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Diarylcyclobutane Analogs of Diethylstilbestrol

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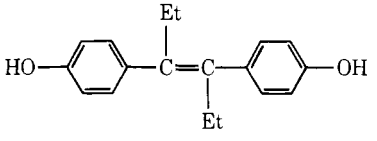
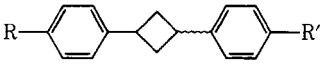
Several 1,3- (and 1,2-) diarylcyclobutanes related to diethylstilbestrol have been prepared. Two compounds, 1,3-bis(*p*-hydroxyphenyl)cyclobutane and its monomethyl ether, showed weak estrogenic and antifertility effects in rats.

Nonsteroidal estrogens can be used for a variety of purposes. In particular, diethylstilbestrol (DES) is effective in treating cancers of the prostate[1] and breast[2] and in controlling various disorders of women.[3] Recently, DES was used successfully as a postcoital contraceptive agent in women.[4]

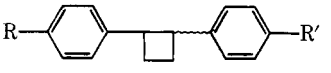
The ethylene unit connecting the phenolic rings of DES can be modified in many ways with retention of estrogenic activity.[5-7] It occurred to us that a cyclobutane ring might effectively replace that ethylene unit. A study of Dreiding models indicated that the aromatic rings and phenolic hydroxyl groups of either *trans*-1,3-bis(*p*-hydroxyphenyl)cyclobutane (*trans*-**1a**) or *trans*-1,2-bis(*p*-hydroxyphenyl)cyclobutane (*trans*-**2a**) can be nearly superimposable upon those of DES. To learn if these cyclobutanes would in fact



DES



1a, R = R′ = OH



2a, R = R′ = OH

behave at least qualitatively like DES, we prepared both of them and several of their derivatives and tested them for estrogenic and postcoital antifertility effects. All examples of **1** actually were obtained as mixtures of cis and trans isomers, while all preparations of **2** were formed as single isomeric entities. Two dialkylaminoethyl ether derivatives of **1** were prepared because some similar derivatives of DES analogs were found to be antiestrogenic.[8] All of the diarylcyclobutanes prepared are listed in Table I.

Chemistry. The 1,3-diarylcyclobutanes (**1**) were prepared according to Scheme I. Conversion of styrene itself to ketone **6** had been reported by Silversmith, *et al.*,[9] and that particular procedure worked for us just as described. The use of *p*-methoxystyrene to prepare ketone **7**, however, required several modifications to cope with the acid sensitivity of the intermediates.

Scheme I

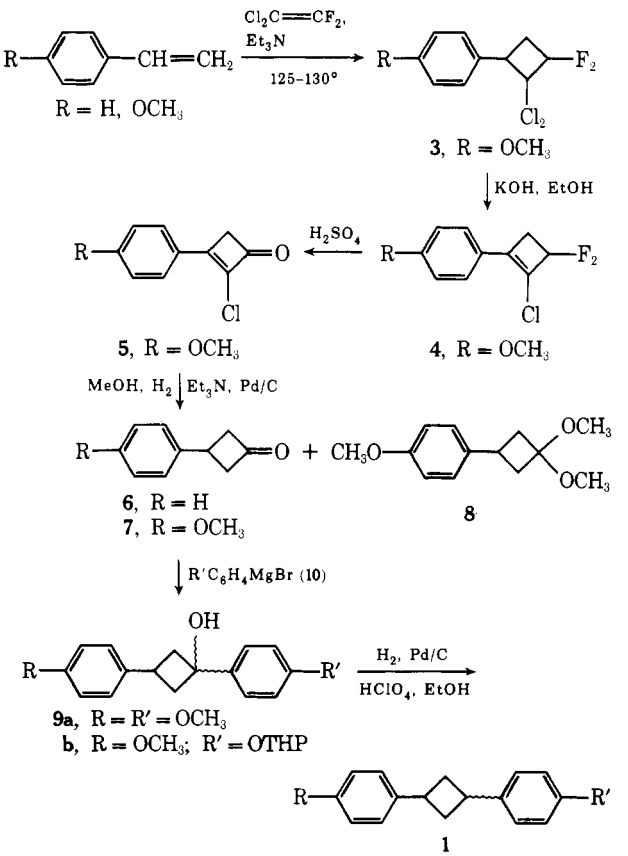
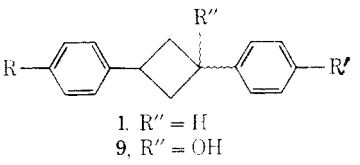
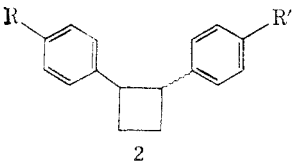


Table I

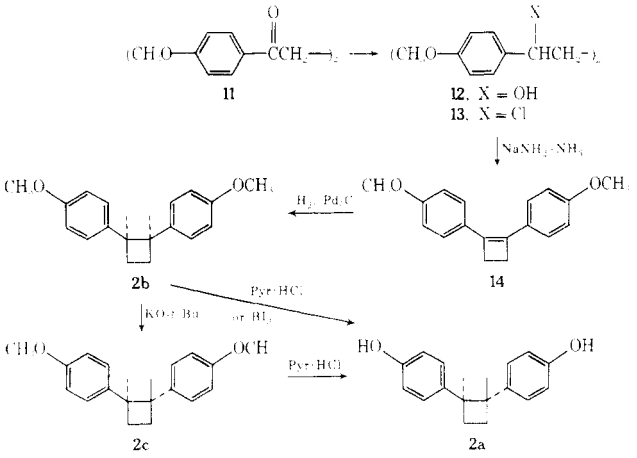




No.	Isomer ratio[a]	R	R'	Prep method	Yield,[b] %	Recrystn solvent[c]	Mp or bp (mm),[d] °C	Formula	Analyses[e]
1a	60:40	HO	HO	D	67	A	148–163.5	$C_{16}H_{16}O_2$	C, H
1b	60:40	CH_3O	HO	B	67	B–C	96–110	$C_{17}H_{18}O_2$	C, H
1c	60:40	H	HO	D	68	D	69.5–79.5	$C_{16}H_{16}O$	C, H
1d	50:50	H	CH_3O	C	44		108–114 (0.01 mm)	$C_{17}H_{18}O$	C, H
1e	50:50	CH_3O	CH_3O	B	55	B	63–83	$C_{18}H_{20}O_2$	C, H
1f		H	$OCH_2CH_2NEt_2$	C	4	B–E	115–127	$C_{22}H_{29}NO \cdot HCl$	C, H, N
1g		CH_3O	$OCH_2CH_2NEt_2$	C	26	B–E	147.5–150.5	$C_{23}H_{31}NO_2 \cdot HCl$	C, H, N
1h	70:30	CH_3CO_2	CH_3CO_2		82	B	76–87.5	$C_{20}H_{20}O_4$	C, H
1i	60:40	KO_3S	KO_3S		72	C	264.5–274.5	$C_{16}H_{14}O_8S_2K_2$	C, H, S
9a		CH_3O	CH_3O	A	36	F	71–75	$C_{15}H_{20}O_3$	C, H
9b		CH_3O	OTHP	A	62	D	72–75	$C_{22}H_{26}O_4$	C, H
2a	Trans	HO	HO	D	71	A	126.5–127	$C_{16}H_{16}O_2$	C, H
2b	Cis	CH_3O	CH_3O		70	G	40.5–41.5	$C_{18}H_{20}O_2$	C, H
2c	Trans	CH_3O	CH_3O		75		170–175 (0.1 mm)	$C_{18}H_{20}O_2$	C, H

[a] In the numerical ratios, no cis or trans assignment is implied; **2a–c** are pure isomers of the configurations indicated. [b] Yields are of analytical material. [c] A, benzene; B, EtOH; C, H_2O; D, heptane; E, $(i\text{-Pr})_2O$; F, cyclohexane; G, MeOH. [d] Corrected. [e] Analyses are within limits of ±0.4% for the elements noted.

Scheme II



Conversion of ketones **6** or **7** to alcohols **9** was done by treating them with Grignard reagents **10** in which R' was variously OCH_3, OTHP, or $OCH_2CH_2NEt_2$. Two of the alcohols (**9a,b**) were purified. To obtain **1**, the OH group of **9** was removed by catalytic hydrogenolysis in the presence of $HClO_4$. The THP-protecting group of **9b** also was removed during this step, and methyl ethers were cleaved subsequently by pyrolysis with pyridine hydrochloride.

Each example of **1** was obtained only as a mixture of the cis and trans isomers. None of the desired pure trans form was isolated in any instance. For several examples of **1** we were able to estimate the ratio of geometrical isomers from the relative nmr intensities of the different aromatic peaks, but we were not able to make any cis or trans assignments within these ratios.

From the bisphenol **1a**, a diacetate **1h** and a dipotassium sulfonate **1i** were prepared with the hope that these derivatives might be biologically active upon oral administration.

trans-1,2-Bis(*p*-hydroxyphenyl)cyclobutane (**2a**) was produced by a route (Scheme II) similar to that used by Dodson and Zielske[11] to prepare the unsubstituted phenyl analogs. As in Scheme I, however, methoxy groups on the aromatic rings compelled us to change some experimental conditions. At first we prepared diketone **11** by the reported[12] Friedel–Crafts acylation of anisole with succinoyl chloride, but the yields were poor (<20%). Subsequently, we made **11** in about 75% overall yield by alkylating ethyl *p*-anisoylacetate with *p*-methoxyphenacyl bromide and decarbethoxylating the intermediate keto ester without isolating it. Reduction of diketone **11** to diol **12** with $NaBH_4$ was straightforward. Conversion of **12** to dichloride **13**, however, required a much more delicate treatment with HCl than reported[11] for the phenyl analog, *i.e.*, 5–10° for 2 hr as opposed to room temperature for 24 hr. If mild conditions were not maintained in preparing **13**, 1,4-bis(*p*-anisyl)-1,4-butadiene formed rapidly.

Cyclization of **13** with $NaNH_2$–NH_3 gave the cyclobutene **14**. Catalytic reduction of this olefin gave the stereochemically pure *cis*-cyclobutane **2b**. Treatment of **2b** with KO-*t*-Bu caused quantitative isomerization to the trans isomer **2c**. Demethylation of **2c** with pyridine hydrochloride at 210° gave the *trans*-diphenol **2a**. We had hoped that demethylation of the *cis*-diether **2b** would give the corresponding *cis*-diphenol. Actually, demethylation of **2b** gave only the *trans*-diphenol **2a** whether it was done under vigorous conditions (pyr·HCl) or under mild conditions with BI_3[13] at room temperature. Molecular models indicate that *cis*-1,2-diphenylcyclobutanes are strained because of the closeness of the aromatic rings. It seems likely, therefore, that relief of strain in this system is the driving force for both the quantitative isomerization of the *cis*- to the *trans*-diether and for conversion of the *cis*-diether to the *trans*-diphenol.

The benzylic protons of **2b** (cis) and **2c** (trans) absorb in the nmr at δ 3.82 and 3.31, respectively, in agreement with the relative peak positions[11] of the corresponding protons of the *cis*- and *trans*-1,2-diphenylcyclobutanes. The benzylic protons of *trans*-diphenol **2a** absorbed at δ 3.29 in the nmr.

The hydrocarbon grouping between the phenolic rings of DES contains a total of six carbon atoms. This suggested to us that in the cyclobutyl compounds, additional alkyl groups might enhance biological activity. In the 1,3 series, we were unable to methylate the benzylic positions of the

diether **1e** under any of the conditions tried. However, we felt that in the 1,2 series methylation ought to occur because the isomerization of **2b** to **2c** must have involved a benzylic carbanion. Unexpectedly, attempts to alkylate **2b** in KO-*t*-Bu–DMSO using CH_3I or dimethyl sulfate gave no alkylated product, but gave only the trans isomer **2c**.

Biological Results. The cyclobutanes in Table I were tested for estrogenicity and for postcoital antifertility activity. In the assay of Rubin, *et al.*,[14] subcutaneously administered **1a** was about 10^{-4} as potent as DES in doubling the uterine weight of immature rats, while the monomethyl ether **1b** was about one-half as potent as **1a**. None of the other cyclobutanes displayed activity at the dose levels tested. In a supplementary test using ovariectomized rats,[15] **1a** was also found to be about 10^{-4} as potent as DES in promoting cornification of the vaginal epithelium. Both **1a** and **1b** were weakly active as postcoital antifertility agents in rats (see Experimental Section). Given subcutaneously for six successive days following coitus, **1a** at 20 mg/kg and **1b** at 40 mg/kg completely prevented pregnancy. For comparison, DES prevented pregnancy at a dose level of 0.004 mg/kg.

Experimental Section

Nmr spectra were recorded on a Varian A-60 spectrometer (Me_4Si). Melting points (capillary, Thomas-Hoover apparatus) of all analytical samples are corrected. Analyses were done for the elements indicated by symbols, and analytical results were within ±0.4% of the calculated values. "Alumina" refers to the A-540 grade of alumina from Fisher Scientific Co.

Antifertility Assay. Groups of ten female rats were given the test compound subcutaneously in corn oil on each of the first 6 days of pregnancy. Day 1 of pregnancy was defined as the day of mating, as verified by the presence of vaginal spermatozoa. The uteri were examined between days 8–12 of pregnancy for the presence and gross appearance of implantation sites. Animals having one or more normal fetuses were considered to be pregnant.

2,2-Dichloro-1,1-difluoro-3-(*p*-anisyl)cyclobutane (3). *p*-Methoxystyrene (40.8 g, 0.30 mol), 1,1-dichloro-2,2-difluoroethylene (55.8 g, 0.42 mol), and Et_3N (3.0 ml, 0.02 mol) were heated in a sealed Carius tube (25 × 615 mm) at 125–130° for 16 hr. The cooled mixture was poured into H_2O, and an Et_2O extract was washed with H_2O, dried ($MgSO_4$), and evaporated to an oil. Distillation of the oil gave 69.0 g (86%), bp 80–85° (0.1 mm), of **3** suitable for use in the next step. Part of the oil was chromatographed (alumina, cyclohexane) and redistilled: bp 81° (0.02 mm); $n^{27}D$ 1.5207. *Anal.* ($C_{11}H_{10}Cl_2F_2O$) C, H.

2-Chloro-1,1-difluoro-3-(*p*-anisyl)-2-cyclobutene (4). Treatment of **3** with KOH–EtOH under the conditions used[9] to prepare the phenyl analog gave a 96% yield of **4** usable as such in the next step. Distillation gave pure material: bp 67° (0.02 mm); $n^{27}D$ 1.5597. *Anal.* ($C_{11}H_9ClF_2O$) C, H.

2-Chloro-3-(*p*-anisyl)-2-cyclobuten-1-one (5). Compound **4** (215 g, 0.93 mol) was poured gradually into 272 ml of concentrated H_2SO_4 with stirring. The rate of addition was adjusted to keep the reaction temperature <40°. When the reaction slowed down, the cooling bath was removed, and stirring was continued for 20 min. The mixture was poured into 3 l. of H_2O, and the precipitated solid was collected on a filter, washed with H_2O, and air-dried. Recrystallization twice from *i*-PrOH gave 128.8 g (66%), mp 96–98°. From another run, an analytical sample was obtained after chromatography of the crude product on alumina (benzene) and recrystallization (heptane): mp 98–100°. *Anal.* ($C_{11}H_9ClO_2$) C, H, Cl.

1,1-Dimethoxy-3-(*p*-anisyl)cyclobutane (8) and 3-(*p*-Anisyl)-cyclobutanone (7). A mixture of **5** (17.4 g, 0.085 mol), Et_3N (11.7 ml, 0.084 mol), and 2.1 g of 10% Pd/C in 300 ml of 10% aqueous MeOH was shaken under H_2 (50 psi) until reduction was complete (30 min). The mixture was filtered and the filtrate was evaporated. An Et_2O solution of the residue was washed (H_2O), dried ($MgSO_4$), and evaporated to give 15.4 g of an oil which was chromatographed on alumina using benzene. The first component (5.3 g) eluted was distilled to furnish 2.5 g (13%) of ketal **8**: bp 94° (0.05 mm); $n^{27}D$ 1.5133. *Anal.* ($C_{13}H_{18}O_3$) C, H.

The second component (4.8 g) was distilled to give 4.3 g (29%) of **7**: bp 93–95° (0.05 mm); $n^{27}D$ 1.5449. *Anal.* ($C_{11}H_{12}O_2$) C, H.

Method A. Grignard Reaction Conditions. The arylmagnesium bromide was prepared in 30 ml of THF from Mg shavings (0.89 g, 0.037 g-atom) and 0.034 mol of aryl bromide. Ketone **7** (6.0 g, 0.034 mol) in 20 ml of THF was added dropwise at room temperature. The mixture was heated at reflux for 2 hr, cooled, and hydrolyzed with 5 ml of saturated aqueous NH_4Cl. The solution was filtered and evaporated to give a residue which was dissolved in Et_2O. The Et_2O solution was washed (H_2O), dried ($MgSO_4$), and evaporated to yield a solid residue which was recrystallized.

Method B. Hydrogenolysis of Cyclobutanols. A mixture of the cyclobutanol (0.046 mol), 3.0 g of 10% Pd/C, 1 ml of 70% $HClO_4$, and 100 ml of 95% EtOH was shaken under 50 psi of H_2 until reduction was complete. The catalyst was removed by filtration and the filtrate was evaporated. A solution of the residue in Et_2O was washed (5% $NaHCO_3$, H_2O) and dried ($MgSO_4$). Evaporation of the Et_2O gave a residue which was recrystallized.

Method C. This procedure combines the features of methods A and B done in succession without purification of the cyclobutanol.

Method D. Cleavage of Ethers with Pyridine Hydrochloride. A mixture of the ether (0.050 mol) and pyridine hydrochloride (0.40 mol) was heated at 210° under N_2 for 30 min and poured into 500 ml of H_2O. Several EtOAc extracts were taken, combined, washed (dilute HCl, H_2O, brine), dried ($MgSO_4$), and evaporated to give the crude product which was recrystallized.

***trans*-1,2-Bis(*p*-hydroxyphenyl)cyclobutane (2a) by Cleavage of *cis*-1,2-Bis(*p*-anisyl)cyclobutane (2b). (a) With Pyr·HCl.** Method D was applied to 9.39 g (0.035 mol) of **2b**. The dark, gummy product was chromatographed on Mallinckrodt SilicAR CC-7 using $(i\text{-Pr})_2O$ to obtain a light yellow oil. Short-path distillation of the latter at 150–200° (0.1 mm) gave again an oil (*ca.* 4.5 g) which crystallized from benzene: 2.70 g (32%) of solid; mp 117–122°. Recrystallization twice from benzene left 1.78 g (21%), mp 125–127°. This product did not depress the melting point of **2a** obtained from the *trans*-diether **2c**.

(b) With BI_3.[13] A solution of BI_3 (0.063 mol) in 200 ml of cyclohexane was prepared under N_2 by the method of Renner[16] from 64 g (0.25 mol) of I_2 and 4.62 g (0.196 mol) of $LiBH_4$. Solid inorganic by-products, however, were not removed by filtration. The BI_3 solution was cooled to 10°, and to it was added 8.05 g (0.030 mol) of **2b**. Stirring was continued for 2 hr at room temperature. The mixture was treated with 50 ml of 3 *N* HCl and extracted with EtOAc. The combined extracts were washed with 10% aqueous Na_2SO_3 and brine, dried ($MgSO_4$), and evaporated to give crude yellow product, 7.40 g. Recrystallization from aqueous MeOH provided 6.00 g (83%), mp 116–118°. This was recrystallized thrice further from aqueous MeOH to obtain 4.68 g (68%), mp 123–124.5°; mixture melting point with **2a** was undepressed.

1,3-Bis(*p*-acetoxyphenyl)cyclobutane (1h). A mixture of **1a** (5.7 g, 0.024 mol), Ac_2O (16.1 ml, 0.161 mol), and 4 drops of pyridine was stirred for 1 hr at room temperature. Evaporation of excess Ac_2O and addition of H_2O to the residue left a solid (7.7 g). Recrystallization from EtOH gave 6.4 g (82%), mp 76–87.5°. Nmr ($CDCl_3$) indicated a 70:30 mixture of isomers. *Anal.* ($C_{20}H_{20}O_4$) C, H.

Dipotassium 4,4′-Bis(1,3-cyclobutylene)diphenol Disulfate (1i). Pyridinesulfuric anhydride[17] was prepared by adding pyridine (25 ml, 0.32 mol) dropwise to a solution of $ClSO_3H$ (10 ml, 0.15 mol) in 200 ml of CCl_4 with stirring at 0° under N_2. Solid **1a** (8.9 g, 0.037 mol) was added gradually. The mixture was stirred for 0.5 hr at room temperature and for 0.5 hr at steam bath temperature. The CCl_4 was decanted, and a solution of 35 g of 85% KOH pellets in 30 ml of H_2O was added to the gummy residue. The pasty mass was cooled, triturated with Et_2O to remove pyridine, and dissolved in 350 ml of boiling H_2O. Chilling overnight produced 16.3 g of solid which was recrystallized twice from H_2O to obtain 13.0 g (72%) of **1i**, mp 264.5–274.5° dec. Nmr (D_2O) suggests a 60:40 isomer ratio. *Anal.* ($C_{16}H_{14}O_8S_2 \cdot K_2$ salt) C, H, S.

1,2-Bis(*p*-anisoyl)ethane (11). Ethyl *p*-anisoylacetate (56.6 g, 0.25 mol) in 50 ml of THF was added during 20 min to a stirred suspension of NaH (10.6 g, 57% dispersion in mineral oil, 0.26 mol) in 500 ml of THF. After H_2 evolution had stopped, there was added in succession 2.16 g (0.013 mol) of KI, 1 l. of acetone, and (in 20 min) 59.6 g (0.26 mol) of *p*-methoxyphenacyl bromide in 150 ml of acetone. The mixture was stirred for 1 hr at room temperature and filtered. Evaporation of the filtrate left an oil which was heated at reflux for 1.25 hr in 600 ml of 3:1 H_2O–EtOH containing 23 g of 85% KOH. This solution was poured into 800 ml of 3 *N* HCl, and steam was passed through the mixture for 5 min.

Cooling and filtration gave a solid which was washed with H_2O and dried: 76.1 g; mp 135–147°. Recrystallization from EtOAc left 56.2 g (75%) of **11**, mp 153–154.5° (lit.[12] mp 154°).

1,4-Bis(*p*-anisyl)butane-1,4-diol (12). Diketone **11** (96.5 g) was reduced with $NaBH_4$ by the method reported[11] for reduction of 1,2-dibenzoylethane. The product was obtained as a mixture of meso and *dl* forms: 93.9 g (96%); mp 104–122°. The diol of this quality was suitable for use in the next step. On one occasion, a single isomeric form of the diol was obtained by repeated recrystallization of the crude product from EtOAc: mp 138.5–139.5° *Anal.* ($C_{18}H_{22}O_4$) C, H.

1,4-Bis(*p*-anisyl)-1,4-dichlorobutane (13). A solution of diol **12** (31.7 g, 0.11 mol) in 800 ml of HOAc–dioxane (4:1) was stirred at 5–10° while a stream of dry HCl gas was bubbled into the liquid at a moderate rate for 2 hr. Heptane (800 ml) was added, and the precipitated solid was collected on a filter and washed with heptane: 32.2 g (90%). Recrystallization (acetone) gave a refined sample. *Anal.* ($C_{18}H_{20}O_2Cl_2$) C, H, Cl. This material decomposed at 124.5°, evolving gas and only partially melting. Complete melting finally occurred at 219°, suggesting thermal conversion of the dichloride to 1,4-bis(*p*-anisyl)-1,4-butadiene (lit.[18] mp 229–231°).

1,2-Bis(*p*-anisyl)cyclobutene (14). Cyclization of **13** was done with $NaNH_2$ by the procedure reported[11] for the phenyl analog. Work-up gave a dark oil which was chromatographed on alumina (benzene). Product-containing fractions (located by tlc) were evaporated to an oil which crystallized from cold MeOH. In a run using 27.2 g of **13** there was obtained 13.5 g (64%), mp 85.5–87°. Recrystallization (EtOH) gave 12.1 g (57%) of **14**, mp 88.5–89.5°. *Anal.* ($C_{18}H_{18}O_2$) C, H.

***cis*-1,2-Bis(*p*-anisyl)cyclobutane (2b).** Cyclobutene **14** (8.15 g, 0.031 mol) was hydrogenated over 0.2 g of 10% Pd/C in 100 ml of dioxane. Filtration and evaporation of the filtrate left an oil which was dissolved in MeOH. Cooling in a Dry Ice–MeOH bath produced **2b**: 7.20 g (88%); mp 38–39.5°. Recrystallization (MeOH) gave 5.75 g (70%): mp 40.5–41.5°; nmr (DMSO-d_6) δ 3.82 (m, 2, benzylic H). *Anal.* ($C_{18}H_{20}O_2$) C, H.

***trans*-1,2-Bis(*p*-anisyl)cyclobutane (2c).** Isomerization of **2b** was effected by KO-*t*-Bu in DMSO as described[11] for the phenyl analog. From 13.68 g of **2b** there was obtained 11.10 g of oily **2c**. Chromatography on alumina (benzene) followed by distillation gave 10.25 g (75%): bp 156–175° (0.1 mm); $n^{25}D$ 1.5783; nmr (DMSO-d_6) δ 3.31 (m, 3, benzylic H). *Anal.* ($C_{18}H_{20}O_2$) C, H.

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Synthesis, Estrogenic Activity, and Electrophilic Reactivity of an *N*-Acetoxy-*N*-acetamido Analog of Diethylstilbestrol

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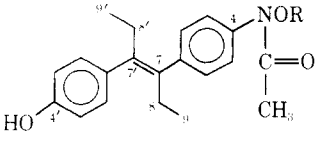
N-Hydroxy- and *N*-acetoxy-4′-hydroxy-7,7′-diethyl-*trans*-*N*-4-stilbenylacetamide were synthesized for study of their carcinogenic and estrogenic activities. These compounds are analogs of diethylstilbestrol and also of the potent carcinogens *N*-hydroxy- and *N*-acetoxy-*N*-4-*trans*-stilbenylacetamide. The hydroxamic acid and the *N*-acetoxyamide exhibited 1/600 and 1/400, respectively, of the estrogenic activity of diethylstilbestrol. The electrophilic reactivity at neutrality of the *N*-acetoxyamide toward methionine was of the same order of magnitude as that of *N*-acetoxy-*N*-4-*trans*-stilbenylacetamide and about 1/10 that of *N*-acetoxy-*N*-2-fluorenylacetamide.

The potent estrogen diethylstilbestrol (4,4′-dihydroxy-7,7′-diethyl-*trans*-stilbene), which is carcinogenic in estrogen target organs of a number of species including the human,[1-3] and the potent carcinogens *N*-hydroxy- and *N*-acetoxy-*N*-4-*trans*-stilbenylacetamide[4,5] share some structural features. The objective of the present work was to design a new carcinogen with specificity for the organ and subcellular targets of the estrogens through combination of the essential structural features of the estrogens and the *trans*-stilbenylacetamide carcinogens. This paper describes the synthesis of *N*-hydroxy- (**10**) and *N*-acetoxy-4′-hydroxy-7,7′-diethyl-*N*-4-*trans*-stilbenylacetamide (**11**). These compounds are estrogenic although much less active than diethylstilbestrol. The *N*-acetoxyamide shows similar electrophilic reactivity to that of *N*-acetoxy-*N*-4-*trans*-stilbenylacetamide, a property which appears to be essential for an ultimate carcinogen.[6,7] The compounds are being assayed for carcinogenic activity.



10, R = H
11, R = C(=O)CH_3

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