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.

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DEPARTMENT OF CHEMISTRY
OHIO UNIVERSITY
ATHENS, OHIO

WILLIAM D. HUNTSMAN
HARRY J. WRISTERS

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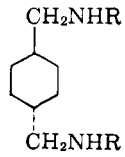
A Novel Mode of Inhibition of Cholesterol Biosynthesis[1]

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.

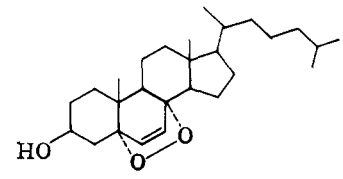


I, R = *o*-$ClC_6H_4CH_2$

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 inter-



II

fering 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]

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).

DEPARTMENT OF BIOCHEMISTRY
AYERST RESEARCH LABORATORIES
MONTREAL, CANADA

D. DVORNIK
M. KRAML
J. DUBUC
M. GIVNER
R. GAUDRY

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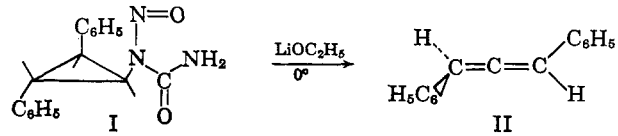
The Conversion of (−)-*trans*-2,3-Diphenylcyclopropane Carboxylic Acid to (+)-1,3-Diphenylallene

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.