Estrogenic Triarylcyclopropanes

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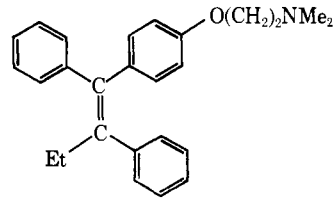
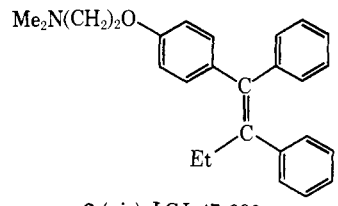
Complex endocrine activity has been reported in certain aminoalkoxytriarylethylenes.[1,2] I.C.I. 46474 (Nolvadex), the trans isomer of 1-*p*-(2-dimethylaminoethoxyphenyl)-1,2-diphenylbut-1-ene, is an example. In rats, this compound is a potent estrogen antagonist but also displays weak and atypical estrogenic activity. It is purely estrogenic in mice, as is the cis isomer (I.C.I. 47699) in both species.[3] The configuration of these isomers as structures 1 and 2 was first proposed on the basis of nmr and dipole moment measurements[4] and later confirmed by an X-ray crystallographic study of the cis isomer.[5,6]



1 (trans), I.C.I. 46,474



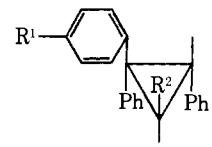
2 (cis), I.C.I. 47,699

It is known that a cyclopropane ring shares some of the chemical and spectroscopic properties of the ethylenic double bond, owing to the fact that the σ electrons in the C–C bond of the ring tend to exhibit the characteristics associated with the mobile π electrons.[7] For instance, chemical and spectroscopic observations (for leading references, see ref 8) show that the cyclopropane ring can have low s character[9] being described as sp^5 hybridized, in agreement with a recent theoretical summary[10] of the description of bonding in cyclopropanes.

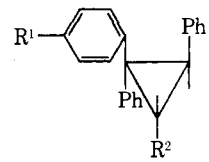
X-Ray crystallographic studies[5,6] have already established that the phenyl rings in the triarylbut-1-enes are twisted at an angle of approximately 60° to the plane of the ethylenic bond. Thus, since there is no conjugation between the phenyl rings and the ethylenic bonds (also confirmed by the appearance in the nmr spectra[4] of the unsubstituted phenyl groups in 1 and 2 as singlets) and therefore no conjugation between the phenyl rings themselves, then introduction of a cyclopropane should not affect any gross electronic distribution in the molecules but might be expected to produce some steric effect. The synthesis of compounds related to 1 and 2 in which the ethylenic double bond was replaced by a cyclopropyl residue was therefore undertaken to see if this variation affected the subtly different biological properties of the triarylbut-1-enes.

Synthesis. Cyclopropanes containing two or three aromatic residues have previously been synthesized by the reaction of a suitably substituted diazomethane with the appropriate olefin to form a pyrazoline which was subsequently decomposed by heating to produce the required cyclopropane. Thus, phenyldiazomethane[11] and phenylethylene gave 1,2-diphenylcyclopropane[12] while diphenyldiazomethane and phenylethylene yielded 1,1,2-triphenylcyclopropane.[13]

The use of phenyldiazomethane and a suitably substituted ethylene seemed to offer the best method of synthesizing desethyl analogs of 1 and 2 containing a cyclopropane ring. The reaction of phenyldiazomethane and 1,1-diphenylethylene was thus shown to give 1,1,2-triphenylcyclopropane (3) in higher yield (62%) than had been obtained by the alternative synthesis. However, much lower yields of the mixed isomers of the alkoxy (**4a,b,** 21%) and the required aminoalkoxy derivates (**5a,b,** 9.4%) were obtained by this route. Separation of the alkoxy isomers was effected by fractional crystallization while for the basic analogous isomers column chromatography was used. The *trans*-aminoalkoxy compound **5b** was obtained as a pale yellow oil and therefore the basic compounds were converted to citrates which were used in biological tests.



3a, $R^1 = H; R^2 = H$
4a, $R^1 = CH_3O; R^2 = H$
5a, $R^1 = (CH_3)_2NCH_2CH_2O; R^2 = H$
6a, $R^1 = (CH_3)_2NCH_2CH_2O; R^2 = CH_3$
7a, $R^1 = CH_3O; R^2 = CO_2C_2H_5$
8a, $R^1 = (CH_3)_2NCH_2CH_2O; R^2 = CO_2C_2H_5$



3b, $R^1 = H; R^2 = H$
4b, $R^1 = CH_3O; R^2 = H$
5b, $R^1 = (CH_3)_2NCH_2CH_2O; R^2 = H$
6b, $R^1 = (CH_3)_2NCH_2CH_2O; R^2 = CH_3$
7b, $R^1 = CH_3O; R^2 = CO_2C_2H_5$
8b, $R^1 = (CH_3)_2NCH_2CH_2O; R^2 = CO_2C_2H_5$

The identity of cis and trans isomers was established by nmr spectroscopy using the same criteria as had been applied to the assignment of the triarylethylenes.[4] Hence, that isomer in which the AA'BB' pattern in the aromatic region and the signal for the protons on the carbon adjacent to the aromatic ether oxygen appeared at higher field was assigned the trans isomer.

It was found that alkyl homologs of these compounds could not be synthesized. In principle methyl homologs of type **6a** and **6b** could be formed by reaction of a substituted 1,1-diphenyldiazomethane with *trans*-ethyl cinnamate and subsequent manipulation of the ester function. However, although the alkoxy esters **7a** and **7b** were formed from 1-(4'-methoxyphenyl)-1-phenyldiazomethane and *trans*-ethyl cinnamate, the required compounds **8a** and **8b** could not be produced since it was found that the intermediate pyrazoline could not be decomposed under any physical or chemical conditions. Further, the reaction of 1 and 2 with carbenes derived from methylene iodide or ethyl diazoacetate did not yield the required cyclopropyl analogs.

Biological. Compounds were evaluated for estrogenic activity by determining their capacity to induce vaginal cornification when given by mouth on three successive

† Dedicated to my former postdoctoral supervisor Professor Alfred Burger in recognition of his interest in cyclopropane derivatives.

Table I. Maximum Dose Levels Given in Biological Tests

Compd	Dose levels (as citrate) in mg/kg/day by mouth	
	Estrogenicity test	Antifertility test
3 citrate	10	5
4a citrate	10	5
4b citrate	1	5
5a citrate	25	10

days to ovariectomized rats. Their antifertility activity was assessed from their capacity to terminate early pregnancy when given by mouth on days 2, 3, and 4 of the pregnancy to rats. Details of the methods used are described elsewhere.[3]

Most of the compounds proved inactive in either sense at the highest dose levels at which they were tested. These doses are shown in Table I. Compound **5b** (citrate) was the exception. In a dose of 25 mg/kg/day it provoked full vaginal cornification in three out of six rats; in the antifertility test it was inactive at 1 mg/kg/day (four rats), but at 5 mg/kg/day it terminated pregnancy in each of four animals. The fact that this compound was fully active in terminating pregnancy at a dose level below that at which it was estrogenic suggests that its effect on pregnancy may have been due to inherent antiestrogenic activity. More extensive testing would be required to establish this conclusively and this was precluded by the amount of material available. In view of the very low potency of the compound both as an estrogen and in terminating pregnancy, where I.C.I. 46,474 is fully active at *ca.* 0.03 mg/kg/day, further pursuit of the matter seemed unjustified.

It thus appears that substitution of an olefinic double bond by a cyclopropyl group profoundly lowers the biological activity of triaryl derivatives although exact analogs of the most biologically interesting triarylbut-1-enes have yet to be synthesized.

Experimental Section

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Nmr spectra were determined on either Varian A-60 or HA-100 spectrometers in $CDCl_3$ or CCl_4 solution (internal Me_4Si) with chemical shifts given in parts per million on the δ scale. Microanalyses were determined using a Technicon CHN analyzer or Pregl, CH, and Coleman N analyzers and were within ±0.4% of the theoretical values.

1,1,2-Triphenylcyclopropane (3). To a solution of 1,1-diphenylethylene (5.50 g, 30.6 mmol) in 15 ml of anhydrous ether was added phenyldiazomethane[10] (3.15 g, 26.7 mmol) in 10 ml of anhydrous ether in a nitrogen atmosphere. The reaction vessel was allowed to stand at room temperature for 3 weeks when the initial red color of the solution had faded to pale yellow. After removal of the ether, the yellow oil was vacuum distilled to remove unchanged 1,1-diphenylethylene (2.65 g), bp 86–92° (0.3 mm). The crude residue was separated from aldazine and other minor impurities by column chromatography on alumina, with petroleum ether (bp 60–80°) as eluent, to yield **1** (2.65 g, 62% based on diphenylethylene), mp 44–46°, which was recrystallized from MeOH as white needles, mp 49–50°. *Anal.* ($C_{21}H_{18}$) C, H.

1-(4′-Methoxyphenyl)-1,2-diphenylcyclopropane. Cis (4a) and Trans (4b) Isomers. A solution of 1-(4′-methoxyphenyl)-1-phenylethylene (3.68 g, 17.5 mmol) in 20 ml of anhydrous ether was added to phenyldiazomethane (1.7 g, 14.4 mmol) in 8 ml of anhydrous ether. The red solution was allowed to stand for 10 days at room temperature when only a pale yellow color remained. After warming on a steam bath for 3 hr to decompose the intermediate pyrazoline, the product was vacuum distilled to remove unchanged olefin (2.1 g), bp 125–140° (0.25 mm). The residue was purified by column chromatography on alumina using 50% benzene–50% hexane as eluent. The first fractions yielded a mixture of cyclopropane isomers (0.5 g, 21%). Repeated crystallization from MeOH produced the pure cis isomer as white feathery needles: mp 74.5–75.5°; nmr ($CDCl_3$) δ 1.80 (m, 2 H, CH_2), 2.80 (q, 1 H, CH, J = 6.0, 8.5 Hz), 3.75 (s, 3 H, OCH_3), 6.75–7.35 (m, 14 H, Ar H). *Anal.* ($C_{22}H_{20}O$) C, H.

Concentration of the mother liquors and fractional crystallization from EtOH produced the pure trans isomer as white needles: mp 69.5–71°; nmr ($CDCl_3$) δ 1.80 (m, 2 H, CH_2), 2.80 (q, 1 H, CH, J = 6.0, 8.5 Hz), 3.67 (s, 3 H, OCH_3), 6.55–7.35 (m, 14 H, Ar H). *Anal.* ($C_{22}H_{20}$) C, H.

4-Dimethylaminoethoxybenzophenone (9). 2-Dimethylaminoethyl chloride, prepared from its hydrochloride (104 g, 720 mmol) by basification with NH_4OH and extraction into benzene, was added as a benzene solution to the sodium salt of 4-hydroxybenzophenone [prepared by dissolving 71.5 g (360 mmol) of *p*-hydroxybenzophenone in an equimolar solution of sodium methoxide and evaporation of the solution *in vacuo* to leave a red oil]. The solution was refluxed with stirring for 18 hr, the precipitate of NaCl was filtered off, and the benzene was removed *in vacuo*. The residual red oil was taken up in dilute HCl, washed several times with benzene, basified with NH_4OH, and $CHCl_3$ extracted. Evaporation of the dried extracts yielded a dark brown oil (69 g, 71%) as crude product. The product could not be crystallized and was used in crude form for the following reaction: nmr ($CDCl_3$) δ 2.25 (s, 6 H NMe_2), 2.66 (t, 2 H, NCH_2), 4.09 (t, 2 H, OCH_2), 6.6–7.8 (m, 9 H, Ar H).

1-Phenyl-1-(4′-dimethylaminoethoxyphenyl)ethylene (10). Sodium hydride (10.0 g, 210 mmol, 50% dispersion in mineral oil) was suspended in dry 1,2-dimethoxyethane (90 ml, freshly distilled from sodium hydride after preliminary standing over calcium hydride) and dimethoxymethylphosphonate (25.8 g, 210 mmol) was added dropwise with stirring in a nitrogen atmosphere. The mixture was stirred for a further 30 min when 4-dimethylaminoethoxybenzophenone (22 g, 80 mmol) in 1,2-dimethoxyethane (50 ml) was added dropwise. Effervescence occurred and the mixture was refluxed for 2 hr. The solution was poured into water, ether extracted, and dried to yield a dark brown oil on evaporation. Ir showed absence of carbonyl bands. The oil was acidified with 2 *N* HCl and ether extracted to remove the mineral oil which had been present in the sodium hydride. The acid layer was then basified with NH_4OH and ether extracted to leave a dark brown oil (8 g) on evaporation. This was chromatographed on alumina using petroleum ether (bp 40–60°) as eluent, first fractions yielding compound **10** as a yellow solid (4.1 g, 18.6%), mp 47–48°. *Anal.* ($C_{18}H_{21}ON$) C, H, N.

1-(4′-Dimethylaminoethoxyphenyl)-1,2-diphenylcyclopropane. Cis (5a) and Trans (5b) Isomers. An ethereal solution of phenyldiazomethane (3.5 g, 30 mmol) was allowed to stand at room temperature in a stoppered flask with compound **10** (5.0 g, 18.7 mmol) for 4 weeks by which time the color of the solution was pale yellow. The ether solution was acidified with HCl and the ether layer separated, yielding aldazine on evaporation. The acid layer was basified with NaOH and ether extracted; the extracts were dried (Na_2SO_4) and evaporated *in vacuo* to leave a red oil (5.5 g). Tlc on alumina in 5% acetone–95% petroleum ether (bp 40–60°) showed *ca.* 50/50 mixture of product and olefin **10**. Vacuum distillation removed most of the olefin, bp 168–176° (0.5 mm) (2.1 g). Cyclopropane isomers were separated from the remaining olefin and other impurities by preparative tlc using alumina GF plates in 5% acetone–95% petroleum ether (bp 40–60°). The cyclopropane isomers were separated by preparative tlc on silica GF using 90% benzene–10% Et_3N. Cis isomer **5a** was obtained as a pale yellow solid (205 mg), mp 51.5–53.5°, and trans isomer **5b** as a pale yellow oil (420 mg, total yield 9.4%): nmr (**5a**, $CDCl_3$) δ 1.80 (m, 2 H, cyclopropyl CH_2), 2.27 (s, 6 H, NMe_2), 2.70 (m, 3 H, NCH_2 + cyclopropyl CH), 4.00 (t, 2 H, OCH_2), 6.7–7.35 (m, 14 H, Ar H); nmr (**5b**, $CDCl_3$) δ 1.85 (m, 2 H, cyclopropyl CH_2), 2.27 (s, 6 H, NMe_2), 2.70 (m, 3 H, NCH_2 + cyclopropyl CH), 3.93 (t, 2 H, OCH_2), 6.55–7.5 (m, 14 H, Ar H).

Citrate salts of both isomers were prepared by adding a hot acetone solution of citric acid (1.1 mmol) to an acetone solution of the isomer (1 mmol). The cis citrate had mp 72°. *Anal.* ($C_{31}H_{35}O_7N\cdot0.5H_2O$) C, H, N. The trans citrate had mp 85°. *Anal.* ($C_{31}H_{35}O_7N\cdot1H_2O$) C, H, N.

1-(4′-Methoxyphenyl)-1,2-diphenyl-3-ethoxycarbonylcyclopropane. Cis (7a) and Trans (7b) Isomers. Ethyl cinnamate (20 ml, 114 mmol) was added to 1-(4′-methoxyphenyl)-1-phenyldiazomethane (21 g, 94 mmol) in a nitrogen atmosphere. The solution was left in a stoppered flask until the deep red color had faded (5 days). The resultant pale orange oil was heated on a steam bath until evolution of nitrogen had ceased and then vacuum distilled to remove unchanged ethyl cinnamate. The residue (27.4 g) was chromatographed on alumina using petroleum ether (75%) (bp

60–80°)-diethyl ether (25%) as eluent. After removal of 1,2-di(4′-methoxyphenyl)-1,2-diphenylethylene in the first fractions, mixed cyclopropane isomers were obtained (4.8 g, crude yield 13.8%). Fractional crystallization from MeOH gave the cis isomer **7a** as white crystals, mp 111–112°, and the trans isomer **7b** as white crystals, mp 98.5–100°. Nmr (**7a**, CCl_4) δ 1.03 (t, 3 H, CH_3 of CO_2Et), 2.96 (d, 1 H, cyp H, J = 6.5 Hz), 3.53 (d, 1 H, cyp H, J = 6.5 Hz), 3.65 (s, 3 H, OCH_3), 3.92 (q, 2 H, OCH_2), 6.6–7.4 (m, 14 H, Ar H). *Anal.* ($C_{25}H_{24}O_3$) C, H. Nmr (**7b**, CCl_4) δ 0.96 (t, 3 H, CH_3 of CO_2Et), 2.90 (d, 1 H, cyp H, J = 7.0 Hz), 3.55 (d, 1 H, cyp H, J = 7.0 Hz), 3.60 (s, 3 H, OCH_3), 3.88 (q, 2 H, OCH_2), 6.4–7.5 (m, 14 H, Ar H). *Anal.* ($C_{25}H_{24}O_3$) C, H.

3-Ethoxycarbonyl-4,5-diphenyl-5-(4-dimethylaminoethoxyphenyl)-2-pyrazoline (11). Ethyl cinnamate (3 ml, 17 mmol) was added in a nitrogen atmosphere to 1-phenyl-1(4′-dimethylaminoethoxyphenyl)diazomethane (3.3 g, 11.7 mmol) [from 4′-dimethylaminoethoxybenzophenone after refluxing for 50 hr with 64% hydrazine and barium oxide in ethanol and shaking of the residual oil from ether extraction with yellow mercuric oxide in petroleum ether (bp 40–60°) for 5 hr. Filtration and evaporation of the petroleum ether left the diazomethane as a red oil]. The mixture was allowed to stand for 6 days by which time the color had faded to pale yellow. No effervescence occurred on heating the mixture, which was then taken up in ether. This was shaken with 2 N HCl and the ether layer separated, washed with water, dried, and evaporated to yield unchanged ethyl cinnamate. The acid layer was basified with 2 N NaOH and ether extracted. Washed, dried extracts yielded a brown oil on evaporation which gave a yellow solid on boiling with petroleum ether (bp 60–80°). Recrystallization from benzene–petroleumn ether (bp 60–80°) gave **11** as white crystals (0.6 g, 11.1%), mp 129–130.5°. *Anal.* ($C_{28}H_{31}O_3N_3$) C, H, N.

Attempts to decompose the pyrazoline by refluxing with benzene, with copper and xylene, and by uv irradiation, were unsuccessful, resulting in unchanged starting materials or tars.

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Book Reviews

Malaria. Roger M. Pinder, Ed. Scientechnica Ltd., Bristol, England. 1973. xii + 316 pp. 17 × 24.5 cm. £10.00.

Writing of malaria, the World Health Organization in 1961 stated that "the clinician has at his disposal a complete series of effective drugs for the treatment of all stages of the disease." Yet this epitaph on antimalarial research tumbled from its pedestal with the increasing emergence of drug-resistant plasmodia and of Anopheles mosquitoes resistant to the insecticides commonly used in malarial vector eradication. In contrast to earlier phases of malaria research, present investigations use many modern tools unavailable even one decade ago. In addition, strong emphasis is being placed on biochemical causation of resistance phenomena and on the biochemical mode of action of chemical agents in chemotherapy and vector eradication. Thus, a whole new set of data has to be considered, and a monograph covering all phases of malariology is a timely and welcome contribution to this broad and overridingly important field of research. The volume by Pinder fulfills the most demanding expectations of such a review. It summarizes, in considerable detail and with meticulous documentation, every aspect of malaria research, from parasitology to experimental and clinical chemotherapy, and from drug resistance to vector control. The author's interest in drug design is emphasized in almost 200 pp of descriptions of the history of antimalarial chemotherapy up to the newest approaches to this work, with strong concern for the mode of action of antimalarial drugs and their effect on plasmodial metabolism. From such data arise quite naturally chapters on multiple attacks on the different stages of plasmodial life cycles by drug combinations and repository antimalarials which form the basis of the routine clinical therapy and prophylaxis of the malarias. Apart from the coverage of every aspect of malariology which will satisfy entomologists, parasitologists, pharmacologists, biochemists, medicinal chemists, clinicians, ecologists, and biostatisticians, the great extra bonus for the reader is the style of this book. The volume presents some of the best English this reviewer has read in scientific books. A vast and fluent vocabulary, a touch of humor, a critical attitude toward debatable practices, and a sense of authoritative knowledge sifting the obsolete from the pertinent will endear this book to anybody interested in the study of one of the oldest and most debilitating scourges of mankind.

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