Tetrahedron Letters No. 32, pp 2797 - 2800, 1976. Pergamon Press. Printed in Great Britain.

NOVEL 5,6-BOND CLEAVAGES OF PENICILLIN SULFOXIDES

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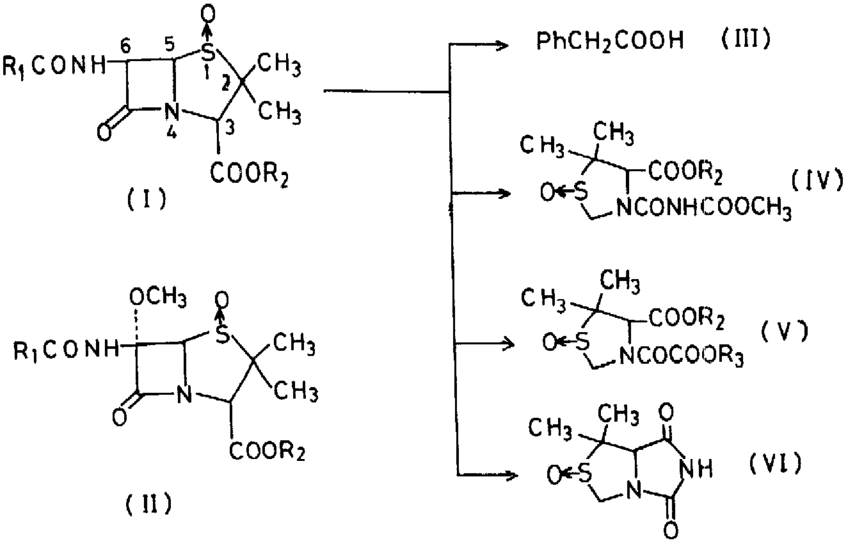
(Received in Japan 31 May 1976; received in UK for publication 21 June 1976)

Since the discovery of a new family of 7-methoxy cephalosporins (Cephamycins), the method of methoxylation of penicillin at 6-position has aroused considerable interest.[1)]

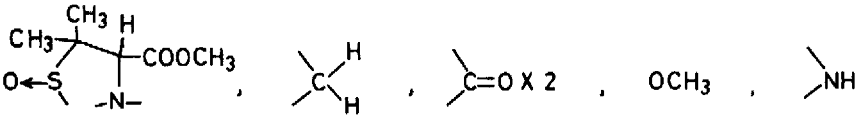
In 1973, Baldwin, et al.[2)] reported that penicillin sulfoxides (I) were easily methoxylated to afford II [R_1: CH_2OPh, R_2: CH_3 and $CH_2C_6H_4(NO_2\text{-}p)$] with tert-butyl hypochlorite in methanol containing sodium borate buffer at 0°C.

Chart 1



However it was revealed that the reaction of I with the same alkoxylating agent gave quite different products under a different reaction condition (especially another temperature), and the reactions were found to be 5,6-bond cleavage of penicillin sulfoxides (I). This paper deals with these reactions.

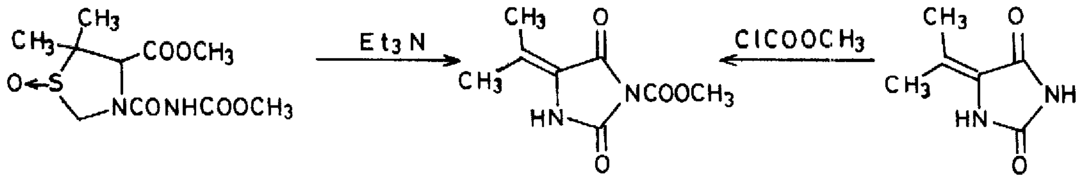
Treatment of benzylpenicillin sulfoxide methylester (Ia, R_1: CH_2Ph, R_2: CH_3) with a 3-fold molar amount of tert-butyl hypochlorite and sodium borate in methanol at 25-26° furnished three products III,IVa and Va. Compound III (51 % yield) was identified with phenylacetic acid by spectral measurements. Compound IVa (R_2: CH_3, 21 % yield), mp 145-148° (ethanol), has the empirical formula of $C_{10}H_{16}N_2O_6S$ and gives peaks in the mass spectrum as follows; m/e (%); 260 (32), 114 (61), 83 (100), 82 (69), 70 (82). The molecular ion peak is not appeared but the elimination of methanol from the molecule gives a peak at m/e 260. The IR spectrum of IVa shows the presence of three carbonyl groups at 1782, 1750 and 1680 cm^{-1}. The NMR spectrum of IVa has signals assigned as follows:$-\overset{|}{\underset{|}{C}}(CH_3)_2$ 1.22 (3H, s) and 1.60 (3H, s), $H-\overset{|}{\underset{|}{C}}-COOMe$ 4.86 (1H, s), $-COO\underline{Me}x2$ 3.77 (3H, s) and 3.80 (3H, s), $-CH_2-$ 4.59 (1H, d, J=13 Hz), and 4.77 (1H, d, J=13 Hz), NH 8.16 (1H, s, disappeared in D_2O). From above data and the structure of the starting material, the following groups would present in VIa:



Thus one of structures composed of the above groups is IVa in chart 1.

The structure of IVa was confirmed as follows. Compound IVa was treated with triethylamine to afford VII, mp 182-185°, $C_8H_{10}N_2O_4$, [mass spectrum m/e: 198 (M^+). IRν_{max}^{KBr} cm^{-1}: 1815, 1765, 1715, 1670. NMR ($CDCl_3$)δ: 1.93 (3H, s), 2.27 (3H, s), 3.98 (3H, s).] in a 29 % yield. Compound VII was identical in all aspects with the acylated product derived from 5-isopropylidenehydantoin (VIII)[3] and methyl chloroformate.

Chart 2



(IVa) (VII) (VIII)

The similarity between IV, V and VI in the NMR and mass spectra suggested that these compounds contained the common skeleton, 5,5-dimethylthiazolidine 1-oxide. Structures of IV, V and VI in chart 1 were proposed.

Compound Va was isolated as the methyl ester after methylation of the acid V (R_2: CH_3, R_3: H) with diazomethane in chloroform.

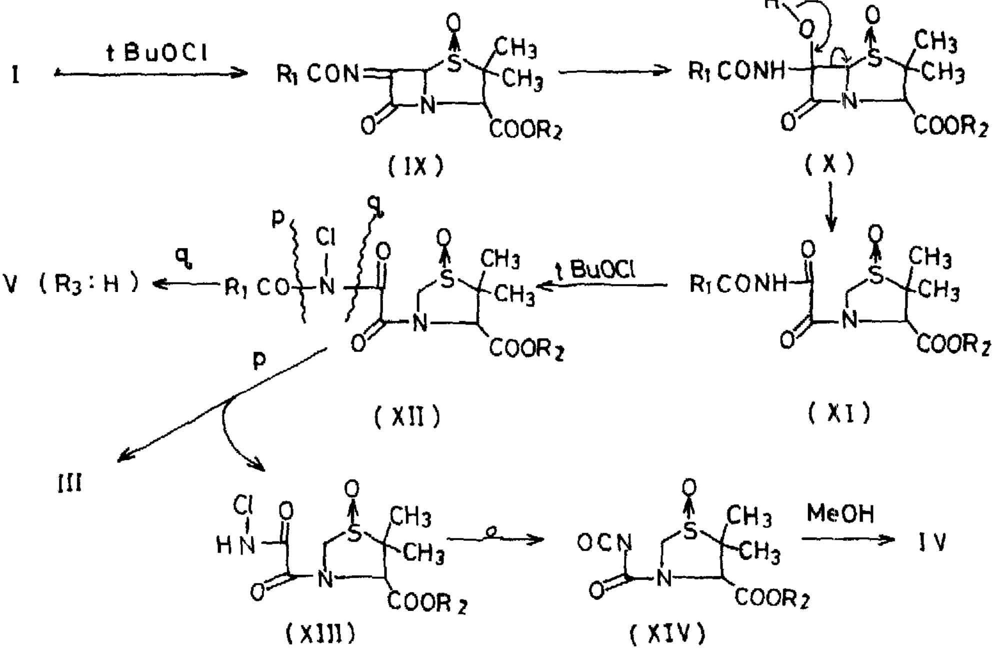
Compound Va (R_3 and R_3: CH_3, 4 % yield), mp 127-128°C (benzene-ether), $C_{10}H_{15}NO_6S$, mass spectrum m/e (%): 277 (M^+, 20), 114 (52), 83 (73), 82 (63), 59 (100), 45 (97). IR ν_{max}^{KBr} cm^{-1}: 1740, 1727, 1675. NMR ($CDCl_3$)[4] δ : 1.23 (3H, s, CH_3), 1.64 (3H, s, CH_3), 3.83 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 4.51 (1H, d, J=14 Hz, HC-), 4.77 (1H, d, 14 Hz, -CH), 4.84 (1H, s, HC-CO).

Similarly, from benzylpenicillin sulfoxide benzyl ester (Ib, R_1 and R_2: CH_2Ph) under the same condition, three products, III, IVb and Vb were obtained. III, 37 % yield. IVb (R_2: CH_2Ph, 54 % yield), mp 142-145°C (ethanol), $C_{16}H_{20}N_2O_6S$, mass spectrum m/e (%): 260 (6), 91 (100), 83 (23), 82 (19), 70 (15). NMR ($CDCl_3$) δ : 1.09 (3H, s), 1.54 (3H, s), 3.75 (3H, s), 4.54 (1H, d, J=13 Hz), 4.74 (1H, d, J=13 Hz), 4.89 (1H, s), 5.14 (1H, d, J=12 Hz), 5.32 (1H, d, J=12 Hz), 7.36 (5H, s). $[\alpha]_D^{25}$ = +137° ($CHCl_3$, c=0.98). Vb (R_2: CH_2Ph, R_3: CH_3), mp 105-107°C (benzene-hexane), $C_{16}H_{19}NO_6S$, mass spectrum m/e (%): 353 (M^+, 2), 91 (100), 83 (10), 82 (9), 59 (13). IR ν_{max}^{KBr} cm^{-1}: 1745, 1730, 1675. NMR ($CDCl_3$)[4] δ : 1.10 (3H, s), 1.58 (3H, s), 3.90 (3H, s), 4.49 (1H, d, J=14 Hz), 4.65 (1H, d, J=14 Hz), 4.86 (1H, s), 5.09 (2H, d, J=14 Hz), 7.39 (5H, s). $[\alpha]_D^{25}$ = +166° ($CHCl_3$, c= 0.97).

In the case of benzylpenicillin sulfoxide trichloroethyl ester (Ic, R_1: CH_2Ph, R_2: CH_2CCl_3), in addition to III (59 % yield), a trans-esterificated product VIa (R_2: CH_3, 13 % yield) and a trace of VI were obtained. VI, mp 213-215°C (dec.) (methanol), $C_7H_{10}N_2O_3S$, mass spectrum m/e (%): 202 (M^+, 15), 153 (62), 83 (80), 82 (100), 55 (39), 41 (93). IR ν_{max}^{KBr} cm^{-1}: 1785, 1720. NMR (DMSO-d_6) δ : 0.94 (3H, s), 1.43 (3H, s), 3.86 (1H, d, J=12 Hz), 4.54 (1H, s), 5.27 (1H, d, J=12 Hz).

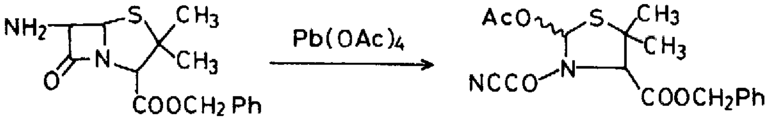
One of possible reaction paths might be summerized in chart 3.

Chart 3



Compound I is oxidized with tert-butyl hypochlorite to form the acylimine$^{2)}$ (IX), which is converted to X by an addition of water contained in borax. Then 5-6 bond fission of X produces XI. The presence of sulfoxide group would accelerate this fission.$^{5)}$ Tert-butyl hypochlorite chlorinates again XI to yield XII and the hydrolysis of XII at q gives V (R_3=H). On the other had, the hydrolysis of XII at p affords III and XIII. Hofmann reaction of XIII followed by an addition of methanol produces IV.

On the 5,6-bond cleavage of penicillin, Stoodley$^{5)}$ has pointed out some possibilities in his review but he described only one example, i.e., XV - XVI. The present work is another example of 5,6-bond cleavage of penicillin derivatives.



(XV) (XVI)

Acknowledgement

The authors are grateful to Drs. S. Minami and H. Uno for their encouragement throughout this work and wish to thank Messrs. S. Arakawa, K. Yoshida and A. Itokawa for the spectral data and the related discussion.

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4) NMR spectra showed that Va and Vb were equilibium mixtures. Data for the main counterpart were described.

5) R.J. Stoodely, Tetrahedron, 31, 2321 (1975).