Journal of Sulfur Chemistry
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713926081

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Jure J. Herak[a]
[a] PLIVA Research Institute, Chemical Synthesis & Technology, Zagreb, Croatia

To cite this Article Herak, Jure J.(1996) '4-Oxoazetidine-2-sulfinic Acid and Its Derivatives', Journal of Sulfur Chemistry, 18: 2, 379 — 392
To link to this Article: DOI: 10.1080/01961779608047901
URL: http://dx.doi.org/10.1080/01961779608047901

Sulfur Reports, Volume 18, pp. 379–392
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4-OXOAZETIDINE-2-SULFINIC ACID AND ITS DERIVATIVES

JURE J. HERAK

PLIVA Research Institute, Chemical Synthesis & Technology, Prilaz baruna Filipovića 25, HR-10000 Zagreb, Croatia

(Received October 9, 1995)

Stereochemically pure 4-oxoazetidine-2-sulfinates and -sulfinamides are readily epimerized in the presence of hydrogen chloride and at the same time transformed by sulfinate-sulfinamide interconversion. Under similar reaction conditions they give 2-azacepham sulfoxides by stereocontrolled intramolecular cyclization. All these reactions accrue *via* equilibrated mixtures of 4-oxoazetidine-2-sulfinyl chlorides as intermediates the presence of which has been confirmed by chemical transformations. The equilibrium ratio between the epimers of the sulfinyl chlorides determinates the enantioselectivity of the processes. The absolute configuration of enantiomerically pure ($2R,S_S$)-1-(1-benzylcarbamoyl-2-methylprop-1-enyl)-4-oxoazetidine-2-sulfinic acid as hydrolysis product of earlier compounds has been confirmed by a single crystal X-ray analysis.

Key words: 2-Azacephams, epimerization, 4-oxoazetidine-2-sulfinic acid.

CONTENTS

1. INTRODUCTION

The discovery of thienamycin, a β-lactam antibiotic with resistance to β-lactamase, clavulanic acid as a powerful β-lactamase inactivator, and other related compounds which inhibit human leukocyte elastase (HLE) has stimulated a growing interest in the chemical synthesis of nonclassical or differently substituted classical bicyclic β-lactam species.

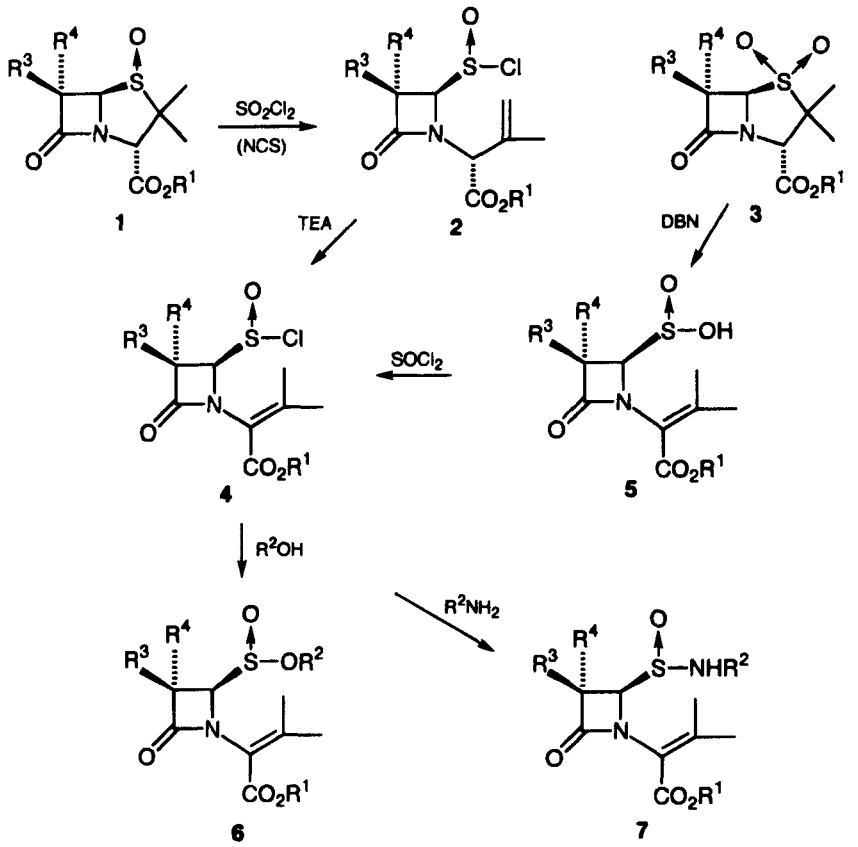
The synthesis usually begins with the construction of a monocyclic β-lactam with an appropriate substituent for a second ring closure. There are numerous methods in the literature for the synthesis of monocyclic β-lactams but the formation of a suitably substituted 2-azetidinone usually requires many steps. The development of short and highly stereocontrolled methods retains a primary importance in β-lactam chemistry.

The penicillin nucleus, because of its low cost and chirality remains the substrate of choice. Methods for the selective cleavage of non-β-lactam-associated bonds of bicyclic penicillanic acid derivatives are of special interest. The products of such reactions could serve as useful intermediates if only the thiazolidine ring degradation could be controlled in an appropriate way. Among these 4-oxoazetidine-2-sulfinic acid derivatives are of interest for the preparation of potential active monobactams, and for the subsequent synthesis of novel fused β-lactams. In order to provide such syntheses and to define the stereochemical consequences their absolute configurations should be known. Therefore the first task is to prepare certain 4-oxoazetidine-2-sulfinic acid derivatives and to determine the configuration on the sulfur atom of the two theoretically possible epimers. 3-Unsubstituted 4-oxoazetidine-2-sulfinates and -sulfinamides with only two asymmetric centers are a good choice.

Compared to sulfoxides, the epimerization and stereochemical transformations of optically active sulfinic acid derivatives has been little investigated, despite their importance in organic sulfur stereochemistry as the main source of optically active sulfoxides.[1,2] It is completely unknown in the β-lactam field.

2. THE SYNTHESIS OF 4-OXOAZETIDINE-2-SULFINATES AND -SULFINAMIDES

There are some reports in the literature on the preparation of 4-oxoazetidine-2-sulfinates **6**[3-5] and -sulfinamides **7**[6-8] according to Scheme 1. The precursors in these reactions are sulfinyl chlorides **4**, prepared from the corresponding penicillanate sulfoxides **1** and sul-



SCHEME 1

furyl chloride or *N*-chlorosuccinimide[6,7] or by the action of thionyl chloride on the corresponding sulfinic acid **5**.[3,4]

The 3-unsubstituted 4-oxoazetidine-2-sulfinyl chlorides **8–9** upon reaction with alcohols yielded the sulfinates **12–15** as diastereoisomeric pairs separable by silica gel column chromatography (Fig. 1). The chiral nature of sulfinate groups has been demonstrated by ^{1}H NMR spectroscopy.[4]

Since the cleavage of the thiazolidine dioxide ring of the penicillanates **10–11** with 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) has been shown to be stereochemically controlled,[9–12] it follows that the individual compounds should be epimeric at sulfur.

Sulfinates with a free carboxyl group **16** were prepared by removal of the ester protecting group with aluminum trichloride-anisole.[13] In these cases it was possible to isolate the carboxylic acids although they were thermally unstable. Treatment of the carboxylic acids **16** with ethyl chloroformate and triethylamine afforded the mixed anhydrides **17** which are stable enough ^{1}H NMR spectroscopic study.[9]

Similarly by the action of amines on the sulfinyl chlorides **8–9** the sulfinamides **18–21**, the free acids **22** and the mixed anhydrides **23** could be prepared (Fig. 1).

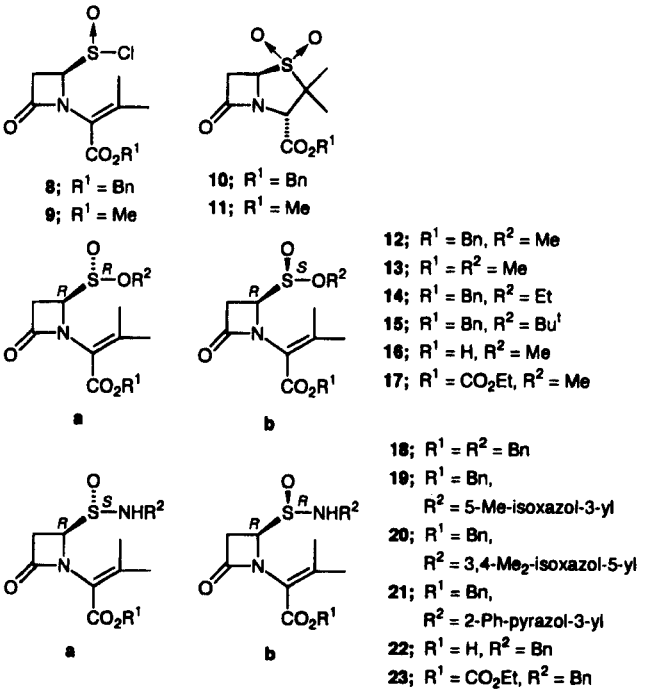


FIGURE 1

3. THE REACTION OF 4-OXOAZETIDINE-2-SULFINYL CHLORIDE WITH 2-MERCAPTOBENZOTHIAZOLE

Using the general procedure for the preparation of sulfinates,[4] starting with the sulfinyl chloride **8** and after treatment with 2-mercaptobenzothiazole,[14] instead of the expected thiosulfinate **28**, the corresponding oxoazetidinyl benzothiazolyl disulfide **26** and bis (benzothiazolyl) disulfide **30**[15] were isolated. Under the same conditions the sulfinyl chloride **9** was transformed into **27** rather than into **29**. The identity of the disulfides **26** and **27** was confirmed by independent synthesis from **24** and **25** (Fig. 2).[16]

4. ^{1}H NMR DETERMINATION OF THE CONFIGURATION OF 4-OXOAZETIDINE-2-SULFINATES AND -SULFINAMIDES

The ^{1}H NMR spectra of the sulfinates **12–17** and the sulfinamides **18–23** (Scheme 2) were measured and the characteristic chemical shifts of hydrogen atoms in position 3 and of the methyl hydrogen atoms are summarized in Table 1. The spectra were assigned on the basis of expected shifts and proton coupling constants.[11,17–18]

There were several well defined differences in the proton chemical shifts for the **a** and **b** compounds. Thus **b** compared with **a** exhibit upfield shifts (Δ_1 values) for the 3β hydrogen

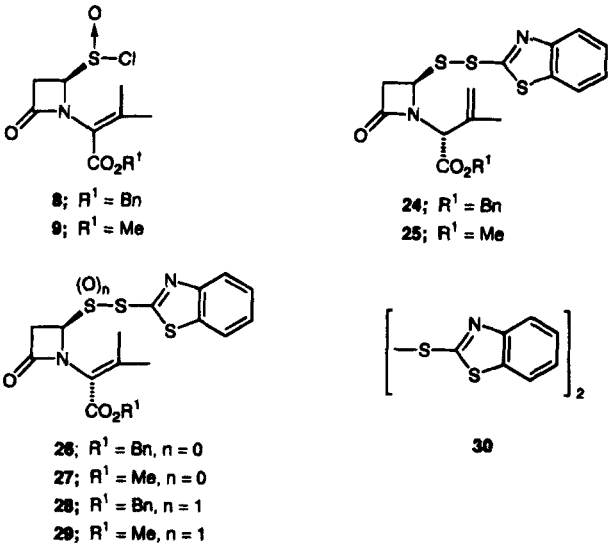


FIGURE 2

TABLE 1 ^{1}H NMR Anisotropy shifts induced by the S → O bond in sulfinates and sulfinamides

Compound	3β-H δ	3β-H (Δ_1)[b]	3α-H δ	3α-H (Δ_2)[b]	Me^1 δ	Me^1 (Δ_3)[b]	Me^2 δ	Me^2 (Δ_4)[b]	Δ_3–Δ_4
12a	3.43		3.09		2.24		2.00		
12b (a–b)	3.10	(+0.33)	3.10	(–0.01)	2.24	(0.00)	2.07	(–0.07)	+0.07
13a	4.49		3.19		2.24		2.00		
13b (a–b)	3.18	(+0.31)	3.21	(–0.02)	2.23	(+0.01)	2.06	(–0.06	+0.07
14a	3.42		3.11		2.24		2.00		
14b (a–b)	3.09	(+0.33)	3.09	(+0.02)	2.23	(+0.01)	2.07	(–0.07)	+0.08
15a	3.40		3.13		2.20	I	.98		
15b (a–b)	3.02	(+0.38)	3.04	(+0.09)	2.22	(–0.02)	2.10	(–0.12)	+0.10
16a	3.45		3.17		2.25		2.02		
16b (a–b)	3.17	(+0.28)	3.21	(–0.04)	2.28	(–0.03)	2.12	(–0.10)	+0.07
17a	3.54		3.24		2.31		2.08		
17b (a–b)	3.15	(+0.39)	3.20	(+0.04)	2.28	(+0.03)	2.16	(–0.08)	+0.11
18a	3.36		3.14		2.24		1.94		
18b (a–b)	2.94	(+0.42)	3.16	(–0.02)	2.21	(+0.03)	2.08	(–0.14)	+0.17
19a	3.51		3.31		2.20		1.98		
19b (a–b)	3.07	(+0.44)	3.26	(+0.05)	2.24	(–0.04)	2.09	(–011)	+0.07
20a	3.29		3.23		2.20		1.97		
20b (a–b)	3.16	(+0.13)	3.29	(–0.06)	2.24	(–0.04)	2.10	(–0.13)	+0.09
21a	3.07		2.96		2.16		1.93		
21b (a–b)	2.80	(+0.27)	2.92	(+0.04)	2.13	(+0.03)	2.01	(–0.08)	+0.11
22a	3.20		3.34		2.20		1.89		
22b (a–b)	3.00	(+0.20)	3.39	(–0.05)	2.16	(+0.04)	2.01	(–0.12)	+0.16
23a	3.34		3.84		2.27		2.00		
23b (a–b)	3.08	(+0.26)	3.26	(+0.58)	2.28	(–0.01)	2.16	(–0.16)	+0.15

[b]Positive and negative signs indicate upfield and downfield shifts, respectively, resulting from the stated process.

atoms and downfield shifts (Δ_4 values) for the higher-field methyl hydrogen atoms (Me^2). The data also show that the differences in chemical shifts for the hydrogen atoms in the two methyl groups are more pronounced in the **a** than in the **b** compounds [(Δ_3–Δ_4) values].

An X-ray structure analysis of a single crystal prepared from a diastereoisomeric mixture of the sulfinates **13a/13b** (the epimer with the chemical shift of the 3β hydrogen atom at lower field) established the absolute configuration $2R,R_S$ for **13a**. It was reasonable to conclude that all diastereoisomers with chemical shifts similar to those in **13a** possess the absolute configuration **a** and that diastereoisomers with higher field values for the 3β hydrogen atom possess the absolute configuration **b**.[9]

An X-ray structure analysis of stereoisomer **18a**[19] confirmed applicability of this rule to the sulfinamide series.

The conformations of **13a** and **18a** are similar (Fig. 3).

Since X-ray studies are carried out in the solid state, it is assumed that the same conformation is maintained in solution. The chemical shifts of the 3β hydrogen atoms are expected to be influenced by shielding of the environment around a sulfoxide bond.[20] In compounds **13a** and **18a** due to free rotation about the C-S bond the oxygen and the sulfur atom of the sulfinyl group are able to lie close to the 3β hydrogen atoms. Consequently, the 3β hydrogen atoms are strongly deshielded and the corresponding signals in the ^1H NMR spectra show downfield shifts.

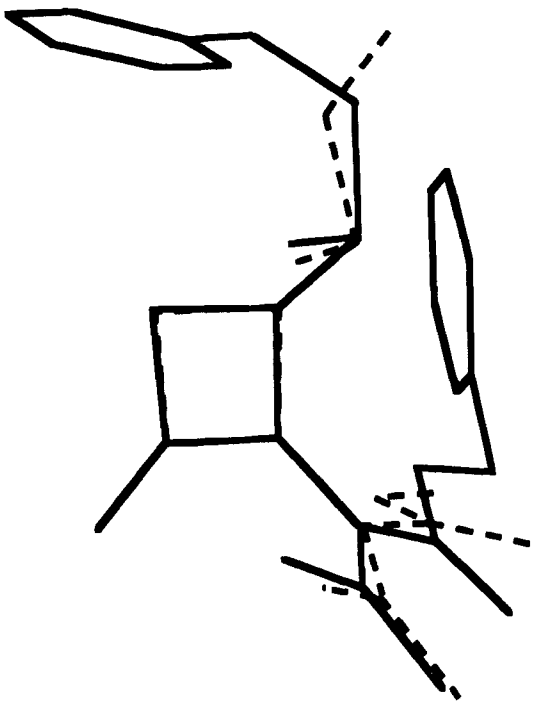


FIGURE 3 OVERLAP drawing of the **13a** (dashed line) and **18a** (solid line) molecules.

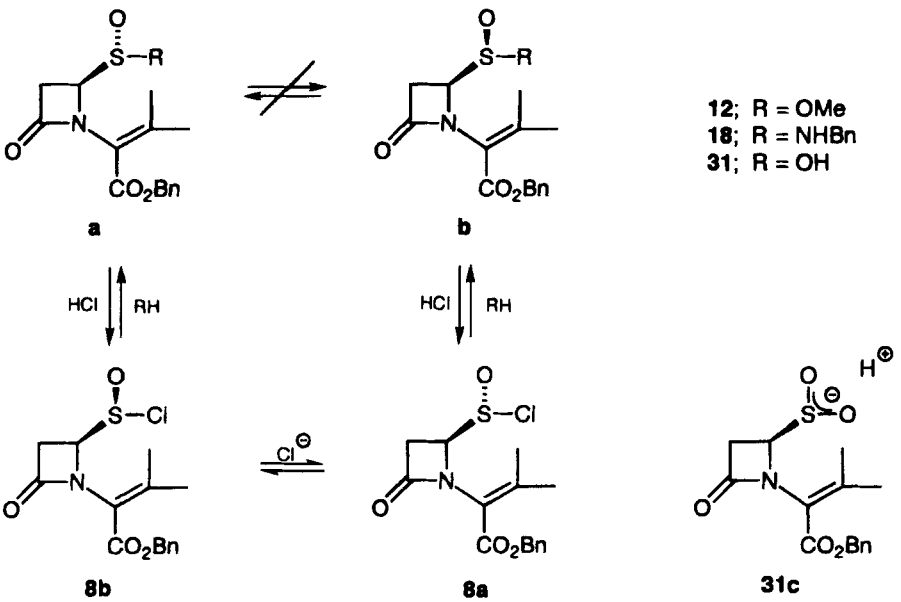
5. STEREOCONTROLLED INTERCONVERSION OF 4-OXOAZETIDINE-2-SULFINIC ACID AND ITS DERIVATIVES

After preparation and separation of enantiomerically pure diastereoisomers of certain 3-unsubstituted 4-oxoazetidine-2-sulfinates and -sulfinamides it was possible to study their transformations by ^{1}H NMR spectroscopy.

It was found that the enantiomerically pure methyl sulfinates **12a** or **12b** and the *N*-benzylsulfinamides **18a** or **18b** are hydrolyzed in strong hydrochloric acid solution and readily epimerized in the presence of anhydrous hydrogen chloride, giving diastereoisomers in the ratio of 2:3 regardless of the starting diastereoisomer. These results imply the formation of a sulfinyl chloride **8a/8b** as the actual intermediate, according to Scheme 2.[21]

Although attempts at the isolation and characterization of these very reactive intermediates from the reaction mixture failed, their presence was confirmed by chemical transformations. The sulfinyl chlorides **8a** and **8b** could be easily converted with water to the sulfinic acid **31**. After the addition of methanol or benzylamine **8a** and **8b** were transformed into a diastereoisomeric mixture of the sulfinates **12a/12b** and the sulfinamides **18a/18b** respectively. Consequently, 4-oxoazetidine-2-sulfinic acids, their sulfinates and sulfinamides can be easily transformed into each other.

The formation of a diastereoisomeric mixture of the sulfinyl chlorides **8a** and **8b** as intermediates, prepared from sulfinic acids, sulfinates or sulfinamides can be either the



SCHEME 2

straightforward result of chloride ion attack on the sulfur of the already epimerized starting compound, or can accrue by later epimerization of the sulfinyl chloride. The sulfinic acid can epimerize by fast proton exchange between **31a** and **31b** *via* the achiral sulfinic acid anion **31c**. The formation of the corresponding methyl sulfone in a short-time reaction of methyl iodide with the sodium salt of the sulfinic acid indicates such a possibility.[22] The sulfinates and sulfinamides could not be epimerized in this way.

The fact that the diastereoisomers **a:b** are obtained by the interconversion sulfinate → sulfinamide in the diastereoisomeric ratio 2:3 regardless of the starting diastereoisomer suggests that epimerization is the result of rapid chloride anion exchange at sulfur between the two epimers **8a** and **8b**. This conclusion is supported by the observation that each isolated epimer of the sulfinates **12** or the sulfinamides **18** when subjected to thermal treatment fails to give the corresponding epimeric mixture. Similarly, action of methanol on the sulfinamides **18** or of benzylamine on the sulfinates **12** does not result in any interconversion in the absence of hydrogen chloride. These results are in agreement with the earlier observation that some acid-catalyzed hydrolyses of sulfinic acid derivatives are accelerated by addition of halide ions.[23-24]

Finally, some published information regarding the racemization of sulfinates[25] and sulfoxides[26] in the presence of hydrogen chloride assumes an equilibrium mixture of sulfinyl chlorides as intermediate.

6. ASYMMETRIC SYNTHESES OF 2-AZACEPHAM SULFOXIDES

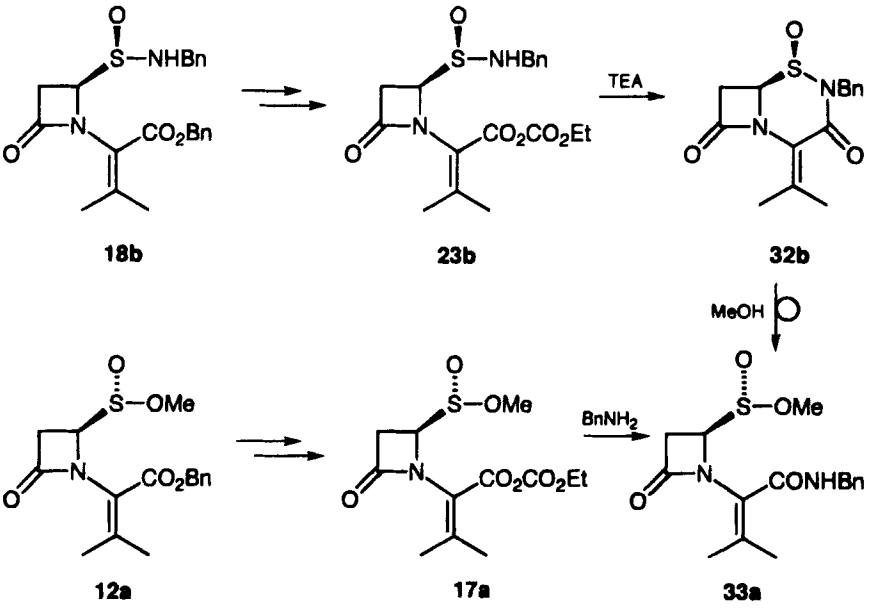
6.1. *Cyclization with a Sulfinamide Group as Nucleophile*

Based on the results that 4-oxoazetidine-2-sulfonamides can be transformed by intramolecular cyclization into the new anhydro-2-azacepham 1,1-dioxides[8] it is possible to use 4-oxoazetidine-2-sulfinamides as precursors (by stereoselective cyclization) to 2-azacepham 1-oxides.[3]

The starting 4-oxoazetidine-2-sulfinamide **18b**, enantiomerically pure, was transformed into the mixed anhydride **23b** by removal of the ester protecting group,[13] followed by the action of ethyl chloroformate in the presence of triethylamine according to Scheme 3. The purification of the mixed anhydride from the reaction mixture failed because of its sensitivity to silica gel and polar solvents, but its formation was observed by ^{1}H NMR analysis of the crude product.

The use of bases such as triethylamine led to cyclization of the mixed anhydride **23b** and formation of the bicyclic compound **32b**. The structure of the new compound was deduced from the spectroscopic data and additionally confirmed by X-ray crystallographic analysis.[27]

Although **32b** could be purified by careful crystallization, it was very unstable. Treatment with methanol resulted in opening of the heterocyclic ring *via* nucleophilic attack on the sulfur to give the methyl sulfinate **33a**. Nucleophilic opening of the ring took place with inversion of the configuration at sulfur, which was confirmed by chemical transformations. Thus, enantiomerically pure **33a** was also obtained by the action of benzylamine on the mixed anhydride **17a**, which was prepared from the methyl sulfinate **12a** by deprotection of the benzyl ester group, followed by activation of the carboxyl group with ethyl chloroformate.[27]



SCHEME 3

The stereo- and regiocontrolled transformation of sulfinamide **18b** into the sulfinates **33a** involves the migration of an amino group from a sulfur to a carbon atom. The substituted 2-azacepham 1-oxide **32** proves to be a convenient and powerful intermediate for new functionalized, well-defined chiral monocyclic β-lactams and a useful precursor for novel 2-azacephams.

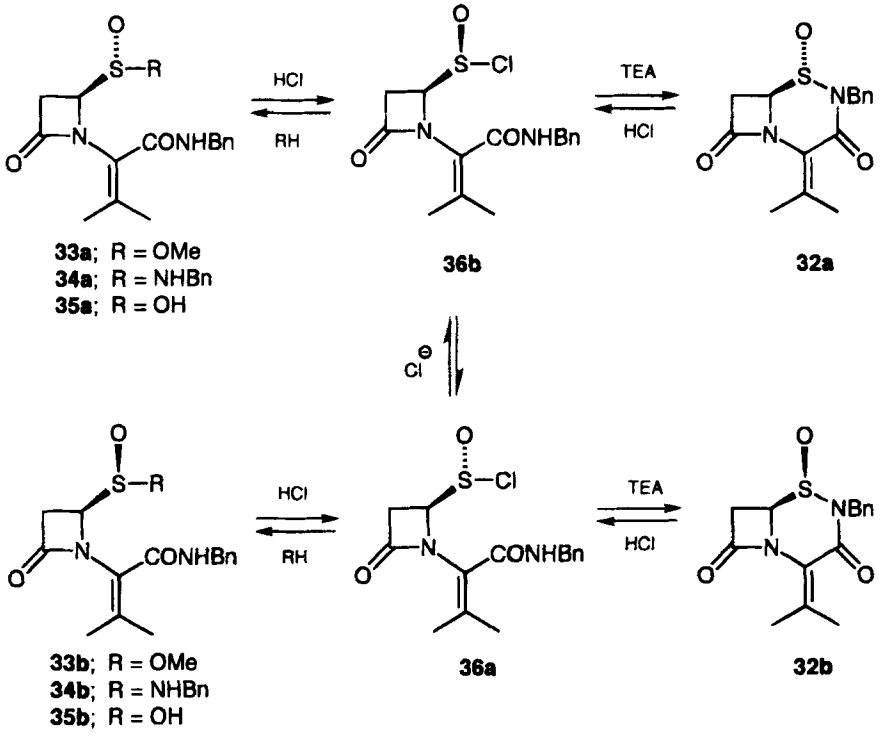
Although diastereoisomerically pure **32b** was obtained this procedure has several disadvantages. The preparation of the mixed anhydride **23b** requires several steps and the crude product is unstable in the presence of silica gel and polar solvents. In addition, during this synthetic sequence, the cleavage of the S-N bound causes destruction of the chiral sulfinamide group and the final overall yield is poor.

6.2. *Cyclization with a Carboxamide Group as Nucleophile*

The use of carbamoyl-sulfinyl chlorides in the key step could lead directly to 2-azacephams **32**.

The knowledge that sulfinyl chlorides **8** are formed in the sulfinate → sulfinamide interconversion[21] enables the use of sulfinic acids or their derivatives as starting compounds for a cyclization.

The sulfinates **33a** or **33b** upon reaction with hydrogen chloride in dry dichloromethane gave a reaction mixture which upon evaporation of the solvent and treatment with triethylamine resulted in the formation of the azacepham **32b** (Scheme 4), contaminated by a small amount of its diastereoisomer **32a** (detectable in the reaction mixture by TLC). From the reaction mixture the diastereoisomerically pure azacepham **32b** (40%) and the starting non-racemic sulfinate **33a** or **33b**, respectively, (30%) were isolated by column chromatography.



SCHEME 4

The reaction of the sulfinamides **34a** or **34b**, better precursors for the generation of sulfinyl chlorides under the same conditions, led to the formation of **32b** as a single β-lactam product in 60% yield.[28]

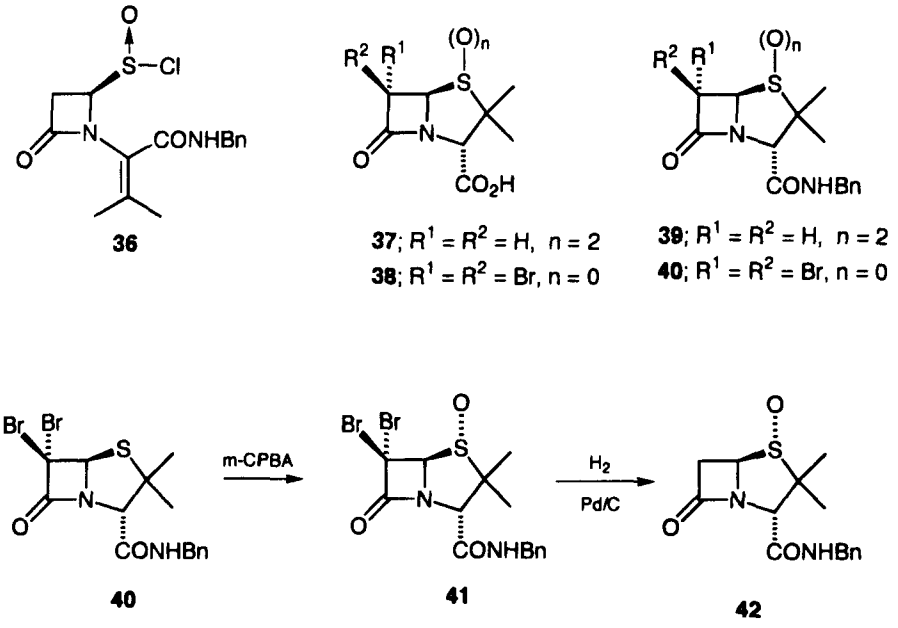
Several attempts to isolate the azacepham **32a** were unsuccessful. This failure was rationalized by the observed instability of the final azacepham **32a**, leading to numerous non-β-lactam compounds under the reaction conditions used for the intramolecular cyclization. At any rate the azacepham **32a** was less stable than **32b**. A similar distinction in the stability between two sulfur diastereoisomers of some other bicyclic sulfinates has been reported earlier.[29]

By analogy[21] this result is due to the fact that an equilibrium mixture of the sulfinyl chlorides **36a/36b** is formed by opening of the thiadiazine ring *via* nucleophilic attack of chloride anion on the sulfur atom.

The azacepham **32b** upon reaction with hydrogen chloride in dry dichloromethane solution, followed by treatment of the non-volatile residue with methanol or benzylamine, also gives a diastereoisomeric mixture of the sulfinates **33a** and **33b** and the sulfinamides **34a** and **34b**, respectively, with predominance of the diastereoisomer **b**.

6.3 *Rearrangement of Penicillamides*

The preparation of the sulfinyl chloride **36** as a suitable precursor for cyclization to an azacepham directly from the bicyclic penicillanic structure has also been investigated. The penicillamides **39–42** were thus prepared according to Scheme 5.



SCHEME 5

The penicillamides **39** and **40** were obtained from the corresponding carboxylic acids **37** and **38** upon addition of ethyl chloroformate, followed by benzylamine. Sulfide **40** upon oxidation with *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane yielded the sulfoxide **41**,[30] which after hydrogenolysis in the presence of 10% Pd-C catalyst gave the sulfoxide **42**. In a convenient and efficient method for the preparation of 4-oxoazetidine-2-sulfinic acids[22] the starting sulfone **39** remained unchanged by DBN and, after a longer reaction time, gave only traces of the sulfinic acid **35**. On the other hand, the sulfoxide **42** in its reaction with *N*-chlorosuccinimide according to a well-established methodology for the preparation of sulfinyl chlorides[7] gave numerous non-β-lactam products.

7. PREPARATION AND DETERMINATION OF THE ABSOLUTE CONFIGURATION OF (2*R*,*S*S)-1-(1-BENZYLCARBAMOYL-2-METHYLPROP-1-ENYL)-4-OXOAZETIDINE-2-SULFINIC ACID

The azacepham **32b** was first treated with anhydrous hydrogen chloride and then with water, or with strong aqueous hydrochloric acid to form the corresponding sulfinic acid **35** in moderate yield. The latter was characterized by its physical and spectroscopic properties. The sulfinic acid **35** could also be obtained from the corresponding sulfinates **33** or sulfinamides **34** under the reaction conditions shown in Scheme 4.

However the ^{1}H NMR spectrum of the sulfinic acid **35** in $CDCl_3$ solution showed achiral behavior around the sulfur atom, and a single crystal of the chiral sulfinic acid was prepared by crystallization from diethyl ether. Its X-ray crystallographic analysis firmly established the 2*R*,*S*S absolute configuration **35b** (Fig. 4).[28]

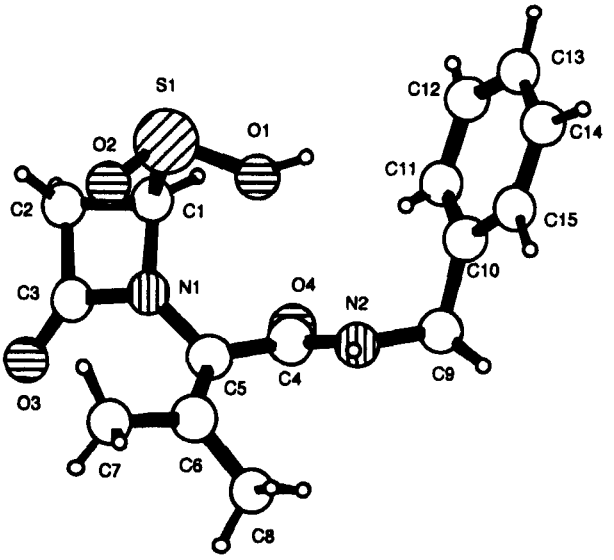


FIGURE 4 Absolute configuration of **35b**.

This behavior implies that the near tetrahedral configuration around the sulfur atom in the sulfinic acid is sufficiently stable in the solid state and that the two diastereoisomeric structures **35a** and **35b** (Scheme 4) should be present. On the other hand in solution the sulfinic acid is achiral for all practical purposes.

Generally, the crystal structures of a number of salts, complexes and other derivatives of sulfinic acids have been determined for some time, but the crystal structure of a sulfinic acid is known only in two cases.[31-32] In one of them[32] methanesulfinic acid molecules are joined to one another by hydrogen bonds in infinite spiral chains along a 2_1 screw axis parallel to *c*. Similar molecular linking in a helix along a 4_1 screw axis is noticed in 4-oxoazetidine-2-sulfinic acid **35b** (Fig. 5).

8. CONCLUSION

4-Oxoazetidine-2-sulfinic acids derivatives are very convenient starting materials for the preparation of potentially active monobactams, and for the subsequent synthesis of novel fused β-lactams. In order to allow such syntheses and to define the stereochemical consequences their absolute configurations should be known.

This review represents a study involving the preparation and structure determination of certain 4-oxoazetidine-2-sulfinic acids and their derivatives on the basis of ^{1}H NMR data confirmed by X-ray structure analysis. The reaction conditions for the epimerization and the stereocontrolled transformation of sulfinates and sulfinamides are also presented as well as their intramolecular cyclization to azacepham systems. All these reactions accrue *via* equilibrium mixtures of 4-oxoazetidine-2-sulfinyl chlorides as intermediates the presence of which was confirmed by chemical transformations. The results presented in this review

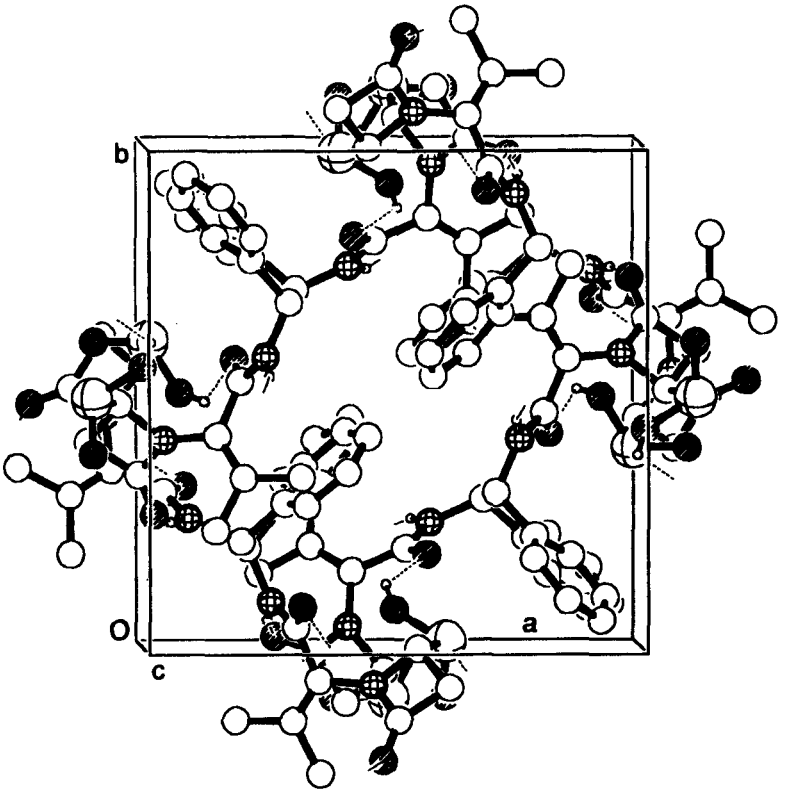


FIGURE 5 Cystal structure of **35b**.

suggest further stereocontrolled synthetic applications of these compounds in the field of β-lactams.

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