N-Quaternary Compounds

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

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In previous reports\textsuperscript{1,2} we have discussed syntheses of the dihydrothiazolo[3,2-a]pyridinium-8-oxide derivatives. In particular it was shown that 8-hydroxy-5-methylidihydrothiazolo[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.

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furan ring resonated as pairs at 4.27 and 4.47 $\tau$ and at 5.48 and 5.52 $\tau$ of about equal intensities, respectively.

The thiazolidine (IV) was subjected to acid catalysed rearrangement in N HCl. The mechanism in this reaction would be protonation with loss of water (V), nucleophilic attack by water on the cation (VI) followed by rupture of the furan ring and cyclisation (II). The mechanism is similar to that postulated in the pyridinium-3-oxide formation. The yield of the dihydrothiazolo [3,2-$\alpha$]pyridinium derivative in this reaction was 4% isolated material. The low yield obtained is mainly due to the instability of the thiazolidine ring in acid solution. A number of highly reactive intermediates are formed leading to a very complex and tarry product mixture. In the strongly water absorbing polyphosphoric acid none of the desired compound (III) was formed which would appear to support the postulated involvement of water in the opening of the furan ring (VI).

In our next approach the correct oxidation level of the furan ring was achieved by electrolytic oxidation of furfural dimethylacetal derivatives. It was difficult to effect selective hydrolysis of the acetal group in the cyclic ketal-acetal derivative (IX) since this molecule was very acid labile. Compounds X and XI were not isolated but are postulated intermediates in the reaction. The experiments were carried out by adding the 2,5-dimethoxy-2,5-dihydrofurfuryl derivative (IX) dropwise to a boiling N HCl solution of cysteine. The yield of the isolated material was about 6%. The mechanism postulated is the same as in the similar pyridinium-3-oxide formation.

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=CH₃) 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 had $[\alpha]_D = -130^\circ$ (NaOH). The postulated $\alpha$-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 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=CH₃) 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:NH₃:H₂O (4:1:2:1) and BuOH:HOAc:H₂O (160:22:50) 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 5.29; N 6.09. Calc. for C₇H₁₃NO₃S: C 49.38; H 5.34; N 5.78). $[\alpha]_D^{38} = -135^\circ$ (c=1.5 in MeOH). $[\alpha]_{D,1}^{62} = -161^\circ$ (c=1.5 in MeOH).

L-(-)-3-Hydroxy-5-methylidihydrothiazolo[3,2-a]pyridinium-3-carboxylate (IIIb). a) A solution of the above prepared 4-carbamethoxy-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 x 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 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 x 30 cm) in the amine form. Water was passed through the column until no more material was eluted as shown by TLC chromato-

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 and the previously synthesized\textsuperscript{1,4} racemic modification. [\(\alpha\)]\textsubscript{D} = \(-132°\) (c = 0.6 in 0.1 N NaOH), [\(\alpha\)]\textsubscript{D} = \(-145°\) (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 x 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 x 100 ml), the combined aqueous extracts washed with ether (3 x 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°; [\(\alpha\)]\textsubscript{D} = \(-153°\) (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. 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.\textsuperscript{1,2} This compound in 0.1 N NaOH aq. was optically inactive.

REFERENCES


Received November 29, 1968.