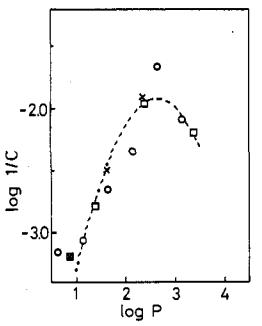

Figure 3. The logarithm of duration (minutes) (C) of the depressant effect of barbiturates (**19**, Table I) as a function of the logarithm of corrected partition coefficients: (○) types III_1; (□) III_2; (x) IIE. The dashed line is calculated from the parabolic equation: $\log (1/C) = -0.511(\log P)^2 + 2.706 \log P - 5.495$.

amphetamines), suggesting that these cases can be explained solely by the hydrophobicity factor correction. For these cases, therefore, the difference in A/A_I between types is responsible for an inadequate estimation of partition coefficients. For the exceptional cases mentioned above there are too few experimental data (Table I) to draw any conclusions. The negative a values of **32** and **33** in Table I probably correspond to the large P region in the parabolic equation.

The correction of a decreased hydrophobicity of double-chain compounds is also important, when the parabolic equation holds. Such an example is shown in Figure 3. In this figure, partition coefficients of types III_2 and IIE of ethyl barbiturates (**19** in Table I) are corrected, employing the observed P value of diethyl barbiturate and assuming that a_{IIS}/a_{IIL1} is equal to a_{IIS}/a_I for type IIS alcohols in Table IV, viz., 0.47. The type dependence seen in Figure 2 disappears in Figure 3.

As relevant structure–activity data are compiled hereafter, the accuracy of prediction will be improved, and applications of the present approach will be extended for various double-chain compounds and various biological activities. The present work is expected to be useful also for predicting the partition coefficients of double-chain compounds, designing drugs, and elucidating the mechanism of pharmacological action of drugs.

Registry No. Butyrylcholinesterase, 9001-08-5.

Inhibition of Prostaglandin Synthetase by Di- and Triphenylethylene Derivatives: A Structure–Activity Study

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The syntheses of new di- and triphenylethylene derivatives are described along with their X-ray analysis and NMR study, which have helped to establish their conformation. Screening of over 50 derivatives for inhibition of prostaglandin synthetase (PGS) activity in bovine seminal vesicle microsomes has revealed that many of the triphenylethylene derivatives are potent inhibitors of PGS. Several even show marked activity at the extremely low concentration (IC_{50}) of about 4×10^{-8} M, which is two orders of magnitude lower than the active concentration of the majority of known nonsteroidal antiinflammatory agents ($IC_{50} \approx 10^{-6}$ M). Unlike the latter, these compounds are not carboxylic acids. Furthermore, in contrast to biphenyl, diphenylmethane, or unsymmetrical, α,α'-diphenylethylene PGS inhibitors, the presence of a β-phenyl ring was an essential requirement for high potency. The best inhibitors possessed a cyanide group (acids, amides, and amines were poor inhibitors), methoxy in preference to hydroxy groups on the α-phenyl rings, and a halogen (F or Cl) in a para position on the β-phenyl ring. These data provide additional insight into the nature of the PGS binding site.

Several triphenylethylene-derived (TPE) compounds, such as clomiphene [1-[*p*-[β-(diethylamino)ethoxy]-phenyl]-1,2-diphenyl-2-chloroethylene], tamoxifen [1-[*p*-[β-(dimethylamino)ethoxy]phenyl]-1,2-diphenylbut-1-ene], and MER-25 [1-[*p*-[2-(diethylamino)ethoxy]-phenyl]-1-phenyl-2-(*p*-methoxyphenyl)ethanol], are known for their antiestrogenic properties and are used clinically for ovulation induction,[1] for the treatment of hormone-dependent cancers,[2] and for diagnostic purposes.[3] However, some of these compounds have also been shown to inhibit prostaglandin synthetase (PGS), and, according to a few authors, this enzyme inhibition could explain part of their biological effects.[4-7]

In a previous study,[8] we reported the synthesis of cyano derivatives of TPE's with affinity for the cytosol estrogen receptor. In the present paper, we describe the synthesis of new derivatives in this series and the results of a structure–activity study on over 50 compounds, in which inhibition of PGS has been measured in bovine seminal

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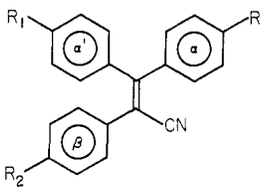
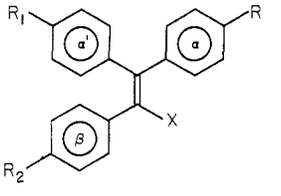
Table I. Physical and Biological Properties of 3,3,2-Triphenylacrylonitriles



no.[a]	R	R_1	R_2	mp,[b] °C	isomers, %	formula	anal. or ref	yield,[c] %	PGS IC_{50},[d] μM
1	H	H	H	166-167		$C_{21}H_{15}N$	16		3.5
2Z	OH	H	H	203-205	95	$C_{21}H_{15}NO$	9[e]		0.2
2E	H	OH	H	193-194	95	$C_{21}H_{15}NO$	9[e]		1.6
3	H	H	OH	229		$C_{21}H_{15}NO$	9		6.6
4	OH	OH	H	249		$C_{21}H_{15}NO_2$	8		2
5	OH	OH	F	244		$C_{21}H_{14}FNO_2$	C, H, N	80	1.3
6Z[f]	OH	CH_3	H	209	96	$C_{22}H_{17}NO$	C, H, N	90	0.8
6E	CH_3	OH	H	192	68	$C_{22}H_{17}NO$	C, H, N		0.08
7Z	OH	H	Cl	177	60	$C_{21}H_{14}ClNO$	9		0.3
8E	OH[g]	Cl	CH_3	184-185	60	$C_{22}H_{16}ClNO$	C, H, N, Cl	84	2
9Z	OH	CH_3	F	201-202	60	$C_{22}H_{16}FNO$	C, H, N	79	1.4
10Z	OH	CH_3	Cl	157	55	$C_{22}H_{16}ClNO$	C, H, N, Cl	45	0.4
11	OH	OH	OH	280		$C_{21}H_{15}NO_3$	C, H, N	30	5.6
12	H	H	OCH_3	148		$C_{22}H_{17}NO$	10		0.5
13Z	OCH_3	CH_3	H	151-152	57	$C_{23}H_{19}NO$	C, H, N	45	0.5
13E	CH_3	OCH_3	H	134-135	65	$C_{23}H_{19}NO$	C, H, N		0.6
14E[f]	CH_3	OCH_3	OCH_3	159-160	80	$C_{24}H_{21}NO_2$	C, H, N	40	0.11
14Z	OCH_3	CH_3	OCH_3	185	90	$C_{24}H_{21}NO$			0.08
15E[f]	CH_3	OCH_3	F	154-156	98	$C_{23}H_{18}FNO$	C, H, N, F	50	0.05
15Z	OCH_3	CH_3	F	160-161	92	$C_{23}H_{18}FNO$			0.04
16E[f]	CH_3	OCH_3	Cl	154	100	$C_{23}H_{18}ClNO$	C, H, N	54	0.03
16Z	OCH_3	CH_3	Cl	176	100	$C_{23}H_{18}ClNO$			0.05
17E	H	OCH_3	Cl	135-136	94	$C_{22}H_{16}ClNO$	C, H, N, Cl	68	0.13
17Z[f]	OCH_3	H	Cl	167-168	100	$C_{22}H_{16}ClNO$			0.17
18E	OCH_3[c]	Cl	CH_3	167	85	$C_{23}H_{18}ClNO$	C, H, N, Cl	43	0.2
19	OCH_3	OCH_3	H	158-159		$C_{23}H_{19}NO_2$	10		0.15
20	OCH_3	OCH_3	F	162		$C_{23}H_{18}FNO_2$	C, H, N, F	50	0.035
21	OCH_3	OCH_3	NH_2	143		$C_{23}H_{20}N_2O_2$	C, H, N	20	0.6
22	OCH_3	OCH_3	OCH_3	176-177		$C_{24}H_{21}NO_3$	17		0.05

[a] Z or E refer to the pure or preponderant isomer. [b] The phenols were recrystallized in acetic acid; the corresponding ethers were recrystallized in isopropyl alcohol. [c] For mixtures of isomers, the percentages refer to the reaction yield. [d] IC_{50} values were determined from the mean curve of percent inhibition against log concentration. The mean curve was obtained from two to four determinations per concentration. [e] The isomers were not separated. [f] Structure established by X-ray crystallography. [g] *E* isomer according to the priority rule.

Table II. Physical and Biological Properties of 1,1,2-Triphenylethylenes



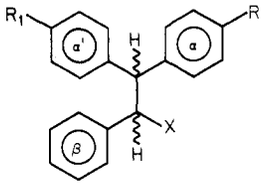
no.	R	R_1	R_2	X	mp, °C	formula	anal. or ref	PGS IC_{50},[a] μM
23	OH	OH	H	H	173	$C_{20}H_{16}O_2$	8	16
4	OH	OH	H	CN	249	$C_{21}H_{15}NO_2$	8	1.8
24	OH	OH	H	CH_2NH_2	110-112	$C_{21}H_{19}NO_2$	8	8
25	OH	OH	H	$CH_2NHCOCH_3$	100	$C_{23}H_{21}NO_3$	8	14
26E	H	OCH_3	Cl	$CONH_2$	258[b]	$C_{22}H_{18}ClNO_2$	C, H, N, Cl	94%[c]
27	OCH_3	OCH_3	H	COOH	169	$C_{23}H_{20}O_4$	15	61%[c]
28	OCH_3	OCH_3	H	$CONH_2$	209	$C_{23}H_{21}NO_3$	18	33

[a] See Table I, footnote d. [b] Recrystallized in acetic acid: yield 75%; isomeric purity 100%, determined by ^1H NMR. [c] Residual activity at 10^{-4} M.

vesicle microsomes. Since inhibition of PGS in vitro is still considered one of the most promising rational approaches for prediction of antiinflammatory activity, our aim was to determine whether these derivatives might not constitute a new class of nonsteroidal antiinflammatory (NSAI) agents, in which case optimization of the structure binding to PGS might lead to a new and highly specific antiinflammatory drug.

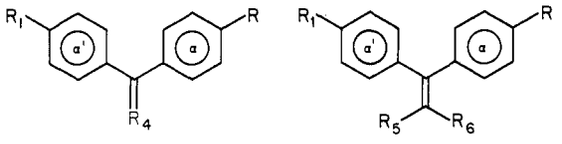
Chemistry. 1,1,2-Triphenylethylene Derivatives (Tables I and II). The isomers or mixtures of isomers

Table III. Physical and Biological Properties of 1,1,2-Triphenylethanes



no.	R	R_1	X	mp, °C	formula	anal. or ref	PGS residual act. at 10^{-4} M, %
29	H	H	CN	102	$C_{21}H_{17}N$	19	75-80
30	OH	OH	CN	98-100	$C_{21}H_{17}NO_2$	C, H, N	76
31	OCH_3	OCH_3	CN	145-146	$C_{23}H_{21}NO_2$	C, H, N	63
32	OH	OH	$CONH_2$	254 (dec)	$C_{21}H_{19}NO_3$	C, H, N	90
33	OH	OH	$CONHCOCH_3$	118-120	$C_{23}H_{21}NO_4$	C, H, N	60

Table IV. Physical and Biological Properties of Bis(*p*-substituted-phenyl)alkenes



no.	R	R_1	R_4	R_5	R_6	mp, °C	formula	anal. or ref	PGS residual act. at 10^{-4} M, %
34	OH	OH				197	$C_{18}H_{18}O_2$	13	53
35a	OH	OH				235	$C_{19}H_{20}O_2$	13	35
36	OH	OH				221-222	$C_{20}H_{22}O_2$	C, H, O	100
37	OH	OH				195-198	$C_{20}H_{22}O_2$	13	35
38	F	OH					$C_{19}H_{19}FO$	C, H	89
35b[a]	OAc	OAc				135-136	$C_{23}H_{24}O_4$	12	40
39	OH	OH		$CH(CH_3)_2$	H	166	$C_{17}H_{18}O_2$	8	26
40	OH	OH		$CH(CH_3)_2$	Cl	169	$C_{17}H_{17}ClO_2$	8	33
41	OH	F		$C(CH_3)_3$	H	124	$C_{18}H_{20}FO$	C, H	78
42	OH	F		C_2H_5	C_2H_5	76	$C_{18}H_{19}FO$	C, H	98

[a] Cyclofenil.

13Z-18E and compounds **12** and **19-22** were prepared by condensation of the appropriate benzophenone and phenylacetonitrile either in 55% NaH/mineral oil under reflux of benzene[9] or in sodium amide under reflux of diethyl ether or benzene.[10] The pure isomers **2E**, **2Z**, and **6Z**, the mixtures of isomers containing predominantly **6E**, **7Z**, **8E**, **9Z**, and **10Z**, and compounds **3-5** and **11** were obtained by demethylation with pyridine hydrochloride of the corresponding methoxy-substituted triphenylacrylonitrile by heating at the reflux temperature for 30 min.[11] The demethylation of **27** gave **23** by decarboxylation.[8]

The amides **26E** and **28** were obtained by heating the corresponding nitrile under reflux for 3 h in isoamyl alcohol containing a caustic soda solution. Acid **27** was similarly prepared but required 70 h of heating because of the high chemical stability of this cyanide group.[10] The amine **24** was the product of selective hydrogenation using Raney nickel as catalyst.[8]

Isomers **6Z** and **6E** were separated by their difference in solubility in acetic acid. The stereoisomers, *E* and *Z*, of **2** and **14-17** were isolated by HPLC on SiO_2 (methylene chloride–heptane for the phenols and chloroform–heptane, 90:10, for the ethers). Because solutions of the phenolic isomers are very photosensitive, they were kept away from light to avoid rapid isomeric equilibration.

2,3,3-Triphenylpropionitrile Derivatives (Table III). 3,3-Bis(4-hydroxyphenyl)-2-phenylpropionitrile (**30**) was obtained by demethylation of compound **31**, the product of the reaction of 4-methoxyphenylmagnesium bromide with 3-(4-methoxyphenyl)-2-phenylpropionitrile.[8] Subsequent alkaline hydrolysis in amyl alcohol gave the

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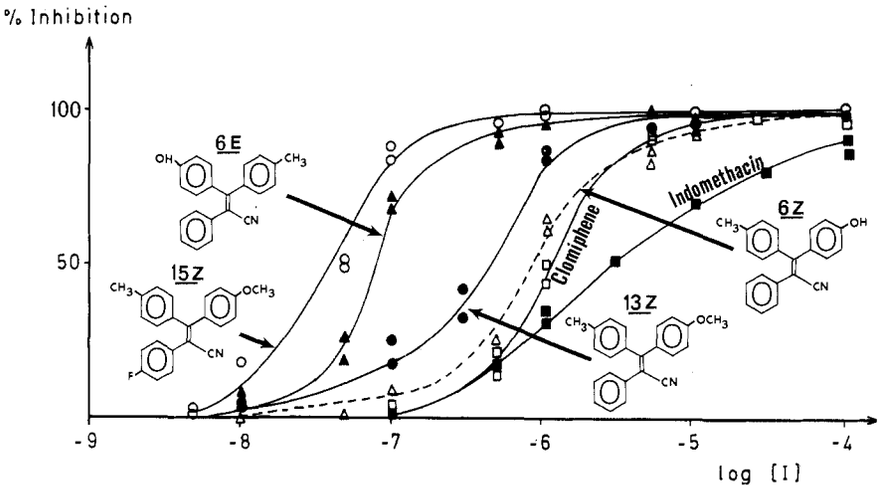

Figure 1. Comparative PGS inhibition curves: (○) **15Z**, (▲) **6E**, (●) **13Z**, (△) **6Z**, (□) clomiphene, (■) indomethacin.

amide **32**.

1,1-Diphenylethylene Derivatives (Table IV). The preparation of compounds **34**, **35a,b**, **37**, **39**, and **40** has been described previously.[8,12,13] Condensation of 4-methoxyphenylmagnesium bromide with 4-fluorophenyl cyclohexyl ketone, followed by demethylation, gave compound **38**. The action of 4-fluorophenylmagnesium bromide on the 4-hydroxyphenyl neopentyl ketone and on the 4-hydroxyphenyl 1-ethylpropyl ketone yielded compounds **41** and **42**, respectively.

X-ray and NMR Analysis. The conformations of isomers **6Z**, **14E**, **15E**, **16E**, and **17Z** were determined by X-ray crystallography. Since nearly all the mixtures of isomers have a methyl or methoxy group in position R or R_1, it was possible, on the basis of the X-ray identification of these *E* and *Z* isomers, to attribute a specific chemical shift to each of these groups: *Z* isomer, $R(OCH_3)$ = 3.84 ppm, $R_1(CH_3)$ = 2.30 ppm; E isomer, $R(CH_3)$ = 2.39 ppm, $R_1(OCH_3)$ = 3.76 ppm. These results are consistent with published observations[14] that have shown that the resonance of protons in substituents para to an aromatic ring in TPE's is at higher fields when this ring is sandwiched between two others on account of the double shielding effect of the ring current. As expected, on account of the homogeneity of this family of compounds, in no case did the absolute chemical-shift values of these groups differ by more than 0.02. We therefore calculated directly the proportion of each isomer in the mixtures. Moreover, the *Z* isomers systematically had a lower R_f value than the *E* isomers on TLC (SiO_2; toluene–heptane, 80:20, for ethers; $CHCl_3$ for phenols), and the melting point of the *Z* isomers was systematically higher than that of the *E* isomers.[15]

Discussion

All compounds were tested for their ability to inhibit prostaglandin synthetase (PGS) in bovine seminal vesicle microsomes. The results are reported in Tables I–IV.

Table V. A Comparison of the Angular Configuration of Several TPE's[a]

molecules	$\hat{\alpha}$, deg	$\hat{\alpha}'$, deg	$\hat{\beta}$, deg
6Z (molecule 1)	49	39	50
6Z (molecule 2)	48	40	53
14E	52	44	55
15E	55	38	58
16E	49	41	45
17Z	45	47	57
(*Z*)-tamoxifen[b]	57	64	51
(*E*)-broparestrol[c]	66	39	54
(*E*)-clomiphene[d]	55	55	58
nafoxidine[e] (molecule 1)	20	76	65
nafoxidine[e] (molecule 2)	17	61	45
nafoxidine[f]	20	89	50
indomethacin[g]			67

[a] See Figure 2. $\hat{\alpha}$, $\hat{\alpha}'$, and $\hat{\beta}$ are the angles between the phenyl ring planes and the central bond plane defined by atoms C4, C7, C8, C9, C27, and C28. The compounds crystallize as racemic mixtures. Only the acute angle ($\hat{\alpha}$ and not $180 - \hat{\alpha}$) was taken into account. [b] Reference 20. [c] Reference 23. [d] Reference 24. [e] Reference 22. [f] Reference 21. [g] Reference 25.

Most known inhibitors of PGS are carboxylic acids. However, although many active compounds were detected among those tested, none had an acid function. Compound **27**, the only test compound with a COOH group, was a poor inhibitor, with 61% residual activity at 10^{-4} M. All the triphenylethane derivatives (Table III) were inactive, indicating that saturation of the double bond results in a loss of activity (compare **30** and **4**, **31** and **19**). Furthermore, all the bis(*p*-substituted-phenyl)alkene derivatives (Table IV) were very poor inhibitors. Thus, the active compounds (Tables I and II, Figure 1) belong exclusively to the triphenylethylene (TPE) series.

Within the TPE series, several features conducive to high inhibitory potency could be distinguished. Thus, for instance, the presence of a cyanide group in the X position enhanced inhibition (**4** > **23**), more so than amino (**24**) or acetylamino (**25**) groups. On the other hand, a carboxylic or amido group was extremely detrimental (**26E** ≪ **17E**, **27**, **28** ≪ **19**). The presence of polar groups in positions R, R_1, and/or R_2 was not an absolute requirement for inhibitory activity, since compound **1** with just hydrogen atoms in all these positions was, nevertheless, a good inhibitor of PGS. However, when a hydroxy group was present, inhibition was greater when this group was situ-

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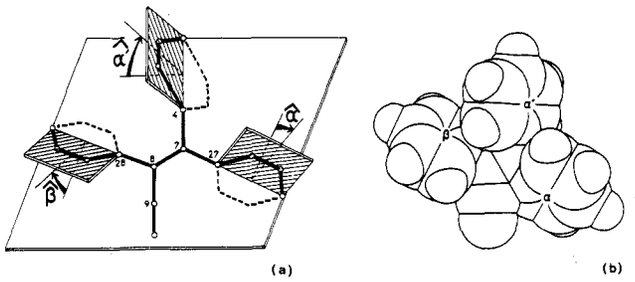


Figure 2. (a) Propeller-like configuration of TPEs; values for angles $\hat{\alpha}$, $\hat{\alpha}'$ and $\hat{\beta}$ are given in Table V. (b) Similarly oriented compact model.

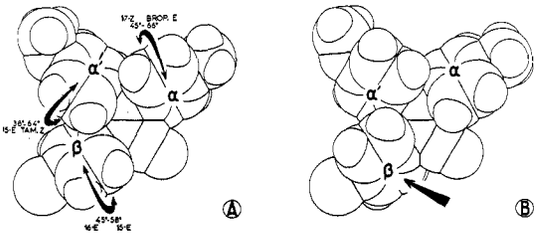
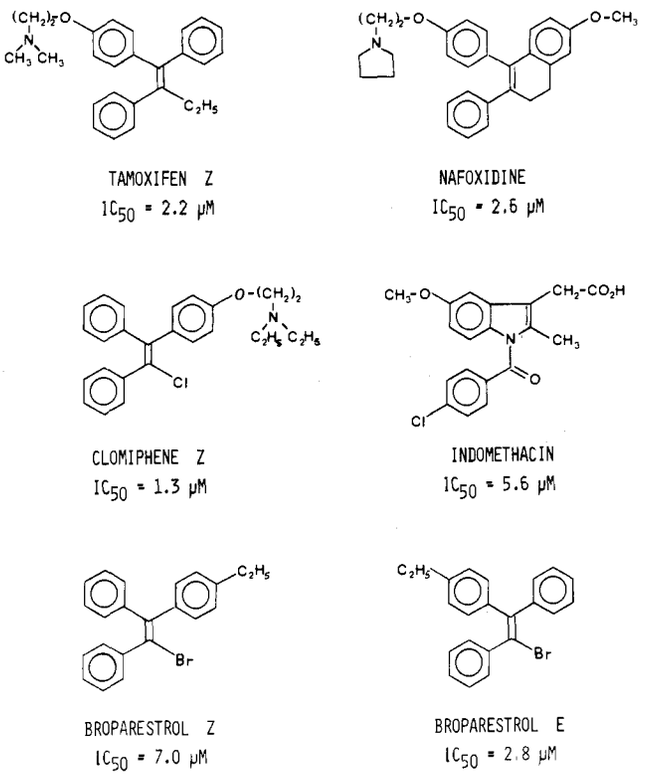


Figure 3. Space-filling representations of both enantiomers (A, B) plotted from crystal coordinates and using the van der Waals radii for **16E**. (A) The angles are the extremes observed for the following compounds: **6Z**, **14E**, **15E**, **16E**, **17Z**, tamoxifen, broparestrol, and clomiphene. (B) The β-phenyl ring is the most accessible and can interact with other atoms or molecules.

ated in either position R or R_1 (**6E** and **6Z**, **2E** and **2Z**) than in position R_2 (**3**). Di- and trihydroxy compounds were rather less active than the monohydroxy derivatives (compare **2**, **4**, and **11**). Methylation of the hydroxy group in position R_2 increased inhibition (**12** > **3**, **22** ≫ **11**). The presence of a halogen (F or Cl) in position R_2 gave rise to the most potent inhibitors in the TPE series as long as the R and R_1 positions were occupied by a methyl or by a methoxy group and not by a hydroxy group [compare **15** (*E* or *Z* isomer), **16** (*E* or *Z* isomer), and **20** with **6Z**, **9Z**, **10Z**, and **13** (*E* or *Z* isomer)]. Finally, bulky substituents in positions R and/or R_1 did not greatly affect inhibitory potency, as exemplified by the well-known related derivatives nafoxidine [1-[2-[4-(3,4-dihydro-6-methoxy-2-phenyl-1-naphthalenyl)phenoxy]ethyl]pyrrolidine], tamoxifen, clomiphene, and broparestrol (*E* or *Z*) [1-(*p*-ethylphenyl)-1,2-diphenyl-2-bromoethylene (Chart I).

The apparent lack of steric hindrance by bulky substituents in R and/or R_1 prompted a comparison of the conformations of five test compounds (**6Z**, **14E**, **15E**, **16E**, and **17Z**) with those reported in the literature for reference substances (Table V, Figures 2 and 3).[20-25] All the isomers crystallized as enantiomorphs, which could not be separated by conventional methods. The comparison confirmed that TPE's are rigid molecules, the positioning of their α, α', and β-phenyl rings restricting rotation. Their conformations were highly analogous. The angle between the β-phenyl ring and the central bond plane, in particular, was found to vary only slightly among substances. An

Chart I



appropriate image to visualize these TPE's might be a propeller with a double bond as the hub. The spatial arrangement of the α, α', and β-phenyl rings thus ressembles three blades situated nearly but not quite symmetrically around a shaft constituted by the perpendicular to the C7–C8 double bond. However, the relative importance of each phenyl ring in PGS inhibition differs as follows: for the α and α' rings, by the variations recorded in the activity of *E* and *Z* isomers (compare **6E** and **6Z**); for the β ring, by the potency conferred by the electronic charge of a halogen in position R_2 (see Table I and several known NSAI agents, e.g., indomethacin [1-(*p*-chlorobenzoyl)-5-methoxy-2-methyl-3-indoleacetic acid], tiaprofenic acid [2-(5-benzoyl-2-thienyl)propionic acid], and diflunisal [2′,4′-difluoro-4-hydroxy[1,1′-biphenyl]-3-carboxylic acid]). Rome and Lands[26] have suggested that this atom may form an irreversible interaction with a residue within the binding site. Indeed, the β ring is not only the most rigid, being able to rotate by just ±6°, but is also the only ring permitting π-electron type interaction. On the basis of these observations, it is tempting to hypothesize that activity in the PGS inhibition test is conditioned by ease of access to this β ring, the α and α' rings acting as more or less polar levers for positioning. That the β ring could act as an anchor by interaction with a hydrophobic region of the site is compatible with the models of Sherrer[27] and Shen.[28,29] However, these models, as well as that of Appleton and Brown,[30] imply a degree

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of steric hindrance not observed in our TPE series and assume the need for an acid group recognized by the cationic site. Potent PGS inhibitors in our TPE series were not acids.

The results obtained on this in vitro enzyme inhibition test have led us to the conclusion that TPE's constitute an interesting new series of PGS inhibitors that are well demarcated from unsymmetrical diphenyl derivatives and from the classical nonsteroid antiinflammatory acids, which represent at present the largest class of PGS inhibitors.

Experimental Section

Melting points were recorded on a Kofler apparatus and are uncorrected (higher than 220 °C on a Maquenne bloc). For mixtures of isomers, instantaneous melting points were determined by projection. Elemental analyses of all new compounds were performed in the Microanalytical Laboratory of the CNRS (Vernaison, France). Results were within ±0.3 of the theoretical values for those elements shown. ^{1}H NMR spectra were recorded in $CDCl_3$ with Me_4Si as internal standard (δ 0) on a Bruker 90-MHz spectrometer. IR spectra were recorded on a Beckman ACCULAB IV. Thin-layer chromatography was performed on silica gel 60 F_{254} precoated aluminium sheets, and HPLC separations were performed on a Jobin Yvon Miniprep equipped with a silica gel 60 15–25 μm (Lichroprep) column. Detection was by UV absorption.

Synthetic Procedures. The following examples have been chosen as illustrations.

2-(4-Chlorophenyl)-3-(4-methoxyphenyl)-3-(4-tolyl)-acrylonitrile (Isomers 16E and 16Z). Twelve grams (54 mmol) of 4-methyl-4′-methoxybenzophenone and 3.7 g of a 55% NaH/mineral oil dispersion were suspended in 200 mL of dry benzene. This suspension was stirred and heated to reflux. A solution of 8.4 g (56 mmol) of 4-chlorophenylacetonitrile in 200 mL of dry benzene was added over a 1-h period. The reflux was maintained for 10 h. The reaction mixture was then poured cautiously into water. The organic layer was washed several times, dried (anhydrous Na_2SO_4), and concentrated. The residue was taken up in 50 mL of isopropyl alcohol, and the crystals were collected (7 g, 38%): mp 149–150 °C (isopropyl alcohol); IR ($CHCl_3$) 2205 (CN) cm^{-1}. The alcohol solution was concentrated and distilled to give 3 g (15%) of the same product: bp 220–225 °C (0.05 mm); TLC showed a double spot (mixture of geometrical isomers), R_f 0.16 and 0.25; ^{1}H NMR ($CDCl_3$) δ 3.84 (s, OCH_3, 55%), 3.77 (s, OCH_3, 45%), 2.39 (s, CH_3, 45%), 2.31 (s, CH_3, 55%). Anal. ($C_{23}H_{18}ClNO$) C, H, N. The isomers were separated in pure form by HPLC, and one of them (**16E**) was identified by X-ray analysis.

2-Phenyl-3-(4-tolyl)-3-(4-hydroxyphenyl)acrylonitrile (Isomers 6Z and 6E). 2-Phenyl-3-(4-tolyl)-3-(4-methoxyphenyl)acrylonitrile (2.2 g, 6 mmol) and pyridine hydrochloride (3 g, 25 mmol) were heated between 220 and 230 °C for 45 min. The reaction mixture was cooled and diluted with water. The solid was filtered and dissolved in 25 mL of warm 5% NaOH. After filtration and cooling, the solution was acidified with HCl. The solid was filtered and the residue was washed and recrystallized in diluted acetic acid. After 2 h, a first crop of crystals was filtered (0.7 g): mp 209 °C (several recrystallizations in acetic acid); TLC (SiO_2; $CHCl_3$), a major spot (R_f 0.04) and a very small spot (R_f 0.14); according to X-ray analysis this solid was primarily composed of isomer *Z*; ^{1}H NMR ($CDCl_3$) δ 7.40–6.78 (m, aromatic), 2.39 (s, CH_3, 4%), 2.30 (s, CH_3, 96%). Anal. ($C_{22}H_{17}NO$) C, H, N. After 48 h, a second crop was filtered (0.5 g): mp 192 °C (recrystallized in diluted acetic acid); TLC, a major spot (R_f 0.14); ^{1}H NMR ($CDCl_3$) δ 7.52–6.55 (m, aromatic), 2.39 (s, CH_3, 68%), 2.30 (s, CH_3, 32%); according to X-ray analysis this solid was a mixture in which the major portion was isomer *E*. A third crop was obtained by dilution of the filtered solution (0.3 g, mp 189–190 °C) containing more isomer *E* than *Z*. The overall yield was 80%.

2-Phenyl-3,3-bis(4-methoxyphenyl)propionitrile (31) (Table III). A solution of 2-phenyl-3-(4-methoxyphenyl)acrylonitrile (18 g, 0.076 mol) in 30 mL of dry THF was slowly added to a Grignard solution prepared from magnesium (2.43 g, 0.1 atom) and 4-methoxyphenyl bromide (20.5 g, 0.11 mol) in dry Et_2O. The reaction mixture was heated to reflux for 5 h, allowed to stand at room temperature for 12 h, and hydrolyzed with dilute HCl. The ether phase was separated. The aqueous solution was extracted with Et_2O. The combined Et_2O extracts were washed until neutral and then dried (anhydrous Na_2SO_4). The solvent was removed and gave an oil, which crystallized on addition of MeOH. Recrystallization from acetic acid gave 11.7 g (45%) of **31**, mp 145–146 °C.

Bis(4-hydroxyphenyl)-2-methylcyclohexylidenemethane (36) (Table IV). Ethyl 2-methylcyclohexanecarboxylate (17 g, 0.1 mol) dissolved in 500 mL of dry Et_2O was added dropwise with vigorous stirring to a Grignard solution of magnesium (7.9 g, 0.3 atom) and 4-methoxyphenyl bromide (56.1 g, 0.3 mol) in 500 mL of dry Et_2O. After the addition, the reaction mixture was refluxed for 2.5 h with stirring and was then cooled. A solution of 10 mol of NH_4Cl in 1 L of water was added. The ether layer was separated, washed, dried over Na_2SO_4, and distilled. The high-boiling fraction was demethylated with pyridine hydrochloride as described previously: 12.3 g (42%) of **36** was collected; mp 221–222 °C. Diacetate derivative: mp 101–103 °C (ethyl alcohol/ligroin). Anal. ($C_{20}H_{22}O_2$) C, H.

1-(4-Hydroxyphenyl)-1-(4-fluorophenyl)-2,2-diethylethylene (42) (Table IV). A solution of 4-methoxyphenyl 1-ethylpropyl ketone (20.6 g, 0.1 mol) dissolved in 100 mL of dry Et_2O was added over 30 min to a Grignard solution prepared from magnesium turnings (2.7 g, 0.11 atom), 4-fluorophenyl bromide (19.25 g, 0.11 mol), and 200 mL of dry Et_2O. After boiling for 1 h with vigorous stirring, the Grignard complex was decomposed with 5 N sulfuric acid. The ether layer was separated, washed with a saturated NaCl solution, dried (anhydrous Na_2SO_4), and concentrated. The residual oil was distilled. The high-boiling fraction was demethylated with pyridine hydrochloride as indicated for **6**: 10.8 g (40%) of crystals was collected; mp 76 °C (ethyl alcohol). Acetate derivative: bp 130–136 °C (0.1 mm); mp 86–87 °C (ethyl alcohol); M_r calcd, 312.39; found, 311.5.

X-Ray Crystallography. Colorless crystals of **6Z**, **14E**, **15E**, **16E**, and **17Z** suitable for X-ray analysis were grown by slow evaporation of 2-propanol or 1:1 methanol–2-propanol solutions. Preliminary cell constants were determined from Weissemberg photographs. All independent reflections corresponding to 2θ (Cu $K\alpha$) <140° were measured on a NONIUS-CAD4 automatic four circle diffractometer using graphite monochromated Cu $K\alpha$ radiation. Cell constants were calculated from least-squares fits of at least 20 reflections. In no case did the two reference reflections monitored every 50 reflections show any significant variation in intensity over the data collection period. The intensity data were corrected for Lorentz-polarization effects. Due to the small size of the crystals, no absorption correction was applied. Measured reflections where $I > 3\sigma(I)$ were considered as observed and were selected for structure analysis. The structures were solved by direct methods with the MULTAN 78 computer programs.[31] Except for the H atoms of the methyl groups of **6Z**, all the atoms were positioned on *E* maps or on subsequent difference Fourrier maps. The structures were refined by block diagonal least squares by using, respectively, isotropic and anisotropic thermal factors for H and non-H atoms. Atomic scattering factors (F, Cl, C, O, and N) were from the "International Tables for X-ray Crystallography",[32] except for H.[33]

Biology. Reagents. [1-^{14}C]Arachidonic acid (58 mCi/mmol) and [^{3}H]PGE_2 (50 Ci/mmol) were purchased from the Radiochemical Centre (Amersham, England). Unlabeled arachidonic acid was from Sigma Chemical Co. (St. Louis, MO) and was stocked at −20 °C in an ethanol solution; glutathion was from Fluka (Switzerland), and hydroquinone was from Prolabo (France). Prostaglandins (PGE_1, PGE_2) were kindly provided by Dr. J. Pike, Upjohn Co. (Kalamazoo, MI). Buffer substances, all analytical grade, were from Merck.

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Preparation of Microsomes. All manipulations were carried out at 4 °C. Frozen bovine seminal vesicles were thawed and then homogenized in a Potter tube with 2 vol of 0.1 M phosphate buffer, pH 7.2, containing 1 mM EDTA and 1 mM cystein. The homogenate was centrifuged for 20 min at 20000*g* in an L 3-50 Beckman centrifuge. The supernatant was centrifuged for 3 h at 100000*g*, and the pellet thus obtained was resuspended in 0.1 M Tris-HCl buffer, pH 8, containing 1 mM EDTA, and resedimented after centrifugation for 3 h at 100000*g*. The washed microsomal fraction was resuspended in this buffer to yield 25 to 30 mg of protein/mL and divided into small fractions, which were stored at −20 °C. Protein concentration was measured[34] with bovine serum albumin as standard.

Prostaglandin Synthetase Assay. Each incubation medium contained bovine seminal vesicle microsomes (2.5–5 mg of protein), [1-^{14}C]arachidonic acid (0.2 μCi/10 μg), reduced glutathion (1 mM), hydroquinone (0.2 mM), human oxyhemoglobin (0.3 μM), and inhibitors (0.1 mM) in 4 mL of 50 mM Tris-HCl buffer, pH 8. The mixture was incubated at 37 °C for 20 min. The reaction was stopped by the addition of 1 M citric acid. At the end of the incubation, [^{3}H]PGE_2 (0.3 μCi/10 μg) was added as an internal standard. Samples were extracted two times with 5 mL of ethyl acetate. The organic phase was washed with water and evaporated to dryness under reduced pressure at 40 °C. The prostaglandins were separated from the arachidonic acid by thin-layer chromatography on silica gel G with benzene–dioxane–acetic acid (20:10:1). The plate was scanned with a Pannax radiochromatogram scanner and exposed to iodine vapor to visualize arachidonic acid and PGE_2. Areas corresponding to the radioactive peaks (arachidonic acid and PGE_2) were scraped and burnt in an Oxymat Intertechnique oxidizer, which separates ^{3}H and ^{14}C. The radioactivity was counted in a Packard Tricarb liquid scintillation spectrometer.

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Acknowledgment. Part of this work was supported by a research grant from PIRMED (CNRS). We express our thanks to A. Sekera and L. Mercklein for their help in the synthesis and testing of these compounds.

Registry No. 1, 6304-33-2; **2Z**, 19460-09-4; **2E**, 84836-12-4; **3**, 16143-90-1; **4**, 66422-14-8; **5**, 82925-18-6; **6Z**, 84836-13-5; **6E**, 84836-14-6; **7Z**, 16144-02-8; **8E**, 84836-15-7; **9Z**, 84836-16-8; **10Z**, 84836-17-9; 11, 76621-40-1; **12**, 16143-89-8; **13Z**, 82925-24-4; **13E**, 84836-18-0; **14E**, 84836-19-1; **14Z**, 84836-20-4; **15E**, 82925-25-5; **15Z**, 82925-26-6; **16E**, 82925-23-3; **16Z**, 84836-21-5; **17E**, 84836-22-6; **17Z**, 84836-23-7; **18E**, 84836-24-8; **19**, 66422-13-7; **20**, 82925-22-2; **21**, 84836-25-9; **22**, 35364-39-7; **23**, 66422-18-2; **24**, 66422-11-5; **25**, 66422-12-6; **26E**, 84836-26-0; **27**, 77799-42-9; **28**, 77799-38-3; **29**, 5350-66-3; **30**, 84836-27-1; **31**, 82925-30-2; **32**, 82925-27-7; **33**, 84836-28-2; **34**, 66422-10-4; **35a**, 5189-40-2; **35b**, 2624-43-3; **36**, 29947-99-7; **37**, 14303-48-1; **38**, 84836-29-3; **39**, 66422-07-9; **40**, 66422-17-1; **41**, 84836-30-6; **42**, 84836-31-7; 4-methyl-4′-methoxybenzophenone, 23886-71-7; 4-chlorophenylacetonitrile, 140-53-4; 2-phenyl-3-(4-methoxyphenyl)acrylonitrile, 5432-07-5; 4-methoxyphenyl bromide, 104-92-7; ethyl 2-methylcyclohexanecarboxylate, 56532-18-4; bis(4-acetoxyphenyl)-2-methylcyclohexylidenemethane, 21327-74-2; 4-methoxyphenyl 1-ethylpropyl ketone, 84836-32-8; 4-fluorophenyl bromide, 460-00-4; 1-(4-acetoxyphenyl)-1-(4-fluorophenyl)-2,2-diethylethylene, 84836-33-9; benzophenone, 119-61-9; 4-methoxybenzophenone, 611-94-9; 4-chloro-4′-methoxybenzophenone, 10547-60-1; 4,4′-dimethoxybenzophenone, 90-96-0; 4,4′-dihydroxybenzophenone, 611-99-4; toluene, 108-88-3; 4-methoxyphenylacetonitrile, 104-47-2; phenylacetonitrile, 140-29-4; 4-fluorophenylacetonitrile, 459-22-3; 4-methylphenylacetonitrile, 2947-61-7; 4-aminophenylacetonitrile, 3544-25-0; prostaglandin synthetase, 9055-65-6.

Supplementary Material Available: The following X-ray crystallography data are available for compounds **6Z**, **14E**, **15E**, **16E**, and **17Z**: cell constants, atomic numbering schemes, and bond lengths and angles (2 pages). Ordering information is given on any current masthead page.