Summary

The resolution of the analgesic drug methadone and related compounds has been described.

RENSSELAER, N. Y. RECEIVED JUNE 4, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

Estrogenic Phenylindane Derivatives[1a]

BY U. V. SOLMSSEN[1b] AND E. WENIS

2-Phenylindene derivatives of the general structure (V, VI) may be considered as analogs to the powerful synthetic estrogens of the stilbene type. For example, 2-(*p*-methoxyphenyl)-3-ethyl-6-methoxyindene (V) may, theoretically, be derived from 4,4'-dimethoxy-α-methyl-β-ethylstilbene by ring closure between the methyl group and a phenyl ring. Because of this structural relationship, a number of 2-phenylindene derivatives were synthesized by Salzer[2a] and Solmssen.[2b]

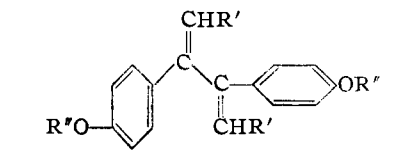
This earlier work, recently reviewed,[3] found that the most active 2-phenylindenes with phenolic hydroxy groups had an estrogenic activity of the same order as the 4,4'-dihydroxystilbene derivatives with isomeric structure. However, such 2-phenylindenes are too unstable for therapeutic usefulness. Acylation of the phenolic hydroxyls resulted in more stable but less active estrogens. Hydrogenation of the indene double bond appeared to be a more promising approach to stable yet highly potent preparations.

In the stilbene series, hydrogenation of the ethylene linkage generally results in unimpaired activity for the *meso* form of the hydrogenation product while the racemic form is much less active. Salzer[2a] reported that hydrogenation of the 2,3-double bond in 2-(*p*-hydroxyphenyl)-3-methyl-6-hydroxy-(2,3)-indene led to complete inactivation. On the other hand, Solmssen[2b] found that saturation of the indene double bond in 2-(*p*-hydroxyphenyl-3-ethyl-6-hydroxy-(2,3)-indene resulted in the corresponding indane (XX) with only slightly decreased activity and satisfactory stability.

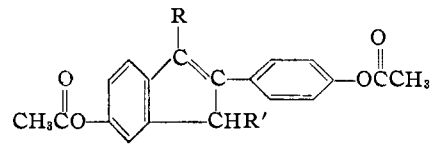
Therefore it was of interest to extend this earlier work[2a] and our first objective was the preparation of a complete series of homologs of the 3-ethylindane (XX). The general method employed for the synthesis is the one described previously[2b] though various steps have been improved materially. Thus, *p*-anisylacetic acid required as an intermediate was prepared from *p*-methoxyacetophenone by Schwenk's[4] variant of the Willgerodt reaction in 49% yield as compared with 18% by the azlactone method from anisaldehyde and hippuric acid, as described previously.[2b] The key intermediate, 2-(*p*-anisyl)-6-methoxyindanone-(3) (II), was obtained in greatly improved yield through Perkin reaction of *p*-anisylacetic acid with *m*-methoxybenzaldehyde, reduction of the resulting crude cinnamic acid by means of Raney nickel, and ring closure of the hydrocinnamic acid (I) with hydrofluoric acid. In analogy with similar observations by Johnson, Anderson and Shelberg[5] this reagent gave practically exclusively the desired isomer (II), m. p. 96°. The other isomer (III) and additional by-products in the ring closure are discussed in the experimental part.

The 3-alkyl substituted dimethoxyindenes (V–X) shown in Table I were again obtained by the Grignard reaction with alkylmagnesium halide. Catalytic reduction of the indene double bond with Raney nickel and demethylation of the crude dimethoxyindanes (XII–XVII) with hydrobromic–acetic acid resulted in the 3-alkyl-2-(*p*-hydroxyphenyl)-6-hydroxy–indanes (XIX–XXIV) as stable, well crystallized substances summarized in Table II.

In the earlier work[2b] five-ring closure had been effected with an unsymmetric starting material and the methoxy or hydroxy group in the fused phenyl ring had been presumed to be in the 6-position. Evidence for the correctness of this assumption has now been furnished by the work of Adler and Hagglund[6] who obtained 2-(*p*-acetoxyphenyl)-3-methyl-6-acetoxy-2,3-indene (XXVII) by means of boron trifluoride cyclization of 2,3-bis-(*p*-acetoxyphenyl)-1,3-butadiene (XXV).



XXV, R' = H, R'' = CH_3CO
XXVI, R' = CH_3 R'' = CH_3CO



XXVII, R = CH_3 R' = H

(1) (a) Presented at the meeting of the American Chemical Society in New York, September 15–19, 1947. (b) Present address: Warner Institute for Therapeutic Research, 113 West 18th Street, New York, 11, N. Y.

(2) (a) W. Salzer, *Z. physiol. Chem.*, **274**, 39 (1942); U. S. Patent 2,281,956 (1942); (b) U. V. Solmssen, THIS JOURNAL, **65**, 2370 (1943).

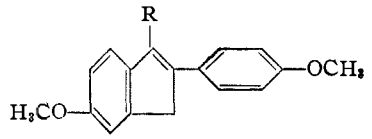
(3) U. V. Solmssen, *Chem. Reviews*, **37**, 481 (1945).

(4) E. Schwenk and E. Bloch, THIS JOURNAL, **64**, 3051 (1942).

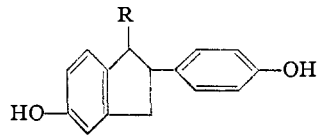
(5) W. S. Johnson, J. M. Anderson and W. E. Shelberg, *ibid.*, **66**, 218 (1944).

(6) E. Adler and B. Hagglund, *Arkiv. Kemi, Mineral. Geol.*, **19A**, No. 23 (1945).

TABLE I



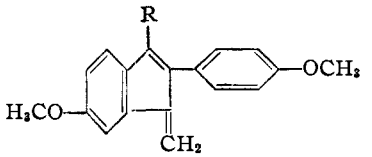
2-(*p*-Anisyl)-3-alkyl-6-methoxy-indene-(2,3)



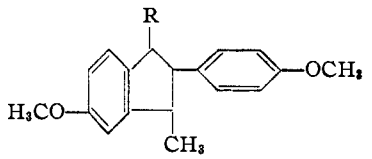
2-(*p*-Hydroxyphenyl)-3-alkyl-6-hydroxy-indane

R	Yield, %	M. p., °C.	Formula	Mol. wt.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Yield, %	M. p., °C.	Formula	Mol. wt.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Methyl	86.1	112–114	$C_{18}H_{18}O_2$	266.3	81.2	81.4	6.8	6.6	66.6	165–166	$C_{16}H_{16}O_2$	240.3	79.9	79.9	6.7	6.8
Ethyl	81.4	87–88	$C_{19}H_{20}O_2$	280.3	81.4	81.7	7.2	7.3	69.0	162–163	$C_{17}H_{18}O_2$	254.3	80.2	80.3	7.2	7.0
n-Propyl	84.4	98	$C_{20}H_{22}O_2$	294.4	81.6	81.9	7.5	7.6	82.0	145–147	$C_{18}H_{20}O_2$	268.3	80.5	80.6	7.5	7.5
Isopropyl	67.4	134–135	$C_{20}H_{22}O_2$	294.4	81.6	80.6	7.5	7.5	86.0	192–194	$C_{18}H_{20}O_2$	268.3	80.5	80.4	7.5	7.4
n-Butyl	53.2	75–76	$C_{21}H_{24}O_2$	308.4	81.8	81.7	7.8	7.7	87.2	187–188	$C_{19}H_{22}O_2$	282.3	80.8	80.7	7.8	7.8
Isobutyl	67.4	134–135	$C_{21}H_{24}O_2$	308.4	81.8	81.7	7.8	7.7	54.6	197–200	$C_{19}H_{22}O_2$	282.3	80.8	80.7	7.8	8.0

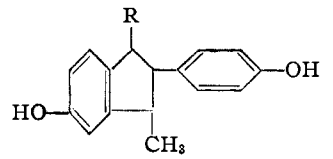
TABLE II



1-Methylene-2-(*p*-anisyl)-3-alkyl-6-methoxyindene-(2,3)



1-Methyl-2-(*p*-anisyl)-3-alkyl-6-methoxyindane



1-Methyl-2-(*p*-hydroxyphenyl)-3-alkyl-6-hydroxyindane

R	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	B. p., °C.	Mm.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	M. p., °C.	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
Methyl	94–95	81.9	82.2	6.5	6.5	170	0.7	80.8	81.0	7.8	7.9	195–196	80.3	80.7	7.1	7.2
Ethyl	96–97	82.0	82.0	6.9	6.6	170	0.6	81.0	80.8	8.1	7.9	195–198	80.6	80.6	7.5	7.4
n-Propyl	68–71	82.3	82.0	7.2	7.0	150–160	0.1	81.2	79.4	8.4	8.0	184–185	80.8	80.3	7.8	8.0
Isopropyl	[a]					[a]						174–181	80.8	81.0	7.8	7.6
n-Butyl	Oil[b]	82.5	79.9	7.5	7.2	175–180	0.2					174–182	81.0	81.1	8.2	8.3

[a] Not isolated in pure form. [b] B. p. 190–200° (0.1 mm.).

TABLE III

2-(*p*-HYDROXYPHENYL)-3-ALKYL-6-HYDROXYINDANES

3-Alkyl	Symbol	No. of rats	E. D. 50[a]
Hydrogen	XVIII	14	>60γ
Methyl	XIX	16	>200γ
Ethyl	XX	18	15γ
n-Propyl	XXI	34	2.1γ
Isopropyl	XXII	59	0.7γ
		50	10γ (oral)
n-Butyl	XXIII	31	>16γ
			<150γ
Isobutyl	XXIV	15	2.8γ

2-(*p*-HYDROXYPHENYL)-1-METHYL-3-ALKYL-6-HYDROXYINDANES

Methyl	XXXIX	6	>16γ
Ethyl	XL	6	>16γ
n-Propyl	XLI	14	>32γ
Isopropyl	XLII	19	1.0γ
n-Butyl	XLIII	14	>32γ

REFERENCE ESTROGENS

Estrone	32	1.7γ
Estradiol	16	0.3γ
Ethinylestradiol	12	3.6γ (oral)
Stilbestrol	16	0.18γ
	12	1.6γ (oral)
Hexestrol	53	0.38γ
Benzestrol	22	0.5γ
	19	>16γ (oral)

[a] Defined as the dose producing full estrus in 50% of the rats, after subcutaneous administration (unless stated otherwise), dissolved in 0.3 cc. corn oil and given in three equal portions.

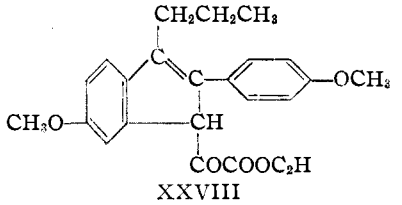
This symmetrical starting material cannot yield an indene with a substituent in the 4-position, but only in the 6-position. The physical data for (XXVII) reported by Adler and Hagglund[6] correspond with Salzer's[2a] and with those reported in the present study. While Salzer reported a relatively high activity for his product, Adler and Hagglund found it inactive and in the present investigation we confirmed the inactivity. Finally, the identity of the product XXVII obtained by the different routes has been established by Adler[7] by a direct comparison of the melting point and mixed melting point of the two preparations. This is proof of the 6-position of one of the methoxy groups in the key intermediate (III) and the synthetic estrogens prepared therefrom.

Salzer's erroneous report that the 3-methylindene had an activity higher than that of the corresponding 3-ethyl derivative led us to prepare also the next lower homolog (IV) without an alkyl substituent in 3-position, by reduction of the 3-keto group in (II) with aluminum isopropoxide, followed by spontaneous dehydration. After demethylation, neither the dihydroxy derivative nor its diacetate were isolated in pure form due to their instability. The corresponding indane (XVIII) was again stable and was prepared without difficulty by Clemmensen reduction of the 3-ketone (II), followed by demethylation. However, its estrogenic activity was low and the comparative activity for the series of compounds

(7) E. Adler, private communication.

(XVIII) to (XXIV) showed that higher rather than lower homologs were likely to yield more potent estrogenic agents. We therefore wished to introduce an additional alkyl group in the free 1-position of the five ring and attempted to methylate 2-(*p*-anisyl)-3-*n*-propyl-6-methoxy-(2,3)-indene (VII) by means of methyl iodide and potassium hydroxide or potassium ethylate. Because no alkylation took place, we then tried to activate the methylene group by introduction of an oxalyl group by means of diethyl oxalate according to Thiele.[8]

The desired 1-ethyloxalyl-3-*n*-propyl derivative (XXVIII) was obtained as a yellow crystalline



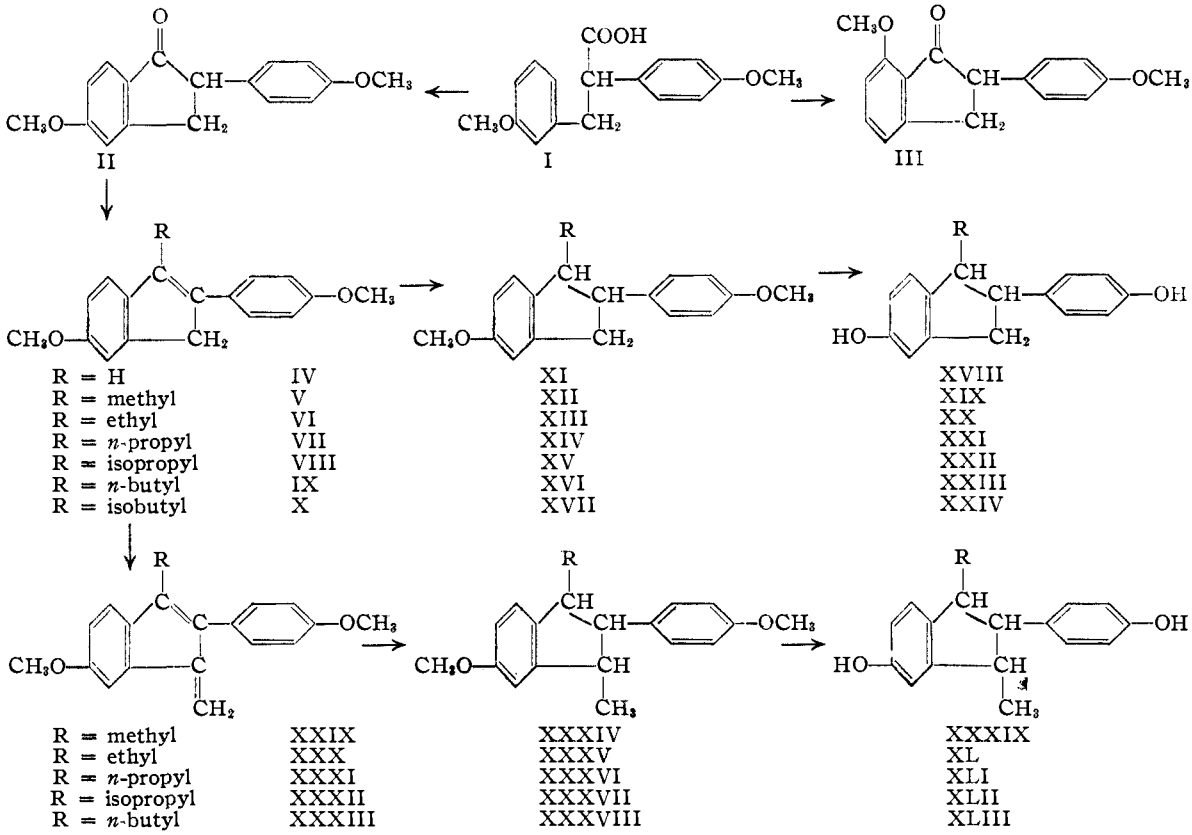
XXVIII

product, but the activated methylene group did not prove to be susceptible to methylation by the means described above. The desired result was finally obtained by reaction of the 3-alkylindenes (V–X) with paraformaldehyde according to Wuest[9] to give the fulvene derivatives (XXIX–XXXIII).

These were isolated in good yields as bright yellow, crystalline, though none too stable, compounds which were hydrogenated without delay to the dimethoxy-1,3-dialkylindanes (XXXIV–XXXVIII). The latter are stable, colorless oils which were demethylated to the crystalline dihydroxy-1,3-dialkylindanes (XXXIX–XLIII) desired for biological assays. The characteristics of intermediates and end-products have been summarized in Table II.

In a few cases the hydroxyl groups have been esterified (see experimental part) but the esters were less active than the corresponding free phenolic compounds.

Since completion of the experimental work Adler and Hagglund[6] reported the synthesis of 1 - methyl - 2 - (*p* - hydroxyphenyl) - 3 - ethyl - 6 - hydroxyindane (XL) from dienestrol (XXVI) and its stereoisomer, isodienestrol, by the method discussed above for the lower homolog (XXVII), followed by hydrogenation and hydrolysis. Very recently Hausmann and Wilder Smith[10] obtained 1 - methyl - 2 - (*p* - hydroxyphenyl) - 3 - ethyl - 6 - hydroxyindene-(2,3) when treating dienestrol with 1 *N* mineral acids.



Estrogenic Activities.—Bio-assays were made on castrated female rats in the Pharmacological Laboratories of Hoffmann–La Roche, Inc. The

(8) J. Thiele, *Ber.*, **33**, 85, 3400 (1900).
(9) H. M. Wuest, *Ann.*, **415**, 291 (1918).
(10) W. Hausmann and A. E. Wilder Smith, *Nature*, **161**, 892 (1948).

results have been listed in Table III, together with comparative assays of a number of estrogens with well-known therapeutic usefulness. Evidently, in both series of 2-phenylindanes with one and two alkyl groups in the five-ring, the maximum activity was reached with the isopropyl group in 3-position.

After subcutaneous administration 2-(*p*-hydroxyphenyl) - 3 - isopropyl - 6 - hydroxyindane (XXII), the most active compound, is about as active as benzestrol while it is one-half as active as hexestrol or one-quarter as active as stilbestrol. After oral administration (XXII) is more active than benzestrol, one-half to one-third as active as ethinyl estradiol while the ratio in comparison with stilbestrol is less favorable than after subcutaneous administration.

While it is true that (XXII) is isomeric with hexestrol and contains the same number of carbon atoms as stilbestrol it is quite obvious that several homologs of (XXII) are less active while they simulate the stilbestrol and hexestrol structure even more closely. Thus it was again confirmed that structural similarity of natural and synthetic estrogens is but one among a number of factors decisive of estrogenic potency.

One reservation, however, should be made regarding this conclusion of structure and estrogenic activity. The compounds of structure (XL–XLIII) have each been obtained in only one form (out of four possible *d,l* forms) and may thus not have the proper stereochemical configuration for highest activity or may not correspond in configuration to the structures (XIX–XXIII).

Experimental

p-Anisylacetic Acid.—Essentially the same method was used as described by Schwenk and Bloch[4] for the *o*- and *m*-isomers. A mixture of 879 g. of *p*-methoxyacetophenone (5.86 moles), 766 g. of morpholine (8.79 moles), and 281.5 g. of sulfur was refluxed with mechanical stirring, for eight to sixteen hours under a good hood. The reaction mixture was poured into 1 l. of warm 2B ethanol (anhydrous ethanol denatured with 2% of benzene used throughout the following experiments). On cooling, a first fraction was obtained, and on evaporation a second fraction of the thiomorpholide of *p*-anisylacetic acid; yield, 1173 g. (80%).

The crude product was divided into two batches, each of 590 g. of thiomorpholide and refluxed for eighteen hours with 6.6 l. of 10% potassium hydroxide solution. After cooling and acidification to congo red indicator, the crystalline product precipitated (287 g.) and was recrystallized from dilute ethanol, after treatment with Norite and adding water to saturation at the boiling point; combined yield, 474 g. (49%).

2-(*p*-Anisyl)-6-methoxyindanone-(3) (II).—Fifty-nine grams of *m*-methoxy-α-(*p*-anisyl)-hydrocinnamic acid (I) was placed in a 4-l. stainless steel beaker. From a cylinder cooled to −20°, fitted with a valve with permanently attached copper tube, 300 g. of anhydrous hydrofluoric acid was run into a beaker. The beaker was covered with an inverted copper funnel with an attached copper tube leading directly into the flue, frequently shaken by hand during five to eight hours and then allowed to stand overnight. It then contained a crystalline, or occasionally gummy, residue which was treated with water and then with sodium carbonate solution and warmed on the steam-bath. Insoluble material was separated by filtration, washed with water and recrystallized from 4:1 methanol–water solution; yield, 45 g. (81.4%) m. p. 93–96°. This product (II) has been previously described.[2b] The 2,4-dinitrophenylhydrazone, recrystallized from ethanol, melted at 216.5–218.5°.

Anal.[11] Calcd. for $C_{23}H_{20}O_6N_4$: C, 61.74; H, 4.5; N, 12.5. Found: C, 61.4; H, 4.4; N, 12.3.

The 5-ring closure had been effected previously[2b] with P_2O_5 in benzene and leads to (II), m. p. 96° and a by-product, m. p. 172°, then assumed to be the 5-methoxy isomer (III) which would be expected as a by-product in the ring closure between the carboxyl group and the two possible positions of the phenyl group. Whereas (II) reacts readily with Grignard reagent and also forms a 2,4-dinitrophenylhydrazone, m. p. 216.5°–218.5°, the formerly obtained by-product, m. p. 172°, has now been found not to give keto derivatives though its structure has not yet been elucidated. This by-product, m. p. 172°, has not been encountered in the ring closure by means of hydrofluoric acid; however, from the mother liquors of several combined batches of 2-(*p*-anisyl)-6-methoxyindanone-(3) two new by-products have been isolated. The one, m. p. 157–160°, was obtained after repeated recrystallization from ethanol, finally from acetone. The analysis of this compound and that of its 2,4-dinitrophenylhydrazone corresponds with the structure (III).

Anal. Calcd. for $C_{17}H_{16}O_3$: C, 76.0; H, 6.0. Found: C, 76.4; H, 5.9.

The 2,4-dinitrophenylhydrazone melted at 205–207°.

Anal. Calcd. for $C_{23}H_{20}N_4O_6$: C, 61.7; H, 4.5; N, 12.5. Found: C, 61.4; H, 4.5; N, 12.6.

The second by-product, isolated in small amounts only, was crystallized from acetone, m. p. 184–185°.

Anal. Found: C, 67.9; H, 5.5; OCH_3, 18.4.

This compound has not been identified. It forms a 2,4-dinitrophenylhydrazone, which was recrystallized from isopropyl alcohol and melted at 256°.

Anal. Found: C, 57.6; H, 4.3; N, 11.2.

2-(*p*-Anisyl)-3-alkyl-6-methoxyindenes-(2,3) (V–X).—The preparation of the 3-ethyl compound (VI) has previously[2b] been described. On repeating this procedure and extending it to other alkyl derivatives, chromatographic purification of the Grignard reaction products was not found to be necessary. Dehydration was effected by cautiously adding dropwise a 50% excess of dilute hydrochloric acid directly to the Grignard reaction mixture. All pertinent data for this series of compounds (V–X) have been summarized in Table I, for the products obtained after recrystallization from ethanol or methanol.

2-(*p*-Hydroxyphenyl)-3-alkyl-6-hydroxyindanes (XII–XVII).—The dimethoxyindenes (V–X), summarized in Table I were hydrogenated to the corresponding dimethoxyindanes. The hydrogenation was carried out at 25° in methanol at atmospheric pressure, with 10% palladium-on-carbon as catalyst, except for the isopropyl and the isobutyl derivatives which were hydrogenated at 60° in cyclohexane with Raney nickel at 500 lb. pressure. Only **2-(*p*-anisyl)-3-isopropyl-6-methoxyindane** (XV) was obtained crystalline. After recrystallization from ethanol, it melted at 87–87.5°.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.1; H, 8.2. Found: C, 81.2; H, 8.0.

Demethylation of the hydrogenation products was effected by refluxing 1 part with 10 parts of a 3:1 mixture of acetic acid and 48% hydrobromic acid, until a sample was soluble in alkali. All pertinent data have been summarized in Table I, for the products obtained after recrystallization from aqueous methanol or ethanol.

2 - (*p* - Hydroxyphenyl) - 6 - hydroxyindane (XVIII).—Twelve grams of mossy zinc (0.37 mole) was activated by shaking for five minutes with 1.2 g. of mercuric chloride, 20 cc. of water, and 0.5 cc. of concentrated hydrochloric acid. The liquid was decanted from the zinc, and to the

(11) All microanalyses were carried out under the direction of Dr. Al Steyermark.

latter was added 7.5 cc. of water, 17.5 cc. of concentrated hydrochloric acid, 10 cc. of toluene and 7.5 g. of 2-(*p*-anisyl)-6-methoxyindanone-(3), (0.0028 mole). The mixture was refluxed for twenty-nine hours while 5-cc. portions of concentrated hydrochloric acid were added after four, eight and twenty-four hours. The toluene was separated, the aqueous layer extracted with ether and the latter combined with the toluene, dried over calcium chloride and evaporated. The sirupy residue (6.2 g.) was refluxed for two and one-half hours with 30 cc. of acetic acid and 10 cc. of 48% hydrobromic acid. The mixture was made alkaline and extracted with ether (discarded). After acidification to congo, the aqueous layer was again extracted with ether and from the latter the crystalline product, melting at 175–176°, was obtained after repeated crystallization from ethanol.

Anal. Calcd. for $C_{16}H_{16}O_2$: C, 79.9; H, 5.7. Found: C, 79.8; H, 5.8.

2-(*p*-Anisyl-6-methoxyindene-(2,3) (IV).—5.36 g. of 2-(*p*-anisyl)-6-methoxyindanone-(3) (II) (0.02 mole), 70 cc. of isopropyl alcohol (distilled over sodium), and 10 g. of aluminum isopropoxide were refluxed under a Vigreux column with the temperature regulated in a way to permit isopropyl alcohol to distil over at a very slow rate, losses being replaced. After twelve hours, no more acetone could be detected in the distillate. The mixture was poured onto ice, made acid to congo with hydrochloric acid, and extracted with ether. After washing, the ether was diluted with ethanol and evaporated until crystallization began while hot. After cooling, 4.1 g. (81.4%) of crude product was obtained and recrystallized from ethanol, m. p. 194–196°.

Anal. Calcd. for $C_{17}H_{16}O_2$: C, 80.9; H, 6.4. Found: C, 80.7; H, 6.1.

Spontaneous dehydration to an indene derivative, as indicated by the analysis, was confirmed by the positive tetranitromethane reaction and the strong blue fluorescence of a benzene solution, characteristic of other indene derivatives.

2-(*p*-Acetoxyphenyl)-3-*n*-propyl-6-acetoxyindane.—Five hundred mg. of the dihydroxy derivative (XXI) was refluxed for one hour with 10 cc. of acetic anhydride and 1 cc. of pyridine. After dilution with water, an oil was extracted with ether, the latter evaporated and the residue distilled, in a molecular pot still, at 230–240°, at 0.5 mm.

Anal. Calcd. for $C_{22}H_{24}O_4$: C, 75.0; H, 6.9. Found: C, 74.9; H, 6.9.

2-(*p*-Propoxyphenyl)-3-*n*-propyl-6-propoxyindane.—Two hundred and fifty mg. of the dihydroxy derivative (XXI) was treated with propionic anhydride in the same manner described above for the acetate; faintly yellow oil, distilled at 230–240° at 0.5 mm.

Anal. Calcd. for $C_{24}H_{28}O_4$: C, 75.8; H, 7.4. Found: C, 76.2; H, 7.6.

1-Methyl-2-(*p*-acetoxyphenyl)-3-isopropyl-6-acetoxyindane.—One gram of the dihydroxy derivative (XLII) was acetylated as described above, crystallized from 50% methanol, m. p. 106.5–109°.

Anal. Calcd. for $C_{23}H_{26}O_4$: C, 75.4; H, 7.15. Found: C, 75.0; H, 7.0.

Ethyl 1-Oxalyl-2-(*p*-anisyl)-3-*n*-propyl-6-methoxyindene (XXVIII).—11.8 g. of 2-(*p*-anisyl)-3-*n*-propyl-6-methoxyindene (VII) was added to a sodium ethylate solution prepared from 1 g. of sodium (10% excess) and 200 cc. of absolute ethanol. Thereto were added 6.4 g. of diethyloxalate (10% excess). The mixture turned yellow almost immediately and was refluxed under nitrogen for two hours. The reaction mixture was poured into 600 cc. of water, cooled, and the crystalline precipitate filtered off. This fraction (3.2 g.) represented a 27% recovery of unreacted starting material, m. p. 92°. The filtrate was acidified to congo and extracted with ether. After evaporating the washed ether extract, an orange gum remained which was dissolved in hot ethanol. The dark-red solution very slowly deposited yellow crystals. After standing for one week in the cold, a total of 4.7 g. (30.4%) of product was obtained, m. p. 120–122° (sinter 117°).

Anal. Calcd. for $C_{24}H_{26}O_5$: C, 73.1; H, 6.6. Found: C, 73.1; H, 6.4.

Later fractions had a slightly lower melting point which was not improved by recrystallization.

1-Methylene-2-(*p*-anisyl)-3-alkyl-6-methoxyindenes-(2,3) (XXIX–XXXIII).—A solution of 0.02 mole 2-(*p*-anisyl)-3-alkyl-6-methoxy-2,3-indene (V–IX) in the necessary amount of absolute ethanol was refluxed with 1.5 to 3 g. of paraformaldehyde and 7.5 cc. of a 28% solution of potassium hydroxide in absolute methanol. The reaction mixtures turned yellow almost immediately, and then became turbid and dark after three-quarters to one and one-half hours at which time the reaction was interrupted. In each case the mixture was diluted with water and the alkaline solution extracted with ether. The ether extract was washed neutral, dried and evaporated in vacuum. The residue was an orange oil which in some instances crystallized in the crude stage, in others only after recrystallization from 80% ethanol. The *n*-butyl derivative could not be obtained crystalline but was purified by distillation. All products required protection from oxidation, and on exposure to air the bright yellow color of the pure preparations darkened within a few days. The pertinent data have been summarized in Table II.

1-Methyl-2-(*p*-anisyl)-3-alkyl-6-methoxyindanes (XXXIV–XXXVIII).—The methylene derivatives (XXIX–XXXIII) were hydrogenated in ethanol with Raney nickel at 40 lb. pressure. The hydrogenation products were obtained as colorless oils. Some were purified, others demethylated directly. All data have been summarized in Table II.

1-Methyl-2-(*p*-hydroxyphenyl)-3-alkyl-6-hydroxyindanes (XXXIX–XLIII).—The demethylation of the above dimethoxy derivatives (XXXIV–XXXVIII) was carried out with acetic acid and hydrobromic acid as described before. In the case of the isopropyl and the *n*-butyl derivative even prolonged refluxing did not result in completely alkali-soluble products. In these cases the small amounts of alkali-insoluble material were removed by ether extraction. The alkaline solution was then acidified to congo and extracted with ether. The residue, after evaporating the ether, was repeatedly recrystallized from 50% methanol. The data pertaining to this series of compounds have been summarized in Table II.

2-(*p*-Acetoxyphenyl)-3-methyl-6-acetoxyindene-(2,3) (XXVII).—The dihydroxy derivative has been prepared by demethylation of the dimethoxy derivative (V) as described earlier[2b] for the ethyl homolog. The crude demethylation product had an unsharp melting point at 170°. After acetylation, the diacetate (XXVII) was recrystallized from methanol, m. p. 129–131°.

Anal. Calcd. for $C_{20}H_{18}O$: C, 74.5; H, 5.6. Found: C, 74.8; H, 5.9.

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Summary

In the search for stable and highly potent estrogens, a series of 2-(*p*-hydroxyphenyl)-3-alkyl-6-hydroxyindanes has been prepared, with the 3-alkyl group being methyl, ethyl, *n*-propyl, isopropyl, *n*-butyl and isobutyl. In another series, an additional methyl group has been introduced in the 1-position of the five-ring. In both series, the 3-isopropyl derivatives were the most active compounds and 2-(*p*-hydroxyphenyl)-3-isopropyl-6-hydroxyindane was found to be active in rats in doses of 0.7 γ (subcutaneously) and 10 γ (orally).

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