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ß-SULTAMS II: SYNTHESIS OF TRI-, TETRA- AND PENTAMETHYLENE-1,2-THIAZETIDINE 1,1-DIOXIDES

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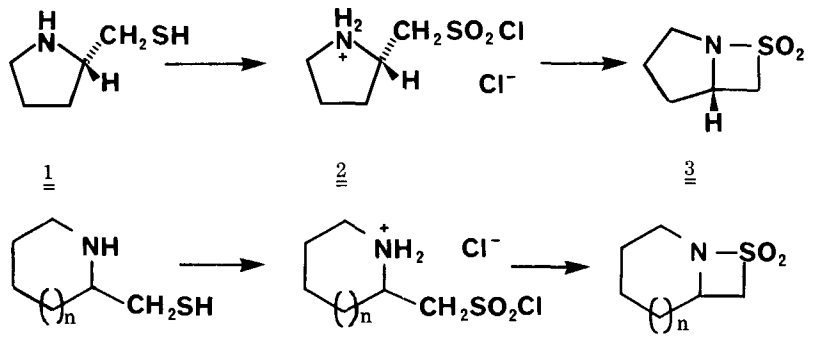
Abstract: The unsubstituted parent structure of sulfone analogs of penicillin and its higher homologs are obtained by base promoted cyclization of cyclic ß-amino-ethanesulfonyl chlorides.

Chemical reactivity and molecular geometry are two fundamental factors contributing to the antimicrobial potency of ß-lactam antibiotics. Substitution of the carbonyl group of the ß-lactam ring by sulfone group results in ß-sultams [1] which are sometimes more reactive than corresponding ß-lactams. The synthesis of biologically not active sulfone analog of penicillin is recently published by Koller et al.[2]. This prompts us to report in this communication on the synthesis of the parent structure 3 of sulfone analog penicillin and of its higher homologs 6 and 9.

(S)-2-Pyrrolidinylmethanethiol (1) was prepared from (S)-proline by reduction with $LiAlH_4$, bromination with PBr_3/ HBr and reaction with thiourea[3,4]. Treatment of its hydrochloride with an excess of chlorine in carbon tetrachloride/ ethanol/ water gave rise to a high yield (84%) of crystalline (S)-2-pyrrolidinylmethanesulfonyl chloride hydrochloride (2) (m.p. 126°C, acetone). The structure of 2 was assigned on the basis of its spectral data as well as by its cyclization with ammonia in chloroform at 0°C producing crystalline (S)-2,3-trimethylene-1,2-thiazetidine 1,1-dioxide (3) (m.p. 56°C, carbon tetrachloride) in 60% yield. The structure of this material was unambiguously confirmed by hydrolysis to the parent sulfonic acid and by its elementary analysis and spectroscopic data[5].
Reaction of (R,S)-2-piperidylmethanethiol (4)[4] with chlorine under similar conditions gave the crystalline (R,S)-2-piperidylmethanesulfonyl chloride

hydrochloride (5) (m.p. 134-135°C, acetone; yield 98%). Treatment of 5 with ammonia in chloroform resulted in formation of the expected (R,S)-2,3-tetramethylene-1,2-thiazetidine 1,1-dioxide (6) (m.p. 57°C, carbon tetrachloride)[5] in 82% yield. We also prepared (R,S)-2-perhydroazepinylmethanethiol (7) (m.p. 60°C, subl.; yield 63%) from (R,S)-2-perhydroazepinylmethanol[6] in three steps by a similar procedure as used for the synthesis of 1. It was converted into the parent sulfonyl chloride hydrochloride 8 (m.p. 121°C, acetone; yield 83%) which could be cyclisized in chloroform with ammonia at 0°C yielding (R,S)-2,3-pentamethylene-1,2-thiazetidine 1,1-dioxide (9)[5] (m.p. 49-50°C, carbon tetrachloride; yield 76%) as colourless crystals.



1 2 3

n=1 4 5 6

n=2 7 8 9

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References and Notes:

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5 all new compounds gave correct elemental analyses; 3: $[\alpha]_D^{21} = -8{,}1$ ($CHCl_3$), SO_2: 1320, 1195 cm^{-1}. 6: SO_2: 1310, 1180 cm^{-1}. 9: SO_2: 1310, 1190 cm^{-1} (KBr)

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