is the pyrrolyl chromophore referred to as ring D in Figure 1.

From the Figure 1, the "dimeric" nature of the salt complex can be characterized as two antibiotic molecules forming a jaw-like structure within which the ammonium salt is bound. The amine is held within the dimer by three hydrogen bonds, to O-3 (3.11 Å) and the carbonyl O-4 (3.05 Å) of one antibiotic molecule and the carboxylate O-1′ (2.77 Å) of the second (prime) molecule. The hydrogen bonds holding the two antibiotic molecules together are from O-1 to NH′ (2.92 Å) and O-1′ to NH (equivalent to the former by the twofold axis) and a third between the two other carboxyl oxygens, O-2 and O-2′ (2.40 Å, an unreliable value owing to the disorder of these oxygen atoms). The 2:1 stoichiometry of the complex results from only one of the molecules of X-14547A (prime in Figure 1) being ionized in the complex, allowing the two O-2 oxygens to be hydrogen bound via the proton on the nonionized carboxyl OH.

The indication from earlier experiments in the polyether class is that the formation of dimeric complexes in the crystalline state is accompanied by an ability to transport divalent as well as monovalent inorganic cations and this was confirmed for X-14547A in the conventional U-tube experiment[13] by demonstrating the transport of radioactive $^{45}Ca^{2+}$ from one aqueous $CaCl_2$ solution to another through a bulk organic phase ($CHCl_3$) on addition of the antibiotic. Subsequently, the calcium salt of X-14547A was formed and crystallized as a hemihydrate, $(C_{31}H_{42}NO_4)_2Ca{\cdot}H_2O$, mp 179 °C, $[\alpha]_D$ −401° (*c* 1, $CHCl_3$). Other divalent polyether antibiotics reported previously are lasalocid,[8] isolasalocid,[14] and lysocellin,[15] but the only other known divalent pyrrole ether (using the recently proposed system of nomenclature[3]) is antibiotic A23187,[4] referred to at the beginning of the report. In addition to the free acid, the calcium salt of A23187 has been analyzed by X-ray crystallography as both an ethanolate[16] and a hydrate[17] and, unlike the polyethers, considerable conformational changes occur on going from the free acid to the salt complex in the case of that particular pyrrole ether.

Supplementary Material Available: Tables of the final positional and thermal parameters (3 pages). Ordering information is given on any current masthead page.

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Structure, Absolute Configuration, and Total Synthesis of an Acid-Catalyzed Rearrangement Product of Bicyclomycin

Sir:

Bicyclomycin (**1**), an antibiotic discovered simultaneously by two Japanese groups,[1,2] possesses a novel structure and an interesting profile of antibacterial activity.[3] The structure was determined by spectroscopic methods[4] and confirmed by X-ray crystallography which also established the *relative* configuration.[5] We report the structure, total synthesis (in racemic form), and absolute configuration of the acid-catalyzed rearrangement products (**2a,b**) of bicyclomycin and therefore the *absolute* configuration of bicyclomycin (**1**).

Our efforts on the total synthesis of **1** prompted us to investigate the stability of the antibiotic under acidic conditions.[6] Heating bicyclomycin in 0.1 N perchloric acid at 100 °C resulted in rapid (~15 min) conversion of the antibiotic into a less polar substance which was the main reaction product. It was isolated in 33% yield by means of chromatography and crystallization.[7] Although only one spot appears on TLC (15% $EtOH/CHCl_3$), the product (**2a,b**) obtained was a mixture of two diastereomers (~1:1) as shown by the doubling of almost every signal in the NMR spectrum.[8]

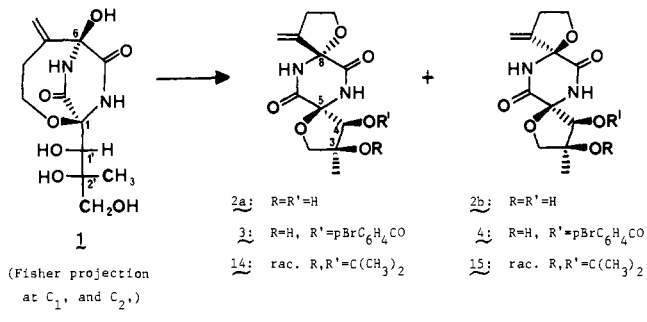
Structures **2a** and **2b** were assigned to the two diastereomers on the basis of a comparison of their NMR, IR, and mass spectra, together with TLC behavior, with those of racemic material obtained independently by total synthesis.

Thus far we have been unable to separate the two diastereomers. However, when the mixture was converted to the *p*-bromobenzoates **3** and **4** (*p*-BrC_6H_4COCl, 4-$(CH_3)_2NC_5H_4N$, dioxane, $(i\text{-}Pr)_2NEt$, room temperature, 72%), the products could be separated by preparative TLC (1:1 $C_6H_6/EtOAc$, three developments). Suitable crystals of the trans isomer **3** for a single-crystal X-ray diffraction analysis were obtained by crystallization from chloroform/hexane.[9] The structure was solved by Patterson and Fourier methods and was refined by full matrix least squares using 1785 reflections ($R = 0.042$, $wR = 0.053$). The absolute configuration was determined by carrying out two refinements, one using the correct value of the imaginary part of the anomalous dispersion correction for bromine ($\Delta f''$) and the other one using $-\Delta f''$. Compound **3** (as depicted in Scheme I) has the 3*S*,4*S*,5*S*,8*R* configuration. Stereodrawings are shown in Figure 1. Compound **4** is accordingly assigned the 3*S*,4*S*,5*S*,8*S* configuration. These results in turn establish the absolute configuration of bicyclomycin as 1*S*,6*R*,1′*S*,2′*S* using the numbering system employed by the earlier investigators.[4]

The rearrangement products **2a,b** were synthesized in racemic form as shown in Scheme II.

N,N-Diacetylglycine anhydride[10] (**5**) was condensed with the aldehyde **6**[11] using conditions reported by Gallina and Liberatori[13] (*t*-BuOK, DMF, 5 °C) to give **7**[14] in 66% yield. Hydrazinolysis ($H_2NNH_2{\cdot}H_2O$, DMF, 99%) removed the remaining *N*-acetyl group and trans ketalization conditions

Scheme I



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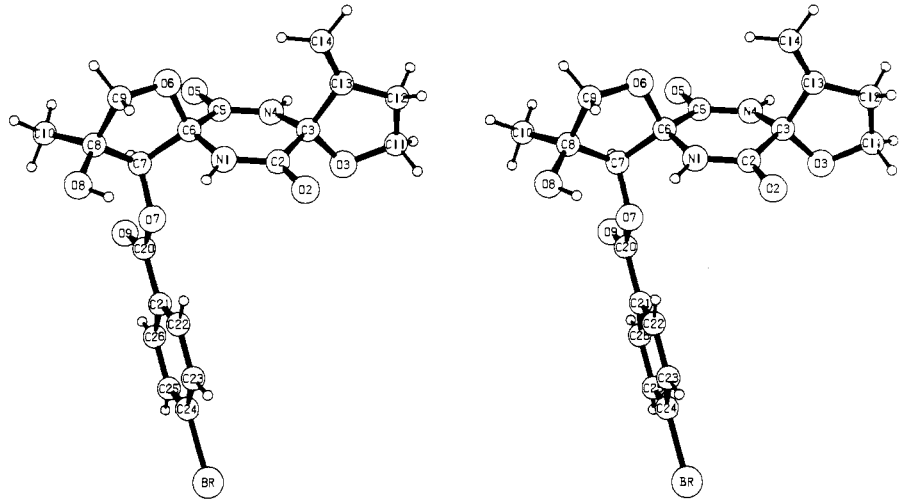
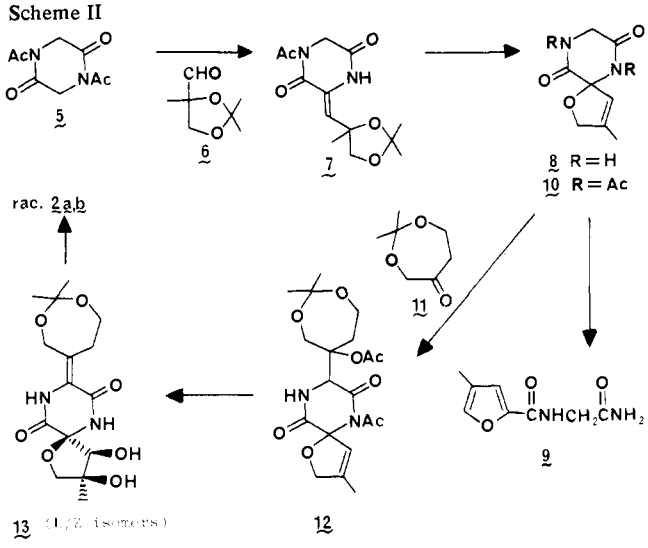


Figure 1. Stereodrawings of a molecule of **3**.

Scheme II



(HOCH$_2$CH$_2$OH, *p*-TsOH, CH$_2$Cl$_2$ reflux, 18 h) gave the spiro diketopiperazine **8** in 52% yield (mp 203–207 °C). Compound **8** undergoes a rearrangement under slightly more vigorous conditions (*p*-TsOH, CHCl$_3$ reflux, 2 hr) to give **9** in 91% yield (mp 175–176 °C).

Conversion of the spiro diketopiperazine **8** to the *N,N*-diacetyl derivative **10** had to be carried out in two identical steps to give satisfactory yields (60–75%) (Ac$_2$O, AcCl, C$_5$H$_5$N, 4-(CH$_3$)$_2$NC$_5$H$_4$N, BaO, room temperature, twice). The anion of **10** was formed at −78 °C with lithium diisopropylamide (THF, HMPA) and was treated with ketone **11**[15] at −78 °C. The mixture was allowed to warm to −40 °C and was then quenched with acetic acid. Compound **12** was obtained as a mixture of isomers in 41% yield. Less than 5% of the product formed by elimination of acetic acid was isolated. The mixture of isomers **12** was converted to **13** (*E/Z* isomers) in three steps in an overall yield of 50%: (1) H$_2$NNH$_2$·H$_2$O, EtOH; (2) OsO$_4$, C$_5$H$_5$N, 0 °C, H$_2$S; (3) DBU/DMF, room temperature. As judged by the NMR spectra, only the isomers having the cis diol on the side of the proximal nitrogen are formed; i.e., the attack of osmium tetroxide is from the less hindered side. Hydrolysis of the ketal (HOAc/H$_2$O, room temperature, 5 min) gave the tetraol (not isolated) which was treated with mesyl chloride in refluxing dioxane in the presence of potassium bicarbonate to give compound **2a,b** (racemic) (mp 208–215 °C) in 32% yield.[17] This racemic material was identical by TLC, NMR, IR, and mass spectra with the material obtained from bicyclomycin. The isomers of **2a,b** (racemic) were separated after conversion to the acetonides **14** and **15** (2,2-dimethoxypropane, *p*-TsOH). The structure of the trans isomer **14** was confirmed by single-crystal X-ray analysis.

Synthesis schemes for bicyclomycin should probably be contrived in a way that circumvents the energy minimum represented by **2**.[18]

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(7) These conditions are not unique. Similar results were obtained using 0.01 N HClO$_4$, 100 °C, 90 min; 1 N H$_2$SO$_4$, 100 °C, 3 min; Hg(OAc)$_2$/HOAc, 60 °C, 4 h.
(8) NMR (Me$_2$SO-d_6) δ 9.03–9.01 (2 br s, 1 H), 7.48–7.42 (2 br s, 1 H), 5.69–5.68 (2 d, J = 7 Hz, 1 H), 5.34–5.03 (m, 3 H), 4.27–4.25 (2 d, J = 7 Hz, 1 H), 3.99 (m, 2 H), 3.74 (m, 2 H), 2.69 (m, 2 H), 1.22 (s, 3 H); IR (KBr) 3485, 3360, 3215, 1687 cm^{-1}; mass spectrum (rel intensity) 284 (1%) (M$^+$), 98 (100%); $[\alpha]^{25}_D$ +1.00° (*c* 0.9, MeOH); mp 238–242 °C (decomposition begins at 220 °C). These spectral data were obtained from a recrystallized sample which appeared to be a 1:2 mixture of **2a** and **2b**.
(9) One mole of chloroform cocrystallized. Crystal data: space group *P*1; a = 6.090, b = 10.102, c = 11.437 Å; α = 113.49, β = 97.56, γ = 102.37°; Z = 1; d_{calcd} = 1.592 g cm^{-3}; μ (Cu Kα) = 59.3 cm^{-1}.
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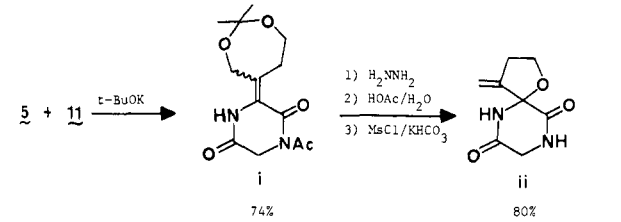

(18) The acid stability determined (bioassay) for bicyclomycin belies the inherent instability of its eight-membered hemiaminal ring.[1] Cf. E. J. Corey, D. J. Brunelle, and K. C. Nicolaou, *J. Am. Chem. Soc.*, **99**, 7359 (1977).

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Elusive Carbenes. Olefinic Capture of Cyclopropylchlorocarbene and Related Species

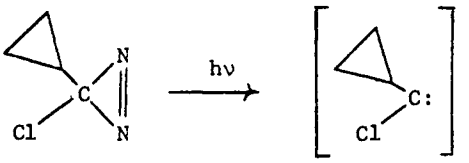
Sir:

Rules are often honored by exceptions. Consider the proposition: "if a singlet carbene has an internal insertion or cycloaddition available, it will not be possible to trap it efficiently with an external reagent".[1] Cyclopropylcarbene, for example, readily ring expands to cyclobutene[2] or fragments to ethylene and acetylene;[2a,c,3] external traps, alkenes in particular, should be hard pressed to compete with these facile intramolecular modes of escape. One way to augment intermolecular carbene capture at the expense of intramolecular immolation is to selectively generate the triplet carbene, which appears to have a lower tendency toward rearrangement than its singlet counterpart. Indeed, *triplet* cyclopropylcarbomethoxycarbene adds to isobutene (but not to *cis*-butene) in up to 33% yield.[2c,4]

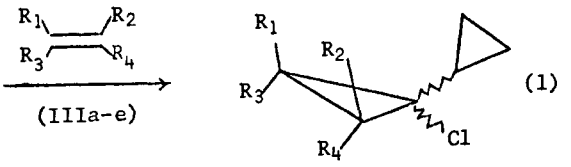
An alternative way to circumvent intramolecular rearrangement would be to stabilize the *singlet* cyclopropylcarbene, prolong its lifetime, and permit intermolecular capture to compete. Cyclopropylchlorocarbene (I) is of immediate interest because chlorine substitution appears to stabilize adjacent singlet carbene centers;[5] note that dichlorocarbene is one of the more selective carbenes in addition to alkenes.[6] The recent literature, however, reports that thermolysis of cyclopropylchlorodiazirine in cyclohexene affords only the intramolecular hydride shift product, chloromethylenecyclopropane.[7]

Nevertheless, we now report that (a) cyclopropylchlorocarbene may be readily generated by photolysis (or thermolysis) of the requisite diazirine and added to a variety of alkenes (including cyclohexene); (b) the principal intramolecular rearrangement of I leads to 1-chlorocyclobutene by ring expansion, and not to chloromethylenecyclopropane by hydride shift; (c) even the parent cyclopropylcarbene can be trapped by isobutene (albeit in low yield); and (d) the intermolecular addition of I is not an isolated phenomenon—*tert*-butylchlorocarbene, another species for which olefinic interception has been vainly sought,[8] also adds to simple alkenes.

3-Cyclopropyl-3-chlorodiazirine (II) was generated[9] from cyclopropylmethylamidinium chloride[10] and condensed into various alkenes (IIIa-e) at −78 °C. Olefinic solutions of II (0.2-1.5 M) were photolyzed in Pyrex vessels at −20 °C with a focussed Osram 200W XE mercury lamp; the decomposition of 3-7 mmol of II, monitored by nitrogen evolution, required 2-4 h. Removal of excess olefin and GC purification provided the product chlorobicyclopropyls IVa-e; cf. eq 1 and Table I.



II I



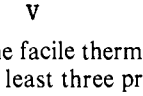
(1)

IVa-e

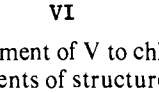
Identities of the addition products were established by structurally consistent IR and ^{1}H NMR spectra[11] and by exact mass spectrometric analyses (±5 mmu on M^+). Additions of I to *cis*- or *trans*-butene were stereospecific within the limits of GC detection. Moreover, additions to *cis*-butene or cyclohexene were stereoselective (cf. Table I), although the isomeric cyclopropanes formed in each case have not yet been configurationally differentiated.[12a]

Although photolytic generation of I is more convenient, thermal decomposition of II in refluxing cyclohexene (~16 h) also afforded adducts IVe in 26% yield (isomer ratio, 3.3).[12b]

Accompanying adducts IV was a minor product, V,[13] which became the major product obtained upon photolysis of II in pentane[14] and the sole product resulting from thermolysis of II in CCl_4 at 100 °C (sealed tube, 2 h). By NMR,[15] V was identical with the unimolecular rearrangement product of I, isolated by Liu and Chien and assigned structure VI.[7] The chlorocyclobutene assignment, V, is preferable, however, be-



V



VI

cause of the facile thermal rearrangement of V to chloroprene. Indeed, at least three prior assignments of structure V to the cyclopropylchlorodiazirine unimolecular decomposition product already exist in the literature.[16-18] The thermal rearrangement of V to chloroprene[17,18] (which we have inde-

Table I. The Addition of Cyclopropylchlorocarbene to Alkenes

alkene	R_1	R_2	R_3	R_4	GC condn[a] Col[b]	GC condn[a] temp, °C	GC condn[a] ret time, min,	yield of IV, %[c]
IIIa	CH_3	CH_3	CH_3	CH_3	A′	100	22	78
IIIb	CH_3	H	CH_3	H	A	110	16	47
IIIc	CH_3	H	H	CH_3	A	100	25	33
IIId	CH_3	CH_3	H	H	B	100	23, 25[d]	37[e]
IIIe	$-(CH_2)_4-$		H	H	C	100	36, 41[f]	44[e]

[a] Gas chromatographic conditions for isolation of IV; He gas flow 60 mL/min. [b] Columns: A, 13 ft × 0.25 in, 14% SF-96 on 80/100 Chromosorb W (A′, 3 ft × 0.25 in, 14% SF-96 on 90/100 Anakrom); B, 15 ft × 0.25 in. 20% QF-1 on 45/60 Gas-Chrom R; C, 10 ft × 0.25 in 10% FFAP on 60/80 Chromosorb W. [c] Yields are based on decomposed II (nitrogen evolution). IV was quantitatively determined in crude photolysis residues by NMR spectroscopy against an internal $CHCl_3$ standard. [d] Two isomers were obtained in 8:1 distribution; the major isomer eluted first. [e] Overall yield. [f] Two isomers were obtained in 3.5:1 distribution; the major isomer eluted first.

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