REACTIONS OF β,β,β-TRICLOROETHYL 6-DIAZOPENICILLANATE WITH ALDEHYDES AND SCHIFF BASES

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Abstract: New 6-substituted penicillins (mainly 6-spiro derivatives) and several non-β-lactam compounds have been prepared by treating aldehydes and Schiff bases with β,β,β-trichloroethyl 6-diazopenicillanate. Identity and stability of the products depend mainly on the nature of the aldehyde components of the starting materials.

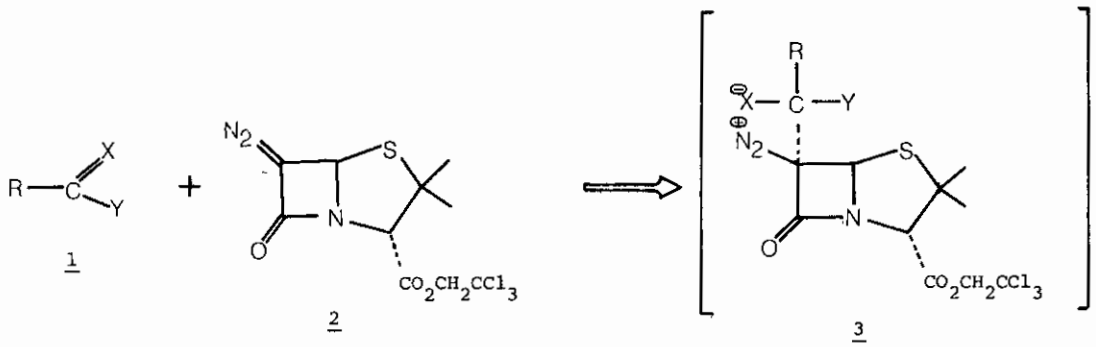
The reactivity of 6-diazopenicillanic acid esters as 1,3-dipolar reagents and nucleophilic reagents resulting in the synthesis of 6-substituted penicillins has been demonstrated recently.[1-5] Synthesis of both stable epoxides (4) and relatively unstable 6-acylpenicillins (5) by treating aliphatic aldehydes with β,β,β-tricholoethyl 6-diazopenicillanate has been described in our previous paper.[2] We wish to report here results of reactions using aromatic aldehydes and Schiff bases with diazocompound 2.

RESULTS AND DISCUSSION

Aldehydes, Schiff bases and methyloxalyl chloride, represented by the general structure 1 react readily with diazoester 2 to yield one or more of the products shown in Scheme I. These reactions, with the sole exception of the one involving methyloxalyl chloride, are catalyzed by a few drops of boron trifluoride etherate. Spiro penicillins 4 are the initial products of most of these reactions according to nmr spectra. However, these highly strained tricyclic compounds (4) are not isolable in all cases: when unstable they rearrange to different non-β-lactam compounds (6, 7 and 8). Products isolated from the reactions are represented in Scheme I by letters in parentheses.

Structural assignments of the products are in agreement with elemental analyses and spectroscopic data[6] (Tables 1 and 2) the salient features of which are the following: Only compounds 4 and 5 exhibited strong β-lactam absorptions in the ir region 1765~1800 cm^{-1}. Compounds 4, 5 and 8 showed the mass spectral fragment 9 (m/e 290) while 6 and 7 did not. Uv spectra of 7f and 8f revealed long wavelength absorptions (320 and 332 nm respectively) whereas those of 8c and 8j did not have appreciable absorption above 270 nm. According to nmr data the OH and NH groups were

Scheme I



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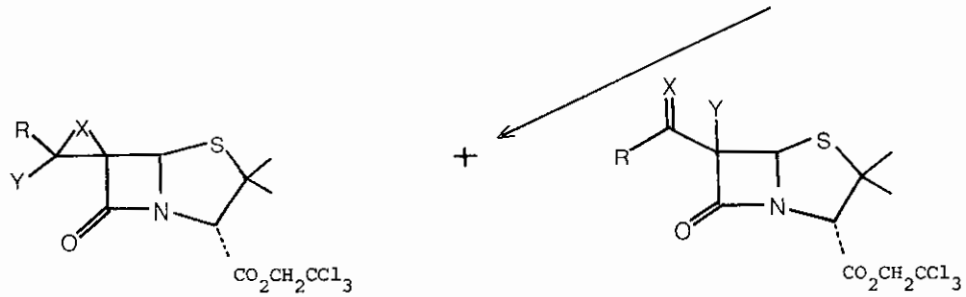
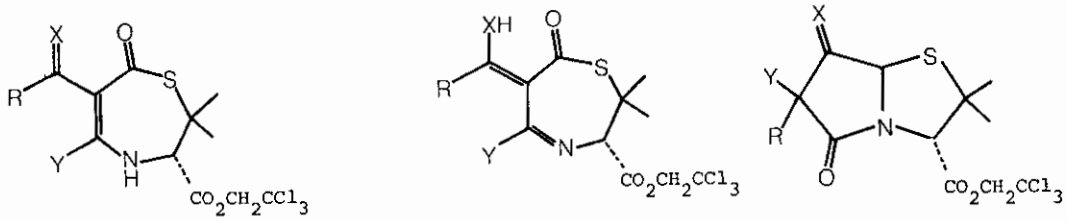


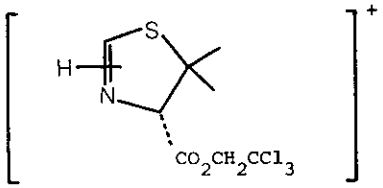
4 (a,b,c,e,f$^+$,h,i$^+$) 5 [e*(trans),j$^+$]



6 (b,f*) 7 (e*,f*,g,h*,i*) 8 (c,d,e,f,i,j)

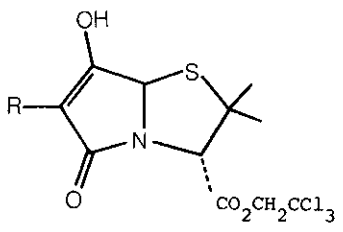
+ Two isomers were isolated, * isolated from pure spiro compound by treating with boron trifluoride etherate.

Compound	a	b	c	d	e	f	g	h	i	j
R	CH_3	$CH_2\phi$	ϕ	ϕOCH_3 (P)	ϕNO_2 (P)	ϕ	ϕOCH_3 (P)	ϕNO_2 (P)	ϕ	CO_2CH_3
X	O	O	O	O	O	Nϕ	Nϕ	Nϕ	NϕOCH$_3$ (P)	O
Y	H	H	H	H	H	H	H	H	H	Cl



9

found to be exchangeable with D_2O. In spite of the acidity of the benzylic protons of 8 (c,d,e), as indicated by their downfield chemical shifts (δ 6.8∿7.8), there was no evidence for the presence of their enol forms 10. However, signals corresponding to the benzylic protons of spiro ethylenimine compounds 8 (f,i) disappeared slowly when small amounts of D_2O and Et_3N were added to the nmr samples. This may indicate the presence of an equilibrium involving the enamines 11 (f,i). Thus it appears that the stability arising from extended conjugation in structure 10 or 11 is not



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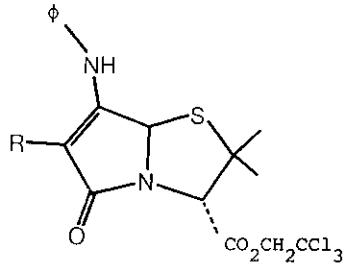

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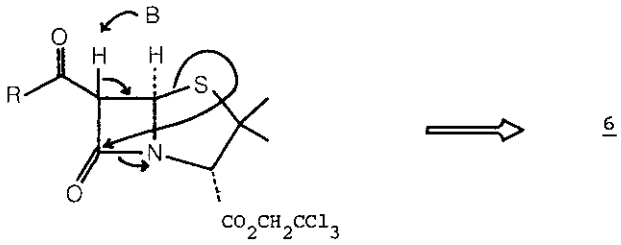
enough to compensate for the strain introduced by replacing an sp_3 carbon with an sp_2 carbon in the rigid five-membered ring.

Mechanisms involved in the reactions of carbonyl compounds and Schiff bases with diazocompounds are well documented.[7,8] Electrophilic carbon of 1 approaching[1] from the least hindered α-face of the β-lactam ring could form 3 as an intermediate which, after N_2 extrusion and ring closure, may give up to four isomeric spiro compounds. Epoxides 4 (a,b,c,e) gave one isomer each and the ethylenimines yielded two isomers (4 (f,i) and 4' (f,i) each. Absolute stereochemistry of the spiro ring in compounds 4 are not known yet. X-ray analyses of these compounds are underway and the results will be reported as they become available.

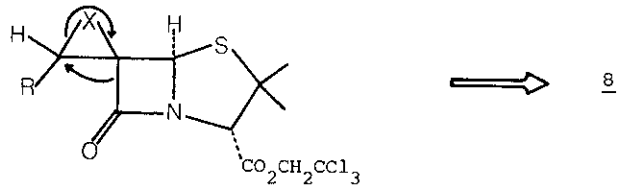
Intermediate 3 could also give 6-acylpenicillins 5 if the hydride or cloride migrates to C-6. We have isolated both isomers of 5j where Cl is the C-6 substituent. But 7-ketocompounds with a hydrogen on the C-6 tend to rearrange[2] to seven-membered ring compounds 6 (with the exception of 5e which was isolated from 4e upon treatment with BF_3). It seems that the proximity of the electron deficient carbonyl group renders the proton on the strained β-lactam ring labile enough to initiate the rearrangement. Stability of the 6-carboxypenicillins (R=OH) synthesized by Rapoport,[9]



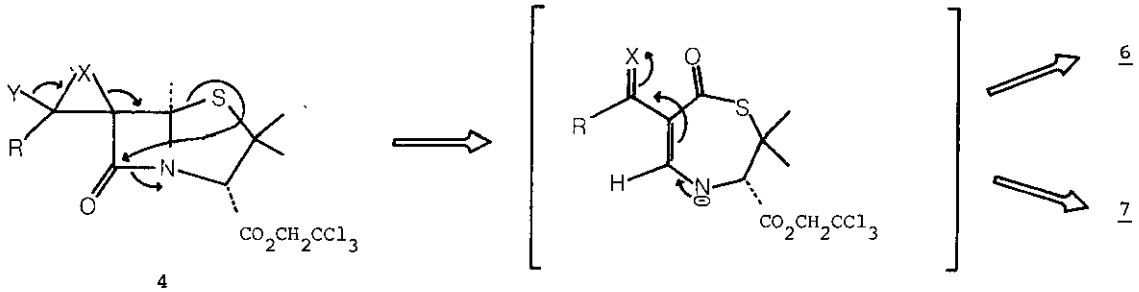
5 ⟹ 6

may be attributed to the lower electrophilicity of the carboxyl group by virtue of the interaction between the carbonyl and the hydroxy group.

Although 6-spiro penicillins (4) appear to be stable when aliphatic aldehydes and Schiff bases are the starting materials, they behave differently when R is a phenyl group or a carbomethoxy group. In these cases, compounds 4 rearrange to non-β-lactam compounds even in neutral solvents. Products marked by a star in Scheme 1 have been isolated in nearly quantitative yields by treating pure spiro compounds with a few drops of boron trifluoride etherate. Compounds of the type 6 and 7 have been reported earlier.[11,12] Possible mechanisms for the conversions of spiro compounds 4 to structures 6, 7 and 8 are indicated in the scheme below. Structure 7 may be viewed as more stable than 6 because in four out of five cases examined it was the former that was formed.



4 ⟹ 8



4 ⟹ [ ] ⟹ 6 + 7

EXPERIMENTAL SECTION

Melting points were determined on a Fisher-Johns melting point apparatus. Nmr spectra were recorded with a Varian Associates T-60 Spectrometer and are reported in parts per million (δ) relative to TMS as internal standard. Ir spectra were recorded on a Perkin-Elmer 237 spectrophotometer. High resolution mass spectra were recorded on a CEC-110B high resolution Mattauch-Herzog mass spectrometer. Microanalysis was performed by Galbraith Laboratories, Inc., Knoxville, Tennessee. Routine thin layer chromatography was run on Bakerflex silica gel 1B-F TLC sheets. Column chromatography was performed with either Mallinckrodt silicic acid (100 mesh) or EM Reagents silica gel 60 (finer than 230 mesh).

Yields, melting points and spectroscopic data of the products are presented in Tables 1, 2 and 3.

Reactions of 2 with Aromatic Aldehydes. To a solution of 2 in CH_2Cl_2 at room temperature was added an equimolar amount of aromatic aldehyde (1(c,d,e)). After stirring the solution for 5 min one drop of boron trifluoride etherate was added. Immediate bubbling followed by fading of the deep yellow color was observed. The solution was stirred for about 15 min, the solvent was removed under reduced pressure and the residue was chromatographed on silica gel using CH_2Cl_2-ether or $CHCl_3$-CCl_4 as the eluent. Epoxides were isolated from the early fractions. The later fractions contained the more polar products 6, 7 etc. A CCl_4-Pet. ether mixture was used for recrystallizations of the crystalline products.

Reactions of 2 with Schiff Bases. The above-described procedure was followed for the reactions of 2 with Schiff bases except that the reactions were carried out at 0-5°C.

Reaction of 2 with Methyloxalyl Chloride. The same procedure as given above for the aromatic aldehydes was used for the reactions of 2 with methyloxalyl chloride except that no catalyst was used.

Reactions of Spiro compounds with BF_3. A few drops of boron trifluoride etherate was added to solutions of the spiro compounds in $CHCl_3$ at room temperature. The mixtures were stirred for 5 min and the solvent was then removed. The residue was subjected to chromatography on silica gel (eluted by $CHCl_3$). A CCl_4-pet. ether mixture was used for recrystallization of crystalline products. Spiro compound 4f on rearrangement yielded 7f while the isomer 4'f gave 6f.

Table 1. The β-Lactam Compounds (4, 4' & 5)

Compound[10]	Yd (%)	mp (°C)	Formula MS, M^+ (m/e)	IR (KBr, cm^{-1})	NMR ($CDCl_3$, δ)
4c	7	146-147	$C_{17}H_{16}Cl_3NO_4S$ 437	1790, 1760	1.42,1.60 (2 s, 6H), 4.26 (s, 1H), 4.60 (s, 1H), 4.80 (s, 2H), 5.60 (s, 1H), 7.26 (m, 5H)
4e	41.5	137-138	$C_{17}H_{15}Cl_3N_2O_6S$ 482	1780, 1760	1.48,1.60 (2 s, 6H), 4.48 (s, 1H), 4.70 (s, 1H), 4.88 (s, 2H), 5.75 (s, 1H), 7.60-8.40 (AA'BB', 4H)
4f	35.2	131-132	$C_{23}H_{21}Cl_3N_2O_3S$ 512	1775, 1748, 1595, 1085	1.45,1.52 (2 s, 6H), 3.85 (s, 1H), 4.68 (s, 1H), 4.60-5.05 (AB, 2H), 5.70 (s, 1H), 6.90-7.90 (m, 10H)
4'f	17.3	175-176	$C_{23}H_{21}Cl_3N_2O_3S$ 512	1778, 1750, 1600, 1085	1.48,1.59 (2 s, 6H), 3.88 (s, 1H), 4.52 (s, 1H), 4.60-5.08 (AB, 2H), 5.61 (s, 1H), 6.90-7.60 (m, 5H), 7.44 (s, 5H)
4h	54.1	99-101	$C_{23}H_{20}Cl_3N_3O_5S$ 557	1785, 1755, 1595, 1085	1.44,1.52 (2 s, 6H), 3.89 (s, 1H), 4.62 (s, 1H), 4.80 (s, 2H), 5.64 (s, 1H), 7.00-7.60 (m, 5H), 7.70-8.40 (AA'BB', 4H)
4i	26.5	126-127	$C_{24}H_{23}Cl_3N_2O_4S$ 542	1765, 1748, 1080	1.45,1.52 (2 s, 6H), 3.85 (s, 3H), 3.86 (s, 1H), 4.70 (s, 1H), 4.64-5.05 (AB, 2H), 5.65 (s, 1H), 6.82-7.20 (AA'BB', 4H), 7.30-7.84 (m, 5H)
4'i	19.4	(amorphous powder)	$C_{24}H_{23}Cl_3N_2O_4S$ 542	1770, 1750, 1075	1.50,1.58 (2 s, 6H), 3.82 (s, 3H), 3.84 (s, 1H), 4.58 (s, 1H), 4.62-5.05 (AB, 2H), 5.62 (s, 1H), 6.84-7.22 (AA'BB', 4H), 7.50 (m, 5H)
5e	32.9	82-84	$C_{17}H_{15}Cl_3N_2O_6S$ 482	1800, 1700, 1600	1.64,1.69 (2 s, 6H), 4.82 (s, 3H), 5.80 (d, J=2 Hz, 1H), 6.26 (d, J=2 Hz, 1H), 7.6-8.1 (AA'BB'), 4H)
5j	27	(oil)	$C_{13}H_{13}Cl_4NO_6S$ 453	1790, 1750	1.62,1.68 (2 s, 6H), 3.94 (s, 3H), 4.70 (s, 1H), 4.85 (s, 2H), 5.64, (s, 1H)
5'j	8.5	(oil)	$C_{13}H_{13}Cl_4NO_6S$ 453	1790, 1760	1.64 (s, 6H), 3.96 (s, 3H), 4.82 (s, 1H), 4.85 (s, 2H), 5.70 (s, 1H)

Table 2. The Non-β-Lactam Compounds (6, 7 & 8)

Compound[10]	Yd (%)	mp (°C)	Formula MS, M^+ (m/e)	IR (KBr, cm^{-1})	NMR ($CDCl_3$, δ)
6f	~100	152-153	$C_{23}H_{21}Cl_3N_2O_3S$ 512	3370, 1760, 1600	1.70 (s, 6H), 3.36 (m, 1H), 3.85 (d, J=9 Hz, 1H), 4.50-5.02 (AB, 2H), 5.90 (d, J=9 Hz, 1H), 6.90-7.70 (m, 10H)
7e	53	210-211	$C_{17}H_{15}Cl_3N_2O_6S$ 482	3300-3400, 1760, 1675-1600	1.50, 1.55 (2s, 6H), 4.86 (s, 2H), 4.99, (s, 1H), 5.92 (s, 1H), 7.42 (s, 1H), 8.20 (m, 4H)
7f	~100	(amorphous powder)	$C_{23}H_{21}Cl_3N_2O_3S$ 512	3180-3350, 1760, 1680, 1625, 1599	1.52 (s, 6H), 4.85 (s, 2H), 5.02 (s, 1H), 6.15 (s, 1H), 7.05-7.80 (m, 11H)
7g	26.2	(amorphous powder)	$C_{24}H_{23}Cl_3N_2O_4S$ 542	3380-3200, 1780, 1680, 1630, 1598	1.55 (s, 6H), 3.84 (s, 3H), 4.90 (s, 2H), 5.05 (s, 1H), 6.20 (s, 1H), 6.90-7.80 (m, 10H)
7h	~100	(amorphous powder)	$C_{23}H_{20}Cl_3N_3O_5S$ 557	3180-3360, 1765, 1685, 1620, 1599	1.55 (s, 6H), 4.84 (s, 2H), 5.00 (s, 1H), 6.10 (s, 1H), 7.00-7.40 (m, 5H), 7.22 (s, 1H), 7.64-8.35 (AA'BB', 4H)
7i	~100	(amorphous powder)	$C_{24}H_{23}Cl_3N_2O_4S$ 542	3200-3400, 1750, 1675, 1620, 1599	1.50 (s, 6H), 3.80 (s, 3H), 4.78 (s, 2H), 4.95 (s, 1H), 5.92 (s, 1H), 6.94 (s, 1H), 6.80-7.70 (m, 9H)
8c	45	(amorphous powder)	$C_{17}H_{16}Cl_3NO_4S$ 437	1760, 1670, 1600	1.60,1.82 (2 s, 6H), 4.80 (s, 2H), 4.98 (s, 1H), 6.75 (s, 1H), 7.21 (m, 6H)
8d	58.7	135-136	$C_{18}H_{18}Cl_3NO_5S$ 467	1755, 1665, 1595	1.58,1.84 (2 s, 6H), 3.78 (s, 3H), 4.00 (s, 2H), 5.02 (s, 1H), 6.90 (s, 1H), 7.35 (s, 1H), 6.88-7.60 (AA'BB', 4H)
8e	16	(amorphous powder)	$C_{17}H_{15}Cl_3N_2O_6S$ 482	1748, 1650 1600	1.55,1.84 (2 s, 6H), 4.80 (s, 2H), 5.00 (s, 1H), 6.90 (s, 1H), 7.46 (m, 5H)
8f	23	(amorphous powder)	$C_{23}H_{21}Cl_3N_2O_3S$ 512	1755, 1630, 1585	1.62,1.72 (2 s, 6H), 4.95 (s, 2H), 5.52 (s, 1H), 7.20-7.90 (m, 12H)
8i	16.3	(amorphous powder)	$C_{24}H_{23}Cl_3N_2O_4S$ 542	1756, 1649, 1598	1.55,1.64 (2 s, 6H), 3.82 (s, 3H), 4.82 (s, 2H), 5.34 (s, 1H), 7.00 (s, 1H), 6.90-7.64 (m, 10H)
8j	13.5	105-106	$C_{13}H_{13}Cl_4NO_6S$ 453	1730-1770, 1685	1.58,1.80 (2 s, 6H), 3.94 (s, 3H), 4.84 (s, 2H), 4.95 (s, 1H) 6.84 (s, 1H)

Table 3. Uv Data

Compound	λmax, nm
7f	243 (ε = 14,470)
	320 (ε = 11,780)
8f	250 (ε = 12,230)
	332 (ε = 9,790)
8j	255 (ε = 5,460)
	270 (ε = 5,040)
8c	228
	270

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References and Notes

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