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Seco-DETHIACEPHALOSPORINS

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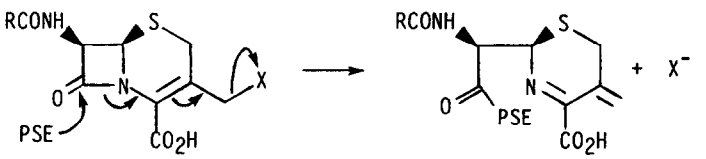
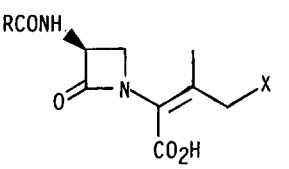
Abstract: Penicillins are converted to "*seco*-dethiacephalosporins" in a sequence consisting of Ra-Ni desulfurization, epoxidation, epoxide rearrangement and introduction of a heteroarylsulfide by nucleophilic substitution.

In the simplest chemical terms, β-lactam antibiotics derive their antimicrobial activity from the electrophilicity of the β-lactam carbonyl group. Reactivity of the β-lactam carbonyl towards nucleophiles (e.g. penicillin sensitive enzymes, PSE's) is enhanced in penicillins due to additional ring strain stemming from fusion with the 5-membered thiazolidine ring.[1] In cephalosporins it is an "electron sink" in the 3'-position, normally an allylic leaving group (as in **1** → **2**), which gives rise to enhanced reactivity of the β-lactam carbonyl.[2] Since the



1 **2**



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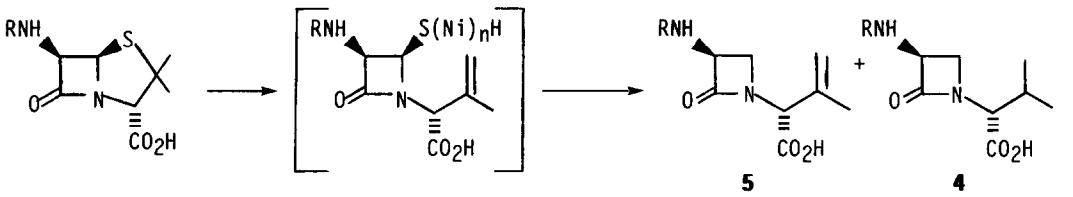
same electronic arrangement as in cephalosporins obtains in the simplified structure **3**, one wonders whether such *seco*-dethiacephalosporins might still retain antibacterial activity. For this reason we undertook the synthesis of some representative examples of this new class. Subsequently we became aware of a patent claiming such compounds as novel antimicrobial agents.[3] Since our own work provides a different and simpler approach to *seco*-dethiacephalosporins and it also lead to a different conclusion regarding the biological properties of these materials, we report here our results.

During a reinvestigation of the Raney nickel desulfurization of penicillins,[4] we found that, in addition to the desthiopenicillins **4**,[5-8] which in earlier reports were described as the sole products, considerable yields of **5** can be obtained under controlled conditions (Scheme 1). Preparation of such *N*-side chain unsaturated azetidinones had previously required multistep syntheses.[3,9]

*Scheme 1**



R	Oil Bath Temp.	Time (min)	Yield (%)	**5** (%)	**4** (%)
a) H	75°	35	31[x]	50	50
b) $\emptyset CH_2\overset{O}{\overset{\|}{C}}-$	175°	15	35[†]	40	60
c) $\emptyset OCH_2\overset{O}{\overset{\|}{C}}-$	175°	15	38[†]	36	64

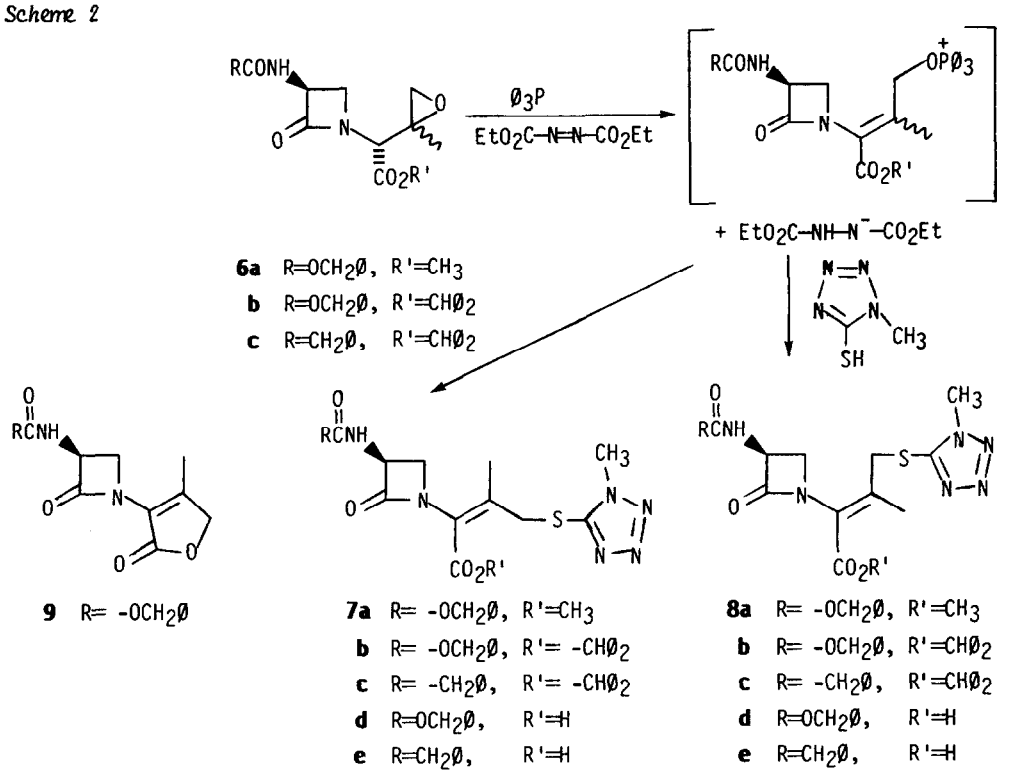
* Desulfurizations were carried out on Na^+ or K^+ salt in H_2O (ca. 0.1 *M*) with a 10-fold amount (by weight) of Ra-Ni, type 28 (Grace) at the specified oil bath temperature. Separation of **5a** from **4a** was achieved, after conversion to the N-carbobenzoxy derivatives, by fractional crystallization from chloroform. In most instances, the removal of **4** is more readily achieved (by HPLC) after further conversion of **5**, e.g. to the epoxide esters **6**. Cf. also ref. 4.

[x] After conversion to the corresponding *N*-carbobenzoxy derivatives.

[†] After conversion to the corresponding benzhydryl ester.

Esterification of **5a**[10] with diazomethane, followed by epoxidation with m-chloroperbenzoic acid (in CH_2Cl_2) afforded **6a** as a mixture of diastereomers (2:1, 68%). Subjection of **6a** to Mitsunobu reaction conditions (triphenylphosphine and diethyl azodicarboxylate in THF at room temperature) was intended to achieve opening of the epoxide ring with concommitant formation of an activated allylic oxygen function, suitable for subsequent nucleophilic substitution by 1-methyl-5-tetrazole thiol, as indicated in Scheme 2. Only trace amounts of the desired products **7a** and **8a** were obtained. The major product of the reaction was the lactone **9**.[11] In contrast, the epoxide **6b**[12] (obtained as a single stereoisomer in 50% yield) with its bulky benzhydryl ester group gave, under the same conditions[13], the desired products **7b**[14] and **8b**[15] (1:1) in 48% yield, accompanied by only trace amounts of the lactone **9**. (Product separation was achieved by two subsequent chromatographies on SiO_2 with EtOAc/hexane, 1:1 and CH_2Cl_2/15% CH_3CN). Compounds **7c** and **8c** (1:1, 42%) were prepared analogously from **6c**.

Scheme 2



Reaction of **7b-c** and **8b-c** with trifluoroacetic acid ($^1/_2$ hr, 0°C) gave the carboxylic acids **7d-e** and **8d-e**. These were tested against a wide spectrum of bacteria, and (in contrast to the cited patent claims) they were found to be practically devoid of antimicrobial activity.

Thus, it appears that the electronic arrangement along the periphery, which is the same in the cephalosporins (**1**) and the *seco*-dethiacephalosporins (**3**), is not sufficient to guarantee antibacterial activity. The conformational regidity imposed on **1** by the thiazine ring and/or the inductive effect contributed by its sulfur atom[16] may be additional requirements.

References and Notes

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5) E. Kaczka, K. Folkers, "The Chemistry of Penicillin", Princeton University Press, Princeton, NJ, 1949, p. 243.

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10) H-NMR [$(CD_3)_2SO$), δ 1.80 (s, $-CH_3$), 3.26 (q, 5.2 Hz, 2.5 Hz, 4β-H), 3.72 (t, 5.2 Hz, 4α-H), 4.67 (m, 3-H), 4.78 (s, $=\!\!<^{H}_{H}$), 4.98 (s, $=\!\!<^{H}_{H}$), 5.06 (s, ØC$\underline{H}_2$-O-), 5.07 (s, -C$\underline{H}$-CO_2H), 7.35 (aromatic -H), 8.06 (d, 8 Hz, -NH); ν_{max} 1757 (β-lactam); $[\alpha]_D^{25}$ = -129.40 (C=1.9728, DMSO, 97% purity as determined by nmr).

11) H-NMR ($CDCl_3$), δ 2.24 (s, $-CH_3$), 3.92 (q, 6.5 Hz, 3 Hz, 4β-H), 4.15 (t, 6.5 Hz, 4α-H), 4.67 (s, lactone -C$\underline{H}_2$-O-), 4.81 (m, 3-H), 5.13 (s, ØC$\underline{H}_2$-O-), 5.49 (d, 7 Hz, -NH), 7.34 (s, aromatic -H).

12) H-NMR ($CDCl_3$), δ 1.36 (s, $-CH_3$), 2.60 and 3.02 (d, 4.2 Hz epoxide -C$\underline{H}_2$-O-), 3.50 (q, 5.8 Hz, 2.5 Hz, 4β-H), 3.82 (t, 5.8 Hz, 4α-H), 4.63 (m, 3-H), 4.68 (s, -C$\underline{H}$-CO_2C$\underline{H}$Ø$_2$), 5.10 (s, ØC$\underline{H}_2$-O-), 5.52 (d, 7.5 Hz, -NH), 6.89 (s, -C$\underline{H}$Ø$_2$), 7.34 (s, aromatic -H); mp 92-95°C.

13) A mixture of triphenylphosphine (1.5 eq.) and diethyl azodicarboxylate (1.5 eq.) in dry THF was stirred at room temperature for 1/2 hr. Subsequently, a solution of **6b** (1 eq.) and 1-methyl-5-tetrazolethiol (1 eq.) in THF was added and stirring continued at room temperature for 2 hr. The structures of **7b-c** and **8b-c** were confirmed by independent synthesis from the corresponding bromide **3** (X=Br).

14) H-NMR ($CDCl_3$), δ 2.14 (s, $-CH_3$), 3.50 (q, 5.8 Hz, 3Hz, 4β-H), 3.74 (t, 5.8 Hz, 4α-H), 3.85 (s, $-NCH_3$), 4.38 (s, -C$\underline{H}_2$-S-), 4.80 (m, 3-H), 5.12 (s, ØC$\underline{H}_2$-O-), 5.42 (d, 8 Hz, -NH), 6.85 (s, -C$\underline{H}$Ø$_2$), 7.31 (s, aromatic -H).

15) H-NMR ($CDCl_3$), δ 2.25 (s, $-CH_3$), 3.45 (q, 5.8 Hz, 3 Hz, 4β-H), 3.78 (t, 5.8 Hz, 4α-H), 3.87 (s, $-N-CH_3$), 4.30 and 4.50 (d, 14 Hz, -C$\underline{H}_2$-S-), 4.88 (m, 3-H), 5.11 (s, ØC$\underline{H}_2$-O-), 5.70 (d, 8 Hz, -NH), 6.89 (s, -C$\underline{H}$Ø$_2$), 7.31 (s, aromatic -H).

16) N.P. Gensmantel, D. McLellan, J.J. Morris, M.I. Page, P. Proctor, G.S. Randahwa, Mechanisms in the Reactions of Some β-Lactam Antibiotics and Their Derivatives, pp. 227-239, in Recent Advances in the Chemistry of β-Lactam Antibiotics, G.I. Gregory, Ed., The Royal Soc. of Chem., London, 1980.

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