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Functional Derivatives of a New Ring System, 1H,4H-Azeto-[2,1-b]thiazolo[3',2':1,5]pyrrolo[3,4-d][1,3]thiazine

István MISKOLCZI,* Katalin E. KÖVÉR, and Zoltán GYÖRGYDEÁK+
BIOGAL Pharmaceutical Works, H-4042 Debrecen, Hungary
+Research Group for Antibiotics of the Hungarian Academy of Sciences, H-4010 Debrecen, Hungary

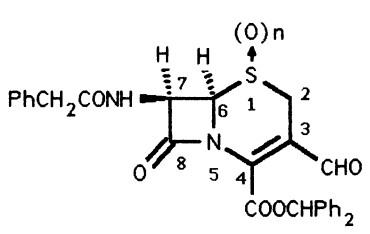
The reaction of 7-β-phenylacetamido-3-formylceph-3-em--4-carboxylic acid benzhydryl ester with D-penicillamine gives rise to a new fused tetracyclic system.

In the field of cephalosporins chemistry many attempts have been made to prepare compounds containing a heterocyclic ring attached directly to the dihydrothiazine moiety at C_3-position because of their interesting chemical and biological features.[1-3] On the other hand, there have been numerous papers which, based on theoretical consideration of analogous β-lactam structures, deal with preparation of γ-lactams[4] having antibacterial activity.[5,6]

Our work combines both the trends mentioned above. We report the preparation and structure elucidation of new compounds **3-8**.

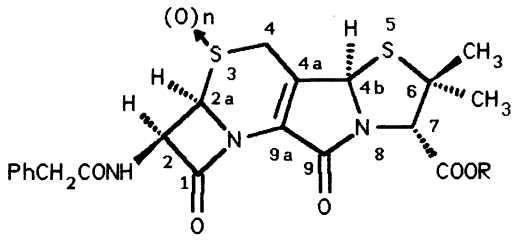
The starting materials were the benzhydryl ester of 7-β-phenyl--acetamido-3-formylceph-3-em-4-carboxylic acid (**1**) and its sulphoxide (**2**). These compounds were prepared by the oxidation of the corresponding 3-hydroxymethyl derivatives with chromic acid.[7,8]

The condensation reactions of **1** and **2** with D-penicillamine in a mixture of methanol-chloroform (3:2) at room temperature led to the stereoselective formation of 2,2a,4b,6,7,9-hexahydro-6,6-dimethyl-1,9--dioxo-1H,4H-azeto[2,1-b]thiazolo[3',2':1,5]pyrrolo[3,4-d][1,3]thiazine-7--carboxylic acids **3** and **5**, respectively. Benzhydryl esters **4** and **6** were subsequently prepared to obtain chromatographically homogeneous substance.[9] When the methyl ester of the penicillamine was used under the same conditions, the formyl group and the β-lactam ring acted as competing reacting groups in the reaction. Thus, the reaction of **1** with D-penicillamine methyl ester gave the compound **7**. In this reaction, the β-lactam ring cleaved and an amide-bond formation took place, along with the formation of thiazolidine-γ-lactam structure.



1 n = 0

2 n = 1

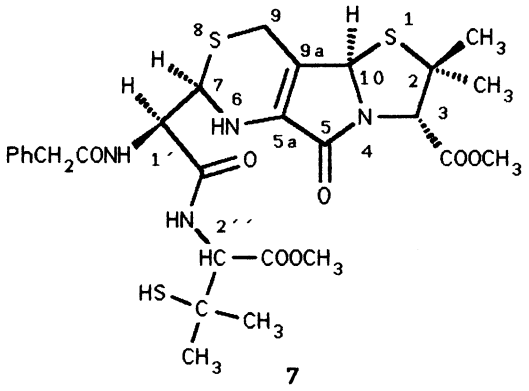


3 n = 0 R = H

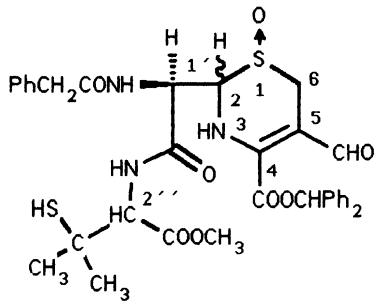
4 n = 0 R = $CHPh_2$

5 n = 1 R = H

6 n = 1 R = $CHPh_2$



7



8A and 8B

(C-2 epimers)

Fig.1.

When 2 was used instead of 1, on the other hand, only the N-acyl derivative 8 was formed with the cleavage of β-lactam ring.

The structures of compounds 1-8 have been established using ^{1}H-NMR data.[10] The C-4b configuration of compound 6 was determined by selective ^{1}H-NOE experiments (Table 1).

Table 1. ^{1}H nuclear Overhauser enhancement data (%) for 6

Proton irradiated	H-4b	H-7(β)	Proton observed CH_3(α, 1.28 ppm)	CH_3(β, 1.42 ppm)
H-4b	-	-	1-2	-
H-7(β)	-	-	-	2-3
CH_3(α)	6.5	2.7	-	-
CH_3(β)	0.8	16.2	-	-

The NOE effects measured between H-4b and $CH_3(\alpha)$ and between H-7 and $CH_3(\beta)$ confirm the trans configuration of protons H-7 and H-4b. Since the stereochemistry of proton H-7 is known, (β), H-4b is situated on the opposite face. Compound **8** is a mixture of C-2 epimers. This is corroborated by the ^{1}H-NMR spectrum which shows two separate sets of multiplets, where the integrated intensities indicate a ratio of 1.4:1 of the two components. The different C-2 configuration is verified by the vicinal coupling constants [J(H-1', H-2) and J(H-2, NH)] of **8A** and **8B**.[10] The occurrence of epimers is in agreement with the chemical expectations evident from previous results described on thiazolidines.[11,12] It is well established that the analogous thiazolidines with NH group give also C-2 epimers via Schiff-bases.

These experiments show that the compounds of thiazolidine γ-lactams are easily formed through the reaction of the esters of β-formyl--carboxylic acids with mercapto amino acids under mild conditions, in contrast to the method of Baldwin[6] in which the rigorous reaction condition (heating in pyridine) leads to side reactions.

The compounds **4-6** are the first members of a new ring system which contains the structural units of cephem, penicilline and γ-lactam in the same molecule. The details of chemistry, biology and structure elucidation of the products will be described in a separate paper.

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9) The purification of **4**, **6-8** were carried out by silica-gel column chromatography [elution with CH_2Cl_2-acetone (9:1)]. R_f **4**: 0.75; **6**: 0.66; **7**: 0.43; **8A**: 0.18; **8B**: 0.30. The compounds gave correct analytical results (S, N, C, H).
10) ^{1}H-NMR data (200 MHz, DMSO-d_6, δ) for new compounds:
Compound **4**: 1.3; 1.46 (2s, 6H, $2CH_3$), 3.53 (s, 2H, $ArCH_2$), 3.59; 3.84 (ABq, J 19.8 Hz, 2H, H-4), 4.68 (s, 1H, H-7), 5.09 (d, 1H, H-2a), 5.81 (dd, J 5 Hz, 1H, H-2), 6.09 (s, 1H, H-4b), 7-7.5 (m, 16H, Ar+$CHPh_2$), 9.22 (d, J 9.1 Hz, 1H, NH)
Compound **6**: 1.28; 1.42 (2s, 6H, $2CH_3$), 3.61 (s, 2H, $ArCH_2$), 3.78; 3.99 (ABq, J 18.2 Hz, 2H, H-4), 4.68 (s, 1H, H-7), 4.88 (d, 1H, H-2a), 5.88 (dd, J 5 Hz, 1H, H-2), 6.16 (s, 1H, H-4b), 7-7.5 (m, 16H, Ar+$CHPh_2$), 8.52 (d, J 8.9 Hz, 1H, NH)
Compound **7**: 1.2-1.4 (4s, 12H, $4CH_3$), 3.03 (s, 1H, SH), 3.47 (s, 2H, $ArCH_2$), 3.5; 3.75 (ABq, J 18 Hz, 2H, H-9), 3.78 (s, 3H, OCH_3), 4.35 (s, 1H, H-3), 4.58 (d, J 8.6 Hz, 1H, H-2''), 4.65 (t, J 6.1 Hz, 1H, H-7), 4.87 (dd, J 6.8 Hz, 1H, H-1'), 5.9 (s, 1H, H-10), 6.22; 8.4; 8.85 (3d, 3H, NH), 7.1-7.4 (m, 5H, Ar)
Compound **8A**: 1.2-1.4 (4s, 12H, $4CH_3$), 2.99 (s, 1H, SH), 3.2-3.6 (m, 4H, H-6, $ArCH_2$), 3.66 (s, 3H, OCH_3), 4.08 (dd, J 7.5; 5.2 Hz, 1H, H-2), 4.55 (d, J 9.1 Hz, 1H, H-2''), 5.12 (t, J 7.5 Hz, 1H, H-1'), 7-7.6 (m, 16H, Ar+$CHPh_2$), 7.92; 8.51; 8.68 (3d, 3H, 3NH), 9.6 (s, 1H, CHO)
Compound **8B**: 1.2-1.4 (4s, 12H, $4CH_3$), 3.04 (s, 1H, SH), 3.2-3.6 (m, 4H, H-6, $ArCH_2$), 3.68 (s, 3H, OCH_3), 4.18 (dd, J 8.2; 2.7 Hz, 1H, H-2), 4.57 (d, 1H, H-2''), 5.27 (t, J 8.2 Hz, 1H, H-1'), 7-7.6 (m, 16H, Ar+$CHPh_2$), 7.93; 8.85; 8.92 (3d, 3H, 3NH), 9.6 (s, 1H, CHO)
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