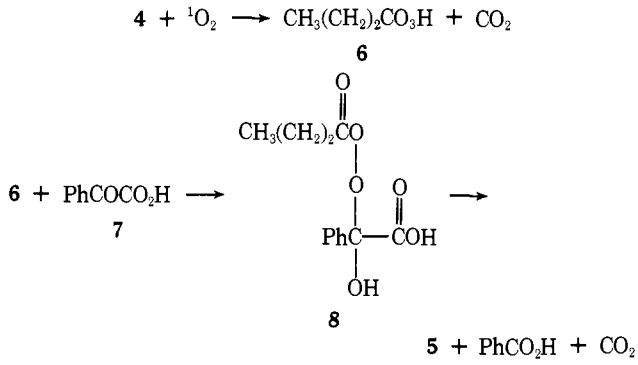
Scheme III

$$PhCO_3H + CH_3(CH_2)_2COCO_2H \longrightarrow \underset{4}{} PhCO_2H + CH_3(CH_2)_2CO_2H + CO_2$$
$$\underset{5}{}$$

Scheme IV



ate were found in 20 and 18% yields, respectively. We conclude that singlet oxygen oxidatively decarboxylates α-ketovaleric acid (**4**) to its peroxy derivative (**6**) leaving phenylglyoxalic acid (**7**) unchanged; however, the two acids rapidly form the appropriate Bayer–Villiger-type intermediate (**8**) which promptly fragments liberating carbon dioxide, benzoic, and butyric acids (**5**) (Scheme IV).

Since α-ketoglutaric acid (**1**) and the peroxyacid (**3**) are mutually destructible, it follows that for selective oxidation of a biological substrate the peracid must be discretely immobilized by being bound to an enzyme. Similarly, sequestering of the peracid should enable it to be identified. This was found to be the case. One gram of α-ketovaleric acid was absorbed on 6 g of anionic exchange resin.[12] The dried resin was suspended in 50 ml of methylene chloride and photooxygenated for 24 h.[13] Carbon dioxide was evolved in 40% yield. Next, the solvent was removed and the resin placed in 10 ml of formic acid and 4 g of cyclohexene. The suspension was heated under reflux for 6 h, cooled, and finally heated with 20 ml of 20% aqueous sodium hydroxide solution for 2 h. Extraction of the mixture with hot ethyl acetate gave 0.11 g of *trans*-cyclohexane-1,2-diol (12% yield).[14]

This work reveals an entirely new facet of singlet oxygen chemistry. It also provides an indication of how α-ketoglutarate-dependent monooxygenase systems may operate, at least in showing that when the spin restriction is removed, molecular oxygen may preferentially attack the α-ketocarboxylic function and not an inactive site on the substrate.

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(8) β-Carotene is an efficient quencher of singlet oxygen in biological systems (C. S. Foote and R. W. Denny, *J. Am. Chem. Soc.*, **90**, 6233 (1968); *ibid.*, **92**, 5216, 5218 (1970).
(9) Hydrogen peroxide reacts readily with α-ketocarboxylic acid (see pp 132–133, ref 3, and pp 327 and 328, ref 10), but there is little or no mention of the reactions of peracids with them; however, a similar reaction course is to be expected.
(10) H. O. House, "Modern Synthetic Reactions", 2d ed, W. A. Benjamin, Menlo Park, Calif., 1972.
(11) Analysis was by gas liquid chromatography using a 1.5 m long 3.5% FFAP column at 60 °C Ethyl benzoate was used to calibrate the yields of methyl benzoate and butyrate.
(12) The resin, IRA-400 obtained from Fluka AG, CH-9470 Buchs, was washed with dry ethanol prior to use.
(13) Our general procedure (ref 6) was followed, but using tetraphenylporphyrin as sensitizer.
(14) The cyclohexanediol was identified with a genuine sample (A. Roebuck and H. Adkins, "Organic Syntheses", Collect. Vol. 3, Wiley, New York, N.Y., 1955, p 217.

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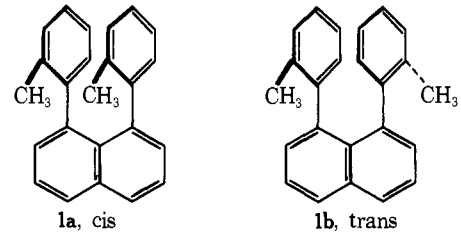
Stable Cis and Trans Rotational Isomers of 1,8-Di-*o*-tolylnaphthalene[1]

Sir:

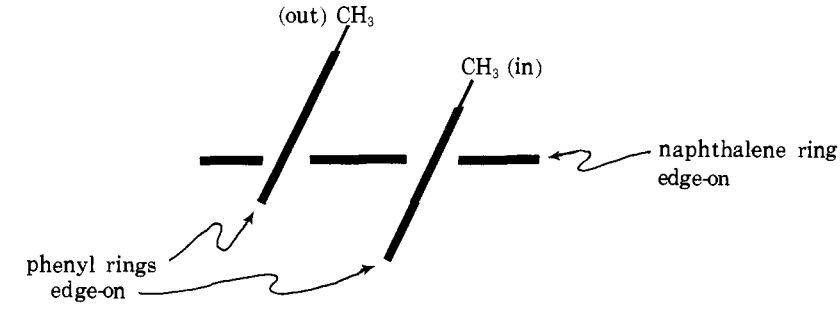
Studies of CPK (Corey–Pauling–Koltun) or similar space-filling models suggest that there should be a very substantial barrier to a 180° rotation about the phenyl–naphthyl bonds in 1,8-diphenylnaphthalene derivatives. This leads to the expectation that such compounds with a substituent at one meta position of each phenyl ring should be expected to exist as stable cis and trans isomer pairs. However, House and co-workers[2] have shown that several such derivatives, including 1,8-bis(3-chlorophenyl)naphthalene and 1,8-bis(3-methylcarboxyphenyl)naphthalene cannot be resolved into stable configurational isomers. Further, proton NMR studies of these derivatives indicate that $\Delta G^{\ddagger}$ for rotation is 15–16 kcal/mol, which corresponds to rather rapid rotation in solution at room temperature.[3]



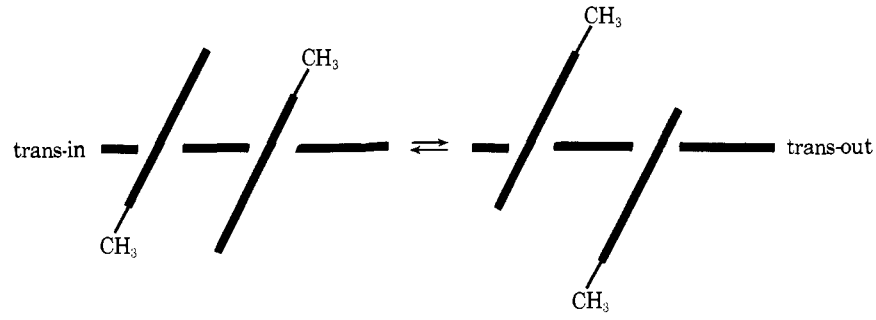
1a, cis **1b**, trans

The possibility of isolating stable cis and trans isomers of this type is an interesting one, and we now have found that 1,8-di-*o*-tolylnaphthalene (**1**) can be so resolved.

1,8-Di-*o*-tolylnaphthalene (**1**) was prepared by a direct coupling of *o*-tolylmagnesium iodide with 1,8-diiodonaphthalene with a nickel acetylacetonate catalyst.[4] The proton NMR spectrum of **1** showed two sharp singlets 1.85 ppm downfield from TMS, which were separated by 2 Hz at 60 MHz. The chemical shift of the methyl groups for **1** is decidedly upfield from the methyl signal of toluene (δ 2.32), presumably because of the ring-current effects of the adjacent phenyl and the naphthalene rings. Two isomers, **1a** and



2



3

1b, were separated from the reaction product by column chromatography on alumina. Each isomer gave a single methyl-group resonance in the proton NMR. Isomer **1a** with the more downfield methyl signal was eluted last. The two isomers are stable in the crystalline state, but have a half-life with respect to interconversion in solution of about 1 day at room temperature. Isomer **1a** has the higher melting point (160–162°), and lower solubility in hexane; fractional crystallization from hexane gave enrichment in **1a.** Isomer **1b** melted over a wide temperature range (120–145°), but when crystals of **1b** were dropped on a hot plate at 135°, they melted immediately. The composition of each isomer was verified by high-resolution mass spectral analysis as well as by elemental analysis.

First-order kinetics were observed for interconversion of the cis and trans forms in $CDCl_3$ at 40° by proton NMR, starting with either a single isomer or a nonequilibrium mixture. The equilibrium constant, **1b/1a,** was found to be 3.21, which corresponds to a free-energy difference between the isomers of 0.73 kcal/mol. Isomer **1b** was the more stable. The rate constant of conversion of **1a** to **1b** is 9.79×10^{-5} s^{-1}. The calculated $\Delta G^{\ddagger}$ for rotation is thus 24.1 kcal/mol (**1a** to **1b**) and about 8 kcal/mol greater than for 1,8-diphenylnaphthalene derivatives lacking the ortho methyl groups.

Assuming the geometry of this compound to be qualitatively similar to that found for other peri-substituted diarylnaphthalenes[5] by x-ray diffraction, the two methyl groups of the cis isomer should occupy different positions, "in" and "out". This is shown in **2,** which is a top view of *cis*-1,8-di-*o*-tolylnaphthalene looking down along the planes of the phenyl rings toward the plane of the naphthalene ring.[6] If the two phenyl rings are flipping rapidly from one side of the naphthalene to the other, interchanging the positions of the two methyl groups, the resultant methyl NMR signal would be a singlet with a shift corresponding to a 1:1 average of the shifts of the methyls in the two possible positions.

The trans isomer should also have "in" and "out" methyl groups, but the trans molecules would have both methyl groups simultaneously "in" or "out", **3.** Thus, there should be two forms, **3,** of the trans isomer, an "in" form and an "out" form. Flipping of the rings back and forth across the plane of the naphthalene ring will interconvert these forms. Rapid interconversion will result in a single signal for the methyl groups of the trans isomer, but the average is not expected to be 1:1, because the in and out forms of the trans rotamer should not have the same energy. Steric considerations suggest that the out isomer is expected to be favored and thus to contribute more heavily to the average signal. Variable-temperature NMR studies at 100 MHz with both isomers of **1** showed no broadening of the methyl-group signals down to −90 °C, indicating an upper limit to the flipping barrier of about 9 kcal/mol. The low barrier (<9 kcal) to the flipping of the aromatic rings of **1** from side to side of the naphthalene plane and the higher barrier (~24 kcal) to ring rotation provides an interesting contrast to the recent study of 1,8-di-*tert*-butylnaphthalene (**2**).[7] For **2,** the barrier to flipping of the *tert*-butyl groups to opposite sides of the naphthalene plane was reported to be >25 kcal, while rotation of the *tert*-butyl groups was <6.5 kcal. These results are not unreasonable. The relatively flat phenyl rings should slide past each other easily (flipping), while the transition state for rotation involves a large increase in crowding with both the adjacent phenyl ring and the nearby naphthyl proton. The *tert*-butyl group may be viewed as relatively spherical, but more bulky and more crowded in the ground state. Rotation does not involve a substantial change in crowding, while flipping of *tert*-butyl groups through the ring place forces these bulky groups closer together.

The NMR spectra of the phenyl ring protons of the cis–trans isomers **1a** and **1b** are strikingly different, while the naphthyl-ring regions are essentially superimposable. **1a** gives a sharp singlet for the phenyl-ring protons, as does 1,8-diphenylnaphthalene, while the phenyl protons of **1b** are a multiplet. This behavior suggests a means of identifying the isomers. For *cis*-1,8-di-*o*-tolynaphthalene, the meta phenyl-ring proton adjacent to the methyl substituent must be positioned over the plane of the adjacent phenyl ring 50% of the time (in), and outside the plane of the adjacent phenyl ring 50% of the time (out). The same will be true of the meta protons on the side of the phenyl ring opposite the methyl group. The meta protons will then experience equal

ring-current effects. However, for the trans isomer, the ring-flip forms are expected to be of unequal energy and, as a result, the meta proton adjacent to the methyl group will spend a different fraction of the time over the plane of the adjacent phenyl ring than for the meta protons opposite the methyl group. Consequently, these meta protons are expected to experience different diamagnetic ring current shifts. The resulting differences in chemical shifts are expected to rise to a multiplet proton spectrum. We therefore assign the trans configuration to isomer **1b** and the cis configuration to isomer **1a.** This assignment is consistent with the observation that **1a** is the less favorable isomer. With rapid flipping of the phenyl rings at room temperature, the trans isomer would be a racemic mixture, while the cis isomer would be achiral. We have not attempted to identify the isomers by resolution.

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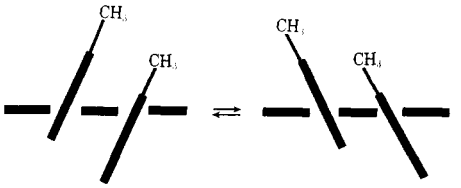

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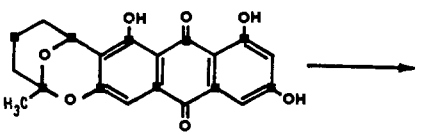
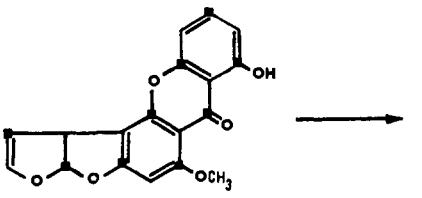
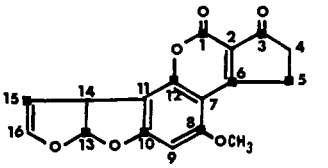


III



II



I

Table I. Comparison of the Signal Intensities of Aflatoxin B_1 and Aflatoxin B_1 Derived From ^{13}C-Labeled Averufin

Carbon no.	δ^9	Peak height (cm) Unlabeled B_1	Labeled B_1	Rel intens
1	155.2	0.6	0.8	1.3
3	201.3	2.5	2.4	1.0
5	29.0	2.7	3.6	1.3
6	177.1	3.8	2.5	0.7
8	161.6	3.5	3.8	1.1
10	165.8	2.8	3.0	1.1
12	153.0	1.4	0.9	0.6
13	113.6	5.0	7.5	1.5
15	102.7	4.6	9.0	2.0
2	117.4	1.5	0.6	0.4
4	35.1	2.8	1.3	0.5
7	104.0	1.4	0.7	0.5
9	90.9	5.0	2.4	0.5
11	107.9	1.7	0.9	0.5
14	47.9	4.4	2.3	0.5
16	145.4	5.9	3.2	0.5
OCH_3	56.6	3.6	1.9	0.5

Origin of the Bisfuran Ring Structure in Aflatoxin Biosynthesis

Sir:

The biogenetic origin of the bisfuran ring structure in the molecule of aflatoxin B_1 (I) has been a subject of disagreement among investigators. Based upon the apparent difference in labeling density between the bisfuran ring and the xanthone moiety in sterigmatocystin (II) derived from ^{14}C-labeled acetate,[1] it was proposed that the two moieties have separate biogenetic origins and II is formed through the fusion of a C_4 and C_{14} unit. II was shown to be convertible into I by *Aspergillus parasiticus*[2] and was recognized as a precursor of I. Specific chemical degradations of I[3] synthesized from [1-^{14}C]- and [2-^{14}C]acetate, however, revealed a uniform label distribution throughout the molecule I. Thus a biosynthetic scheme was advanced in which I is derived from a single C_{18} polyketomethylene unit and the bisfuran ring system was proposed to be formed through endoperoxidation of the terminal phenyl group of a polyhydroxynaphthacene intermediate. However, the recent finding that averufin (III), a C_{20} polyketide, can be readily converted into I by *A. parasiticus*[4,5] indicates the biosynthesis of I involves a C_{20} rather than a C_{18} intermediate. This implies (1) the C_6 side chain of averufin is converted into the bisfuran ring system or (2) the C_6 side chain is removed and replaced by a C_4 acetoacetate unit which is converted into the bisfuran ring system.

In the present study we subjected ^{13}C-labeled I derived from ^{13}C-labeled III to ^{13}C NMR analysis in order to show that nine of the ten carbon atoms in III originating from [1-^{13}C]acetate are incorporated into I.

The ^{13}C-labeled III was synthesized by cultures of *A. parasiticus* ATCC 24551 supplemented with [1-^{13}C]acetate.[6] The purified ^{13}C-labeled III was then converted into I by the mycelium of *A. parasiticus*.[5] Previous ^{13}C NMR analysis of ^{13}C-labeled III has revealed that III is biosynthesized through a head-to-tail assembly of ten acetate units,[7] with the labels occupying alternating positions throughout the molecule.

Comparison of the relative signal intensities of I and I derived from ^{13}C-labeled III, as shown in Table I, indicates that the ratios of the intensities (last column) for the ex-