evidence of containing some lactone. The nature of these compounds will be further investigated.

Summary

A practical synthesis of substituted 1-cyclopentenealdehydes has been developed and applied to 1-cyclopentenealdehyde, 3-*n*-propyl-1-cyclopentenealdehyde and 3,5-di-*n*-propyl-1-cyclopentenealdehyde.

The substituted 1-cyclopentenealdehydes have been shown to undergo the Reformatski reaction.

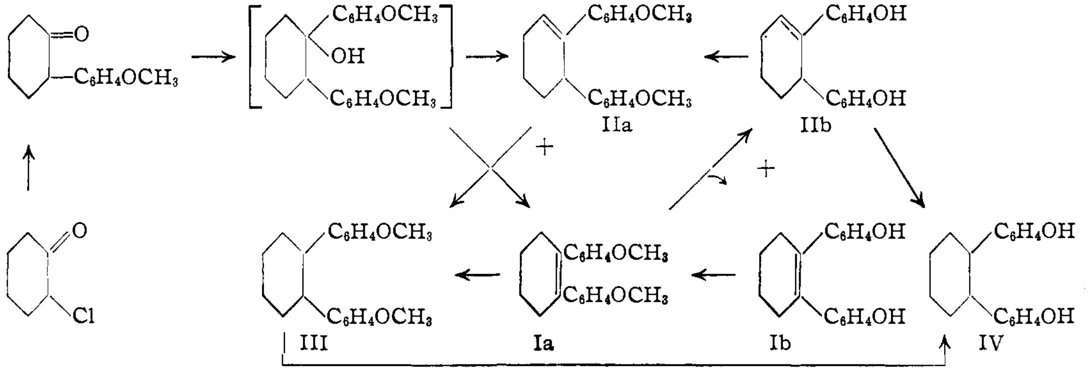
NEW HAVEN, CONNECTICUT RECEIVED MARCH 17, 1949

[CONTRIBUTION NO. 67 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TENNESSEE]

Synthesis of Cyclohexestrol[1]

BY GEORGE P. MUELLER AND ROY MAY[2]

Much of the search for new synthetic estrogens has consisted either of substituting groups within the essentially intact hexestrol skeleton, or of building other structures also supposedly capable of simulating the nuclear form of the estrogenic hormone. The synthesis of the cyclohexane analog, for which previous attempts have been reported,[3] has been completed.



The formation of 2-substituted cyclohexanones from 2-chlorocyclohexanones has been studied more recently by Mousseron[4] and by Newman[5] who have shown that the alkyl or aryl group from an attacking Grignard reagent may become attached either to the carbonyl or the halogen-bearing carbon. Our results indicate further either that a 2-substituted cyclohexanone or cyclohexene oxide is formed and subject to further attack as in the formation of tertiary alcohols from carboxylic esters, or that the halogen-bearing and carbonyl carbons are attacked simultaneously. Thus, although clean separations of products were difficult, a 2:1 mole ratio of *p*-methoxyphenylmagnesium bromide to 2-chlorocyclohexanone favored the formation of bis-(*p*-methoxyphenyl)-cyclohexenes, Ia and IIa, over that of 2-*p*-methoxyphenylcyclohexanone,[6] and conversely for a 1:1 ratio.

The mixture of cyclohexenes must have been formed by spontaneous dehydration during the reaction or on hydrolysis of the magnesium salts, since the isomer Ia was on one occasion crystallized directly from the crude products before application of the usual dehydrating conditions. Parmerter[7] obtained a 1,2-diphenylcyclohexene after dehydrating the crude hydrolysis product from phenylmagnesium bromide and 2-phenylcyclohexanone, but he did not confirm the actual presence of a carbinol. Further evidence of the activating effect of the *p*-methoxyphenyl group in this connection was observed during a synthesis of 2-*p*-methoxyphenylcyclohexanone through perbenzoic acid oxidation of 1-*p*-methoxyphenylcyclohexene. Here, distillation of the acid-free oxidation product to purify the 1-*p*-methoxyphenylcyclohexene oxide yielded instead the cyclohexanone. 1-Phenylcyclohexene oxide was reported however as being purified in this way and requiring acid catalysis to effect the rearrangement.[8]

Two bis-(*p*-methoxyphenyl)-cyclohexenes, Ia and IIa, were isolated and separately hydrogenated to the same cyclohexane, III, which was demethylated in alcoholic alkali to 1,2-bis-(*p*-hydroxyphenyl)-cyclohexane IV. We have called

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[1] The main portion of this paper was presented at the American Chemical Society meeting at Washington, D. C., September, 1948.

[2] Present address: T. V. A., Health and Safety Dept., Wilson Dam, Alabama.

[3] (a) Price and Mueller, THIS JOURNAL, **66**, 628 (1944); (b) **66**, 632 (1944).

[4] Mousseron, Granger, Winternitz and Combes, *Bull. soc. chim.*, **610** (1946).

[5] Newman and Booth, *J. Org. Chem.*, **12**, 737 (1947).

[6] Shortly after its preparation in this laboratory this ketone was reported by Bachmann and Wick at the American Chemical Society Meeting, Chicago, Ill., 1948.

[7] Parmerter, THIS JOURNAL, **71**, 1127 (1949).

[8] Sherwood, Short and Woodcock, *J. Chem. Soc.*, 323 (1936).

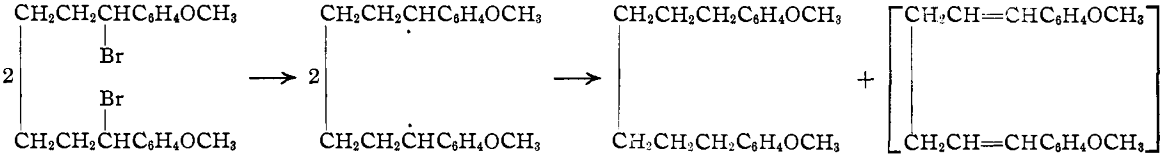
the latter "cyclohexestrol," although its low physiological activity may, perhaps, not warrant such a cognomen. Similar demethylation of the cyclohexene, Ia, gave both of the phenolic cyclohexenes, Ib and IIb, identified with the methoxy-isomers by remethylation. The skeletal structure of the series was confirmed through dehydrogenation of the mixed bis-(*p*-methoxyphenyl)-cyclohexenes to 4',4''-dimethoxy-*o*-terphenyl.[3b]

Placement of the double bond in the isomeric series, I and II, as shown is provisional. It seems likely that the carbinol intermediate would have a *trans* configuration favorable to the formation of Ia, as the preponderant isomer, by *trans* elimination of water.[9] Conflicting evidence arises from the appearance of the two phenolic cyclohexenes during alkaline demethylation at 200° of the isomer Ia. If there were not some doubt, arising from isolation difficulties and hence the qualitative nature of the experiment, one could only conclude that migration of the bond from the unsymmetrical to the symmetrical and completely conjugated position had occurred.[10] Establishment of these structures through oxidation studies is continuing.

The two phenolic cyclohexenes as well as cyclohexestrol were tested and found to possess definite, though weak, estrogenic activity. Whether the latter has the *dl* or *meso* configuration can only be inferred from hydrogenation experiments with diethylstilbestrol.[11] Up to this date the compound has eluded resolution.

Several attempts to synthesize cyclohexestrol by ring-closure of 1,6-bis-(*p*-methoxyphenyl)-hexane derivatives were unsuccessful but yielded curious results which illustrate the steric resistance offered by aryl substituents on the carbons to be joined. The methods tried were analogous to those previously used in preparing hexestrol, dienestrol and related compounds.[12]

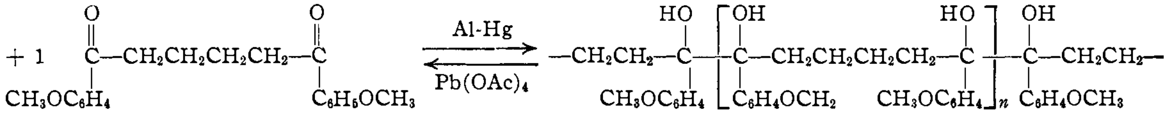
Treatment of 1,6-bis-(*p*-methoxyphenyl)-1,6-dibromohexane with phenylmagnesium bromide and cobaltous chloride was expected to produce a 1,6-diradical and then a 1,2-bis-(*p*-methoxyphenyl)-cyclohexane. We submit that while the mechanism of free radical formation here was that previously suggested, the disposition of the radical itself may rather be the result of a disproportionation.[13]



$$2\begin{array}{l}\mathrm{CH_2CH_2CHC_6H_4OCH_3}\\ \qquad |\\ \qquad \mathrm{Br}\\ \qquad \mathrm{Br}\\ \qquad |\\ \mathrm{CH_2CH_2CHC_6H_4OCH_3}\end{array} \longrightarrow 2\begin{array}{l}\mathrm{CH_2CH_2\dot{C}HC_6H_4OCH_3}\\ \\ \mathrm{CH_2CH_2\dot{C}HC_6H_4OCH_3}\end{array} \longrightarrow \begin{array}{l}\mathrm{CH_2CH_2CH_2C_6H_4OCH_3}\\ \\ \mathrm{CH_2CH_2CH_2C_6H_4OCH_3}\end{array} + \left[\begin{array}{l}\mathrm{CH_2CH{=}CHC_6H_4OCH_3}\\ \\ \mathrm{CH_2CH{=}CHC_6H_4OCH_3}\end{array}\right]$$

The isolation and positive identification of 1,6-bis-(*p*-methoxyphenyl)-hexane, aside from the ever-present biphenyl and *p*-terphenyl, was all that could be accomplished with the intractable, highly unsaturated products. Again, treatment of the dibromohexane with sodium, magnesium and sodium amide led in each case to unsaturated oils from which no recognizable compound could be isolated.

Another approach to the ring-closure was the aluminum-amalgam reduction of 1,4-bis-(*p*-methoxybenzoyl)-butane to the anticipated 1,2-bis-(*p*-methoxyphenyl)-1,2-dihydroxycyclohexane.[14] Similar cyclic 1,2-diaryl pinacols have been formed in which the ring was already extant.[15] Only a polymeric product was recovered, however, despite attempts to isolate crystalline material from the purification liquors. This resin was poly-1,6-bis-(*p*-methoxyphenyl)-1,6-dihydroxyhexamethylene, as shown by its rapid and quantitative oxidation with lead tetraacetate to the original 1,6-diketone.



$$n + 1\ \underset{\mathrm{CH_3OC_6H_4}}{\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}}\mathrm{{-}CH_2CH_2CH_2CH_2{-}}\underset{\mathrm{C_6H_5OCH_3}}{\overset{\overset{\mathrm{O}}{\|}}{\mathrm{C}}} \underset{\mathrm{Pb(OAc)_4}}{\overset{\mathrm{Al\text{-}Hg}}{\rightleftarrows}} \mathrm{{-}CH_2CH_2{-}}\underset{\mathrm{CH_3OC_6H_4}}{\overset{\mathrm{HO}}{\mathrm{C}}}\left[\underset{\mathrm{C_6H_4OCH_2}}{\overset{\mathrm{OH}}{\mathrm{C}}}\mathrm{{-}CH_2CH_2CH_2CH_2{-}}\underset{\mathrm{CH_3OC_6H_4}}{\overset{\mathrm{HO}}{\mathrm{C}}}\right]_n\underset{\mathrm{C_6H_4OCH_3}}{\overset{\mathrm{OH}}{\mathrm{C}}}\mathrm{{-}CH_2CH_2{-}}$$

The formation of this interesting polypinacol under such mild conditions and the facile reversal of the reductive-polymerization offers attractive possibilities. The study of this reaction and of the chemical and physical properties of the product is continuing.

Experimental

Reduction of 1,4-bis-(*p*-Methoxybenzoyl)-butane.—1,4-bis-(*p*-Methoxybenzoyl)-butane, 25.0 g., was hydrogenated in 125 ml. of ethyl alcohol over copper-chromium oxide at 2000 p. s. i. and 100°, giving 22.4 g. of crystalline material, m. p. 100-140°. After three recrystallizations from methyl alcohol the melting point was 132-150°. Similar mixtures were obtained by using Raney nickel at 2000 p. s. i. and 130°. Aluminum isopropoxide reduction of 9.9 g. of the diketone and recrystallization of the product once from benzene gave 7.5 g. of solid, m. p. 105-140°. In order to confirm the reduction work, 48.6 g. of magnesium turnings, 216 g. of freshly-distilled tetramethylene bromide and 408 g. of anisaldehyde were treated in a man-

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[9] Price and Karabinos, THIS JOURNAL, **62**, 1159 (1940).

[10] Farmer, *Trans. Faraday Soc.*, **38**, 356 (1942).

[11] Wessely and Welleba, *Ber.*, **74**, 777, 785 (1941).

[12] (a) Kharasch and Kleiman, THIS JOURNAL, **65**, 491 (1943); (b) Docken and Spielman, *ibid.*, **62**, 2163 (1940); (c) Bernstein and Wallis, *ibid.*, **62**, 2871 (1940); (d) Kharasch, Nudenberg and Fields, *ibid.*, **66**, 1276 (1944).

[13] Kharasch, Sayles and Fields, *ibid.*, **66**, 481 (1944).

[14] *Cf.* (a) Dodds, Golberg, Lawson and Robinson, *Nature*, **141**, 247 (1938); (b) Newman, THIS JOURNAL, **62**, 1683 (1940); (c) Niederl and Silverstein, *J. Org. Chem.*, **14**, 10 (1949).

[15] Maitei and Bogdan, *Ber.*, **67B**, 1834 (1934).

ner similar to that of Schmidt,[16] yielding 100 g. of the 1,6-glycols, m. p. 115-138°, after two recrystallizations from ethyl alcohol. Oxidation of 3.3 g. of such a product with 10 g. of concentrated sulfuric acid, 5 g. of potassium dichromate and 20 ml. of water at 100° for twenty-five minutes yielded 1 g. of 1,4-bis-(*p*-methoxybenzoyl)-butane, identified through mixed melting points of the diketone and its oxime with authentic samples. The glycols, therefore, were mixtures of *dl* and *meso* forms of 1,6-bis-(*p*-methoxyphenyl)-1,6-dihydroxyhexane.

1,6-bis-(*p*-Methoxyphenyl)-1,6-dibromohexane.—The mixture of 1,6-bis-(*p*-methoxyphenyl)-1,6-dihydroxyhexanes, 5 g., was suspended in 20 ml. of dry benzene and dry hydrogen bromide was introduced, causing solution of the glycol accompanied by slight warming. The water formed was removed and the solution cooled overnight; the white, crystalline powder was collected and weighed 5.5 g.; m. p. 99-102°. An additional recovery by concentrating the benzene solution *in vacuo* made the total yield 6.2 g. (88%). This bromide, recrystallized from anhydrous ether, melted at 102-103° with decomposition.

Anal. Calcd. for $C_{20}H_{24}O_2Br_2$: C, 52.65; H, 5.30. Found: C, 52.84; H, 5.36.

At room temperature the bromide decomposed in a few days, but was stable for several months under refrigeration. A dark green oil was the impurity associated with the bromide, either accompanying certain preparations or appearing on decomposition after standing or melting. Since the pure bromide was not greatly soluble in boiling ether, although more so in ether-acetone mixtures, from which it crystallized less completely, purification for preparative purposes was best accomplished by washing with a very little cold acetone and several times with ether. The colored material was thus removed, leaving generally 85-90% of white crystalline material from very impure-looking preparations. Decomposition accompanied attempts to recrystallize from hot benzene or ethyl alcohol. A pure sample precipitated silver bromide instantly from alcoholic silver nitrate.

The oily residues remaining from crystallization of the solid 1,6-glycols yielded 76% of the same pure dibromohexane.

1,6-bis-(*p*-Methoxyphenyl)-1,6-dichlorohexane.—The mixture of solid 1,6-glycols, 10 g., was suspended in 20 ml. of dry benzene and 20 ml. of petroleum ether (b.p. 95-96°); 8 g. of thionyl chloride was added and the solution warmed gently at reflux for forty-five minutes until gas evolution had ceased and the solid dissolved. After cooling overnight 7.2 g. (65%) of gray-white crystals were collected; m. p. 105-108°. After five recrystallizations from dry ether the dichlorohexane melted at 108-112°, or up to 116° upon rapid heating, with decomposition. *Anal.* Calcd. for $C_{20}H_{24}O_2Cl_2$: C, 65.40; H, 6.59. Found: C, 65.35; H, 6.79. It gave instantaneous precipitation in alcoholic silver nitrate. As before, the oily 1,6-glycols by the same procedure yielded 53% of the dichloro compound.

Attempts to Cyclize 1,6-bis-(*p*-Methoxyphenyl)-1,6-dibromohexane.—Using a procedure similar to that of Kharasch and Kleiman for coupling anethole hydrobromide,[11] the dibromohexane, 22.8 g., was suspended in 300 ml. of dry benzene and 300 ml. of dry ether. This suspension was added to a solution of 75 ml. of phenylmagnesium bromide (0.15 mole) in ether which had previously been treated with 1.0 g. of freshly-fused, powdered cobaltous chloride and cooled in ice-hydrochloric acid. The cooling bath was then removed, stirring continued five hours at room temperature and the mixture finally decomposed with 300 g. of ice and 10 ml. of concentrated hydrochloric acid. The dried ethereal extracts yielded 23.2 g. of an oil which was distilled to give 8.1 g. of biphenyl, b. p. 107-120° (8-11 mm.), m. p. 69-70° and 10.13 g. of an oil, b. p. 210-250° (1 mm.). Subjection of the latter fraction to a long series of distillations and crystallizations from toluene, ether, ligroin and methyl alcohol permitted isolation of 0.4 g. of *p*-terphenyl, m. p. 209-211°, and 0.5 g. of 1,6-bis-(*p*-methoxyphenyl)-hexane, m. p. 70.1-72.5°. The mixed melting points of the latter with biphenyl and with 1,2-bis-(*p*-methoxyphenyl)-cyclohexane (see below) were depressed, but not with a synthetic sample of the known 1,6-bis-(*p*-methoxyphenyl)-hexane,[17] for which compound the analysis also was correct.

Pinacol Reduction of 1,4-bis-(*p*-Methoxybenzoyl)-butane.—A suspension of 25 g. of the diketone in 400 ml. of moist ethyl acetate was added to 9.5 g. of aluminum foil, freshly amalgamated. The temperature remained at 38° with stirring, for two hours as the reaction proceeded slowly, then rose to 48° and finally had dropped back to 30° after four hours. The mixture was worked up in the usual way, the organic solution dried over anhydrous magnesium sulfate and evaporated *in vacuo* leaving 20.7 g. of a tan-colored glass, soluble in warm ethyl acetate and precipitated therefrom by benzene or petroleum ether. The product was not soluble in methyl alcohol, ethyl alcohol or acetone. It was dissolved in 100 ml. of ethyl acetate and the resulting solution filtered into 250 ml. of methyl alcohol. The freshly precipitated polymer was gummy, but on standing in the mother liquors became friable and when dried resembled colorless rosin. The dry polymer was introduced into 100 ml. of ethyl acetate where it first swelled, then formed a gel and finally dissolved on heating; it was precipitated again in 250 ml. of methyl alcohol, collected and dried. The powdered polymer was hygroscopic and difficult to dry to a constant weight even over phosphorus pentoxide. It melted at 170-185° with foaming until residual moisture had evaporated. The viscous amber liquid cooled to form a brittle glass. *Anal.* Calcd. for $C_{20}H_{24}O_4$: C, 73.15; H, 7.37. Found: C, 72.03; H, 7.39; redried: C, 72.14; H, 7.64. The finely-powdered polymer, 0.66 g. (0.002 mole), and 0.90 g. (0.002 mole) of lead tetraacetate gave a heavy, insoluble suspension in 5 ml. of glacial acetic acid. However, on stirring, the entire mass was brought into solution in two minutes. After centrifuging to remove traces of insoluble matter, this was poured into cold water and the precipitated solid collected and dried, giving 0.66 g. of ketone. This was recrystallized twice from ethyl acetate and melted at 144.0-146.0°, not depressing the melting point of an authentic sample of 1,4-bis-(*p*-methoxybenzoyl)-butane.

2-(*p*-Methoxyphenyl)-cyclohexanone.—The procedure used previously in preparing phenylmethylcyclohexanones served as a guide.[5] 2-Chlorocyclohexanone,[18] 41 g. (0.31 mole), in 100 ml. of dry ether was added with stirring and cooling to the Grignard reagent prepared from 56 g. (0.30 mole) of *p*-bromoanisole and 7.55 g. (0.31 mole) of magnesium in 100 ml. of ether. Xylene, 155 ml., was added to the mixture on the next day and ether distilled away until the internal temperature reached 95-100°, when heating was continued at total reflux with stirring for eight hours. The cooled mixture was hydrolyzed with ammonium chloride solution and the organic layer removed, washed, dried and distilled, yielding 19.9 g. (33%) of 2-(*p*-methoxyphenyl)-cyclohexanone; b. p. 156-166° (1 mm.), m. p. 88.5-89.5° after crystallization from ligroin. *Anal.* Calcd. for $C_{13}H_{16}O_2$: C, 76.43; H, 7.89. Found: C, 76.01, 75.97; H, 7.65, 7.77. This ketone failed either to form a bisulfite addition compound or to react with Schiff reagent. It did react slowly with Fehling solution and the usual ketone reagents. The 2,4-dinitrophenylhydrazone was prepared and recrystallized three times from ethyl alcohol; m. p. 143-144°. *Anal.* Calcd. for $C_{19}H_{20}O_5N_4$: C, 59.37; H, 5.25. Found: C, 59.10; H, 5.25. Its structure was confirmed by oxidizing 1.0 g. of the ketone suspended in 25 ml. of water and heated to 90° with the dropwise addition of 1.0 g. of potassium permanganate in 25 ml. of water. The cooled solution was extracted with ether and the residual ether removed from the aqueous solution which was then acidified with dilute sulfuric acid and permitted to stand in the cold until crystallization of the δ-(*p*-methoxy-

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(16) Schmidt, *Ann.*, **547**, 103 (1941).

(17) Plant and Tomlinson, *J. Chem. Soc.*, 1092 (1935).

(18) Newman, Farbman and Hipsher, *Org. Syntheses*, **25**, 22 (1945).

benzoyl)-valeric acid was complete. This was collected and recrystallized successively from alcohol and ethyl acetate; 0.5 g., m. p. 127.0-127.5°,[17] neutral equivalent 238 (calcd., 236).

Another preparation of 2-(*p*-methoxyphenyl)-cyclohexanone involved oxidation of 1-(*p*-methoxyphenyl)-cyclohexene[19] with perbenzoic acid in chloroform solution. However, the oxidation products from 19.3 g. were oily and yielded as crystalline products 2 g. of an unidentified substance, m. p. 122-124° [*Anal.* Calcd. for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60. Found: C, 73.65, 73.51; H, 6.77, 6.62] and only 2 g. of the desired cyclohexanone after distillation at 3 mm. of the unpurified oxide intermediate.

The bis-(*p*-Methoxyphenyl)-cyclohexenes, Ia and IIa.—A solution of 19 g. (0.093 mole) of 2-(*p*-methoxyphenyl)-cyclohexanone in 300 ml. of dry ether was added to the Grignard reagent prepared from 18 g. (0.096 mole) of *p*-bromoanisole and 2.34 g. (0.096 mole) of magnesium in 40 ml. of ether, slowly, to maintain gentle refluxing. The mixture stood overnight, was hydrolyzed with ammonium chloride solution and the crude product recovered as an oil from the dry ethereal extract. This oil was heated at reflux for one hour with 20 g. of acetic anhydride. Removal of the excess anhydride and acetic acid left an oil, separable into 10.9 g. of viscous, greenish-yellow oil, b. p. 209-214° (1 mm.), crystallizing slowly on dilution with alcohol. The yield was 9.1 g. (33%) of crystalline product, m. p. 75-87°. Microscopic observation showed two crystal forms present after eight recrystallizations from ethyl alcohol, which raised the melting point to 86-88°. The analysis was correct for a mixture of bis-(*p*-methoxyphenyl)-cyclohexenes; this mixture was almost entirely the isomer Ia with very little IIa.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.59; H, 7.54. Found: C, 81.30, 81.46; H, 7.39, 7.44.

In an alternative preparation 21 g. (0.16 mole) of 2-chlorocyclohexanone in 50 ml. of dry ether was added to the Grignard reagent prepared from 61 g. (0.32 mole) of *p*-bromoanisole and 7.9 g. (0.32 mole) of magnesium in 100 ml. of ether; 150 ml. of xylene was used in the manner described above. After hydrolysis and separation, the dried xylene extracts were treated with 10 ml. of acetic anhydride for three hours at room temperature and the solvent and acetic acid removed *in vacuo*. Fractional distillation yielded 2.1 g. (6.4%) of 2-(*p*-methoxyphenyl)-cyclohexanone and 17.8 g. of green oil, b. p. 210-215° (1 mm.), of which 9.2 g. (19.7%) crystallized readily from alcohol. This was the principal product, melting at 88.5-90.0° (micro)[20] after three recrystallizations. This was bis-(*p*-methoxyphenyl)-cyclohexene, Ia.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.59; H, 7.54. Found: C, 81.44; H, 7.43.

The mother liquors from purification of the isomer Ia yielded 0.25 g. of the other isomer, m. p. 88.0-89.5° (micro) after five crystallizations from alcohol. This was bis-(*p*-methoxyphenyl)-cyclohexene, IIa; a mixture of equal weights of Ia and IIa melted at 67-86°.

Anal. Calcd. for $C_{20}H_{22}O_2$: C, 81.59; H, 7.54. Found: C, 81.57; H, 7.49.

In an attempt to isolate the intermediate, 1,2-bis-(*p*-methoxyphenyl)-cyclohexanol, the acetic anhydride treatment was omitted, but instead the heavy oil remaining after removal of the xylene *in vacuo* allowed to stand until partly crystallized. With the aid of petroleum ether some crystals were freed from oil and purified from methyl alcohol. They proved to be the cyclohexene, Ia.

Dehydrogenation of 0.3 g. of the mixture of cyclohexenes, m. p. 75-87°, was accomplished by heating with 0.065 g. of sulfur for five hours at 200-250°. Zinc dust was added at 250° to destroy excess sulfur and the melt cooled and extracted with hot methyl alcohol. The recovery of white needles, m. p. 103-105° was 0.14 g.; when purified further from methyl alcohol this product melted at 105-106° and did not depress the melting point of 4′,4″-dimethoxy-*o*-terphenyl.[3b]

The bis-(*p*-Hydroxyphenyl)-cyclohexenes, Ib and IIb.—A solution of 3.0 g. of bis-(*p*-methoxyphenyl)-cyclohexene, Ia, m. p. 86-88°, in 25 ml. of ethyl alcohol and 10 g. of potassium hydroxide was heated in a steel autoclave at 200-210° for twenty-four hours.[18a] Acidification of the cooled, diluted solution precipitated 2.65 g. (98%) of crude phenols, m. p. 165-220°. Fractional crystallization from methyl alcohol finally gave two pure products, the first isolated being bis-(*p*-hydroxyphenyl)-cyclohexene, IIb, 0.4 g., crystallizing in long needles and subliming into short staffs at 224° just before melting at 226.6-228.6° (micro). *Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.18; H, 6.81. Found: C, 81.14; H, 6.77. The diacetate resulted from heating 50 mg. of the phenol with 2 ml. of acetic anhydride and 0.1 g. of fused sodium acetate. It was purified from methyl alcohol; m. p. 149.0-150.4° (micro). *Anal.* Calcd. for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.07; H, 6.65. This phenolic cyclohexene, IIb, did not depress the melting point of 4′,4″-dihydroxy-*o*-terphenyl. However, 4′,4″-diacetoxy-*o*-terphenyl, m. p. 186°[3b] was clearly different from and depressed the melting point of the cyclohexane derivative. Moreover, saponification of the acetate, in 5% sodium hydroxide, m. p. 149-150°, gave the original phenol almost quantitatively. Methylation of 50 mg. of this phenol, m. p. 224-228°, by alternate addition in two portions of a total of 2 ml. of 20% sodium hydroxide and 2 ml. of dimethyl sulfate, destroying the excess with concentrated ammonia, yielded a gummy, white solid. This was recrystallized three times from methyl alcohol; m. p. 90.8-91.4° (micro); m. m. p. with bis-(*p*-methoxyphenyl)-cyclohexene, Ia, 70-87°; m. m. p. with the cyclohexene, IIa, 89.5-90.9° (micro). Hydrogenation of the phenolic cyclohexene, IIb, 18 mg., over 10% palladium-on-charcoal catalyst[21] in ethyl alcohol at 80 p. s. i. yielded 12 mg. of 1,2-bis-(*p*-hydroxyphenyl)-cyclohexane, IV, m. p. 177-179° (see below).

The second compound isolated from the demethylation products crystallized on slow evaporation of the liquors from phenolic cyclohexane IIb. This melted at 160-220° but finally yielded 0.5 g. of micro-needles, m. p. 171.0-173.5° (micro), from the same solvent. It depressed to 158° the melting point of 1,2-bis-(*p*-hydroxyphenyl)-cyclohexane and is bis-(*p*-hydroxyphenyl)-cyclohexene, Ib. *Anal.* Calcd. for $C_{18}H_{18}O_2$: C, 81.18; H, 6.81. Found: C, 81.33, 81.15; H, 6.90, 6.66. The diacetate, prepared as above, was purified from methyl alcohol; m. p. 140.5-141.5° (micro). *Anal.* Calcd. for $C_{22}H_{22}O_4$: C, 75.41; H, 6.33. Found: C, 75.45; H, 6.36. Methylation of this phenol in like manner furnished bis-(*p*-methoxyphenyl)-cyclohexene, Ia, m. p. 88.8-89.8° (micro); m. p., with the isomer Ia isolated from the Grignard reaction, 88.3-90.4° (micro).

1,2-bis-(*p*-Methoxyphenyl)-cyclohexane, III.—The mixture of bis-(*p*-methoxyphenyl)-cyclohexenes, 3.2 g., in 50 ml. of acetone was shaken with 0.5 g. of 10% palladium-on-charcoal catalyst for six hours at 50 p. s. i. of hydrogen. Following filtration and removal of acetone the residue was crystallized from alcohol, giving 2.9 g. (90%) of 1,2-bis-(*p*-methoxyphenyl)-cyclohexane, m. p. 67-69°. *Anal.* Calcd. for $C_{20}H_{24}O_2$: C, 81.02; H, 8.17. Found: C, 80.92, 80.91; H, 8.06, 7.92. Hydrogenation, likewise, of the pure isomeric bis-(*p*-methoxyphenyl)-cyclohexenes, Ia and IIa, resulted in the same cyclohexane from each in comparable yields.

1,2-bis-(*p*-Hydroxyphenyl)-cyclohexane, IV.—Demethylation of 8.0 g. of 1,2-bis-(*p*-methoxyphenyl)-cyclohexane with 20 g. of potassium hydroxide in 150 ml. of alcohol at 200-210° for twenty-four hours yielded 7.0 g. of acid-precipitated product, m. p. 176-178°. Two recrystallizations from 50% aqueous methyl alcohol, with

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[19] This was prepared by dehydration of the carbinol, *cf.* Sherwood, *et al.*, *J. Chem. Soc.*, 1832 (1932); 323 (1936), and the melting point was as given by v. Braun, *Ann.*, **472**, 1 (1929).

[20] All micro-melting points were observed at fifty magnifications in the Kofler apparatus as supplied by the Arthur H. Thomas Co., Philadelphia, Pa., and calibrated in terms of standard samples accompanying the instrument.

[21] Hartung, THIS JOURNAL, **50**, 3370 (1928).

addition of Norite, gave 6.5 g. (88%) of the phenol, m. p. 177.5-179.5°, which produced no color with ferric chloride. *Anal.* Calcd. for $C_{18}H_{20}O_2$: C, 80.54; H, 7.53. Found: C, 80.56, 80.54; H, 7.41, 7.20.

1,2-bis-(*p*-Acetoxyphenyl)-cyclohexane, m. p. 114.8-116.2° (micro), was prepared and purified just as described for the corresponding unsaturated compounds. *Anal.* Calcd. for $C_{22}H_{24}O_4$: C, 74.96; H, 6.88. Found: C, 74.88, 75.00; H, 6.81, 6.75.

Physiological Activity.—On subcutaneous injection into rats[22] of an oil solution, bis-(*p*-hydroxyphenyl)-cyclohexene, Ib, showed 300 I. U./mg.; bis-(*p*-hydroxyphenyl)-cyclohexene, IIb, 150 I. U./mg.; and 1,2-bis-(*p*-hydroxyphenyl)-cyclohexane, 200 I. U./mg. of estrogenic activity.

Summary

1,2-bis-(*p*-Hydroxyphenyl)-cyclohexane and two intermediate cyclohexenes together with their methyl and acetyl derivatives have been prepared. The phenols have moderate estrogenic activity. The hindrance to ring closure of 1,6-diarylhexamethylene derivatives has been indicated and the formation of a polypinacol discussed.

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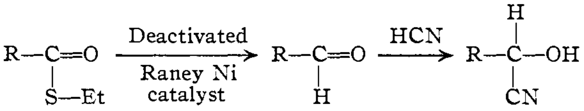
[22] We are grateful to Parke Davis and Company, Detroit, Michigan, for testing these compounds.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

Steroid Acids and their Transformation Products. VI. Some New Aldehydes and Their Derived Cyanohydrins

BY A. VERN MCINTOSH, ANNA MAE SEARCY, ELIZABETH M. MEINZER AND ROBERT H. LEVIN

Preparation of steroid aldehydes by the desulfurization of thiol esters of 3β-hydroxy-5-cholenic acid, 3β-hydroxybisnor-5-cholenic acid and desoxycholic acid with acetone deactivated W-1[1] Raney nickel catalyst has been reported in previous papers of this series.[2] We have now prepared aldehydes starting with the thiol esters of nor-desoxycholic acid, lithocholic acid, 12α-hydroxycholanic acid, and 3α-hydroxy-11-cholenic acid, in yields of 39 to 78%. These aldehydes have been converted to cyanohydrins in excellent yields, completing the sequence of reactions



$$\begin{array}{c}\text{R—C=O}\\ |\\ \text{S—Et}\end{array} \xrightarrow[\text{Raney Ni catalyst}]{\text{Deactivated}} \begin{array}{c}\text{R—C=O}\\ |\\ \text{H}\end{array} \xrightarrow{\text{HCN}} \begin{array}{c}\text{H}\\ |\\ \text{R—C—OH}\\ |\\ \text{CN}\end{array}$$

Ethyl 3α,12α-diacetoxynorthiolcholanate has been used as a model for the study of variations in the desulfurization procedure. The information gained from the experiments on the desulfurization of this compound is summarized very briefly below, excluding data which have been previously reported in this series.

A number of attempts were made to prepare 3α,12α-diacetoxynorcholan-23-al from the thiol ester without deactivation of the nickel. It was found that five parts of W-4 Raney nickel, or twenty parts of W-1 or commercial active Raney nickel, would reduce the thiol ester in alcohol quantitatively to 3α,12α-diacetoxynorcholan-23-ol at either room temperature or at reflux. When ten parts of W-1 Raney catalyst was heated with one part of ester in alcohol solution, a mixture of 3α,12α-diacetoxynorcholan-23-ol and ethyl 3α,12α-diacetoxynorthiolcholanate was obtained, besides about a 1% yield of aldehyde isolated as the semicarbazone.

Next, an experiment was devised to analyze the products obtained by use of Raney nickel which had been deactivated by reaction with the thiol ester. A mixture of Raney nickel and Celite filter-aid was placed in a chromatogram column and a solution of the thiol ester was filtered through and collected in portions. When 10 g. of W-4 Raney nickel was used, 2.1 g. of very pure 3α,12α-diacetoxynorcholan-23-ol was obtained in the first several fractions, then alcohol–ester mixtures followed. The time of contact of the solution in the column was about a minute, indicating a very rapid reaction at room temperature. Using W-1 Raney nickel, a little less than half the yield of alcohol given by the W-4 nickel was obtained, followed by some gummy mixtures, then the pure thiol ester. A very small amount of aldehyde semicarbazone was obtained on working up the mixtures, besides both alcohol and ester.

Without deactivation of the Raney nickel before the reaction with the thiol ester not more than 1% of aldehyde was obtained, isolated as the semicarbazone. Pretreatment of the Raney nickel in acetone under reflux proved by far the most suitable of the methods of deactivation tried.[2] When deactivated with acetone W-1 and W-4 Raney nickels, prepared in this Laboratory, and a commercial active Raney nickel[3] were used successfully as desulfurizing agents. A commercial pelleted Raney catalyst was found to be entirely inactive. Within experimental error the yields obtained when the commercial active Raney nickel was used were the same as were obtained with the W-1 catalyst. The W-4 catalyst gave consistently lower yields of aldehyde although different deactivation and reaction times were tried. However, for reduction of thiol esters to alcohols the W-4 nickel was best, giving nearly quantitative

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[1] Adkins and Pavlic, THIS JOURNAL, **69**, 3039 (1947).

[2] (a) Spero, McIntosh and Levin, *ibid.*, **70**, 1907 (1948); (b) McIntosh, Meinzer and Levin, *ibid.*, **70**, 2955 (1948).

[3] Raney Active Nickel Catalyst, in water, obtained from the Gilman Paint and Varnish Co., Chattanooga, Tenn. This catalyst is analogous to W-1 or W-2 catalysts in activity.