relationship of his theory and our results will be treated in a future publication.
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(9) For a review of polar cycloadditions, see R. Gompper, *Angew. Chem., Int. Ed. Engl.*, **8**, 312 (1969).
(10) D. A. Labianca, G. N. Taylor, and G. S. Hammond, *J. Am. Chem. Soc.*, **94**, 3679 (1972).
(11) Since [anthracene*:DMHD] exciplex still exhibits some polar character (ref 5), the results suggest that stepwise $4\pi_s + 2\pi_s$ photocycloadditions of 1,3-dienes to anthracene may occur concurrently with $4\pi_s + 4\pi_s$ additions under certain conditions. These have been found in photocycloadditions of highly unsymmetrical dienes and polar 1,3-dienes, J. Libman and T. Hamada, unpublished results.
(12) Guggenheim Fellow, 1974–1975.

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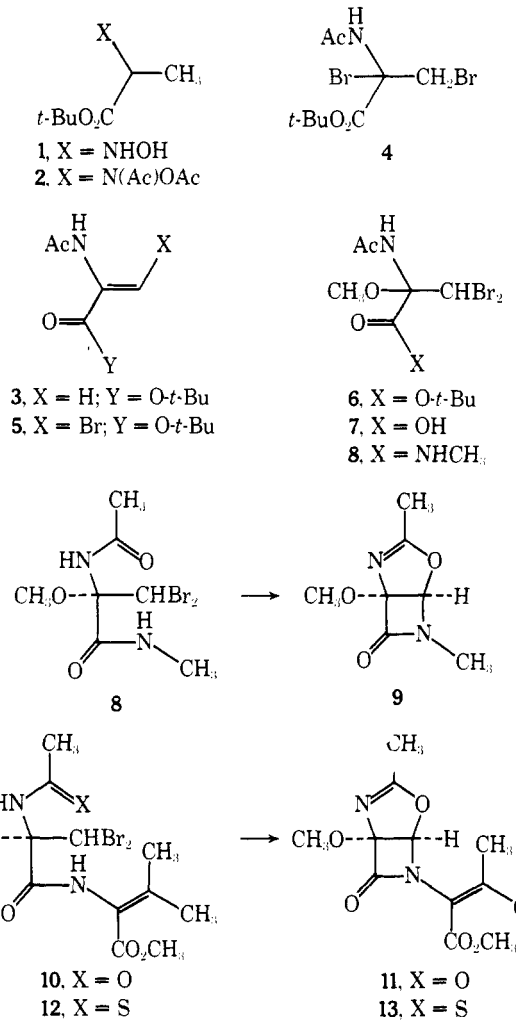
Biogenetic-Type Synthesis of Penicillin–Cephalosporin Antibiotics. I. A Stereocontrolled Synthesis of the Penam- and Cephem-Ring Systems from an Acyclic Tripeptide Equivalent

Sir:

Several magnificent total syntheses of penicillin–cephalosporin antibiotics have been completed,[1] but to our best knowledge none of them was achieved on the basis of the biosynthetic pathways[2] of the antibiotics. This series of papers is concerned with a biogenetic-type synthesis[3] of the bicyclic penicillin–cephalosporin antibiotics from an acyclic tripeptide[2a] equivalent. Our synthetic scheme is mainly based on the biosynthetic pathways suggested by Cooper[2d] in 1972.

2-Bromopropionyl bromide was converted to the hydroxylamine[5] **1** (mp 74–5°) in 85% yield by two steps (i.e., (1) *t*-BuOH–Py,[4] (2) $NH_2OH{\cdot}HCl$–$NaOCH_3$ in CH_3OH). Acetic anhydride treatment of **1** at 100° for 30 min yielded the diacetate[5] **2** (oil), which was converted to *N*-acetyldehydroalanine *tert*-butyl ester[5] (**3**) (oil) by triethylamine treatment in 72% overall yield from **1**. Bromine reacted smoothly with **3** in methylene chloride at room temperature, to give the dibromide **4** which was not isolable but clearly detectable by NMR analysis. Triethylamine treatment of **4** gave *N*-acetylbromodehydroalanine *tert*-butyl ester[5,6] (**5**) (mp 106–107°) in 90% overall yield from **3**. **5** reacts with bromine in a mixture of methylene chloride and methanol at room temperature, to yield the methoxydibromide *tert*-butyl ester[5] **6** (mp 115–116°) in 82%. Removal of the carboxylic acid blocking group of **6** under acidic conditions gave the methoxy dibromo acid[5] **7** (mp 143–144°) in 80% yield. A standard DCC procedure on **7** and methylamine in dioxane at room temperature afforded the methoxydibromodiamide[5] **8** (mp 114–115°) in 74% yield.[7]

On treatment with 2 equiv of sodium or potassium hydride in THF at room temperature, the methoxydibromodiamide **8** was cleanly converted to the β-lactam oxazoline **9**.[8]



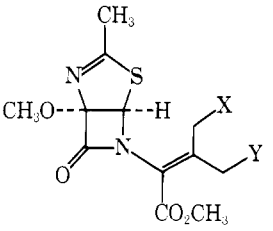
The yield of the substance homogeneous on TLC was about 70%. The crystalline substance[5] (mp 84–85°) was isolated in about 40% yield. Structure **9** was assigned to the product on the basis of the spectroscopic data ($\delta_{ppm}^{CDCl_3}$ 2.13 (3 H, s), 2.91 (3 H, s), 3.58 (3 H, s), and 5.56 (1 H, s); $\nu_{max}^{CH_2Cl_2}$ 1785 and 1650 cm^{-1}) and the elemental analysis data. The double cyclization reaction (KH or NaH, THF, room temperature) worked cleanly on the dehydrovaline derivative **10**[5,9] (mp 150–151°), to afford the β-lactam oxazoline derivative **11**[5] (oil; $\delta_{ppm}^{CDCl_3}$ 1.86 (3 H, s), 2.14 (3 H, s), 2.28 (3 H, s), 3.63 (3 H, s), 3.79 (3 H, s), and 5.88 (1 H, s); $\nu_{max}^{CH_2Cl_2}$ 1785, 1728, and 1650 cm^{-1}) in 40% yield.[10]

To extend the new double cyclization reaction to a biogenetic-type synthesis of the antibiotics, cyclization was examined on the monothioamide **12**. Thus, the dehydrovaline derivative **10**, was treated with phosphorus pentasulfide in THF at 50° for 2 hr and the unpurified[11] monothioamide **12** was subjected to the double cyclization reaction under sodium hydride conditions. A preparative TLC separation of the products on aluminum oxide plates gave the β-lactam thiazoline derivative[5] **13** (oil) in 12% overall yield from **10**. The synthetic substance was identified with an authentic sample, synthesized from 6-aminopenicillanic acid[12] by following Koppel's[13] and then Cooper's[14] procedures, by comparison of NMR, ir, TLC (aluminum oxide and silica gel plates), and HLC (Corasil I).

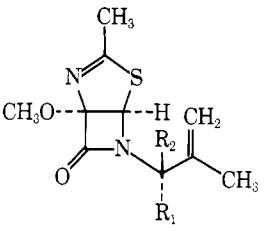
NBS bromination of **13** in the presence of a small amount of α,α′-azobisisobutyronitrile in carbon tetrachloride (1.5 hr, 75°), followed by a preparative TLC separation on aluminum oxide plates, gave the monobromides **14** and **15** (70% yield), the dibromide **16** (10% yield), and the

starting material **13** (10%). Zinc–acetic acid reduction of the mixture of the monobromides **14** and **15** (25 min at room temperature) gave a mixture of the deconjugated ester with *natural* configuration **17**[5] (oil), the deconjugated ester with *unnatural* configuration **18**[5] (oil), and the conjugated ester **13** in 90% yield.[15] The structure assignment to the deconjugated ester with *natural* configuration was confirmed from comparison (NMR, ir, TLC, HLC) of the synthetic substance with the authentic sample, synthesized from 6-aminopenicillanic acid by following Koppel's[13] and Cooper's[14] procedures. The ratio of **17:18:13** was 3:4:5, but this is not a serious problem for synthetic purposes, because by triethylamine treatment **18** can easily be isomerized to **13** and **13** can be recycled.

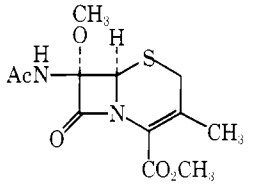
Following Cooper's method,[2d] the deconjugated ester with *natural* configuration **17** was subjected to *m*-chloroperbenzoic acid oxidation in benzene containing a catalytic amount of trifluoroacetic acid, to yield a complex mixture of products. After the entire products mixture was treated with phosphorus trichloride, the products were separated by a preparative TLC on silica gel plates, to give the 3-deacetoxy-7-methoxycephalosporin derivative **19**[5] in about 5% yield and 6-methoxypenicillin derivative **20**[5] in about 1% yield. The synthetic cephalosporin and penicillin derivatives were identified with authentic substances[16,17] by comparison of NMR, ir, TLC, and HLC. A process induced by a radical initiator was recently found to be extremely effective for selective transformation of β-lactam thiazoline sulfoxides (i.e., sulfoxides of **17** type compounds) to penam sulfoxides (60–90% yield).[18]



13, X = Y = H
14, X = Br; Y = H
15, X = H; Y = Br
16, X = Y = Br



17, $R_1 = CO_2CH_3$; $R_2 = H$
18, $R_1 = H$; $R_2 = CO_2CH_3$



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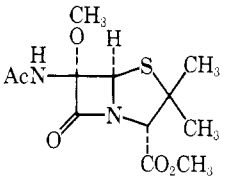

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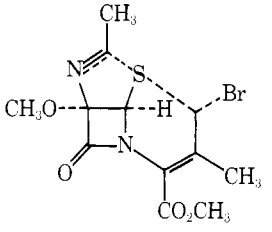

21

An alternative method to convert the β-lactam thiazoline into the cephem-ring system was developed. The monobromide **14** was readily separated from the isomeric monobromide **15** by HLC, using Corasil I in an ethyl acetate–hexane system. The ratio of **14:15** obtained by NBS bromination was about 2:3. When the methylene chloride solution of **14** was allowed to evaporate to dryness under atmospheric pressure and left to stand at room temperature for 3 days, the starting material completely disappeared and a new product appeared. Isolation of the product by preparative TLC on silica gel plates gave the 3-deacetoxy-7-methoxycephalosporin derivative **19** in 40% yield. To carry out this transformation efficiently, the thickness of the evaporated film is obviously important. Under the same conditions, the isomeric monobromide **15** was recovered unchanged. These results suggest the transformation from **14** to **19** would proceed through a transition state **21**, which allows the assignment of the stereochemistry of the monobromides **14** and **15** as indicated. The recovered monobromide **15** can be converted to **19** through recycling back to the conjugated ester **13**.[19]

From the synthetic point of view, the 3-deacetoxy-7-methoxycephalosporin derivative **19** may be considered essentially equivalent to 7-methoxycephalosporin C, because Webber and his coworkers[20] have already established a procedure for converting 3-deacetoxycephalosporin C to cephalosporin C. Furthermore, 3-deacetoxy-7-methoxycephalosporin C was recently isolated from natural sources.[21] Further modification on the synthetic route along the biogenetic pathways, particularly the oxidative ring construction of the β-lactam thiazoline system, is reported in the following paper.[22-24]

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(3) For the attempted biogenetic-type syntheses of the penam and cephem antibiotics, see N. J. Leonard et al., *J. Am. Chem. Soc.*, **86**, 5307 (1964); *Tetrahedron Lett.*, 1471 (1964); *J. Org. Chem.*, **32**, 677 (1967); J. E. Baldwin, S. B. Haber, and J. Kitchin, *J. Chem. Soc., Chem. Commun.*, 790 (1973); J. Cheney, C. J. Moores, J. A. Raleigh, A. I. Scott, and D. W. Young, *J. Chem. Soc., Chem. Commun.*, 47 (1974).

(4) M. S. Newman and F. J. Evans, *J. Am. Chem. Soc.*, **77**, 946 (1955).

(5) Satisfactory spectroscopic data (MS, NMR, ir, uv) were obtained for this substance.

(6) The entire products mixture contains a small amount (<5%) of the *cis*-bromodehydroalanine. In the corresponding methyl ester series, the ratio of trans:cis was about 2:1.

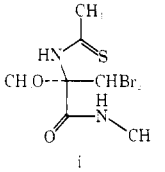
(7) The diamide **8** could also be synthesized from **3** through the acid[5] (X = Br, Y = OH in **3**; mp 142° dec) and then the diamide[5] (X = Br, Y = $NHCH_3$ in **3**; mp 145–146° dec) in better overall yield (60%).

(8) Cyclization of N-substituted 3-halo-3-phenylpropionamides to β-lactams under strong basic conditions is known: I. L. Knunyants and N. P. Gambaryan, *Izv. Akad. Nauk SSSR, Otdel. Khim. Nauk*, 1037 (1955); 834 (1957); 527 (1960); 83 (1961).

(9) The compound **10** was synthesized from the methoxydibromo acid **7** and penicillamine methyl ester in 30% overall yield in three steps (i.e., (1) DCC in dioxane, (2) tosylchloride and pyridine, and (3) triethylamine).

(10) The choice of the C_6 (penam numbering) methoxy group was made because the acid **7** was readily synthesized in our hands and also because 7-methoxycephalosporins are naturally occurring antibiotics. The double cyclization reaction was recently found effective even for the C_6–H series; S. Nakatsuka, H. Tanino, and Y. Kishi, a manuscript for publication in preparation.

(11) The monothioamide i, structurally similar to **14**, was found to be an unstable substance; its half-life in methylene chloride at room temperature was about 2 hr.



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(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

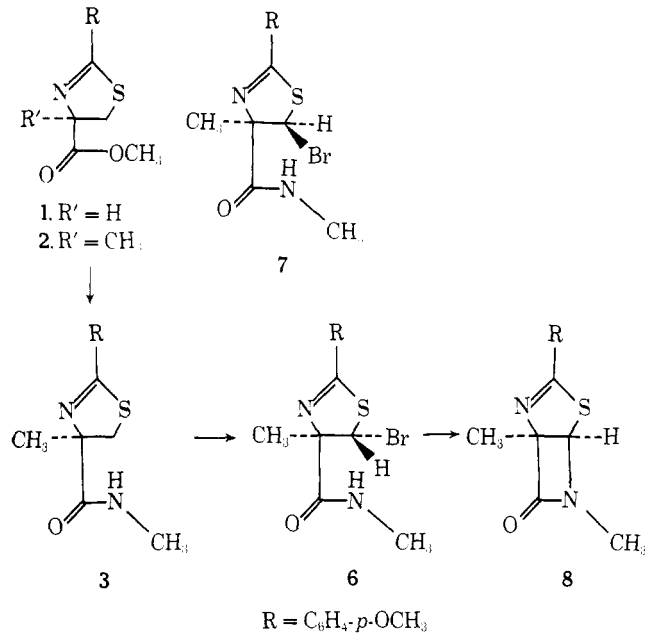
Sir:

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)