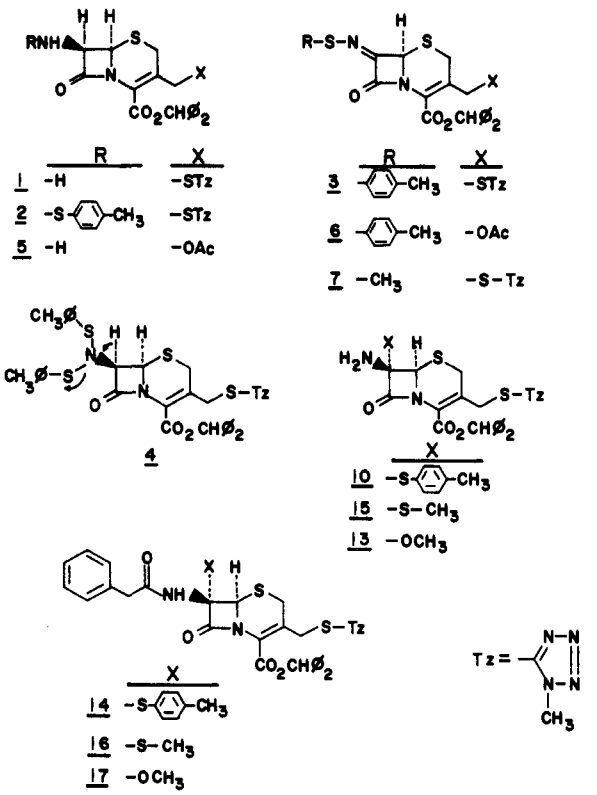
## Sulfenyl Transfer Rearrangement of Thiooximes. A Novel Conversion of Cephalosporins to 7α-Methoxycephalosporins

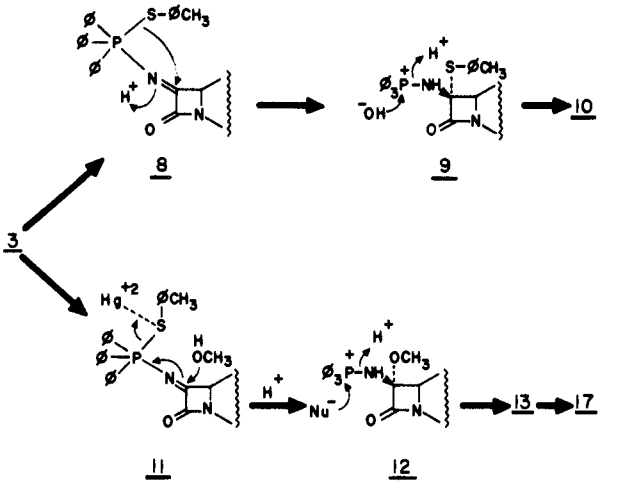
*Sir:*

7α-Methoxycephalosporins are a new class of β-lactam antibiotics[1] which are particularly effective against gram-negative bacteria,[2] and consequently much effort has been expended to provide a practical synthetic route to these substances.[3] We wish to report procedures by which cephalosporins may be converted to 7α-methoxycephalosporins via the intermediacy of new thiooxime (sulfenimine) β-lactams. Such thiooximes undergo a novel sulfenyl transfer rearrangement which can be controlled to afford high yields of either 7α-methoxycephems[4] or 7α-aryl- (or -alkyl-) thiocephems.

Sulfenamide **2** can be conveniently prepared in high yield from cephalosporin amine ester **1** by reaction with a stoichiometric amount of *p*-toluenesulfenyl chloride (TSC)[5] in the presence of acid scavengers (propylene oxide, pulverized molecular sieves (4A), or $NaHCO_3$). Treatment of **1** with **3** molar equiv of TSC (0 °C, $CH_2Cl_2$, propylene oxide, pulverized molecular sieves (4A), 3 h) directly afforded bright yellow thiooxime **3**[6] (80%)[7] (mp 154–155 °C; NMR ($CDCl_3$) δ 2.36 (s, 3 H), 3.68 (s, 2 H), 3.78 (s, 3 H), 4.13, 4.43 (d of d, 2 H, *J* = 13 Hz), 5.25 (s, 1 H), 6.90 (s, 1 H), 7.26 (m, 14 H); UV (MeOH) 261 nm (ε 3700), 355 (3900); IR (KBr) 1770, 1715 $cm^{-1}$) and *p*-tolyl disulfide. Thiooxime **3** presumably derives by further sulfenylation of **2**; the fugitive sulfenimide **4** is not observed or isolated, owing to its presumed proclivity toward β elimination.[8] In theory, 3 molar equiv of sulfenyl halide should be optimum to effect this conversion: 2 equiv are consumed to form **3**, whereas the third can act as a convenient trap for liberated thiol. Formation of thiooxime **3** is stereospecific; however, the oxime geometry is presently unknown. In a similar manner 7-ACA-benzhydryl ester (**5**) is converted to thiooxime **6** (77%, yellow oil). Treatment of **1** with freshly prepared methylsulfenyl chloride[10] under the above conditions led to methyl thiooxime **7** (76%, white crystals): mp 213–214 °C; NMR ($CDCl_3$) δ 2.88 (s, 3 H), 3.67 (s, 2 H), 3.81 (s, 3 H),




Scheme I



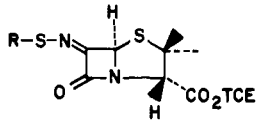

4.18, 4.46 (d of d, *J* = 13 Hz), 5.23 (s, 1 H), 6.94 (s, 1 H), 7.36 (m, 10 H); IR ($CHCl_3$) 1770, 1710 $cm^{-1}$. Thiooximes **3**, **6**, and **7** all form stereospecifically, are stable at 26 °C, and do not readily add nucleophiles (alcohols, thiols) at C-7 under neutral conditions.

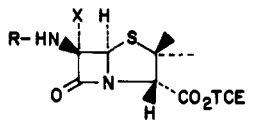
The aforementioned thiooximes undergo a novel sulfenyl transfer reaction. Thiooxime **3** reacted with 3 molar equiv of triphenylphosphine to afford stereospecifically, after silica gel chromatography, good yields of 7α-arylthioamine **10** as a white foam: NMR ($CDCl_3$) δ 2.00 (br s, 2 H, exchanges with $D_2O$) 2.30 (s, 3 H), 3.60 (s, 2 H), 3.76 (s, 3 H), 4.11, 4.38 (d of d, 2 H, *J* = 13 Hz), 4.73 (s, 1 H), 6.86 (s, 1 H), 7.30 (m, 14 H); IR ($CHCl_3$) 1775, 1715 $cm^{-1}$. A suggested mechanism for this rearrangement is outlined in Scheme I. Reaction of **3** with triphenylphosphine did not proceed directly to **10** (NMR) without the intervention of an acidic catalyst (silica gel). Subsequent experiments ($^{13}C$ NMR, $^1H$ NMR, TLC) indicated that a reversible equilibrium is established between thiooxime **3** and triphenylphosphine leading to a complex, which may have a structure equivalent to **8**.[11] Protonation of **8** initiates transfer of the sulfenyl moiety from phosphorus to carbon; subsequent hydrolysis of the resulting aminophosphorane affords **10** and triphenylphosphine oxide, which has also been isolated from these reactions. In practice, silica gel may be introduced directly into the reaction mixture without detrimental effect. The net effect of combining thiooxime **3**, triphenylphosphine (3 equiv), and silica gel[12] ($CH_2Cl_2$, 26 °C) is a rapid (<3 h) sulfenyl transfer from nitrogen to carbon resulting in stereospecific formation of 7α-arylthioamine **10** in excellent yield (NMR). Acylation ($PhCH_2COCl$, $PhN(Et)_2$, $CH_2Cl_2$) of **10** affords **14** (80%). Alternatively, the crude rearrangement product may be acylated in situ to yield **14** (≃80% from **3**). In a similar manner, methyl thiooxime **7** undergoes sulfenyl transfer rearrangement to 7α-methylthioamine **15** (≃90%, NMR). Substance **15** is identical with an authentic sample prepared via methylthiolation of the corresponding *p*-nitrobenzylideneaminocephalosporin.[13] Such procedures are known to afford 7α-sulfenylated products.[3d] Steric requirements and comparison (NMR) of amines **10** and **15** strongly suggest that **10** is also α substituted. Acylation ($PhCH_2COCl$, propylene oxide, $CH_2Cl_2$, 0 °C) of **15** gave **16** (80%). Both **14** and **16** could be converted to a mixture of 7α-methoxycephalosporin ester **17** and its 7β-methoxyl isomer (73%, 2/1 α/β; 67%, 5/1 α/β, respectively, by NMR analysis) via the procedure of Slusarchyk, et al. [3d]

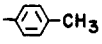
Performing sulfenyl transfer rearrangement of **3** in methanol yielded only a trace of 7α-methoxyamine **13**, as did quenching of preformed complex **8** with methanol. Methoxyamine **13** could be obtained by mercury ($Hg^{+2}$) catalyzed methanolysis[3e]

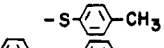
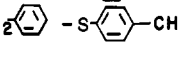
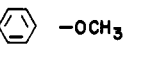
of **10** or **15**, but the preferred procedure is a modification of the sulfenyl transfer rearrangement in which either thiooxime is reacted with triphenylphosphine (3 equiv), mercuric acetate (1 equiv), methanol, and methylene chloride (26 °C, 3–5 h). Following removal of methanol, acylation of this mixture ($PhCH_2COCl$, propylene oxide, −10 °C) afforded 7α-methoxycephem ester **17** (90% from **7**) as a white foam: NMR ($CDCl_3$) δ 3.46 (s, 3 H), 3.50 (s, 2 H), 3.66 (s, 2 H), 3.93 (s, 3 H), 4.20, 4.50 (d of d, 2 H, $J$ = 13 Hz), 5.00 (s, 1 H), 6.33 (br s, 1 H), 6.90 (s, 1 H), 7.33 (s, 15 H); IR ($CHCl_3$) 1780, 1715, 1690 $cm^{-1}$. It is noteworthy that no β-methoxylation is observed.[14] A proposed pathway for this transformation is illustrated in Scheme I (**3** → **11** → **12** → **13** → **17**).

The methodology discussed above has been generalized to include the penam nucleus. Thus, trichloroethyl 6-aminopenicillanate *p*-toluenesulfonate salt was converted to thiooximes **18** (80%)[15a] and **19** (43%).[15b] Substance **18**, in





| | R |
|---|---|
| **18** |  |
| **19** | $-CH_3$ |

| | R | X |
|---|---|---|
| **20** | −H |  |
| **21** |  |  |
| **22** |  | $-OCH_3$ |

analogy with the cephalosporin example, underwent sulfenyl transfer rearrangement to **20** (≃90% by NMR, one isomer) which was acylated ($PhCH_2COCl$, $PhN(Et)_2$, $CH_2Cl_2$, 0 °C) to yield **21**. In addition, subjection of thiooxime **18** to the above modified rearrangement conditions, followed by acylation, afforded 6α-methoxypenam **22** (91% from **18**).[16,17] We are continuing to investigate the scope and mechanism of these transformations.

**Acknowledgment**. The authors wish to express their gratitude to Dr. William H. Koster and Dr. William A. Slusarchyk for useful discussions during the course of this research. We also wish to thank the Squibb Institute Analytical Department for their assistance, especially Dr. M. Puar for obtaining and interpreting NMR data.

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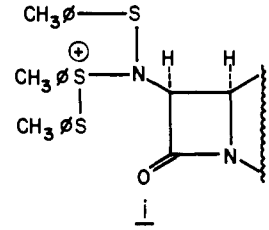
(4) For a different synthesis of 7α-methoxycephalosporins from thiooximes, see the accompanying paper of Dr. Tetsuo Hiraoka and his colleagues at Sankyo Company, Japan.

(5) T. L. Cairns, Ed., *Org. Synth.*, **35**, 99, 1955.

(6) All new compounds gave satisfactory elemental analyses and spectral data.

(7) All yields refer to quantities actually isolated, unless otherwise stated.

(8) Similar sulfenimides (of 6-APA) have been isolated by Welch;[9] however, these reactions were performed in aqueous media and did not lead to thiooxime products. An alternate route to **3** might involve activation of sulfenimide **4** toward β elimination through a structure of type I.



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(9) W. M. Welch, *J. Org. Chem.*, **41**, 2220 (1976).

(10) I. B. Douglass, *J. Org. Chem.*, **24**, 2004 (1959).

(11) There is ample analogy for insertion of trivalent phosphorous between an N–S bond in sulfenamide chemistry. See T. Mukaiyama, *Angew. Chem., Int. Ed. Engl.*, **15**, 94 (1976).

(12) Mallinckrodt SilicAR CC-4 was used, although numerous brands were satisfactory.

(13) Personal communication from Dr. W. A. Slusarchyk of these laboratories. We thank him for providing this sample.

(14) The α configuration of methoxyl at C-7 is confirmed by comparison of **18** with an authentic sample prepared by a route known to give exclusive α-methoxylation.[3k,13]

(15) (a) Yellow crystals; mp 77–79 °C; NMR ($CDCl_3$) δ 1.60 (br s, 6 H), 2.36 (s, 3 H), 4.73 (s, 1 H), 4.80 (s, 2 H), 5.73 (s, 1 H), 7.16, 7.46 (d of d, 4 H, $J$ = 8 Hz); IR ($CHCl_3$) 1780, 1760 $cm^{-1}$; UV (MeOH) 226 nm (ε 8300), 267 (3600), 338 (3600); mass spectrum *m/e* 466 ($M^+$). (b) White crystals; mp 129–130 °C; NMR ($CDCl_3$) δ 1.60 (s, 6 H), 2.91 (s, 3 H), 4.76 (s, 1 H), 4.86 (s, 2 H), 5.81 (s, 1 H); IR (KBr) 1770, 1755 $cm^{-1}$; mass spectrum *m/e* 390 ($M^+$). Both **18** and **19** form stereospecifically and are stable entities at 26 °C.

(16) Introduction of C-6 methoxyl occurs stereospecifically, the configuration of which was expected to be α on the basis of steric effects and analogy with the cephalosporin example. This was confirmed by conversion of **22** to the known 7α-methoxy-7-phenylacetamidodeacetoxycephalosporanic acid.[3d] Details will be given in the full paper.

(17) A typical procedure for rearrangement of **18** to **22** is as follows. Thiooxime **18** (16.1 g, 34.5 mmol) and triphenylphosphine (27.6 g, 103.6 mmol) are dissolved in methylene chloride (600 ml) and stirred at 26 °C. A solution of mercuric acetate (11.0 g, 34.5 mmol) in methanol (150 ml) is immediately added and the reaction mixture is allowed to stir for 3.5 h. The mixture is evaporated to dryness under reduced pressure and then redissolved in methylene chloride (600 ml) and propylene oxide (150 ml). This solution is chilled to −10 °C and phenylacetyl chloride (25.8 g) in methylene chloride (80 ml) is added dropwise with stirring. After 3 h, the reaction mixture is concentrated to an oil and chromatographed on silica gel (Mallinckrodt SilicAR CC-7) to yield **22** as a clear, colorless oil (15.49 g, 91%).

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*Received April 4, 1977*

## A Novel Synthetic Route to 7α-Methoxycephalosporins

*Sir:*

Much attention has been focused on 7-methoxycephalosporins after isolation of the cephamycin group from cultures of a *streptomyces* species[1] and subsequent modification of the original compound to those with enhanced activity.[2] Several methods have been developed for introduction of a methoxy group at the seven position of cephalosporins starting from 7-aminocephalosporins or 7-acylaminocephalosporins.[3] However, some difficulty still remains in the synthesis of 7α-methoxycephalosporins having a complex 7β-acylamino side chain.[4] Our object was directed toward the synthesis of