2-Chloro-1-phenylindene from 1,1-Dichloro-*trans*-2,3-diphenylcyclopropane

ROBERT ARMEN MAGARIAN*▲, STUART MELTON‡, and GERRY NATARELLI†

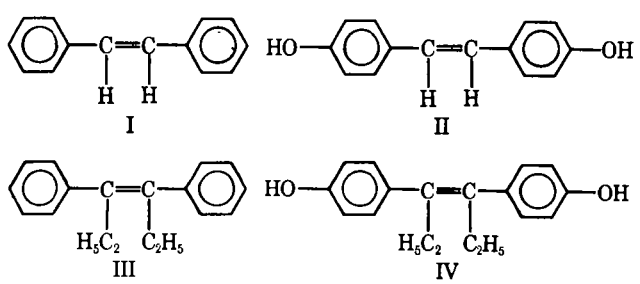
Abstract □ An indene derivative was isolated from the reaction of *trans*-stilbene and sodium trichloroacetate in diglyme and tetrachloroethylene. The chemical and spectral studies indicate that the product isolated is 2-chloro-1-phenylindene, which originated from 1,1-dichloro-*trans*-2,3-diphenylcyclopropane *via* an ionized rearrangement.

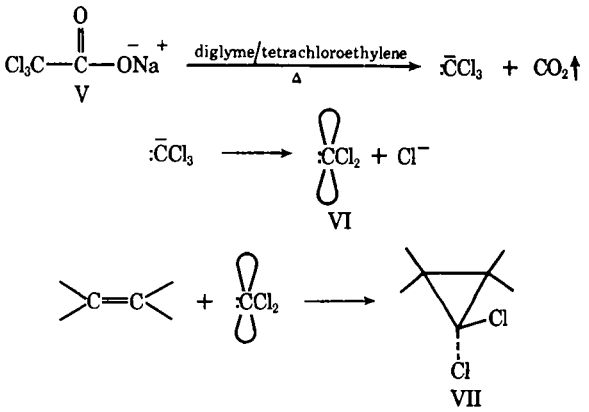
Keyphrases □ 1,1-Dichloro-*trans*-2,3-diphenylcyclopropane—intermediate in the formation of 2-chloro-1-phenylindene from *trans*-stilbene and sodium trichloroacetate in diglyme and tetrachloroethylene □ 2-Chloro-1-phenylindene—synthesis from *trans*-stilbene and sodium trichloroacetate in diglyme and tetrachloroethylene *via* 1,1-dichloro-*trans*-2,3-diphenylcyclopropane □ *trans*-Stilbene reaction with sodium trichloroacetate—isolation, PMR identification of 2-chloro-1-phenylindene □ PMR spectroscopy—identification, 2-chloro-1-phenylindene □ Receptor theory—cyclopropyl rigid ring system, geometric isomers of stilbene, isolation and identification of 2-chloro-1-phenylindene

Several workers have used rigid ring systems to lock functional groups into a desired conformation in order to elucidate specific receptors (1, 2). Similarly, our interest in the cyclopropane moiety arose from our work in the area of estrogenic "receptor" elucidation. This interest prompted us to look at stereospecific methods of synthesis for the preparation of cyclopropyl derivatives of the geometric isomers of stilbene (I), 4,4′-dihydroxystilbene (II), 1,2-diethylstilbene (III), and diethylstilbestrol (IV).

The interesting reaction between a carbene and an olefin described by Fieser and Sachs (3) was selected for the preparation of the isomeric cyclopropanes. This reaction involves a thermal decomposition of sodium trichloroacetate (V) in diglyme and tetrachloroethylene to generate dichlorocarbene (VI) (Scheme I).

The reaction is monitored by the evolution of carbon dioxide, and the dihalocarbene is known to be a singlet methylene that adds stereospecifically to olefins, producing a *gem*-dichlorocyclopropane (VII). In view of the ease with which dihalocarbenes can be generated in the presence of olefins, it would appear that the application of these reagents to the preparation of cyclopropanes would be limited only by the nucleophilic character of the double bond (4–6). Prior to the use of this procedure, we became aware of the weak nucleophilic character of





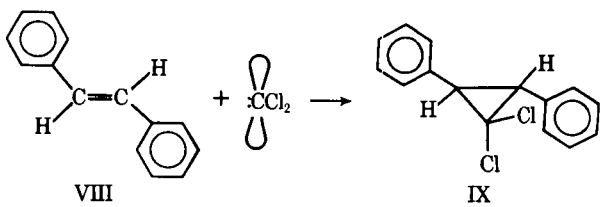
Scheme I

the double bond in *trans*-stilbene when no products were isolated after a number of trials using the Simmons–Smith (7) reaction and upon employing diazomethane as one reagent in the liquid phase (8–10). The primary interest in the *gem*-dichlorocyclopropane VII was to establish only the generality of the stereospecific reaction as a method for preparing intermediates to be reduced to their corresponding cyclopropane derivatives using sodium in methanol (11).

To test this reaction, the simplest olefin in the series, *trans*-stilbene (VIII), was selected in hopes of producing 1,1-dichloro-*trans*-2,3-diphenylcyclopropane (IX) (Scheme II).

EXPERIMENTAL[1]

The method of synthesis was adapted from the procedure described in the literature (3). A mixture of 7.2 g. (0.04 *M*) of *trans*-stilbene[2], 14.5 g. (0.078 *M*) of sodium trichloroacetate (3), 10 ml. of diglyme[3], and 20 ml. of tetrachloroethylene[3] in a 250-ml. round-bottom flask, fitted with a condenser and mercury trap, was heated near boiling (120°). The mixture was stirred magnetically with continued heating until the evolution of carbon dioxide ceased (4 hr.). The very dark-brown reaction mixture was cooled, 90 ml. of 95% ethanol was added, and the mixture was filtered by suction. The cake containing an organic solid was washed with cold methanol



Scheme II

[1] Melting points were taken on a Thomas-Hoover capillary melting-point apparatus and are corrected. The microanalysis was carried out by Midwest Microlab Ltd., Indianapolis, IN 46226

[2] Aldrich.

[3] Fisher.

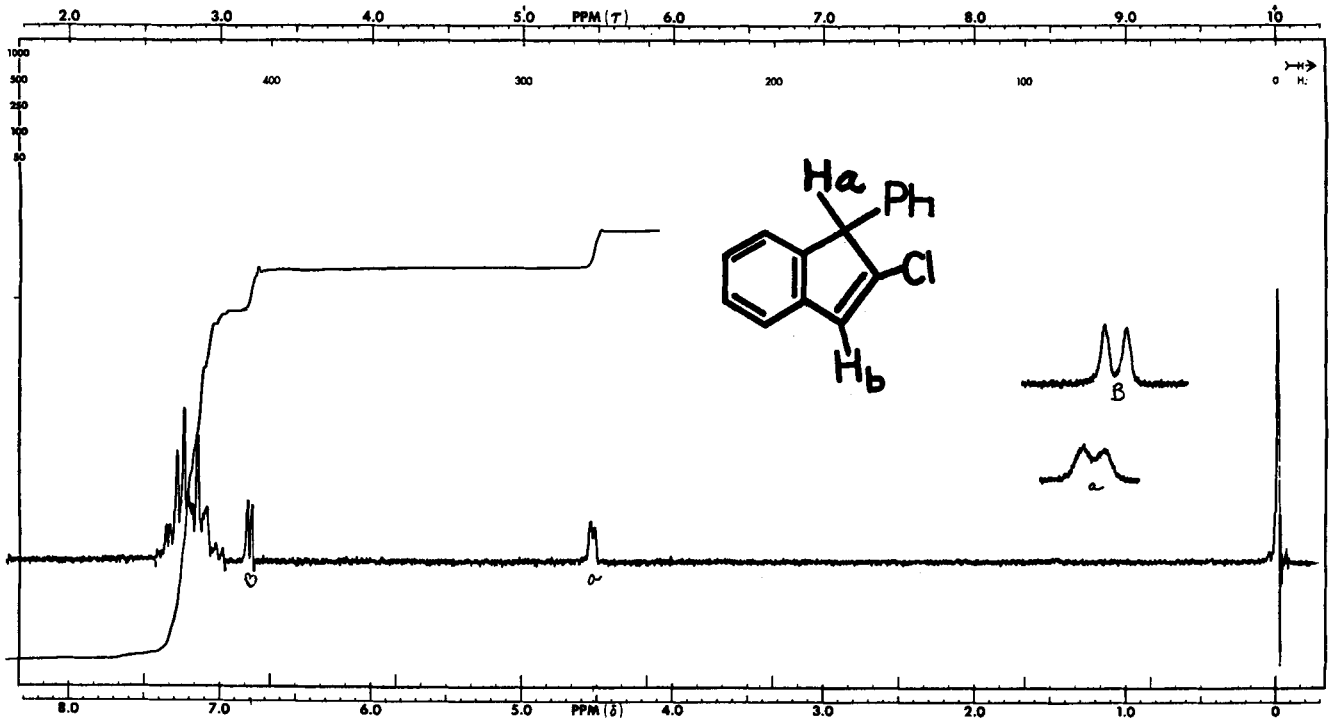


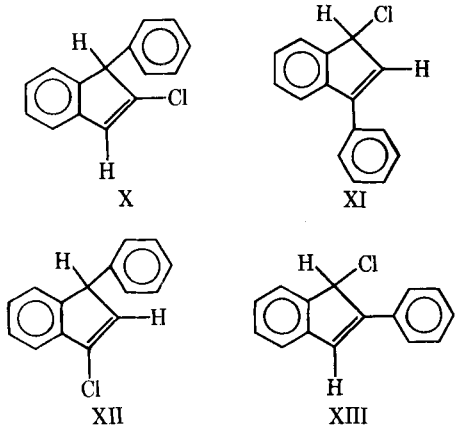
Figure 1—*PMR spectrum of 2-chloro-1-phenylindene.*

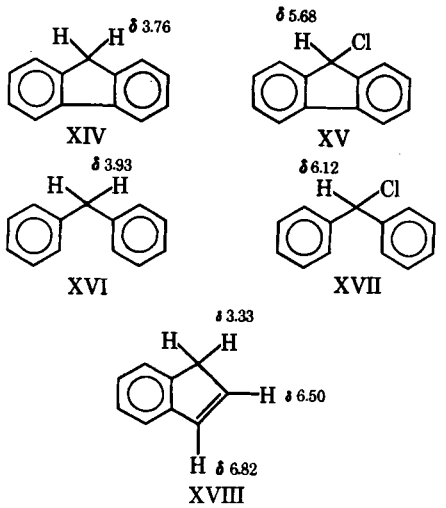
to remove the dark mother liquor and to give unreacted *trans*-stilbene (3.0 g.). The filtrate was evaporated on a rotary evaporator, leaving a thick, dark-brown oil, which yielded additional *trans*-stilbene (0.5 g.) when cooled thoroughly in an ice bath. The solid was filtered by suction and the brown filtrate, when stripped of its liquid using a rotary evaporator, afforded 12.0 g. of a reddish-brown oil. This oil was fractionally distilled, yielding a light-yellow oil (139°/2 mm.). Refractionation of the yellow oil provided 1.5 g. (33% based on *trans*-stilbene) of white solid, m.p. 61.5–62.0°, from methanol.

Anal.—Calc. for $C_{15}H_{11}Cl$: C, 79.48; H, 4.89; Cl, 15.64. Found: C, 79.50; H, 5.06; Cl, 15.53.

RESULTS AND DISCUSSION

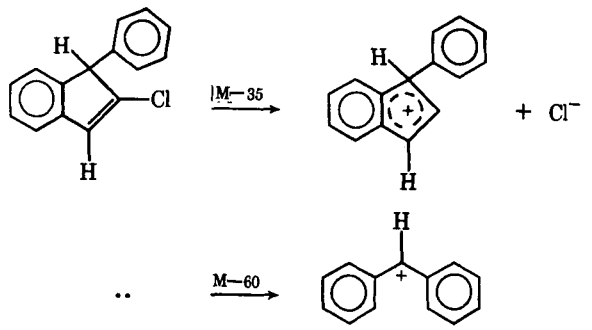
A reddish-brown oil was isolated from the reaction mixture, which was spotted on TLC[4] to monitor any unreacted olefin; four spots[5], one of which was *trans*-stilbene, were detected when developed in carbon tetrachloride and viewed under UV light (3660 Å). Upon fractional distillation under vacuum, a yellow oil[6] was collected which tested for chlorine in alcoholic silver nitrate solution and reacted with potassium permanganate solution, but it did not discolor the solution of bromine in carbon tetrachloride. The reaction of isomeric *gem*-dibromocyclopropanes with warmed alcoholic silver nitrate solution appears in the literature (12). The yellow oil was refractionated under vacuum, and a colorless liquid was collected which solidified upon exposure to air. A pungent odor of hydrogen chloride was noted in the condenser. The solid product[7] failed to react when warmed with alcoholic silver nitrate and with bromine in carbon tetrachloride solution, but it reacted with the potassium permanganate solution. The empirical formula, $C_{15}H_{11}Cl$ (mol. wt. 226.7), arrived at from the elemental analysis indicated that a hy-





Scheme III— PMR models showing relevant chemical shifts

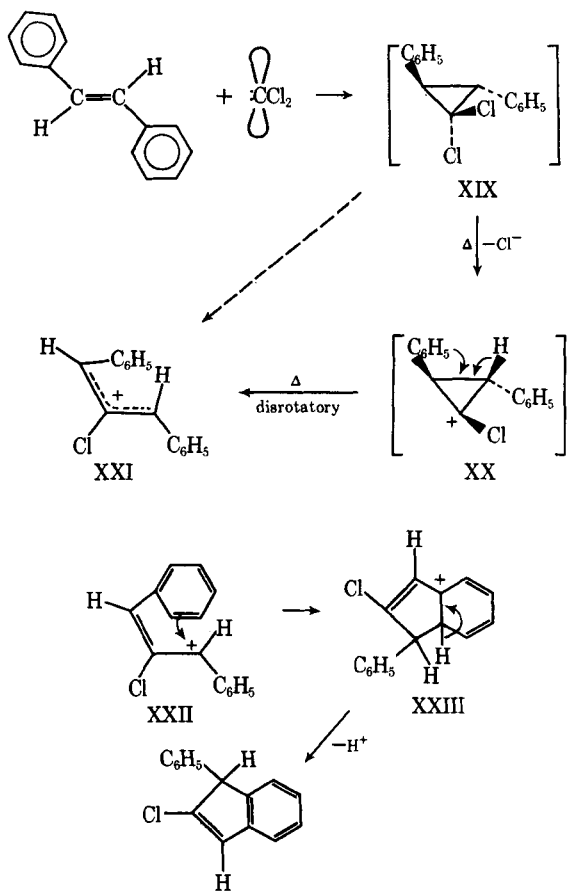
[4] Eastman silica gel F chromagram.
[5] R_f 0.17, 0.42, 0.17 (*trans*-stilbene, yellowish orange), and 0.85 (purple).
[6] Remnants of the oil changed from light yellow to orange when left in clear glass containers.
[7] Reacts with plastic lids and containers, resulting in a yellow discoloration.



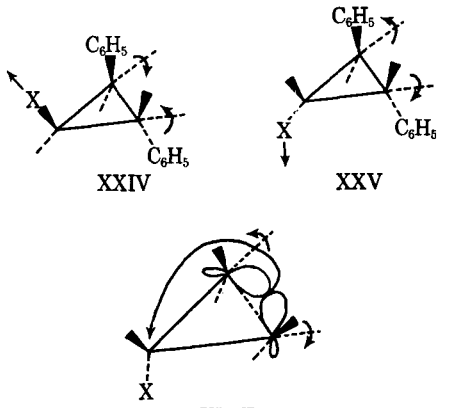
Scheme IV

drogen and chlorine atom were removed from the expected product, IX[8]. The chemical and spectral data led to the determination of the structure as 2-chloro-1-phenylindene (X).

The IR spectrum[9] (KBr disk) showed absorptions at 3060 (aromatic C—H), 3030 (C=C—H), 2875 (C—H), 1455 and 1495 (benzene ring), and 735 and 760 (*o*-disubstituted benzene) cm.$^{-1}$. The proton magnetic resonance (PMR) spectrum[10] ($CDCl_3$) (Fig. 1) is in disagreement with cyclopropane proton signals, which appear at an unusually high field at 0.22 p.p.m. except when substituted by electronegative groups, bringing about increased chemical shifts based upon decreased magnetic screening of the cyclopropane protons that remain (13, 14). Seyferth *et al.* (15) reported the PMR absorption of Structure IX[11]. In Fig. 1 the resonance absorption for the



Scheme V



XXIV XXV XXVI

benzylic proton (H_a) appears as a doublet at 4.55 p.p.m., and the vinylic proton (H_b) doublet is at 6.80 p.p.m. The aromatic multiplet is downfield at 7.20 p.p.m., and the integration ratio is 9:1:1. The expected coupling constant (J_{ab}) range for the spin–spin interaction between benzylic and vinylic protons is 0.5–2.0 Hz. (16, 17), and the observed is an agreeable 1.7 Hz.

There are five reasonable isomeric structures of the indene X, of which only one (XI)[12] was reported previously (18). Only four of the isomers are listed below, since indenes bearing equivalent geminal protons at C_1 need not be considered. Even if their geminal protons were nonequivalent, the coupling constant would be from 12 to 15 Hz., much too large for the indene X (19). Isomers XI and XII have vicinal protons at C_1—C_2 and an expected coupling constant from 4 to 10 Hz., which is much larger than the observed (16, 17). Structure X is the proposed compound; the chemical shift of the benzylic proton of XIII, although having the same coupling constant as X, would be further downfield at approximately 6.0 p.p.m., as inferred from the PMR models shown in Scheme III[13]. Structure XIII was ruled out also on mechanistic grounds. The PMR spectrum of the indene X is in close agreement with the chemical shift of the vinylic proton absorption for the unsubstituted indene XVIII.

The mass spectrum (nitrogen internal standard) exhibited a molecular ion peak at *m/e* 227. The two expected *m/e* fragment peaks were seen: 167 (M − 60), the loss of C_2HCl from the parent ion, and 192 (M − 35) from the loss of Cl (Scheme IV).

CONCLUSION

The evidence cited here supports the formation of 2-chloro-1-phenylindene, and the mechanism for its formation is illustrated in Scheme V. Although any mechanistic interpretation must be regarded as speculative without additional data, one plausible explanation is presented based upon modern electronic theory (20).

The departure of a chloro group from the 1,1-dichloro-2,3-diphenylcyclopropane (XIX) intermediate to form the cyclopropyl cation XX and the bond-breaking electrocyclic reaction to give the benzylic cation XXI are concerted. This is apparent when it is realized that the 2,3-bond is broken by either inward (XXIV) or outward (XXV) rotation. The electron density of that bond shifts either below or above (XXVI) the plane, depending on the mode of rotation, and is then available for backside displacement of the chloro group. This reaction is a normal S_N2 displacement of the leaving group by the electrons of the backbone sigma bond in the cyclopropyl ring.

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[8] m.p. 39–40.5° (15).

[9] IR spectrum was recorded on a Beckman IR-20A spectrophotometer.

[10] PMR spectrum was determined on a Varian A-60-A spectrometer, using tetramethylsilane as an internal standard.

[11] Aromatic protons (10 H's) at 7.37 p.p.m. and methylene protons (2 H's) at 3.15 p.p.m.

[12] m.p. 70–71°.

[13] Sources: XIV, XV, and XVII, "The Sadtler Standard Spectra," Sadtler Research Laboratories, Philadelphia, Pa.; XVI and XVII, Werner Brugel, "Nuclear Magnetic Resonance Spectra and Chemical Structure," Academic, New York, N. Y., 1967; and XVIII, Varian Associates, "High Resolution NMR Spectra Catalog," vol. 1, 1962; R. M. Silverstein and G. C. Bassler, "Spectrometric Identification of Organic Compounds," 2nd ed., Wiley, New York, N. Y., 1967.

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ACKNOWLEDGMENTS AND ADDRESSES

Received April 26, 1971, from the **Department of Medicinal Chemistry, College of Pharmacy, University of Oklahoma, Norman, OK 73069*, and † *Mallinckrodt Chemical Co., St. Louis, MO 63160*

Accepted for publication April 12, 1972.

Presented to the Medicinal Chemistry Section, APhA Academy of Pharmaceutical Sciences, San Francisco meeting, March 1971.

Supported in part by a Mead Johnson grant and in part by NSF Grant GY-5896, National Science Foundation, Washington, D. C.

The authors are indebted to Dr. Alan Marchand, Chemistry Department, University of Oklahoma, for his helpful suggestions, and to Dr. Jim McChesney, School of Pharmacy, University of Kansas, for the mass spectrum.

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Application of Salivary Salicylate Data to Biopharmaceutical Studies of Salicylates

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Abstract □ Concentrations of salicylic acid in saliva and plasma were measured in three subjects following the administration of 650 mg. of aspirin. Concentrations of salicylic acid in saliva were proportional to concentrations in plasma, saliva–plasma ratios in the three subjects being 0.0293 ± 0.0013, 0.0303 ± 0.0033, and 0.0394 ± 0.0043. The saliva–plasma ratios were independent of the plasma concentrations of salicylic acid observed in this study, the maximal concentration being 50 mcg./ml. Measurement of salivary concentrations of salicylic acid may be a useful technique in the evaluation of different formulations of aspirin or other salicylates. In the present study, delayed release of aspirin from enteric-coated tablets was demonstrated from the time course of the concentration of salicylic acid in saliva.

Keyphrases □ Salivary excretion—relationship between salicylic acid concentration in saliva and plasma after aspirin administration, man □ Salicylic acid levels after aspirin administration—relationship between saliva and plasma concentrations, man □ Absorption, aspirin—relationship between salicylic acid concentration in saliva and plasma, man □ Aspirin absorption—relationship between salicylic acid concentration in saliva and plasma, man

The secretion of drugs and other foreign compounds in saliva is well known. The salivary excretion of weak acids such as salicylate (1), sulfonamides (2, 3), and barbiturates (3, 4) has been investigated in some detail. Killman and Thaysen (2) found that the concentrations of several sulfonamides in human saliva were proportional to the concentration of the unbound drug in plasma. These observations indicated that measurement of concentrations of drugs in consecutive samples of saliva may be a useful technique in investigations of the kinetics of absorption and elimination of drugs, although difficulties may arise if the plasma binding characteristics of the drugs varied significantly during the time course of the experiments.

In the present study, the relationship between the concentrations of salicylic acid in saliva and plasma was investigated at various times after aspirin administration. Furthermore, the measurement of salicylic acid levels in serial samples of saliva was examined as a technique in the evaluation of aspirin preparations, although the different preparations were not evaluated thoroughly. The aim of the present work was to develop a technique that would obviate the need for collecting blood samples in some biopharmaceutical studies with salicylates. All studies were conducted using mixed saliva. It was considered that methods of collecting saliva should be as simple as possible if measurements of salivary levels of salicylic acid were to have practical value in the evaluation of different pharmaceutical formulations.