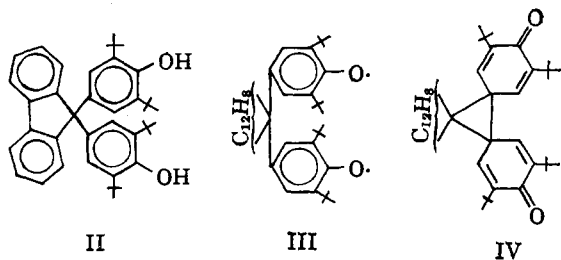


Fig. 1.—E.p.r. of II in a rigid glass.

(IV) were present. There are three strong bands in the 6- μ region. The pair of bands at 6.0 and 6.2 μ is assigned to IV, and the band at 6.4 μ is attributed to III. There is ample analogy for these assignments.³ The oxidation product reacted rapidly with oxygen and gave a mixture of products which was not characterized. The infrared spectrum of the total crude product was consistent with the expected cyclic peroxide being the major component. The optical spectra of solutions of the oxidation products of II were determined at various stages of oxidation but no definitive interpretation could be made.



The oxidation of II (methyltetrahydrofuran solution) was also effected by lead dioxide in a sealed, degassed system. The e.p.r. spectrum was monitored as oxidation proceeded. Initially the simple three-line spectrum ($a = 1.65$ gauss) of the monoradical appeared. As oxidation proceeded the intensity of the signal increased and then decreased markedly but it could not be made to vanish entirely. When this solution was frozen to a rigid glass (*ca.* -180°), the e.p.r. spectrum (Fig. 1) revealed the presence of a triplet species. There are two sets of $\Delta m = 1$ lines, about $g = 2$, at ± 63 and ± 15 gauss as well as a half-field ($\Delta m = 2$) absorption. The larger splitting is attributed to biradical III and the smaller to a dimer containing two molecules of III, probably linked by a peroxide bond. Such bond formation would be rather unusual, since phenoxy radicals bearing three very bulky substituents

are generally thought to be monomeric. An examination of scale molecular models indicated that peroxide bond formation is feasible. The low temperature at which the spectrum was determined would also favor the dimer. This explanation is supported by the concentration dependence of the zero field splitting. Upon dilution the intensity of the smaller splitting decreases much more rapidly than that of the larger and finally disappears completely while the larger splitting is still intense. The positions of these lines indicate that the average distance between electrons in III is 6 Å. while it is 9.8 Å. in the dimer.⁴

The zero field splitting behaved unusually as the sample was heated. The satellite lines decreased in intensity and finally disappeared in the base line. The failure of these lines to reappear as a single broad line at $g = 2$ is attributed to the rapid interconversion of III and IV.

Acknowledgment.—We wish to thank Professor S. I. Weissman for helpful discussions of this work.

(4) G. E. Pake, *J. Chem. Phys.*, **16**, 327 (1948).

BELL TELEPHONE LABORATORIES, INC. EDWIN A. CHANDROSS
MURRAY HILL, NEW JERSEY
DEPARTMENT OF CHEMISTRY ROBERT KREILICK
WASHINGTON UNIVERSITY
ST. LOUIS, MISSOURI

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Glutarimide Antibiotics. IV. The Total Synthesis of *dl*- and *l*-Cycloheximide

Sir:

Cycloheximide (I), a mold metabolite possessing potent fungicidal, antitumor, and rodent-repellent properties, has been the subject of a number of attempted syntheses in recent years.¹⁻⁴

Lack of knowledge of the stereochemistry of cycloheximide and its isomers was a major reason for the failure of these attempts to produce intermediates closely related to I. Clarification of the orientation of the substituents on the cyclohexanone ring of I has recently been forthcoming^{5,6} and in conjunction with our own structure studies⁶ in this area we have maintained a concurrent synthetic effort. This now has led to the total synthesis of I, reported below.

Catalytic reduction⁷ of 2,4-dimethylphenol with palladium on charcoal led directly to *cis*-2,4-dimethylcyclohexanone⁸ (II) which was then converted in excellent yield to the morpholine enamine (III), using a Dowex-50 resin catalyst, b.p. $97-98^\circ$ (3.0 mm.), n_D^{25} 1.4930. *Anal.* Found: C, 73.8; H, 10.7; N, 7.3.

Acylation of III by 3-glutarimidylacetyl chloride (IV) in chloroform followed by decomposition of the intermediate product (V) by means of an acidic buffer led to a 35% yield of *dl*-dehydrocycloheximide (VI),^{6,9} m.p. $180-181^\circ$. *Anal.* Found: C, 64.5; H, 7.6; N, 5.2. The solution infrared spectrum of this material was identical with that of dehydrocycloheximide derived

(1) M. A. Acitelli, Ph.D. Thesis, Cornell University, 1957.

(2) B. C. Lawes, *J. Am. Chem. Soc.*, **82**, 6413 (1960).

(3) T. Okuda, M. Suzuki, and Y. Egawa, *J. Antibiotics* (Tokyo), Ser. A, **14**, 158 (1961).

(4) F. Johnson, W. D. Gurowitz, and N. A. Starkovsky, *Tetrahedron Letters*, 1167 (1962).

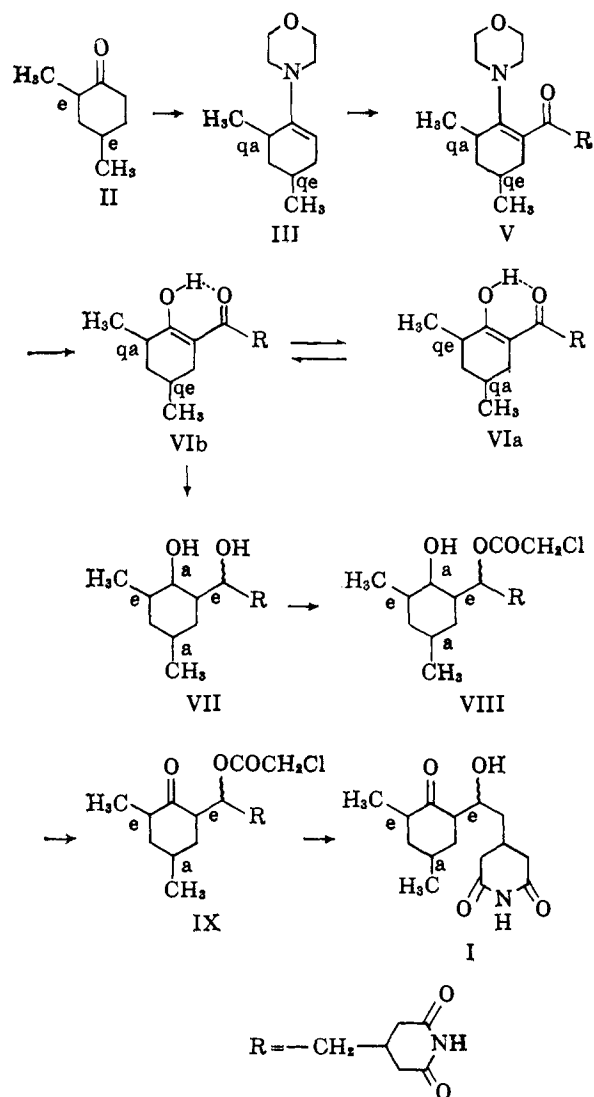
(5) T. Okuda and M. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **9**, 1014 (1961).

(6) F. Johnson and N. A. Starkovsky, *Tetrahedron Letters*, 1173 (1962).

(7) The large scale reductions were carried out by W. B. Trapp and H. E. Hennis of the Midland Division of The Dow Chemical Co., and we gratefully acknowledge their assistance.

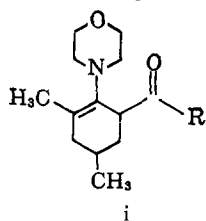
(8) The product contained 7% of the *trans* form as estimated by g.l.c. analysis.

(9) The methyl groups in dehydrocycloheximide already have been shown to be *trans* to one another [A. J. Lemin and J. H. Ford, *J. Org. Chem.*, **25**, 344 (1960)].



by chromic acid oxidation of cycloheximide itself. It appears that VI is almost the exclusive product of C-acylation.^{10,11} Catalytic reduction of VI in acetic acid over platinum then afforded *dl*-dihydrocycloheximide (VII)¹² in 52% yield, m.p. 164–165°. *Anal.* Found: C, 63.3; H, 8.9; N, 4.9.

(10) In an article which appears to have been largely ignored [see, however, M. Kuehne, *J. Am. Chem. Soc.*, **81**, 5400 (1959)], W. R. N. Williamson [*Tetrahedron*, **3**, 314 (1958)] has suggested that the inability of alkyl halides to C-alkylate the enamines of 2-alkyl cyclohexanones was due in part to the steric effects of the 2-alkyl substituent. The latter, he postulated; assumed a quasi-axial position in the dipolar form of the enamine. The results of our synthetic work now seem to support these ideas, and it would appear that enamines of 2-alkylated cyclohexanones do indeed have the 2-alkyl group in a quasi-axial position. Thus, these materials present possibilities for accomplishing syntheses where an endergonic process is called for. Whereas the authors prefer the above argument, an alternative reason for appearance of *trans*-methyl groups in VI could be found if it is assumed that the product of acylation has the structure shown in i, and that the decomposition step is a kinetically controlled process and leads to the more unstable configuration for the 2-methyl group.



(11) After this work was completed, the synthesis of optically active dehydrocycloheximide was reported by H. J. Schaeffer and V. K. Jain [*J. Pharm. Sci.*, **52**, 509 (1963)], who used the optically active piperidine enamine derived from (+)-*trans*-2,4-dimethylcyclohexanone.

Thus, in two relatively simple steps we were able to establish *stereoselectively five asymmetric centers*, four of which were required in the final product.

The conversion of VII to I by partial oxidation proceeded with only a small yield, and the following procedure proved much more satisfactory.

Monoacylation of VII with chloroacetyl chloride¹³ in dioxane-pyridine led to a 65% yield of VIII, m.p. 183–184° (*Anal.* Found: C, 56.5; H, 7.0; Cl, 10.2; N, 4.1), which on oxidation with chromium trioxide in aqueous acetone containing a little acetic acid afforded *dl*-cycloheximide chloroacetate (IX), m.p. 137–138° in good yield. *Anal.* Found: C, 56.8; H, 6.6; Cl, 10.2; N, 3.9.

Hydrolysis of IX with aqueous potassium bicarbonate than gave racemic cycloheximide (I), m.p. 139–140°, whose solution infrared spectrum and n.m.r. spectra in deuteriochloroform and pyridine were identical with those of the natural product. *Anal.* Found: C, 64.3; H, 8.1; N, 5.0.

When the above synthetic sequence was repeated using *cis-dl*-2,4-dimethylcyclohexanone, *l*-cycloheximide, m.p. 114–115°, [α]_D²⁵ −33° (*c* 1.0, chloroform), was obtained. *Anal.* Found: C, 63.9; H, 8.2; N, 5.1. This was identical in all respects with the naturally occurring material.

This work represents a *total synthesis* of optically active I since *cis-dl*-II has been resolved previously.¹⁴ In addition it formally represents a total synthesis of *d*-naramycin-B and a new synthesis of *d*-isocycloheximide,^{14,15} since *l*-I has been isomerized to these two substances by Okuda, *et al.*¹⁶

A full paper dealing with this synthesis and the stereochemical problems involved will appear at a later date.

(12) Infrared evidence suggests that VI exists in the enolic form depicted! Thus, two conformers, VIa and VIb, present themselves for reduction, and Dreiding models suggest that VIb would be the one most easily reduced since it should present much less steric hindrance to the approach of the catalyst in the area of the molecule where reduction is taking place.

(13) Considerable difficulty was experienced in finding a protecting group for the side-chain hydroxylic group which would not be transferred easily to the ring hydroxyl by anchimeric assistance, but which could be subsequently hydrolyzed without destroying the acid- and base-sensitive aldol and glutarimide functions in I. The group in question filled these requirements.

(14) E. C. Kornfeld, R. G. Jones, and T. V. Parke, *J. Am. Chem. Soc.*, **71**, 150 (1949).

(15) A. J. Lemin and J. H. Ford, *J. Org. Chem.*, **25**, 344 (1960).

(16) T. Okuda, M. Suzuki, T. Furumai, and H. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **10**, 639 (1962).

THE DOW CHEMICAL COMPANY
EASTERN RESEARCH LABORATORY
FRAMINGHAM, MASSACHUSETTS

FRANCIS JOHNSON
N. A. STARKOVSKY
A. C. PATON
A. A. CARLSON

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Restricted Rotation in Aromatic Aldehydes

Sir:

The evidence¹ available suggests that benzaldehyde (I) is planar, presumably because of resonance interaction² of the type Ia ↔ Ib. This interaction should also give rise to an appreciable barrier to internal rotation about the C₁C_α bond; however, the magnitude

(1) E. A. Braude in E. A. Braude and F. C. Nachod, "Determination of Organic Structures by Physical Methods," Academic Press, Inc., New York, N. Y., 1955, p. 172; R. Bramley and R. J. W. LeFèvre, *J. Chem. Soc.*, 56 (1962).

(2) However, the resonance energies of benzene (36 kcal./mole) and of benzaldehyde (35 kcal./mole) obtained from combustion data are virtually the same [G. W. Wheland, "Resonance in Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1955, pp. 99, 108]. Dispersion forces may also stabilize the planar form; cf. the calculations of W. T. Simpson, *J. Am. Chem. Soc.*, **73**, 5363 (1951), on butadiene; see also R. S. Mulliken, *Tetrahedron*, **6**, 68 (1959), and W. F. Yates, *J. Phys. Chem.*, **65**, 185 (1961).