SYNTHESIS OF 6-SULFONYLMETHYLENE, 6-SULFINYLMETHYLENE- AND SPIROPYRAZOLINE-PENICILLANIC ACIDS [1]

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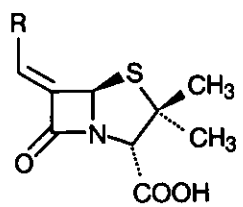
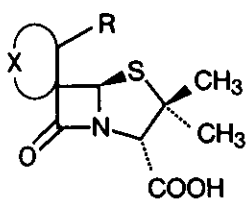
Abstract - The synthesis of the title compounds **1** , analogs of 6-acetylmethylenepenicillanic acid, and their products of diazomethane addition **2** are described. Their ß-lactamase inhibiting activity is briefly discussed.

As sensitive ß-lactam antibiotics are hydrolyzed by ß-lactamases[2] they are ineffective against bacterial strains that harbor these enzymes. Work involved in the retention of the efficacy of susceptible, but otherwise potent antibiotics, led to the isolation and synthesis of a number of molecules that inhibit or inactivate ß-lactamases[3]. One of these compounds is 6-acetylmethylenepenicillanic acid (Ro 15-1903) **1** (R: $COCH_3$), an inhibitor of many of the chromosomally and R-factor mediated ß-lactamases[4,5]. A similar compound, 6-methoxymethylenepenicillanic acid was recently found to irreversibly inactivate RTEM-2 ß-lactamase from E.coli[6].





1 R: $COCH_3$ (Ro 15-1903) $S(O)_n R^0$

2 R: COR^0 X: CH_2N_2 $S(O)_nR^0$ CH_2N_2

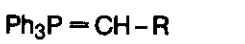
Although penicillanic acids **1** (R: $S(O)_nR^o$) with a S-substituted 6-methylene group have not been synthesized, they may be of interest due to the variability inherent in the sulfur oxidation levels. Moreover, the electron deficient methylene function should present a possibility for synthesizing new structures (e.g. **2**) via 1,3-dipolar cycloaddition.

In this paper the synthesis of compounds of type **1** and the diazomethane adducts **2** are reported. In addition, their ability to protect mezlocillin from hydrolysis by various enzymes, will be briefly discussed.

In order to synthesize compounds of type **1**, the Wittig strategy was adopted as 6-oxopenicillanates[7] are known to readily react with carbonyl-stabilized phosphonium ylids[8,9]. The new allyl 6-oxopenicillanate **6**[10] was chosen as a suitable intermediate, allowing the smooth palladium(0)-catalyzed cleavage of the ester[11] at the end of the synthesis. In contrast to the synthesis of compounds **1**, with a carbonyl substituted methylene group (R: COR°), it appeared to be more difficult to synthesize those compounds with a heteroatom-substituted methylene group. For example, it was not possible to isolate ß-lactam containing products from the reaction between benzyl 6-oxopenicillanate and methoxymethyl triphenylphosphorane or the corresponding phosphonate-stabilized anion[6]. It was hoped that the application of S-analogs under Wittig-Horner conditions[12] would not present similar problems.

The phosphonates **3** and phosphoranes **4** are, apart from a new (allyloxycarbonylmethylene)triphenylphosphorane **4h**[10,13], known from the literature sources.

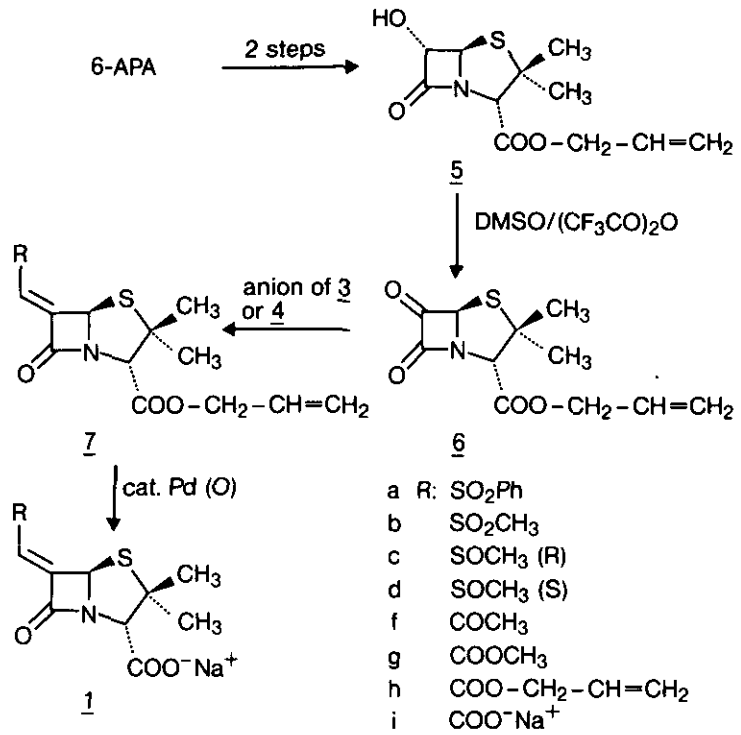
3	a	R: SO_2Ph [14]
	b	SO_2CH_3 [15]
	c, d	$SOCH_3$(R,S) [16]
	e	SCH_3 [17]

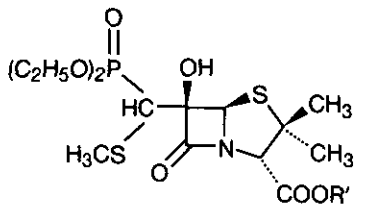


4	f	R: $COCH_3$ [18]
	g	$COOCH_3$ [18]
	h	$COO-CH_2-CH=CH_2$ [13]

Thus, the allyl ester **5** (mp 68°C)[10], prepared by esterification of 6-α-hydroxypenicillanic acid[19] (NEt_3, C_3H_5Br, 2M in DMF, 0°C → r.t.) was oxidized[9] (DMSO, $(CF_3CO)_2O$, CH_2Cl_2, 30 min, -65°C then NEt_3) almost quantitatively to yield the dione **6**, which was used immediately for the Wittig (-Horner) transformations (scheme 1). Deprotonation of the phosphonates **3a** and **3b** using 1 equiv. of LDA in THF at -78°C followed by the addition of an equimolar amount of the dione **6** in

Scheme 1:





8 R': -CH2-CH=CH2
9 Na

THF within a few minutes produced the olefins **7a** and **7b** which were isolated in moderate yield (34% and 35% respectively after chromatography). Deprotonation with n-butyllithium or sodium hydride as well as inverse addition did not improve the yield. Reacting **6** with (racemic) diethyl methylsulfinylmethylphosphonate **3c,d** yielded a 1:1 mixture (41%) of the diastereomeric sulfoxides **7c** and **7d** . The latter were separated by chromatography[21]. One of the two possible isomers of the olefinic products **7** was either formed exclusively or predominantly. In this case, it was possible to unambigiously assign the stereochemistry of the double bond using NMR spectroscopy: The olefinic protons of the Z-isomers of similar compounds absorb about 0.5 ppm lower field than the E-isomers[6,9,22]. The Z-geometry of the esters can be assigned on comparing these data (c.f. table 1). The Z-isomers also possess biological activity in the corresponding free acids[5,6].

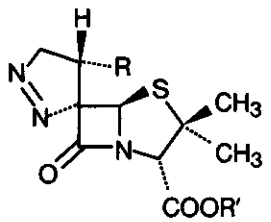
table 1 : Chemical shifts of the olefinic protons in Z-esters **7**

Z-ester **7**	δ(ppm) in $CDCl_3$
a	6.78
b	6.90
c	6.86
d	6.88
f	6.55
g	6.32
h	6.32

In contrast to the sulfonyl- and sulfinylmethylphosphonates, the reaction of **6** with diethyl methylthiomethylphosphonate **3e** stopped at the addition product stage **8** . The remaining intermediates **7f-h** were obtained in the usual manner[4,9] by means of the phosphoranes **4f-h** .

1,3-Dipolar cycloaddition of diazomethane in ether to the electron deficient double bonds of the esters **7** at 0°C yielded spiropyrazolinepenicillanates. Although all additions took place in a regio- and stereochemical uniform manner, the sulfomethylene derivatives **7a-c** added exactly in the opposite sense to the carbonylmethylene congeners **7f,g** [23].

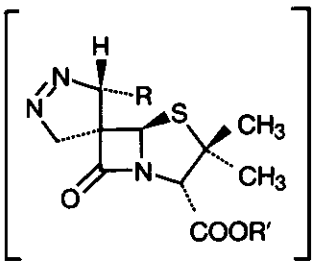
Δ^1-Pyrazolines **10a-c** (62, 70, and 65% respectively after chromatography) were obtained from the esters **7a-c** , while Δ^2-pyrazolines **13f,g** (72 and 63% respectively) resulted from **7f,g** . The primarily formed Δ^1-pyrazolines **12f,g** could not be isolated under the reaction conditions[24].



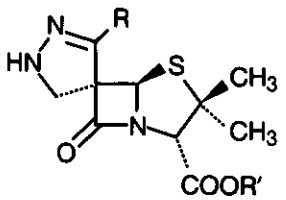
10 a R': $-CH_2-CH=CH_2$
b $-CH_2-CH=CH_2$
c $-CH_2-CH=CH_2$

11 a R': Na
b Na
c Na

a R: SO_2Ph
b SO_2CH_3
c $SOCH_3$ (R)
f $COCH_3$
g $COOCH_3$



12 f R': $-CH_2-CH=CH_2$
g $-CH_2-CH=CH_2$



13 f R': $-CH_2-CH=CH_2$
g $-CH_2-CH=CH_2$

14 f R': Na
g Na

Finally, palladium(0)-catalyzed cleavage[11] of the allyl esters **7a-d, f-h, 8, 10a-c** and **13f, g** afforded the corresponding sodium salts **1a-d, f, g**[25], **i**[26], **9, 11a-c** and **14f, g** in 60-90% yield[27].

Except for **1f**, only the sulfones **1a** and **1b** exhibited considerable ß-lactamase inhibiting activity. They protected mezlocillin from hydrolysis by ß-lactamases from Staph. aureus and Prot. vulgaris. They were however inferior to **1f** (Ro 15-1903). None of the sodium salts synthesized exhibited antibacterial activity.

ACKNOWLEDGEMENTS

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20. Selected physical data: **1a** : ν (KBr) 1767, 1600, 1318, 1151 cm^{-1}; δ (DMSO) 1.41 (s, 3H, CH_3), 1.46 (s, 3H, CH_3), 4.01 (s, 1H, H-3), 6.02 (s, 1H, H-5), 7.48 (s, 1H, =CH-SO_2), 7.7-7.8 (m, 3H, Ph), 7.95 (m, 2H, Ph). **1b** : ν (KBr) 1782, 1590, 1317, 1140 cm^{-1}; δ (DMSO) 1.45, 1.46 (s, 6H, CH_3), 3.18 (s, 3H, SO_2CH_3), 4.06 (s, 1H, H-3), 5.96 (s, 1H, H-5), 7.30 (s, 1H, =CH-SO_2). **1c** : ν (KBr) 1787, 1600, 1560 cm^{-1}; δ (DMSO) 1.43, 1.45 (s, 6H, CH_3), 2.80 (s, 3H, $SOCH_3$), 4.0 (s, 1H, H-3), 6.0 (s, 1H, H-5), 7.24 (s, 1H, =CH-SO). **1d** : ν(KBr) 1755, 1600, 1400, 1310 cm^{-1}; δ(DMSO) 1.43 (s, 3H, CH_3), 1.48 (s, 3H, CH_3), 2.80 (s, 3H, $SOCH_3$), 4.0 (s, 1H, H-3), 5.90 (s, 1H, H-5), 7.22 (s, 1H, =CH-SO). **1i** : ν (KBr) 1755, 1600 cm^{-1}; δ (D_2O) 1.55 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 4.32 (s, 1H, H-3), 5.96 (s, 1H, H-5), 6.38 (s, 1H, =CH-COO). **7a** : ν ($CHCl_3$) 1775, 1738 cm^{-1}; δ ($CDCl_3$) 1.52 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 4.60 (s, 1H, H-3), 4.71 (m, 2H, $-CH_2-$), 5.3-5.5 (m, 2H, $=CH_2$), 5.9-6.05 (m, 1H, $-\underline{CH}=CH_2$), 6.24 (s, 1H, H-5), 6.78 (s, 1H, $=CH-SO_2-$), 7.6-7.8 (m, 3H, Ph), 8.03 (m, 2H, Ph). **7b** : ν ($CHCl_3$) 1778, 1737, 1670 cm^{-1}; δ ($CDCl_3$) 1.51 (s, 3H, CH_3), 1.63 (s, 3H, CH_3), 3.15 (s, 3H, CH_3SO_2), 4.65 (s, 1H, H-3), 4.72 (m, 2H, $-CH_2-$), 5.35-5.5 (m, 2H, $=CH_2$), 5.9-6.1 (m, 1H, $-\underline{CH}=CH_2$), 6.20 (s, 1H, H-5), 6.90 (s, 1H, $=CH-SO_2-$); m/e 332 (M^+). **7c** : ν ($CHCl_3$) 1772, 1740 cm^{-1}; δ ($CDCl_3$) 1.50 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 2.87 (s, 3H, CH_3SO), 4.58 (s, 1H, H-3), 4.70 (m, 2H, $-CH_2-$), 5.3-5.5 (m, 2H, $=CH_2$), 5.9-6.05 (m, 1H, $-\underline{CH}=CH_2$), 6.20 (s, 1H, H-5), 6.88 (s, 1H, =CH-SO); m/e 315 (M^+). **9** : δ(DMSO) 1.24 (t, J=7 Hz, 6H, $CH_2\underline{CH_3}$), 1.44, 1.46 (s, 6H, CH_3), 2.28 (s, 3H, SCH_3), 3.25 (d, J=17 Hz, CHP), 3.88 (s, 1H, H-3), 4.07 (q, J=7 Hz, 4H, $\underline{CH_2}CH_3$), 5.40 (s, 1H, H-5), 6.12 (bs, 1H). m/e (FAB) 436 (M+H), 458 (M+Na). **10a** : ν ($CHCl_3$) 1788, 1744, 1312, 1153 cm^{-1}; δ ($CDCl_3$) 1.60 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 4.09 (d, J=7.5 Hz, 1H, $CHSO_2$), 4.41 (dd, J=20 Hz, 7.5 Hz, 1H, NCH_2), 4.50 (s, 1H, H-3), 4.71 (m, 2H, $-\underline{CH_2}-CH=CH_2$), 5.2-5.4 (m, $=CH_2$), 5.41 (d, J=20 Hz, CH_2N) together 3H, 5.9-6.05 (m, 1H, $-\underline{CH}=CH_2$), 6.35 (s, 1H, H-5), 7.6-7.9 (m, 5H, Ph). **10b** : ν (KBr) 1785, 1741, 1311, 1131 cm^{-1};

δ($CDCl_3$) 1.58 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 3.18 (s, 3H, SO_2CH_3), 3.92 (d, J=7.5 Hz, 1H, $\underline{CH}SO_2CH_3$), 4.56 (dd, J=18 Hz, 7.5 Hz, 1H, CH_2N), 4.58 (s, 1H, H-3), 4.73 (m, 2H, $-\underline{CH_2}-CH=CH_2$), 5.3-5.5 (m, 2H, $=CH_2$), 5.79 (d, J=18 Hz, 1H, CH_2N), 5.9-6.1 (m, 1H, $-\underline{CH}=CH_2$), 6.40 (s, 1H, H-5); m/e (FAB) 374 (M+H). **11a** : ν (KBr) 1769 1613, 1321, 1149 cm^{-1}; δ (DMSO) 1.41, 1.44 (s, 6H, CH_3), 3.96 (s, 1H, H-3), 4.38 (dd, J=18 Hz, 7.5 Hz, 1H, CH_2N), 4.76 (d, J=7.5 Hz, 1H, $\underline{CH}SO_2Ph$), 5.19 (d, J=18 Hz, 1H, CH_2N), 6.15 (s, 1H, H-5), 7.7-7.9 (m, 5H, Ph); m/e (FAB) 418 (M+H), 440 (M+Na). **11b** : ν (KBr) 1765, 1607, 1306, 1134 cm^{-1}; δ(DMSO) 1.50, 1.57 (s, 6H, CH_3), 3.29 (s, 3H, SO_2CH_3), 4.00 (s, 1H, H-3), 4.37 (dd, J=20 Hz, 7.5 Hz, 1H, CH_2N), 4.68 (d, J=7.5 Hz, 1H, $\underline{CH}SO_2CH_3$), 5.54 (d, J=20 Hz, 1H, CH_2N), 6.16 (s, 1H, H-5): m/e (FAB) 356 (M+H), 378 (M+Na). **13g** : mp 143°C; ν (KBr) 3305, 1784, 1755, 1711 cm^{-1}; δ ($CDCl_3$) 1.51 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 3.88 (s, 3H, CO_2CH_3), 4.16 (s, 2H, CH_2N), 4.63 (s, 1H, H-3), 4.72 (m, 2H, $-\underline{CH_2}-CH=CH_2$), 5.3-5.5 (m, $=CH_2$), 5.42 (s, H-5) together 3H, 5.9-6.1 (m, 1H, $-\underline{CH}=CH_2$), 6.50 (bs, exchangeable, 1H, NH); m/e (CI,NH_3) 354 (M+H), 371 ($M+NH_4$). **14f** : ν (KBr) 3431, 1760, 1655, 1605 cm^{-1}; δ(DMSO) 1.36 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 2.18 (s, 3H, $COCH_3$), 3.96 (s, 1H, H-3), 3.76, 4.11 (AB, J=12 Hz, 2H, CH_2N), 5.21 (s, 1H, H-5), 9.18 (bs, 1H, NH). **14g** : ν (KBr) 3344, 1762, 1713, 1607 cm^{-1}; δ(DMSO) 1.39 (s, 3H, CH_3), 1.53 (s, 3H, CH_3), 3.60 (s, 3H, CO_2CH_3), 3.90 (s, 1H, H-3), 3.67, 4.11 (AB, J=12.5 Hz, 2H, CH_2N), 5.27 (s, 1H, H-5), 8.89 (s, 1H, NH).

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26. Performed as described in ref. 11 but employing 1.96 *equiv.* sodium 2-ethylhexanoate.
27. Sodium salts not crystallizing from the reaction mixture were precipitated by addition of ether and subjected to Diaion HP-20 chromatography.

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