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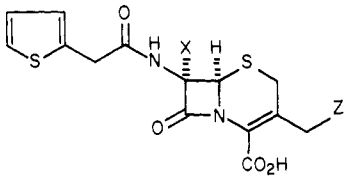
Communications to the Editor

Nuclear Analogues of β-Lactam Antibiotics. 4.[1] Total Synthesis of Bisnorisopenicillins[2] from Antibacterially Active Monocyclic β-Lactam Precursors

Sir:

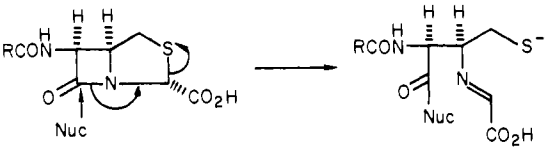
In the cephalosporin field of β-lactam antibiotics there has been considerable interest in the relationship of the substituent at C-3′ to antibacterial activity. Various studies have indicated that the electronegativity of the C-3′ substituent might influence the antibacterial activity by altering the stability of the β-lactam bond to nucleophilic cleavage.[3] For many related cephalosporins [e.g., cephalothin (**1a**) and its ADCA analogue **1b**] there is an ap-



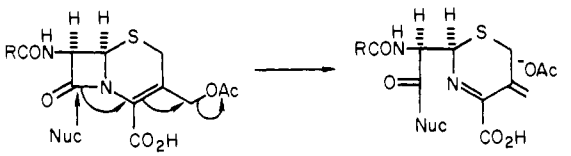
1a, X = H; Z = OAc
b, X = H; Z = H
c, X = OMe; Z = OAc
d, X = OMe; Z = H

parent correlation between in vitro activity and the ability of the substituent at C-3′ to function as a leaving group;[3d] the compound with the better leaving group usually exhibits better activity. This trend appears to be more pronounced in the cephamycins (7α-methoxycephalosporins) since it has been reported that **1c** exhibits in vitro activity similar to cephalothin (**1a**),[4] while its deacetoxy analogue **1d** is virtually inactive.[5] The apparent beneficial influence of a good leaving group at C-3′ on in vitro activity of cephalosporins caused us to consider the possibility of constructing penicillin nuclear analogues with a potential leaving group incorporated directly into the ring system. Bisnorisopenicillin I[2] is representative of this type of nuclear analogue since the sulfur atom is situated such that it might be expelled as mercaptide in a manner comparable to the vinylogous acetate of cephalosporins II[6].

Based on this premise, we were hopeful that bisnorisopenicillins I might exhibit the increased antibacterial spectrum characteristic of the cephalosporin antibiotics.



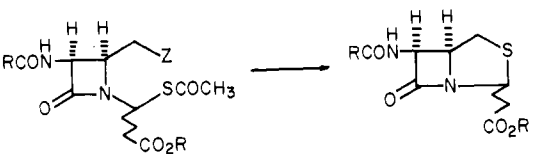
I



II

In this communication we report the total synthesis of bisnorisopenicillin and a monocyclic precursor, both of which display potent antibacterial action.

Our synthetic plan was based on the selective cleavage of the thioacetate ester in monocycle III to the corresponding thiol which was expected to cyclize via intramolecular displacement of halogen (Z) to afford the desired 3-thia-1-azabicyclo[3.2.0]heptane nucleus IV. The initial steps in the preparation of monocylic precursors such as III followed our previously reported synthetic approach to β-lactam nuclear analogues.[1]



III IV

Acid-catalyzed addition[7] of benzyl glyoxylate to **2**[1b] (2 equiv of boron trifluoride etherate, 3 equiv of $OHCCO_2CH_2Ph$, THF, 22 °C, 1 h) afforded the hydroxy iodide **3**[8] as a 1:1 mixture of carboxylate epimers. Treatment of this mixture with 1 equiv of thionyl chloride[9] (1 equiv of pyr, THF, −20 °C, 0.5 h) afforded the unstable chloro intermediate which was converted in situ ($KSCOCH_3$, DMF–THF, −20 °C to room temperature, 1 h) to the thioacetate **4** [55% from **2**: IR (Nujol) γ_{max} 5.63 (β-lactam), 5.69 (ester), 5.84 (thioacetate), and 6.01 nm (amide); NMR ($CDCl_3$–Me_2SO-d_6) δ 2.37 (s, SAc), 3.77 (s,

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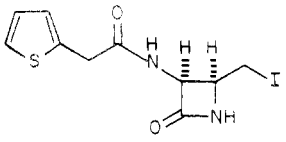
Table I. Minimum Inhibitory Concentrations (MIC) Expressed in μg/mL and nmol/mL[a]

Compd	(1) S.a.[d]	(2) S.f.[e]	(3) E.c.[f]	(4) E.c.[g]	(5) K.p.[h]	(6) S.m.[i]	(7) P.m.[j]	(8) E.a.[k]
6[b]	3.1 (5.5)	50 (88)	6.3 (11)	12.5 (22)	3.1 (5.5)	50 (88)	50 (88)	12.5 (22)
11[b]	6.3 (7.4)	50 (59)	25 (30)	25 (30)	25 (30)	200 (236)	>200 (>236)	25 (30)
Thienylpenicillin[c]	0.2 (0.5)	1.6 (3.7)	12.5 (29)	12.5 (29)	25 (58)	50 (116)	>200 (>464)	25 (58)
Cephalothin (1a)	0.1 (0.2)	6.3 (14)	3.1 (7.0)	3.1 (7.0)	1.6 (3.6)	>200 (>453)	>200 (>453)	6.3 (14)

[a] The antibacterial activity expressed in nmol/mL is enclosed in parentheses. The nmol/mL calculation is based on the carboxylic acid form of each compound. [b] Racemic. [c] R. R. Chauvette et al., *J. Am. Chem. Soc.*, 84, 3401 (1962). [d] *S.a.* = *Staphylococcus aureus* SK&F 23390. [e] *S.f.* = *Streptococcus faecalis* HH 34358. [f] *E.c.* = *Escherichia coli* SK&F 12140. [g] *E.c.* = *Escherichia coli* HH 33779. [h] *K.p.* = *Klebsiella pneumoniae* SK&F 1200. [i] *S.m.* = *Serratia marcescens* ATCC 13880. [j] *P.m.* = *Proteus morgani* 179. [k] *E.a.* = *Enterobacter aerogenes* ATCC 13048.

thienyl CH_2CO), 5.14 and 5.16 (s, CO_2CH_2Ph), 5.99 and 6.05 (s, $CHCO_2CH_2Ph$)] which was also a 1:1 mixture of carboxylate epimers.[10] In an attempt to effect selective cleavage of the thioacetate group, monocycle **4** was subjected to mild hydrolysis (K_2CO_3, H_2O–THF, 0 °C to room temperature, 1 h) followed by acidification (H_3PO_4) to afford a crude reaction mixture which exhibited antibacterial activity.[11] Isolation and purification revealed that the monocyclic acid **5**[12] [75%; IR (Nujol) γ_{max} 5.66 (β-lactam), 5.74 (acid), 5.89 (thioacetate), and 6.00 nm (amide); NMR ($CDCl_3$–Me_2SO-d_6) δ 2.43 (s, SAc), 3.78 (s, thienyl CH_2CO), 5.34 (dd, J = 5, 9 Hz, C-3′ β-lactam H), 5.95 and 6.05 (s, $CHCO_2H$)], not the bisnorisopenicillins **8** or **9**, was the principal reaction product as well as the major antibacterially active component. The predominant formation of **5** via selective hydrolysis of the benzyl ester in the presence of the thioacetate group was unexpected.[13] The sodium salt (**6**) of acid **5** could be prepared by a standard method ($NaHCO_3$, H_2O, and lyophilization).



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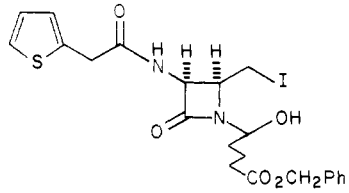
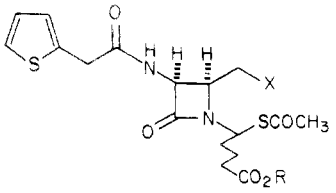
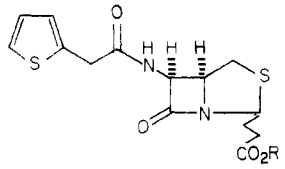


3



4, X = I; R = CH_2Ph
5, X = I; R = H
6, X = I; R = Na
7, X = Br; R = Na



8, R = CH_2Ph
9, R = H
10, R = Na
11, R = H_3N-C_6H_{13}

The desired cleavage–cyclization reaction was ultimately achieved by treatment of **4** with 2 equiv of cyclohexylamine[14] (CH_2Cl_2, 0 °C, 1 h) to afford the bicyclic ester **8** as a mixture of carboxylate epimers. The major isomer could be purified by fractional crystallization to afford a crystalline product [60%; mp 160–161.5 °C; IR (Nujol) γ_{max} 5.62 (β-lactam), 5.74 (ester), and 6.04 nm (amide); NMR ($CDCl_3$) δ 3.77 (s, thienyl CH_2CO), 4.65 (m, C-5 H), 5.12 (s, CO_2CH_2Ph), 5.37 (dd, J = 5, 8 Hz, C-6 H), and 5.52 (s, $CHCO_2CH_2Ph$); m/e (FD) 402 (M^+)]. Mild hydrolysis of **8** [$NaHCO_3$–Na_2CO_3 (pH 9.2), H_2O–THF, 0 °C, 1 h] followed by acidification (H_3PO_4) afforded the highly unstable acid **9**.[15] The sodium salt (**10**) of acid **9** was found to be considerably more stable; however, all attempts to purify **10** directly from the hydrolysis reaction mixture were unsuccessful. The problem was eventually solved by taking advantage of the cyclohexylamine-mediated cleavage–cyclization reaction. When the monocyclic salt **7**[16] was treated with excess cyclohexylamine (CH_2Cl_2, 0 °C, 1 h) the bisnorisopenicillin salt **11** was obtained, contaminated only with excess cyclohexylamine, *N*-cyclohexylacetamide, and sodium bromide. Successive triturations with hexane and ether removed the amine and amide impurities. A sample of **11** [95%; IR (Nujol) γ_{max} 5.66 (β-lactam), 6.01 (amide), and 6.18 nm (carboxylate)] prepared in this manner (containing 1 equiv of sodium bromide) was suitable for preliminary antibacterial testing.

The in vitro activities of **11** and its monocyclic precursor **6** are compared with those of the corresponding penicillin and cephalosporin in Table I. Compounds **6**[17] and **11** exhibit activity against gram-negative bacteria (organisms 3–8) which is comparable to that of thienylpenicillin. Unfortunately, this trend does not continue against the gram-positive bacteria (organisms 1–2), since **6** and **11** are substantially less active against *Staphylococcus aureus* and *Streptococcus faecalis* than either their penicillin or cephalosporin counterparts. Since compounds **6** and **11** are not only racemic but also a mixture of carboxylate epimers, it is possible that a single stereoisomer of **6** or **11** might exhibit in vitro activity which was two to four times better than that shown in Table I.

Acknowledgment. We are grateful to Drs. J. Gleason and C. Perchonock for helpful discussions during the course of this work. We thank D. Jakas for the preparation of authentic thienylpenicillin, C. Perchonock for a supply of analytically pure **7**, and J. Guarini for the in vitro results reported in this paper.

References and Notes

(1) (a) For previous papers in this series, see W. F. Huffman, K. G. Holden, T. F. Buckley, III, J. G. Gleason, and L. Wu, *J. Am. Chem. Soc.*, **99**, 2352 (1977); (b) D. B. Byran, R. F. Hall, K. G. Holden, W. F. Huffman, and J. G. Gleason, *ibid.*, **99**, 2353 (1977); (c) J. Finkelstein, K. G. Holden, R. Sneed, and C. D. Perchonock, *Tetrahedron Lett.*, 1855 (1977).

(2) The trivial name of bisnorisopenicillin has been used for the 6-acylamino-3-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate nucleus as suggested by the publications of M. S. Manhas and A. K. Bose, "Synthesis of Penicillin, Cephalosporin C, and Analogs", Marcel Dekker, New York, N.Y., 1969, and J. Hoogmartens, P. J. Claes, and H. Vanderhaeghe, *J. Med. Chem.*, **17**, 389 (1974).

(3) The following publications as well as references cited therein should provide ample background for this subject: (a) C. H. O'Callaghan, S. M. Kirby, A. Morris, R. E. Waller, and R. E. Duncombe, *J. Bacteriol.*, **110**, 988 (1972); (b) R. B. Hermann, *J. Antibiot.*, **26**, 223 (1973); (c) W. C. Topp and B. G. Christensen, *J. Med. Chem.*, **17**, 342 (1974); (d) J. M. Indelicato, T. T. Norvilas, R. R. Pfeiffer, W. J. Wheeler, and W. L. Wilhan, *ibid.*, **17**, 523 (1974); (e) D. B. Boyd, R. B. Hermann, D. E. Presti, and M. M. Marsh, *ibid.*, 18, 408 (1975); (f) J. M. Indelicato, A. Dinner, L. R. Peters, and W. L. Wilham, *ibid.*, **20**, 961 (1977).

(4) L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Am. Chem. Soc.*, **94**, 1408 (1972).

(5) T. Jen, J. Frazee, and J. R. E. Hoover, *J. Org. Chem.*, **38**, 2857 (1973).
(6) The material found in ref 3 as well as in the following publications [(a) A. D. Russell and R. H. Fountain, *J. Bacteriol.*, **106**, 65 (1971), and (b) C. H. O'Callaghan, R. B. Sykes, and S. E. Staniforth, *Antimicrob. Agents Chemother.*, **10**, 245 (1976)] indicates that the substituent at C-3′ is actually expelled concomitant with opening of the β-lactam ring.
(7) The thermal addition of glyoxylates to β-lactams is described by R. Scartazzini, H. Peter, H. Bickel, K. Heusler, and R. B. Woodward, *Helv. Chim. Acta*, **55**, 408 (1972).
(8) All new compounds were characterized by spectroscopic methods. Satisfactory elemental analyses were obtained for compounds **4**, **6**, **8**, and **11**.
(9) See the paper cited in ref 7.
(10) Although one of the carboxylate epimers of **4** could be purified by fractional crystallization to give a single diastereoisomer [mp 165–169 °C dec; NMR ($CDCl_3$–Me_2SO-d_6) δ 5.14 (s, CO_2CH_2Ph), 5.25 (dd, J = 5, 9 Hz, C-3′ β-lactam H), 5.99 (s, $CHCO_2CH_2Ph$)], its stereochemical integrity was lost during ester cleavage (see ref 12).
(11) Compounds were tested in a disk assay against *B. subtilis*.
(12) Acid **5** was a 1:1 mixture of carboxylic acid epimers. Hydrolysis of the crystalline diastereoisomer of **4** (ref 10) under a variety of conditions always resulted in epimerization to give the same 1:1 epimeric ratio of carboxylic acids.
(13) Thioacetate esters are known to hydrolyze rapidly when treated with mild base according to T. C. Bruice in "Organic Sulfur Compounds", Vol. I, N. Kharasch, Ed., Pergamon Press, New York, N.Y., 1961, Chapter 35.
(14) The facile cleavage of thioesters by amines is described by J. J. Godfrey, U.S. Patent 3 086 049 (1963), and G. Fuchs, *Acta Chem. Scand.*, **19**, 1490 (1965), as well as by T. C. Bruice as cited in ref 13.
(15) Substantial decomposition of **9** took place in a matter of minutes and thus made extremely difficult any isolation or purification techniques which required the intermediacy of **9**.
(16) Although **5** and **6** could be converted to the bisnorisopenicillin 11, for our large-scale work we chose to use the bromo derivative **7** which was prepared in a manner similar to that for iodide **6** (C. D. Perchonock, unpublished results).
(17) It is our belief that the monocycle **6** exhibits antibacterial activity due to its in situ conversion to bisnorisopenicillin (**10**). Evidence for this theory will be the subject of a forthcoming publication.

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Articles

Analgesics. 1. Synthesis and Analgesic Properties of *N-sec*-Alkyl- and *N-tert*-Alkylnormorphines

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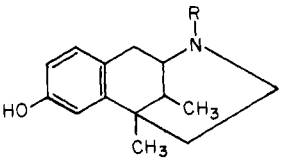
A series of *N-sec*- and *N-tert*-alkylnormorphines was synthesized and evaluated for analgesic potency, antagonist activity, and opiate receptor binding. Computer-assisted conformational analysis profiles were utilized to assist in the selection of compounds for synthesis and correlation of receptor events with in vivo observations. *N-tert*-Alkylnormorphines **5a–c** were devoid of agonist activity; however, some *sec*-alkyl analogues showed interesting mixed agonist–antagonist actions. *N-sec*-Butyl- and *N*-(α-methylallyl)normorphine were separated into *R* and *S* isomers, which exhibited quantitative pharmacological differences. The *N-sec*-butyl *S* isomer **10a** showed analgesia approximating morphine with nalorphine-like antagonist activity. Preliminary testing indicates only slight evidence for physical dependence with this compound.

It is generally acknowledged that compounds possessing potent analgesic activity yet having some degree of antagonist properties are good candidates for clinically useful analgesics with low addition potential. N-Substituents of fused ring opiates play a central role in determining the relative analgesic agonist/antagonist potencies of these molecules and in a given compound, this ratio is directly related to drug–receptor events. The success achieved with the drug pentazocine (Id),[1] a mixed agonist–antagonist, suggested that the nitrogen substituent of appropriate opiate bases should be investigated further. Archer and co-workers[2] have compared the antagonist protencies of a number of N-substituted 5,9-dimethylbenzazocines I. It was found that the *N*-propyl (Ia, AD_{50} = 0.019) and *N*-cyclopropylmethyl (Ib, AD_{50} = 0.019) analogues were more antagonistic than the *N*-allyl compound (Ic, 0.047). The AD_{50} values for dimethylallyl (Id) and dichloroallyl (Ie)



Ia, R = n-C_3H_7
b, R = c-C_3H_5-CH_2-
c, R = CH_2=$CHCH_2$-
d, R = $(CH_3)_2C$=$CHCH_2$-
e, R = Cl_2C=$CHCH_2$-
f, R = *cis*-ClCH=$CHCH_2$-

compounds were 3.9 and 5.1, respectively, whereas the *cis*-3-chloroallyl analogue If was also a strong antagonist, AD_{50} = 0.018. Since the compounds with saturated N-substituents were equal to or more antagonistic than the vinyl analogues, it would appear that the spatial ar-

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