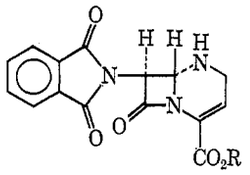
Communications

See Editorial, *J. Org. Chem.* **37**, No. 19, 4A (1972).

Studies on Lactams. XXIX.[1] Synthesis of Aza Analogs of Cepham

Summary: The synthesis of several novel aza analogs of cephams has been accomplished by the reaction of N-acylated 1,4,5,6-tetrahydropyrimidines with different acid chlorides in presence of triethylamine.

Sir: Recently Wolfe, *et al.*,[2] have reported the conversion of penicillin to 1-aza-6-epidethiocephem (**1**).



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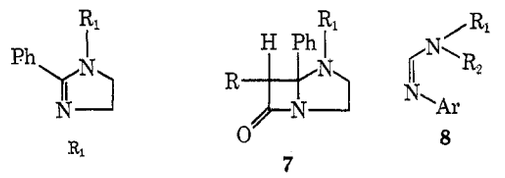
Prompted by the disclosure of this partial synthesis we describe here the results of our studies on the total synthesis of analogous compounds. In view of our earlier success with the "acid chloride–imine" method[3] for preparing various α-substituted β-lactams including 6-epipenicillin methyl ester,[4] we investigated the use of this synthetic approach to penam and cepham analogs in which S has been replaced by N.

Our initial attempt involved the reaction of 2-phenylimidazoline (**2**) with azidoacetyl chloride in presence of triethylamine. The reaction product appeared to contain the expected bicyclic β-lactam (**7**, R = N_3; R_2 = $COCH_2N_3$) on the basis of ir and nmr spectral data. However, **7** could not be obtained in the pure form: attempts at purification led to its decomposition and only an *N*-acylimidazoline **3** could be isolated. This was not surprising in view of our earlier experience[5] with unstable β-amino-β-lactams **9** obtained from amidines **8** and diphenylketene. Reaction of **3** with an acid chloride and triethylamine was no more successful in leading to pure **7**. Several other *N*-acyl derivatives, such as **4**, **5**, and **6**, fared no better than **3** for obtaining pure 1-azapenam analogs.

Next we condensed **10**, the higher homolog of **2**, with phenoxyacetyl chloride and triethylamine in methylene chloride solution. The desired β-lactam **13** was obtained in 72% yield: mp 131–132°; ir ν_{max} 1775 (β-lactam CO), 1667 cm^{-1} (amide CO); nmr ($CDCl_3$) τ 2.3–3.4 (m, 15 H), 4.25 (s, 1 H), 5.25 (s, 2 H), 5.68–6.5 (br, 2 H), 6.5–7.2 (br, 2 H), 7.9–8.78 (br, 2 H); mass spectrum M^+ at *m/e* 428. Calcd for $C_{26}H_{24}N_2O_4$: C, 72.89; H, 6.54; N, 5.60. Found: C, 72.75; H, 6.77; N, 5.96. Under similar conditions azido acetyl chloride (**10**) and triethylamine gave the diazido-β-lactam (**14**). Catalytic hydrogenation of **14** on Pd/C produced a diamino-β-lactam (**15**) which upon acylation with phenoxyacetyl chloride (2 mol) provided the cepham analog **16** with two phenoxyacetamido side chains. It is possible to have two different side chains: conversion of **10** to **11** and **12** prior to reaction with phenoxyacetyl chloride and triethylamine led to the β-lactams **17** and **18**, respectively. Because of the presence of several substituents in close proximity in compounds **13–18**, assignment of configuration of these β-lactams on the base of nmr data does not appear to be possible.

It is reasonable to expect that the various routes described previously for placing[6] and modifying[7] α substituents in monocyclic β-lactams prepared by the

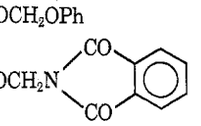


Compd R_1

2 H

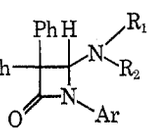
3 $COCH_2N_3$

4 $COCH_2OPh$



5 $COCH_2N$

6 p-$SO_2C_6H_4CH_3$



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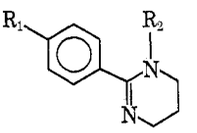
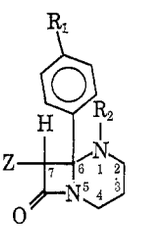


Compd	R_1	R_2
10	H	H
11	H	p-$SO_2C_6H_4CH_3$
12	CO_2Et	$COCH_2Ph$



Compd	Z	R_1	R_2
13	OPh	H	$COCH_2OPh$
14	N_3	H	$COCH_2N_3$
15	NH_2	H	$COCH_2NH_2$
16	$NHCOCH_2OPh$	H	$COCH_2NHCOCH_2OPh$
17	OPh	H	p-$SO_2C_6H_4CH_3$
18	OPh	CO_2Et	$COCH_2Ph$

(1) For part XXVIII, see A. K. Bose, J. C. Kapur, B. Dayal, and M. S. Manhas, *Tetrahedron Lett.*, in press.

(2) S. Wolfe, J. Ducep, G. Kannengiesser, and W. S. Lee, *Can. J. Chem.* **50**, 2902 (1972).

(3) A. K. Bose, B. Anjaneyulu, S. K. Bhattacharya, and M. S. Manhas, *Tetrahedron*, **23**, 4769 (1967).

(4) A. K. Bose, G. Spiegelman, and M. S. Manhas, *J. Amer. Chem. Soc.*, **90**, 4506 (1968).

(5) A. K. Bose and I. Kugajevsky, *Tetrahedron*, **23**, 957 (1967).

(6) M. S. Manhas and A. K. Bose, "beta-Lactams: Natural and Synthetic," part 1, Wiley-interscience, New York, N. Y., 1971.

(7) A. K. Bose, H. P. S. Chawla, B. Dayal, and M. S. Manhas, *Tetrahedron Lett.*, 2503 (1973).

"acid chloride–imine" method would also be applicable to the synthesis of bicyclic β-lactams from suitable tetrahydropyrimidine derivatives. The striking increase in stability in going from the 1-azadethiopenam to the corresponding cepham series, of course, facilitates the synthesis of cepham analogs. The extension of this general synthetic approach to other bicyclic β-lactams is in progress.

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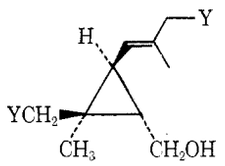
Asymmetric Induction in a [2,3] Sigmatropic Rearrangement. A Biogenetic Model

Summary: Treatment of achiral *S*-methyl-*S*,*S*-bis(γ,γ-dimethylallyl)sulfonium fluoroborate with chiral bases produces artemisia methyl thioether with 5–12% asymmetric induction.

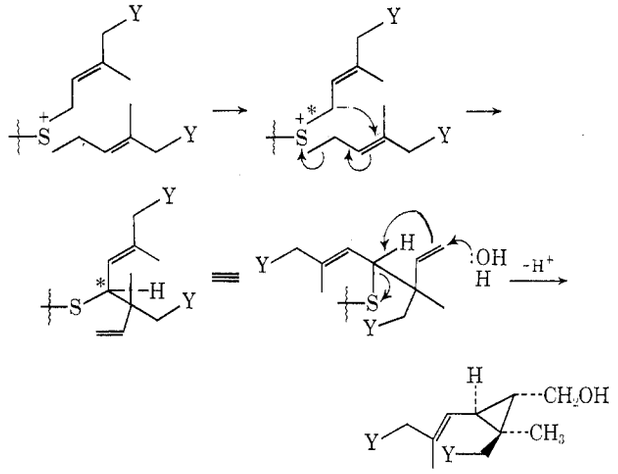
Sir: The discovery that the direct biological precursors of squalene[1,2] and phytoenes[3] possess the cyclopropane structures **1b** and **1c**, respectively, suggests a link to the monoterpene analog chrysanthemol (**1a**).



1a, Y = H
b, Y = geranyl
c, Y = farnesyl

Among the biogenetic schemes considered for the formation of these compounds,[4] that based on the [2,3] sigmatropic rearrangement of sulfur ylides possesses exceptional fascination (see Scheme I).[4g,5] In this scheme, the chirality of the biogenetic intermediates **1a–c** is determined by a single event—the conversion of an achiral sulfonium salt into a chiral ylide.

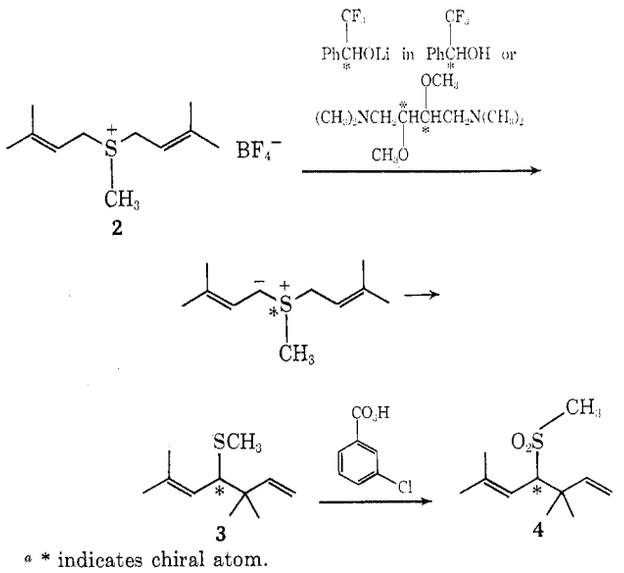
SCHEME I
[2,3] SIGMATROPIC REARRANGEMENT BIOGENETIC HYPOTHESIS



In experiments designed to examine various facets of this scheme, consideration of the stereochemistry of the process was undertaken to determine whether (1) simple chiral bases could discriminate between the enantiotopic[6] arms of the achiral sulfonium salt, (2) the ylide thus generated could rearrange faster than it loses its asymmetry, and (3) the chirality at sulfur could be faithfully translated into chirality at carbon.

Treatment of *S*-methyl-*S*,*S*-bis(γ,γ-dimethylallyl)-sulfonium fluoroborate (**2**) with *n*-butyllithium–sparteine complex[7] or lithium 1-(−)-menthoxide in tetrahydrofuran led to artemisia methyl thioether **3** with no observable optical rotation (see Scheme II). On the

SCHEME II
REARRANGEMENT IN MODEL SYSTEM[a]



[a] * indicates chiral atom.

(1) (a) L. J. Altman, R. C. Kowerski, and H. C. Rilling, *J. Amer. Chem. Soc.*, **93**, 1782 (1971); (b) H. C. Rilling, C. D. Poulter, W. W. Epstein and B. Larsen, *ibid.*, **93**, 1783 (1971); (c) W. W. Epstein and H. C. Rilling, *J. Biol. Chem.*, **245**, 4597 (1979); (d) H. C. Rilling and W. W. Epstein, *J. Amer. Chem. Soc.*, **91**, 1041 (1969).

(2) (a) J. Edmond, G. Popjak, S.-M. Wong, and V. P. Williams, *J. Biol. Chem.*, **246**, 6254 (1971); (b) R. V. M. Campbell, L. Crombie, and G. Pattenden, *Chem Commun.*, 218 (1971); (c) R. M. Coates and W. H. Robinson, *J. Amer. Chem. Soc.*, **93**, 1785 (1971).

(3) L. J. Altman, L. Ash, R. C. Kowerski, W. W. Epstein, B. R. Larsen, H. C. Rilling, F. Muscio, and D. E. Gregonis, *J. Amer. Chem. Soc.*, **94**, 3257 (1972).

(4) (a) E. E. van Tamelen and M. A. Schwartz, *J. Amer. Chem. Soc.*, **93**, 1780 (1971); (b) R. M. Coates and W. H. Robinson, *ibid.*, **94**, 5920 (1972), and references therein; (c) C. D. Poulter, O. J. Muscio, C. J. Spillner, and R. G. Goodfellow, *ibid.*, **94**, 5921 (1972); (d) C. D. Poulter, *ibid.*, **94**, 5515 (1972); (e) L. Crombie, P. A. Frith, R. P. Houghton, D. A. Witing, and D. K. Woods, *J. Chem. Soc., Perkin Trans. 1*, 642 (1972); (f) A. F. Thomas and W. Pawlak, *Helv. Chim. Acta*, **54**, 1822 (1971); (g) B. M. Trost, P. Conway, and J. Stanton, *Chem. Commun.*, 1639 (1971); (h) R. B. Bates and D. Feld, *Tetrahedron Lett.*, 4875 (1967).

(5) (a) J. E. Baldwin, R. E. Hackler, and D. P. Kelley, *J. Amer. Chem. Soc.*, **90**, 4758 (1968); (b) G. E. Risinger and H. D. Durst, *Tetrahedron Lett.*, 3133 (1968); (c) B. M. Trost and R. LaRochelle, *ibid.*, 3327 (1968); (d) G. M. Blackburn, W. D. Ollis, C. Smith, and I. O. Sutherland, *Chem. Commun.*, 99 (1969).

(6) In actuality, this terminology is incorrect. Since the carbanion may be tetrahedral the ylide may exist in one of four diastereomeric forms in which case the two arms are diastereotopic. Making the reasonable assumption that the carbanion center is at least "effectively" planar owing to rapid inversion simplifies the discussion. No conclusions are affected by this assumption.

(7) H. Nozaki, T. Aratani, and T. Toraya, *Tetrahedron Lett.*, 4097 (1968).