synthesis,[15] this point remains to be defined for β-sitosterol.

(15) L. W. Parks, *J. Am. Chem. Soc.*, **80**, 2023 (1958).

(16) Postdoctoral trainee in the training program for Steroid Biochemistry.

DEPARTMENT OF CHEMISTRY
CLARK UNIVERSITY
WORCESTER, MASSACHUSETTS
AND
THE WORCESTER FOUNDATION FOR EXPERIMENTAL BIOLOGY
SHREWSBURY, MASSACHUSETTS

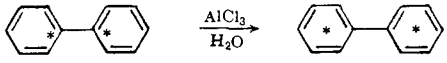
MARGARET CASTLE[16]
GEORGE BLONDIN[16]
WILLIAM R. NES

RECEIVED MAY 16, 1963

The Rearrangement of Diphenyl[1]

Sir:

We wish to report unequivocal evidence for the water promoted, aluminum chloride induced intramolecular rearrangement of the benzene rings in diphenyl

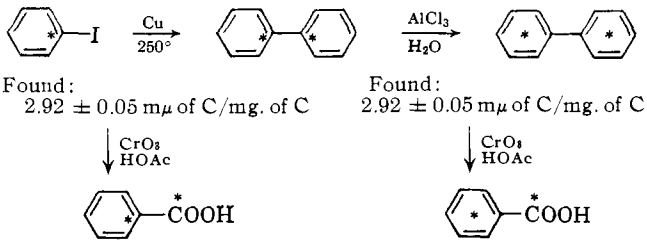


(1)

When diphenyl-1,1′-C^{14}, prepared in 80% yield *via* an Ullmann reaction[2] on iodobenzene-1-C_1^{14}, was heated to 100° for 30 min. with 10 mole % of aluminum chloride and 1 mole % of water, the radioactivity, originally localized at the two connecting carbons, had been randomly distributed. Recovered active diphenyl was also shown to be randomized when the reaction was carried out for 12 hr. in a refluxing benzene solution. The degradation method used is outlined in Scheme I.

SCHEME I

SYNTHESIS AND DEGRADATION OF ACTIVE DIPHENYL



Calcd. for no rearrangement: 4.99 mμ of C/mg. of C
Found: 4.95 ± 0.06 mμ of C/mg. of C

Calcd. for complete rearrangement: 2.92 mμ of C/mg. of C
Found: 2.92 ± 0.05 mμ of C/mg. of C

The view that the reaction is intramolecular[3] is supported by the following facts: (1) The inactive benzene used in the solvent experiments was devoid of activity at the end of a run within the precision of our assay methods.[4] (2) A rearrangement carried out with inactive diphenyl in benzene-1-C_1^{14} yielded diphenyl having an activity indicating less than 0.001% intermolecularity.

The isomerizations in benzene were carried out by refluxing 0.5 g. of diphenyl-1,1′-C^{14} in 10 ml. of benzene containing 50–100 mg. of aluminum chloride and 5–10 mg. of water for various periods of time. The diphenyl, isolated after quenching the reaction mixture and evaporating the benzene, was oxidized[5] by stirring for 5 hr. at 40–50° with 3.0 g. of chromium trioxide in 35 ml. of glacial acetic acid, furnishing benzoic acid in 35–47% yields.

As a secondary check on the exchange, radioactive benzene alone was treated with the aluminum chloride–water catalyst. Carrier diphenyl was added after the reaction had been quenched. The isolated and purified diphenyl had an activity indicating a benzene to diphenyl conversion of less than 0.01%.[6]

Our experimental data do not allow us to distinguish between a hydrogen abstraction[7] mechanism and a proton addition[8] mechanism to develop the positive charge on the *ortho* carbon. The latter pathway followed by a 1,2-shift and proton loss seems to us the simplest explanation, although other mechanisms cannot be excluded at this stage. If a proton addition mechanism is operative during this facile rearrangement of diphenyl in the presence of a water promoted Lewis acid, some doubt is thrown on the stability of polyaryls[9] under conditions of electrophilic substitution reactions. Furthermore it seems to us that the significance of isomer distribution in diphenyl[10] would require some re-examination.

(1) Research performed under the auspices of the U. S. Atomic Energy Commission.

(2) The benzoic acid obtained by oxidation of the unrearranged diphenyl-1,1-C^{14} showed no loss in specific activity. This indicated *inter alia* that the Ullmann reaction proceeds without rearrangement. The iodobenzene-1-C_1^{14} was prepared in 76% yield from aniline-1-C_1^{14} (*cf.* H. J. Lucas and E. R. Kennedy, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 351) supplied by Nuclear Research Chemicals, Inc., Orlando, Florida.

(3) G. A. Olah and M. W. Meyer, *J. Org. Chem.*, **28**, 1912 (1963).

(4) D. R. Christman, M. E. Day, P. R. Hansell, and R. C. Anderson, *Anal. Chem.*, **27**, 1935 (1955). The authors are indebted to Dr. D. R. Christman and Mrs. C. T. Paul for the activity assays.

(5) J. C. Colbert and C. L. Hensley, *J. Am. Chem. Soc.*, **62**, 3257 (1940).

(6) The yield of diphenyl from benzene in the absence of diphenyl may well be greater than in the presence of diphenyl, the latter presumably complexing better with the catalyst than benzene.

(7) A. Streitwieser, Jr., and L. Reif, *J. Am. Chem. Soc.*, **82**, 5003 (1960).

(8) R. H. Allen, *ibid.*, **82**, 4856 (1960); *cf.* H. C. Brown and C. R. Smoot, *ibid.*, **78**, 2176 (1956); H. Steinberg and F. L. J. Sixma, *Rec. trav. chim.*, **81**, 185 (1962); E. Ünseren and A. P. Wolf, *J. Org. Chem.*, **27**, 1509 (1962).

(9) P. Kovacic and F. W. Koch, *ibid.*, **28**, 1864 (1963).

(10) M. J. S. Dewar, T. Mole, D. S. Urch, and E. W. T. Warford, *J. Chem. Soc.*, 3572 (1956); L. M. Stock and H. C. Brown, *J. Am. Chem. Soc.*, **84**, 1242 (1962); R. Baker, R. W. Bott, and C. Eaborn, *J. Chem. Soc.*, 2136 (1963).

(11) Visiting professor at Brookhaven National Laboratory, June 14, 1963–September 4, 1963, from University of Groningen, Holland.

DEPARTMENT OF CHEMISTRY
BROOKHAVEN NATIONAL LABORATORY
UPTON, L. I., NEW YORK

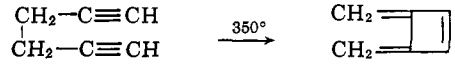
HANS WYNBERG[11]
A. P. WOLF

RECEIVED AUGUST 28, 1963

3,4-Dimethylenecyclobutene by Thermal Rearrangement of 1,5-Hexadiyne

Sir:

We have found that 1,5-hexadiyne (I) rearranges at 350° giving 3,4-dimethylenecyclobutene (II) in 85% yield. The reaction is conducted in a flow system, using



I II

a Pyrex tube (12 mm. × 65 cm.) packed with glass helices as the reaction vessel. The diyne is vaporized and swept through the reaction tube in a stream of nitrogen. It is important that the hydrocarbon be vaporized before it reaches the reaction zone. If the liquid is allowed to drop directly onto the helices, it ignites each time a drop hits, and after a short time a vigorous reaction occurs filling the apparatus with soot. This trouble is not experienced when the hydrocarbon is vaporized first. Complete conversion of I occurs at 350° using a hydrocarbon feed rate of 6 ml./hr. and a nitrogen flow of 2400 ml./hr. The v.p.c. tracing of the product shows a single peak.

The infrared and ultraviolet spectra are in agreement with those reported for II by Blomquist and Maitlis.[1] The boiling point which we observe (72°) is substan-

(1) A. T. Blomquist and P. M. Maitlis, *Proc. Chem. Soc.*, 332 (1961).

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.

DEPARTMENT OF CHEMISTRY
OHIO UNIVERSITY
ATHENS, OHIO

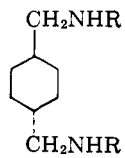
WILLIAM D. HUNTSMAN
HARRY J. WRISTERS

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.

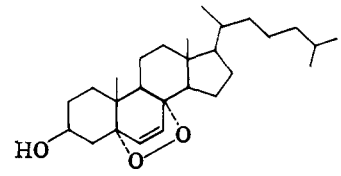


I, R = *o*-$ClC_6H_4CH_2$

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).

DEPARTMENT OF BIOCHEMISTRY
AYERST RESEARCH LABORATORIES
MONTREAL, CANADA

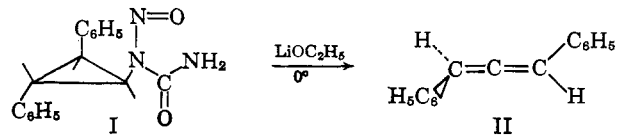
D. DVORNIK
M. KRAML
J. DUBUC
M. GIVNER
R. GAUDRY

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.