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CHEMISTRY OF SECOPENICILLINS. PART I: THE NAYLER REACTION REVISITED

Ching-Pong Mak and Hans Fliri
SANDOZ Forschungsinstitut
Brunnerstraße 59, A-1235 Wien, Austria

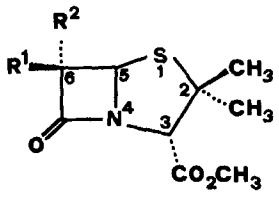
Abstract: Reaction of several penicillin derivatives 1a-1g with sodium hydride/methyl iodide gave secopenicillins 2a-2g. A mechanism for this reaction is proposed.

In 1971, Nayler and coworkers[1a] reported a novel ring cleavage reaction of methyl 6ß-(triphenylmethylamino)penicillanate 1a with strong anhydrous base (NaH, K^tOBu) and methyl iodide to give the secopenicillin 2a. Subsequently they also showed that this reaction is applicable to 6,6-dibromopenicillanate 1b but not to acylaminopenicillins, methyl penicillanate and 6α-bromopenicillanate, and the principal products obtained are of structure 3[1b,c]. Details of this reaction are not well understood[2].

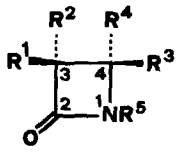
The advent of the nonclassical ß-lactams[3] and the obvious potential of penicillin as precursor for their synthesis has prompted many workers to study this reaction with different C6 substituents. Silylethers of 1c have been successfully used in this process by the Merck group[4] in their synthesis of thienamycin from penicillin and by Hirai and coworkers[5]; in addition the latter group discovered that 2b obtained from 1b is completely racemic ! We have been making extensive use of 1b in connection with our carbapenem program[6] and have independently investigated the scope and mechanism of the Nayler reaction. Table I summarizes our results.

In order to rationalize the formation of racemic 2b and the diastereomeric mixtures 2f/2f' and 2g/2g' from the corresponding optically and diastereomerically pure precursors under these conditions, either base catalyzed racemization/epimerization at C5/C4 has to occur, or an intermediate must be involved where C5 of the precursors has become trigonal. Base catalyzed epimerization can be excluded based on results obtained by the original authors[1c]. Hirai[5] assumed reversible dissociation of the C5-S bond in a preformed sulphonium salt of 1b[2] for the formation of racemic 2b . In our opinion, however, this is not very likely for the following reasons: i) treatment of 1b with methyl iodide in the absence of base (entry 3) gave no seco product and no sulphonium salt[2]; optically pure 1b was recovered quantitatively. Even when performing the experiment in the presence of base, besides racemic 2b, optically pure 1b could be recovered (entry 2); ii) if sulphonium salt formation indeed preceeded elimination, why should the products not be alkylated further ?

We are in favor of a mechanism which involves an anion-induced, concerted non-synchonous[7] [3+2] cycloreversion to give acyclic thioaldehyde 4, which subsequently either enolizes to give vinylthiolate 7, or recyclizes by addition of the enamide anion to give cyclic thiolates 5/6, depending on the respective relative rates (scheme 1). This ring closure is controlled by the nature of the substituents R^1/R^2, leading to racemic products from achiral 4 ($R^1 = R^2$) and



1



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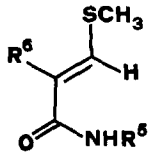


3

R^5 = $C{=}C(CH_3)_2$ | $COOCH_3$

R^6 = acylamino, H, Br

TABLE I

ENTRY	start. mat. No	R^1	R^2	product No	R^1	R^2	R^3	R^4	recov. 1 [%]	yield of 2 [%]
1	1a	$Ø_3CNH$	H	2a	$Ø_3CNH$	H	SCH_3	H	40	25
2	1b*	Br	Br	2b	Br	Br	SCH_3	H		78
3	1b**	Br	Br						100	
4	1b***	Br	Br	disulfides 10/10' (20 %) were isolated					40	
5	1c*	H	HO MeCH (R)	2c	H	OH MeCH (R)	SCH_3	H	20	63
6	1d	≠SiO MeCH (R)	H	2d	≠SiO MeCH (R)	H	H	SCH_3		42
7	1e*	Br	H	2e	H	Br	SCH_3	H	8	8
8	1f*	OH MeCH (R)	Br	2f	OH MeCH (R)	Br	SCH_3	H	2f/2f'=56/44	78
				2f'	OH MeCH (R)	Br	H	SCH_3		
9	1g*	Br	=SiO MeCH (S)	2g	Br	OH MeCH (S)	H	SCH_3	2g/2g'=37/63	63
				2g'	Br	OH MeCH (S)	SCH_3	H		

1b* in a parallel experiment the reaction was stopped on purpose to check the properties of recovered 1b.

1b** reaction performed in the absence of base.

1b*** 1b was exposed to sodium hydride in furan as a solvent; after 5 days 1% 2-propanol was added.

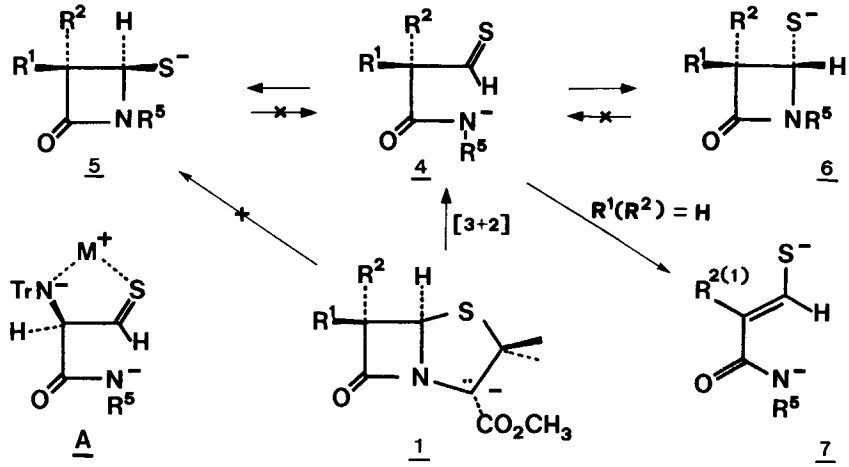
1c*,1f* the OH group was in situ protected as trimethylsilylether; acidic work up.

1e* 2e is racemic; in addition 9 % 3 (R^6=Br) and 8 % methyl 6α - bromopenicillanate were isolated; we assume that 1e was equilibrated to a mixture of 6α/6ß-bromo isomers.

1g* acidic work up

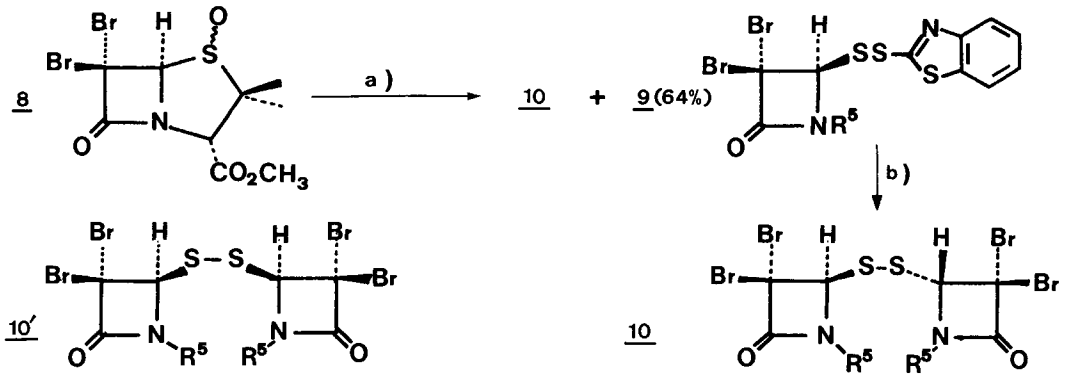
to chiral products from chiral 4; formation of the thermodynamically less stable cis-product 2a from 1a is probably due to a chelated dianionic species A.

scheme 1



Stepwise formation of 4 via 5 is disregarded for the following reason: the disulfide 10 obtained from 1b by exposure to sodium hydride in the absence of methyl iodide (entry 4) was shown to be an inseparable, optically inactive mixture of meso (10') and d,l (10) isomers[8]; this must have been formed by oxidative dimerization of the racemized thiolate 5/6. On the other hand, optically active 10 ($[\alpha]^{D}_{21}$ = + 171°) could be obtained via 8 under conditions which presumably involve thiolate 5[9] (scheme 2); in order to give optically active 10, 5 must be configurationally stable[10].

scheme 2



a) i) 1 eq. 2-mercaptobenzthiazole, toluene, 90° [13]; ii) cat. Et_3N, CH_2Cl_2, r.t.

b) cat. Et_3N/2-mercaptobenzthiazole, CH_2Cl_2, r.t.

There is ample precedence for cycloreversion reactions of saturated five membered heterocycles bearing a negative charge[11] and we believe that such a mechanism is also operative in related cases[12]. A more detailed investigation on this principle is presently being undertaken in our laboratory. These results, together with synthetic applications of the Nayler process, will be reported shortly.

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8. Selected physical properties: (NMR spectra were taken in $CDCl_3$; coupling constants (J) were given in Hz) 2d: 0.10(s,6),0.90(s,9),1.34(d,3,J=6.5),2.00(s,3),2.12(s,3),2.22 (s,3),3.27(dd,1,J=5,2.5),3.78(s,3),4.27(dq,1,J=6.5),5.00(d,1,J=2.5). 2e: 2.02(s,3),2.18 (s,3),2.28(s,3),3.80(s,3),4.71(d,1,J=2.2),5.09(d,1,J=2.2). 2f: 1.58(d,3,J=6),2.04(s,3), 2.23(s,3),2.30(s,3),2.46(d,1,J=4.5),3.81(s,3),4.26(dq,1,J=6;4.5),5.24(s,1). 2f': 1.45-(d,3,J=6),2.06(s,3),2.15(s,3),2.30(s,3),2.53(d,1,J=4.5),3.80(s,3),4.24(dq,1,J=6;4.5), 5.26(s,1). 10: 2.02(s,3),2.34(s,3),3.84(s,3),5.67(s,1); ^{13}CNMR: 22.2(=$\frown$Me), 23.7 - (=$\frown^{Me}$), 52.3(OCH_3),54.8(C3),84.7(C4),117.5($\succ$C=),158.3($\succ$=CMe_2),158.4(O=C-N),162.8 (CO_2Me). 10': 2.01(s,3),2.35(s,3),8.84(s,3),5.67(s,1).
   MS(FAB): m/e 402/404/406($C_9H_{10}Br_2NO_3S_2$); m/e 338/340/342($C_9H_{10}Br_2NO_3$).
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