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Synthesis of Cyclopropyl Analogs of Stilbene and Stilbenediol as Possible Antiestrogens

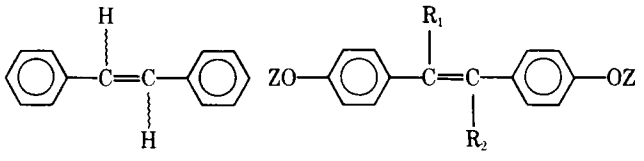
ROBERT A. MAGARIAN ˣ **and ERIC JOEL BENJAMIN** *

Abstract □ Conformationally rigid analogs of stilbene and stilbenediol were prepared *via gem*-dichlorocyclopropyl precursors utilizing two different synthetic methods: a two-phase catalytic method and an organomercurial method. These precursors were reduced to the corresponding cyclopropyl analogs using sodium and methanol. All compounds are being tested to discriminate between estrogenic and antiestrogenic activity, to determine estrogen binding ability, and to evaluate tissue culture anticancer activity.

Keyphrases □ Cyclopropyl analogs of stilbene and stilbenediol—synthesis as potential antiestrogens □ Stilbene and stilbenediol cyclopropyl analogs—synthesis as potential antiestrogens □ Antiestrogens, potential—synthesis of cyclopropyl analogs of stilbene and stilbenediol

A previous publication (1) discussed the cyclopropane moiety in connection with work on estrogen receptor elucidation. The preparation of *gem*-dichlorocyclopropyl analogs of the stilbene (I) and stilbenediol (II) series (Table I), using two different synthetic methods, and their subsequent reduction to the corresponding cyclopropyl analogs (Table II) are reported here.

Antiestrogens that arrest epithelial proliferation caused by estrogens in the uterus or vagina could have some utility in a particular uterine or vaginal cancer. Furthermore, certain antiestrogens may prove effective against other hormonal-dependent cancers such as breast cancer. Effective chemotherapeutic agents against such solid, hormone-sensitive tumors have not been fully developed and the duration of chemotherapeutic remissions is not as long lasting as those induced by endocrine manipulation.



I II

Currently, the compounds reported in Tables I and II are being tested to discriminate between their estrogenic and antiestrogenic activities and for their estrogen binding ability, and they are being evaluated in a tissue culture anticancer assay[1].

DISCUSSION

A two-phase catalytic method (2) and an organomercurial method (3–7) have proven effective as applied to olefins of low reactivity (*e.g.*, *trans*-stilbene) toward dichlorocarbenes generated by other procedures. Of practical significance is the fact that yields are usually high by these two routes.

The *gem*-dichlorocyclopropyl analogs of stilbene were prepared according to both methods, while the stilbenediols were subjected only to the latter mercurial method since the phenolic groups were sensitive to strong base and some stilbenediols were poorly soluble in chloroform. The *gem*-dichlorocyclopropane precursors listed in Table I were subsequently reduced with sodium metal and methanol (8, 9).

The general reaction developed by Simmons and coworkers (10–12) for the stereospecific synthesis of cyclopropane derivatives involves the treatment of olefins with diiodomethane and zinc–copper couple. This convenient method could have allowed omission of the reductive step; however, in spite of various modifications (13–17), this method does not consistently produce respectable yields when the olefins are weak nucleophiles. Olefins in which the nucleophilic character of the double bond has been reduced by electron-withdrawing groups should react less readily with carbenes than those in which the nucleophilic character has been increased by electron-donating groups (18–20).

Method A—All reports of the syntheses of *gem*-dihalocyclopropane derivatives have stressed the necessity of operating under strictly anhydrous conditions because of the rapid hydrolysis of dichlorocarbene. On the other hand, the method established by Makosza and Wawrzyniewicz (2) and improved by Dehmlow and Schonefeld (21, 22) (Scheme I) generates dichlorocarbene in the reaction among chloroform, a concentrated solution (50%) of sodium hydroxide, and a catalytic amount of triethylbenzylammonium chloride, thus allowing the preparation of *gem*-dichlorocyclopro-

[1] Tests are being performed by the Cancer Section, Oklahoma Medical Research Foundation, Oklahoma City, and the College of Pharmacy, University of Oklahoma, Norman, Okla.

Table I—*gem*-Dichlorocyclopropanes

Compound	R_1	R_2	R_3	R_4	Melting Point	Yield, % Method A	Yield, % Method B	Crystallization Solvent	Formula	Analysis[a], %	Calc.	Found
III	H	C_6H_5	C_6H_5	H	38–40°[b]	86	86	—[c]	$C_{15}H_{12}Cl_2$		—	—
IV	H	C_6H_5	H	Ph	51–52°	69	86	—[d]	$C_{15}H_{12}Cl_2$	C	68.45	68.32
										H	4.59	4.71
										Cl	26.94	26.66
V	H	C_6H_4—OCH_3	C_6H_4—OCH_3	H	88–89°	—[e]	52	Ethanol	$C_{17}H_{16}Cl_2O_2$	C	63.17	63.46
										H	4.99	5.13
										Cl	21.93	21.98
VI	CH_2CH_3	C_6H_4—OCH_3	C_6H_4—OCH_3	CH_2CH_3	111–112°	74.7	59[f]	Methanol	$C_{21}H_{24}Cl_2O_2$	C	66.49	66.21
										H	6.38	6.31
										Cl	18.69	18.78
VII	CH_2CH_3	C_6H_4—$OCOCH_3$	C_6H_4—$OCOCH_3$	CH_2CH_3	137–137.5°[g]	—[h]	72[f]	Ethanol	$C_{23}H_{24}Cl_2O_4$	C	63.45	63.28
										H	5.56	5.58
										Cl	16.29	16.43
VIII	CH_2CH_3	C_6H_4—OH	C_6H_4—OH	CH_2CH_3	147.5–148°		84[i]	Benzene	$C_{19}H_{20}Cl_2O_2$	C	64.96	64.81
										H	5.74	5.87
										Cl	20.19	20.01

[a] Elemental analyses were performed by Midwest Microlab. Ltd., Indianapolis, Ind. [b] Lit. (5, 6) mp 39–40.5°, 90%; lit. (21, 22) mp 39°, 96%. [c] Distillation. [d] Sublimation. [e] Method A was not used because of the insolubility of the olefin in chloroform. [f] Product was obtained by a double run; yields are based on the olefin. [g] See *Experimental* for melting-point behavior. [h] No reaction. [i] *gem*-Dichlorocyclopropane was obtained from the hydrolysis of VII.

pane derivatives with retention of configuration by the addition of dichlorocarbene to olefins.

Although the reaction is carried out in an aqueous medium, only a small fraction of the generated dichlorocarbene is hydrolyzed. This result may be explained by the catalytic mode of action of the quaternary ammonium compound (2). In concentrated sodium hydroxide solution, triethylbenzylammonium chloride is transformed into the hydroxide, which is insoluble in the reaction medium. Thus, the quaternary ammonium hydroxide migrates to the boundary between the aqueous and organic phases, where it reacts with chloroform to yield the quaternary ammonium derivative of the trichloromethyl anion. After diffusion into the organic phase, the derivative is transformed into dichlorocarbene and the ammonium chloride (Scheme II).

The dichlorocarbene reacts rapidly with the olefin present in the organic layer, whereas the quaternary ammonium chloride passes to the phase boundary and reenters the transformation cycle. Thus, dichlorocarbene is only slightly hydrolyzed. On the other hand, the high degree of dichlorocarbene utilization, despite the use of stoichiometric amounts of olefin and chloroform, is due to the fact that the quantity of dichlorocarbene that can be formed at one time is small and does not exceed the amount of the catalyst, *i.e.*, 1%. Consequently, dichlorocarbene is always confronted with a large excess of olefin.

This catalytic method seems to be the simplest procedure used so far, and the isolation of the resulting products appears to present no difficulties. The yields of the products obtained by this method are high, and no excess of the olefin is required; the ratio of olefin to chloroform is 2:1 to 1:2, depending on the availability of the olefin.

Excellent yields were obtained by this method for olefins that gave either no product or poor yields by other methods (8, 23–26). For example, the *gem*-dichlorocyclopropyl analog of *trans*-stilbene was not isolated using the Doering and Hoffman procedure (8); it was produced in 90% yield by the Seyferth *et al.* method (5, 6) and in 96% yield by the Dehmlow and Schonefeld method (21, 22). In most cases, high yields (74–86%) were obtained by this method when commercially available olefins were used.

This basic method, however, was not suited for diphenolic olefins such as diethylstilbestrol (II, $R_1 = R_2 = CH_2CH_3$, Z = H) due to salt formation from the concentrated sodium hydroxide solution. The enormous decrease in solubility of diethylstilbestrol in chloroform posed a problem. The diacetate ester of diethylstilbestrol, which was soluble in chloroform, was tried at room temperature, but it too was hydrolyzed to the salt and thrown out of organic phase and thus was unavailable for reaction with the dichlorocarbene.

Method B—Seyferth and coworkers (3–7) reported that phenyl(trihalomethyl)mercury compounds were very useful and versatile reagents as sources for dihalocarbenes; they reacted with olefins to give *gem*-dihalocyclopropanes in high yields. It was found that phenyl(bromodichloromethyl)mercury is far superior to phenyl(trichloromethyl)mercury in its reaction with olefins to produce exclusively 1,1-dichlorocyclopropanes (3). This mercurial route does not involve basic reaction conditions and does not proceed *via* nucleophilic intermediates (such as trichloroacetate or trichloro-

Scheme I

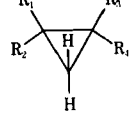


Table II—Cyclopropyl Analogs of Stilbene and Stilbenediol

Compound	R_1	R_2	R_3	R_4	Boiling Point/ Melting Point	Yield, %	Crystallization Solvent	Formula	Analysis[a], %	
									Calc.	Found
IX*a*	H	C_6H_5	C_6H_5	H	90° (0.01 mm)[b]	69[c]	—	$C_{15}H_{14}$	C 92.74 H 7.26	92.62 7.29
IX*b*	H	C_6H_5	H	C_6H_5	38–38.5°[d]	68[c]	Sublimation	$C_{15}H_{14}$	C 92.74 H 7.26	92.45 7.35
X	CH_2CH_3	C_6H_4—OH	C_6H_4—OH	CH_2CH_3	139–141°	70[e]	Benzene	$C_{19}H_{22}O_2$	C 80.81 H 7.85	81.00 7.66
XI	H	C_6H_4—OCH_3	C_6H_4—OCH_3	H	70.5–71.5°[f]	67[c]	Ethanol	$C_{17}H_{18}O_2$	C 80.28 H 7.13	80.01 7.19
XII	CH_2CH_3	C_6H_4—OCH_3	C_6H_4—OCH_3	CH_2CH_3	75–76°	77[c]	Methanol	$C_{21}H_{26}O_2$	C 81.25 H 8.44	81.41 8.45

[a] Elemental analyses were performed by Midwest Microlab. Ltd., Indianapolis, Ind. [b] Lit. (37–40) bp 144–145.3° (3.8 mm). [c] Obtained by sodium–methanol reduction of *gem*-dichlorocyclopropane. [d] Lit. (37–40) mp 38.0–38.5°. [e] Obtained by demethylation of dimethyl ether XII with boron tribromide. [f] Lit. (41) mp 70.5–71.5°.

methide ion); high yields at lower temperatures are obtained. The conversion of *cis*- and *trans*-olefins to *gem*-dichlorocyclopropanes proceeds with retention of configuration, as illustrated in the preparation of 1,1-dichloro-*trans*-2,3-diphenylcyclopropane in 90% yield from *trans*-stilbene (Scheme III).

The preparation of the Seyferth reagent, phenyl(bromodichloromethyl)mercury, is time consuming and tedious, involving anhydrous conditions. A special high-speed stirring apparatus is needed since both the phenylmercuric halide and the potassium *tert*-butoxide (in the form of its monosolvate) have very low solubility in the solvent system, and a large excess of the haloform (bromodichloromethane) is needed (3, 4). The monosolvate was found to produce high yields. Seyferth and Lambert (4) succeeded in eliminating the need for preparing potassium *tert*-butoxide–*tert*-butyl alcohol monosolvate by modifying the original procedure so that commercial potassium *tert*-butoxide could be substituted; however, the modified procedure resulted in 5% yields in this laboratory. Consequently, freshly prepared potassium *tert*-butoxide as the monosolvate with *tert*-butyl alcohol was used and yields increased to 69%. During the crystallization of this reagent, the first crop of crystals was contaminated with unchanged phenylmercuric chloride. Hence, the procedure was modified in this laboratory to prevent the contamination.

This was the method of choice in preparing the *gem*-dichlorocyclopropane derivatives of 4,4′-dimethoxystilbene (II, $R_1 = R_2 = H$, $Z = CH_3$), dimestrol (II, $R_1 = R_2 = CH_2CH_3$, $Z = CH_3$), and diethylstilbestrol diacetate (II, $R_1 = R_2 = CH_2CH_3$, $Z = COCH_3$). In the reactions using dimestrol or diethylstilbestrol diacetate, the PMR spectrum of the product indicated the presence of a considerable amount of unchanged olefin. Despite a twofold quantity of reagent, the yield did not improve. Since all attempts to separate the mixture failed, it was necessary to remove the precipitated phenylmercuric bromide and rerun the reaction using the original mixture (unused olefin and product) with additional amounts of the Seyferth reagent to induce the reaction to go to completion. Using this variation, Compounds VI and VII were obtained in 59 and 72% yields, respectively.

Minor limitations in the Seyferth method were reported (27). Phenyl(bromodichloromethyl)mercury reacted with carboxylic acids in benzene at 60–80° to give dichloromethyl esters in high yields, and the mercurial reagent reacted with alcohols to form dichloromethyl ethers and a mixture of products. Refluxing diethylstilbestrol with phenyl(bromodichloromethyl)mercury in benzene at 80° yielded a dark liquid from which no product was isolated. This promoted the use of dimestrol and diethylstilbestrol diacetate as substrates (Scheme IV).

$$CHCl_3 + (CH_3CH_2)_3\overset{+}{N}CH_2C_6H_5\ \overset{-}{O}H \rightleftharpoons \overset{-}{C}Cl_3(CH_3CH_2)_3\overset{+}{N}CH_2C_6H_5 + H_2O$$

$$\overset{-}{C}Cl_3(CH_3CH_2)_3\overset{+}{N}CH_2C_6H_5 \longrightarrow :CCl_2 + (CH_3CH_2)_3\overset{+}{N}CH_2C_6H_5\overset{-}{C}l$$

Scheme II

Reduction of aliphatic *gem*-dihalocyclopropyl compounds by sodium in wet methanol was originated by Doering and Hoffman (8). All *gem*-dichlorocyclopropanes involved in this study were reduced by this method (Scheme V) except VII and VIII. The 2,3-dialkyl derivatives were difficult to reduce, but increasing the equivalent amount of sodium metal and the quantity of methanol brought about good yields (Table II).

Being unable to reduce VII and VIII completely to the corresponding cyclopropyl analogs because of hydrolysis, it was of interest to search for a method that would bring about demethylation of XII to the analog X. Demethylation of aryl methyl ethers can be effected by a variety of reagents (28, 29), but usually it is necessary to employ high temperatures and acidic reagents. These conditions are too drastic for the cyclopropyl ring. Aromatic ethers have been cleaved at room temperature or lower using boron tribromide (30–32) (Scheme VI). The reactants are mixed in methylene chloride or *n*-pentane at −80°, and the mixture is allowed to warm to room temperature with continuous stirring for 15–20 hr. Methylene chloride is reported to have the most powerful solvent action and is preferred.

Even though cyclopropanes are sensitive to Lewis acids, boron tribromide was used successfully as a demethylating agent on XII.

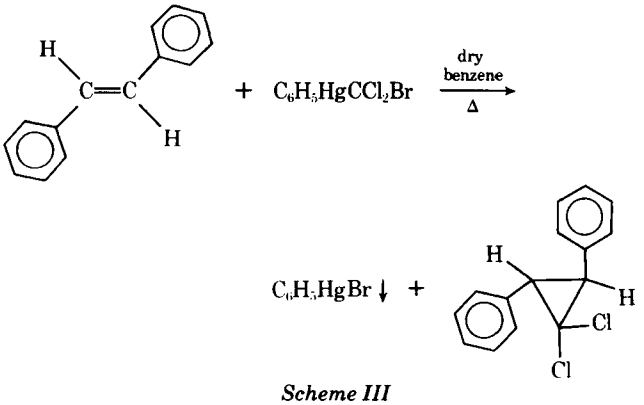
EXPERIMENTAL[2]

Phenyl(bromodichloromethyl)mercury—The procedure described by Seyferth and Lambert (4) was modified. Phenylmercuric chloride[3] (31.25 g, 0.1 mole) and bromodichloromethane[3] (25 g, 0.15 mole) were dissolved in 600 ml of tetrahydrofuran (dried with calcium hydride and distilled from lithium aluminum hydride[4]) in a flame-dried, 1-liter, three-necked flask. The flask was equipped with a mechanical stirrer, a nitrogen inlet tube, and an air condenser fitted with a mercury trap. The mixture was stirred and cooled in a dry ice–acetone bath. To a 500-ml conical flask in a dry box under anhydrous nitrogen was added 24 g (0.13 mole) of potassium *tert*-butoxide–*tert*-butyl alcohol monosolvate (33).

[2] Methods A and B are representative for the preparation of most compounds listed in Table I. Analyses and physical properties for all compounds are reported in Tables I and II. All IR spectra were recorded on a Beckman IR-20A, using polystyrene film as a standard to ascertain reproducibility. The NMR spectroscopic analyses were performed on a Varian T-60 MHz instrument. Most spectra were reported in either $CDCl_3$ or CD_3OD with tetramethylsilane as the internal standard. Mass spectra were taken with a Hitachi-RMU-6E mass spectrometer. Melting points were taken on a Hoover capillary melting-point apparatus and are uncorrected. Yields are based on pure samples. Research chemicals were of the purest grade and, in all cases, were used without further purification. Solvents were reagent grade and most were purchased from Eastman Chemical Co., Rochester, NY 14650

[3] Aldrich Chemical Co.

[4] Pflatz and Bauer, Flushing, NY 11368



Scheme III

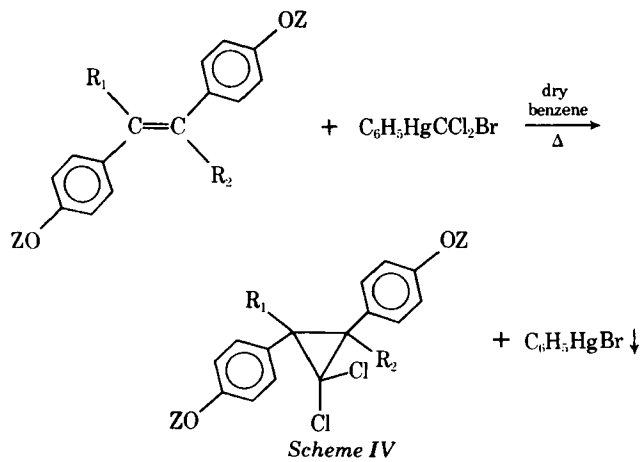
The conical flask was connected to the 1-liter three-necked flask by 2.54-cm (1-in.) Tygon tubing, and the contents were transferred to the reaction mixture slowly over 30 min. After addition, the mixture was stirred for 15 min at −55° and transferred to a 2-liter single-necked flask. The solvent was removed *in vacuo* (3 mm) through a dry ice–acetone trap without heating the flask until most of the solvent had evaporated. The remaining solvent was removed on a water bath at 20°, yielding a gray solid to which was added 500 ml of benzene.

The mixture was agitated until a partial solution was effected. Then 100 ml of water was added, the mixture was shaken vigorously, and 8.0 g of gray solid was collected. The layers were separated, and the aqueous phase was extracted with three 100-ml portions of benzene. All of the organic layers were collected, and benzene was removed *in vacuo*. To the white solid was added 500 ml of hot hexane–chloroform (3:1) solution in small portions with swirling and occasional heating on a steam bath until most of the solid dissolved. The flask was then placed at 0°, and 4.0 g of unreacted phenylmercuric chloride was collected on filter paper.

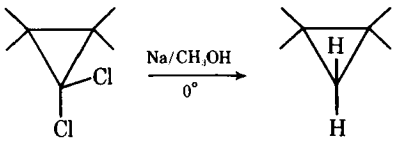
The clear filtrate was placed in the refrigerator at 0°. Crystals formed and were collected, yielding 22.74 g of white needles, mp 108–110° dec. Concentrating the mother liquor and placing the residue into the refrigerator yielded another 7.4 g of the mercurial reagent; the total yield was 30.14 g (68.5%).

1,1-Dichloro-*trans*-2,3-diphenylcyclopropane (III) (Method A)—Following the method reported (21, 22), 16.0 g (0.09 mole) of *trans*-stilbene[3] and 2.0 g (0.008 mole) of triethylbenzylammonium chloride[3] were dissolved in 300 g of chloroform contained in a 1-liter three-necked flask fitted with a mechanical stirrer, condenser, and dropping funnel. The flask was cooled in an ice water bath, and 200 g of ice-cold 50% sodium hydroxide solution was added dropwise. The mixture was stirred at 10–20° for 6 hr and then at room temperature for 2 days. The dark-brown mixture was diluted with 100 ml of water and filtered. Two layers were separated, and the aqueous layer was washed with three 50-ml portions of methylene chloride.

All organic extracts were combined, washed with water, and dried over anhydrous magnesium sulfate. The drying agent was filtered, and the chloroform was evaporated under reduced pressure,



Scheme IV



Scheme V

yielding 28 g of a dark-brown oil. Distillation of the crude oil at 140° (0.5 mm) gave 20 g (86%) of a light-yellow liquid, which solidified after several days at 5°, mp 38–40° [lit. (5, 6) mp 39–40.5°]. In subsequent reactions the distilled compound was passed through neutral alumina (activity I)[5], using petroleum ether (bp 30–60°) as the eluent to remove a small amount of the decomposed products; ν_{max} (mineral oil mull): 3095 (weak), 3060 (medium), 3025 (medium), 1610 (medium), 1503 (strong), 1220 (weak), 1175 (medium), 1108 (weak), 1095 (strong), 1060 (medium), 1035 (medium), 915 (weak), 865 (strong), 755 (strong), 743 (weak), and 695 (strong) cm^{-1}; $\delta_{60\ MHz}$ ($CDCl_3$): 3.15 (s, 2H) and 7.37 (s, 10H).

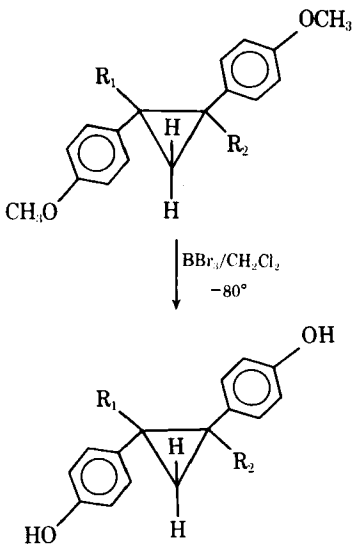
1,1-Dichloro-*cis*-2,3-diphenylcyclopropane (IV)—*Method A*—To a cold solution of 0.50 g (0.002 mole) of triethylbenzylammonium chloride and 110 g of chloroform in a three-necked flask was added 6.0 g (0.33 mole) of *cis*-stilbene[3], and the solution was stirred to dissolve the stilbene. A 50% sodium hydroxide solution (75 g) was added carefully through a dropping funnel; it was stirred at 10–20° for 6 hr and then at room temperature for 24 hr by means of a magnetic stirrer. The mixture was diluted with 100 ml of water, and a dark-brown chloroform layer separated. The aqueous phase was extracted with three 50-ml portions of methylene chloride, and the organic layers were collected and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* yielded 7.5 g of dark-brown oil.

The crude oil was purified by placing it on a 1.3 × 33-cm column of alumina (activity I)[5] and eluting with purified petroleum ether (bp 30–60°). A cream-colored oil, 6.0 g (69%), solidified at 0°, mp 48–49°.

The IR and NMR spectra were identical to those obtained using Method B.

Method B—According to the literature method (5, 6), 3.6 g (0.02 mole) of *cis*-stilbene[3] was added to 10.0 g (0.022 mole) of phenyl(bromodichloromethyl)mercury in benzene. After the resulting solution was refluxed with stirring under dry nitrogen and maintained at 82–88° in an oil bath for 1.5 hr with stirring, phenyl mercuric bromide precipitated (7.2 g, 92%) and the reaction mixture turned yellow. The relative proton absorption in the NMR spectrum showed small quantities of the unchanged olefin.

The mixture then was refluxed with stirring for an additional hour. The NMR spectrum of this mixture indicated that the olefin



Scheme VI

[5] E. Merck ag Darmstadt.

had reacted. Benzene was removed on a flash evaporator, yielding 6.5 g of crude product, which was dissolved in petroleum ether (bp 30–60°) and filtered to remove a small amount of white precipitate, mp 175° dec. The crude product was purified through a 2 × 18-cm column of neutral alumina (activity I)[5] using purified petroleum ether (bp 30–60°). A cream-colored oil was eluted, which solidified after standing in a refrigerator overnight. The solid had a melting-point range of 49–51° and weighed 4.5 g (86%).

An analytical sample was obtained by sublimation. The sublimator was kept at 45° (0.03 mm) in an oil bath while the inner cold finger was maintained at −5° by a cold water pump. The white needles melted at 50–51.5°; ν_{max} (neat): 3065 (medium), 3050 (strong), 1960 (weak), 1890 (weak), 1810 (weak), 1609 (medium), 1587 (weak), 1500 (strong), 1453 (strong), 1386 (weak), 1250 (weak), 1160 (weak), 1080 (medium), 1050 (medium), 1035 (medium), 1005 (weak), 958 (weak), 927 (medium), 840 (weak), 813 (strong), 754 (strong), 721 (weak), 700 (strong), 648 (weak), and 626 (weak) cm^{-1}; $\delta_{60\ MHz}$ ($CDCl_3$): 3.28 (s, 2H) and 7.18 (m, 10H).

1,1-Dichloro-*trans*-2,3-diethyl-2,3-(4,4′-dimethoxyphenyl)-cyclopropane (VI)—*Method A*—In 150 g of chloroform were dissolved 9.0 g (0.03 mole) of dimestrol[3] (34) and 0.75 g (0.0032 mole) of triethylbenzylammonium chloride in a three-necked flask, fitted with a condenser and a dropping funnel. The mixture was cooled in an ice water bath, and 75 g of a 50% sodium hydroxide solution was added dropwise while the mixture was agitated with a magnetic stirrer. Then the mixture was stirred at 10–20° for 6 hr and at room temperature for an additional 40 hr.

To the dark mixture was added 100 ml of water, and the solution was transferred to a separator. A dark-brown chloroform layer was separated after the phases were allowed to separate. The aqueous layer was neutralized with dilute hydrochloric acid and extracted with two 50-ml portions of chloroform. The chloroform extracts were combined and dried over anhydrous magnesium sulfate, and the drying agent was filtered. Evaporation of chloroform at reduced pressure gave 13.0 g of a dark-brown oil, which solidified on cooling.

This dark-brown solid was refluxed with 200 ml of petroleum ether (bp 30–60°) for 15–20 min, and the hot mixture was filtered from 2.5 g of a dark-brown solid, mp 170° dec. The light-brown solution was concentrated to about 40 ml at reduced pressure until crystallization occurred. After cooling and stirring, 8.0 g of a yellow solid was collected, mp 109–110°. Another 2.0 g was isolated from further concentration of the filtrate, bringing the total yield to 10 g.

This crude product was crystallized from 200 ml of hot methanol, yielding 8.5 g (74.7%) of light-yellow crystals, mp 110–111°. In a subsequent reaction, the product was purified using a neutral alumina column (activity I)[5] and *n*-hexane as the eluent.

Repeated crystallization from hot methanol gave an analytical sample, mp 111–112°; ν_{max} (CCl_4): 3038 (weak), 2975 (strong), 2940 (strong), 2920 (weak), 2880 (weak), 2835 (medium), 1613 (strong), 1580 (weak), 1508 (strong), 1463 (strong), 1445 (medium), 1415 (weak), 1375 (medium), 1333 (weak), 1293 (strong), 1245 (strong), 1175 (strong), 1110 (medium), 1090 (weak), 1035 (strong), 960 (weak), 925 (weak), 885 (weak), 845 (strong), 830 (strong), and 655 (medium) cm^{-1}; $\delta_{60\ MHz}$ ($CDCl_3$): 0.8 (t, 6H), 1.5 (m, 4H), 3.8 (s, 6H), and 7.12 (m, 8H).

Method B—A mixture of 3.4 g (0.011 mole) of dimestrol (34) and 5.5 g (0.013 mole) of phenyl(bromodichloromethyl)mercury in 35 ml of dry benzene was stirred and refluxed at 85–87° (oil bath) under dry nitrogen for 2.0 hr. During refluxing, phenylmercuric bromide precipitated and the reaction mixture turned yellow. The NMR spectrum showed a considerable amount of unchanged olefin. The mixture was stirred and refluxed for an additional 2 hr, but a considerable amount of unchanged olefin was still present as ascertained by NMR spectroscopy.

From the mixture was filtered 3.8 g (87%) of phenylmercuric bromide. Benzene was evaporated under reduced pressure, and a cream-colored solid (3.0 g) was stirred and refluxed under dry nitrogen with 3.0 g of phenyl(bromodichloromethyl)mercury in benzene for 2.0 hr. At this time no unchanged olefin was present in the NMR spectrum. The cream-colored solid (2.8 g) was dissolved in cold chloroform and filtered to remove a small amount of white precipitate. Evaporation of the chloroform and recrystallization of the cream-colored solid from hot methanol gave 2.5 g (59%) of white crystals, mp 110–112°. The NMR and IR spectra were identical to those obtained using Method A.

1,1-Dichloro-*trans*-2,3-diethyl-2,3-(4,4′-diacetoxyphenyl)-cyclopropane (VII) (Method B)—A mixture of 6.0 g (0.016 mole) of diethylstilbestrol[6] diacetate (35, 36) and phenyl(bromodichloromethyl)mercury (8.8 g, 0.02 mole) in 30 ml of dry benzene was refluxed for 5 hr (oil bath) with stirring, using a magnetic stirrer under dry nitrogen. The solution turned yellow and phenylmercuric bromide (6.65 g, 93%) precipitated. An NMR spectrum of the mixture indicated the presence of a small amount of unreacted olefin.

The benzene was evaporated *in vacuo*, and the solid collected was dissolved in 30 ml of dry benzene and refluxed with 4.4 g of phenyl(bromodichloromethyl)mercury under dry nitrogen at 87–90° for 3 hr. At this time, the NMR spectrum showed no unchanged olefin, and the mixture was warmed; 3.65 g (91%) of phenylmercuric bromide was collected. The solvent was removed under vacuum, yielding 6.5 g of a yellow solid.

The crude yellow compound was stirred with cold ethanol to dissolve the unreacted mercurial reagent. A light-yellow solid (5.5 g) was collected, mp 134–180° (melted with partial decomposition at 134° and another melt at 180°). Recrystallization from hot ethanol yielded 5.0 g (72%) of cream-colored crystals, mp 135–137°.

An analytical sample, mp 137–137.5°, was obtained from additional recrystallizations from hot ethanol; ν_{max} (CCl_4): 3050 (weak), 2290 (strong), 2948 (medium), 2795 (weak), 1775 (very strong), 1610 (weak), 1508 (strong), 1465 (medium), 1448 (weak), 1418 (weak), 1377 (strong), 1340 (weak), 1312 (weak), 1205 (very strong), 1170 (strong), 1115 (weak), 1092 (weak), 1022 (strong), 948 (medium), 915 (strong), 852 (strong), 705 (weak), 658 (weak), 618 (medium), and 565 (weak) cm^{-1}; $\delta_{60\ MHz}$ ($CDCl_3$): 0.8 (t, 6H), 1.53 (m, 4H), 2.3 (s, 6H), and 7.28 (q, 8H).

1,1-Dichloro-*trans*-2,3-diethyl-2,3-(4,4′-dihydroxyphenyl)-cyclopropane (VIII)—In 50 ml of methanol on a steam bath was dissolved 4.35 g (0.01 mole) of VII with stirring. After complete solution was obtained, 10 g of 15% sodium hydroxide solution was added dropwise to the warm solution with stirring for 10 min. Then the solution was poured over an ice water bath with vigorous stirring. This mixture was neutralized carefully with 7 ml of 36% HCl. The gum which appeared was collected on a filter paper, dissolved in 80 ml of hot benzene, and left at 37° for crystallization. White needles, mp[7] 143–145° dec, 2.95 g (84%), were obtained.

An analytically pure sample, mp 147.5–148° dec.[7] (with melting) was obtained by a second recrystallization from hot benzene; ν_{max} (KBr): 3400 (strong and broad), 3040 (weak), 2980 (medium), 2940 (weak), 2880 (weak), 1610 (strong), 1600 (strong), 1505 (strong), 1435 (strong), 1380 (strong), 1333 (strong), 1295 (weak), 1230 (strong), 1170 (strong), 1110 (medium), 1088 (weak), 1030 (weak), 1015 (medium), 965 (weak), 934 (medium), 895 (weak), 835 (strong), 789 (weak), 750 (weak), 670 (medium), 630 (weak), 560 (medium), and 498 (weak) cm^{-1}; $\delta_{60\ MHz}$ ($CDCl_3$ + CD_3OD): 0.80 (t, 6H), 1.50 (q, 4H), 3.80 (s, 2H), and 7.03 (m, 8H).

1,1-Dichloro-*trans*-2,3-(4,4′-dimethoxyphenyl)cyclopropane (V) (Method B)—To 150 ml of dry benzene (distilled with calcium hydride) under nitrogen was dissolved 2.4 g (0.01 mole) of 4,4′-dimethoxystilbene (light brown in color, mp 210°) with stirring (magnetic bar). The solution was refluxed using an oil bath and cooled to 85°. Then 6.0 g (0.014 mole) of phenyl(bromodichloromethyl)mercury was added, and the mixture was refluxed with stirring under nitrogen for 2.5 hr. The mixture turned yellow-brown with a large quantity of precipitate.

From the warm solution was filtered 3.3 g (68%) of light-brown phenylmercuric bromide. Benzene was removed under vacuum, yielding a waxy, dark-blue substance, which solidified on standing. The solid was stirred with 20 ml of chloroform to effect a partial solution, which was allowed to stand at 0° for 3 hr. The starting olefin was collected, 1.0 g (41%), and the filtrate was transferred to a 100-ml flask. The chloroform was evaporated *in vacuo*, leaving a yellow oil, which solidified.

To the solid was added 50 ml of hot ethanol; this mixture was heated on a steam bath to effect a partial solution and was filtered. The yellow filtrate was cooled slowly, and 1.7 g (52%) of light-yellow crystals, mp 86–88°, was collected. The crystals were dissolved in hot ethanol and treated with activated charcoal. After filtering

[6] Nutritional Biochemical Corp., Cleveland, OH 44128

[7] To obtain an accurate melting point, the bath was first heated to 135° and the capillary was introduced.

and cooling, 1.5 g (45%) of cream-colored needles, mp 88–89.5°, was obtained. An analytical sample was prepared from hot ethanol; ν_{max} (CCl_4): 3045 (weak), 3000 (medium), 2960 (medium), 2940 (weak), 2910 (weak), 2840 (medium), 1610 (strong), 1585 (weak), 1505 (strong), 1465 (medium), 1440 (medium), 1300 (medium), 1250 (very strong), 1175 (strong), 1105 (medium), 1070 (weak), 1045 (strong), 870 (strong), and 825 (medium) cm^{-1}; $\delta_{60\ MHz}$ (CCl_4): 2.95 (s, 2H), 3.7 (s, 6H), and 6.96 (q, 8H).

***trans*-1,2-Diphenylcyclopropane (IX*a*)**—The reductive method of Dale and Swartzentruber (9) was used. To a 250-ml three-necked flask, fitted with a dry ice–acetone condenser and a dropping funnel, were added 3.3 g (0.012 mole) of 1,1-dichloro-*trans*-2,3-diphenylcyclopropane (III) and 40 ml of ether. This solution was stirred (magnetic stirrer) and cooled in an ice water bath. Sodium metal (5.5 g, 0.25 g-atom) was added in small pieces as 60 ml of methanol–water (100:3.3 ml) was added dropwise. The sodium reacted after 2 hr, and a white solid was observed. When all of the sodium had reacted, 20 ml of water was added and the aqueous layer was extracted with two 30-ml portions of ether.

The aqueous phase was neutralized slowly and carefully on an ice–salt bath with concentrated hydrochloric acid and extracted with two 20-ml portions of ether. The ether extracts were dried over anhydrous magnesium sulfate and filtered. The solvent was evaporated at reduced pressure, and the light-yellow liquid was distilled and collected in three fractions at 0.01 mm.

Fraction 1 (bp 38–52°) was kerosene (used for storing sodium), fraction 2 (bp 67°) was a mixture, and fraction 3 (bp 90–92°) yielded 1.6 g (69%) of 1,2-diphenylcyclopropane.

An analytical sample was obtained by refractionation, bp 90° (0.01 mm) [lit. (37–40) mp 15.3°, bp 144–145.3°(3.8 mm)]; ν_{max} (neat): 3065 (medium), 3030 (strong), 2938 (medium), 2860 (weak), 1948 (medium), 1875 (weak), 1795 (weak), 1605 (very strong), 1585 (medium), 1495 (very strong), 1450 (strong), 1280 (weak), 1212 (strong), 1183 (medium), 1158 (weak), 1118 (strong), 1072 (strong), 1030 (strong), 1002 (weak), 989 (weak), 940 (medium), 905 (strong), 840 (weak), 775 (medium), 750 (strong), and 695 (very strong) cm^{-1}; $\delta_{60\ MHz}$ ($CDCl_3$): 1.4 (m, 2H), 2.15 (m, 2H), and 7.18 (s, 10H).

***cis*-1,2-Diphenylcyclopropane (IX*b*)**—A solution of 2.0 g (0.008 mole) of IV and 30 ml of ether in a 250-ml three-necked flask, fitted with a dry ice–acetone condenser, was stirred (magnetic stirrer) in an ice water bath. Sodium metal (6.9 g, 0.3 g-atom) was added in small pieces over 1.5 hr, and 60 ml of wet methanol (2 ml of water) was introduced slowly through a dropping funnel with stirring (magnetic stirrer). After all of the sodium metal reacted, 20 ml of water was added and the aqueous layer was extracted with two 30-ml portions of ether.

The aqueous phase was neutralized slowly with concentrated hydrochloric acid on an ice–salt bath and extracted with two 30-ml portions of ether. The ether extracts were dried over anhydrous magnesium sulfate and filtered. Evaporation of ether at 30° under vacuum yielded 1.5 g of a yellow oil, which solidified when left at 0°. Sublimation at 40–50° (0.04–0.05 mm) with the cold finger at −40° yielded 1.0 g (68%) of white needles, mp 38–38.5° [lit. (37–40) mp 38–38.5°]; ν_{max} (neat): 3015 (strong), 1950 (medium), 1880 (weak), 1805 (weak), 1603 (strong), 1580 (weak), 1493 (strong), 1443 (strong), 1380 (weak), 1362 (medium), 1200 (medium), 1160 (medium), 1110 (weak), 1073 (strong), 1030 (strong), 915 (medium), 833 (medium), 775 (medium), 760 (medium), 720 (medium), 690 (medium), and 625 (medium) cm^{-1}; $\delta_{60\ MH_z}$ ($CDCl_3$): 1.42 (m, 2H), 2.5 (t, 2H), and 7.0 (s, 10H).

1,2-Diethyl-*trans*-1,2-(4,4′-dimethoxyphenyl)cyclopropane (XII)—To 150 ml of ether in a 1-liter three-necked flask, fitted with a dry ice–acetone condenser, dropping funnel, and mechanical stirrer, was added 8.34 g (0.02 mole) of VI. To this stirred mixture was added 40 g (1.7 g-atom) of sodium metal in small portions over 3.5 hr, along with 300 ml of wet methanol (10 ml of water), which was introduced slowly through a dropping funnel.

After all of the sodium metal had reacted, 100 ml of water was added slowly and carefully and the aqueous layer was extracted with two 50-ml portions of ether. The aqueous phase was neutralized with concentrated hydrochloric acid slowly on an ice–salt bath and extracted twice with 50 ml of ether. Ether extracts were collected and dried over anhydrous magnesium sulfate and filtered. Evaporation of ether *in vacuo* yielded 8.4 g of a yellow-brown oil, which solidified on standing at 0°. The crude compound was dissolved in hot methanol, treated with activated charcoal, filtered, and allowed to remain at 37° until crystals formed. Light-yellow crystals were obtained in four different crops[8], totaling 5.25 g (77%), mp 75–78°.

An analytical sample was obtained through sublimation at 70° (0.03 mm), mp 75–76°; ν_{max} (CCl_4): 3030 (weak), 2985 (medium), 2955 (strong), 2935 (medium), 2870 (weak), 2835 (weak), 1605 (strong), 1575 (weak), 1503 (strong), 1455 (medium), 1435 (medium), 1368 (weak), 1300 (weak), 1285 (medium), 1235 (very strong), 1165 (strong), 1103 (medium), 1063 (weak), 1033 (strong), 825 (strong), 692 (weak), and 608 (medium) cm^{-1}; $\delta_{60\ MHz}$ ($CDCl_3$): 0.6 (m, 6H), 0.95 (s, 2H), 1.48 (m, 4H), 3.78 (s, 6H), and 7.03 (q, 4H); mass spectrometry M^+: *m/e* 310.

1,2-Diethyl-*trans*-1,2-(4,4′-dihydroxyphenyl)cyclopropane (X)—A reported demethylation procedure (30–32) was followed; 3.1 g (0.01 mole) of XII was dissolved in 60 ml of anhydrous methylene chloride (dried and distilled from anhydrous calcium hydride) contained in a 250-ml, flame-dried, single-necked flask fitted with a dropping funnel with a calcium chloride drying tube. The single-necked flask was placed in a dry ice–acetone bath (−80°); then 4.7 g (0.019 mole) of boron tribromide[3], which was weighed in the hood and quickly diluted with 60 ml of dry methylene chloride and transferred to the dropping funnel, was added dropwise to the dimethyl ether solution over 10–15 min while the mixture was stirred (magnetic stirrer).

After 15 min, the cooling bath was removed and the reddish mixture was stirred at room temperature for 20 hr. The resulting pale-brown mixture was placed in an ice water bath and decomposed slowly with 100 ml of water. The organic material was extracted with two 100-ml portions of ether, and the combined ether layers were extracted with 150 ml of 2 *N* sodium hydroxide solution.

The alkaline solution was neutralized with dilute hydrochloric acid and extracted with ether. The ether was washed with water, dried over anhydrous magnesium sulfate, and filtered. Evaporation of the ether *in vacuo* yielded a pale-brown oil, which was dissolved in hot chloroform, treated with activated charcoal, filtered, and cooled, yielding 1.98 g (70%) of white crystals, mp 138–140°.

Recrystallization from hot benzene provided an analytical sample, mp 139–141°; ν_{max} (KBr): 3300 (broad), 3043 (weak), 2960 (medium), 2872 (weak), 2792 (weak), 2074 (weak), 1890 (medium), 1764 (weak), 1607 (strong), 1592 (strong), 1507 (strong), 1432 (strong), 1347 (strong), 1307 (weak), 1292 (weak), 1222 (strong), 1164 (weak), 1097 (medium), 1067 (medium), 1034 (medium), 1007 (medium), 963 (weak), 952 (weak), 922 (weak), 892 (weak), 860 (weak), 827 (strong), 764 (weak), 734 (weak), 672 (weak), 612 (weak), and 522 (weak) cm^{-1}; $\delta_{60\ MHz}$ (CCl_4–CD_3OD): 0.6 (m, 6H), 0.95 (s, 2H), 1.55 (m, 4H), 2.55 (s, 2H), and 6.98 (q, 8H); mass spectrometry M^+: *m/e* 282.

***trans*-1,2-Bis(*p*-methoxyphenyl)cyclopropane (XI)**—The method reported by Doering and Hoffman (8) was followed; 1.6 g (0.005 mole) of V and 6.0 g (0.26 g-atom) of sodium metal were added to 60 ml of wet methanol in 30 ml of ether. A light-yellow oil (1.2 g), which solidified when absolute ethanol was added, was obtained. The mixture was heated on a steam bath and filtered. The solution was allowed to cool slowly and was stored at 0° overnight. A white solid (0.42 g), mp 66–68°, was collected. The filtrate was concentrated by evaporation and placed into a refrigerator. Another 0.6 g of white crystals, mp 68–70°, brought the total yield to 1.02 g (78%).

Sublimation at 70–75° (0.05 mm) with the cold finger at −5° (ammonium chloride–sodium nitrate–sodium chloride–ice–water mixture) yielded 0.86 g (67%) of a white solid, mp 70.5–71.5° [lit. (41) mp 70.5–71.5°]; $\delta_{60\ MHz}$ ($CDCl_3$): 1.3 (M= 2H), 2.05 (m, 2H), 3.78 (s, 6H), and 6.95 (q, 8H).

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[8] Cooling of the concentrated solution at 0° caused separation of oil instead of crystals; therefore, it was necessary to crystallize first at room temperature and then at 10°. The concentration of the mother liquor gave an additional crop of crystals.

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Effect of pKb on Lipophilic Binding of Disopyramide Derivatives to Human Plasma

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Abstract □ The extent of plasma binding, the partition coefficient, and the pKb of 13 disopyramide derivatives were determined. The structural variation on the diisopropylaminoethyl group of disopyramide molecules influenced these physical parameters to varying degrees. Results demonstrated that the extent of interaction between drugs and human plasma was a linear function of their lipophilicity and inversely proportional to the magnitude of the pKb value.

Keyphrases □ Disopyramide derivatives—determination of plasma binding, partition coefficient and pKb, relationship between pKb and binding □ Lipophilic binding of 13 disopyramide derivatives to human plasma—relationship to pKb □ Plasma binding, 13 disopyramide derivatives—determination, relationship to pKb □ Partition coefficients, 13 disopyramide derivatives—determination

Previously, it was reported (1) that the extent of plasma binding for 20 disopyramide derivatives was linearly related to their lipophilicity, log (p.c.), as defined by the following relationship:

$$\log (D_b/D_f) = \log (D_b/D_f)_0 + \log (\text{p.c.}) \qquad \text{(Eq. 1)}$$