(12) We are indebted to the Fujisawa Pharmaceutical Company in Osaka for the generous gift of 6-aminopenicillanic acid.
(13) G. A. Koppel and R. E. Koehler, *J. Am. Chem. Soc.*, **95**, 2403 (1973).
(14) R. D. G. Cooper and F. L. Jose, *J. Am. Chem. Soc.*, **92**, 2575 (1970); J. E. Baldwin, F. J. Urban, R. D. G. Cooper, and F. L. Jose, *ibid.*, **95**, 2401 (1973).
(15) Transformation of **13** into **17** could be effected by kinetically controlled protonation on the monoanion of **13**, but the results were less satisfactory than the present procedure.
(16) 3-Deacetoxy-7-methoxycephalosporin (**19**) was synthesized from 6-aminopenicillanic acid by Koppel's procedure[13] and then modified Morin reaction.
(17) 6-Methoxypenicillin (**20**) was synthesized from 6-aminopenicillanic acid by Koppel's procedure.[13]
(18) H. Tanino, S. Nakatsuka, and Y. Kishi, a manuscript for publication in preparation.
(19) This cyclization is also effective for preparation of 3-deacetoxy-7*H*-cephems. The dibromide **16**, available from **13** in 70% yield by NBS (2.2 equiv) bromination, similarly cyclizes to 3-bromomethyl-7-methoxycephems, but the yield is much lower than for the monobromide case, obviously because the expected product decomposes under these conditions.
(20) J. A. Webber, E. M. Van Heyningen, and R. T. Vasileff, *J. Am. Chem. Soc.*, **91**, 5674 (1969).
(21) Fujisawa Pharmaceutical Co., Japan Patent, 25488 (1974).
(22) This paper was read in the 9th IUPAC Symposium on Chemistry of Natural Products, Ottawa, Canada, 1974, and the 1st IUPAC Conference on Organic Synthesis, Louvain-la-Nueuve, Belgium, 1974, by Y. Kishi.
(23) S. Nakatsuka, H. Tanino, and Y. Kishi, *J. Am. Chem. Soc.*, following paper in this issue.
(24) Financial assistance by Harvard University, the National Institutes of Health, the National Science Foundation, and the Pharmaceutical Division of CIBA-GEIGY is gratefully acknowledged.

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Biogenetic-Type Synthesis of Penicillin–Cephalosporin Antibiotics. II. An Oxidative Cyclization Route to β-Lactam Thiazoline Derivatives

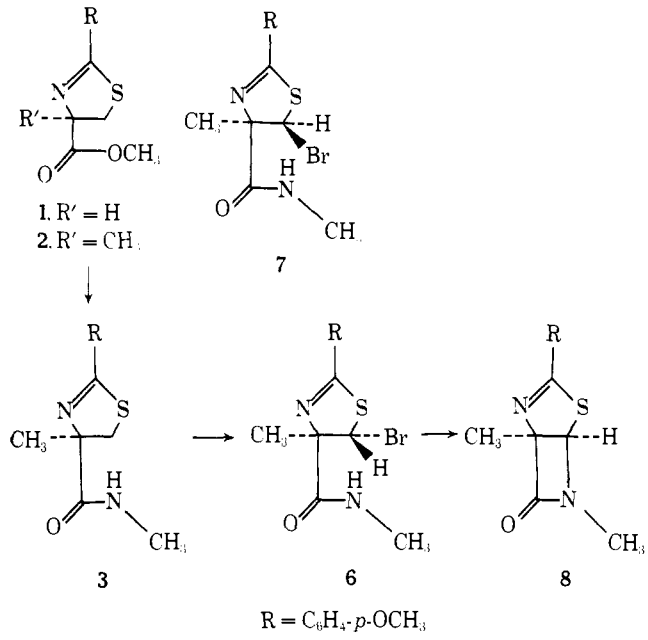
Sir:

In the preceding paper,[1] we reported a selective and stereocontrolled synthesis of the penam and cephem derivatives from an acyclic tripeptide[2] equivalent. One of the crucial steps of the synthesis was the double cyclization reaction to construct the β-lactam thiazoline system. In this communication, we report an oxidative cyclization method to construct the β-lactam thiazoline ring system. A synthesis of the β-lactam thiazoline dehydrovaline **10**, using the oxidative cyclization by a key step, could present a solution for the biogenetic-type synthesis of penicillins and cephalosporins, which would be closer than the previous approach to the biosynthetic pathways suggested by Cooper.[3]

The thiazoline **1**[4] (mp 57–58°), which corresponds to the dehydrated form of *N*-acylcysteine,[5] was synthesized in 90% yield from L-cysteine by two steps ((1) CH_3OH–HCl, (2) *p*-$CH_3OC_6H_4C(OEt)$=NH·HCl in CH_3OH).[6] Treatment of **1** with 1.05 equiv of sodium methoxide in methanol, followed by methyl iodide (excess) treatment, gave the methylthiazoline **2**[4] (oil) in 74% yield. The ester group in **2** was converted to the corresponding amide group by three steps ((1) NaOH in aqueous CH_3OH, (2) $(COCl)_2$, (3) H_2NR); thus, the amide **3**[4] (mp 132–133°; 85% overall yield), **4**[4] (oil as a diastereomeric mixture; 86% overall yield), and **5**[4] (oil; 83% overall yield) were synthesized from **2** (Scheme I).

NBS bromination of the amide **3** in CCl_4 containing α,α′-azobisisobutyronitrile at 90° gave a ca. 1:1 mixture of the bromides **6** and **7**.[7] The bromides 6 ($\delta_{ppm}^{CDCl_3}$ 1.92 (3 H, s), 2.74 (3 H, d, J = 5 Hz), 3.83 (3 H, s), 6.53 (1 H, s), and 6.88 and 7.75 (2 H + 2 H, AB, J = 9 Hz)) and **7** ($\delta_{ppm}^{CDCl_3}$ 1.53 (3 H, s), 2.91 (3 H, d, J = 5 Hz), 3.83 (3 H, s), 5.84 (1 H, s), and 6.88 and 7.73 (2 H + 2 H, AB, J = 9 Hz)) were isolable, although **6** and **7** were readily hydrolyzed to the corresponding alcohols. Assignment of the stereochemistry was made from the following cyclization experiments. Namely, potassium hydride treatment[1] of **6** gave cleanly the β-lactam thiazoline **8**[4] (mp 138–139°; $\delta_{ppm}^{CDCl_3}$ 1.80 (3 H, s), 2.83 (3 H, s), 3.81 (3 H, s), 5.19 (1 H, s), and 6.84 and 7.71 (2 H + 2 H, AB, J = 9 Hz); ν_{max}^{KBr} 1752 cm^{-1}) in high yield, but under the same conditions the isomeric bromide **7** was recovered unchanged. These results indicate the cyclization reaction takes place in an SN2 process and allows one to assign the stereochemistry to the bromides **6** and **7**. The bromide **7**, which was recovered under the above conditions could be converted to the β-lactam thiazoline **8** by potassium hydride in THF containing lithium bromide and lithium perchlorate. The conversion of **3** into **8** could be best achieved without isolation of the unstable bromides **6** and **7** in about 20% overall yield.

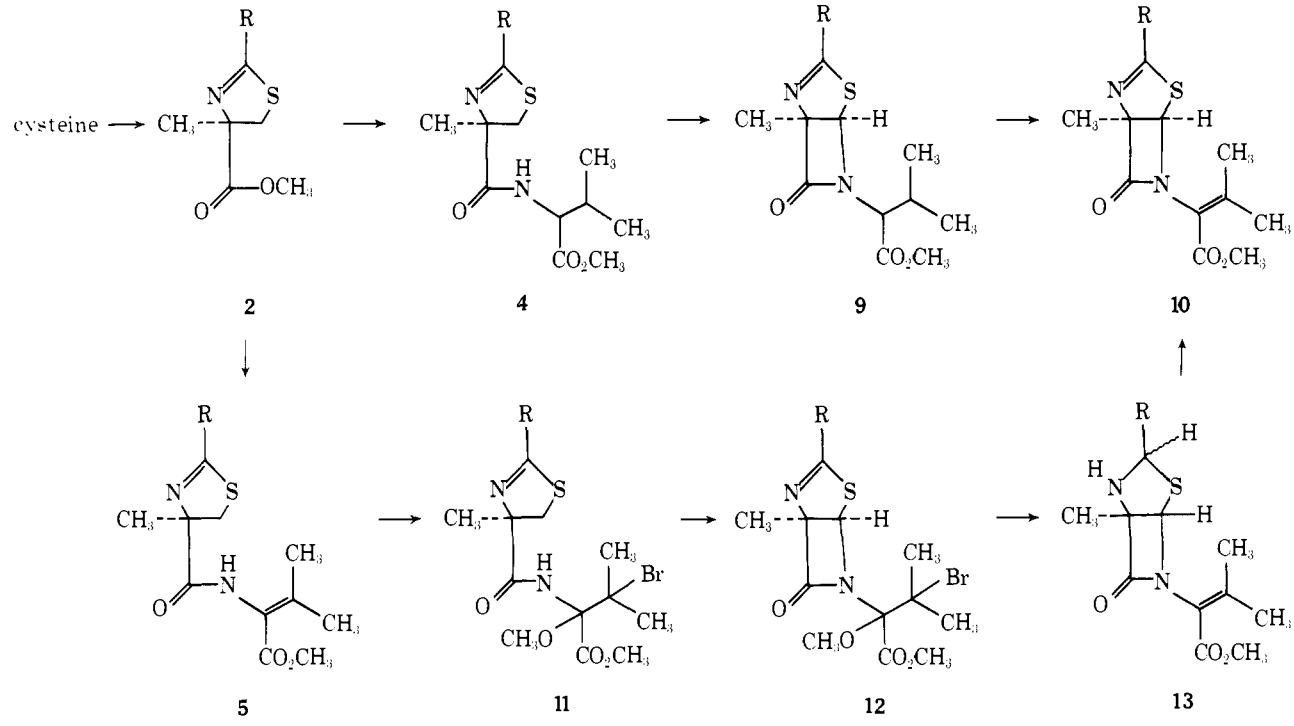
Scheme I



Similarly, NBS (1.3 equiv) bromination of the amide **4**, followed by potassium hydride treatment in THF containing $LiClO_4$, yielded the β-lactam thiazoline valine derivative **9**[4] (melting point of the one diastereomer 127–129°; ν_{max}^{KBr} 1757 and 1740 cm^{-1}; the other diastereomer is an oil) in 15% overall yield. Successive treatment of **9** with NBS (2.0 equiv) in CCl_4 containing α,α′-azobisisobutyronitrile at 90°,[8] zinc–acetic acid at room temperature,[9] and triethylamine in methylene chloride, yielded the β-lactam thiazoline dehydrovaline derivative **10**[4] (mp 107–108°; $\delta_{ppm}^{CDCl_3}$ 1.84 (6 H, s), 2.24 (3 H, s), 3.76 (3 H, s), 3.84 (3 H, s), 5.61 (1 H, s), and 6.91 and 7.79 (2 H + 2 H, AB, J = 9 Hz); ν_{max}^{KBr} 1762 and 1726 cm^{-1}) in 70% overall yield (Scheme II). This sequence of the reactions corresponds to one possible sequence of the suggested biosynthetic pathways; namely, the β-lactam ring construction is followed by oxidation of the valine moiety. The β-lactam thiazoline **10** can selectively be transformed to a 6-methylpenam and a 7-methylcephem by the method described in the preceding paper.[1]

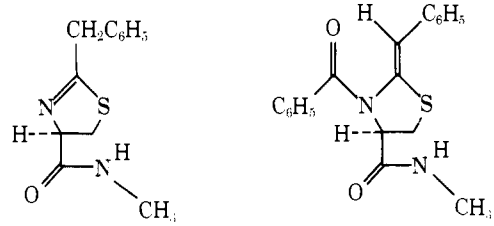
The other possibility concerning the sequence of the biosynthetic pathways (i.e., oxidation of the valine moiety is followed by the β-lactam ring construction) could be demonstrated in the following ways. Bromination of **5** with bromine in methylene chloride and methanol work-up gave the bromomethoxyamide **11**[4] (oil as a diastereomeric mixture)

Scheme II



in 93% yield. NBS bromination of **11**, followed by KH-$LiClO_4$ treatment in THF, afforded the bromomethoxythiazoline β-lactam **12**[4] (melting point of one diastereomer 183–184°; ν_{max}^{KBr} 1781 and 1761 cm^{-1}; the other diastereomer is an oil, $\nu_{max}^{CH_2Cl_2}$ 1771 and 1745 (sh) cm^{-1}) in 22% overall yield. Aluminum amalgam reduction of **12** gave the β-lactam thiazolidine **13**[4] (mp 107–108°; $\delta_{ppm}^{CDCl_3}$ 1.80 (3 H, s), 2.04 (3 H, s), 2.25 (3 H, s), 3.78 (3 H, s), 3.80 (3 H, s), 5.52 (1 H, s), 5.59 (1 H, broad), and 6.89 and 7.43 (2 H + 2 H, AB J = 9 Hz); ν_{max}^{KBr} 1752 and 1726 cm^{-1}) in 71% yield.[10] DDQ dehydrogenation of **13** in benzene afforded the β-lactam thiazoline **10**[4] (mp 107–108°) in 40% yield.

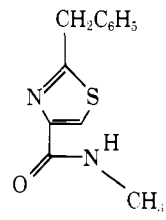
The C_4-methyl group in the amide **3**, **4**, or **5** was important to avoid thiazole formation during NBS bromination. Therefore, straight application of the described procedure for a synthesis of naturally occurring 6*H*-penicillins or 7*H*-cephalosporins seems to be less promising. However, this difficulty was overcome as follows—note the amide side chain of penicillin G. The benzylthiazolineamide **14**[4,11] (mp 80–81°) was converted to the benzoate **15**[4] (mp 156–157°) by benzoyl chloride-triethylamine treatment in 80% yield. *m*-Chloroperbenzoic acid oxidation of **15** in methylene chloride afforded the sulfoxide **16**[4] (mp 220–221°) in 95% yield. Acetic anhydride treatment of **16** at 110° overnight gave a mixture of acetates **17**[4] (mp 188–189°; $\delta_{ppm}^{CDCl_3}$ 2.12 (3 H, s), 2.87 (3 H, d, J = 5 Hz), 5.36 (1 H, s), 5.92 (1 H, s), 6.72 (1 H, s), and 7.0–7.8 (10 H, m)), and **18**[4] (oil; $\delta_{ppm}^{CDCl_3}$ 2.04 (3 H, s), 2.90 (3 H, d, J = 5 Hz), 5.21 (1 H, d, J = 8 Hz), 6.10 (1 H, s), 6.68 (1 H, d, J = 8 Hz), and 7.0–7.7 (10 H, m)). The stereochemistry of the acetates was concluded from analysis of the NMR spectra (i.e., $J_{4,5}$ = 0 Hz in **17**, while $J_{4,5}$ = 8 Hz in **18**), and also from the fact that the acetate **18** readily aromatizes to the thiazole **19**[4] (mp 112–113°), while the acetate **17** is stable under these conditions. Transformation of **16** to **17** was best achieved by acetic anhydride-acetic acid (1:1) treatment at 110° overnight in 40% yield.[12] The acetate **17** can be cyclized to a β-lactam thiazoline derivative by the similar method described before.[13]



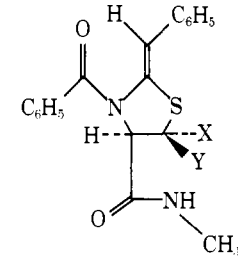
14

15

16. sulfoxide of 15



19



17, X = OAc; Y = H

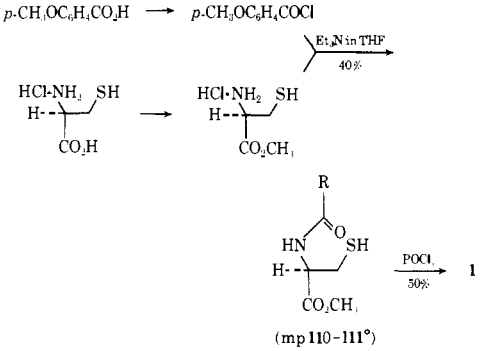
18, X = H; Y = OAc

Further extensions and modifications of the synthetic route, and also a possibility that demonstrated synthetic schemes may be involved in actual biosyntheses of the antibiotics, are currently being studied in our laboratories.[14]

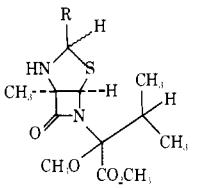
References and Notes

(1) Part I of this series: S. Nakatsuka, H. Tanino, and Y. Kishi, *J. Am. Chem. Soc.*, preceding paper in this issue.
(2) H. R. V. Arnstein and J. C. Crawhall, *Biochem. J.*, **67**, 180 (1957).
(3) R. D. G. Cooper, *J. Am. Chem. Soc.*, **94**, 1018 (1972). The present oxidative cyclization method to construct the β-lactam thiazoline ring system corresponds to the process from the cysteinylvaline derivative to the β-lactam thiazoline derivative in the Cooper's suggestion.
(4) Satisfactory spectroscopic data (MS, NMR, ir, uv) were obtained for this substance.
(5) The *p*-methoxyphenyl group as the substituent R was chosen from the following two reasons; i.e., (1) the sulfur atom in this thiazoline system can easily be oxidized to the corresponding sulfoxide, and (2) this thiazoline system is considerably stable under acidic and basic conditions.
(6) The thiazoline **1** could be synthesized from L-cysteine and *p*-methoxy-

benzoic acid in the following procedures, which would be closer to the biosynthetic pathways but are less efficient.



(7) NBS bromination of **3** in CH_2Cl_2 at room temperature gave exclusively the *N*-bromoamide, which yielded a mixture of the bromides **6** and **7** on refluxing in CCl_4 containing radical initiator.
(8) The major product at this stage was a mixture of the allylic monobromides (see ref 1).
(9) The product at this stage was a mixture of the conjugated and deconjugated ester (see ref 1).
(10) Aluminum amalgam reduction of the one diastereomer ("oil") of **12** gave exclusively **13**, but the other ("crystal") gave a ca. 1:1 mixture of **13** and i.



i

(11) This compound was synthesized by the method similar to the one adopted for the synthesis of **3**.
(12) In addition of **17** (40% yield), the thiazole **19** was isolated in 40% yield. **19** would be formed through **18**.
(13) S. Nakatsuka, H. Tanino, and Y. Kishi, a manuscript for publication in preparation.
(14) Financial assistance by Harvard University, the National Institutes of Health, the National Science Foundation, and the Pharmaceutical Division of CIBA-GEIGY is gratefully acknowledged.

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Facile, Aerial Oxidation of Coordinated Ammonia

Sir:

Considerable interest has arisen over the past decade concerning the fixation of atmospheric nitrogen to ammonia.[1,2] Although it is a challenging chemical problem, it has convincingly been demonstrated that the fixation of N_2 to NH_3 could only have a marginal effect[3,4] on the cost of ammonia now being produced by the Haber process. Economically, the chemical fixation of nitrogen directly into organonitrogen derivatives or more reactive forms of nitrogen such as hydroxylamine is much more important. Both Van Tamelen[5] and Volpin[6,7] have demonstrated that molecular nitrogen can be activated and incorporated into organic molecules. Unfortunately, the addition of N_2 and H_2 to benzene (to yield aniline) is highly endoergic.[8] As a result, the production of numerous inorganic and organonitrogen compounds often occurs by way of a variety of circuitous routes. One classic example is the oxidation of ammonia (>800° over Pt/Rh)[9] to produce NO_x (NO, NO_2, N_2O_3) which is then reduced (Raschig process)[10] to hydroxylamine. Yet, the direct aerial oxidation of NH_3(aq) to NH_2OH(aq) (at 25° and atmospheric pressures) is only slightly endoergic (+0.8 kcal).[11] Thus, it is apparent that *even* if one starts from NH_3, simple, straightforward processes are unknown for the production of a variety of inorganic and organonitrogen compounds. The possibility remains that catalytic systems can be devised to activate nitrogen or even ammonia to produce NH_2OH (coordinated), NO^+, NO, NO_2^-, or NO_3^-. We wish to report the rapid, facile oxidation of ammonia coordinated to ruthenium, using air at room temperatures and atmospheric pressures (pH ≥11). The final product is a nitrosyl: $Ru(NH_3)_5NO^{3+}$. We have also succeeded in preparing this same nitrosyl in higher yields and at even lower pH's using a HO_2^-/H_2O_2 buffer without the requirement of an external source of oxygen. Similar nitrosyls have been produced by Broomhead and Taube[12] by the action of ClO_4^- upon $Ru(NH_3)_6^{3+}$, at steam-bath temperatures. Recently, Diamond and Taube[13] have reported that at lower pH's (7-9) organic amines on ruthenium are oxidized to amides.

Previously, we have demonstrated[14] that this nitrosyl can be converted into alkylnitroso compounds in the presence of alcohol by means of ionizing radiation. Several additional examples of reactive metal nitrosyls can be found in the literature, namely, (1) disproportionation (Stanko[15] has shown that $RhCl_3$ catalyzes the disproportionation of NO (via rhodium nitrosyls) to yield N_2O and ethyl nitrite (in the presence of ethanol), (2) protonation (excess HCl is also known to reduce[16] $Ir(NO)(PPh_3)_3$ to $IrCl_3(NH_2OH)(PPh_3)_2$), (3) oxidation (Laing and Roper[17] have demonstrated that $Ru(NO)_2L_2$ is oxidized by O_2 to yield the nitrate: $RuO_2(NO_3)(NO)L_2$), (4) reductive coupling (Bottomley[18] has shown that $Ru(NH_3)_5NO^{3+}$ reacts with NH_2OH to yield $Ru(NH_3)_5(N_2O)^{2+}$ and with N_2H_4 to yield $Ru(NH_3)N_2^{2+}$), (5) aromatic substitution (Meyer et al.[19] have prepared N-bound nitroso arene complexes by the addition of secondary and tertiary anilines to $Ru(bipyr)_2NOX^{2+}$), and (6) reduction (catalytic reduction of the "coordinated nitrosyl" by CO[20] (yielding N_2O and CO_2) over rhodium and iridium catalysts has recently been reported). Thus it is apparent that the generation of metal-nitrosyls can serve as important intermediates for the production of other organonitrogen derivatives.

Maintaining a continual oxygen purge through solution of $Ru(NH_3)_6X_3$ (X^- = Cl^- or Br^-, 2×10^{-5} to 0.05 *M*) at pH 13 (using KOH or NaOH as the only buffer), we have obtained the $Ru(NH_3)_5NO^{3+}$ complex in greater than 30% yield within 15 min (at room temperature). We have characterized the nitrosyl by the following methods. (1) Rotary evaporation of the acidified product mixture to dryness results in the appearance of a strong band at 1908 cm^{-1} (ν_{NO}) and a weaker band at 600 cm^{-1} (ν_{Ru-NO}) indicative of $Ru(NH_3)_5NO^{3+}$.[21] (2) With an NH_3 buffer, we have separated the $Ru(NH_3)_5NO^{3+}$ by ion exchange chromatography (moves as a +3 ion on Dowex 50W X-2, 200-400 mesh or on Sp-Sephadex).[22] The eluent displays a uv spectrum[21] characteristic of $Ru(NH_3)_5NO^{3+}$. (3) Evaporation of the +3 eluent (in HCl) produced an orange solid displaying ir and uv spectra indicative of $Ru(NH_3)_5NO^{3+}$.[21,23,24]

Using 5 *M* NH_3 as a buffer followed by acidification with HCl and evaporation to dryness produces $Ru(NH_3)_5Cl^{2+}$ (48%),[25] *t*-$Ru(NH_3)_4Cl_2^+$ (18%),[25] and a mixture of ruthenium nitrosyls (34% over 12 hr). The use of ammonia as a buffer permits us to use lower pH's (11) to obtain substantial yields of the nitrosyls. This can probably be attributed to competitive aquation reactions whose equilibria are favorably shifted by the high concentration of NH_3. From the ion exchange analysis, we have determined that the main competitive processes are confined primarily to base hydrolysis. Both $Ru(NH_3)_5OH_2^{3+}$ and *t*-$Ru(NH_3)_4(OH_2)_2^{3+}$ have been observed in the acidified product solutions. The latter species do not yield substantial