CHEMICAL STUDIES ON THE TRANSFORMATION OF PENICILLINS - I: SYNTHESIS OF CYCLIC DISULFIDES AND THIOSULFINATES RELATED TO ASPARAGUSIC ACID

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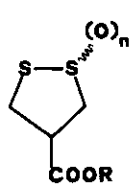
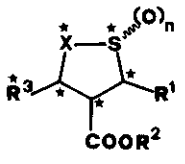
Abstract - The synthesis of cyclic disulfides and thiosulfinates related to Asparagusic acid from penicillin sulfoxides are described.

In connection with our synthetic program on immunomodulating disulfides 1a and thiosulfinates 1b[2a] related to Asparagusic acid 1c[2b], we have initiated studies in the preparation of various substituted analogs of the general structure A. Availability of these derivatives might provide insight into the understanding of the mode of action as well as structure-activity relationships of this interesting class of compounds. In addition, we are intrigued by the possibility of preparing such compounds from readily available starting materials of type B[3], which is derived from 6-aminopenicillanic acid (6-APA). Herein we report some of our preliminary results.

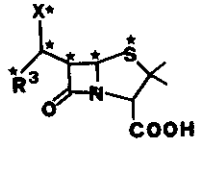


1a n = 0
1b n = 1
1c n = 0, R = H



A

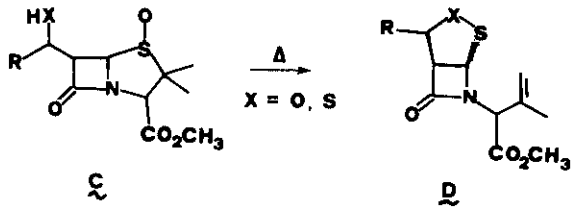
X = O, S



B

Our strategy was based on the Morin reaction[4a] in which a penicillin sulfoxide is thermolysed and undergoes a "retro-ene" reaction to give a sulfinic acid, which could then be captured by an internal or external nucleophile (or electrophile) to give new penams and cephams structures. One important application of this process is the trapping of the sulfenic acid with mercaptans to form disulfides[4b].

We envision that by subjecting 6-substituted penicillin sulfoxides of type C to similar thermolytic conditions, we could obtain bycyclic β-lactams[5] of type D, which should enable us to further elaborate into our desired products (Scheme I).

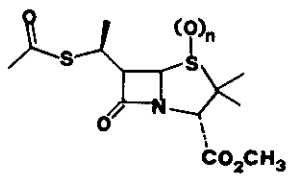


C D

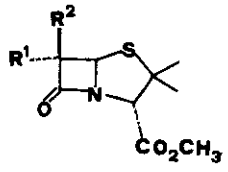
Scheme I

6-[1-Acetylthioethyl]penicillanates 2b/c appeared to be attractive targets because their synthesis should be straightforward from the corresponding hydroxyethyl analogs, which are important intermediates in the synthesis of penems and carbapenems[6]. Thus, the acetylthioethyl-sulfide 2a[7] was obtained in 73 % yield (based on recovery of starting material) from 3a[3] using the Mitsunobu/Volante conditions[8] [2 equiv triphenylphosphine, 2 equiv diethylazodicarboxylate (DEAD), 1.2 equiv thioacetic acid]. In contrast, the corresponding (S)-isomer 3c[3] failed to give any substitution product[9].

Oxidation of 2a with sodium metaperiodate, (THF/water/2-propanol) gave an easily separable mixture of the isomeric sulfoxides 2b and 2c (31 % and 53 % respectively), together with only 4 % of the sulfone 2d. We thought that the deprotection to generate the free mercaptan function is not necessary if the acetyl group could be removed after the cyclization.



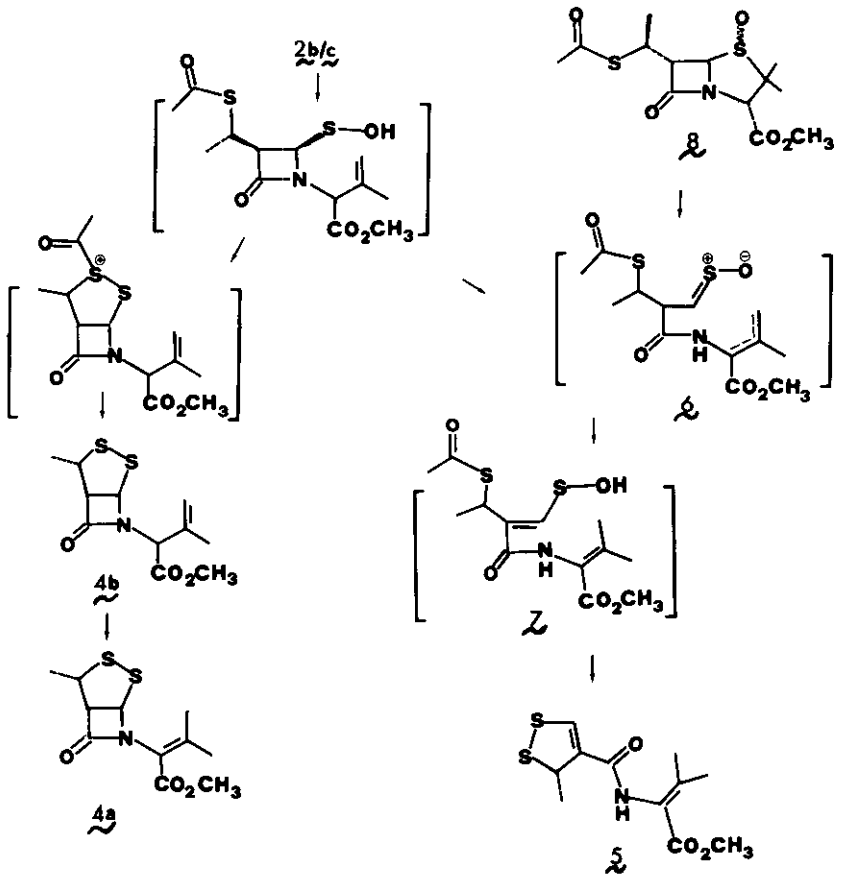
2a n = 0
b n = 1, (α)
c n = 1, (β)
d n = 2



3a R^1 = H R^2 = OH
b R^1 = OH R^2 = H
c R^1 = H R^2 = HO

Indeed, heating a mixture of either the α- or β-sulfoxide with imidazole (2.1 equiv) in dioxane (3h/100°C) gave the bicyclic β-lactam 4a in 20 % yield, together with 8 % of the unstable unsaturated disulfide 5 (Scheme II). On the other hand, refluxing a solution of 2b or 2c in toluene (20 h) was sufficient to produce the unconjugated disulfide 4b in 40 % yield. However, the most expedient method for the preparation of 4b was heating a solution of the sulfoxide in dioxane (120°C, 16 h, 1 g/10 ml, 78 %) with approximately two equiv of water. Disulfide 4b was then isomerized into 4a quantitatively by stirring a methylene chloride solution of 4b for 1 h, in the presence of a catalytic amount of triethylamine.

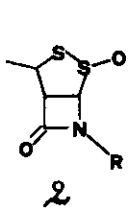
Scheme II



The formation of disulfide 5 in slightly basic medium[10] could best be explained by the intermediacy of the sulfine 6[11] (Scheme II), which underwent subsequent isomerization to the unsaturated sulfenic acid 7. Taking this into account, we prepared analogously the trans-6(S)-[1(S)-acetylthioethyl] sulfoxide 8 from 3b[3]. Treating 8 under similar conditions (120°C, dioxane, 1.2 equiv imidazole), disulfide 5 was obtained as the exclusive product, although in low yield (18 %)[12]. The competing cyclization reaction as observed before in the cis-isomer could not have taken place in the latter case.

4a was converted to a mixture of the thiosulfinates 9a/10a by sodium metaperiodate oxidation and they were isolated in 20 % and 40 % yields after column chromatography. Ozonolysis of 9a/10a (dichloromethane/-78°C), followed by reductive work-up (dimethylsulfide, methanol/triethylamine) gave the N-unsubstituted derivatives 9b/10b in 50 % and 30 % yields respectively[13]. Alternatively ozonlysis of 4a (dichloromethane/-78°C) followed by the usual reductive work-up afforded directly 9b/10b in 61 % overall yield, and in the ratio of 3:1, with preference for the isomer 9b. It is interesting to note that the α-sulfoxides are formed predominately[14], and is probably due to preferential attack of the oxidants from the sterically less hindered side.

These bicyclic thiosulfinates are stable crystalline compounds and the β-lactam nitrogen behave similarly to the other mono and bicyclic azetidinones[15]. More noteworthy is the reaction with benzyl chloroformate (dichloromethane/triethylamine/20°C) to give the N-carbobenzyloxy derivatives 9c/10c. In spite of their seemingly high reactivity (ν_{CO}: 1840 cm^{-1}), they could be isolated in moderate yield by silica gel chromatography (49 % and 37 % from 9b and 10b respectively). The corresponding monocyclic amides 11 (57 %) and 12 (45 %) were obtained directly from 9b and 10b respectively when the reaction was performed in the presence of one equiv of cyclohexylmethylamine.



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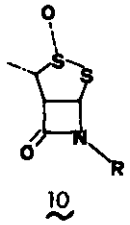

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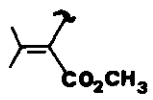
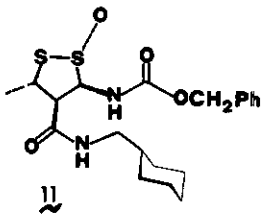
a R = 

b R = H

c R = CO_2CH_2Ph



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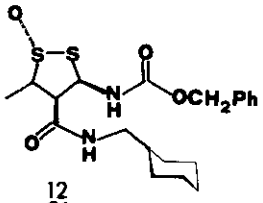

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The biological properties of these derivatives are being evaluated and will be reported in due course.

ACKNOWLEDGEMENT

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NOTES AND REFERENCES

1. Present address: Chemical Development Pharma/Agro, Sandoz AG, Basel, Switzerland.
2. a) Belgian Patent Application, BE-900854 A, 1983. b) H. Yanagawa, T. Kato, and Y. Kitahara, Tetrahedron Lett., 1973, 14, 1073, and references cited therein.
3. V.M. Girijavallabhan, A.K. Ganguly, S.W. McCombie, P. Pinto and R. Rizvi, Tetrahedron Lett., 1981, 22, 3485.
4. a) R.B. Morin, B.G. Jackson, R.A. Mueller, R.E. Lavagnino, M.B. Scanlon and S.L. Andrews, J.Am.Chem.Soc., 1983, 85, 1896. b) T. Kamiya, T. Teraji, Y. Saito and M. Hashimoto, Tetrahedron Lett., 1973, 14, 3001.
5. Intramolecular trapping of the sulfenic acid intermediate by sulfur nucleophiles has been described. See for example: H. Tanida, R. Muneyuki and T. Tsushima, Tetrahedron Lett., 1975, 16, 3063.

6. H. Fliri and C.P. Mak, J.Org.Chem., 1985, 50, 3438.

7. Selected physical data:

2a) mp 116-118°C, $[\alpha]^{20}_D$ +266.5° (c 0.89, CH_3OH)

2b) Nmr($CDCl_3$) δ 1.33 (s, 3), 1.60 (d, 3, J = 6.5 Hz), 1.62 (s, 3), 2.40 (s, 3), 3.82 (s, 3), 3.87 (dd, 1, J = 12.5, 4 Hz), 3.91 (dq, 1, J= 12.5, 6.5 Hz), 4.35 (s, 1), 4.60 (d, 1, J = 4 Hz).

2c) Nmr($CDCl_3$) δ 1.21 (s, 3), 1.56 (d, 3, J = 7 Hz), 1.68 (s, 3), 2.35 (s, 3), 3.81 (s, 3), 4.02 (dd, 1, J= 12.5, 5 Hz), 4.21 (dq, 1, J = 12.5, 7 Hz), 4.59 (s, 1), 4.69 (d, 1, J = 5 Hz).

4a. Nmr($CDCl_3$) δ 1.37 (d, 3, J = 7.5 Hz), 2.10 (s, 3), 2.27 (s, 3) 3.79 (s, 3), 3.92 (dq, 1, J = 7.5, 0.8 Hz), 3.98 (dd, 1, J = 4, 0.8 Hz), 5.83 (d, 1, J = 4 Hz).

4b. Nmr($CDCl_3$) δ 1.34 (d, 3, J = 7 Hz), 1.91 (br s, 3), 3.78 (s, 3), 3.87 (dq, 1, J = 7, 0.8 Hz), 3.91 (dd, 1, J = 3.5, 0.8 Hz), 4.86 (s, 1), 4.97 (br s, 1), 5.15 (br d, 1, J = 1 Hz), 5.86 (d, 1, J = 3.5 Hz).

5. Uv(CH_3OH) λ max: 220 (14210), 267 (sh, 5790), 311 (5580), 376 (1580), nmr($CDCl_3$) δ 1.58 (d, 3, J = 6.8 Hz), 1.86 (s, 3), 2.18 (d, 3, J = 0.5 Hz), 3.66 (s, 3), 4.80 (dq, 1, J = 6.8, 0.5 Hz), 6.97 (br, 1), 7.12 (d, 1, J = 0.5 Hz).

9a. Nmr($CDCl_3$) δ 1.73 (d, 3, J = 7 Hz), 1.91 (s, 3), 2.24 (s, 3), 3.82 (s, 3), 4.38 (dq, 1, J = 7, 0.8 Hz), 4.60 (dd, 1, J = 3.5, 0.8 Hz), 5.97 (d, 1, J = 3.5 Hz).

10a. Nmr($CDCl_3$) δ 1.44 (d, 3, J = 7 Hz), 2.29 (s, 3), 2.45 (s, 3), 4.00 (s, 3), 4.51 (dq, 1, J = 7, 0.8 Hz), 4.76 (dd, 1, J = 4.5, 0.8 Hz), 6.57 (d, 1, J = 4.5 Hz).

9b. Nmr($CDCl_3$) δ 1.70 (d, 3, J = 7.2 Hz), 4.32 (dd, 1, J = 7.2, 0.8 Hz), 4.58 (dd, 1, J = 3, 0.8 Hz), 5.62 (d, 1, J = 3 Hz), 6.50 (br, 1).

10b. Nmr($CDCl_3$) δ 1.22 (d, 3, J = 7.2 Hz), 4.36 (dd, 1, J = 7.2, 0.8 Hz), 4.52 (dd, 1, J = 3.8, 0.8 Hz), 6.06 (d, 1, J = 3.8 Hz), 6.40 (br, 1).

9c. Ir(KBr) 1830, 1740, 1380, 1330 cm^{-1}; nmr($CDCl_3$) δ 1.73 (d, 3, J = 7 Hz), 4.40 (dq, 1, J = 7, 1 Hz), 4.54 (dd, 1, J = 4, 1 Hz), 5.30 (s, 2), 5.86 (d, 1, J = 4 Hz), 7.40 (s, 5).

10c. Nmr($CDCl_3$) δ 1.42 (d, 3, J = 7 Hz), 4.40 (dq, 1, J = 7, 1 Hz), 4.48 (dd, 1, J = 5, 1 Hz), 5.26 (d, 1, J = 12.5 Hz), 5.34 (d, 1, J = 12.5 Hz), 6.21 (d, 1, J = 5 Hz), 7.40 (m, 5).

11. Nmr($CDCl_3$) δ 0.9-1.83 (m, 11), 1.52 (d, 3, J = 7 Hz), 3.12 (m, 2), 3.41 (dd, 1, J = 11.5, 10 Hz), 4.46 (dq, 1, J = 10, 7 Hz), 4.92 (d, 1, J = 12.5 Hz), 5.14 (d, 1, J = 12.5 Hz), 5.58 (dd, 1, J = 11.5, 9 Hz), 6.90-7.10 (br, 2), 7.42 (s, 5).

12. Nmr($CDCl_3$) δ 0.80-1.80 (m, 11), 1.44 (d, 3, J = 6.5 Hz), 3.12 (m, 2), 3.77 (m, 2), 5.09 (s, 2), 6.23 (m, 1), 6.52 (br, d, 1, J = 7.5 Hz), 7.02 (br, 1), 7.33 (m, 5).

8. P.R. Volante, Tetrahedron Lett., 1981, 22, 3119, and references cited therein.

9. Only olefinic products were obtained.

10. Similar results were obtained when the thermolysis was performed in the presence of one equiv of pyridine.

11. J.E. Baldwin, S.R. Herchen, G. Schulz, C.P. Falshaw and T.J. King, J.Am.Chem.Soc., 1980, 102, 7815.

12. This compound is unstable on silca gel.

13. Yields were not optimized.

14. We have observed in a sample of 9a, proton signals (< 5 %) which could be attributed to the β-isomer. Structural assignment of these thiosulfinates was based mainly on evidences derived from the NMR chemical shifts of the respective compounds.

15. Unpublished results: e.g. alkylation at nitrogen with bromoacetates.

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