tially higher than the value (51°) reported by these authors.

Samples of II obtained directly from the thermal isomerization reaction have been stored under nitrogen in the refrigerator for several days without appreciable polymerization. Upon being exposed to the air, however, the triene polymerizes rapidly. When the partially polymerized material is exposed to air and rubbed with a spatula, it ignites, often with detonation.

Studies of the mechanism and scope of the thermal rearrangement reaction are underway.

Acknowledgment.—This work was supported by the National Science Foundation under Grant 25089.

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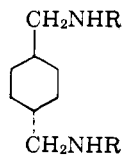
RECEIVED SEPTEMBER 5, 1963

A Novel Mode of Inhibition of Cholesterol Biosynthesis[1]

Sir:

We wish to report on a novel mode of interference with the endogenous synthesis of cholesterol. Evidence is reported herewith that *trans*-1,4-bis(2-dichlorobenzylaminomethyl)cyclohexane dihydrochloride (AY-9944)[2] (I) prevents the conversion of 7-dehydrocholesterol to cholesterol.

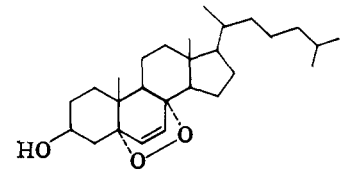


I, R = *o*-$ClC_6H_4CH_2$

In vitro, at a final concentration of 1×10^{-6} *M*, I inhibits the incorporation of 2-C^{14}-mevalonate into cholesterol[3,4] by liver homogenates[5] of rat (81),[6] dog (21), and monkey (59%). In contrast, at a final concentration of 1×10^{-5} *M*, which completely blocked incorporation of mevalonate into cholesterol, I did not significantly affect the synthesis from 2-C^{14}-mevalonate of (a) squalene[7] by rat[8] and trout[9] liver homogenates and (b) of lanosterol[10] by rat liver homogenates.[11]

In vitro, at a final concentration of 1×10^{-5} *M*, compound I had no effect on the conversion of 26,27-C^{14}-desmosterol to cholesterol by rat liver homogenates.[12]

Investigation of the serum of rats treated with I revealed the presence of "fast-acting" sterols[13] showing ultraviolet absorption bands characteristic of steroid homoannular 5,7-dienes.[14] This, together with the isolation from livers of rats treated with I of a "fast-acting" sterol which was identified as the transannular peroxide of 7-dehydrocholesterol (II)[15] indicates that I inhibits the hepatic synthesis of cholesterol by interfering with the conversion of 7-dehydrocholesterol to cholesterol. This was corroborated by the fact that I inhibits the reduction of the Δ^7-bond of 7-dehydrocholesterol by rat liver homogenates when assayed according to Kandutsch.[16] Our findings indicate that *7-dehydrocholesterol is a precursor on the major pathway of the hepatic synthesis of cholesterol*[17] and is not its metabolite.[14b]



II

Given orally to experimental animals AY-9944 significantly lowers their serum cholesterol levels.

Acknowledgment.—We acknowledge, with appreciation, the discussions with Dr. K. Wiesner.

(1) Part IV of a series entitled "Agents Affecting Lipid Metabolism." Part III: D. Dvornik and M. Kraml, *Proc. Soc. Exptl. Biol. Med.*, **112**, 1012 (1963).

(2) Dr. L. Humber, to be published.

(3) *Cf.* P. A. Tavormina and M. Gibbs, *J. Am. Chem. Soc.*, **79**, 758 (1957).

(4) Isolated with addition of carrier, brominated [*cf.* L. Fieser, *ibid.*, **75**, 5421 (1953)], and crystallized to radiochemical purity.

(5) All liver homogenates were prepared by the technique of N. L. R. Bucher, *ibid.*, **75**, 498 (1953) and incubated [*cf.* N. L. R. Bucher and K. McGarrahan, *J. Biol. Chem.*, **222**, 1 (1956)] in the presence of cofactors as described by G. Popjak, R. H. Cornforth, and K. Clifford, *Lancet*, I, 1270 (1960).

(6) In liver homogenates of rats treated with I, 2 hr. after one oral dose of 10 μmoles/kg., incorporation of mevalonate into cholesterol was depressed by 92% and 48 hr. later by 55%.

(7) Isolated with addition of carrier and purified by chromatography, thiourea adduct formation, and dissociation [*cf.* O. Isler, R. Rüegg, L. Choppard-dit-Jean, H. Wagner, and K. Bernhard, *Helv. Chim. Acta*, **39**, 897 (1956)], followed by hexahydrochloride formation [*cf.* I. M. Heilbron, E. D. Kamm, and W. M. Owens, *J. Chem. Soc.*, 1630 (1926)] which was crystallized to radiochemical purity [*cf.* R. G. Langdon and K. Bloch, *J. Biol. Chem.*, **200**, 129 (1953)].

(8) *Cf.* J. W. Cornforth, R. H. Cornforth, G. Popjak, and T. Youhotsky-Gore, *Biochem. J.*, **69**, 146 (1958).

(9) *Cf.* E. Schwenk, G. J. Alexander, and C. A. Fish, *Arch. Biochem. Biophys.*, **58**, 37 (1955). We thank Mr. Bernard Vincent, Department of Games and Fisheries, Province of Quebec, for a gift of gray trout.

(10) Isolated with addition of carrier, acetylated, brominated, and crystallized to radiochemical purity [*cf.* D. A. Lewis and J. F. McGhie, *Chem. Ind.* (London), 550 (1956)].

(11) To accumulate labeled lanosterol, 1×10^{-3} *M* arsenite was added [*cf.* M. L. Moller and T. T. Tchen, *J. Lipid Res.*, **2**, 342 (1961)].

(12) *Cf.* D. Steinberg and J. Avigan, *J. Biol. Chem.*, **235**, 3127 (1960).

(13) Color development in the Liebermann–Burchard reaction after 1.5 min. (*cf.* P. R. Moore and C. A. Baumann, *ibid.*, **195**, 615 (1952)].

(14) (a) L. Dorfman, *Chem. Rev.*, **53**, 47 (1953); (b) E. I. Mercer and J. Glover, *Biochem. J.*, **80**, 552 (1961).

(15) We thank Dr. J. Bagli for an authentic sample of II.

(16) A. A. Kandutsch, *J. Biol. Chem.*, **237**, 358 (1962).

(17) *Cf.* (a) A. A. Kandutsch and A. E. Russell, *ibid.*, **235**, 2256 (1960); (b) D. S. Goodman, J. Avigan, and D. Steinberg, *ibid.*, **238**, 1287 (1963); (c) M. E. Dempsey, J. D. Seaton, and R. W. Trockman, *Fed. Proc.*, **22**, 529 (1963).

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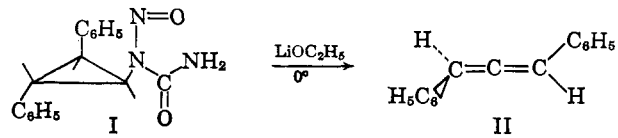
RECEIVED SEPTEMBER 4, 1963

The Conversion of (−)-*trans*-2,3-Diphenylcyclopropane Carboxylic Acid to (+)-1,3-Diphenylallene

Sir:

We wish to report our finding that the reaction of optically active N-nitroso-N-(*trans*-2,3-diphenylcyclopropyl)urea (I) with lithium ethoxide alcoholate in heptane gives 1,3-diphenylallene[1] (II) which exhibits a high degree of rotation. (Crude product $[\alpha]^{25}D$ +419°; recrystallized material, $[\alpha]^{24}D$ +797°.)



I II

This observation constitutes not only a potentially general method for the synthesis of optically active allenes[2] (in which the resolving "handle" has been

(1) For other examples of allene formation from cyclopropane precursors, see: W. M. Jones, M. H. Grasley, and W. S. Brey, Jr., *J. Am. Chem. Soc.*, **85**, 2754 (1963), and references cited therein.

(2) For a review of other methods for generating optically active allenes, see E. L. Eliel, "The Stereochemistry of Carbon Compounds," McGraw-Hill Book Company, Inc., New York, N. Y., 1962, Chapter 11.

removed in the course of the reaction) but also a potential method for relating the absolute configurations of allenes to the configurations of their cyclopropane progenitors.[3]

The optically active nitrosourea[4] (I) was synthesized from optically active *trans*-2,3-diphenylcyclopropane carboxylic acid[5] by the same reaction scheme used for the synthesis of the 2,2-diphenyl analog.[1]

Treatment of the nitrosourea with lithium ethoxide (alcoholate) in heptane at 0° gave a hydrocarbon-soluble material that showed an ultraviolet spectrum that was identical with that of pure, racemic 1,3-diphenylallene prepared by the method of Jacobs and Danker.[6] From the ultraviolet spectrum, the yield of allene was calculated to be 79.2%. Evaporation of the hydrocarbon-soluble fraction gave a pale yellow granular solid, m.p. 35–42°. The infrared spectrum (KBr) of this material was identical with that of pure racemic material (KBr) except for the presence of a low intensity broad absorption centering at about 5.9 μ and the absence of a distinct peak at 11.3 μ (overlapping with a peak at 11.4 μ). Assuming the crude pale yellow solid is pure allene, the material showed $[\alpha]^{25}D$ +419° (ethanol). Recrystallization of this material from pentane gave white needles, m.p. 52–56°; $[\alpha]^{24}D$ +797° (ethanol).[7] The infrared (KBr) and ultraviolet spectra of this material were identical with the corresponding spectra of pure racemic 1,3-diphenylallene except between 11.0 and 11.5 μ.

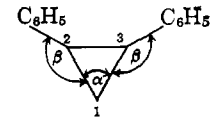
The precursor or precursors to the allene have not yet been conclusively determined. However, by analogy to the base-induced decomposition of N-nitroso-N-(2,2-diphenylcyclopropyl)urea,[1] the reaction scheme most likely involves initial formation of the diazocyclopropane that can either decompose in a concerted fashion to the allene or proceed first to the cyclopropylidene that can then collapse to give the allene.

It is naturally of interest to speculate as to the origin of the optical activity in the allene as well as to attempt to examine what the retention of asymmetry means with regard to the more intricate details of the mechanism of formation of the allene from its precursors. Some insight into both of these problems can be gained by considering individually the various structural and geometrical changes that must occur during the conversion of either the diazocyclopropane or the cyclopropylidene to the allene. Four changes of real significance must take place. The bond between C_2 and C_3 (Scheme I) must break, the β-angle must increase from about 150 to 180°, the α-angle must increase from 60 to 180°, and, finally, planes A and B (Scheme II) must rotate 90° with respect to each other.

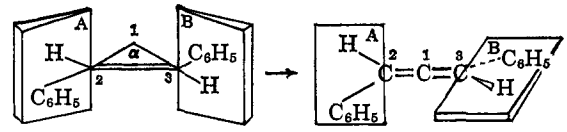
Now, if the α- and β-angles increase to 180° before planes A and B rotate, the allene must be inactive, since this sequence entails a symmetrical intermediate. Thus, the mere fact that the allene is optically active demonstrates unequivocally that rotation of planes A and B must at least begin before α and β increase to 180°.

Furthermore, the fact that rotation of the two planes precedes collinearity of carbons 1, 2, and 3 immediately suggests that the source of the optical activity of the allene resides in steric effects that affect the direction of rotation of the planes A and B. Thus,

SCHEME I



SCHEME II



rotation of plane A or plane B in a counterclockwise direction leads to one enantiometric allene. However, either of these changes brings a phenyl group into opposition with the phenyl and hydrogen described by the other plane. On the other hand, rotation of plane A or plane B in a clockwise direction leads to the other enantiomer and brings a hydrogen in one plane into opposition with the phenyl and hydrogen in the other plane. This analysis suggests that this system might well be useful for relating the absolute configurations of optically active allenes with their cyclopropane precursors. However, the situation is not quite as straightforward as it appears at first glance. Thus, the major portion of the optically active allene might well result from the concerted collapse of a diazocyclopropane in which a nitrogen molecule partially bonded to C-1 could conceivably present a steric effect that is in opposition to the effect described before. We are presently engaged in experiments that we hope will clarify this point and will demonstrate whether or not this is truly a potentially general method to relate the absolute configurations of allenes to optically active cyclopropane acids.

Acknowledgment.—The authors are indebted to the National Science Foundation and to the U. S. Army Research Office (Durham) for their generous support of this work.

(3) For references to configurational correlations between optically active allenes and their nonallenic precursors, see ref. 2, pp. 315–316.

(4) Correct analyses were obtained for all new optically active compounds except for the nitrosourea which was unstable enough at room temperature to preclude sending away for analysis.

(5) L. A. D'yakonov, M. I. Komendantov, Fu Gui-siya, and G. L. Korichev, *J. Gen. Chem. USSR*, **32**, 917 (1962).

(6) T. L. Jacobs and D. Danker, *J. Org. Chem.*, **22**, 1424 (1957).

(7) 1,3-Diphenylallene of low optical purity has been previously prepared by Jacobs and Danker[6] ($[\alpha]^{22}D$ +2.48; −1.24° (CCl_4)).

(8) Alfred P. Sloan Fellow.

(9) N.S.F. summer research participant, 1962.

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RECEIVED AUGUST 14, 1963

Enzymatic Stereospecifity in the Dehydrogenation of Stearic Acid to Oleic Acid[1]

Sir:

The enzyme-catalyzed conversion of stearic acid to oleic acid (*cis*-Δ^9-octadecenoic acid) shows positional and geometrical specificity. We now have found that in *Corynebacterium diphtheriae* this enzyme system has the further property of selectively removing one particular hydrogen from each pair of hydrogens at carbon atoms 9 and 10 of the polymethylene chain.

This investigation has been made possible by the finding that methyl 9-hydroxyoctadecanoate,[2] prepared by catalytic hydrogenation of the naturally occurring Δ^{12}-9-hydroxyoctadecenoic acid,[3] is optically active and has the same sign of rotation as synthetic methyl 9D-hydroxyoctadecanoate.[4] We have also

(1) Supported by grants-in-aid from the National Science Foundation, the United States Public Health Service, the Life Insurance Medical Research Fund, and the Eugene Higgins Trust Fund of Harvard University.

(2) A generous gift from Dr. A. J. Fulco.

(3) F. D. Gunstone, *J. Chem. Soc.*, 1274 (1952).

(4) We are indebted to Professor Gunstone for a gift of synthetic 9D-hydroxyoctadecanoic acid. Our finding that both the "natural" and the synthetic samples are levorotatory confirms the assignment of the D-configuration to the "natural" acid made by Baker and Gunstone on the basis of mixture melting point data: C. D. Baker and F. D. Gunstone, *J. Chem. Soc.*, 759 (1963).