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# PREPARATION OF A MONO HEMI-KETAL OF A THIOSULFONATE ESTER

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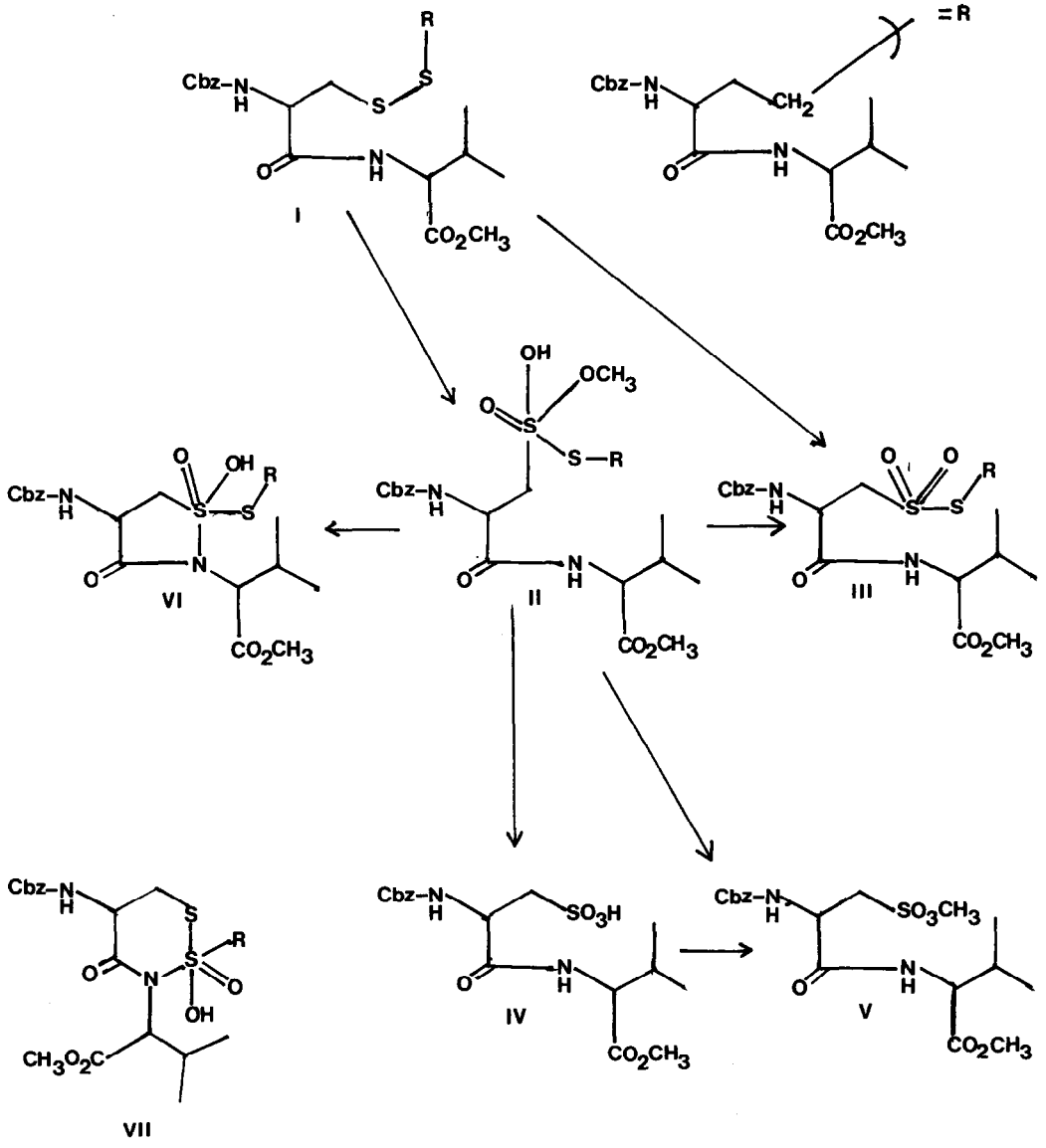
In the course of a study designed to explore potentially viable biosynthetic routes to the β-lactam antibiotics, we desired to prepare α-oxidized N-acyl cystinyl-valine dipeptides. Several reports have recently appeared in the literature describing the methoxylation of various penicillin and cephalosporin derivatives at the 6 and 7 position respectively.[1] In these transformations, t-butyl hypochlorite has been successfully employed as a selective oxidant when sulfur was present in the form of sulfide, sulfoxide, sulfone, and thiolactone. No reported examples in the previous investigations have included molecular sulfur present as a disulfide. We now report some divergent results obtained by employing similar oxidative means on N,N'-dicarbobenzyloxy-L-cystinyl-L-valine methyl ester (I).[2]

Treatment of I with lithium methoxide and t-butyl hypochlorite in THF at -20° led rapidly to two new products in good yield. After preparative tlc (ϕH/EtOAc, elute 3x), the major product was isolated, crystallized ($CHCl_3$/$Et_2O$/Hexane), and identified as II [m.p. 105-107°; pmr ($CDCl_3$) δ 0.87 (d, 6H, J - 4Hz), 0.93 (d, 6H, J = 4Hz), 2.20 (m, 2H), 3.40 (m, 4H), 3.76 (S, 6H), 3.80 (S, 3H), 4.52 (d of d, 2H, J = 8Hz), 4.80 (m, 2H), 5.19 (S, 4H), 6.52 (d, 1H, d = 8Hz), 6.60 (d, 1H, J = 8Hz), 7.24 (m, 2H), 7.40 (S, 10H); $\nu_{max}^{CHCl_3}$ 3395, 2990, 2950, 1735, 1715, 1680, 1499, 1295, 1240, 1180, 960; cmr ($CDCl_3$) 17.40, 18.68, 30.70, 49.26, 50.23, 51.89, 54.63, 56.98, 57.37, 67.12, 127.88, 128.26, 135.78, 155.60, 155.89, 169.46, 171.52].[3,4] The minor component (slightly higher $R_f$) although not crystalline, was similar in all respects to II and likely only differs in the configuration at hexavalent sulfur. A more suitable and efficient approach for large scale preparation of II involved performing the oxidation with t-butyl hypochlorite in absolute methanol at -80°. The same mixture of diasteromeric materials were obtained in > 95% yield. If preparative tlc was not employed both isomers could be induced to co-crystallize. When co-crystallized material, in the solid state stood at 26° for several days, tlc and nmr revealed complete conversion to one isomer (lower $R_f$, major initial product).

In addition to the spectral data, confirmatory evidence for structure II was derived from the following transformations. Substance II was inert to thermolysis (80°) in dry benzene for extended periods. However, in the presence of a catalytic amount of p-toluenesulfonic acid, the aforementioned conditions caused a quantitative conversion of II to thiosulfonate ester III [m.p. 129-130°; pmr ($CDCl_3$) δ0.99 (d, 12H, 5 = 7Hz), 2.18 (m, 2H), 3.73 (S, 6H), 3.76 (broad m, 4H), 4.55 (d of d, 2H, J = 9,9Hz), 5.10 (broad m, 2H),


Cbz–N H
R
S
S
O
N H
CO2CH3
I
=R
CH2
OH
OCH3
S–R
II
III
VI
VII
IV
V
SO3H
SO3CH3
CH3O2C
OH

5.15 (S, 4H), 6.22 (d, 2H, J = 8Hz), 7.34 (S, 5H), 7.61 (broad m, 2H); $\nu_{max}^{CHCl_3}$ 3410, 3325, 2950, 1738, 1718, 1675, 1497, 1340, 1130, 1049].[3] The physical data for III were completely in accord with a separate sample of III prepared by direct oxidation of I (m-chloroperbenzoic acid, $CH_2Cl_2$, 26°). Acidic aqueous hydrolysis of II (THF/HCl, 12 hr) afforded sulfonic acid IV [pmr (dmso-$d_6$) $\delta$0.92 (d, 6H, J = 7Hz), 2.18 (m, 1H), 2.95 (m, 2H), 3.76 (S, 3H), 4.31 (m, 1H), 4.48 (m, 1H), 5.20 (S, 2H), 7.59 (S, 5H), 8.39 (m, 1H), 8.60 (m, 1H)]. Due to its insoluble nature, substance IV was esterified ($CH_2N_2/Et_2O/CHCl_3$) and characterized as the methyl sulfonate ester (V) [m.p. 90-92°; m/e 430 ($M^+$); pmr ($CDCl_3$) $\delta$ 0.84 (d, 3H, J = 8Hz), 0.88 (d, 3H, J = 8Hz), 2.18 (m, 1H), 3.78 (S, 3H), 3.78 (d, 2H, J = 6Hz), 3.88 (S, 3H), 4.52 (d of d, 1H, J = 8, 8 Hz), 4.76 (m, 1H), 5.20 (S, 2H), 6.14 (d, 1H, J = 8Hz), 7.16 (d, 1H, J = 10Hz), 7.44 (S, 5H); $\nu_{max}^{CHCl_3}$ 3420, 2960, 1735, 1718 (sh), 1675, 1498, 1368, 1210, 1178, 1048, 995; cmr ($CDCl_3$) 17.75, 18.84, 31.03, 49.58, 51.05, 52.23, 56.52, 57.89, 67.47, 75.66, 78.88, 128.21, 128.59, 136.03, 156.02, 168.83, 171.86].[3] Compound V could also be directly derived in high yield from I by treatment with excess oxidant (t-BuO Cl, MeOH, -80°). Likewise, II gave V under similar conditions.

Base catalyzed elimination of methanol was efficiently effected in substance II by heating under reflux in benzene containing some anhydrous potassium carbonate. The resultant, non-crystalline product, presumably a mixture of diastereoisomers, is tentatively assigned structure VI [pmr ($CDCl_3$) $\delta$ 0.90 (d, 6H, J = 7Hz), 1.04 (d, 6H, J = 7Hz), 2.20 (m, 2H), 3.60 (6nm, 4H), 3.80 (S, 6H), 4.60 (d, 1H, J = 10Hz), 5.04 (m, 2H), 5.16 (S, 2H), 5.20 (S, 2H), 5.60 (m, 1H), 7.44 (s, 10H); $\nu_{max}^{CHCl_3}$ 3400, 3965, 1735, 1720, 1675 (sh), 1500, 1205, 1100]. The $\alpha$-valyl proton on one side of the dimer is clearly present in the nmr spectra as a doublet, indicating substitution has occurred on amido nitrogen. Structure VII however cannot be ruled out at this time. Substance VI was inert to $CH_2N_2/Et_2O$ as was II. The only identifiable product of reduction of II with $NaBH_4$/EtOH/0° was Cbz-cysteinyl valine methyl ester.

In summary: substance II, an unusual mono hemi-ketal derivative of a thiosulfonate ester has been synthesized by oxidation of a peptide disulfide (II), and its structure proven by spectroscopic and chemical means.[5]

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2. Prepared by coupling with N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline. B. Belleau and G. Malek, J. Amer. Chem. Soc., 90, 1652 (1968).

3. Satisfactory elemental analysis was obtained for this compound.

4. CMR spectra taken in $CDCl_3$. Chemical shifts are expressed as parts per million downfield from TMS.

5. The preparation of this functionality in a cyclic peptide disulfide has been achieved and will be discussed in a future paper.