extra lines in the spectrum of $Al_2(Cl)_{5.5}(OH)_{0.5}$ correspond to interplanar distances of aluminum chloride hexahydrate. However, the intensities of most of these lines are not in accord with the expected upper limit to the concentration of hexahydrate set by the composition of the catalytically active material. The extra lines in the spectrum of $Al_2(Cl)_{5.5}(OH)_{0.5}$ do not correspond to lines in the spectra of any of the alumina hydrates which have been studied in these laboratories or in the published spectra.[10]

Although the X-ray data are not definitive, they do provide corroborating evidence for the existence of one or more hydroxyaluminum chlorides.

It is apparent that a comparison of the catalytic activity of aluminum chloride and bromide as isomerization catalysts for naphthenes must be made with extreme care. It is likely that several aluminum hydroxy halides exist and that each has its own specific activity as a catalyst. If, as is suggested by certain experiments (as noted above), the equilibria between the various molecular species are affected by the quantity of hydrogen halide present, it becomes virtually impossible to determine hydroxyl halides, let alone to compare the activities of particular chlorides and bromides. Furthermore, the evidence that at 60° (and below) the aluminum chloride catalysis is heterogeneous in part, while the aluminum bromide catalysis is homogeneous, results in the lack of really common ground for a comparison of activities.

(10) Hanewalt, A. S. T. M. X-Ray Diffraction Data Cards.

Acknowledgments.—The authors wish to acknowledge the assistance of Mr. Donald Mayers and Mrs. Jane H. Morgan in carrying out the many experiments, of which those reported herein form but a small fraction. The X-ray photographs were made under the direction of Mr. A. E. Smith. The infrared spectrophotometric analytical method for cyclohexane and methylcyclopentane was developed under the direction of Dr. F. S. Mortimer.

Summary

The results of a study of the isomerization of cyclohexane and methylcyclopentane in the presence of aluminum chloride and bromide are presented. The experiments confirm the lack of catalytic activity on the part of aluminum halides in the absence of a promoter.

It is shown that at 60° for the isomerization of cyclohexane and methylcyclopentane: (1) Hydrogen halides have no promotional affect on the isomerizing activity of aluminum halides. (2) Water is a promoter of isomerization activity in aluminum halides. (3) The catalysis by the aluminum bromide–water complex is homogeneous. (4) The catalysis by the aluminum chloride–water complex is partially homogeneous and partially heterogeneous.

New evidence for the existence of an intermediate compound (or compounds) of the form $Al_2X_{6-n}(OH)_n$ $(1 \leq n \leq 5)$ is presented, and it is suggested that any or all of the intermediates have catalytic activity.

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CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE WASHINGTON SQUARE COLLEGE OF NEW YORK UNIVERSITY]

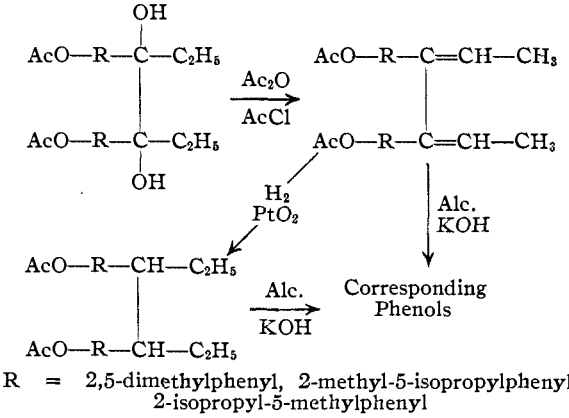
Synthetic Estrogens. Tetraalkyl Substituted Analogs of Dienestrol and Hexestrol[1,2]

BY JOSEPH B. NIEDERL AND PHILIP WEISS[3]

In continuation of studies in the introduction of alkyl[5,6] and aryl[4] groups into the benzene nuclei of dienestrol and hexestrol, it was decided to synthesize tetra alkyl substituted analogs of dienestrol and hexestrol. The phenols used were *p*-xylenol, thymol and carvacrol.

The following method of synthesis[7] was used in preparing the substituted dienestrols and hexestrols. The phenols were esterified with propionyl chloride, and the resulting esters were subjected to the Fries rearrangement to give the cor-

FLOW SHEET



R = 2,5-dimethylphenyl, 2-methyl-5-isopropylphenyl, 2-isopropyl-5-methylphenyl

(1) Abstracted from a dissertation submitted by Philip Weiss to the Faculty of the Graduate School of New York University in partial fulfilment of the requirements for the degree of Doctor of Philosophy.

(2) Presented before the Medicinal Chemistry Division of the American Chemical Society at New York, N. Y., September, 1947.

(3) Present address: Wallace and Tiernan Products, Inc., Belleville, New Jersey.

(4) J. B. Niederl and R. M. Silverstein, THIS JOURNAL, **70**, 619 (1948).

(5) V. Niederl and co-workers, *ibid.*, **70**, 508 (1948).

(6) E. Kaiser and co-workers, *ibid.*, **68**, 636 (1946); paper presented before the Medicinal Chemistry Division of the American Chemical Society at New York, N. Y., September, 1947.

(7) E C. Dodds and co-workers, *Proc. Roy. Soc.*, **B127**, 140 (1939).

TABLE OF COMPOUNDS

Number	Compounds	Formula	M. p., °C. (uncor.)	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found	Overall yields, %
	Phenyl propionates							
I	2,5-Dimethyl	$C_{11}H_{14}O_2$	[a]	74.16	74.38	7.86	7.74	96
II	2-Isopropyl-5-methyl	$C_{13}H_{18}O_2$	[b]	75.72	75.46	8.73	8.77	95
III	2-Methyl-5-isopropyl	$C_{13}H_{18}O_2$	[c]	75.72	75.68	8.73	8.64	93
	Propiophenones							
IV	2,5-Dimethyl-4-hydroxy	$C_{11}H_{14}O_2$	128	74.16	74.43	7.86	7.74	70
V	2-Methyl-4-hydroxy-5-isopropyl	$C_{13}H_{18}O_2$	113	75.72	75.61	8.73	8.87	85
VI	2-Isopropyl-4-hydroxy-5-methyl	$C_{13}H_{18}O_2$	110	75.72	75.51	8.73	8.91	87
VII	2,5-Dimethyl-4-acetoxy	$C_{13}H_{16}O_3$	[d]	70.90	70.74	7.27	7.43	68
VIII	2-Methyl-4-acetoxy-5-isopropyl	$C_{15}H_{20}O_3$	[e]	72.58	72.49	8.06	8.15	80
IX	2-Isopropyl-4-acetoxy-5-methyl	$C_{15}H_{20}O_3$	[f]	72.58	72.41	8.06	8.19	81
	-3,4-hexanediols							
X	3,4-bis-(2',5'-Dimethyl-4'-acetoxyphenyl)	$C_{26}H_{34}O_6$	179	70.58	70.51	7.69	7.98	21
XI	3,4-bis-(2'-Methyl-4'-acetoxy-5'-isopropylphenyl)	$C_{30}H_{42}O_6$	152	72.28	72.32	8.43	8.65	17
XII	3,4-bis-(2'-Isopropyl-4'-acetoxy-5'-methylphenyl)	$C_{30}H_{42}O_6$	184	72.28	72.02	8.43	8.70	4
	-2,4-hexadienes							
XIII	3,4-bis-(2',5'-Dimethyl-4'-acetoxyphenyl)	$C_{26}H_{30}O_4$	155	76.84	76.53	7.38	7.38	16
XIV	3,4-bis-(2'-Methyl-4'-acetoxy-5'-isopropylphenyl)	$C_{30}H_{38}O_4$	156	77.92	78.22	8.22	8.45	13
XV	3,4-bis-(2'-Isopropyl-4'-acetoxy-5'-methylphenyl)	$C_{30}H_{38}O_4$	117	77.92	78.09	8.22	8.41	3
XVI	3,4-bis-(2',5'-Dimethyl-4'-hydroxyphenyl)	$C_{22}H_{26}O_2$	206	81.99	81.73	8.07	8.40	14
XVII	3,4-bis-(2'-Methyl-4'-hydroxy-5'-isopropylphenyl)	$C_{26}H_{34}O_2$	169	82.53	82.39	8.99	9.26	11
XVIII	3,4-bis-(2'-Isopropyl-4'-hydroxy-5'-methylphenyl)	$C_{26}H_{34}O_2$	163	82.53	82.24	8.99	9.14	2
XIX	3,4-bis-(2',5'-Dimethyl-4'-propionoxyphenyl)	$C_{28}H_{34}O_4$	169	77.87	77.63	7.82	7.97	14
XX	3,4-bis-(2'-Methyl-4'-propionoxy-5'-isopropylphenyl)	$C_{32}H_{42}O_4$	137	78.36	78.21	8.57	8.78	12
XXI	3,4-bis-(2'-Isopropyl-4'-propionoxy-5'-methylphenyl)	$C_{32}H_{42}O_4$	126	78.36	78.14	8.57	8.83	2
XXII	3,4-bis-(2',5'-Dimethyl-4'-benzoxyphenyl)	$C_{36}H_{34}O_4$	186	81.51	81.41	6.41	6.53	12
XXIII	3,4-bis-(2'-Methyl-4'-benzoxy-5'-isopropylphenyl)	$C_{40}H_{42}O_4$	183	81.91	81.73	7.16	7.38	10
XXIV	3,4-bis-(2'-Isopropyl-4'-benzoxy-5',5'-methylphenyl)	$C_{40}H_{42}O_4$	179	81.91	81.69	7.16	7.43	1.8
	-hexanes							
XXV	[g]3,4-bis-(2',5'-Dimethyl-4'-acetoxyphenyl)	$C_{26}H_{34}O_2$	163	76.09	76.36	8.29	8.14	14
XXVI	3,4-bis-(2'-Methyl-4'-acetoxy-5'-isopropylphenyl)	$C_{30}H_{42}O_4$	134	77.25	77.41	9.01	9.30	12
XXVII	3,4-bis-(2'-Isopropyl-4'-acetoxy-5'-methylphenyl)	$C_{30}H_{42}O_4$	140	77.25	77.38	9.01	9.24	2
XXVIII	[g]3,4-bis-(2',5'-Dimethyl-4'-hydroxyphenyl)	$C_{22}H_{30}O_2$	216	80.98	81.14	9.20	9.01	14
XXIX	3,4-bis-(2'-Methyl-4'-hydroxy-5'-isopropylphenyl)	$C_{26}H_{38}O_2$	177	81.67	81.89	9.94	9.73	12
XXX	3,4-bis-(2'-Isopropyl-4'-hydroxy-5'-methylphenyl)	$C_{26}H_{38}O_2$	171	81.67	81.55	9.94	9.68	2
XXXI	[g]3,4-bis-(2',5'-Dimethyl-4'-propionoxyphenyl)	$C_{28}H_{38}O_4$	104	76.71	76.94	8.67	8.41	14
XXXII	3,4-bis-(2'-Methyl-4'-propionoxy-5'-isopropylphenyl)	$C_{32}H_{46}O_4$	128	77.73	77.84	9.31	9.05	12
XXXIII	3,4-bis-(2'-Isopropyl-4'-propionoxy-5'-methylphenyl)	$C_{32}H_{46}O_4$	133	77.73	77.84	9.31	9.18	2
XXXIV	[g]3,4-bis-(2',5'-Dimethyl-4'-benzoxyphenyl)	$C_{36}H_{38}O_4$	204	80.89	81.13	7.11	6.91	11
XXXV	3,4-bis-(2'-Methyl-4'-benzoxy-5'-isopropylphenyl)	$C_{40}H_{46}O_4$	192	81.35	81.18	7.79	8.01	10
XXXVI	3,4-bis-(2'-Isopropyl-4'-benzoxy-5'-methylphenyl)	$C_{40}H_{46}O_4$	183	81.35	81.29	7.79	7.93	1.7

B. p., °C. (uncor.): [a] 124.5–125.5° (17 mm.). [b] 133.5–134.5° (13 mm.). [c] 135–136.5° (12.5 mm.). [d] 188° (30 mm.). [e] 177–179° (16 mm.). [f] 184–186° (16 mm.). [g] Active estrogens.

responding 2,5-dialkyl-4-hydroxypropiophenone. Esterification of the propiophenone and reduction with aluminum amalgam yielded the pinacol. The substituted dienestrol was obtained by dehydration of the pinacol. The hexestrol was synthesized by catalytic hydrogenation of the hexadiene. The method of synthesis used is presented in the accompanying flow sheet.

Experimental

Propionylation.—1,4,2-Xylenol, thymol and carvacrol were esterified by refluxing with an excess of propionyl chloride. The residue was distilled under reduced pressure to yield I, II, and III, respectively.

Fries Rearrangement.—Compounds IV, V and VI were synthesized by the Fries rearrangement[8] of the corresponding esters. One mole of the ester (I, II, III) was dissolved in 600 ml. of dry nitrobenzene. After cooling the solution in an ice-bath, one and one-third moles of anhydrous aluminum chloride was added in small portions to the reaction mixture. The reaction was set aside at room temperature for a minimum of twenty-four hours. The green solution was poured into an ice–water mixture, and then acidified with dilute hydrochloric acid. The hydrolyzed aluminum chloride complex was extracted with ether, and the combined nitrobenzene–ether extracts were extracted with 10% sodium hydroxide. After washing with several portions of ether to remove traces of nitro-

(8) K. W. Rosenmund and W. Schnurr, *Ann.*, **460**, 56 (1928)

benzene, the alkaline solution was acidified with dilute hydrochloric acid to yield the crude 2,5-dialkyl-4-hydroxypropiophenone. The solid was filtered, washed well with water, and then recrystallized from dilute methanol.

Pinacol Reduction.—The 2,5-dialkyl-4-hydroxypropiophenones (IV, V, VI) were esterified by refluxing with acetic anhydride using pyridine as a catalyst. After removing the acetic acid and anhydride, the esters (VII, VIII, IX) were distilled under vacuum, and then used in the pinacol reduction.

One hundred grams of the pure 2,5-dialkyl-4-acetoxypropiophenone (VII, VIII, IX) was dissolved in 750 ml. of moist ethyl acetate. The solution was treated at once with amalgamated aluminum which was freshly prepared from thirty-eight grams of aluminum foil. The reaction mixture was stirred continuously, and no water was added during the course of the reaction. The progress of the reaction was followed exclusively by the change in temperature, and the reaction was allowed to continue until the temperature rise reached a maximum and then decreased 5°. The actual change in temperature amounted to 39°, and the time required to complete the reduction was one and one-half hours. The reaction mixture was filtered, the residual aluminum amalgam was washed with ethyl acetate, and the combined ethyl acetate fractions were dried over anhydrous magnesium sulfate. After filtering the ethyl acetate solution, the filtrate was concentrated in a water pump vacuum, and the gummy residue was crystallized by adding a small amount of low-boiling petroleum ether. A white crystalline product (X, XI, XII) was obtained by washing the crude solid with cold benzene.

Dehydration of the Pinacol.—Compounds XIII, XIV, and XV were synthesized in the following manner. Five grams of the hexanediol (X, XI, and XII) was dissolved in 15 ml. of acetic anhydride and 10 ml. of acetyl chloride. The mixture was refluxed for four hours, and after cooling the solution it was poured into an ice-water mixture. Solid sodium bicarbonate was added until the mixture was alkaline and on standing overnight, a semi-solid mass separated. The partially solidified material was washed well with water, and then crystallized by triturating with a small amount of ice cold methanol. Recrystallization from methanol yielded a white crystalline solid.

Saponification of XIII, XIV, XV was effected by heating at 80° for twenty minutes with a 50% alcoholic potassium hydroxide solution. The solution was stored at room temperature for two days, diluted with water, and then filtered. The filtrate was acidified, and the precipitate was filtered, washed, and recrystallized from dilute ethanol to yield the tetra alkyl substituted dihydroxy hexadienes XVI, XVII and XVIII.

Catalytic Hydrogenation.—The hexadiene diacetate (XIII, XIV, XV) was dissolved in glacial acetic acid, platinum oxide was added and the mixture was shaken with hydrogen at 40 lb. pressure for seven hours. The solution was filtered and the filtrate was concentrated *in vacuo*. The residue was crystallized and recrystallized from dilute methanol.

The hexane diacetate (XXV, XXVI and XXVII) obtained by catalytic hydrogenation of the corresponding hexadienes (XIII, XIV, XV) was saponified in the same manner as under XVI, XVII and XVIII.

Esters.—The dipropionates (XIX, XX, XXI, XXXI, XXXII, XXXIII) were prepared by refluxing the 2,5-dialkyl dienestrol (XVI, XVII, XVIII) and the 2,5-dialkyl hexestrol (XXVIII, XXIX, XXX), respectively, with propionic anhydride. These compounds were recrystallized from dilute ethanol. The dibenzoates (XXII, XXIII, XXIV, XXXIV, XXXV, XXXVI) were prepared by the Schotten–Baumann method from (XVI, XVII, XVIII, XXVIII, XXIX, XXX) and were recrystallized from dilute ethanol.

Physiological.—The assays were carried out by administering subcutaneously a solution of the test sample in oil to ovariectomized female rats. At the 50 microgram dose level, the 3,4-bis-(2′-isopropyl-4′-hydroxy-5′-methylphenyl)-hexane showed no estrogenic activity, while the 3,4-bis-(2′-methyl-4′-hydroxy-5′-isopropylphenyl)-hexane gave a 10% oestrus response.

Contrary to the above and indicative of the high degree of specificity in these types of compounds, the 3,4-bis-(2′,5′-dimethyl-4′-hydroxyphenyl)-hexane, the compound prepared from *p*-xylenol, gave 100% positive oestrus response at 50 and at 5 microgram dose levels, and almost as good a response at 2 and 1 microgram dose levels. Thus this tetramethyl hexestrol compares favorably with its dimethyl analog, the 3,4-bis-(5′-methyl-4′-hydroxyphenyl)-hexane prepared from *o*-cresol.[5]

Acknowledgment.—The authors are indebted to the Pharmacological Laboratories of Reed and Carnrick, Jersey City, N. J., and of the Lederle Laboratories, Pearl River, N. Y., for the estrogenic assays.

Summary

Studies in the introduction of alkyl- and aryl-groups into the benzene nuclei of synthetic estrogens have been extended to include the preparation of tetra-alkylated dienestrols and hexestrols from *p*-xylenol, thymol and carvacrol.

The tetra-alkylated hexestrols derived from thymol and carvacrol showed only feeble estrogenic activity, while the tetramethyl hexestrol obtained from *p*-xylenol is a fully active estrogen with a favorable therapeutical index.

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