Anal. Calcd. for $C_{33}H_{46}O_4N_4$: C, 70.43; H, 8.24; N, 9.96. Found: C, 70.61; H, 8.19; N, 10.01.

Chlorination of Δ^5-Cholesten-3-one.—Δ^5-Cholesten-3-one (1.92 g.) was dissolved in acetic acid (15 ml.) and treated with one portion of *t*-butyl hypochlorite (0.7 ml.). The mixture was allowed to stand overnight. To the yellow solution was added a solution of 2,4-dinitrophenylhydrazine in acetic acid and the mixture was boiled for 30 minutes. The 2,4-dinitrophenylhydrazone of $\Delta^{4,6}$-cholestadien-3-one, m.p. 231–232° (from ethanol–ethyl acetate) was obtained, identical with the product described above.

Chlorination of Δ^4-Cholesten-3-one.—Δ^4-Cholesten-3-one (0.9 g.) was dissolved in acetic acid (7 ml.) and treated with *t*-butyl hypochlorite (0.4 ml.). After the mixture had stood overnight, a solution of 2,4-dinitrophenylhydrazine in acetic acid was added and the mixture was boiled for 30 minutes. The precipitate was filtered, dissolved in chloroform and chromatographed over alumina. The 2,4-dinitrophenylhydrazone of Δ^4-cholesten-3-one, m.p. 232–233°, was obtained as the major product, identical with an authentic sample, showing that very little chlorination had taken place. A second 2,4-dinitrophenylhydrazone was obtained, m.p. 257° dec. (from ethanol–chloroform) and was not investigated further. No 2,4-dinitrophenylhydrazone of $\Delta^{4,6}$-cholestadien-3-one was obtained.

CAMBRIDGE, MASS.

[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RESEARCH LABORATORIES, THE WM. S. MERRELL COMPANY]

Synthetic Estrogens. Halotriphenylethylene Derivatives

BY R. S. SHELTON, M. G. VAN CAMPEN, JR., D. F. MEISNER, S. M. PARMERTER, E. R. ANDREWS, R. E. ALLEN AND K. K. WYCKOFF

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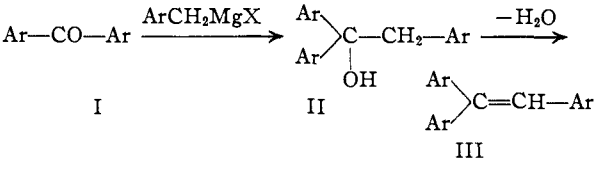
A series of halotriphenylethylene derivatives has been prepared and screened for estrogenic activity. Several of the products obtained showed a high order of estrogenic activity combined with a long duration of action.

A number of non-steroidal compounds have been shown to have estrogenic activity.[1a,b] Hydroxy or alkoxy substitution is one means of obtaining highly potent, short-acting, synthetic estrogens.[2] Robson and Schönberg[3] reported that triphenylethylene and chlorotriphenylethylene were estrogens of low potency but of unusual duration of action. The authors, as well as Robson, Schönberg, Dodds and others,[4-13] have shown that increased potency is obtained in various alkoxy-substituted halotriphenylethylenes.

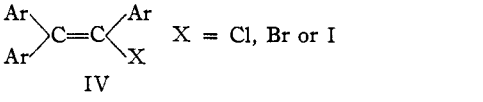
The work reported here deals principally with the synthesis and estrogenic activity of triphenylethylene derivatives having hydroxy or alkoxy substituents on all three benzene nuclei.

Most of the compounds were prepared by the reaction of appropriate benzylmagnesium halides with suitable diaryl ketones I followed by dehydration of the resulting carbinols II to triarylethylenes III



I II III

The triarylethylenes were then halogenated to obtain halotriarylethylenes IV.



X = Cl, Br or I

IV

In a few cases, the halogen was replaced by hydroxy, carboxy or alkyl substituents.

Tris-(*p*-alkoxyphenyl)- and tris-(*p*-aralkoxyphenyl)-ethylenes were converted to hydroxy derivatives by three types of dealkylation reactions: (1) demethylation with potassium hydroxide at elevated temperatures, (2) debenzylation by hydrogenolysis and (3) debenzylation with methylmagnesium iodide. In some cases, the hydroxy derivatives were then esterified.

The first debenzylation reactions were carried out with hydrogen and 10% palladium on charcoal. Recent work has shown, however, that this reaction can be effected more smoothly and consistently if a catalytic amount of hydrochloric acid is added to the reaction mixture as a promoter. For example, catalytic debenzylation of 1,1-bis-(*p*-benzyloxyphenyl)-2-(*p*-methoxyphenyl)-ethanol (compound 4), with concurrent or subsequent dehydration, gave 1,1-bis-(*p*-hydroxyphenyl)-2-(*p*-methoxyphenyl)-ethylene (compound 12) in a higher yield than did the Grignard cleavage of 1,1-bis-(*p*-benzyloxyphenyl)-2-(*p*-methoxyphenyl)-ethylene (compound 24). The controlled hydrogenolysis of bromo-2,2-bis-(*p*-benzyloxyphenyl)-1-(*p*-methoxyphenyl)-ethylene (compound 26) gave bromo-2,2-bis-(*p*-hydroxyphenyl)-1-(*p*-

(1) (a) J. W. Cook, E. C. Dodds and C. L. Hewett, *Nature*, **131**, 56 (1933); (b) for a review of synthetic estrogens see U. V. Solmssen, *Chem. Revs.*, **37**, 481 (1945).

(2) E. C. Dodds and W. Lawson, *ibid.*, **137**, 996 (1936).

(3) J. M. Robson and A. Schönberg, *ibid.*, **140**, 196 (1937).

(4) E. C. Dodds, L. Goldberg, W. Lawson and R. Robinson, *Proc. Roy. Soc. (London)*, **B127**, 140 (1939).

(5) A. Schönberg, J. M. Robson, W. Tadros and H. A. Fahim, *J. Chem. Soc.*, 1327 (1940).

(6) J. M. Robson and A. Schönberg, *Nature*, **150**, 22 (1942).

(7) J. M. Robson and M. Y. Ansari, *J. Pharmacol. Exptl. Therap.*, **79**, 340 (1943).

(8) E. C. Dodds, L. Goldberg, E. J. Grünfeld, W. Lawson, C. M. Saffes and R. Robinson, *Proc. Roy. Soc. (London)*, **B132**, 83 (1944).

(9) J. S. H. Davies and Imperial Chemical Industries, Ltd., British Patent 549,200 (November, 1942).

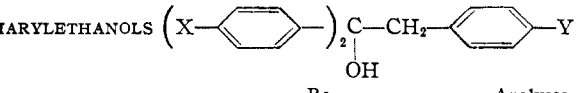
(10) J. S. H. Davies, Leslie A. Elson and Imperial Chemical Industries, Ltd., British Patent 549,353 (November, 1942).

(11) C. R. Thompson and H. W. Werner, *Proc. Soc. Exptl. Biol. Med.*, **77**, 494 (1951).

(12) R. S. Shelton and M. G. Van Campen, Jr., U. S. Patent 2,430,891 (November, 1947).

(13) R. S. Shelton and M. G. Van Campen, Jr., U. S. Patent 2,571,954 (October, 1951).

TABLE I

INTERMEDIATE 1,1,2-TRIARYLETHANOLS 

No.	X	Y	Formula	Yield, %	M.p., °C.	Recryst. solvent[a]	Analyses, % Carbon Calcd.	Carbon Obsd.	Hydrogen Calcd.	Hydrogen Obsd.
1	CH_3O–	H	$C_{22}H_{22}O_3$	77	143–144[b]	A	79.01	78.97	6.63	6.59
2	CH_3O–	CH_3O–	$C_{23}H_{24}O_4$	80	130–131[c]	A	75.85	75.85	6.65	6.52
3	CH_3O–	$C_6H_5CH_2O$–	$C_{29}H_{28}O_4$	50	123–125	B	79.05	79.10	6.41	6.40
4	$C_6H_5CH_2O$–	CH_3O–	$C_{35}H_{32}O_4$	80	120–121	A	81.38	81.65	6.24	6.32
5	$C_6H_5CH_2O$–	$C_6H_5CH_2O$–	$C_{41}H_{36}O_4$	76	165–166	C	83.10	82.93	6.12	6.27

[a] Recrystallization solvents: A, 95% ethanol containing a trace of NH_4OH; B, 95% ethanol; C, butanone. [b] A. Orekhoff, *Bull. soc. chim.*, **25**, 174 (1919). [c] R. S. Shelton and M. G. Van Campen, Jr., U. S. Patent 2,430,891 (November, 1947).

methoxyphenyl)ethylene (compound 14), which also was prepared in a good yield by the reduction of bromo-2,2-bis-(*p*-propionoxyphenyl)-1-(*p*-methoxyphenyl)-ethylene (compound 31) with lithium aluminum hydride.

Attempts to prepare the analogous tri-allyloxy substituted compounds were unsuccessful. The Grignard reagent, prepared from *p*-allyloxybenzylmagnesium halide, decomposed spontaneously due to the susceptibility of allyloxy aryl ethers to ether cleavage.[14,15]

Physical constants and estrogenic activity of these compounds are given in the accompanying tables. Several known compounds have been included for comparative purposes.

The halotris-(*p*-alkoxyphenyl)-ethylenes retained the characteristic long duration of action of chlorotriphenylethylene but showed a marked increase in potency. Chlorotris-(*p*-methoxyphenyl)-ethylene (compound 18), one of the most active and interesting compounds prepared, was unusual in that it produced a true estrogenic response with very little effect upon the adrenal or pituitary gland weight of rats.[11–13] Replacement of alkoxy by hydroxy or acyloxy groups in these compounds occasionally produced an increase in potency with a concomitant decrease in duration of action (compare compounds 14, 30, 31). The tris-(*p*-benzyloxyphenyl)-ethylenes were inactive as estrogens (compounds 27, 28).

Halogenation of the triarylethylenes generally produced an increase in estrogenic potency. This was in agreement with the reports of Robson and others.[3,16,17] The exceptions were those compounds which contained a *p*-benzyloxyphenyl group on the carbon atom to which the halogen was also attached (compare compounds 21, 22 and 27, 28). In these cases, the expected increase in potency due to the introduction of the halogen appeared to be eliminated or overshadowed by the potency-decreasing effect of the benzyloxy group. There was no marked difference in activity when one halogen was substituted for another (compounds 18, 19, 20). This was contrary to the report of Barbier, Rumpf and Roland[18] that activity in the halotriarylethylene series varied with the particular halogen.

Experimental[19]

The reactions used in the preparation of triarylcarbinols, triarylethylenes and halotriarylethylenes are illustrated by specific examples. Preparations which varied from the general methods are described separately, and new intermediates are given at the end of the Experimental part. Some of the triarylethylenes were obtained as crystalline solvates and appropriate drying conditions for the compounds involved are given in footnotes to Table II.

The intermediate triarylcarbinols which were isolated are recorded in Table I. Unlisted carbinols were not purified, but were dehydrated directly to triarylethylenes. The triarylethylenes and triarylethanes prepared are listed in Table II, and the estrogenic activity data are listed in Table III. Compounds 13 and 23 were not tested for estrogenic activity. The remaining compounds, not listed in Table III, were inactive when tested at dose levels of 100 mcg.

Carbinol Preparation. 1,1,2-Tris-(*p*-methoxyphenyl)-ethanol (Compound 2).—A hot solution of 18 g. (0.075 mole) of 4,4′-dimethoxybenzophenone in 50 ml. of dry benzene was diluted with 100 ml. of anhydrous ether. The resulting fine suspension was stirred while a solution of 0.08 mole of *p*-methoxybenzylmagnesium chloride[20] in 225 ml. of anhydrous ether was added over a 90-minute period. After the addition, the mixture was heated to reflux for an additional 15 minutes, then decomposed by pouring into a mixture of 25 g. of ammonium chloride, 100 ml. of crushed ice and 5 ml. of 28% ammonium hydroxide. The ether layer was separated, washed once with water and evaporated at a temperature not exceeding 50°. Recrystallization of the residue from 200 ml. of ethanol containing 1 ml. of 28% ammonium hydroxide gave 22 g. (80%) of pure product which melted at 130–131°.[21]

Compounds containing allyloxy and benzyloxy groups in place of the methoxy substituents were prepared from 4,4′-diallyloxybenzophenone[22] and 4,4′-dibenzyloxybenzophenone,[22] respectively.

Dehydration of Carbinols. Tris-(*p*-methoxyphenyl)-ethylene (Compound 15).—A mixture of 83 g. (0.228 mole) of 1,1,2-tris-(*p*-methoxyphenyl)-ethanol and 90 ml. of 85% phosphoric acid was stirred and heated on a steam-bath for three hours, then poured into a mixture of 400 ml. of ice-water and 300 ml. of chloroform. After the two layers were separated, the aqueous phase was extracted twice with 100-ml. portions of chloroform. The combined chloroform extracts were washed once with water, then with a saturated solution of sodium bicarbonate and finally with water. After the chloroform was evaporated, the residual oil was crystallized from 500 ml. of a 1:4 mixture of acetone and 95% ethanol to give 67 g. (85%) of pure product, m.p. 100–101°.

(14) A. Lüttringhaus, G. v. Sääf and K. Hauschild, *Ber.*, **71**, 1673 (1938).

(15) R. I. Meltzer and J. A. King, THIS JOURNAL, **75**, 1355 (1953).

(16) J. M. Robson, A. Schönberg and H. A. Fahim, *Nature*, **142**, 292 (1938).

(17) J. M. Robson, J. S. H. Davies and W. Tebrick, *Brit. J. Pharmacol.*, **5**, 376 (1950).

(18) P. Barbier, P. Rumpf and M. Roland, *Bull. soc. chim. biol*, **31**, 286 (1949).

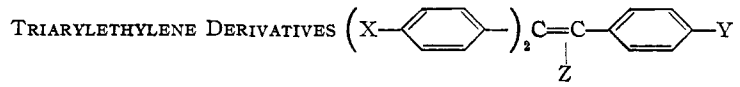
(19) All temperatures are uncorrected.

(20) Substituted benzyl Grignard reagents were prepared by the method of M. G. Van Campen, S. M. Parmerter and D. F. Meisner, THIS JOURNAL, **70**, 2296 (1948).

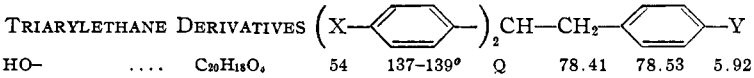
(21) The above procedure is outlined because it was the general method used for preparing the carbinols, but a more economical preparation of 1,1,2-tris-(*p*-methoxyphenyl)-ethanol has been developed in these laboratories utilizing the reaction of *p*-methoxyphenylmagnesium bromide with desoxyanisoin.

(22) W. Tadros, *J. Chem. Soc.*, 442 (1949).

TABLE II

TRIARYLETHYLENE DERIVATIVES 

No.	X	Y	Z	Formula	Yield, %	M.p., °C.	Recryst. solvent[a]	Carbon Calcd.	Carbon Obsd.	Hydrogen Calcd.	Hydrogen Obsd.	Halogen Calcd.	Halogen Obsd.
6	H	H	H	$C_{20}H_{16}$	72	69–70[b]	D	93.71	93.64	6.29	6.26	...	...
7	H	H	OH	$C_{20}H_{16}O$[c]	13	135–136	E	88.20	88.39	5.92	6.03	...	...
8	H	H	Cl	$C_{20}H_{15}Cl$[d]	..	116–117	B	82.61	82.67	5.20	5.30	12.19	11.92
9	CH_3O–	H	H	$C_{22}H_{20}O_2$	97	62–64[e]	B	83.51	83.76	6.37	6.46	...	...
10	CH_3O–	H	Br	$C_{22}H_{19}BrO_2$	81	114–115[f]	D	66.84	66.90	4.85	4.66	20.22	20.29
11	HO–	HO–	H	$C_{20}H_{16}O_2$[g]	70	189–191[h]	G	78.93	78.88	5.30	5.40	....	...
12	HO–	CH_3O–	H	$C_{21}H_{18}O_2$	47	192–193	H	79.22	79.29	5.70	5.87	...	...
13	HO–	CH_3O–	Cl	$C_{21}H_{17}ClO_2$	91	164	H	71.49	71.39	4.86	4.87	10.04	9.80
14	HO–	CH_3O–	Br	$C_{21}H_{17}BrO_2$	77	160–161[i]	H	63.50	63.50	4.30	4.50	20.12	20.03
15	CH_3O–	CH_3O–	H	$C_{23}H_{22}O_2$	85	100–101[j]	I	79.72	80.00	6.40	6.41	...	...
16	CH_3O–	CH_3O–	C_2H_5	$C_{25}H_{26}O_3$[k]	32	87–88	D	80.18	80.36	7.00	7.02	...	...
17	CH_3O–	CH_3O–	COOH	$C_{24}H_{22}O_4$	34	202–203	J	73.9	73.7	5.70	5.45	[l]	...
18	CH_3O–	CH_3O–	Cl	$C_{23}H_{21}ClO_2$	67	113–114[j]	D	72.53	72.63	5.56	5.33	9.31	9.30
19	CH_3O–	CH_3O–	Br	$C_{23}H_{21}BrO_2$	93	119–121[m]	D	64.95	64.75	4.97	4.94	18.82	18.80
20	CH_3O–	CH_3O–	I	$C_{23}H_{21}IO_2$	85	114–115	B	58.48	58.54	4.48	4.64	26.87	26.83
21	CH_3O–	$C_6H_5CH_2O$–	H	$C_{29}H_{26}O_3$	73	139–140	K	82.44	82.61	6.20	6.36	...	...
22	CH_3O–	$C_6H_5CH_2O$–	Br	$C_{29}H_{25}BrO_3$	87	165–166	C	69.48	69.48	5.03	5.04	15.94	16.10
23	CH_2=CH—CH_2O	CH_3O–	H	$C_{27}H_{26}O_2$	73	101–103	L	81.38	81.39	6.58	6.65	...	...
24	$C_6H_5CH_2O$–	CH_3O–	H	$C_{36}H_{30}O_3$	83	83–84	F	84.31	84.30	6.01	5.94	...	...
25	$C_6H_5CH_2O$–	CH_3O–	Cl	$C_{36}H_{29}ClO_3$	65	145–146	F	78.86	78.89	5.48	5.54	6.67	6.65
26	$C_6H_5CH_2O$–	CH_3O–	Br	$C_{36}H_{29}BrO_3$	84	152–153	F	72.79	72.92	5.06	5.21	13.88	14.00
27	$C_6H_5CH_2O$–	$C_6H_5CH_2O$–	H	$C_{41}H_{34}O_3$	86	134–135	F	85.70	85.67	5.96	5.97	...	...
28	$C_6H_5CH_2O$–	$C_6H_5CH_2O$–	Br	$C_{41}H_{33}BrO_3$	87	140–141	F	75.35	75.43	5.09	5.16	12.23	12.02
29	CH_3COO–	CH_3COO–	H	$C_{26}H_{22}O_6$	29	138–140	M	72.55	72.60	5.15	5.08	...	...
30	CH_3COO–	CH_3COO–	Br	$C_{26}H_{21}BrO_6$	17	151–153	D	61.31	61.19	4.16	4.35	15.50	15.65
31	C_2H_5COO–	CH_3O–	Br	$C_{27}H_{25}BrO_3$	40	118–120	B, N	63.67	63.65	4.95	5.03	15.69	15.82
32	C_2H_5COO–	C_2H_5COO–	H	$C_{28}H_{28}O_6$	17	96–98	O	73.71	73.60	5.93	5.98	...	...
33	$(CH_3)_2N$–	CH_3O–	H	$C_{25}H_{25}N_2O$	35	106–108[j]	P	80.61	80.32	7.58	7.77	[n]	...

TRIARYLETHANE DERIVATIVES 

34	HO–	HO–	....	$C_{20}H_{18}O_4$	54	137–139[o]	Q	78.41	78.53	5.92	6.06	...	...
35	HO–	CH_3O–	....	$C_{21}H_{20}O_3$	63	134–135	H	78.73	78.48	6.29	6.43	...	...
36	CH_3O–	HO–	....	$C_{22}H_{22}O_3$	15	117–118	M	79.02	79.01	6.64	6.69	...	...
37	CH_3O–	CH_3O–	....	$C_{24}H_{24}O_2$	88	86–87	L	79.28	79.25	6.94	6.95	...	...

[a] Recrystallization solvents: A, 95% ethanol containing a trace of NH_4OH; B, 95% ethanol; C, butanone; D, methanol; E, methanol–benzene; F, acetone; G, xylene; H, benzene; I, acetone–methanol; J, dilute acetic acid; K, 95% ethanol–butanone; L, absolute ethanol; M, benzene–petroleum ether; N, ethyl ether; O, ether–petroleum ether; P, chloroform–ethyl ether; Q, toluene. [b] H. Staudinger and N. Kon, *Ann.*, **384**, 38 (1913), reported a m.p. of 72°, and C. Stadnikoff, *Ber.*, **47**, 2133 (1914), found a m.p. of 72–73°. [c] Prepared using the method of H. Biltz, *Ber.*, **32**, 650 (1899). [d] Prepared using the method of A. Schönberg, *et al.*[5] [e] A. Orekhoff, *Bull. soc. chim.*, **25**, 174 (1919), reported a m.p. of 62–63°. [f] C. F. Koelsch, THIS JOURNAL, **54**, 2487 (1932), reported a m.p. of 109–111°. [g] R. S. Shelton and M. G. Van Campen, Jr., U. S. Patent 2,571,954 (October, 1951). [h] Dried at 78° and 20 mm. over P_2O_5 and paraffin. [i] Melts with decomposition. [j] R. S. Shelton and M. G. Van Campen, Jr., U. S. Patent 2,430,891 (November, 1947). [k] Prepared using the method described in U. S. Patent 2,301,260. [l] Neut. equiv. calcd. for $C_{24}H_{22}O_5$: 390. Found, 387. [m] J. S. H. Davies, Brit. Patent 549,200 (January, 1942). [n] *Anal.* Calcd. for $C_{25}H_{25}N_2O$: N, 7.52. Found: N, 7.38. [o] Dried six hours *in vacuo* at 110° over P_2O_5 and paraffin.

Halogenation. Chlorotris-(*p*-methoxyphenyl)-ethylene (Compound 18).—To a vigorously stirred solution of 10 g. (0.029 mole) of tris-(*p*-methoxyphenyl)-ethylene in 35 ml. of carbon tetrachloride was added, over a 90-minute period, a solution of 2 g. (0.056 mole) of chlorine in 50 ml. of carbon tetrachloride. After the solvent was evaporated, the residue was recrystallized from 400 ml. of methanol to give 8 g. (67%) of pure chlorotris-(*p*-methoxyphenyl)-ethylene which melted at 113–114°.

Iodotris-(*p*-methoxyphenyl)-ethylene (Compound 20).—A few drops of ethyl bromide were added to a stirred mixture of 3.48 g. (0.143 gram atom) of magnesium turnings and 30 ml. of anhydrous ether. When the reaction had started, a solution of 20 g. (0.047 mole) of bromotris-(*p*-methoxyphenyl)-ethylene in 30 ml. of anhydrous benzene was added to the stirred mixture over a 90-minute period. The mixture was then heated to reflux, and a solution of 10.5 g. (0.096 mole) of ethyl bromide in 350 ml. of anhydrous ether was added. Stirring and a gentle rate of reflux were maintained for two hours after which time most of the magnesium had reacted. The solution was decanted from the excess magnesium into a dropping funnel and added dropwise, over a 30-minute period, to a vigorously stirred solution of 35.4 g. (0.140 mole) of iodine in 500 ml. of anhydrous ether. The solution was refluxed for 30 minutes, concentrated to 600 ml. and poured into a mixture of ice and dilute hydrochloric acid. The two layers were separated, and the aqueous layer extracted with ether. The combined ether layers were washed three times with 50-ml. portions of sodium thiosulfate solution and once with water, then dried over anhydrous magnesium sulfate. After the solvent was evaporated, the residue was dissolved in 250 ml. of hot methanol and 10 ml. of chloroform. The yellow prisms (20 g.) which separated from the cool solution melted at 113–114°. One recrystallization from a solution of methanol and chloroform gave 19.2 g. (85%) of the product, m.p. 113.5–114.5°. A second recrystallization from a solution of one part acetone and three parts methanol raised the melting point to 114–115°.

1,1,2-Tris-(*p*-hydroxyphenyl)-ethane (Compound 34).—A suspension of 11.5 g. (0.02 mole) of 1,1,2-tris-(*p*-benzyloxyphenyl)-ethylene and 2 g. of 10% palladium on charcoal in 200 ml. of absolute ethanol was shaken for three hours at room temperature under hydrogen at an initial pressure of 45 p.s.i. After the catalyst was removed by filtration, the filtrate was evaporated to dryness, and the residue was dissolved in benzene, diluted with petroleum ether (75–90°) and chilled at 5° for several days. The crystalline precipitate was recrystallized from toluene to give 3.3 g. (54%) of the product, which melted at 137–139° after it had been dried for six hours at 110° *in vacuo* to remove solvent of crystallization.

TABLE III

ESTROGENIC ACTIVITY

No.	Potency R.U. in mcg.[b] Oral	Subcutaneous	Duration of action[a] Oral Dose, R.U.	Oral Duration, days	Subcutaneous Dose, R.U.	Subcutaneous Duration, days
8	*Ca.* 25	86	10	2	10	15
			100	4	100	11–13
10	28.5	113	35	2	10	14
			175	11	100	12
14	30	0.99	1	1	10	1
			10	4	100	1
			166	3	5000	2
18	18[c]	55	52	2	18.5	>57
			260	17		
19	*Ca.* 25	*Ca.* 50	10	1	10	5–7
			100	7–10	100	7–10
20	2 26[d]	...	..	...	....	...
25	75	185	10	1	10	1
			100	6		
26	116	500	10	1	....	...
			100	3		
29	Inactive	66	..	...	10	1
					100	30
31	15	15	..	...	1	12
32	Inactive	80	..	...	10	4
Diethylstilbestrol	1.0	0.3	..	...	100	14
Hexestrol	12.0	0.35	20	1	....	...
			200	4	10	1
			1650	4	100	2
					4545	2

[a] Duration of estrogenic activity was determined in groups of twelve castrate female rats. The duration was taken as the length of time in which one-half of the animals no longer showed an estrus type vaginal smear. [b] Rat unit (R.U.): The dose required to cause vaginal cornification in 50% of the animals comprising a dose group (fifteen to twenty castrate female rats). The compounds were administered by the indicated route in three equal doses at four-hour intervals. Rat units were determined by using three dose levels for each compound. [c] Activity in mouse units was 1.78 mcg. Mouse unit (M.U.): The dose required to cause a 100% increase in uterine weight of immature mice. The compounds were administered subcutaneously three times a day for three days. The uteri were dissected out and weighed on a torsion balance 24 hours after the last injection. The mouse units were determined by using three dose groups of five animals each. [d] Activity in mouse units.

1,1-Bis-(*p*-hydroxyphenyl)-2-(*p*-methoxyphenyl)-ethane (compound 35) and 1,1-bis-(*p*-methoxyphenyl)-2-(*p*-hydroxyphenyl)-ethane (compound 36) were prepared similarly from the corresponding benzyloxyphenylethylenes.

1,1-Bis-(*p*-hydroxyphenyl)-2-(*p*-methoxyphenyl)-ethylene (Compound 12). A. Cleavage by Hydrogenolysis.—A solution of 30 g. (0.058 mole) of 1,1-bis-(*p*-benzyloxyphenyl)-2-(*p*-methoxyphenyl)-ethanol, 1 ml. of concentrated hydrochloric acid and 300 ml. of ethyl acetate was shaken with 2 g. of 10% palladium on charcoal under hydrogen at an initial pressure of 45 p.s.i. The theoretical amount of hydrogen (0.116 mole) was absorbed in one hour. The catalyst was removed by filtration. The filtrates from four runs, in which a total of 120 g. (0.233 mole) of the ethanol was used, were combined and evaporated to dryness. The residue was dissolved in ether and extracted with 5% sodium hydroxide solution. Acidification of the alkaline solution with dilute hydrochloric acid gave an oil which slowly solidified. Recrystallization from benzene gave 44.5 g. (60%) of a light tan product, m.p. 187–189°.

B. Grignard Cleavage.—A solution of 0.037 mole of methylmagnesium iodide in ether was added to a suspension of 5 g. (0.01 mole) of 1,1-bis-(*p*-benzyloxyphenyl)-2-(*p*-methoxyphenyl)-ethylene in 200 ml. of anhydrous ether. After evaporation of the solvent, the residue was heated for five hours on the steam-bath, cooled, and treated with an excess of saturated ammonium chloride solution. The mixture was extracted with ether and the combined ether extracts were, in turn, extracted with dilute aqueous sodium hydroxide. Saturation of the alkaline solution with carbon dioxide gave a gummy precipitate which melted at 192–193° after two recrystallizations from benzene; yield 1.5 g. (47%). The product was identical with that obtained by method A.

Bromo-2,2-bis-(*p*-propionoxyphenyl)-1-(*p*-methoxyphenyl)-ethylene (Compound 31).—A mixture of 75 g. (0.236 mole) of 1,1-bis-(*p*-hydroxyphenyl)-2-(*p*-methoxyphenyl)-ethylene, 240 ml. of dry pyridine and 240 ml. of propionic anhydride was heated for three hours on a steam-bath, then poured into two liters of ice-water. The mixture was extracted with ether and the ether solution was extracted with dilute acid, then dilute sodium hydroxide solution, dried over anhydrous magnesium sulfate and evaporated.

To a stirred solution of the residue in 700 ml. of dry carbon tetrachloride was added, during a three-hour period, a solution of 37.7 g. (0.236 mole) of bromine in 500 ml. of carbon tetrachloride. The mixture was stirred an additional 12 hours. After washing with dilute sodium bisulfite solution, then dilute alkali, the solution was dried over anhydrous magnesium sulfate and evaporated. Recrystallization of the oily residue from absolute ethanol, then twice from dry ether gave 48.2 g. (40%) of product which melted at 118–120°.

Bromo-2,2-bis-(*p*-hydroxyphenyl)-1-(*p*-methoxyphenyl)-ethylene (Compound 14). A. Cleavage by Ester Reduction.—A solution of 2.0 g. (0.0039 mole) of bromo-2,2-bis-(*p*-propionoxyphenyl)-1-(*p*-methoxyphenyl)-ethylene in 100 ml. of anhydrous ether was added, over a ten-minute period, to a stirred solution of 0.21 g. (0.0055 mole, 50% excess) of lithium aluminum hydride in 100 ml. of ether. The mixture was stirred for ten minutes after the addition, then decomposed by adding dropwise 5 ml. of water followed by 25 ml. of 10% hydrochloric acid. The ether layer was separated, dried over anhydrous magnesium sulfate and evaporated under reduced pressure at a temperature not exceeding 40°. Higher temperatures resulted in decomposition of the product.

The residual oil was rubbed under petroleum ether (40–60°) until solid, then recrystallized from 50 ml. of benzene to yield 1.2 g. (77%) of pure product, m.p. 160–161° (dec.).

B. Cleavage by Hydrogenolysis.—A mixture of 4 g. (0.0034 mole) of bromo-2,2-bis-(*p*-benzyloxyphenyl)-1-(*p*-methoxyphenyl)-ethylene, 2 g. of 10% palladium on charcoal and 100 ml. of absolute ethanol was shaken under hydrogen at an initial pressure of one atmosphere. The calculated amount of hydrogen (0.0068 mole) was absorbed in 20 minutes. After removal of the catalyst by filtration, the solution was evaporated to dryness at room temperature under a stream of air. Recrystallization of the residue from benzene gave 1.8 g. (81%) of product, m.p. 158–159° (dec.).[23]

The melting point of a mixture of this material with the same compound prepared by method A was not depressed.

The corresponding chloro derivative (compound 13) was prepared in the same manner.

Tris-(*p*-acetoxyphenyl)-ethylene (Compound 29).—A mixture of 34.6 g. (0.1 mole) of tris-(*p*-methoxyphenyl)-ethylene and a solution of 100 g. of 85% potassium hydroxide in 500 ml. of 95% ethanol was heated at 190–195° under pressure in a rocking autoclave for 24 hours. The mixture was rinsed from the autoclave with a liter of water, filtered and concentrated on a steam-bath. After the residual aqueous solution had been chilled, it was acidified with hydrochloric acid, and the oil which precipitated was extracted with ether. The combined ether extracts were washed with water, dried over anhydrous magnesium sulfate and evaporated.

The residue was acetylated using acetic anhydride in pyridine by the method described above for compound 31, to give 10 g. (29%) of product which melted at 138–140°.

Tris-(*p*-hydroxyphenyl)-ethylene (Compound 11).—A mixture of 8.6 g. (0.02 mole) of tris-(*p*-acetoxyphenyl)-ethylene and 250 ml. of 10% aqueous potassium hydroxide solution was heated to reflux for five hours, filtered and acidified with acetic acid. The precipitated oil crystallized on standing and was filtered, washed with water and air-dried. Recrystallization from 200 ml. of benzene containing a small amount of ethanol gave a red oil and colorless crystals which separated above the oil. The crystalline material was recrystallized twice from xylene to give 4.3 g. (70%) of a crys-

(23) Difficulty was encountered is reproducing this debenzylation unless a catalytic amount of hydrochloric acid was present. Occasionally bromine was removed from the molecule.

talline solvate which melted at 153–157° with frothing. An analytical sample, dried over phosphorus pentoxide and paraffin at 78° and 20 mm., melted at 189–191°.

The trihydroxy compound was converted to tris-(*p*-propionoxyphenyl)-ethylene (compound 32) by reaction with propionic anhydride in pyridine solution as described above for the triacetoxy derivative.

Bromotris-(*p*-acetoxyphenyl)-ethylene (Compound 30).—To a stirred solution of 5 g. (0.012 mole) of tris-(*p*-acetoxyphenyl)-ethylene in 60 ml. of chloroform was added 2.1 g. (0.012 mole) of N-bromosuccinimide. After 15 minutes, the solution was heated to reflux for 20 hours, cooled and shaken with 250 ml. of cold water. The chloroform layer was separated, washed with cold water and evaporated. Three recrystallizations of the residue from methanol (charcoal decolorization) gave 1 g. (17%), m.p. 151–153°.

1,1,2-Tris-(*p*-methoxyphenyl)-ethane (Compound 37).—A mixture of 17.3 g. (0.05 mole) of tris-(*p*-methoxyphenyl)-ethylene and 1 g. of 10% palladium on charcoal in 200 ml. of ethyl acetate was hydrogenated at room temperature at an initial pressure of 30 p.s.i. Hydrogen absorption ceased in one hour. After the catalyst was removed and the solvent evaporated, the residue was recrystallized from absolute ethanol to give 15.2 g. (88%) of pure product, m.p. 86–87°.

Tris-(*p*-methoxyphenyl)-acrylic Acid (Compound 17).—A Grignard solution was prepared from 10 g. (0.0257 mole) of bromotris-(*p*-methoxyphenyl)-ethylene in the manner described above for the preparation of compound 20. The solution was decanted from the excess magnesium onto 25 g. of powdered, solid carbon dioxide. The complex was decomposed with 10% sulfuric acid, and the ether layer was separated and evaporated. The residue was chilled, and the solid material which separated was removed by filtration and dissolved in dilute, aqueous sodium hydroxide solution. The alkaline solution was extracted with ether, then poured onto a mixture of ice and concentrated hydrochloric acid. Recrystallization of the precipitated solid from dilute acetic acid gave a 34% yield of pure product, m.p. 202–203°.

1,1-Bis-(*p*-dimethylaminophenyl)-2-(*p*-methoxyphenyl)-ethylene (Compound 33).—To a stirred, hot solution of 20 g. (0.0766 mole) of Michler ketone in dry benzene was added, over a 20-minute period, a solution of 0.294 mole of *p*-methoxybenzylmagnesium chloride in 350 ml. of anhydrous ether. After the addition was complete, the mixture was heated to reflux for 16 hours, then decomposed with a solution of 30 g. of ammonium chloride in 150 ml. of water. The mixture was filtered, and the ether layer was evaporated.

The filter cake and the residue from the ether layer were combined and recrystallized from methanol containing a trace of ammonium hydroxide to give the carbinol, m.p. 150–151°. The carbinol was dehydrated by mixing with one-tenth its weight of thymolsulfonic acid and heating under vacuum in an oil-bath until effervescence ceased. The mixture was cooled, dissolved in chloroform and washed with 5% sodium hydroxide solution. The chloroform solution was evaporated and the residue was recrystallized from ether to give 10 g. (35%) of the pure ethylene, m.p. 106–108°.

***p*-Benzyloxybenzyl Alcohol.**[24]—A mixture of 600 ml. of dry isopropyl alcohol, 42.4 g. (0.2 mole) of *p*-benzyloxybenzaldehyde[25] and 10 g. (0.48 mole) of aluminum isopropoxide was heated at a rate such that the acetone distilled as it was formed. When no more acetone distilled,[26] most of the solvent was removed and the residue was poured onto a mixture of 300 g. of ice and 30 ml. of concentrated hydrochloric acid. The solid product retained water tenaciously. It was therefore extracted with 1300 ml. of boiling petroleum ether (75–90°). The solid which separated upon cooling was recrystallized from petroleum ether (75–90°) to give 31 g. (72%) of pure product, m.p. 86–87°.

Anal. Calcd. for $C_{14}H_{14}O_2$: C, 78.48; H, 6.58. Found: C, 78.70; H, 6.56.

***p*-Benzyloxybenzyl Chloride.**—A solution of 21.4 g. (0.1 mole) of *p*-benzyloxybenzyl alcohol in 300 ml. of anhydrous ether was chilled to 5°, saturated with dry hydrogen chloride, and the mixture was maintained at 5° for 16 hours. An equal volume of an ice-water mixture was added. The ether layer was separated, and the aqueous layer was extracted three times with ether. The combined ether solutions were washed with water, then with a saturated sodium carbonate solution, and dried over anhydrous sodium carbonate. After removal of the solvent, the residue was recrystallized from petroleum ether to give 20 g. (86%) of white plates, m.p. 79–80°.

Anal. Calcd. for $C_{14}H_{13}OCl$: C, 72.28; H, 5.63; Cl, 15.25. Found: C, 72.54; H, 5.88; Cl, 15.06.

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(24) The synthesis of this compound was mentioned by W. Tadros and L. Ekladius, *Nature*, **166**, 525 (1950), but no physical constants were reported.

(25) E. D. Bergmann and M. Sulzbacher, *J. Org. Chem.*, **16**, 84 (1951).

(26) The distillate was checked for acetone with 2,4-dinitrophenylhydrazine solution.

CINCINNATI 15, OHIO

[CONTRIBUTION NO. 1821 FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY[1]]

On the Catalytic Hydrogenation of 3,4-Benzpyrene

BY W. LIJINSKY AND L. ZECHMEISTER

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Total catalytic hydrogenation of purified 3,4-benzpyrene yields the perhydro derivative. By partial hydrogenation 1′,2′,3′,4′-tetrahydro-3,4-benzpyrene was isolated; yield 40%. A by-product was tentatively identified as 6,7-dihydro-3,4-benzpyrene.

Although some partially reduced benzpyrenes have been prepared by indirect synthesis, no direct catalytic hydrogenation of 3,4-benzpyrene seems to have been carried out. We became interested in this process because of the occurrence of hydrogenated polycyclic hydrocarbons in some natural tars, a report on which will appear elsewhere.[1a]

At room temperature and in the presence of platinum oxide the complete saturation of 3,4-benzpyrene with 10 mols of hydrogen takes place without difficulty. The resulting perhydro compound, probably a mixture of stereoisomers, formed a colorless oil most of which crystallized after long standing.

When the reduction process had been interrupted after the uptake of 2 mols of hydrogen and the resulting mixture resolved chromatographically in ultraviolet light, a well-crystallized tetrahydro derivative was isolated. It was found to be identical with a colorless sample of 1′,2′,3′,4′-

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