

SYNTHESIS OF METHYLENE (R)-6-ACETONYLIDENE-3-METHYL-7-OXO-4-THIA-
1-AZABICYCLO[3.2.0]HEPT-2-ENE-CARBOXYLATE PIVALATE

Solange Adam

Pharmaceutical Research Department, F. Hoffmann-La Roche and Co. Ltd.,
CH-4002 Basel, Switzerland

Abstract—Methylene (Z)-6-acetonylidene-penicillanate pivalate (1 b)
a powerful inhibitor of β -lactamases, is converted efficiently
into the title compound.

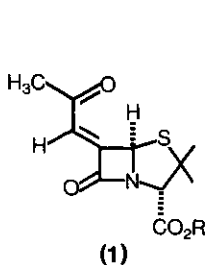
Reports from our laboratories have described the synthesis and the exceptional β -lactamase activity of 6-acetylmethylenepenicillanic acid (1 a)¹⁻⁶. This compound was shown to be more potent than clavulanic acid and sulbactam. As part of a programme directed towards the synthesis of nuclear analogs, we now report the transformation of (1 b) into the analogous penem (11).

Treatment of methylene (Z)-6-acetonylidene-penicillanate pivalate (1 b) with m-chloroperbenzoic acid (1.1 equiv., tetrahydrofuran, 20°C) gave the β -sulfoxide (2)⁷ (90%). Reaction of (2) with thiophenol (1 equiv.) in the presence of catalytic amounts of DBN in dichloromethane at 20°C, followed by flash chromatography, gave the adducts (3) (35%) and (4) (30%). Compound (3) was obtained as a diastereomeric mixture. When (4) was heated with 2-mercaptobenzothiazole (1 equiv., toluene, reflux 7h), using the Kamiya⁸ procedure, disulfide (5) was obtained in almost quantitative yield. Base-catalysed isomerisation^{9,10} (triethylamine, 0.1 equiv., dichloromethane, 4h, 20°C) gave (6 a). Crude disulfide (6 a) was dissolved in a mixture of acetic acid-acetic anhydride (ratio 1:3) and treated at -20°C with triphenylphosphine (1 equiv.) followed by pyridine. The crystalline acetylthio derivative (6 b) was then isolated, after flash chromatography (73%). The isopropylidene compound (6 b) was then ozonised, in dichloromethane at -78°C, to give the oxalyl derivative (7). Reduction of (7) with Zn and acetic acid in dichloromethane at 5°C gave the hemiaminal (8 a) which was subsequently converted by thionyl

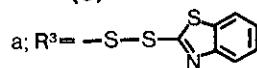
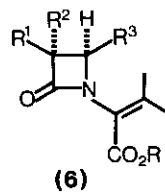
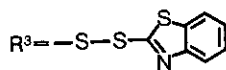
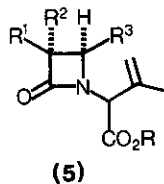
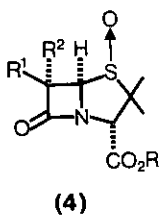
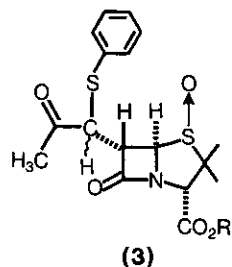
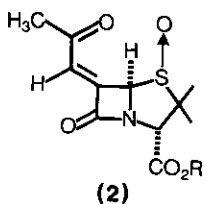
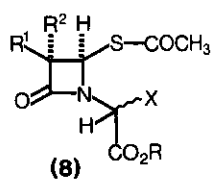
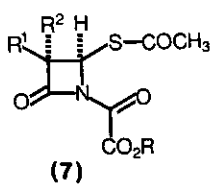
chloride-pyridine (1.5 equiv.) in dichloromethane at -20°C to an oily chloride (8 b). The phosphorane (9) was obtained in 80% yield when (8 b) was treated with triphenylphosphine (dichloromethane, reflux 20h). When heated in toluene under reflux (12h) (9) cyclised to the oily penem (10) which was isolated, after flash-chromatography, in 60% yield. The ^1H n.m.r. spectra showed the expected resonances for the pivaloyloxymethyl group together with signals at δ (CDCl_3) 2.18 (=Me), 2.27 (CO-Me), 3.18 and 3.38 (C(8)-H, 2xd, J 18Hz), 5.62 (C(5)-H) and 7.5 (Ar). The double bond at C(6) was reintroduced in the following manner: (10) was treated with m-chloroperbenzoic acid (1 equiv.) in tetrahydrofuran at -15°C and the mixture was allowed to warm-up to ambient temperature (2h). The (Z)-acetylmethylene penem¹¹ (11) formed smoothly and was isolated, after flash chromatography, as an orange oil in 80% yield. No (E) isomer was detected. The ^1H n.m.r. spectra showed the expected resonances for the pivaloyloxymethyl group together with signals at δ (CDCl_3) 2.36 (=Me and CO-Me), 6.21 (C(5)-H quite a d J 1Hz), 6.61 (C(8)-H); ν_{max} (CHCl_3) 1793, 1752, 1725 and 1715 cm^{-1} . Penem (11) was found to inhibit a number of cell-free β -lactamases derived from both Gram-positive and Gram-negative organisms; it turned out to be more potent against the β -lactamase of *Proteus vulgaris* 1028 than the corresponding penam (1 b). Compound (11) was devoid of any antibacterial activity.

ACKNOWLEDGEMENTS

I thank Drs. R.L. Then and P. Angehrn for the biochemical and synergy studies.

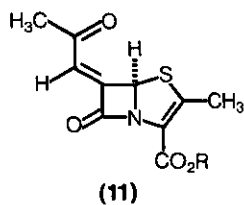
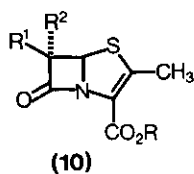
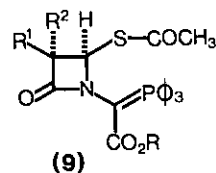


a; R = H

b; R = $-\text{CH}_2\text{OCOC}(\text{CH}_3)_3$

b; R³ = $-\text{S}-\text{COCH}_3$


a; X = OH

b; X = Cl


R = $-\text{CH}_2\text{OCOC}(\text{CH}_3)_3$

R¹ = $-\text{CH}_2\text{COCH}_3$

R² = $-\text{S}-$

REFERENCES AND NOTES

1. Europ.Pat.Applic.Publi. No. 50805 (F. Hoffmann-La Roche Ltd.)
2. M. Arisawa and R.L. Then, J. Antibiot., 1982, 35, 1578.
3. P. Angehrn and M. Arisawa, J. Antibiot., 1982, 35, 1584.
4. M. Arisawa and S. Adam, Biochem. J., 1983, 211, 447.
5. M. Arisawa and R.L. Then, J. Antibiot., 1983, 36, 1372.
6. M. Arisawa and R.L. Then, Biochem. J., 1983, 209, 609.
7. S. Adam, W. Arnold and P. Schöholz, Tetrahedron, 1983, 39, 2485.
8. T. Kamiya, T. Teraji, Y. Saito, M. Hashimoto, O. Nakaguchi and T. Oku, Tetra. Lett., 1973, 3001.
9. R.B. Woodward, "Recent Advances in the Chemistry of β -Lactam Antibiotics" ed. J. Elks, Special Publication No 28, The Chemical Society, London, 1977, p. 167.
10. I. Ernest, J. Gosteli, C.W. Greengrass, W. Holick, D.E. Jackmann, H.R. Pfaendler and R.B. Woodward, J. Am. Chem. Soc., 1978, 100, 8214.
11. Stereochemical assignment for (11) is based on comparison of its n.m.r. properties with those of related compounds: (1 b) and the corresponding 6 (E) isomer.

Received, 28th March, 1984