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SULFOXIDES OF PENICILLANATES WITH NON CLASSICAL SUBSTITUENTS IN THE 6-POSITION†

S. ADAM*
Department of Pharmaceutical Research

and

W. ARNOLD and P. SCHÖNHOLZER
Central Research Units, F. Hoffmann-La Roche & Co., Ltd., Basle, Switzerland

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Abstract—(6*Z* and 6*E*)-6-acetonylidenepenicillanates and (6*R*)-6-acetonylpenicillanates were prepared and the directing influence of the keto-group on the stereochemical course of the oxidation at the S with *m*-chloroperbenzoic acid was determined.

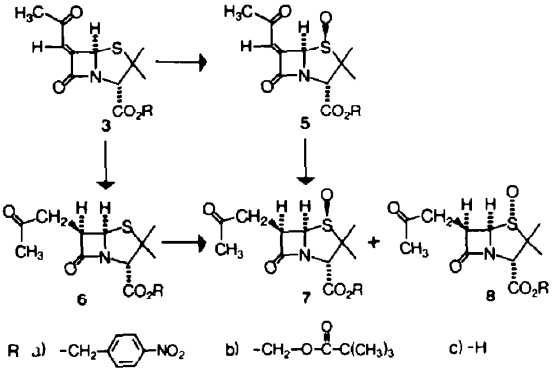
It is known that the oxidation of penicillins and cephalosporins by a wide variety of oxidizing agents gives rise preferentially to the formation of the (*S*)-sulfoxide as a result of the directing influence of the amido side chain which is considered to form a H-bond with the oxidant thus allowing "reagent approach control" from the more hindered β face of the molecule.[1]

Such a directing effect is not possible in the 6β-phthalimidopenicillanate and hence the sulfoxide possesses the *R*-configuration.[1] Similarly 6β-ethylpenicillanate is reported to give the (*R*)-sulfoxide in 90% yield.[2] In these two cases oxidation occurs from the sterically more accessible α face.

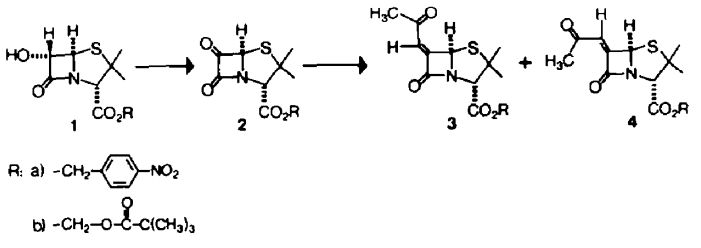
We would like to report here the results of some studies of the oxidation of related penicillanates with non-classical substituents in position 6,6-Acetonylidenepenicillanates **3** and **4** were synthesized as outlined in Scheme 1. Oxidation of the alcohol **1** with dimethyl sulfoxide–trifluoroacetic anhydride at −65° gave the ketone **2**, which in turn reacted at 20° with 1-triphenylphosphoranylidene-2-propanone to give **3** as the major product accompanied with a small amount of **4**.

Treatment of *p*-nitrobenzyl (6*Z*)-6-acetonylidenepenicillanate **3a** with 1.2 equiv. of *m*-chloroperbenzoic acid in THF or dichloromethane at 20° afforded after recrystallization a single sulfoxide **5a** in over 90% yield (Scheme 2).

No thermal epimerization could be detected by refluxing this sulfoxide in benzene during 24 hr, thus showing its thermodynamic stability. In order to obtain more information about the stereochemical course of the oxidation, we catalytically reduced the double bond of **3a** in the presence of Wilkinson's catalyst, and isolated *p*-nitrobenzyl (6*R*)-6-acetonylpenicillanate **6a** as the only product in very high yield. The β-orientation of the side chain was confirmed by the ^{1}H-NMR spectrum of the product ($J_{5,6}$ = 5 Hz). When **6a** was treated with an equimolar amount of *m*-chloroperbenzoic acid in THF at 20° a 1:1 mixture of the two sulfoxides was obtained, which could be readily separated by flash chromatography.[3] The less polar being crystalline could



Scheme 2.



Scheme 1.

†Dedicated to Prof. Dr. Albert Hürlimann on his 60th birthday.

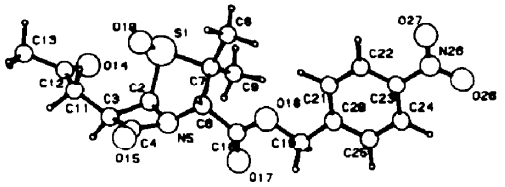
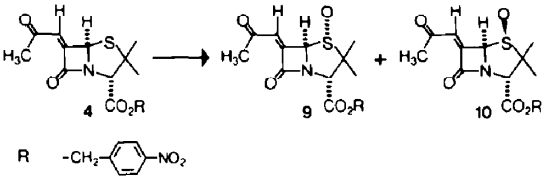


Fig. 1. A computer generated drawing of **7a**.



Scheme 3.

be shown by X-ray analysis to be the (*S*)-sulfoxide **7a** (Fig. 1).

The thiazoline ring has the same conformation as in the classical penicillin sulfoxides.[4] In addition to the X-ray analysis for **7a**, ^{13}C-NMR spectroscopy was used to confirm the configuration of some of the penicillin sulfoxides, the results being consistent with the data given:[5] in the (*R*)-sulfoxides there is a larger shift difference for the geminal Me groups (23–25 ppm and 15–17 ppm), while in the (*S*)-sulfoxides both Me groups resonate at nearly the same frequencies (~17.5–20 ppm).

The second product, an amorphous solid was consequently assigned structure **8a**. In refluxing benzene during 24 hr it was slowly converted into **7a**. **7a** under the same conditions remained unchanged, indicating that the *S*-configuration is thermodynamically more stable. Catalytic reduction of **5a** under the same conditions as for **3a** provided a single compound which could be readily identified as **7a**.

The following considerations allow the assignment of the *S*-configuration to **5a**: as reported above, the sulfoxide is thermodynamically stable; furthermore during the catalytic hydrogenation **5a**→**7a** the conditions are such that no epimerization of the sulfoxide can occur. Additional evidence of this structure came from the ^{13}C-NMR data: the geminal Me groups resonate at 18.50 ppm and 19.55 ppm. The same sequence of reactions was applied to methylene (6*Z*)-6-acetonylidenepenicillanate pivalate **3b**.[6] Oxidation of **3b** gave, after work-up, a single crystalline sulfoxide **5b**, which in turn was hydrogenated to **7b**. Catalytic reduction of the double bond in **3b** afforded **6b**. Oxidation of **6b** with *m*-chloroperbenzoic acid furnished a mixture of the (*R*)- and (*S*)-sulfoxides **7b** and **8b** (ratio: ~ 1:1), which could be separated by flash chromatography[3] and were assigned by NMR.

In order to confirm that only one sulfoxide **5a** or **5b** was formed during the oxidation and that the other isomer was not lost during the work-up, we performed the oxidation directly in $CDCl_3$ and analysed subsequently the crude mixture by NMR. From these spectra it was shown that the crude mixture also contained a small amount of the (*R*)-sulfoxide, the ratio (*S*):(*R*) being 9:1, in both cases. Because the (*R*)-sulfoxide in the saturated series is less stable than the (*S*)-sulfoxide, the recovery after work-up and chromatography was in general not a reliable measure for the proportions of the epimers in the crude mixture. During work-up of the oxidation reactions much care had to be taken, especially during the decomposition of any excess of peracid and treatment with bicarbonate, so that losses due to decomposition could be minimized. The flash chromatography also had to be carried out as quickly as possible.

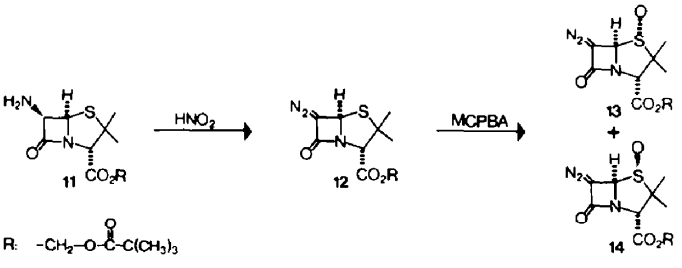
From the above results it is apparent[2] that the ketone CO in **5** as well as in **7** exerts a significant directive effect on the course of the oxidation. To further substantiate this conclusion we extended the oxidation to the *E*-olefin (Scheme 3).

Because here the keto group is more distant from the S than in the *Z*-olefin, the oxidation selectivity was expected to be lower and the ratio (*R*):(*S*)-sulfoxides to be higher than in the case of the *Z*-olefins. Consequently, we treated **4a** with *m*-chloroperbenzoic acid in $CDCl_3$ and found that the ratio (*R*)-:(*S*)-sulfoxide was 3:7, confirming our expectation.

In the case of methylene 6-diazopenicillanate pivalate **12**[7] the oxidation with one equivalent of *m*-chloroperbenzoic acid gave rise to a 1:1 mixture of the two sulfoxides **13** and **14** (Scheme 4).

Rapid flash chromatography allowed the separation of the two isomers. The more polar **14** with the *S*-configuration was a yellow crystalline compound, but the (*R*)-sulfoxide was not crystalline. Also in this series the (*R*)-sulfoxide was less stable than the (*S*)-sulfoxide, decomposing faster in solution at room temperature than the (*S*)-sulfoxide.

The preferential formation of the (*S*)-sulfoxide in the acylmethylene series is noteworthy. Models show that steric hindrance towards β attack is less important than in the case of classical penicillins, or in the case of the (*R*)-6-acetonylpenicillanates **7** and **8**,



Scheme 4.

where this hindrance is quite marked. It is possible that non bonded repulsive effects as well as electrostatic interactions of the ketone may favour the transition state leading preferentially to the β-sulfoxide. It has been reported that the presence of remote polar substituents can influence the stereochemistry of the oxidation with peracids.[8]

The catalytic reduction of the *p*-nitrobenzyl esters **7a** and **8a** with Pd–C gave the corresponding acids **7c** and **8c**. Submitted to biological testing the (*S*)-sulfoxide **7c** lacked antibacterial activity whereas the (*R*)-sulfoxide **8c** showed some activity in vivo against *Streptococcus haemolyticus*. These results confirmed the statement that the (*R*)-sulfoxides are much more active than the (*S*)-sulfoxides.[9a,b]

EXPERIMENTAL

The ^{1}H-NMR spectra were run on a Varian A60D or on a Bruker WP 80 CW machine. The ^{13}C-NMR spectra were run on a Bruker WM 400 equipped with an Aspect 2000 computer (80 K memory). s = singulet, d = dublet, t = triplet, q = quartet, m = multiplet. Mass spectra were recorded on a Manchester MS 9, AEI instrument. IR spectra were recorded on a Beckmann 9 spectrometer. Solvents were purified and dried by standard methods. Where indicated, solutions were degassed by evacuation with stirring. Flash chromatography was performed on Merck Kieselgel 60 (40–63 μm). M.ps were measured on a Büchi 510 apparatus.

p-*Nitrobenzyl* (6E)-6-*acetonylidenepenicillanate* **4a** *and* p-*nitrobenzyl* (6Z)-6-*acetonylidenepenicillanate* **3a**

A stirred soln of 4.2 ml (59 mmole) DMSO destilled over CaH_2 in 60 ml CH_2Cl_2 was treated at −65° under argon with a soln of 4.9 ml (35.6 mmole) trifluoroacetic anhydride in 40 ml CH_2Cl_2. To this mixture a soln of 10.5 g (29.7 mmole) *p*-nitrobenzyl (6*S*)-6-hydroxypenicillanate in 70 ml CH_2Cl_2 was then added dropwise. After 30 min the orange soln was treated dropwise with 9.4 ml (71.2 mmole) Et_3N. The cooling bath was removed and the mixture was stirred during 40 min. The crude mixture was then treated with 11.3 g (35.65 mmole) acetonylidenetriphenylphosphorane. After 10 min the solvent was evaporated and the residue was purified by flash chromatography using cyclohexane–EtOAc (7:3) as eluent, yield: 0.14 g of **4a** as orange oil and 7.5 g of **3a** as yellowish crystals m.p. 82–84°.

Compound **4a**. ^{1}H-NMR ($CDCl_3$, 80 MHz): 1.45 ppm and 1.62 ppm, 2 xs, 2-C–CH_3; 2.61 ppm, s, –$COCH_3$; 4.65 ppm, s, 3-C$\underline{H}$; 5.30 ppm, s, –OCH_2–; 5.75 ppm, ~s, broadened by long range coupling, 5-C$\underline{H}$; 6.54 ppm, ~s, broadened by long range coupling, 8-C$\underline{H}$; 7.56 ppm and 8.24 ppm, centers of AA′BB′-spectrum, aromatic H.

Compound **3a**. IR (KBr) 1777, 1767, 1740, 1662, 1606. MS 390, 347, 319, 316. ^{1}H-NMR ($CDCl_3$, 80 MHz): 1.45 ppm and 1.59 ppm, 2 × s, 2-C–CH_3; 2.35 ppm, s, –$COCH_3$; 4.64 ppm, s, 3-C$\underline{H}$; 5.31 ppm, center of AB-spectrum, J_{gem} = 13 Hz, nearly a s, –OCH_2–; 6.00 ppm, d, J_{58} = 1 Hz, 8-C$\underline{H}$; 7.58 ppm and 8.26 ppm, centers of AA′BB′-spectrum, aromatic H.

p-*Nitrobenzyl* (6Z)-6-*acetonylidenepenicillanate* (S)-S-*oxide* **5a**

A soln of 7.9 g (20.2 mmole) **3a** in 10 ml THF was treated under stirring with 4.1 g (21.3 mmole) *m*-chloroperbenzoic acid at 20°. After 2 hr the mixture was treated with a soln of Na_2SO_3 in order to destroy the excess of peracid. The mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc and water. The organic phase was separated and washed successively with dilute cold $NaHCO_3$aq and water, dried ($MgSO_4$), filtered and evaporated. The crystalline residue was recrystallized from EtOAc–Et_2O. Yield: 7 g of yellow crystals. IR 1784, 1749, 1735, 1040. ^{1}H-NMR ($CDCl_3$, 80 MHz): 1.22 ppm and 1.68 ppm, 2 × s, 2-C–CH_3; 2.41 ppm, s, –CO–CH_3; 4.75 ppm, s, 3-C$\underline{H}$; 5.35 ppm, AB-spectrum J_{gem} = 13 Hz, nearly a s, –OCH_2–; 5.72 ppm, d, J_{58} = 1.6 Hz, 5-C$\underline{H}$; 6.88 ppm, d, J_{58} = 1.6 Hz, 8-C$\underline{H}$; 7.59 ppm and 8.26 ppm, centers of AA′BB′-spectrum, aromatic H.

^{13}C-NMR ($CDCl_3$, 100.6 MHz broad band and cw offset decoupled): 18.50 ppm and 19.55 ppm, 2 × q, 2-C–$\underline{C}H_3$; 31.41 ppm, q, –$CO\underline{C}H_3$; 66.31 ppm, t, –$O\underline{C}H_2$–; 66.70 ppm, d, 3-C; 73.61 ppm, s, 2-C; 81.59 ppm, d, 5-C; 123.08 ppm, d, 8-C; 123.99 ppm, 128.95 ppm, 141.84 ppm and 148.16 ppm, aromatic C ortho, meta, para and ipso to –NO_2, respectively; 144.29 ppm, s, 6-C; 165.94 ppm and 167.83 ppm, 2 × s, 7-CO and 3-C–$\underline{C}O$ or vice versa; 196.52 ppm, s, $CH_3\underline{C}O$–.

p-*Nitrobenzyl* (6R)-6-*acetonylpenicillanate* (S)-S-*oxide* **7a**

A stirred mixture of 5.7 g (14 mmole) **5a**, 4 g of Wilkinson's catalyst in 200 ml EtOAc and 200 ml MeOH (degassed solvents) was hydrogenated at room temp. in the dark for 3 hr. After filtration and evaporation of the filtrate the residue was purified by flash chromatography and yielded 5 g of **7a**, using cyclohexane–EtOAc (1:1) as eluent. IR ($CHCl_3$) 1794, 1759, 1717, 1060. MS 390 (M-H_2O), 321, 293, 277, 210. ^{1}H-NMR ($CDCl_3$, 80 MHz): 1.18 ppm and 1.64 ppm, 2 × s, 2-C–CH_3; 2.20 ppm, s, –CO–CH_3; 2.95 ppm, dd, J_{gem} = 18.5 Hz, J_{68} = 6 Hz and 3.58 ppm, dd, J_{gem} = 18.5 Hz, $J_{68'}$ = 10.2 Hz, 8-CH_2; ~4.0 ppm, m, 6-C$\underline{H}$; 4.64 ppm, s, 3-C$\underline{H}$; 5.03 ppm, d, J_{56} = 5 Hz, 5-C$\underline{H}$; 5.33 ppm, AB-spectrum, J_{gem} = 13 Hz, nearly a s, –OCH_2–; 7.58 ppm and 8.26 ppm, centers of AA′BB′-spectrum, aromatic H.

p-*Nitrobenzyl* (6R)-6-*acetonylpenicillanate* **6a**

A soln of 5.15 g (13.2 mmole) **3a**, 2.5 g Wilkinson's catalyst in 100 ml EtOAc and 100 ml MeOH (degassed solvents) was hydrogenated at room temp. in the dark for 2 hr. After filtration, evaporation of the filtrate gave an oil. Flash chromatography with cyclohexane–EtOAc (6:4) as eluent gave 5 g of **5a** as an orange oil. IR ($CHCl_3$) 1778, 1765, 1720. MS 392, 349, 821, 295. ^{1}H-NMR ($CDCl_3$, 80 MHz): 1.43 ppm and 1.63 ppm, 2 × s 2-C–CH_3; 2.20 ppm, s, –CO–CH_3; ~2.90 ppm, dd, J_{gem} = 18 Hz, J_{68} = 6.5 Hz and ~3.10 ppm, dd, J_{gem} = 18 Hz, $J_{68'}$ = 9 Hz, 8-CH_2; 4.00 ppm, ddd, J_{56} = 4.5 Hz, 6-C$\underline{H}$; 4.48 ppm, s, 3-C$\underline{H}$; 5.30 ppm, AB-spectrum, J_{AB} = 13 Hz, nearly a s, –OCH_2–; 5.60 ppm, d, J_{56} = 4.5 Hz, 5-CH; 7.58 ppm and 8.26 ppm, centers of AA′BB′-spectrum, aromatic H.

p-*Nitrobenzyl* (6R)-6-*acetonylpenicillanate* (S)-S-*oxide* **7a** *and* p-*nitrobenzyl* (6R)-6-*acetonylpenicillanate* (R)-S-*oxide* **8a**

A mixture of 3.6 g (9.25 mmole) **6a** in 70 ml THF was treated under stirring at 20° with 1.86 g (9.7 mmole) *m*-chloroperbenzoic acid. After 40 min the excess of peracid was destroyed under cooling at 5° with $NaHSO_3$aq. After concentrating under reduced pressure the residue was partitioned between EtOAc and water. The organic phase was separated and washed successively with dilute cold $NaHCO_3$aq. and water, dried ($MgSO_4$), filtered and evaporated.

Separation of the two sulfoxides by flash chromatography using cyclohexane–EtOAc (1:1) as eluent gave 2 g of **7a** as white crystals. IR (KBr) 1790; 1757, 1711, 1050. MS 390 (M-H_2O), 348, 321, 284. ^{1}H-NMR: data are given above.

1 g **8a** was obtained as white foam. IR (MBr) 1790, 1760, 1712, 1060. MS 390 (M-H_2O), 348, 307, 279. ^{1}H-NMR ($CDCl_3$, 80 MHz): 1.31 ppm and 1.61 ppm, 2 × s, 2-C–CH_3; 2.26 ppm, s, –$COCH_3$; ~3.08 ppm, center of AB-part of ABX-spectrum, nearly a d, J_{vic} ~ 8 Hz, –CO–CH_2; 4.20 ppm, m, ΣJ = 20 Hz, 6-C$\underline{H}$; 4.46 ppm, s, 3-C$\underline{H}$; 4.80 ppm, d, J_{56} = 4.8 Hz, 5-C$\underline{H}$; 5.35 ppm, s, –OCH_2–; 7.61 ppm and 8.29 ppm, centers of AA′BB′-spectrum, aromatic H.

Recrystallization of **7a** from EtOAc and Et_2O gave the crystals for the X-ray analysis.

Methylene (6R)-6-*acetonylpenicillanate pivalate* (S)-S-*oxide* **7b**

A stirred mixture of 6.4 g (16.6 mmole) **5b**,[5] 4 g Wilkinson's catalyst in 150 ml EtOAc and 150 ml MeOH (both solvents being degassed) was hydrogenated at room temp. and in the dark for 2 hr. After filtration the filtrate was evaporated. Purification of the dark oily residue by flash chromatography gave 6 g of **7b** using cyclohexane–EtOAc (1:1) as eluent. IR ($CHCl_3$) 1793, 1761, 1714, 1060. ^{1}H-NMR ($CDCl_3$, 80 MHz): 1.23 ppm, s, $(CH_3)_3C$–; 1.24 ppm and 1.61 ppm, 2 × s, 2-C–CH_3; 2.18 ppm, s, –CO–CH_3; 2.93 ppm, dd, J_{gem} = 18.5 Hz, $J_{6\beta}$ = 6 Hz and 3.56 ppm, dd, J_{gem} = 18.5 Hz, $J_{6\beta}$ = 10.8 Hz, 8-CH_2; 3.97 ppm, ddd, J = 10.8 Hz, J = 6 Hz, J = 4.9 Hz, 6-CH; 4.56 ppm, s, 3-CH; 4.99 ppm, d, J_{56} = 4.9 Hz, 5-CH; 5.68 ppm, d and 5.92 ppm, d, J_{gem} = 5.5 Hz, –O–CH_2O–. ^{13}C-NMR ($CDCl_3$, 100.6 MHz, broad band and cw offset decoupled): 18.72 ppm and 19.36 ppm, 2 × q, 2-C–CH_3; 26.92 ppm, q, $(CH_3)_3$C–; 29.54 ppm, q, –COCH_3; 36.99 ppm, t, –CO–CH_2–; 38.84 ppm, s, $(CH_3)_3$C–; 46.48 ppm, d, 6-C; 64.92 ppm, d, 3-C; 74.04 ppm, s, 2-C; 74.46 ppm, d, 5-C; 80.43 ppm, t, –OCH_2O–; 167.33 ppm, s, 3-C–CO–; 173.72 ppm, s, 7-C; 176.74 ppm, s, –CO–C$(CH_3)_3$; 206.11 ppm, s, CH_3–CO–.

Methylene (6R)-6-*acetonylpenicillanate pivalate* **6b**

A stirred mixture of 3.69 g (10 mmole) **3b**, 3 g Wilkinson's catalyst in 100 ml EtOAc and 100 ml MeOH (degassed solvents) was hydrogenated at room temp. for 2 hr. After filtration and evaporation of the filtrate the residue was purified by flash chromatography yielding 3.2 g of **6b** as a brown oil. Eluent cyclohexane–EtOAc (7:3). IR (film) 1767, 1717. MS 371, 341, 328, 274. ^{1}H-NMR ($CDCl_3$, 80 MHz): 1.21 ppm, s, $(CH_3)_3$C–; 1.48 ppm and 1.61 ppm, s, 2-C–CH_3; 2.18 ppm, s, –CO–CH_3; ~1.95 ppm, center of AB-part of ABX-spectrum, J_{gem} = 18 Hz, $J_{6\beta}$ = 9 Hz, $J_{6\alpha}$ = 6.5 Hz, 8-CH_2; 3.95 ppm, ddd, J_{56} = 4.4 Hz, 6-CH; 4.37 ppm, s, 3-CH; 5.54 ppm, d, J_{56} = 4.4 Hz, 5-CH; 5.73 ppm and 5.81 ppm, 2 × d, J_{gem} = 6 Hz, –OCH_2O–.

Methylene (6R)-6-*acetonylpenicillanate pivalate* (S)-S-*oxide* **7b** *and methylene* (6R)-6-*acetonylpenicillanate pivalate* (R)-S-*oxide* **8b**

A soln of 2.7 g (7.25 mmole) **6b** in 50 ml THF was treated under stirring with 1.38 g (7.25 mmole) *m*-chloroperbenzoic acid at 20°. After 10 min the mixture was treated under stirring at 5° with a few drops of Na_2SO_3aq. in order to destroy any excess of peracid. The mixture was concentrated under reduced pressure. The residue was partitioned between EtOAc and water. The organic phase was separated and washed successively with dilute cold $NaHCO_3$aq. and water, dried ($MgSO_4$), filtered and evaporated. Separation of the two sulfoxides by flash chromatography using cyclohexane–EtOAc (1:1) as eluent furnished 1.7 g of **7b**. IR (film) 1796, 1765, 1719, 1060. MS 369 (M-H_2O), 273, 256, 238, 228. ^{1}H- and ^{13}C-NMR data are given above.

Additionally 0.3 g of **8b** were obtained. IR (KBr) 1800, 1766, 1755, 1070. MS 369 (M-H_2O), 353, 327, 373, 238, 228. ^{1}H-NMR ($CDCl_3$, 80 MHz): 1.23 ppm, s, $(CH_3)_3$C–; 1.34 ppm and 1.60 ppm, 2 × s, 2-C–CH_3; 2.23 ppm, s, –COCH_3; 3.03 ppm, ~d, J ~ 7.5 Hz, –CO–CH_2–; ~4.1 ppm, m, 6-CH; 4.31 ppm, s, 3-CH; 4.70 ppm, d, J_{56} = 4.6 Hz, 5-CH; 5.71 ppm and 5.88 ppm, 2 × d, J_{gem} = 5.5 Hz, –OCH_2–O–. ^{13}C-NMR ($CDCl_3$, 100.6 MHz, broad band and cw offset decoupled): 15.31 ppm and 24.13 ppm, 2 × q, 2-C–CH_3; 26.92 ppm, q, –C$(CH_3)_3$; 29.70 ppm, q, CH_3CO–; 38.86 ppm, s, –C$(CH_3)_3$; 39.93 ppm, t, 8-C; 46.85 ppm, d, 6-C; 63.18 ppm, d, 3-C, 76.76 ppm, d, 5-C, 80.34 ppm, t, –OCH_2O–; 166.19 ppm, s, 3-C–CO; 171.99 ppm, s, 7-CO–; 176.74 ppm, s, –CO–C$(CH_3)_3$; 203.30 ppm, s, CH_3CO–.

p-*Nitrobenzyl* (6E)-6-*acetonylidenepenicillanate* (R)-S-*oxide* **9** *and* p-*nitrobenzyl* (6E)-6-*acetonylidenepenicillanate* (S)-S-*oxide* **10**

A soln of 0.14 g (2.55 mmole) **4a** in 1.4 ml $CDCl_3$ was treated with 49 mg *m*-chloroperbenzoic acid. After 20 min, the mixture was extracted with cold $NaHCO_3$aq., then with water. The organic layer was separated and dried ($MgSO_4$), filtered and evaporated. Separation of the two sulfoxides by flash chromatography using cyclohexane–EtOAc (1:1) as eluent furnished 20 mg of **9**. ^{1}H-NMR ($CDCl_3$, 80 MHz): 1.43 ppm and 1.45 ppm, 2 × s, 2-C–CH_3; 2.59 ppm, s, –COCH_3; 4.68 ppm, s, 3-CH; 5.24 ppm, d, J = 1 Hz, 5-CH; 5.30 ppm, s, –OCH_2–; 6.34 ppm, ~s, broadened by long range coupling, 8-CH; 7.58 ppm and 8.25 ppm, centers of AA'BB'-spectrum, aromatic H.

^{13}C-NMR ($CDCl_3$, 100.6 ppm, broad band and cw offset decoupled): 16.80 ppm, q, and 24.27 ppm, q, 2-C–CH_3; 30.07 ppm, q, CH_3CO–; 66.58 ppm, t, –O–CH_2–; 67.45 ppm, d, 3-C; 73.32 ppm, s, 2-C; 85.09 ppm, d, 5-C; 124.01 ppm and 129.16 ppm, d, aromatic C ortho and meta to $-NO_2$; 132.03 ppm, d, 8-C; 141.43 ppm, s, aromatic C para to $-NO_2$; 144.61 ppm, s, 6-C; the signal of remaining carbon atoms are of too low intensity to be assigned unambiguously.

30 mg of **10** were obtained additionally. ^{1}H-NMR ($CDCl_3$, 80 MHz): 1.21 ppm and 1.70 ppm, 2 × s, 2-C–CH_3; 2.64 ppm, s, –COCH_3; 4.75 ppm, s, 3-CH; 5.35 ppm, s, –OCH_2–; 5.44 ppm, ~s, broadened by long range coupling, 5-CH; 6.15 ppm, ~s, broadened by long range coupling, 8-CH; 7.56 ppm and 8.28 ppm, centers of AA'BB-spectrum, aromatic H.

^{13}C-NMR ($CDCl_3$, 100.6 MHz): 18.44 ppm and 19.65 ppm, 2 × q, 2-C–CH_3; 30.01 ppm, q, –COCH_3; 66.43 ppm, t, –OCH_2–; 66.77 ppm, d, 3-C; 75.17 ppm, s, 2-C; 77.40 ppm, d, 5-C; 124.04 ppm, 129.02 ppm and 148.22 ppm, aromatic C ortho, meta and ipso to $-NO_2$, respectively; 141.63 ppm and 142.64 ppm, 2 × s, 6-C and aromatic C para to $-NO_2$ or vice versa; 164.11 ppm, s, 7-CO; 167.63 ppm, s, 3-C–CO; 195.98 ppm, s, CH_3–CO–.

Methylene 6-*diazopenicillanate pivalate* (R)-S-*oxide* **13** *and methylene*-6-*diazopenicillanate pivalate* (S)-S-*oxide* **14**

A stirred soln of 17.05 g (50 mmole) freshly prepared **12** in 150 ml CH_2Cl_2 was treated at room temp. with 9.5 g *m*-chloroperbenzoic acid (50 mmole). External cooling was applied in order to maintain a temp. of 20°. The mixture was stirred at this temp. for 3 hr and then filtered. The filtrate was extracted with cold dilute $NaHCO_3$aq., then with water, dried ($MgSO_4$), filtered and evaporated at 20°. The orange residue was quickly flash chromatographed. Elution with EtOAc gave 4.5 g of yellow foamy **13**. IR (KBr) 2105, 1760, 1061. ^{1}H-NMR ($CDCl_3$, 80 MHz): 12.4 ppm, s, $(CH_3)_3$C–; 1.46 ppm and 1.52 ppm, 2 × s, 2-C–CH_3; 4.41 ppm, s, 3-CH; 5.68 ppm, s, 5-CH; 5.80 ppm and 5.90 ppm, 2 × d, J_{gem} = 5 Hz, –OCH_2O–.

4 g of yellow crystalline **14** were also isolated. IR (KBr) 2112, 1774, 1749, 1059. ^{1}H-NMR ($CDCl_3$, 80 MHz): 1.24 ppm, s, $(CH_3)_3$C–; 1.29 ppm and 1.67 ppm, 2 × s, 2-C–CH_3; 4.40 ppm, s, 3-CH; 5.75 ppm and 6.00 ppm, 2 × d, J_{gem} = 5.5 Hz, –OCH_2O–; 5.88 ppm, s, 5-CH. ^{13}C-NMR ($CDCl_3$, 100.6 MHz, broad band and cw offset decoupled): 18.09 ppm and 20.10 ppm, q, 2-C–CH_3; 26.90 ppm, q, $(CH_3)_3$C–; 38.81 ppm, s, –C$(CH_3)_3$; 63.89 ppm, d, 3-C; 74.07 ppm, s, 2-C; 80.45 ppm, t, –O–CH_2O–; 80.59 ppm, d, 5-C; 165.20 ppm, s, 7-CO–; 167.37 ppm, s, 3-C–CO–; 176.77 ppm, s, –CO–C$(CH_3)_3$.

(6R)-6-*Acetonylpenicillanic acid* (R)-S-*oxide sodium salt* **8c**

To a stirred suspension of 1.5 g prereduced Pd–C in 20 ml EtOAc, a soln of 1.85 g (4.5 mmole) **8a** in 50 ml EtOAc was added at room temp. The stirred mixture was hydrogenated at atmospheric pressure for 2.5 hr. The catalyst was removed by filtration through $MgSO_4$. The filtrate was concentrated to a volume of 5 ml. Under cooling and stirring

Table 1. Final fractional coordinates for **7a** with estimated standard deviations in parenthesis for **7a**

Atoms	x	y	z
S(1)	0.3905 (1)	0.4955 (0)	0.2537 (1)
C(2)	0.4273 (3)	0.5464 (9)	0.3704 (4)
C(3)	0.3852 (3)	0.6938 (11)	0.4198 (4)
C(4)	0.4432 (4)	0.8183 (13)	0.3801 (5)
N(5)	0.4880	0.6737	0.3560
C(6)	0.5277 (3)	0.6581 (10)	0.2724 (4)
C(7)	0.4901 (3)	0.4943 (12)	0.2211 (4)
C(8)	0.4870 (4)	0.5168 (17)	0.1171 (4)
C(9)	0.5241 (4)	0.3179 (12)	0.2525 (7)
O(10)	0.3570 (3)	0.6630 (8)	0.2165 (3)
C(11)	0.3004 (4)	0.7283 (11)	0.4013 (5)
C(12)	0.2517 (4)	0.5698 (14)	0.4126 (5)
C(13)	0.1683 (4)	0.6040 (16)	0.4239 (7)
O(14)	0.2773 (3)	0.4226 (11)	0.4102 (5)
O(15)	0.4502 (3)	0.9729 (10)	0.3674 (4)
C(16)	0.6116 (3)	0.6284 (10)	0.2933 (4)
O(17)	0.6428 (2)	0.5922 (10)	0.3656 (3)
O(18)	0.6487 (2)	0.6410 (7)	0.2172 (2)
C(19)	0.7299 (3)	0.6126 (13)	0.2288 (4)
C(20)	0.7623 (3)	0.5988 (9)	0.1378 (4)
C(21)	0.7198 (3)	0.6279 (9)	0.0561 (4)
C(22)	0.7537 (3)	0.6116 (10)	-0.0264 (4)
C(23)	0.8298 (3)	0.5652 (10)	-0.0234 (4)
C(24)	0.8730 (3)	0.5348 (10)	0.0578 (4)
C(25)	0.8386 (3)	0.5552 (10)	0.1383 (4)
N(26)	0.8648 (3)	0.5409 (10)	-0.1084 (4)
O(27)	0.8282 (3)	0.5703 (11)	-0.1794 (3)
O(28)	0.9308 (3)	0.4850 (10)	-0.1061 (3)
H(1)-C(2)	0.4322	0.4201	0.4046
H(1)-C(3)	0.3761	0.6833	0.4913
H(1)-C(6)	0.5228	0.7780	0.2325
H(1)-C(8)	0.4556	0.6368	0.1011
H(2)-C(8)	0.4591	0.4071	0.0815
H(3)-C(8)	0.5443	0.5300	0.0963
H(1)-C(9)	0.5330	0.3053	0.3256
H(2)-C(9)	0.5785	0.3263	0.2235
H(3)-C(9)	0.4933	0.2041	0.2250
H(1)-C(11)	0.2901	0.7757	0.3323
H(2)-C(11)	0.2843	0.8290	0.4481
H(1)-C(13)	0.1601	0.7455	0.4247
H(2)-C(13)	0.1527	0.5483	0.4874
H(3)-C(13)	0.1330	0.5472	0.3681
H(1)-C(19)	0.7567	0.7217	0.2661
H(2)-C(19)	0.7410	0.4914	0.2662
H(1)-C(21)	0.6605	0.6654	0.0564
H(1)-C(22)	0.7211	0.6335	-0.0906
H(1)-C(24)	0.9323	0.4977	0.0580
H(1)-C(25)	0.8716	0.5362	0.2024

Table 2. Anisotropic thermal parameters for **7a**

$T = \exp - (B_{11} h^2 + B_{22} k^2 + B_{33} l^2 + B_{23} kl + B_{13} hl + B_{12} hk)$

Atoms	B_{11}	B_{22}	B_{33}	B_{23}	B_{13}	B_{12}
S(1)	0.0033	0.0256	0.0050	-0.0019	0.0008	-0.0036
C(2)	0.0035	0.0233	0.0038	0.0030	0.0018	-0.0005
C(3)	0.0040	0.0262	0.0046	-0.0000	0.0029	0.0001
C(4)	0.0040	0.0298	0.0052	-0.0049	0.0021	-0.0029
N(5)	0.0033	0.0241	0.0038	-0.0005	0.0014	-0.0021
C(6)	0.0036	0.0221	0.0031	0.0005	0.0016	-0.0021
C(7)	0.0032	0.0287	0.0049	-0.0054	0.0019	-0.0041
C(8)	0.0054	0.0504	0.0039	-0.0074	0.0026	-0.0100
C(9)	0.0038	0.0280	0.0112	-0.0053	0.0028	-0.0020
O(10)	0.0043	0.0349	0.0054	0.0039	-0.0013	0.0024
C(11)	0.0043	0.0283	0.0067	-0.0013	0.0033	0.0035
C(12)	0.0040	0.0299	0.0058	0.0047	0.0024	-0.0012
C(13)	0.0037	0.0395	0.0112	0.0069	0.0025	-0.0003
O(14)	0.0050	0.0303	0.0119	0.0026	0.0052	-0.0015
O(15)	0.0064	0.0251	0.0107	-0.0056	0.0064	-0.0044
C(16)	0.0033	0.0241	0.0042	0.0004	0.0009	-0.0039
O(17)	0.0035	0.0510	0.0044	0.0025	0.0007	-0.0013
O(18)	0.0032	0.0316	0.0036	0.0037	0.0018	0.0011
C(19)	0.0029	0.0402	0.0048	0.0023	0.0010	0.0018
C(20)	0.0030	0.0177	0.0048	0.0002	0.0015	-0.0003
C(21)	0.0027	0.0212	0.0048	0.0009	0.0005	0.0001
C(22)	0.0027	0.0244	0.0049	0.0032	0.0012	0.0003
C(23)	0.0029	0.0200	0.0054	-0.0019	0.0020	-0.0030
C(24)	0.0024	0.0283	0.0055	-0.0005	0.0006	0.0008
C(25)	0.0030	0.0239	0.0050	0.0005	-0.0002	-0.0009
N(26)	0.0035	0.0328	0.0057	-0.0015	0.0023	-0.0030
O(27)	0.0050	0.0637	0.0049	0.0017	0.0025	-0.0001
O(28)	0.0037	0.0443	0.0078	-0.0071	0.0041	-0.0001

this soln was treated with 2.25 ml 2N soln of sodium 2-ethylcaproate in EtOAc. Addition of 100 ml dry Et_2O precipitated the Na salt. The crystalline salt was filtered, thoroughly washed with ether and dried to give 1.2 g of yellowish crystals **8c**. IR (MBr) 1770, 1719, 1619, 1410, 1046, 1035. ^{1}H-NMR (D_2O with DSS as internal standard, 60 MHz): 1.36 ppm and 1.68 ppm, 2 × s, 2-C–CH_3; 2.14 ppm, s, –$COCH_3$; ~3.27 ppm, ~d, J ~ 8 Hz, 8-CH_2; ~4.15 ppm, m, 6-CH; 4.23 ppm, s, 3-CH; 4.92 ppm, d, J = 4 Hz, 5-CH.

^{13}C-NMR (D_2O, 100.6 MHz): 20.74 ppm and 21.83 ppm, 2 × q, 2-C–CH_3; 31.45 ppm, q, –$COCH_3$; 38.97 ppm, t, 8-CH_2; 47.24 ppm, d, 6-C; 69.23 ppm, d, 3-C; 76.18 ppm, d, 5-C; 77.08 ppm, s, 2-C; 175.84 ppm and 179.04 ppm, 2 × s, 7-CO and 3-C–CO or vice verse; 212.43 ppm, s, CH_3CO–.

(6R)-6-*Acetonylpenicillanic acid* (S)-S-*oxide sodium salt* **7c** was analogously obtained. IR (KBr) 1770, 1715, 1620, 1400, 1050, 1024. ^{1}H-NMR (D_2O, with DSS as internal standard, 60 MHz): 1.32 ppm and 1.66 ppm, 2 × s, 2-C–CH_3; 2.27 ppm, s, –$COCH_3$; ~3.25 ppm, m, ~d, J ~ 8 Hz, 8-CH_2; 4.18 ppm, m, 6-CH; 4.31 ppm, s, 3-CH; 5.27 ppm, d, J = 4.8 Hz, 5-CH.

X-ray structure determination of p-*nitrobenzyl* (6R)-6-*acetonylpenicillanate* (S)-S-*oxide* **7a**

Crystal data. Formula $C_{18}H_{20}N_2O_7S$; M = 408.43. The crystals are monoclinic, they belong to the space group C2, Z = 4, with a = 17.584(6), b = 7.565(3), c = 14.725(5) Å, β = 94.34(3)°, V = 1953.17 Å^3. Calculated density = 1930 kgm^{-3}, μ = 164 m^{-1} (λ = 0.71069 Å). Crystal size: 0.25 × 0.5 × 0.5 mm^3. T = 293° K.

Intensity measurements. Intensities were measured up to θ = 28 degrees with the help of a computer (PDP 8) controlled four circle diffractometer (Hilger and Watts Y290) operating in the $\omega/2\theta$ scan mode using zirconium filtered molybdenum radiation.

Table 3. Bond lengths (A) with standard deviations in parentheses for **7a**

Atoms	Lengths	Atoms	Lengths
C(2)-S(1)	1.832(6)	C(13)-C(12)	1.510(10)
C(7)-S(1)	1.852(6)	O(14)-C(12)	1.203(10)
O(10)-S(1)	1.484(6)	O(17)-C(16)	1.193(7)
C(3)-C(2)	1.550(9)	O(18)-C(16)	1.341(7)
N(5)-C(2)	1.465(8)	C(19)-O(18)	1.442(7)
C(4)-C(3)	1.535(10)	C(20)-C(19)	1.498(8)
C(11)-C(3)	1.519(9)	C(21)-C(20)	1.385(8)
N(5)-C(4)	1.409(10)	C(25)-C(20)	1.380(8)
O(15)-C(4)	1.193(10)	C(22)-C(21)	1.399(8)
C(6)-N(5)	1.466(7)	C(23)-C(22)	1.382(8)
C(7)-C(6)	1.571(10)	C(24)-C(23)	1.386(8)
C(16)-C(6)	1.500(8)	N(26)-C(23)	1.448(7)
C(8)-C(7)	1.537(8)	C(25)-C(24)	1.381(8)
C(9)-C(7)	1.519(12)	O(27)-N(26)	1.206(7)
C(12)-C(11)	1.490(11)	O(28)-N(26)	1.232(7)

Table 4. Bond angles with standard deviations in parentheses for **7a**

Angles	Degrees	Angles	Degrees
C(7)-S(1)-C(2)	88.3(3)	C(9)-C(7)-C(8)	112.6(7)
O(10)-S(1)-C(2)	105.6(3)	C(12)-C(11)-C(3)	114.0(7)
O(10)-S(1)-C(7)	105.4(3)	C(13)-C(12)-C(11)	116.4(8)
C(3)-C(2)-S(1)	116.4(4)	O(14)-C(12)-C(11)	121.4(7)
N(5)-C(2)-S(1)	102.3(3)	O(14)-C(12)-C(13)	122.1(8)
N(5)-C(2)-C(3)	88.5(5)	O(17)-C(16)-C(6)	126.6(5)
C(4)-C(3)-C(2)	84.7(5)	O(18)-C(16)-C(6)	110.5(5)
C(11)-C(3)-C(2)	122.5(6)	O(18)-C(16)-O(17)	122.8(5)
C(11)-C(3)-C(4)	119.8(7)	C(19)-O(18)-C(16)	115.5(4)
N(5)-C(4)-C(3)	91.2(6)	C(20)-C(19)-O(18)	110.2(5)
O(15)-C(4)-C(3)	137.8(8)	C(21)-C(20)-C(19)	123.2(5)
O(15)-C(4)-N(5)	130.9(7)	C(25)-C(20)-C(19)	116.6(5)
C(4)-N(5)-C(2)	92.6(5)	C(25)-C(20)-C(21)	120.2(5)
C(6)-N(5)-C(2)	117.9(5)	C(22)-C(21)-C(20)	120.2(5)
C(6)-N(5)-C(4)	125.8(6)	C(23)-C(22)-C(21)	118.0(5)
C(7)-C(6)-N(5)	104.9(5)	C(24)-C(23)-C(22)	122.5(5)
C(16)-C(6)-N(5)	111.3(4)	N(26)-C(23)-C(22)	118.6(5)
C(16)-C(6)-C(7)	110.6(5)	N(26)-C(23)-C(24)	118.9(5)
C(6)-C(7)-S(1)	104.1(4)	C(25)-C(24)-C(23)	118.3(5)
C(8)-C(7)-S(1)	107.2(4)	C(24)-C(25)-C(20)	120.8(5)
C(8)-C(7)-C(6)	111.9(7)	O(27)-N(26)-C(23)	119.5(5)
C(9)-C(7)-S(1)	106.4(5)	O(28)-N(26)-C(23)	118.7(6)
C(9)-C(7)-C(6)	113.9(5)	O(28)-N(26)-O(27)	121.7(5)

Table 5. Torsion angles for **7a**

Angles	Degrees	Angles	Degrees
S1(C2-N5)C6	-30.1	C2(C3-C11)C12	54.6
C2(N5-C6)C7	-0.8	C3(C11-C12)C13	161.9
N5(C6-C7)S1	31.2	O15(C4-N5)C6	-35.8
C6(C7-S1)C2	-42.4	C4(N5-C6)C16	123.1
C7(S1-C2)N5	40.6	N5(C6-C16)O18	-170.7
C2(C3-C4)N5	-12.8	C6(C16-O18)C19	-179.3
C3(C4-N5)C2	13.5	C16(O18-C19)C20	170.2
C4(N5-C2)C3	-13.4	O18(C19-C20)C21	6.0
N5(C2-C3)C4	12.3	C19(C20-C21)C22	-179.6
S1(C2-C3)C11	31.6		

Structure determination and refinement. Independent data for 2529 planes were used to solve the structure with the help of Multan 78 (10) and 1589 with $I > 2.5\sigma$ (I) for the refinement by full-matrix least-squares (11) with anisotropic temperature factors for the non-H atoms.

The calculated parameters of the H atoms were included in the structure factor calculation but not refined. The final discrepancy values are $R = 0.053$ and $RW = 0.0605$. The principal results: final parameters, bond lengths, bond angles and some torsion angles are set out in the Tables 1–5.

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