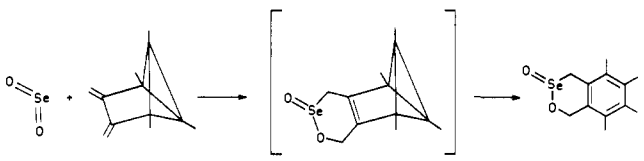
clic and aromatic sulfinic esters **4** and **5** by isolation from their solutions at 20° in the former and at 100° in the latter case of the corresponding tetracyanoethylene (TCNE) adducts **9**[7,16] (7%) and **8**[8] (isolated 90%), respectively (instead of the corresponding sulfones **10** and **7**), on addition of TCNE.



3 11 12

The addition of sulfur dioxide thus bears a close resemblance to the reported selenium dioxide addition to 1,3-dienes. Also with diene **3** at room temperature in chloroform a seleninic ester **12**[17] was formed probably via the intermediacy of **11**, and was isolated in 70% yield. Heating of compound **12** to 180° in *o*-dichlorobenzene did not lead to any rearrangement to the corresponding selenone.

The established reaction sequence as stated in Scheme I suggests that at least in the case of highly reactive dienes more examples of kinetically controlled (2 + 4) ($\pi + \pi\pi$) vs. thermodynamically controlled (2 + 4) (n + $\pi\pi$) cycloadditions of sulfur dioxide are to be expected.

Acknowledgment. We are grateful to Professor J. Strating for a discussion of the subject and for reading the manuscript.

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(9) If benzene is chosen as the solvent the same applies.
(10) ^{1}H NMR ($CDCl_3$, 30°) δ 1.24 (s, 3 H), 1.34 (s, 3 H), 1.52 (s, 3 H), 1.60 (s, 3 H), 5.07 and 5.25 (SCH_2, 2 H), 5.59 and 5.76 (OCH_2, 2 H); ^{13}C NMR ($CDCl_3$, 30°; δ relative to internal Me_4Si; noise decoupled) δ 3.4, 4.2, 8.5, and 11.9 (CH_3-carbons), 44.0, 57.0, 71.5, and 87.3 (quaternary carbons), 105.5 and 106.9 (CH_2-carbons), 146.7 and 147.6 (sp^2-carbons). Too unstable (i.e., isomerization to **5**) to be isolated.
(11) ^{1}H NMR ($CDCl_3$, 30°) δ 2.23 (s, 6 H), 2.25 (s, 6 H), 3.50 and 4.41 (AB-quartet, J_{AB} = 16 Hz, 2 H), 5.18 (s, 2 H). If dissolved in *o*-dichlorobenzene an asymmetric solvent-induced shift (ASIS) occurs, revealing a second AB-system; ^{1}H NMR (*o*-dichlorobenzene, 30°) δ 1.58 (s, 6 H), 1.66 (s, 6 H), 2.96 and 3.73 (AB-quartet, J_{AB} = 16 Hz, 2 H), 4.57 and 4.74 (AB-quartet, J_{AB} = 14 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 30°, δ relative to internal Me_4Si; noise decoupled) δ 14.5, 15.4, 16.2, and 16.6 (CH_3-carbons), 53.1 and 60.4 (CH_2-carbons), 121.2, 128.8, 129.5, 132.3, 134.5 and 135.1 (sp^2-carbons); ir (Nujol mull) 1105 cm^{-1} (S=O); MS M$^+$ peak at *m/e* 224. Anal. Calcd for $C_{12}H_{16}SO_2$: C, 64.25; H, 7.19; S, 14.29. Found: C, 64.24; H, 7.22; S, 14.31. Compound **5** rearranges prior to melting.
(12) ^{1}H NMR ($CDCl_3$, 30°) δ 1.69 (s, 6 H), 1.71 (s, 6 H), and 3.44 (s, 4 H). Too unstable (i.e., isomerization to **7**) to be isolated.
(13) If the diene **3** is added to liquid sulfur dioxide, condensed at −50° in an open tube, only the aromatic sulfinic ester **5**, due to a sulfur dioxide catalyzed rearrangement, can be isolated; the same isomerization can be induced by treating the polycyclic ester **4** with $AgClO_4/Na_2CO_3$ or with CCl_3COOH. Compare ref 8.
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(15) ^{1}H NMR ($CDCl_3$, 30°) δ 2.13 (s, 6 H), 2.18 (s, 6 H), and 4.27 (s, 4 H); ^{13}C NMR ($CDCl_3$, 37°, δ relative to internal Me_4Si; noise decoupled) δ 16.1 and 17.2 (CH_3-carbons), 57.1 (CH_2-carbons), 127.2, 130.3, and 135.6 (sp^2-carbons); ir (Nujol mull) 1300 and 1130 cm^{-1} (O=S=O); MS M$^+$ peak at *m/e* 224. Anal. Calcd for $C_{12}H_{16}SO_2$: C, 64.25; H, 7.19; S, 14.29. Found: C, 64.29; H, 7.17; S, 14.26; mp 212.0–212.5 °C.
(16) Since no recombination to sulfone **10** is observed in this experiment it is concluded that in the absence of TCNE the rearrangement via **10** to **7** proceeds in 7% yield. The isomerization of **4** to **5** occurs thus in 93% yield. The data are obtained by comparing the relative areas of the absorptions due to the methylene protons in **9** and **5**, respectively, these compounds being the only products formed under these conditions.
(17) ^{1}H NMR ($CDCl_3$, 30°) δ 2.28 (s, 6 H), 2.33 (s, 6 H), 3.43 (d, J = 14 Hz, 1 H), 4.93 (d, J = 14 Hz, 1 H), 4.99 and 5.40 (AB-quartet, J_{AB} = 13 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 37°, δ relative to internal Me_4Si; noise decoupled) δ 15.3; 15.9, 16.8, and 17.0 (CH_3-carbons), 55.4 and 62.4 (CH_2-carbons), 123.3, 130.8, 132.5, 134.3, 135.3, and 135.8 (sp^2-carbons); ir (Nujol mull) 838 cm^{-1} (Se=O); MS M$^+$ peaks at *m/e* 268, 269, 270, 272, and 274 ($_{34}Se^{76}$ = 9.02, $_{34}Se^{77}$ = 7.58, $_{34}Se^{78}$ = 23.52, $_{34}Se^{80}$ = 49.82, $_{34}Se^{82}$ = 9.19% natural abundance). Anal. Calcd for $C_{12}H_{18}SeO_2$: C, 53.15; H, 5.95; Se, 29.11. Found: C, 52.83; H, 5.81; Se, 28.71. Compound **12** decomposes prior to melting (T > 170°).

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Synthesis of 2-Methyl-3-cephem Derivatives[1]

Sir:

In the past decade there has been considerable interest in the chemical modification of penicillins and cephalosporins. We also have developed a useful procedure for the preparation of modified β-lactam derivatives from penicillins via disulfide **1** and penam bromide **2**.[2] In the preceding paper we reported on the synthesis of a new tricyclic β-lactam **3** from **2**;[3] we now report the conversion of **3** via intramolecular cyclopropane ring opening into 2-methyl-3-cephem derivative **4**. The key step, opening the cyclopropane ring while preserving the labile β-lactam ring, was achieved with Lewis acids[4] and yielded all of the possible stereoisomers **4, 5, 6,** and **7** of the 2-methylcephem systems.

Treatment of tricyclic sulfide **3** in CH_2Cl_2 with $AlBr_3$ for 1 h at 0 °C gave a mixture of 3-cephems **4** and **5**, and 2-cephem **6**. Chromatographic separation afforded in 80% yield 2α-methyl-3-cephem **4**, mp 175–178 °C (ir 1790 cm^{-1} (β-lactam C=O); NMR δ (in $CDCl_3$) 1.46 (d, J = 7.5 Hz, 2-CH_3), 3.62 (m, 2-H), 6.66 (d, J = 6 Hz, 3-H), 4.92 (d, J = 4.5 Hz, 6-H), 5.94 (dd, J = 4.5 and 9 Hz, 7-H)), and in 2–3% yields, respectively, 2β-methyl-3-cephem **5**, mp 120–122 °C (ir 1775 cm^{-1} (β-lactam C=O); NMR δ (in $CDCl_3$) 1.50 (d, J = 8 Hz, 2-CH_3), 3.88 (m, 2-H), 6.41 (d, J = 2 Hz, 3-H), 5.11 (d, J = 5 Hz, 6-H), 5.85 (dd, J = 5 and 9 Hz, 7-H)), and 2-methyl-2-cephem **6**, mp 136–137 °C (ir 1780 cm^{-1} (β-lactam C=O); NMR δ (in $CDCl_3$) 1.94 (t, J = 1.5 Hz, 2-CH_3),[5] 5.00 (m, 4-H), 5.59 (m, 3-H), 5.18 (d, J = 4.5 Hz, 6-H), 5.70 (dd, J = 4.5 and 9 Hz, 7-H)).

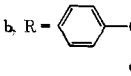
The configuration of **4** was based on the NMR analysis of its β-sulfoxide **8**,[6] mp 173–175 °C, prepared by oxidation with *m*-chloroperbenzoic acid ($CHCl_3$, 0°, 1.5 h); similarly, **5** was oxidized (*m*-chloroperbenzoic acid, $CHCl_3$, 0°, 1 h) to β-oxide **9**,[6] mp 160–161 °C.

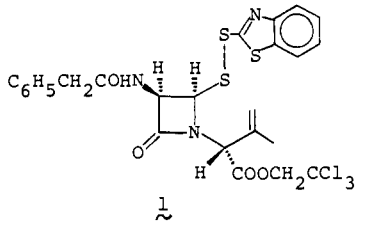
The 2-methyl configuration was assigned α for **4** and β for **5** on the following evidence: (i) the 2-CH_3 signal of **8** (1.25 ppm) is more shielded than that of **9** (1.63 ppm);[7] (ii) in **8**, a 1.0 Hz long-range coupling is present between 2-H and 7-H,[8] and furthermore, a 7% NOE is observed between 6-H and 2-CH_3; (iii) in **9**, on the other hand, 1.5 Hz long-range coupling is present between 2-H and 6-H;[9,10] and (iv) the $J_{2,3}$ values of 6 Hz for **8** and 2 Hz for **9** are in agreement with dihedral angles estimated from molecular models.

In contrast, treatment of **3** in CH_2Cl_2 with $TiCl_4$ for 2.5 h at room temperature gave selectively 2-cephem **7**, mp 108.5–110.5 °C (ir 1770 cm^{-1} (β-lactam C=O); NMR δ (in $CDCl_3$) 1.99 (t, J = 1 Hz, 2-CH_3),[5] 4.68 (m, 4-H), 5.68 (m, 3-H), 5.06 (d, J = 4 Hz, 6-H), 5.56 (m, 7-H)), 70%

Table I. Minimum Inhibitory Concentrations (MIC) Expressed in μg/ml

Compd[a]	*Staphylococcus aureus* 209P JC-1	*Staphylococcus aureus* 213	*Escherichia coli* 324	*Escherichia coli* 327	*Shigella flexneri* 2A	*Salmonella enteritidis*
10a	0.78	1.56	25	25	25	12.5
10b	0.78	1.56	12.5	6.25	6.25	25
12a	3.13	12.5	>100	>100	100	100
12b	12.5	25	100	50	25	100

[a] a, R =  ; b, R =



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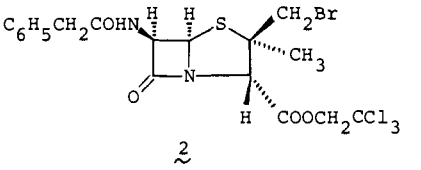

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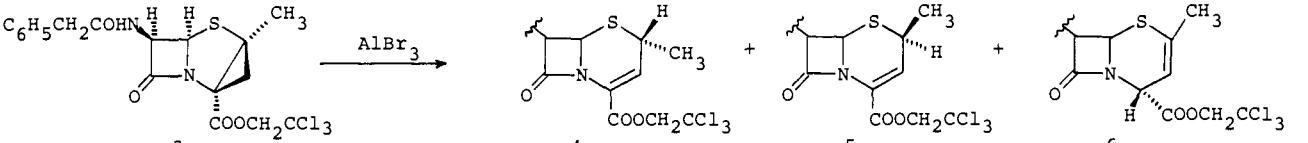
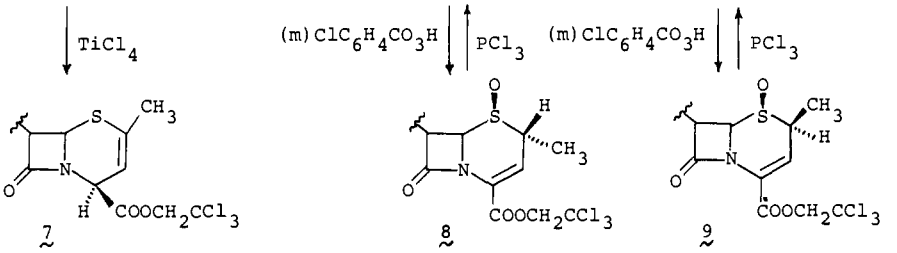
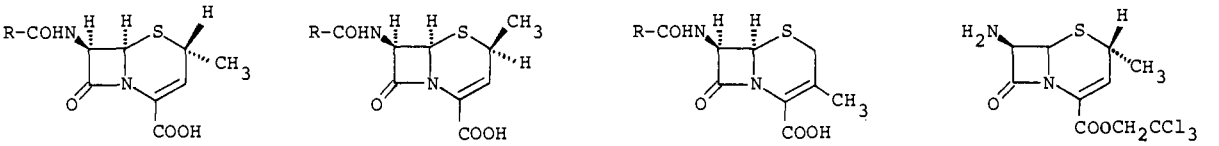


3 4 5 6



7 8 9



10 11 12 13

yield. Spectral data showed that **6** and **7** are stereoisomers. Moreover, the observation that in **7**, 4-H and 7-H are long-range coupled[11] by 1.5 Hz indicates that 4-H is α in **7**, and hence β in **6**. This was corroborated by the following results: (i) **7** was converted quantitatively into the more stable isomer **6** when treated with Et_3N (CH_2Cl_2, room temperature, 1 h); (ii) *m*-chloroperbenzoic acid oxidation of **6** (CH_2Cl_2, 0°, 1 h) gave in 90% yield a 2:1 mixture of **8** and **9**, whereas the same oxidation of **7** (CH_2Cl_2, 0°, 1 h) gave in 86% yield a 1:2 mixture of **8** and **9**.

As far as we are aware, compounds such as **7** in which the carboxyl group adopts the unstable β-configuration have not been reported previously in the 2-cephem series. It is presumed that $TiCl_4$ complexes with both the 4-carboxyl and β-lactam carbonyl groups, and that this leads to the β-configuration of the carboxyl group. Both **8** and **9** were reduced, respectively, to **4** and **5**, in high yields with PCl_3/DMF (−10°, 1 h).

Removal of the trichloroethyl protective group from **4** and **5** by zinc dust reduction (DMF/AcOH, 0°, 1.5 h) gave acids **10** (R = $CH_2C_6H_5$) and **11** (R = $CH_2C_6H_5$); the former showed greater antimicrobial activity than the natural desacetoxycephalosporin derivative **12** (R = $CH_2C_6H_5$), while the latter showed activity of the same order or slightly less than **12** (R = $CH_2C_6H_5$). The 7-phenylacetyl side chain of **4** was removed by the usual manner (i.e., PCl_5 etc.)[12] to give amine **13**, hydrochloride mp 185–187 °C, from which various 7-acyl derivatives **10** were prepared by conventional methods (i.e., (1) acylation, (2) reductive deesterification with zinc dust). Independent of the 7-acyl groups, **10** exhibited stronger activity against both G(+) and G(−) bacteria as compared to **12** (see Table I). The different activities between 2-methyl-3-cephem **10** and 3-methyl-3-cephem **12** are presumably due to differences in the reactivities of the β-lactam moiety.[13]

We have thus been able to derive 2-methyl-3-cephems in a facile manner from penicillin, and also to gain additional information on the structure-activity relationships in the cephalosporin series.

Acknowledgment. We thank Dr. M. Nishida for the in vitro results reported in this paper.

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(5) A spin-decoupling experiment confirmed that, in both **6** and **7**, 2-CH_3 is long-range coupled with 3-H and 4-H (allylic and homoallylic coupling, respectively).
(6) The oxide configuration of **8** and **9** was determined by comparison with their α-sulfoxide isomers: α-oxide of **4**, mp 146–148 °C; α-oxide of **5**, mp 183–185 °C, prepared by oxidation with trichloroisocyanuric acid (CH_2Cl_2/acetone/pyridine/H_2O, −20°, 45 min). Details will be dealt with in a forthcoming full paper.
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(12) Cf. (a) B. Fechtig, H. Peter, H. Bickel, and E. Visher, *Helv. Chim. Acta*, **51**, 1108 (1968); (b) F. M. Huber, R. R. Chauvette, and B. G. Jackson, "Cephalosporins and Penicillins: Chemistry and Biology", E. H. Flynn, Ed., Academic Press, New York, N.Y., 1972, pp 39–55, and references therein.
(13) There are many reports on correlations between the chemical reactivity of the β-lactam moiety and its antibiotic activity in the penicillin and cephalosporin field; cf. M. Gorman and C. W. Ryan, ref 12b, pp 536–542, and references therein.

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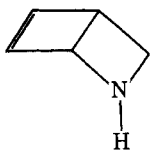
A Synthesis of N-Substituted 1,2-Dihydropyridines

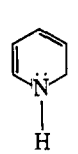
Sir:

Although dihydropyridines have been known since the last century, derivatives without stabilizing electron-withdrawing groups on the ring are very rare and little information is available on their chemistry.[1] There has been recent interest[2] in the synthesis of the 1,2-dihydropyridine ring system because of its implication as a pivotal intermediate in the biosynthesis of indole alkaloids.[3] These biosynthetic studies suggest that 1,2-dihydropyridines may provide a very efficient synthetic route to the indole alkaloids and related compounds.[4]

Previous syntheses of reactive 1,2-dihydropyridines without stabilizing electron-withdrawing groups on the ring essentially have been limited to the *careful* reduction of pyridine or pyridinium ions.[1] We have developed a more versatile nonreductive synthetic method involving 2-azabicyclo[2.2.0]hex-5-ene (**1**) as a key intermediate. Compound **1** is a valence isomer of the parent 1,2-dihydropyridine. In contrast to the parent 1,2-dihydropyridine, which has never been isolated, its valence isomer **1** does not possess the dienamine functionality and is relatively stable to polymerization and oxidation.

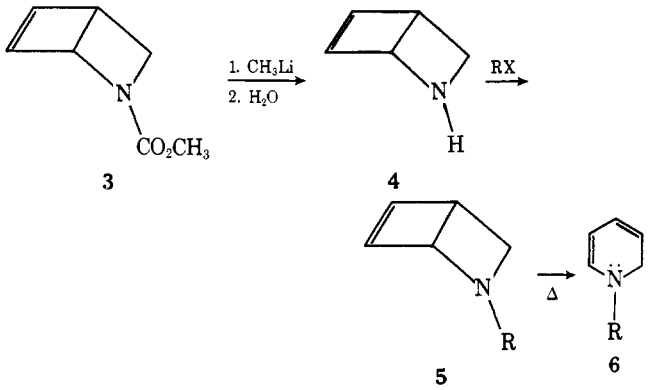


1



2

The preparation of **1** is most conveniently carried out[5] by the slow addition of carbamate **3**[6] to methyllithium in dry tetrahydrofuran at −15°. After 5 min the reaction is quenched by the addition of H_2O. Alkylating agents relatively stable to hydrolysis, e.g., benzyl chloride and 6-bromo-1-hexene, are added in equimolar amounts, and the reaction mixture is allowed to reflux until the disappearance of the alkylating agent ceases. This procedure produces bicyclic amines **5a** and **b** in 40–60% overall isolated yields from carbamate **3**.[7]



3 4 5 6

a, R = $PhCH_2$–
b, R = $CH_2{=}CH(CH_2)_4$–
c, R = $CH_3O_2C(CH_2)_5$–
d, R = $CH_2{=}CHCH_2$–
e, R = $PhCH_2CH_2$–
f, R = $C_2H_5O_2CCH_2$–

If the alkylating agent is sensitive to hydrolysis, e.g., methyl 6-bromohexanoate, then the bicyclic amine **1** is isolated by first extracting the reaction mixture with ether and then by removing most of the solvent by distillation through an efficient column. This procedure produces the bicyclic amine in yields of 20–25%. Treatment of **4** with methyl 6-bromohexanoate and an excess of diisopropylamine produces **4c** in 90–95% yield.

The ring opening of the bicyclic amines is induced thermally.[8] Initial studies on the gas phase ring opening indicated the reaction rate to be sensitive to the substituent on nitrogen. In contrast to the *N*-carbomethoxy derivative **4d** (R = CO_2CH_3, $t_{1/2} \simeq 0.5$ h at 165°), the *N*-methyl derivative **4e** (R = CH_3) exhibits a $t_{1/2} \simeq 0.5$ h at only 122°. Compounds **4a–c** showed similar kinetic behavior to the *N*-methyl derivative **4e.** A more detailed kinetic study of the ring opening of **4a** and **d** in benzene solution gives results similar to the above.[9]

This synthetic scheme has many advantages over the direct reduction of pyridine and its derivatives as an entry into the 1,2-dihydropyridine ring system. Whereas the reduction of pyridine derivatives can produce both 1,4- and 1,2-dihydropyridines,[1] as well as tetrahydropyridines,[10] the ring opening is efficient in giving only the 1,2-dihydropyridine free of side products. Finally, the 2-azabicyclo[2.2.0]hex-5-ene ring system present in **4a–c** is a masked 1,2-dihydropyridine. The greater chemical stability of the 2-azabicyclo[2.2.0]hex-5-enes (**4a–c**) compared to the isomeric dihydropyridines will allow for the development of synthetic schemes leading to biologically interesting molecules that normally would be prohibited using the more reactive 1,2-dihydropyridines.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation (MPS74-23700).

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