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ON THE PREPARATION OF 4-MERCAPTO-AZETIDINONES

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4-Dithioazetidinone and 4.7-diaza-2-thiabicyclo[3.2.0]hept-2-en-6-one derivatives were prepared from penam-3-isocyanates, which are useful intermediates to 4-mercapto-azetidinones.

Azetidinone compounds of types II and IV play key roles in the synthesizing of new β-lactam antibiotics and thienamycin analogues. An important step in obtaining these compounds is the removal of the β-lactam N-substituent moiety. This can usually be done by oxidation with $KMnO_4$[1], OsO_4[1], ozone[2] or $Pb/OAc/_4$[3], or via pyrazoline formation[4]. Another approach is the conversion of the 3-COOH group to the hydroxy function through -NHR or -OR derivatives[5]. As these carbinolamide derivatives are in equilibrium with their open forms, they also give an opportunity for obtaining II or IV.

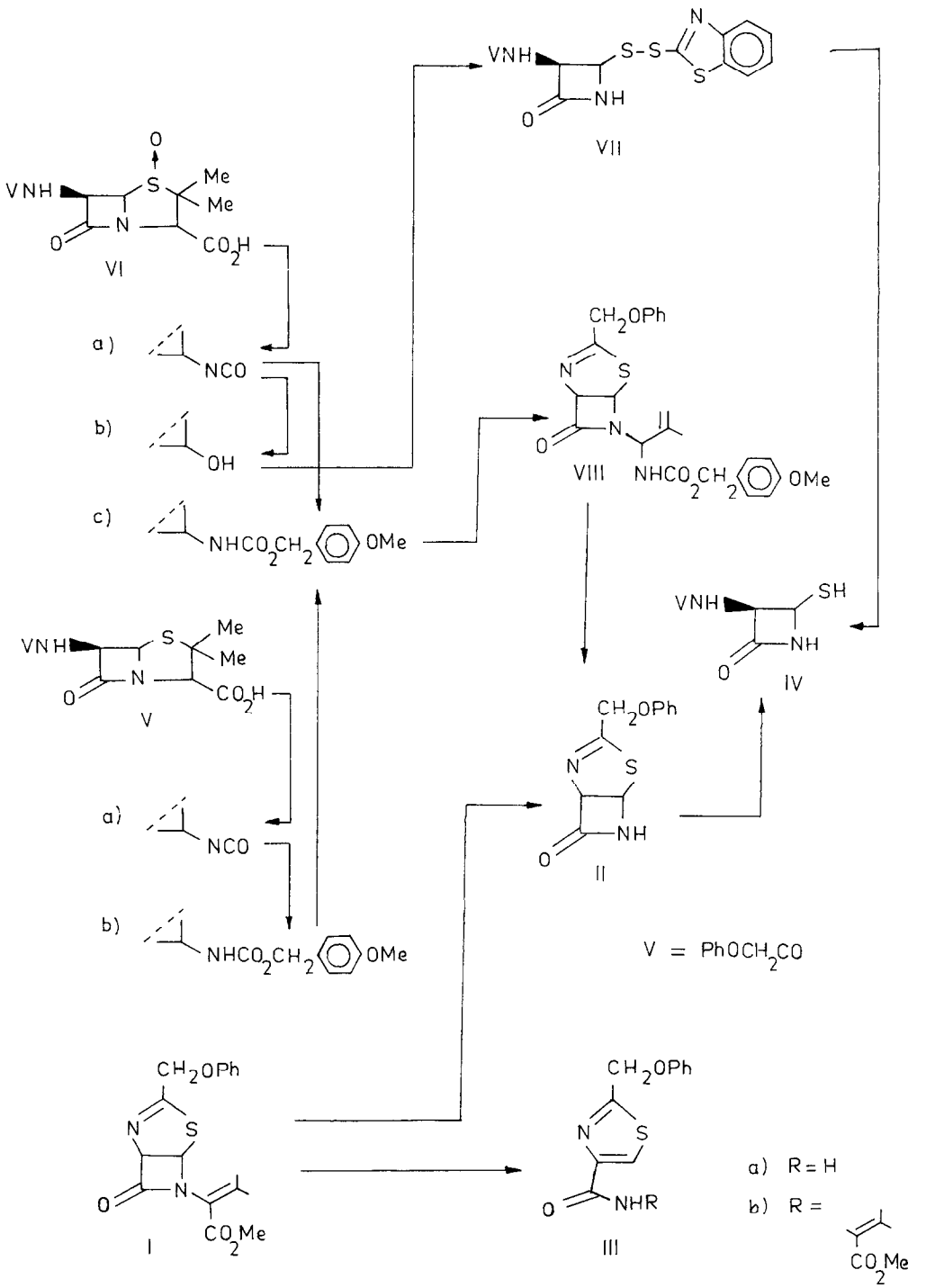
The oxidation of the olefin side-chain of I with $KMnO_4$ yields II, but this reaction is accomplished by various amounts of by-products, in our case IIIa /m.p.:168 °C, IR/KBr/: 3450, 3127, 1696, 1665, 1500 cm^{-1}; PMR /DMSO-d_6, 100 MHz/ δ : 5,13/s,2H/, 6,5-7,2 /m,5H+2H/, 7,78 /s,H/; MS M^+: 234,27/[11] and IIIb /m.p. 129-30 °C, IR/KBr/: 3326, 3109, 1710, 1666, 1540 cm^{-1}; PMR /CCl_4+DMSO-d_6, 100 MHz/ δ : 1,78 /s,3H/, 2,04 /s,3H/, 3,50 /s,3H/, 5,16 /s,2H/, 6,5-7,0 /m,5H/, 7,85 /s,H/, 8,72 /s,H//. Under other reaction conditions /$KMnO_4$, 18-crown-6/ CH_2Cl_2 or $/C_8H_{15}/_3$ $/i\text{-}C_3H_7/N^+ \cdot MnO_4^-$/benzene/, these were the dominant products. Analogues of IIIa have already been reported as by-products of the acid hydrolysis of analogues of II[6,7].

Penicillin V was converted to its isocyanate[5] with $ClCOOiBu/LiN_3$ and subsequently to the p-methoxybenzyl urethane /Vc/ /m.p.: 156-8 °C; IR/KBr/: 3340, 1785, 1715, 1693, 1517 cm^{-1}; PMR /DMSO-d_6, 100 MHz/ δ : 1,44 /s, 2x3H/, 3,76 /s,3H/, 4,46 /d,H, J=6Hz/, 4,6 /s,2H/, 5,0 /s,2H/, 5,37-5,50 /m,2xH/, 6,8-7,32 /m,9H/, 8,02 /d,H, J=12 Hz/, 8,36 /d,H, J=6 Hz/; MS: m/e /%/: 485/0,6/M, 408 /0,1/, 364/0,2/, 347/1,3/, 332/2,3/, 250/8,8/, 191/3,9/, 157/16/, 137/8,4/, 121/100/, 114/12/, 107/19/, 77/24//. We attempted to prepare this compound via

the direct method of Shioiri et al.[8], using diphenylphosphoryl azide + p-methoxybenzyl alcohol, but because of side-reactions the yield of Vc was low. Oxidation of Vc with m-chloroperbenzoic acid resulted in a 3:2 mixture of /S/- and /R/-sulphoxides /VIc/. The alternative procedure, i.e. starting from the penicillin V sulphoxide /VI/, also led to the desired VIc, as practically pure /S/ isomer /m.p.: 149 °C; IR/KBr/: 3378, 1793, 1728 /sh/, 1698, 1516 cm^{-1}; PMR /DMSO-d_6+ $CDCl_3$, 100 MHz/ δ: 1,23 /s,3H/, 1,44 /s,3H/, 3,76 /s,3H/, 4,55 /s,2H/, 5,03 /s,2H/, 5,14 /d,H, J=6 Hz/, 5,75 /d,H,J=9 Hz/, 5,90 /dd,H/, 6,76-7,4 /m,9H/, 7,75 /d,H,J=6 Hz/, 8,15 /d,H,J=9 Hz//.

Treatment of VIc with trimethyl phosphite[9] in benzene led to VIII /m.p.: 144--45 °C; IR/KBr/: 3320, 1742, 1720, 1516 cm^{-1}; PMR /DMSO-d_6, 100 MHz/ δ : 1,65 /s,3H/, 3,76 /s,3H/, 4.96-5,11 /m,3x2H/, 5,58-5,68 /m,3H/, 5,94 /d,H/, 6,8-7,4 /m,9H/, 8,18 /d,H, J=4 Hz/; MS: m/e /%/: 467/0,2/M, 424/0,2/, 234/5,3/, 191 /9,4/, 190/4,2/, 137/32/, 121/100/, 98/13/, 94/15/, 77/16//. In contrast with the reaction in compounds of type I, the exo double bond in the N-side chain of VIII does not isomerize to the enamide on treatment with triethylamine. If trifluoroacetic acid alone is used to remove the urethane function, and thus the whole side-chain, the reaction is accomplished with considerable rupture of the β-lactam ring, but the CF_3COOH/CH_2Cl_2/ anisole system at 0 °C produces II in about 70% yield, which gives rise to IV by acid hydrolysis[7].

Compound VIa opens an alternative route to IV. VIa was hydrolyzed to alcohol VIb[12]. Owing to the reactivity of the sulphenic acid form of this hydroxypenam sulphoxide[4b,10], its reaction in refluxing tert.-butanol or dioxan with mercapto-benzthiazole gave the crystalline disulphide VII, which proved identical /m.p., PMR/ with the recently-described intermediate of Woodward et al[2b]. Mild hydrogenolysis of this compound /methanol/buffer, $NaBH_4$/ led to IV.


VNH
S-S
N
S
NH
O
VII
O
S
Me
Me
N
CO2H
VI
a)
NCO
b)
OH
c)
NHCO2CH2
OMe
CH2OPh
VIII
NHCO2CH2
OMe
SH
IV
V
II
I
CO2Me
III
NHR
V = PhOCH2CO
a) R = H
b) R =

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