SYNTHESIS OF 3-SUBSTITUTED CEPHEMS FROM PENICILLINS VIA 4-DITHIO-2-AZETIDINONE INTERMEDIATES

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This paper is dedicated to Doctor Ken'ichi Takeda on the seventies anniversary of his birth.

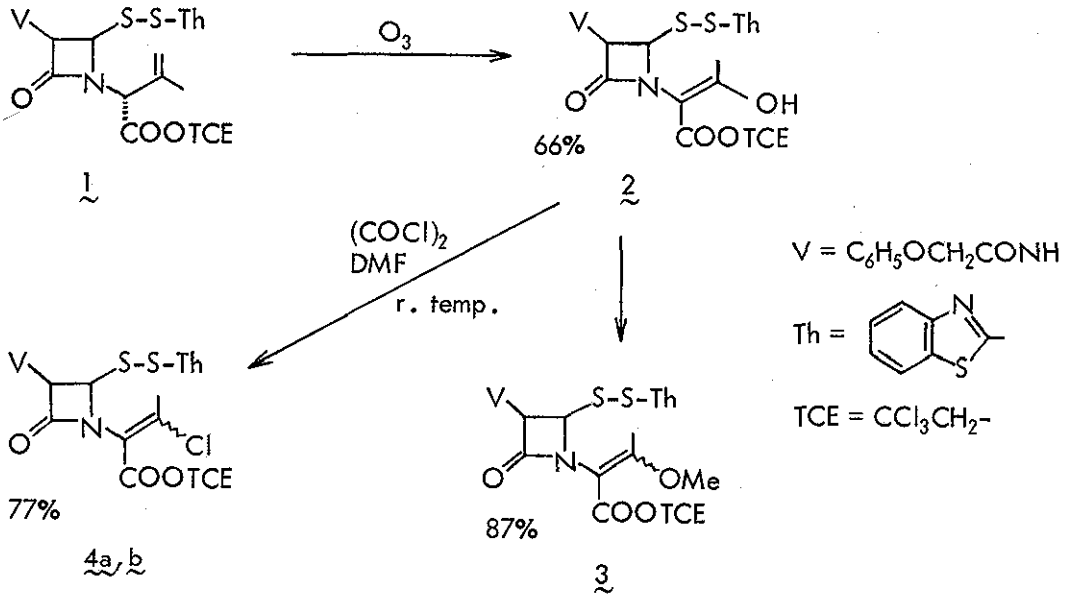
Cyclization of monocyclic dithioazetidinones 9 to the 3-substituted cephems is accomplished. When substituents at the β position of esters 9 are electron withdrawing such as chloro or sulfonyloxy, the benzothiazol-2-ylthio group migrates to position 3 of the cephem nucleus to give 3-thio derivatives 5 and 6. In contrast, when the substituents at the β position are weakly electron withdrawing, normal cyclization occurs giving 3-acyloxy derivatives 10. Reaction of γ-bromo-β-keto ester 16 with sodium borohydride and successive treatment with triphenylphosphine affords 3-hydroxy-cephem 11 albeit in poor yield. Base treatment of γ-bromo

enamino ester 15 or γ-bromo-β-acetoxy ester 20 gives the corresponding 2,3-bis-substituted cephems 18 or 21.

In the past decade there has been considerable interest in chemical modification of penicillins and cephalosporins. We have been interested in 3-halo- and 3-methoxy-7-phenylglycylaminoceph-3-em-4-carboxylic acids[1] that have been reported to be superior to cephalexin in antibacterial activities. The precedent synthesis involves reduction of 7-substituted cephalosporanic acids to the 3-methylene cephams,[2] ozonolysis of the 3-methylene to the 3-oxo function, and subsequent conversion into the 3-chloro- or the 3-methoxycephem-4-carboxylates.[1] More recently, a successful direct synthesis of 3-halo- or 3-methoxycephems from a 4-benzothiazol-2'-yldithio-2-azetidinone has been described.[3] 4-Benzothiazol-2'-yldithio-2-azetidinones have also been used as the key intermediates in syntheses of 2β-substituted methylpenicillins,[4] 3β-substituted cephams,[4] 3-methyl-3-cephems, and 2-methyl-3-cephems.[5] We also planned to use these disulfides as the key intermediates for the synthesis of 3-substituted cephems from penicillins.

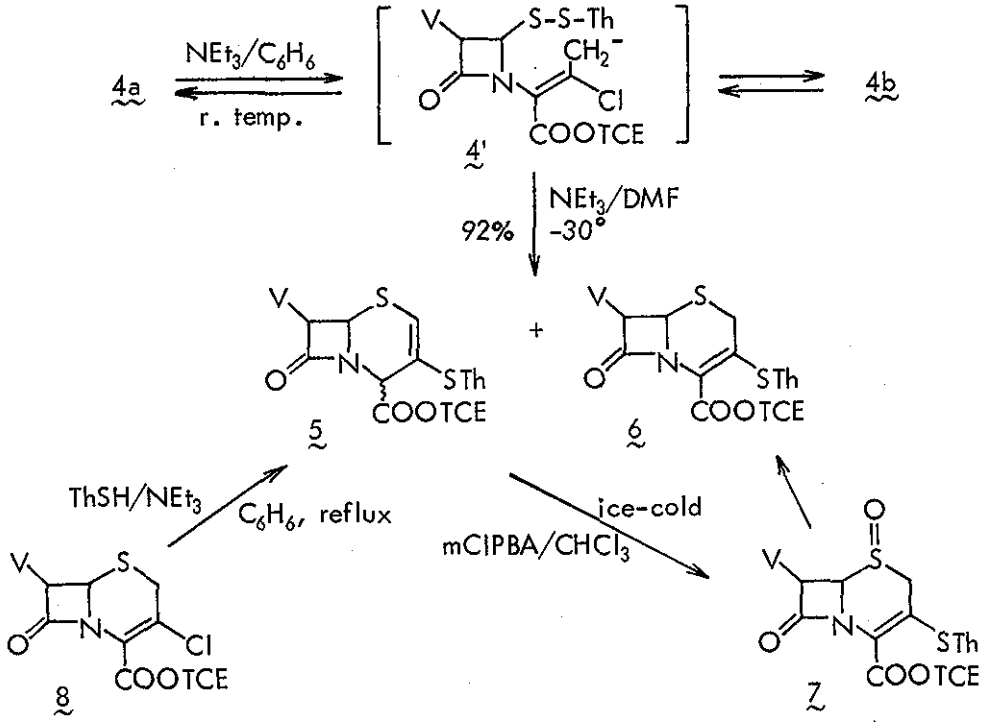
Upon ozonolysis the azetidinone disulfide 1 afforded β-keto ester 2[6a] as a single isomer, which easily reacted with diazomethane giving β-methoxy derivative 3 as a mixture of two geometrical isomers. Direct cyclization reaction of 2 or 3 in basic media was unsuccessful though some successful results were recorded in a patent literature[6a] in similar cases. Therefore, we intended to change the enol hydroxy group to other suitable groups in order to effect easier formation of the carbanion at the γ position. Treatment of 2 in dimethylformamide with oxalyl chloride afforded the β-chloro derivatives 4 as a mixture of two geometrical isomers. Chromatographic

separation of the mixture gave 4a as a major product, mp 102-104°; ir: 1781 cm^{-1} (β-lactam C=O); nmr δ (in $CDCl_3$) 2.63 (s, CH_3), 4.57 (s, $C_6H_5OCH_2$), 4.45, 4.70 (ABq, CH_2CCl_3, J = 12 Hz), 5.03 (dd, C_3-H, J = 5.0, 8.0 Hz), 5.70 (d, C_4-H, J = 5.0 Hz), 6.8-8.0 (m, 10H), and 4b as a minor product, foam; ir: 1781 cm^{-1} (β-lactam C=O); nmr δ (in $CDCl_3$) 2.63 (s, CH_3), 4.52 (s, $C_6H_5OCH_2$), 4.71, 4.79 (ABq, CH_2CCl_3, J = 11 Hz), 5.5-5.8 (m, C_3-H, C_4-H), 6.8-8.0 (m, 10H).



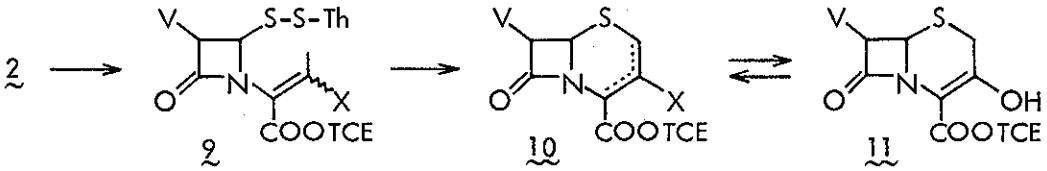
When 4a was treated with triethylamine in benzene, isomerization to 4b was observed. This result suggests that the carbanion 4' is generated with this base. This carbanion is expected to attack the sulfur atom to give the cephem nucleus effecting the desired cyclization. In fact, treatment of 4a in dimethylformamide with excess triethylamine for 2 hr at -30° gave a mixture of cyclized products. However, it turned out that the products had the unexpected 3-benzothiazol-2'-ylthiocephem structures 5 and 6. On similar treatment with triethylamine the methanesulfonyloxy-

or p-toluenesulfonyloxy derivative of 2 prepared in the usual manner were converted into the cyclized products 5 and 6 in good combined yield. Chromatographic separation afforded in 80% yield 5; ir: 1790 cm^{-1} (β-lactam C=O); nmr δ (in $CDCl_3$) 4.56 (s, $C_6H_5OCH_2$), 4.73 (s, CH_2CCl_3), 5.43 (d, C_6-H, J = 4.0 Hz), 5.60 (d, C_4-H, J = 1.0 Hz), 5.75 (dd, C_7-H, J = 4.0, 8.0 Hz), 6.8-8.0 (m, 10H), and in 12% yield 6; ir: 1795 cm^{-1}; nmr δ (in $CDCl_3$) 3.64, 3.96 (ABq, C_2-CH_2, J = 18 Hz), 4.50 (s, $C_6H_5OCH_2$), 4.85, 5.02 (ABq, CH_2CCl_3, J = 12 Hz), 5.12 (d, C_6-H, J = 5.0 Hz), 5.95 (dd, C_7-H, J = 5.0, 9.0 Hz), 6.75-8.05 (m, 10H). The structure of 5 was determined from the above described ir and nmr spectral data and by chemical conversions as described below. Oxidation of 5 with m-chloroperbenzoic acid gave the sulfoxide 7, which was reduced (acetyl chloride-$SnCl_2 \cdot 2H_2O$ in DMF)[7] to the 3-cephem 6. Furthermore, it was found that both 5 and 6 were derived from the



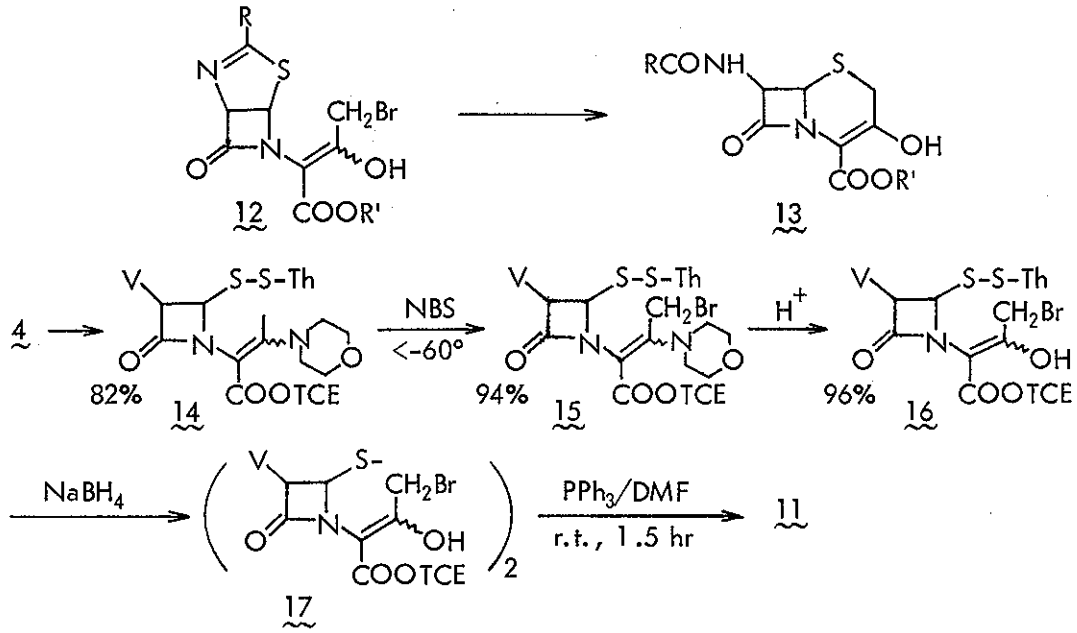
3-chloroceph-3-em 8.

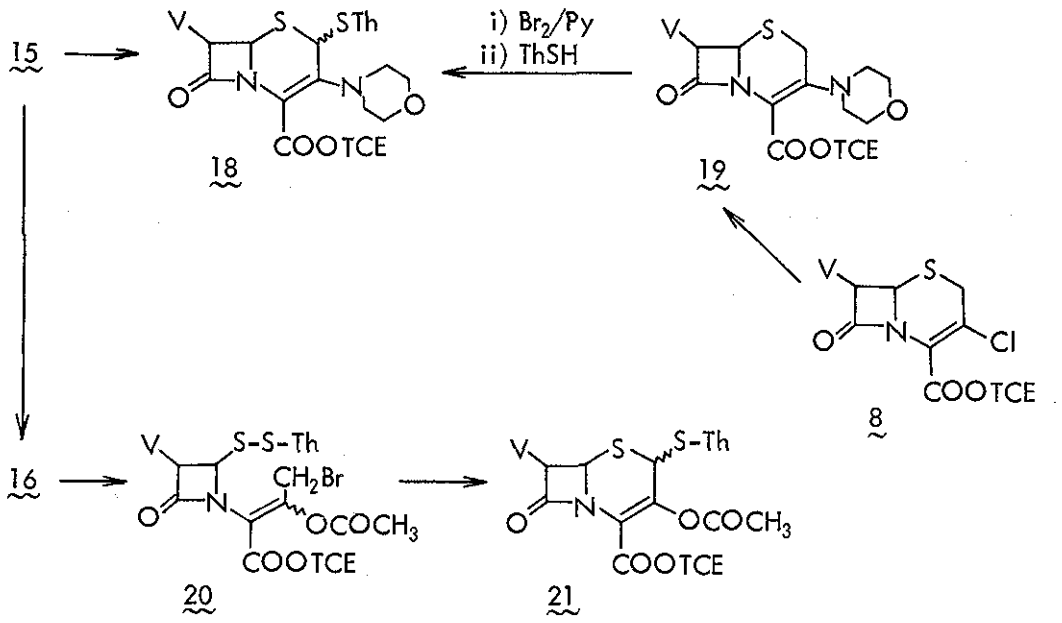
The formation of these 3-benzothiazolylthiocephems can be interpreted by initial formation of the 3-chloro- or 3-sulfonyloxycephem-4-carboxylate followed by replacement of the electron-withdrawing (good leaving) group by the concomitantly formed benzothiazol-2-ylsulfide ion giving the Δ^2 and Δ^3 cephems 5 and 6. Apparently the former product was formed by isomerization of the latter with base. It was expected that rather weakly electron-withdrawing groups at the β position would not be replaced by the benzothiazolylthio group and thus the initial cyclization products could be obtained. In fact, when compounds 9 [X = $OCOCH_3$, $OCOOCH_2$◁, and $OP(O)(OEt)_2$] were treated with triethylamine in a similar manner, the expected 3-substituted cephems 10 were obtained as mixtures of Δ^2 and Δ^3 isomers. Treatment of 10 (X = $OCOOCH_2$◁) with aluminum chloride in dichloromethane-nitromethane at room temperature afforded 3-hydroxyceph-3-em 11 in a good yield.



Recently, it was found in our research group that thiazoline γ-halo-β-keto esters 12 were easily and quantitatively cleaved with acids and were recyclized to give 3-hydroxycephems 13.[8] Therefore, we attempted to synthesize the 3-hydroxycephems in a similar way from the disulfides containing γ-halo-β-keto ester function. γ-Bromo-β-keto ester 16 was obtained in a good overall yield by bromination of the enamine 14 derived from 4 and successive hydrolysis of the resulting bromo enamine 15. Treatment of the disulfide 16 with sodium borohydride did not give the desired 3-hydroxy-

cephem 11 but gave the symmetric disulfide 17, which was reductively cleaved with triphenylphosphine giving the cephem 11 although in a poor yield (~5%). On the contrary, treatment of 15 with triethylamine in dimethylformamide at 0° afforded in quantitative yield 2-benzothiazol-2'-ylthio-3-morpholinocephem 18, mp 191-192°; ir: 1783 cm^{-1}; nmr δ (in $CDCl_3$) 3.27-3.83 (m, morpholino), 4.23, 4.50 (ABq, $C_6H_5OCH_2$, J = 15 Hz), 4.63, 4.97 (ABq, CH_2CCl_3, J = 12 Hz), 5.43 (d, C_6-H, J = 4.0 Hz), 5.65 (dd, C_7-H, J = 4.0, 8.0), 6.40 (s, C_2-H), 6.77-7.92 (m, 5H). The assigned structure of 18 was confirmed by its independent synthesis from 8 via 19 as illustrated in the scheme. The benzothiazol-2-ylthio group at C_2 is tentatively assigned to take the thermodynamically stable α configuration, as further information is not available. Hydrolysis and subsequent acylation of 15 gave the acetoxy derivative 20, which reacted similarly with triethylamine giving the corresponding cephem 21 in quantitative yield.





We have thus been successful in synthesizing 3-substituted ceph-3-ems in a facile manner from penicillins. Recently, successful syntheses of 3-substituted cephems from penicillins involving a similar synthetic route have been reported by other research groups.[6)]

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