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ALKYLATION OF PENICILLANATES:PREPARATION AND ISOLATION OF PENAM SULPHONIUM SALTS

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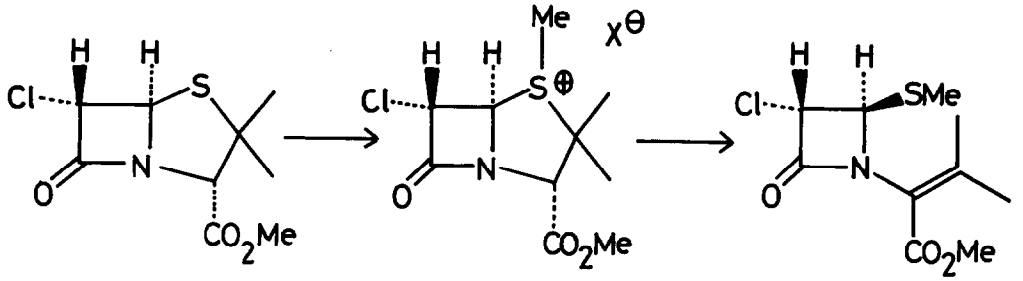
The chemistry of penicillins and cephalosporins has been studied extensively in recent years. During this work it has been observed that the sulphur atom of penicillin is comparatively unreactive towards electrophilic attack.[1] Although a cephalosporin derivative has recently been converted into a rearranged sulphonium salt,[2] there are no reports in the literature of the preparation of sulphonium salts derived from penicillins. We wish to report the efficient preparation and isolation of several penicillin derived sulphonium salts, together with some aspects of their chemistry.

Treatment of methyl 6-α-chloropenicillanate (1) with a slight excess of trimethyloxonium tetrafluoroborate in nitromethane for six hours at room temperature gave an almost quantitative yield of tetrafluoroborate (2a). Although crude (2a) was sufficiently pure for most purposes, an analytically pure sample (m.p. 151-152.5°) was obtained by recrystallization from nitromethane;[3] $\nu_{max.}$ 1810, 1750 cms^{-1}; $[\alpha]_D^{20}$ + 105° (nitromethane); nmr (CD_3NO_3;δ) 1.86 (6H,s), 3.28 (3H,s), 3.94 (3H,s), 5.11 (1H,s), 5.80 (1H,d, J = 1.5 Hz), and 5.96 (1H,d, J = 1.5 Hz). When a solution of (2a) in nitromethane was treated with anhydrous sodium carbonate for one hour at room temperature, the 1,2-seco-penicillanate (3) was obtained in excellent yield (95%) and was purified by distillation (b.p. 160°/ 0.05 mm.Hg) or by silica-gel chromatography. The seco-penicillanate was identified from analytical and spectroscopic data;[3] $\nu_{max.}$ 1780, 1720, 1630 cms^{-1}; nmr ($CDCl_3$,δ) 2.00 (3H,s), 2.17 (3H,s), 2.27 (3H,s), 3.80 (3H,s), 4.69 (1H,d, J = 2.0 Hz), 5.03 (1H, d, J = 2.0 Hz); m/e 263,265 (M^+), 108 (M^+-155, base peak). Methyl 6-α-chloropenicillanate (1) was also converted into seco-penicillanate (3) in 95% yield without isolation of the intermediate sulphonium salt by treatment of a solution in nitromethane with trimethyloxonium tetrafluoroborate (room temp., 6 hrs.) and then with anhydrous sodium carbonate (room temp., 1 hr.).

Methyl 6-α-chloropenicillanate (1) was converted into fluorosulphonate (2b) using methyl fluorosulphonate in refluxing dichloromethane. This reaction was slower than the reaction of (1) with trimethyloxonium tetrafluoroborate,the fluorosulphonate (2b) gradually crystallizing out of the reaction mixture (80% isolated after 72 hrs.). The nmr spectrum of the fluorosulphonate (2b) was identical to that of the tetrafluoroborate (2a), and the fluorosulphonate was converted into seco-penicillanate (3) by treatment with sodium carbonate.[3]

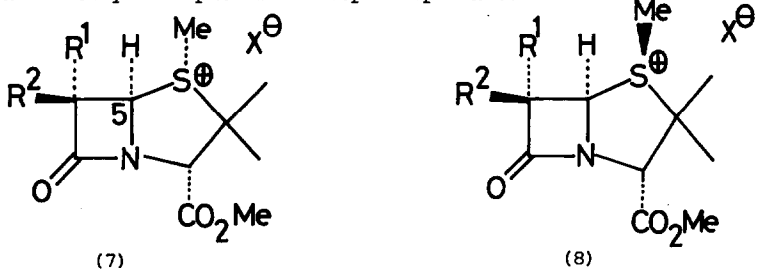


(1) (2a): X = $BF_4^{\ominus}$ (3)

(2b): X = $FSO_3^{\ominus}$

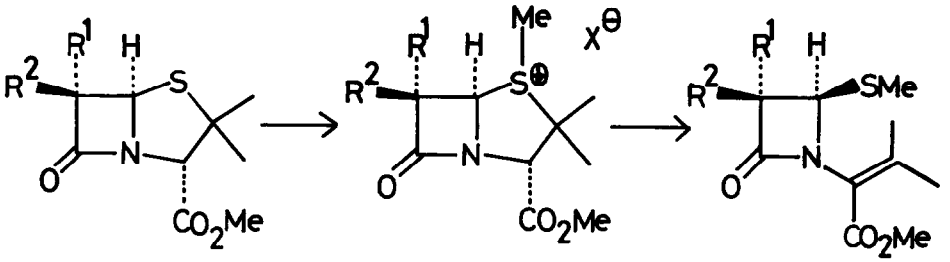
These reactions have been applied to other penicillanates, and our results to date are summarized in the table (see scheme). Methyl 6-α-phthalimido-, methyl 6,6-dibromo-, and methyl 6-α-chloropenicillanates were converted into their methyl sulphonium salts in excellent yields by trimethyloxonium tetrafluoroborate in nitromethane or by methyl fluorosulphonate in refluxing dichloromethane. The tetrafluoroborates were easily handled crystalline solids which could be recrystallized from nitromethane and stored for several weeks in a refrigerator without decomposition. The fluorosulphonates were less easy to handle and decomposed when exposed to the atmosphere for a few hours. Both the fluorosulphonates and the tetrafluoroborates were converted into seco-penicillanates by anhydrous sodium carbonate (nitromethane solution, one hour, room temperature). However a sulphonium salt could not be isolated from the reaction between methyl 6-β-phthalimido-penicillanate (4; R^1 = H, R^2 = phthalimido) and trimethyloxonium tetrafluoroborate. A complex reaction mixture was obtained from which the desired seco-penicillanate (6; R^1 = H, R^2 = phthalimido) was isolated after treatment with anhydrous sodium carbonate.[4]

Alkylation of methyl penicillanates on sulphur could lead to the formation of diastereoisomeric sulphonium salts, (7) or (8). For all the alkylations we have studied so far, only one of the two possible sulphonium salts was detected by nmr in the crude alkylation mixture. Thus it would appear that these alkylation reactions have been extremely stereoselective. For the dibromo-tetrafluoroborate (5; R^1 = R^2 = Br, X = BF_4^-), a significant NOE effect (25%) was observed between -S-methyl and the proton attached to C-5. Therefore in this case the sulphonium salt has tentatively been assigned the configuration depicted in (7). This stereoselectivity agrees with that observed for alkylation of methyl 7-α-phthalimidocephalosporanate.[2]



(7) (8)

Scheme



(4) (5): X = $BF_4^{\ominus}$, $FSO_3^{\ominus}$ (6)

Table

Methyl Penicillanate (4)		Alkylating Agent	Conditions of alkylation	Yield of crude sulphonium salt (%)	Yield of crude seco-penicillins (%)
R^1	R^2				
Cl	H	$Me_3O^{\oplus}BF_4^{\ominus}$	room temp./6 hrs.	90	95
Cl	H	FSO_3Me	CH_2Cl_2 reflux/3 days	80	95
Phthal	H	$Me_3O^{\oplus}BF_4^{\ominus}$	room temp./4 hrs.	87	94
Phthal	H	FSO_3Me	CH_2Cl_2 reflux/3 days	65	90
H	Phthal	$Me_3O^{\oplus}BF_4^{\ominus}$	room temp./2 hrs.	-	30
Br	Br	$Me_3O^{\oplus}BF_4^{\ominus}$	room temp./12 hrs	90	90

The formation of a complex product mixture upon attempted alkylation of methyl 6-β-phthalimidopenicillanate (4; R^1 = H, R^2 = phthal.)contrasts with the extremely clean formation of sulphonium salt from its 6-α-epimer. This may be due to instability of penam sulphonium salts with a proton in the α-position at C-6. These may undergo a facile trans-elimination to give an azetinone which then reacts further.[7]

Further work is in progress in this area.[8]

Acknowledgments.

We thank Professor C. B. Reese for drawing our attention to this problem and Beecham Pharmaceuticals for a generous gift of starting material.

Notes and References.

1. E. H. Flynn (ed.), Cephalosporins and Penicillins, Academic Press, 1972.

2. D. K. Herron, Tetrahedron Letters, 1975, 2145.

3. Satisfactory spectroscopic data was obtained for all new compounds. Satisfactory analytical data was obtained for all new seco-penicillanates and tetrafluoroborates, but could not be obtained for the fluorosulphonates. The fluorosulphonates were identified by comparison of their nmr spectra with the corresponding tetrafluoroborates and by clean conversion to the seco-penicillanates.

4. The cis-disubstituted phthalimido-seco-penicillanate (6; R^1 = H, R^2 = phthalimido) was also prepared by treatment of methyl 6-β-phthalimidopenicillanate-1-oxide with trimethylphosphite (see ref. 1, page 201) and from the corresponding isobutyl disulphide following the procedure described by Barton.[5] It was epimerized to the trans-phthalimido-seco-penicillanate (6; R^1 = phthalimido, R^2 = H) by DBN in refluxing benzene.[6]

5. R. D. Allan, D. H. R. Barton, M. Girijavallabhan, P. G. Sammes, and M. V. Taylor, J. C. S. Perkin I, 1973, 1182.

6. A. K. Bose, C. S. Narayanan, and M. S. Manhas, J. C. S. Chem. Comm., 1970, 975.

7. G. Kretschmer and R. N. Warrener, Tetrahedron Letters, 1975, 1335; A Brandt, L. Bassignani, and L. Re, Tetrahedron Letters, 1976, 3975.

8. We thank the S.R.C. for support (to PMD)).