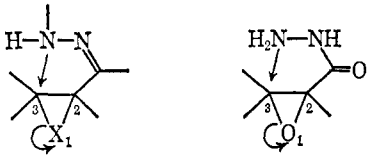
The reactions of **2** and **4** stand in sharp contrast to those of structurally similar heterocyclic systems (*e.g.*, **12** and **13**). In these systems rearrangement apparently



12,[12] X = O, NR **13**[13]

proceeds *via* attack at C-3 with resultant formation of a five-membered ring. Electronegativity of the heteroatom and steric factors are among the variables which might be expected to influence the direction and ease of rearrangement. The scope, utility, and detailed mechanism of this and similar rearrangements are under further investigation.

Acknowledgment. Support of this research by a National Science Foundation Grant (GP-5531) and by a NASA traineeship to S. C. C. (1965–1968) is gratefully acknowledged.

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Biosynthetic Studies. II.[1] The Mode of Incorporation of Phenylalanine into Gliotoxin

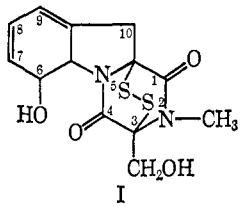
Sir:

In our recent studies on biosynthesis,[1,2] we have employed precursors enriched with stable isotopes (^{15}N, ^{13}C) and spectral methods for the determination of the site and extent of labeling. We report here our findings from a series of experiments using intermolecularly doubly labeled amino acids (see Table I) which provide some insight into the biotransformations of phenylalanine, an important precursor of many families of natural products.

It has been reported[3] that phenylalanine is incorporated efficiently into gliotoxin (I). We have found[1] that during the production of gliotoxin by *Trichoderma viride* in a chemically defined medium, if [^{15}N]glycine be added to the substrate,[4] both nitrogen atoms in I are labeled although to unequal extents.[1] The presence of [^{15}N]phenylalanine in the substrate, however, leads to the labeling of only N-5 in I. It is difficult to determine whether phenylalanine is incorporated intact into I to any appreciable extent, but the wide divergence in the isotope dilution observed (see Table I) when a mixture of [1-^{14}C]phenylalanine and [^{15}N]-phenylalanine is used indicates that extensive deamination and reamination must occur. Aspartic acid causes labeling at both nitrogen atoms in gliotoxin without contributing to the carbon skeleton. Glutamic acid also serves as the source of both nitrogen atoms in I. One has to conclude that, in the system under examination, phenylalanine and N-methylserine (or serine) readily participate in a nitrogen pool but the exchange of the amino group between phenylalanine and serine (or its equivalent) is limited.

Table I

Precursor	Gliotoxin: Isotope level, %	Gliotoxin: Isotope dilution
[1-^{13}C]Phe	^{13}C, 6	8.4 ×
[1-^{14}C]Phe		8.1 ×
[1-^{13}C]Phe	^{13}C, 5	10.0 ×
[3-^{14}C]Phe		10.3 ×
[1-^{14}C]Phe	^{15}N, 9	4.4 ×
[^{15}N]Phe		11.1 ×
[^{15}N]Asp	^{15}N, 2.5	
[1-^{14}C]Asp	^{14}C, 0	
[^{15}N]Glu	^{15}N, 2.5	
[1-^{14}C]L-Phe	^{15}N, 9	4.3 ×
[^{15}N]DL-Phe		11.1 ×
[1-^{14}C]D-Phe	^{15}N, 11	2.6 ×
[^{15}N]DL-Phe		9.1 ×



I

The experiment with phenylalanine labeled at C-1 with ^{13}C as well as with ^{14}C established that there is no appreciable isotope effect during incorporation, as is to be expected. Therefore, the observation that [1-^{13}C]phenylalanine and [3-^{14}C]phenylalanine are incorporated with the same isotope dilution (within limits of experimental error) signifies that the carbon skeleton of phenylalanine remains intact during deamination and reamination. At present there is insufficient information for determining whether the C-6,C-3 unit is in the form of phenylpyruvic or cinnamic acids or their equivalents. However, the finding that both L- and D-phenylalanines are equally efficient precursors of gliotoxin is compatible with an optically inactive intermediate.

The significantly higher dilution of ^{15}N compared to ^{13}C or ^{14}C during incorporation is indicative of a larger nitrogen pool than carbon pool. The only source of nitrogen in the medium used is NH_4^+. Since the concentration of this ion is quite large,[4] it is remarkable that a ^{15}N-enrichment level as high as 9% was obtained.

Work is in progress for obtaining further details about the incorporation of phenylalanine and *m*-tyrosine into gliotoxin.

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(1) Part I: A. K. Bose, K. G. Das, P. T. Funke, I. Kugajevsky, O. P. Shukla, K. S. Khanchandani, and R. J. Suhadolnik, *J. Am. Chem. Soc.*, 90, 1038 (1968).

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(4) In each experiment 50 mg of the labeled compound was added to about 1.5 l. of medium. For experimental details see ref 1.

Suhadolnik and Dr. M. Anchel for valuable discussions and help with some aspects of the experimental work.

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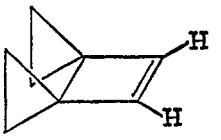
Dispiro[2.0.2.2]oct-7-ene

Sir:

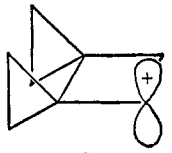
There have been reported in the literature no examples of the highly interesting dispiro[2.0.2.2]oct-7-ene system (**1**). This molecule is ideally conducive to various



1

studies of the interaction of cyclopropyl groups with conjugated π systems since it possesses the minimum-energy bisected geometry[1] in which the planes of both cyclopropane rings are normal to the nodal plane of the adjacent double bond. This should allow maximum delocalization between the π system and the p-character bonds of the cyclopropane rings.

Among various possible probes into the chemical nature of this system, the thermal and photochemical reorganizational reactions as well as the study of the carbonium ion chemistry of the dispiro[2.0.2.2]oct-7-ene system should prove of significant theoretical value to organic chemists. The molecule should prove rather resistant to thermal rearrangement since all of the modes of decomposition that have previous analogy are unfavorable here. Indeed the cyclobutene → butadiene, vinylcyclopropane → cyclopentene, and bicyclopropyl → cyclohexene conversions each have obvious drawbacks when applied to this system. Generation of the carbonium ion **2** should also bring about

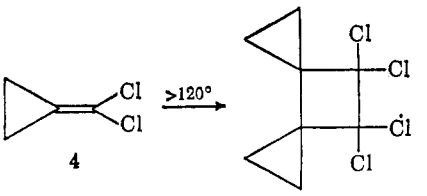


2

intriguing results, since **2** has the ideal geometry for maximum overlap between the vacant p orbital and the π-like orbitals of the cyclopropane ring.[2] A symmetrical homoallylic structure would be predicted for the species, and one would expect a great resistance to skeletal rearrangement such as that observed by Winstein in a similar system.[3]

The first synthesis of this system was accomplished *via* our observation of the heretofore unknown thermal dimerization reaction of dichloromethylenecyclopropane (**4**).

Decomposition of sodium trichloroacetate in the presence of allene provided 2,2-dichloromethylenecyclopropane (**3**), in ~20% yield.[4] **3**, on heating in the gas



4 **5**

phase at 215° for 1 hr, was converted quantitatively to dichloromethylenecyclopropane (**4**);[5] the nmr spectrum showed a singlet at 1.51 ppm and the mass spectrum, a parent peak at *m/e* 122. Longer heating or direct heating of **3** in the liquid phase results in quantitative conversion to 7,7,8,8-tetrachlorodispiro[2.0.2.2]octane (**5**) which had two symmetrical multiplets in the nmr centered at 0.64 and 1.13 ppm and a mass spectrum with a parent peak at *m/e* 244. Treatment of **5** with zinc in ethanol leads, in 85% yield, to 7,8-dichlorodispiro[2.0.2.2]-oct-7-ene (**6**), which showed two symmetrical multiplets in the nmr centered at 0.50 and 0.85 ppm; a mass spectrum with a parent peak at *m/e* 174; λ_{max} (hexane) 203 mμ (ϵ 1.0 × 10^3). Reduction of **6** with sodium–tetrahydrofuran–*t*-butyl alcohol results in the formation, in 80% yield, of the desired dispiro[2.0.2.2]-oct-7-ene, which showed two symmetrical multiplets in the nmr centered at 0.47 (4 H) and 0.73 (4 H) ppm and a singlet at 6.13 (2 H) ppm; bands, *inter alia*, in the ir (12 mm, gas phase) at 3080, 3010, 1014, 933, 876, and 737 cm^{-1}; λ_{max} (ethanol) 203 mμ (ϵ 5.72 × 10^3); a mass spectrum with a parent peak at *m/e* 106. Ozonolysis of **1** followed by treatment with performic acid results in >80% yield of bicyclopropyl-1,1′-dicarboxylic acid,[6] displaying two symmetrical multiplets in the nmr at 0.62 (4 H) and 1.01 (4 H) ppm and a broad singlet at 12.7 (2 H) ppm.

As might be expected, dispiro[2.0.2.2]oct-7-ene is thermally stable at temperatures up to 300°. We will report results from our investigation of its thermal rearrangement and other aspects of its chemistry.

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Ion-Pair Return in Racemization and Isomerization of Sulfinate Esters

Sir:

Sulfinate esters of aliphatic alcohols are known to undergo isomerization to sulfones when the nature of the alkyl moiety is such as to give rise to a comparatively stable carbonium ion.[1,2] Structure and solvent effects indicate that the isomerization is likely to occur by an ionization process, which appears to involve an ion-pair intermediate.[2] Since the sulfinate anion is

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