Synthetic Antigonadotropins. IV. Bromotriphenylethylenes

H. H. Fox,[1] J. T. GIBAS, H. L. LEE, AND A. BORIS

Research Laboratories, Hoffmann-La Roche, Inc., Nutley, New Jersey

Received February 12, 1965

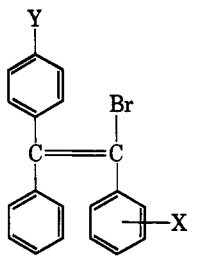
A series of bromotriphenylethylene derivatives has been prepared, every member of which tested so far has shown marked antigonadotropic and estrogenic activity.

Previous work in this continuing study[2] has shown that the antigonadotropic activity of triarylethylenes was closely dependent upon maintaining the integrity of the basic triphenylethylene structure.

$$(C_6H_5)_2\overset{1}{C}=\overset{2}{C}HC_6H_5$$

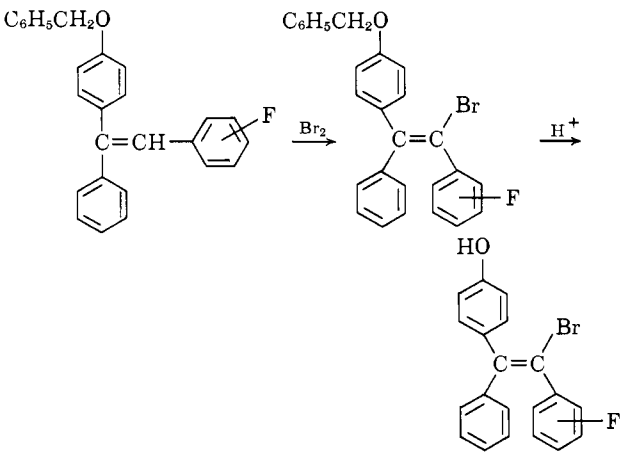
Activity was lost when (1) a pyridine ring or cycloalkyl group was substituted for one of the phenyl groups at C-1; (2) the two phenyl groups at C-1 were bridged; (3) a cyclopropyl group was substituted for the ethylene link; or (4) a nitrogen atom was substituted for C-2. However, the fact that a compound possessed a triphenylethylene structure was no guarantee of activity since activity was also lost in the presence of certain substituents on the phenyl groups.[3]

On the basis of earlier work in this field, it was decided that of the various changes which could be made in the triphenylethylene structure pictured above, one that seemed most desirable would be the replacement of the hydrogen at C-2 with a halogen to produce halotriphenylethylenes. The halogen chosen was bromine and the present report concerns the synthesis of bromotriphenylethylenes of the following structure.



X = F, CF_3, Cl
Y = H, OH, CH_3O, $C_6H_5CH_2O$

These compounds were prepared, in general, by treating the appropriate triphenylethylene in glacial acetic acid solution with 1 molecular equiv. of bromine at room temperature. After standing for 0.5–1 hr., the reaction mixture was refluxed for 2–3 hr., the solvent was removed, and the solid product was recrystallized from the appropriate solvent (usually ethanol). The above procedure was not applicable to those compounds in which Y = OH. Attempts to brominate the hydroxylated compounds directly gave anomalous results, probably due to bromination of the phenolic ring. To circumvent this difficulty attempts were made to demethylate the methoxy analogs. When these attempts also failed, recourse was had to benzyloxy derivatives of the triphenylethylenes. Bromination of the benzyloxy derivatives using acetic acid as a solvent resulted in considerable decomposition with the odor of benzaldehyde much in evidence. Chloroform proved satisfactory as a solvent in these cases and bromination was carried out by the addition of bromine at the reflux temperature of chloroform followed by debenzylation to give the desired hydroxylated bromo derivatives. This sequence of reactions is illustrated in the following equation.



The compounds of this series exist as *cis–trans* isomers. In some instances, both isomeric forms were isolated and arbitrarily identified as "α" and "β" forms. No effort was made to determine their absolute configuration. With the exception of 1,1-diphenyl-2-bromo-2-(*p*-chlorophenyl)ethylene which had previously been prepared by Tadros, *et al.*,[4] all of the compounds reported here and listed in Table I are new.

Pharmacology.—All of the bromotriphenylethylene derivatives prepared in this study showed marked antigonadotropic and marked estrogenic activity when tested as previously described.[2,5] It was apparent that bromination of the triphenylethylene enhanced both the antigonadotropic and estrogenic activity inasmuch as the brominated derivatives were many times more active than their unbrominated precursors. Indeed, three triphenylethylene derivatives which had no activity, namely, 1,1-diphenyl-2-(*m*-trifluoromethylphenyl)ethylene, 1-(*p*-benzyloxphenyl)-1-phenyl-2-(*p*-fluorophenyl)ethylene, and 1-(*p*-benzyloxyphenyl)-1-phenyl-2-(*m*-fluorophenyl)ethylene, all gave active bromo derivatives.

The antigonadotropic and estrogenic activities of the compounds described herein are listed in Table II. Where the estrogenic dose was 0.1 mg., ovariectomized rats were used. The antigonadotropic activity of these

(1) Cyclo Chemical Corp., Los Angeles, Calif.

(2) (a) H. H. Fox, J. T. Gibas, H. L. Lee, and A. Boris, *J. Med. Chem.*, **7**, 306 (1964); (b) H. H. Fox, J. T. Gibas, H. L. Lee, and A. Boris, *ibid.*, **7**, 790 (1964).

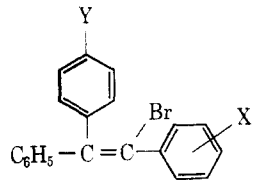
(3) H. H. Fox, J. T. Gibas, H. L. Lee, and A. Boris, *ibid.*, **8**, 250 (1965).

(4) W. Tadros, K. Farahat, and J. M. Robson, *J. Chem. Soc.*, 439 (1949).

(5) A. Boris and H. H. Fox, *Arch. intern. Pharmacodyn.*, **151**, 475 (1964).

Table I

Bromotriphenylethylene Derivatives



No.	Y	X	Form	M.p. or b.p., °C(mm.)	Calcd., % C	Calcd., % H	Calcd., % Br	Found,[a] % C	Found,[a] % H	Found,[a] % Br
I	H	*p*-Cl	...	115–116	...	...	...	...	...	...
II	H	*m*-CF_3	...	153–153.5	62.6	3.5	...	62.3	3.6	...
III	H	*m*-F	...	129–130	68.0	4.0	22.6	67.9	4.3	22.7
IV	H	*o*-F	...	100.5–102	68.0	4.0	22.6	68.1	4.0	22.7
V	H	*p*-F	...	113–114	68.0	4.0	22.6	68.3	4.4	22.4
VI	CH_3O	*o*-F	Mix.	195 (0.15)	65.8	4.2	20.9	65.2	4.3	21.2
VIa	CH_3O	*o*-F	α	100.5–102	65.8	4.2	...	65.6	4.4	...
VII	CH_3O	*p*-F	α	125–126	65.8	4.2	20.9	66.0	4.2	20.8
VIII	CH_3O	*p*-F	β	103–105	65.8	4.2	20.9	65.9	4.6	20.8
IX	CH_3O	*p*-Cl	α	134.5–135	63.1	4.0	28.9[b]	62.8	4.0	29.1[b]
X	CH_3O	*p*-Cl	β	96.5–97.5	63.1	4.0	28.9[b]	63.2	4.2	28.8[b]
XI	CH_3O	*m*-F	Mix.	183 (0.15)	65.8	4.2	20.9	65.8	4.2	20.9
XIa	CH_3O	*m*-F	α	111.5–113	65.8	4.2	20.9	65.9	4.4	20.3
XII	$C_6H_5CH_2O$	*m*-F	α	96–99	70.6	4.4	17.4	70.9	4.6	17.0
XIII	$C_6H_5CH_2O$	*m*-F	β	122–123	70.6	4.4	17.4	70.4	4.4	17.3
XIV	$C_6H_5CH_2O$	*p*-F	α	110–113	70.6	4.4	17.4	70.4	4.1	17.8
XV	$C_6H_5CH_2O$	*p*-F	β	152–153	70.6	4.4	17.4	70.4	4.6	17.1
XVI	$C_6H_5CH_2O$	*o*-F	α	125–128	70.6	4.4	17.4	69.9	4.4	17.4
XVII	$C_6H_5CH_2O$	*o*-F	β	146–147	70.6	4.4	17.4	70.7	4.4	17.5
XVIII	HO	*m*-F	...	134–135	65.0	3.8	21.7	65.0	3.8	22.1
XIX	HO	*p*-F	...	155–156	65.0	3.8	21.7	64.6	3.9	21.6
XX	HO	*o*-F	...	134–142	65.0	3.8	21.7	65.5	4.0	21.8

[a] The authors are indebted to Dr. A. Steyermark and his staff for the microanalyses. [b] Halogen. [c] Not clear.

Table II

No.	Antigonadotropic activity Dose, mg./kg./day (% change) Testes	Prostate	Estrogenic activity Dose[a] (% change in uterus)
I	50 (−58)	50 (−38)	5 (+35)
II	50 (−67)	50 (−75)	5 (+138)
III	50 (−76)	50 (−73)	5 (+79)
IV	25 (−64)	25 (−67)	5 (+219)
V	25 (−66)	25 (−73)	5 (+131)
VI	50 (−68)	50 (−65)	5 (+222)
VIa	1 (−66)	1 (−78)	0.1 (+192)
VII	50 (−70)	50 (−66)	5 (+108)
VIII	50 (−73)	50 (−75)	5 (+123)
IX	50 (−73)	50 (−76)	5 (+156)
X	1 (−44)	1 (−63)	0.1 (+150)
XI	1 (−64)	1 (−80)	0.1 (+131)
XIa	1 (−74)	1 (−75)	0.1 (+178)
XII	50 (−75)	50 (−75)	0.1 (+246)
XIII	50 (−75)	50 (−73)	0.1 (+83)
XIV	50 (−64)	50 (−63)	0.1 (+94)
XVI	50 (−69)	50 (−75)	0.1 (+156)
XVII	50 (−73)	50 (−78)	0.1 (+82)
XVIII	50 (−60)	50 (−61)	0.1 (+256)
XIX	50 (−66)	50 (−64)	0.1 (+229)
XX	50 (−72)	50 (−73)	0.1 (+294)

[a] Dose in mg./rat/day.

compounds was so marked that the screening dose was lowered to 25 mg./kg./day and subsequently to 1 mg./kg./day. It is interesting to note that the *cis-trans* isomers showed no significant difference in activity in either parameter.

Experimental[6]

Bromination. General Method.—To a stirred solution of 0.01 mole of the triphenylethylene derivative in about 30 ml. of glacial acetic acid was added dropwise, at room temperature, 0.01 mole of bromine in 15 ml. of glacial acetic acid. The mixture was permitted to stand at room temperature for 0.5 hr. and was then refluxed for 2 hr. The product was obtained by removal of the acetic acid under vacuum and recrystallization of the residue from ethanol. In general, the residues were solids, but in two instances, removal of the solvent acetic acid left liquids which were distilled and which showed a correct analysis for the desired compounds (VI and XI). Subsequently, ethanol solutions of both these liquids on standing for several days yielded precipitates which were identified as one of the two possible isomeric forms (VIa and XIa, respectively). The other methoxy derivatives were separated into their isomeric forms by recrystallization from ethanol.

Bromination of Benzyloxytriphenylethylene Derivatives.—To a refluxing solution of 0.01 mole of the benzyloxytriphenylethylene derivative in 30 ml. of $CHCl_3$ was added dropwise, 0.01 mole of bromine in 10 ml. of $CHCl_3$. Refluxing was continued for 15 min.; the solvent was removed, and the residue was treated with hot methanol. A portion of the residue dissolved in the methanol and on cooling gave a precipitate of the α-form (XII and XIV). The methanol-insoluble portion on recrystallization from acetonitrile gave the β-form (XIII and XV). In the case of 1-(*p*-benzyloxyphenyl)-1-phenyl-2-bromo-2-(*o*-fluorophenyl)ethylene, the α-form (XVI) was recrystallized from methanol and the β-form (XVII) from diethyl ether.

Hydrolysis of the Benzyloxybromotriphenylethylene Derivatives.—Only the α-forms of the benzyloxybromotriphenylethylene derivatives were hydrolyzed. The hydrolysis was effected by refluxing the appropriate compound with an excess of 20% 2-propanolic HCl overnight. The solvent was then removed and the residue was recrystallized from a CCl_4-hexane mixture (XVIII and XX) or from dilute methanol (XIX).

(6) All melting points are corrected; the boiling points are uncorrected.