic complication since the center is removed again during the aromatisation of VIII. The NMR spectrum in CDCl<sub>3</sub> showed that the two diastereomers (IV, R' = H) were formed in about equal amounts. Thus both the methine proton on the C-2 carbon in the thiazolidine ring and the *O*-methylene protons attached to the



The isolation of the desired component of the reaction product involved several steps. After removing the tarry products the aromatic constituents were extracted into aqueous phenol from the aqueous solution at pH 3.5. Around the isoelectric point the zwitterion is more soluble in the organic phase. Addition of ether to the phenol extracts separated out the water containing the zwitterion (III) from the phenol-ether phase. Other aromatic derivatives formed in the reaction including any decarboxylated derivative of III remained largely in the phenol-ether layer. The product thus obtained was further purified by passage through a column of DEAE-Sephadex A-25 in the amine form. Any remaining decarboxylated material was eluted with water while the zwitterion (III) was eluted with 0.01–0.10 N formic acid.

The optical rotation of IIIb (R=CH<sub>3</sub>) obtained from the 5-hydroxymethyl derivative (IV) was  $[\alpha]_D^{25} = -132^\circ$  (NaOH), in the second approach  $[\alpha]_D^{25} = -153^\circ$  (NaOH). The substance isolated from the liver hydrolysates<sup>3</sup> had  $[\alpha]_D = -130^\circ$  (NaOH). The postulated<sup>7</sup> L-configuration, as found by chemical degradation of the liver hydrolysate product (IIIb), is therefore confirmed.

The desmethyl derivative (IIIa, R=H) prepared under the same conditions as IIIb from L-cysteine *via* the 2,5-dimethoxy-2,5-dihydrofuran approach was totally inactive. Our explanation<sup>9</sup> for this is as follows: The methine proton on the asymmetric carbon is highly activated and therefore readily abstracted. The carbanion formed would tend to invert and becomes planar in the transition state. But in a planar or nearly planar state there will be steric interaction between the methyl group in IIIb (R=CH<sub>3</sub>) and the carboxylic acid group, and therefore the carbanion of this molecule is prevented from assuming a planar state. Thus the molecule is optically stable since it must be reprotonated from the same side as the proton was lost.

## EXPERIMENTAL

Paper chromatography or TLC on silica gel in the systems BuOH:EtOH:NH<sub>3</sub>:H<sub>2</sub>O (4:1:2:1) and BuOH:HOAc:H<sub>2</sub>O (100:22:50) has been used in this work.

*4-Carbomethoxy-2-(5-hydroxymethyl-2-furyl)thiazolidine (IV)*. L-Cysteine methyl ester hydrochloride (1.44 g, 0.008 mole), 5-hydroxymethylfurfural (1.00 g, 0.008 mole), and potassium acetate (0.84 g, 0.008 mole) were dissolved in 50% aqueous ethanol (14 ml). The solution was left in the cold for a week, some solid precipitate filtered off, the filtrate evaporated until most of the ethanol had been removed and the solid precipitate collected. The solid fractions were combined and recrystallised from ethanol-water; yield 1.60 g (90%), m.p. 80–81°. (Found: C 49.46; H 5.20; N 6.09. Calc. for C<sub>10</sub>H<sub>13</sub>NO<sub>4</sub>S: C 49.38; H 5.34; N 5.78).  $[\alpha]_D^{25} = -135^\circ$  (*c*=1.5 in MeOH).  $[\alpha]_{546}^{25} = -161^\circ$  (*c*=1.5 in MeOH).

*L-(-)-8-Hydroxy-5-methyl-dihydrothiazolo[3,2-*a*]pyridinium-3-carboxylate (IIIb)*. a) A solution of the above prepared 4-carbomethoxy-2-(5-hydroxymethyl-2-furyl)thiazolidine (30.0 g, 0.119 mole) in methanol was added dropwise over 1 h with stirring to N HCl (700 ml) under reflux. The reaction mixture was kept at 100° for 48 h, the tarry product removed by filtration, the filtrate concentrated to about 75 ml, the pH adjusted to 3.5 and filtered again to remove insoluble material. The filtrate was then extracted with 90% phenol (3 × 50 ml), the phenol extracts washed with water (50 ml), ether (600 ml) added to the phenol extracts, the aqueous layer separated and the phenol-ether layer extracted repeatedly with water (in all 160 ml). The combined water extracts were washed with ether (50 ml) to remove any phenol, concentrated to about 25 ml and applied on a DEAE-Sephadex A 25 column (2.5 cm × 30 cm) in the amine form. Water was passed through the column until no more material was eluted as shown by TLC chromatog-

raphy. The desired material was eluted with 0.005 N formic acid. Evaporation and crystallisation from water furnished 1.0 g (4 %) of a solid, m.p. 153–154°, which had the same properties as the product isolated from liver hydrolysates<sup>3</sup> and the previously synthesized<sup>1,2</sup> racemic modification.  $[\alpha]_D^{25} = -132^\circ$  ( $c = 0.6$  in 0.1 N NaOH),  $[\alpha]_{546}^{25} = -145^\circ$  ( $c = 0.6$  in 0.1 N NaOH).

b) 2,5-Dimethoxy-2,5-dihydro-5-methylfurfural dimethyl acetal (59.0 g, 0.27 mole), prepared from 5-methylfurfural and methyl orthoformate, was added dropwise with stirring over 90 min to a boiling solution of L-cysteine (32.6 g, 0.27 mole) in N HCl (1700 ml). The brown solution was then concentrated to about 800 ml, a little charcoal added, the stirring continued for 1 h, filtered and the pH adjusted to 3.5 with 2 N NaOH. The resultant solution was extracted with 90 % phenol ( $3 \times 160$  ml), the phenol extracts washed with water (30 ml), ether (1500 ml) added, the aqueous layer separated, the phenol-ether layer extracted with water ( $3 \times 100$  ml), the combined aqueous extracts washed with ether ( $3 \times 50$  ml) and freeze-dried. The product thus obtained was further purified by chromatography on DEAE-Sephadex as described under a). The yield was 3.0 g (6 %), m.p. 163–165°, of a chromatographically homogeneous product. Recrystallisation from water gave yellowish white crystals, m.p. 160–161°;  $[\alpha]_D^{25} = -153^\circ$  ( $c = 1.7$  in 0.1 N NaOH aq.).

8-Hydroxydihydrothiazolo[3,2-a]pyridinium-3-carboxylate (IIIa). 2,5-Dimethoxy-2,5-dihydrofurfural dimethyl acetal was prepared from furfural dimethyl acetal by electrolytic methoxylation.<sup>8</sup> The furan derivative was then reacted with cysteine as described above under b).

The yield in this reaction was 5 % of a product, m.p. 191–192°, whose properties were the same as for the title compound previously synthesized.<sup>1,2</sup> This compound in 0.1 N NaOH aq. was optically inactive.

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