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SYNTHESIS AND PROPERTIES OF ß-SULTAMS

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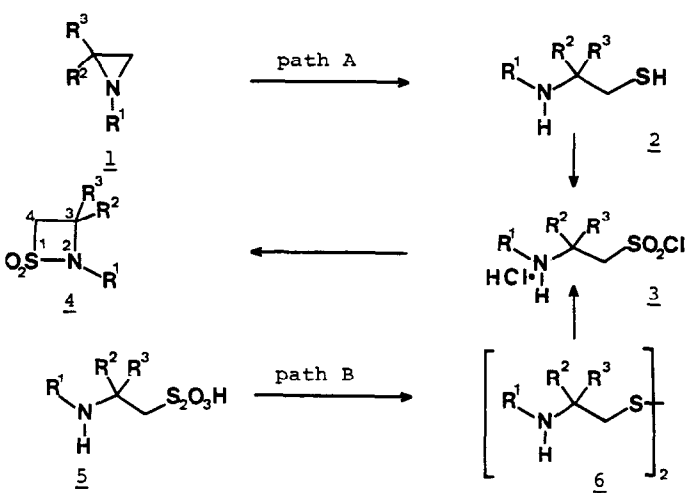
Abstract: ß-Sultams substituted in 2- and 3-position including bicyclic ß-sultams were prepared and some of their reactions are reported.

In contrast to ß-lactams little attention has previously been paid to ß-sultams.[1] Scanning the literature[2] chlorination of amino-mercaptans (2) and -disulfides (6) in the presence of alcohol to sulfochlorides (3) (CCl_4/EtOH/Cl_2/+10°) followed by cyclisation to ß-sultams (4) (Et_3N, CH_2Cl_2, 0°) proved to be the most versatile method for the preparation of this biologically interesting class of compounds. The amino-mercaptans (2) were obtained from aziridines (1) with H_2S (path A)[3], and the disulfides (6) from aminothiosulfates (5) with iodine (path B).[4]

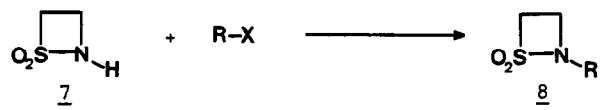


The ß-sultams thus prepared are listed in table 1.[4b,5] Since the corresponding thiosulfate was obtained from natural S-prolin the bicyclic ß-sultam (4h) is optically active and has the same absolute configuration at the bridgehead as the ß-lactam antibiotics.[7]

Table 1

	R^1	R^2	R^3	yield	path
4a	H	CH_3	H	69 %	A
4b	H	CH_3	CH_3	74 %	A
4c	CH_2CH_2OH	H	H	26 %	A
4d	$CH_2CH_2CO_2C_2H_5$	H	H	96 %	A
4e	$CH_2CH_2C_6H_5$	H	H	95 %	A
4f	$CH_2CH_2CH_3$	H	H	44 %	A
4g	CH_2CH_2CN	H	H	75 %	B
4h		$-CH_2CH_2CH_2-$	H	78 %	B
4i		$-CH_2CH_2CH_2CH_2-$	H	63 %	B

The chemical properties of ß-sultams are in many respects comparable with those of ß-lactams. For example, it was possible to alkylate the ß-sultam (7) according to a phase-transfer method which had been developed for ß-lactams.[8] Activated alkyl halides such as allylbromide and benzylbromide reacted quickly. With α-bromoacetic esters, which are partially hydrolyzed under these conditions the yield tended to be lower, and secondary alkyl halides such as isopropyl iodide were hardly converted. The ß-sultams (8) which were obtained by phase-transfer alkylation are listed in table 2.



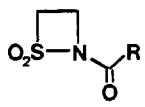
7 8

table 2

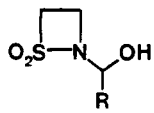
	R	X	yield
8a	CH_3	J	50 %
8b	$n\text{-}C_6H_{13}$	Br	76 %
8c	$-CH_2CH{=}CH_2$	Br	72 %
8d	$-CH_2C_6H_5$	Br	76 %
8e	$i\text{-}C_3H_7$	J	3 %
8f	$-CH_2CO_2CH_2C_6H_5$	Br	47 %
8g	$-CH_2CO_2C_2H_5$	Br	31 %
8h	$-CH_2CO_2CH_3$	Br	22 %

Since acylation of the ß-sultam (7) in 2-position causes destabilisation of the 4-membered ring the yield of isolated products tended to be low. A good yield of (10a) was obtained by the reaction of (7) with methylchloroformate ($ClCO_2CH_3/Et_3N/CH_2Cl_2/0°$). Small amounts of (10b) and (10c) were prepared by acylation of the sodium salt (7) with acetyl chloride and benzoyl chloride respectively. The compounds (10a-c) decomposed at room temperature but it was possible to store them in a freezer for several weeks.

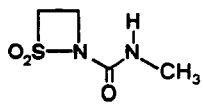
The β-sultam (7) reacted with paraformaldehyde ($MeOH/Et_3N/(CH_2O)_n$) to (12a) and with glyoxylic acid ($H_2O/KHCO_3/(OH)_2CHCO_2H$) to (12b). Conversion of (7) with methylisocyanate ($CH_2Cl_2/CH_3NCO/Et_3N$) gave the urea derivative (13). Silylation of (7) to (14) readily occurred with chlorotrimethyl-silane ($CH_2Cl_2/CH_3SiCl/Et_3N/5$-$20°$).



10a R=OCH_3 82 %
10b R=CH_3 27 %
10c R=Ph 2 %

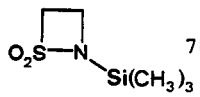


12a R=H 100 %
12b R=CO_2K 57 %



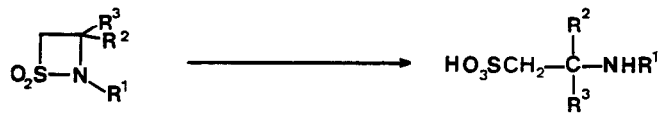
87 %

13



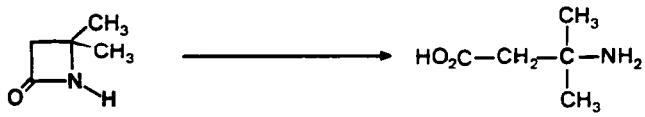
78 %

14



7 $R^1=R^2=R^3=H$
8a $R^1=CH_3$, $R^2=R^3=H$
4b $R^1=H$, $R^2=R^3=CH_3$

15a $R^1=R^2=R^3=H$
15b $R^1=CH_3$, $R^2=R^3=H$
15c $R^1=H$, $R^2=R^3=CH_3$



16

17

4i

18

In order to find out more about the stability of ß-sultams we investigated the ring opening of (7), (8a) and (4b) to (15a), (15b) and (15c) in aqueous solutions and compared the ß-sultam (8a) with the ß-lactam (16).[9] At pH 13 the half life of (8a) was 45 min. The ring opening of (7) was slower by a factor of 8 and the ring opening of (4b) slower by a factor of 300.[9] The ß-lactam (16) was converted only half as fast as (4b) at pH 13. The difference in stability between ß-sultams and ß-lactams was even more drastic in acidic solutions. The half life of (4b) at pH 2.3 is 12 min wheras (16) remained unchanged in an aqueous solution at this pH for more than 24 h. Compound (16) was readily converted to (17) at 90° with an equivalent amount of HCl. Like the ß-lactam (16) the investigated ß-sultams were stable towards amines in aprotic solvents at room temperature. The bicyclic ß-sultam (4i) could only be converted to (18) with benzylamine at temperatures above 140°. The synthesis of a bicyclic ß-sultam whose structure is related to that of penicillin will be reported shortly.[10]

1) According to the JUPAC nomenclature the systematic name for ß-sultam is 1,2-thiazetidin-1,1-dioxide

2a) H.Baganz, G.Dransch, Chem.Ber. 93, 784 (1960).
2b) B.J.R.Nicolaus, E.Bellasio, E.Testa, Helv.Chim.Acta 45, 717 (1962).
2c) G.M.Atkins, E.M.Burgess, J.Am.Chem.Soc. 89, 2502 (1967) and 90, 4744 (1968).
2d) O.Tsuge and S.Iwanami, Bull.Chem.Soc.Jpn. 43, 3543 (1970).
2e) A.Le Berre, J.Petit, Tetrahedron Lett. 3, 213 (1972).
2f) T.Nagai, T.Shingaki, M.Inagaki, T.Ohshima, Bull.Chem.Soc.Jpn. 52, 1102 (1979).

3a) H.Bestian, German Patent 710.267 (1941).
3b) H.Bestian, Ann.Chem. 566, 210 (1950).
3c) E.J.Mills, M.T.Bogert, J.Am.Chem.Soc. 62, 1173 (1943).

4a) D.Rosenthal, G.Brandrup, K.H.Davis, Jr., M.E.Wall, J.Org.Chem. 30, 3689 (1965).
4b) J.R.Piper, T.P.Johnston, J.Org.Chem. 28, 981 (1963).

5) All compounds gave spectral data (IR, ^{1}H and ^{13}C NMR, and MS) in accordance with their structures. The unusual α-carbon deshielding in four-membered ring sulfonyl compounds[6] was also revealed in ß-sultams by ^{13}C NMR. $\delta(CDCl_3)$ (7) 61.2; (4a) 66.4; (4b) 70.8 and (4h) 64.7 ppm.

6) E.Bock, A.A.Bazzi, J.B.Lambert, S.M.Wharry, K.K.Andersen, D.C.Ditmer, B.H.Patwardhan, D.J.H.Smith, J.Org.Chem. 45, 4807 (1980).

7) (4h): m.p. 51-52°, $[\alpha]_D$=2.2° (in methanol c=1).

8) D.Reuschling, H.Pietsch, A.Linkies, Tetrahedron Lett. 615 (1978).

9) The reactions were monitered by NMR at 30°.

10) F.Cavagna, W.Koller, A.Linkies, H.Rehling, D.Reuschling, Angew.Chem.Suppl., 1982, 1201-1212

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