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NUCLEOPHILIC S_N2 DISPLACEMENTS ON PENICILLIN-6- AND CEPHALOSPORIN-7- TRIFLATES; 6β-IODOPENICILLANIC ACID, A NEW β-LACTAMASE INHIBITOR

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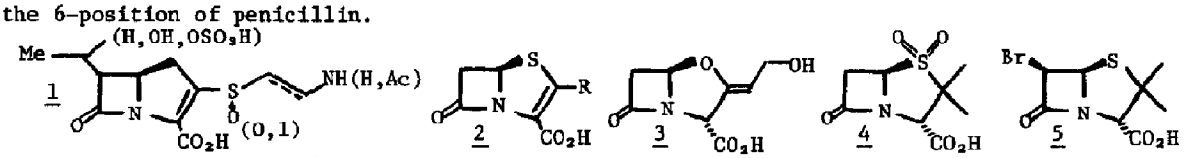
Abstract Triflate or nonaflate esters of alkyl 6α (or β) hydroxypenicillanates are substituted (with inversion) by the soft nucleophiles iodide, bromide, chloride, azide, arylselenoxide,[1] thiocyanate, thiols, and thiolacids; carbon nucleophiles fail. Methoxide (hard) attacks the lactam bond, opening both rings to give a known[11] 1,4 thiazine. Iodide substitutes 7α-trifloxycephalosporins, giving 7β-iodocephalosporins.

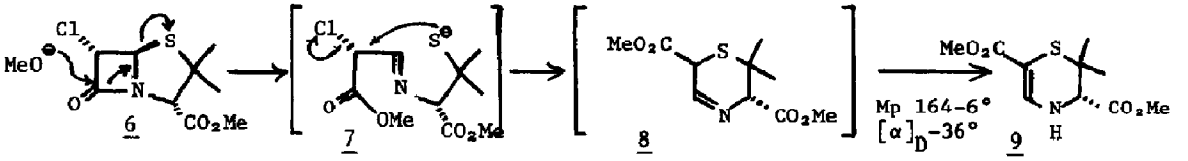
INTRODUCTION The advent of antimicrobial carbapenems[2] 1 containing carbon-linked side chains at C6, and of penems[3,4] 2 and β-lactamase inhibitors 3,[5] 4[6] and 5[7,8,9] also lacking the classical acylamino side chain, has encouraged us in a broad exploration of the chemistry of the 6-position of penicillin.



We set out to achieve S_N2 nucleophilic displacements, as such reactions would allow stereospecific synthesis of a variety of 6α or 6β substituted compounds, starting from appropriate precursors of the inverse stereochemistry. The β-lactamase inhibitor 5, and its iodine analogue, were important target compounds.

Classical S_N2 displacements on penicillins and cephalosporins, monosubstituted next to the carbonyl, have eluded chemists for over a decade,[10,11,12] though such reactions have been achieved on stabilized Δ^2-cephem[13] or cepham[14] derivatives. 6-Diazopenicillins and 7-diazocephalosporins do react, giving a variety of monosubstituted (chiefly α-oriented) and disubstituted compounds;[10-12,15-18] only in the case of substitution by thiols, under photolytic conditions, have β-substituted products been reported.[19] Disubstituted 6-methoxy (or azido) 6-bromopenicillins also react with certain nucleophiles, giving further disubstituted compounds[15] which, however, are not readily converted into 6β-monosubstituted compounds related to 5. The several attempts to displace a 6α-halo or 6α-sulphonoxy substituent on a penicillin each resulted in loss of the β-lactam ring: the following (Scheme 1) seems to be the most characteristic reaction mode.[11]

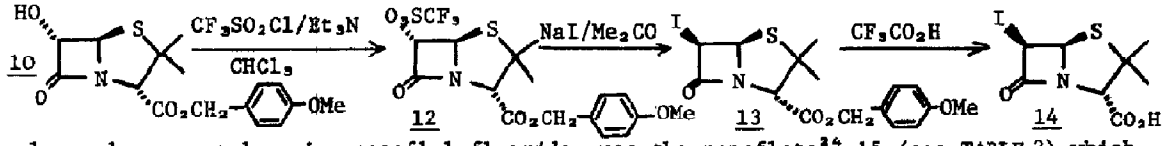
Scheme 1



Triflate[20,21] is over 10,000 times as reactive a leaving group as tosylate, allowing displacements on even the intensely unreactive nortricyclyl system,[22] and we report below successful S_N2 reactions on 6-trifloxy penicillins such as 12.

CHEMISTRY Benzhydryl 6-α-hydroxypenicillanate[23] and related C(3) esters such as 10 yielded novel C(6) triflate esters 11 and 12 (TABLE 2) which reacted with sodium iodide to give esters of 6β-iodopenicillanic acid; deprotection gave the free acid [sodium salt: $(\alpha)_D^{25}$ -232.6°(c 1% in water)] (Scheme 2). The β-orientation was confirmed by the $J_{5,6}$ coupling of 4Hz.

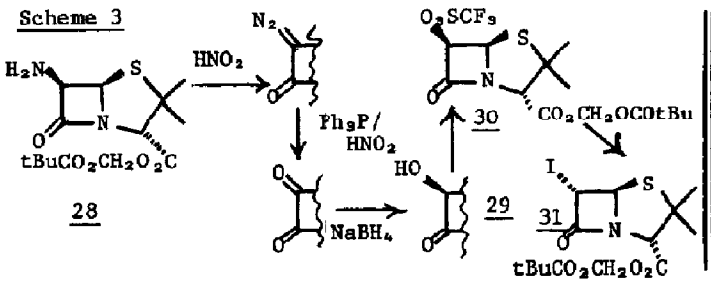
Scheme 2



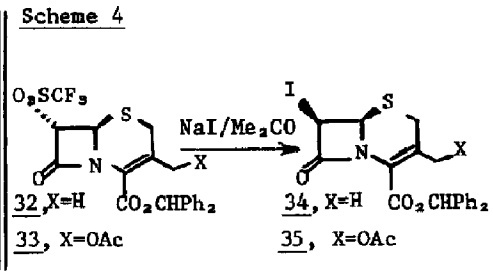
Analogously prepared, using nonaflyl fluoride, was the nonaflate[24] 15 (see TABLE 2) which reacted similarly. Compounds 12 and 15 and alternative C(3) ester analogues reacted also with bromide and chloride ion, the pseudohalogens azide and thiocyanate (the thiocyanates produced were distinct from the known[25] isothiocyanates), and with a variety of other sulphur (and selenium[1]) nucleophiles, giving products 16 to 27. Excess of the sulphur nucleophiles had to be avoided or some α-substituted product (e.g. 21) was formed. [We believe this epimerization to occur via proton abstraction (ref. 7 and papers cited therein) rather than via a second nucleophilic displacement].

Pivaloxymethyl 6β-aminopenicillanate[26] (28) was converted (Scheme 3), by a sequence previously used on other esters,[27,28] to the 6β-hydroxy compound 29, which yielded the 6β-triflate 30. This triflate reacted with sodium iodide to give the 6α-iodo compound 31.

Scheme 3



Scheme 4

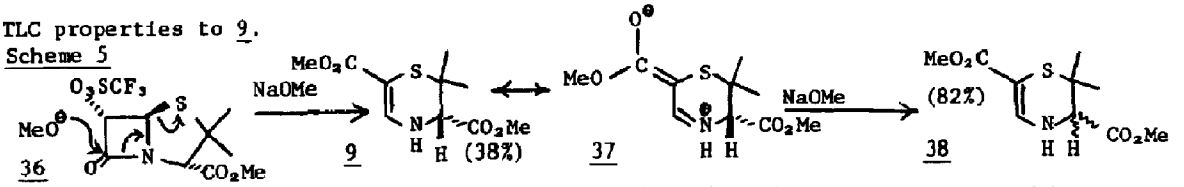


Cephalosporin triflates[29] 32 and 33 (Scheme 4) reacted analogously to the penicillins with sodium iodide in acetone, giving the new 7β-iodocephalosporins 34 and 35.

Our successful reactions were all with relatively soft nucleophiles,[30] and we therefore tried several carbon nucleophiles. None succeeded; most carbon nucleophiles are rather strong bases: exceptions to this, such as Meldrum's acid (isopropylidene malonate) are probably too sterically hindered to react. Azide and bromide are harder than our other successful nucleophiles, and do yield some products of ring opening in THF. Still harder nucleophiles such as amines and methoxide yielded only ring opened products, but we have investigated the details of the reaction only in the case of methoxide, which gave the thiazine 9 discussed earlier.[11] Excess methoxide on 36 or 9 gave the (new) racemic thiazine 38 [$[\alpha]_D^{25}$ + 1.2°; -1.5°(two samples) (c 1.0% in $CHCl_3$); m.p. 139-140°] which has identical IR, UV, NMR, CHN &

TLC properties to 9.

Scheme 5



This hitherto unreported racemization is presumably mediated by ionization at C(3) promoted by an electronic contribution from structure 37, for which there is IR evidence.[31]

BACTERIOLOGY 6β-Iodopenicillanic acid (14), Pfizer Code No. UK-38,006, is a potent, broad spectrum, β-lactamase inhibitor showing the following IC_{50} on isolated enzyme, pre-incubated at 30°C for 15 mins, (TABLE 1).

TABLE 1

Source of Enzyme:	E. coli (TEM 1)	Klebsiella 54	B. cereus	[Substrate: 100μM Nitrocefin]
IC_{50} (nanomoles/l):	0.54	17.0	3.5	

In a 1:1 combination with ampicillin it gave an MIC of 6.25μg/ml (of each drug) against E. coli 198; the individual drugs were inactive at 100μg/ml.

EXPERIMENTAL (REPRESENTATIVE COMPOUNDS)[32]

4-Methoxybenzyl 6α-hydroxypenicillanate (10). Anisyl chloride (50.6 g) was added to 6-α-hydroxypenicillanic acid[10] (71 g) in DMF (540 ml) and Et_3N (57 g); the mixture was stirred 17 hr. at 20°, partitioned between water (1l) and EtOAc (1l). The organic phase was washed (H_2O), dried ($MgSO_4$) and evaporated to give an oil which on short path medium pressure column chromatography on silica (SPC/SiO_2), eluting with petrol (bp 60-80°) gave 10 (15 g).

4-Methoxybenzyl 6α-trifloxypenicillanate (12). CF_3SO_2Cl (0.70 g) in $CHCl_3$ (2 ml) was added dropwise to ice-cold 10 (0.93 g) and Et_3N (0.55 g) in $CHCl_3$ (50 ml). After 15 mins. the solution was washed (H_2O), dried ($MgSO_4$), filtered, and evaporated: the residue yielded (SPC/SiO_2, eluting with C_5H_{12} then C_5H_{12}/CH_2Cl_2) pure 12 (0.70 g).

4-Methoxybenzyl 6β-iodopenicillanate (13). 12 (5 g), NaI (12.5 g) and Me_2CO (100 ml) were stirred at 20° for 46 hr. The mixture was concentrated to 10 ml, and partitioned between H_2O (200 ml) and Et_2O (200 ml); the Et_2O layer on evaporation gave 13 (4.8 g).

6β-Iodopenicillanic Acid (14). 13 (2.4 g) in CH_2Cl_2 (120 ml) was treated with CF_3CO_2H (12 ml) and stirred for 40 min., evaporated, and the residue yielded (SPC/SiO_2, eluting with petrol then 25% AcOEt/petrol) an eluate from which 14 (504 mg) crystallized after evaporation to low bulk.

We thank Mrs. B.J. Newman for technical help, Drs. B. Moore and S. Jevons and their colleagues for biological data, and Drs. D.A. Cox and C.W. Greengrass for their interest and discussions.

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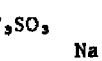
PENICILLANIC ACID DERIVATIVES

TABLE 2

Cpd No	C3	Substituent C6	Solvent *Ion		hr	Yield %	Mp	IR(film) βlac	NMR($CDCl_3$) ppm downfield from internal Me_4Si; J in Hz 2αMe	2βMe	3H	5H + 6H	$J_{5,6}$	C(3)CO_2R	Anal: Found C%	H%	N%	Anal: Calc. C%	H%	N%
10	M	α-HO				13	oil		1.35	1.50	4.42	4.87 5.23		3.78(s3)5.09(s2)6.84(d2J=8.8)7.27(d2)						
11	B	α-CF_3SO_3				82	44-5	1795	1.32[A]	1.59	4.85	5.74[z]5.89[z]	1.4	6.91(s1)7.1→7.5(m10)[in deuteroacetone]						
11									1.25	1.53	4.65	5.53 5.53		7.00(s1)7.40(s10)[in deuterochloroform]						
12	M	α-CF_3SO_3				55	69-71	1798[k]	1.36	1.53	4.52	5.48 5.48		3.80(s3)5.12(s2)6.89(d2J=8.7)7.29(d2)	43.6	3.8	2.6	43.5	3.8	3.0
13	M	β-I	Na	a	48	Q	66-70	1768[k]	1.39	1.69	4.86	5.43 5.65	4.2	3.86(s3)5.18(s2)6.95(d2J=9.2)7.36(d2)						
14	H	β-I				29	120dec	1798[k]	1.57	1.74	4.57	5.39 5.65	4.0	9.0(bsCO_2H)	29.6	2.9	4.1	29.4	3.1	4.3
15	B	α-$C_4F_9SO_3$				50	74-6	1793[k]	1.36	1.65	4.69	5.58 5.58		6.99(s1)7.37(bs10)	45.0	2.8	2.2	45.1	3.0	2.1
16	P	β-	Na	d	3	49	106-7	1796	1.51	1.67	4.50	5.56 5.74	4.5	1.20(s9)5.8(bs2) C(6)Me:3.57(s3)	44.5	5.5	16.1	44.8	5.4	16.3
17	B	β-Br	Li	d	17	21	oil	1795	1.26	1.65	4.61	5.30 5.67	4.0	6.95(s1)7.35(bs10)						
18	B	β-Cl	Li	d	17	40	oil	1795	1.25	1.61	4.56	5.16 5.66	4.0	6.92(s1)7.33(bs10)						
19	N	β-N_3	Li	d	336	42	foam	1790	1.43	1.57	4.52	4.96 5.47	4.0	5.28(s2)7.57(d2J=8.7)8.25(d2)[Azide IR 2130]						
20	P	β-NCS	K	a	64	25	oil	1790	1.49	1.6[s]	4.55	5.02 5.63	4.3	1.22(s9)5.82(bs2)[SCN IR 2155]						
21	P	α-NCS	K	a	64	41	oil	1790	1.49	1.6[s]	4.58	4.42 5.42	1.5	1.22(s9)5.82(bs2)[SCN IR 2155]	NMR C(6) substituent					
22	B	β-MeCOS	K	t	17	50	gum	1787	1.24	1.57	4.52	5.36 5.60	4.3	6.93(s1)7.31(s10)	2.32(s3)					
23	N	β-PhS	K	t	24	76	oil	1790	1.42	1.58	4.55	4.79 5.59	4.4	5.26(s2)7.1→7.55(m)8.2(d2J=8.8)	7.1→7.55[m7incl.2 from C(3)R]					
24	P	β-PhCOS	Na	d	17	60	oil	1788	1.52	1.67	4.51	5.55 5.64	4.3	1.22(s9)5.72(d1J=5.3)5.80(d1J=5.3)	7.2→7.6(m3)7.8→8.0(m2)					
25	P	β- 	Na	d	2	54	gum	1780	1.29	1.65	4.50	5.70 5.70		1.21(s9)5.68(d1J=5.4)5.75(d1J=5.4)	6.9→7.2(m1)8.4(d2J=4.9)					
26	B	β-Et_2NCS_2	Na	t	17	58	oil	1785	~1.2	1.58	4.50	5.76 5.88	4.1	6.92(s1)7.3(bs10)	1.18(t6J=7)3.83(q4J=7)					
27	B	β-EtOCS$_2$	K	t	17	72	oil	1790	1.24	1.57	4.53	5.52 5.69	4.0	6.94(s1)7.32(s10)	1.38(t3J=7)4.59(q2J=7)					
30	P	β-CF_3SO_3				5	gum	1815	1.48	1.60	4.52	5.65 5.90	4.0	1.22(s9)5.85(AB2)						
31	P	α-I	Na	a	168	86	oil	1788	1.75	1.90	4.82	5.25 5.71	2.0	1.48(s9)6.09(s2)						

CEPHALOSPORANIC ACID DERIVATIVES (all benzhydryl esters)

		C7						2αH	2βH	$J_{2\alpha\beta}$	6H + 7H	$J_{6,7}$	C(4)CO_2CHPh$_2$	C(3) substituent
32	D	α-CF_3SO_3			-	oil	1790	3.57[A]	3.57		5.43 6.05	1.8	6.99(s1)7.3→7.66(m10)	2.24(s3)
33	C	α-CF_3SO_3			-	oil	1795	3.56	3.34	18.6	4.96 5.08	~2	6.99(s1)7.2→7.5(m10)	2.0(s3)4.77(d1J=14.4)5.01(d1J=14.4)
34	D	β-I	Na	a	17	Q	oil	1770	3.63[A]	3.40	19	5.08 6.04	4.4	6.98(s1)7.3→7.64(m10)	2.02~2.12(within solvent peaks)
35	C	β-I	Na	a	17	83	oil	1780	3.4	3.4		4.47 5.61	4.9	6.94(s1)7.3→7.4(bs10)	2.0(s3)4.74(d1J=13.7)5.00(d1J=13.7)

NOTES: REAGENT & CONDITIONS for the S_N2 reactions: done at room temp. in conc. soln. (up to 20% w/v). *Ion column: the counterion for the incoming anionic C(6) or C(7) substituent. A deuteroacetone. a. acetone. B benzhydryl. C cephalosporanic acid derivative. D desacetoxycephalosporanic acid derivative. d dimethylformamide. H hydrogen. k KBr disc. M 4-methoxybenzyl ester. N 4-nitrobenzyl ester. P pivaloxymethyl ester. Q quantitative. t tetrahydrofuran. z J_{6F} =0.55: confirms assignment; β-lactam protons of other compounds not assigned.

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32. See also TABLE 2.