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MODEL STUDIES TOWARDS THE SYNTHESIS OF 2-β-HYDROXYMETHYL PENICILLIN N

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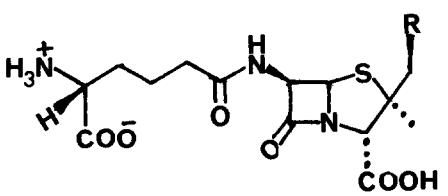
Abstract: The synthesis of 2-β-hydroxymethyl penicillin V sulfoxide is described as a model study towards the synthesis of 2-β-hydroxymethyl penicillin N.

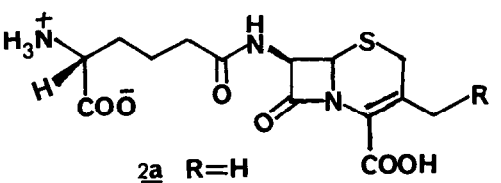
As part of our interest in 2-β-hydroxymethyl penicillin N 1b[1] as a possible intermediate in the cell-free ring expansion of penicillin N 1a into desacetoxy-cephalosporin C 2a[2,3,4] we report here the synthetic attempts towards the title compound.

The only report of 2-β-hydroxymethyl penicillin is by Cooper[5] when he isolated 2-β-hydroxymethyl penicillin V sulfoxide 4 as one of a "plethora of products" by peracidic oxidation of a thiazoline derivative 3. The approach followed in our studies stems from the observation made by Kamiya[6] of isolation of penicillin and cephalosporin derivatives when the disulfide 5, was treated with Ag^+ in the presence of a nucleophile. Thus the disulfide 5, prepared by Kamiya's[7] procedure, when treated with the silver salt of a carboxylic acid[8] in the presence of a large excess of the corresponding carboxylic acid gave penicillin derivatives (6a-c) and cephalosporin derivatives (7a-c). The results are summarised in Table 1 and the chemical shifts of various characteristic protons are given in Table 2.

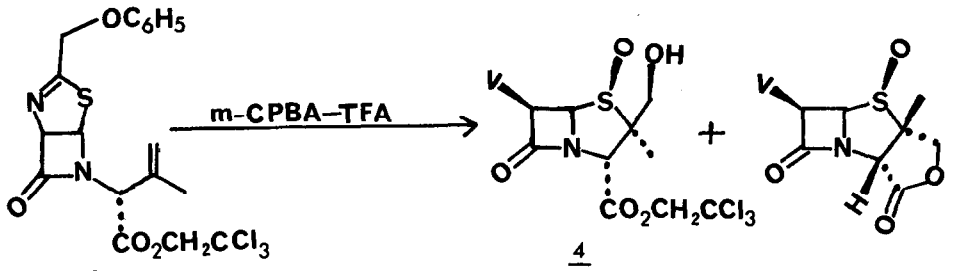
Penicillin derivatives (6a-c) and cephalosporin derivatives (7a-c) were obtained in the ratio given in Table 1 when the disulfide 5 was treated with silver salts of o-nitrophenyl acetic acid, o-nitrocinnamic acid and chloroacetic acid respectively. The reduction of penicillin derivatives (6a & b) with 10% Pd-C resulted in the corresponding amino derivatives (in 6b, the double bond



1a R=H
1b R=OH

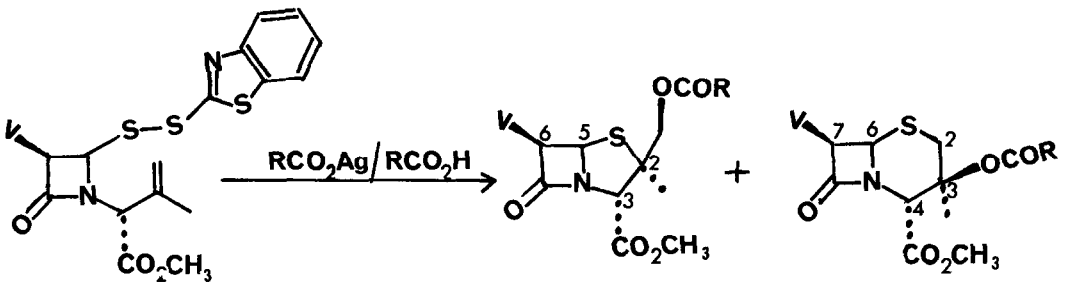


2a R=H
2b R=OH
2c R=OCOCH$_3$



3 4

V = $C_6H_5OCH_2CONH$



5 6 7

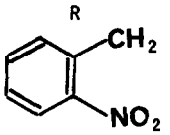
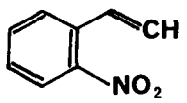
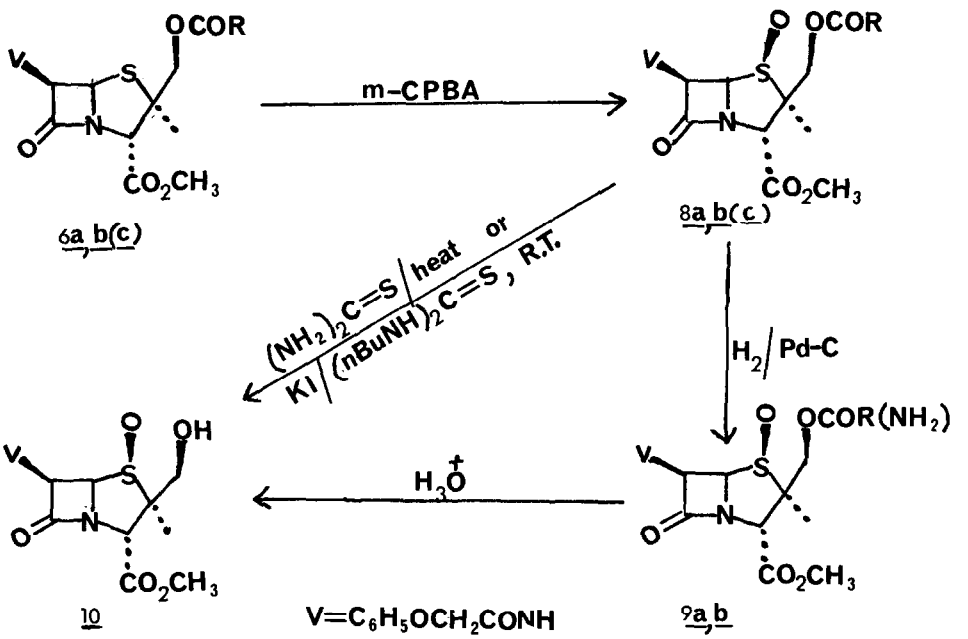
	R	Reaction condition	Ratio (6:7)	Overall Yield (%)
a		Benzene, R.T., 38 hrs.	2:1	60.8
b		DMF, R.T., 70 hrs.	1.5:1:2(7, R= H)	59.5
c	$ClCH_2$	Benzene, R.T., 17 hrs. or CH_2Cl_2, R.T., 4 hrs.	1:1	70.2

Table 1



Comparison of chemical shifts in 6 and 7

	Ring CH_3	2β-CH_2(H_6)/H_2(7)	H_3(6)/H_4(7)	H_5,H_6(6)/H_6(7)	H_7(7)
6a	1.43	4.62, 4.98 (ABq) J_{AB} = 12Hz	4.67	5.63-5.8 (m)	
7a	1.50	3.40 (s)	4.75	5.3 (d) J = 4Hz	5.7 (d of d) J = 4,10Hz
6b	1.53	3.93, 4.53 (ABq) J_{AB} = 11Hz	4.8	5.53-5.8 (m)	
7b	1.65	3.55 (s)	4.8	5.3 (d) J = 4Hz	5.6 (d of d) J = 4, 10Hz
6c	1.50	4.01, 4.3 (ABq) J_{AB} = 11Hz	4.66	5.56-5.8 (m)	
7c	1.60	3.46 (s)	4.8	5.33 (d) J = 4Hz	5.70 (d of d) J = 4, 10Hz

Table 2

is also reduced), which upon treatment with acid yielded only complex mixtures. The penicillin derivatives 6a, b & c were oxidised to the corresponding sulfoxides 8a, b & c in 86.3, 94.2 and 75.8% yield respectively. Compounds 8a & b on hydrogenation with 10% Pd-C afforded the corresponding amino derivatives 9a & b (the double bond in 8b is also reduced) in quantitative yields. Subsequent treatment with dil. HCl yielded 2-β-hydroxymethyl penicillin V sulfoxide methyl ester (10) in 49.4 and 68.2% yield respectively [n.m.r. ($CDCl_3$): 1.23 (s, 2-CH_3), 3.86, 4.16 (ABq, CH_2-O), 5.0 (s, H_3), 5.03 (d, 4Hz, H_5), 6.16 (d of d, 4Hz, 10Hz, H_6); i.r. ($CHCl_3$): 1800, 1745, 1690 cm^{-1}; mass spectrum M^+ = 396]. Since we have established the instability of 2-β-hydroxymethyl penicillin, a milder method for deprotection was sought. 2-β-Chloroacetoxymethyl penicillin sulphoxide 8c on heating with thiourea in absolute ethanol gave the compound 10 in 70% yield after chromatography.[10] The same conversion was more conveniently achieved by treating penicillin derivative 8c with KI followed by N,N'di-n-butylthiourea in acetone at R.T. in 74% yield.

We are presently investigating the application of the above procedure to the synthesis of 2-β-hydroxymethyl penicillin N.

Acknowledgments

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