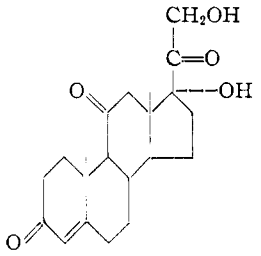
[CONTRIBUTION FROM THE LABORATORY OF PHARMACEUTICAL CHEMISTRY OF THE UNIVERSITY OF KANSAS SCHOOL OF PHARMACY]

Steroidal Hormone Relatives. I. The Conversion of 3,4-Bis-(*p*-hydroxyphenyl)-2-hexanone to 3,4-Bis-(4-oxocyclohexyl)-2-hexanone, and a Synthesis of *meso*-Hexestrol

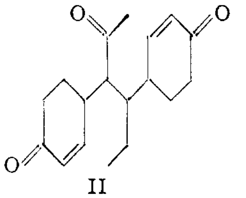
BY J. H. BURCKHALTER AND JOSEPH SAM

Principally as a means of providing a background for further chemical studies, certain open model compounds were synthesized so as to provide a carbonyl function in a position to correspond with that of position 11 of cortisone. 3,4-Bis-(*p*-methoxyphenyl)-2-hexanone (VIc) was prepared from the corresponding nitrile. After demethylation, it was first reduced catalytically and then oxidized with chromic acid to give 3,4-bis-(4-oxocyclohexyl)-2-hexanone (V). VIc, as well as its demethylation product (VId), was converted by means of the Wolff–Kishner reduction to *meso*-hexestrol. VId has been found to be a powerful estrogen.

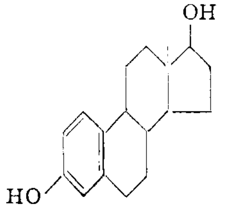
The importance of the carbonyl group at position 11 in cortisone (I) has suggested the synthesis of certain open model compounds which would possess the oxygen function in a corresponding position.[1] One of the desired substances (II) might be considered to bear a structural relationship to cortisone (I) similar to that which hexestrol (IV) bears to estradiol (III).



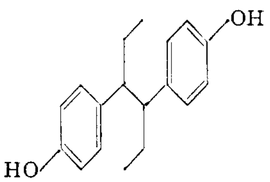
I



II

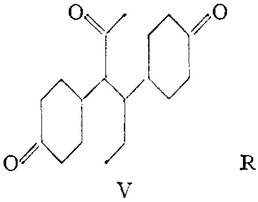


III

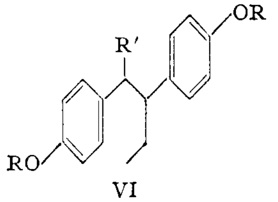


IV

One approach to II required the preparation of triketone V. *p*-Methoxyphenylacetonitrile was condensed with anisaldehyde by the general method of Kohler[2] to give α,β-bis-(*p*-methoxyphenyl)-acrylonitrile in 95% yield.[3] The latter compound, when treated with at least a molar excess of ethylmagnesium bromide, was converted in 42% yield to a solid (VIa) and in 49% yield to a liquid (VIa') which represent the two *dl*-forms of α,β-bis-(*p*-methoxyphenyl)-valeronitrile.[3] Isomer VIa and a five-molar excess of methylmagnesium iodide gave ketone VIc in 87% yield,[3a] and a very small amount of the other *dl*-form (VIc') was isolated in one experiment. VIc was also obtained by treatment of the acid chloride of the higher melting acid (VIb) with ethoxymagnesiummalonic ester according to the method of Hauser.[4] The results of Hunter and Korman[3] who obtained a lower melting isomeric acid (VIb') could not be duplicated. Hence, VIc' could not be prepared *via* the acid chloride. Attempts to make VIc' by treatment of nitrile VIa' with the methyl Grignard reagent gave only oils which failed to meet analytical requirements.



V



VI

	R	R'	M.p.
a	CH_3	CN	131
a'			Oil
b	CH_3	CO_2H	182
b'			165
c	CH_3	$COCH_3$	143
c'			104
d	H	$COCH_3$	220
d'			Oil
e	$COCH_3$	$COCH_3$	144
e'			104

When demethylation procedures using hydrobromic acid, pyridine hydrochloride and aluminum chloride were found to be unsatisfactory, VIc was converted by aluminum bromide to 3,4-bis-(*p*-hydroxyphenyl)-2-hexanone (VId) in yields ranging between 50 and 71%. A considerable amount of additional phenolic material could not be satisfactorily purified. It was assumed to be the other *dl*-form (VId') resulting from isomerization *via* enol formation. Distinctive crystalline diacetates (VIe and e') were made of both *dl*-isomers. However, an attempt to recover the pure isomeric phenols by basic hydrolysis of the acetates gave mixtures from which it was possible to isolate in pure form, in both cases, only VId. It is assumed that the difficulties of isolation resulted from isomerization *via* carbanion formation.

Reduction of 3,4-bis-(*p*-hydroxyphenyl)-2-hexanone (VId) at elevated temperature and pressure gave a mixture of isomeric 3,4-bis-(4-hydroxycyclohexyl)-2-hexanols which was directly converted by chromic acid oxidation to the triketone V (41% yield based upon the mixture of alcohols).[5]

Attempts to convert V to II through bromination and dehydrobromination[5c,6] were fruitless. However, the failure to isolate a pure product was not

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[1] Others have apparently had the same objective in mind: (a) D. R. Satriana, A. Loter and M. M. Baizer, THIS JOURNAL, **73**, 866 (1951); (b) K. Rorig, Abstracts of Papers, 119th Meeting, American Chemical Society, Boston, Mass., April 1 to 5, 1951, p. 20 M.

[2] E. P. Kohler, *Am. Chem. J.*, **35**, 399 (1906).

[3] J. H. Hunter and J. Korman, THIS JOURNAL, **70**, 3424 (1948).

[3a] A similar experiment by Rorig failed[1b] possibly because he did not use an excess of the Grignard reagent. As pointed out by Rorig,[1b] nitrile VIa contains an α-hydrogen which is probably sufficiently acidic to attack a Grignard reagent.

[4] H. G. Walker and C. R. Hauser, THIS JOURNAL, **68**, 1386 (1946).

[5] *Cf.* Methods of A. L. Wilds and C. H. Shunk, *ibid.*, **71**, 3946 (1949); (b) D. M. Musser and H. Adkins, *ibid.*, **60**, 664 (1938); (c) W. Schoeller, *et al.*, U. S. Patent 2,392,864 (Jan. 15, 1946).

[6] H. E. Ungnade and P. W. Tucker, *ibid.*, **71**, 1381 (1949).

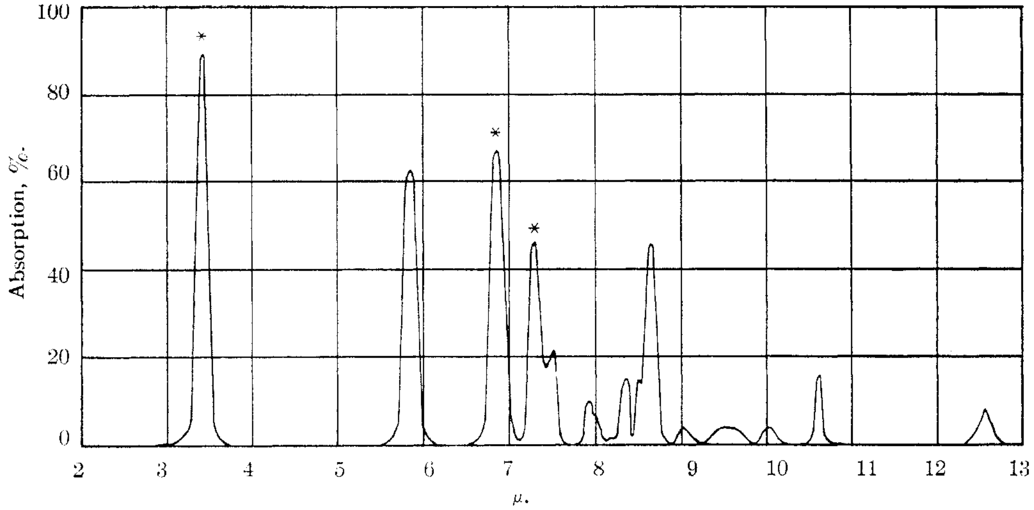
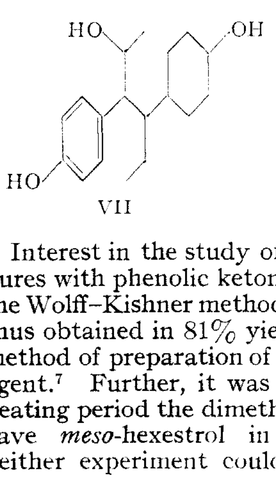


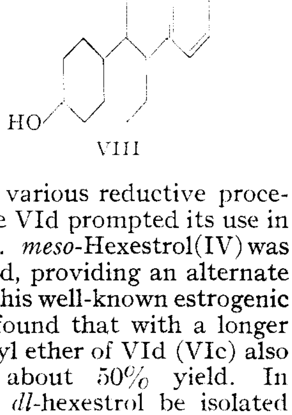
Fig. 1.—Infrared absorption spectrum of 3,4-bis-(4-oxocyclohexyl)-2-hexanone (V): * represents nujol absorption.

surprising in view of the several possibilities for the formation of isomers and by-products.

Microanalyses and qualitative tests indicate that V possesses the carbonyl function but do not eliminate the possibility of the presence of a hydroxyl instead of a carbonyl group at position 2. The infrared absorption curve (Fig. 1), however, does not reveal a hydroxyl band near 3 μ, the expected wave length, but it does show the expected carbonyl band at 5.8 μ. Hence, V has been designated as a triketone.

At one stage in the catalytic reduction of 3,4-bis-(*p*-hydroxyphenyl)-2-hexanone (VId), a small amount of a phenolic white crystalline solid was isolated. Elementary analysis does not exclude a carbonyl function, but the absence of a typical carbonyl band near 5.8 μ and the presence of a typical hydroxyl band at 3 μ indicates the oxygen to be present as hydroxyl groups (Fig. 2). These data suggest either 4-(4-hydroxycyclohexyl)-3-(4-hydroxyphenyl)-2-hexanol (VII) or 3-(4-hydroxycyclohexyl)-4-(4-hydroxyphenyl)-2-hexanol (VIII) as the intermediate reduction product of VId.


VII


VIII

Interest in the study of various reductive procedures with phenolic ketone VId prompted its use in the Wolff–Kishner method. *meso*-Hexestrol(IV) was thus obtained in 81% yield, providing an alternate method of preparation of this well-known estrogenic agent.[7] Further, it was found that with a longer heating period the dimethyl ether of VId (VIc) also gave *meso*-hexestrol in about 50% yield. In neither experiment could *dl*-hexestrol be isolated from the reaction mixture. The related Clemmensen procedure failed with VIc.

Although *meso*-hexestrol was the product of reduction of both VIc and VId, an assignment of configuration to these ketones upon that basis would be open to question because of the severity of the conditions of the Wolff–Kishner reaction. Nevertheless, it is interesting to observe that the series of unprimed lettered compounds of general formula VI consists of the higher melting isomers which were converted always in yields of at least 50% to the higher melting and presumably the more stable isomeric derivative. Possible isomerizations within the group of VI compounds may be explained by carbanion or enol formation effected, respectively, by the basic or acidic conditions.

Attempts were made to convert ketone VIc to compounds of type II by means of the Birch reduction.[8,9] This method, which employs sodium and liquid ammonia followed by acid hydrolysis, gave a solid which could not be purified. Because alcoholic groups have been shown to increase the solubility and reactivity of certain compounds in the Birch reduction,[9] there was reason to replace VIc with 3,4-bis-(*p*-methoxyphenyl)-2-hexanol in the same procedure. However, only a pure acetate of the latter could be obtained from which it was impossible to isolate a pure alcohol by hydrolysis because of isomerization.

With the thought in mind of preparing 3-(*p*-methoxyphenyl)-4-ethyl-7-methoxy-2-tetralone, 1-diazo-3,4-bis-(*p*-methoxyphenyl)-2-hexanone was made from the acid chloride of VIb and converted to the 1-bromo and 1-acetoxy derivatives. The prospect of conversion of these compounds to a tetralone in appreciable amount, however, was discouraging in view of the observations of others.[10]

Biological Results.—Only one of the compounds has been studied biologically. 3,4-Bis-(*p*-hydroxyphenyl)-2-hexanone (VId) has been described by Charles A. Winter, of Merck Institute for Thera-

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(7) Other methods apparently require fewer steps. See, for example, M. S. Kharasch, H. McBay and W. H. Urry, *J. Org. Chem.*, **10**, 401 (1945); A. L. Wilds and W. B. McCormack, *ibid.*, **14**, 45 (1949); N. P. Buu-Hoi and N. Hoan, *ibid.*, **14**, 1023 (1949); M. S. Kharasch, U. S. Patent 2,392,852 (Jan. 15, 1946).

(8) This experiment was undertaken upon the suggestion of Dr. A. L. Wilds, of the University of Wisconsin.

(9) A. J. Birch and S. M. Mukherji, *J. Chem. Soc.*, 2531 (1949).

(10) C. D. Gutsche and W. S. Johnson, This Journal, **68**, 2239 (1946).

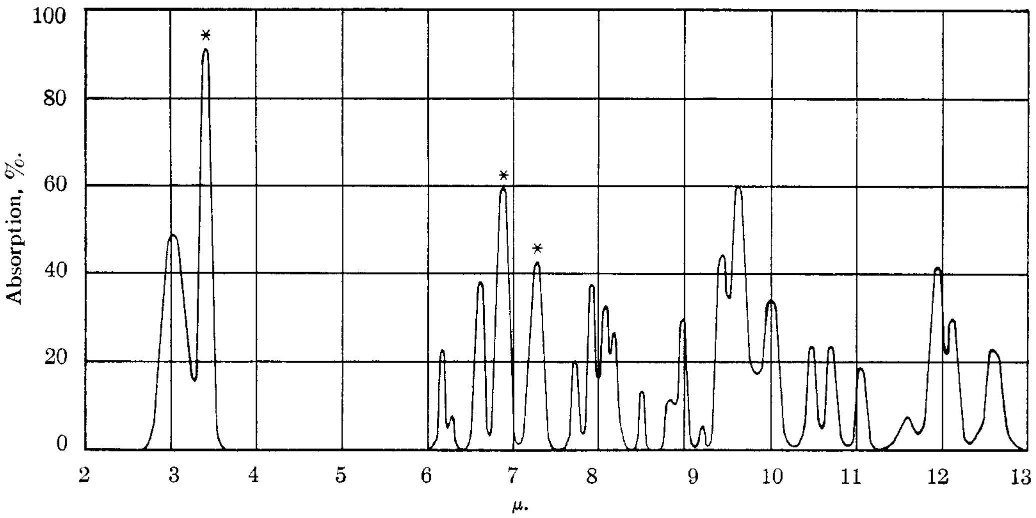

Fig. 2.—Infrared absorption spectrum of 4-(4-hydroxycyclohexyl)-3-(4-hydroxyphenyl)-2-hexanol (VII) or its isomer (VIII): * represents nujol absorption.

peutic Research, as "a powerful estrogen, though not quite as potent as diethylstilbestrol." When screened concurrently in a modification of the Selye test, as well as in other standard test methods, VId and diethylstilbestrol both possessed some of the effects of cortisone. However, the remote structural relationship of VId to cortisone does not suggest any promise for the compound as a substitute.

Acknowledgments.—The authors are grateful to Research Corporation for financial support of the project, to Drs. Charles A. Winter and Robert H. Silber, of Merck Institute, for biological studies; and to Mr. Bruce Scott, of Parke, Davis and Co., for infrared absorption spectra determinations and interpretations.

Experimental[11]

***p*-Methoxybenzyl Chloride.**—This intermediate was made consistently in about 90% yield using essentially the procedure of Livshits, *et al.*[12] No solvent was needed, but it was important to use freshly distilled *p*-methoxybenzyl alcohol (anisic alcohol, Givaudan–Delawanna) and redistilled thionyl chloride. The crude chloride decomposes readily with the evolution of hydrogen chloride. Even after one distillation it polymerizes readily upon standing. However, after redistillation the compound is stable for months. Rorig,[13] employing the procedure of Shriner and Hull, reports satisfactory results without distilling the chloride when it is used at once.

***p*-Methoxyphenylacetonitrile.**—The procedure of Livshits, *et al.*,[12] or the Rorig modification[13] of the Shriner and Hall procedure gave yields of 80 to 90% based on the chloride. These methods require benzene and dioxane as a solvent. However, the product of Lee, *et al.*,[14] who used acetone as a solvent, appeared to be impure. The nitrile prepared by their procedure gave only a 43% yield of the acrylonitrile described in the following experiment.

α,β-Bis-(*p*-methoxyphenyl)-acrylonitrile.—By the general procedure of Kohler,[2] this compound was prepared and recrystallized from alcohol in 95% yield, m.p. 105–107°.[15]

α,β-Bis-(*p*-methoxyphenyl)-valeronitrile (VIa).—The procedure followed was that of Kohler[2] for the preparation of α,β-diphenylvaleronitrile. Hydrolysis of the complex made from 159 g. of α,β-bis-(*p*-methoxyphenyl)-acrylonitrile and the ethyl Grignard reagent gave a yellow solid. Washing with a little ether and recrystallization from alcohol gave 74 g. (42% yield) of the solid isomer (VIa); m.p. 130–131° (same as reported[3]).

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17. Found: C, 76.80; H, 6.84.

The aqueous solution was extracted with ether and the extracts combined with the alcohol filtrate. Removal of the solvent and distillation of the residue gave 87 g. (49% yield) of the liquid isomer, b.p. 205° (1 mm.) [reported[3] bath temperature 220–230° (0.3 mm.)].

Anal. Found: C, 77.22; H, 7.27.

α,β-Bis-(*p*-methoxyphenyl)-valeryl Chloride.—α,β-Bis-*p*-methoxyphenylvaleric acid (m.p. 181–183°) was prepared from the solid nitrile (VIa) by the method of Hunter and Korman.[3] A mixture of 3.1 g. of the acid and 5 ml. of thionyl chloride was refluxed on a steam-bath for four hours. The excess thionyl chloride was removed *in vacuo* and the residual solid was recrystallized from Skelly solvent. Two grams (60% yield) of the acid chloride was obtained, m.p. 136–137°.

Anal. Calcd. for $C_{19}H_{21}ClO_3$: C, 68.57; H, 6.36. Found: C, 68.78; H, 6.44.

3,4-Bis-(*p*-methoxyphenyl)-2-hexanone (VIc). Method A.—The general procedure of Kohler[2] was followed. Fifty grams (0.17 mole) of solid nitrile (VIa), dissolved in 300 ml. of dry benzene, was added slowly to a boiling and well-stirred ethereal solution of methylmagnesium iodide, prepared from 24 g. (1 mole) of magnesium, 140 g. (1 mole) of methyl iodide and 200 ml. of anhydrous ether. The ether was then removed and the resulting benzene solution refluxed for three hours. The mixture was cooled and slowly added to a solution of 200 ml. of concentrated hydrochloric acid. Although cooled at first, the mixture was allowed to become hot to ensure complete hydrolysis. The aqueous layer was separated with ether and the extracts combined with the benzene layer. After removal of the solvent, an oily solid remained. Recrystallization from alcohol gave 46 g. (87% yield) of 3,4-bis-(*p*-methoxyphenyl)-2-hexanone, m.p. 142–143°.

Anal. Calcd. for $C_{20}H_{24}O_3$: C, 76.89; H, 7.74. Found: C, 76.90; H, 7.76.

A **2,4-dinitrophenylhydrazone** was prepared and recrystallized from alcohol, m.p. 167–169°.

Anal. Calcd. for $C_{26}H_{28}N_4O_6$: C, 63.76; H, 5.93. Found: C, 63.61; H, 5.85.

In one run of the same experiment a mixture of isomeric ketones was noted. Fractional crystallization from alcohol gave a small amount of the **isomeric 3,4-bis-(*p*-methoxyphenyl)-2-hexanone (VIc′)**, m.p. 103–104°.

Anal. Found: C, 77.02; H, 7.89.

Method B.—The Hauser and Walker method for the synthesis of methyl ketones was followed.[4] The diethyl

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[11] Microanalyses by Mr. C. W. Beazley, Skokie, Illinois.

[12] R. S. Livshits, *et al.*, *J. Gen. Chem.* (*U. S. S. R.*), **17**, 1671 (1947); *C. A.*, **42**, 2607 (1948).

[13] K. Rorig, THIS JOURNAL, **73**, 1290 (1951).

[14] J. Lee, *et al.*, *C. A.*, **41**, 6252 (1947).

[15] See also ref. 3 and J. B. Niederl and A. Ziering, THIS JOURNAL, **64**, 886 (1942).

ethoxymagnesium malonate was prepared from a mixture of 0.5 g. of magnesium, 1 ml. of absolute alcohol and 0.1 ml. of carbon tetrachloride in ether and 3.5 g. of diethyl malonate and 2 ml. of absolute alcohol in ether. To the resulting solution an ethereal solution of 1.6 g. of α,β-bis-(*p*-methoxyphenyl)-valeryl chloride was added. Following the procedure of Hauser and Walker gave 0.8 g. (53% yield) of the same hexanone VIc, m.p. 139–141°, as shown by mixed melting point.

3,4-Bis-(*p*-hydroxyphenyl)-2-hexanone (VId).—A mixture of 10 g. of 3,4-bis-(*p*-methoxyphenyl)-2-hexanone (VIc), 45 g. of aluminum bromide and 200 ml. of dry thiophene-free benzene was refluxed with stirring for five and a half hours. The mixture was allowed to cool and excess hydrochloric acid was added. The aqueous layer was extracted with ether, and the combined ether solution was extracted with 10% sodium hydroxide solution. Excess hydrochloric acid was added to the basic solution, the precipitated phenolic material was extracted with ether, the extracts were washed with dilute sodium bicarbonate solution and then with water, and the ether was removed leaving 9.5 g. of crude semi-solid product. Recrystallization from a water–alcohol mixture gave 4.5 g. of VId, m.p. 216–219°, and 4.5 g. of crude material, m.p. 155–175°. Washing the latter with chloroform left an additional 2.5 g. of VId. Recrystallization of the total of 7 g. from a water–alcohol mixture gave 6.5 g. (71% yield) of VId, m.p. 218–220°.

Anal. Calcd. for $C_{18}H_{20}O_3$: C, 76.03; H, 7.09. Found: C, 75.41; H, 7.25.

The diacetate (VIe) of VId was prepared and recrystallized from alcohol, m.p. 143–144°.

Anal. Calcd. for $C_{22}H_{24}O_5$: C, 71.72; H, 6.56. Found: C, 71.80; H, 6.66.

The isomeric diacetate (VIe′) was prepared from the oily phenolic material recovered from the filtrates of VId. Recrystallized from alcohol, it melted at 103–104°.

Anal. Found: C, 71.90; H, 6.76.

3,4-Bis-(4-hydroxycyclohexyl)-2-hexanol.—A mixture of 6.7 g. of 3,4-bis-(*p*-hydroxyphenyl)-2-hexanone (VId), 1.5 g. of Raney nickel and 100 ml. of absolute alcohol was treated with hydrogen at 2700 p.s.i. and 160–165° for 36 hours.[16] The bomb was allowed to cool and the catalyst was removed by filtration. Evaporation of the alcohol left a white viscous oil, which was dissolved in ether and extracted with 50 ml. of 5% sodium hydroxide solution. On removal of the ether, 5 g. of alkali insoluble oil was obtained. No attempt was made to separate the isomers, and the material was used for the preparation of the triketone V.

3,4-Bis-(4-oxocyclohexyl)-2-hexanone (V).—A mixture of 8 g. of chromic acid, 10 ml. of water and 40 ml. of glacial acetic acid was added slowly with stirring to a cooled solution of 5 g. of the isomeric alcohol mixture in 50 ml. of glacial acetic acid. The temperature was kept between 20 and 25° during the addition. After standing at room temperature for 22 hours, the mixture was poured into 300 ml. of water. The aqueous solution was extracted with ether, the extracts washed with 10% sodium hydroxide solution and then with water. Removal of the ether left 3.5 g. of an oily solid which was recrystallized from Skelly solvent (b.p. 87–97°) to give 2 g. (41% yield) of the triketone, m.p. 139–140°.

Anal. Calcd. for $C_{18}H_{28}O_3$: C, 73.94; H, 9.65. Found: C, 73.72; H, 9.91.

A bis-semicarbazone of V was prepared.[17] Because of insolubility in the usual solvents, it was purified only by boiling with alcohol, m.p. 290–292°.

Anal. Calcd. for $C_{20}H_{34}N_6O_3$: C, 59.09; H, 8.43. Found: C, 58.73; H, 8.56.

Conversion of VId and VIc to *meso*-Hexestrol (IV).[18]—A mixture of 2.6 g. of 3,4-bis-(*p*-hydroxyphenyl)-2-hexanone (VId), 5 ml. of 85% hydrazine hydrate, 25 ml. of triethylene glycol and 1.8 g. of potassium hydroxide was refluxed for an hour. The condenser was removed and the water and excess hydrazine hydrate was removed by heating until the temperature reached 200°. The mixture was then refluxed for three hours, after which it was cooled, acidified with hydrochloric acid and poured into 150 ml. of water. The precipitated white solid was collected on a filter and recrystallized from benzene to give 2 g. (81% yield) of crude *meso*-hexestrol, m.p. 172–176°. Recrystallization from benzene raised the melting point to 187–189°. There was no depression with an authentic sample.

3,4-Bis-(*p*-methoxyphenyl)-2-hexanone (VIc) in the foregoing procedure underwent demethylation and reduction directly to *meso*-hexestrol when the reflux period was extended to 48 hours. However, the yield was only 48 to 52%.

3,4-Bis-(*p*-methoxyphenyl)-2-hexanol.—The method of Nystrom and Brown was followed.[19] A mixture of one gram of lithium aluminum hydride and 100 ml. of ether was placed in a flask above which was located the thimble of a Soxhlet extractor containing 9.4 g. of 3,4-bis-(*p*-methoxyphenyl)-2-hexanone (VIc). The mixture was heated at reflux temperature until all the ketone had been removed from the thimble. To decompose the excess lithium aluminum hydride and alcoholate, 100 ml. of water was slowly added to the stirred mixture, which was then poured into 100 ml. of ice-water. After the addition of 100 ml. of 10% sulfuric acid, the aqueous layer was extracted with ether and the ether layers combined. Removal of the ether gave 9 g. of white solid, m.p. 115–130°. Fractional crystallization failed to separate satisfactorily the possible isomeric hexanols.

An acetate, prepared from the mixture of isomeric hexanols, was recrystallized from alcohol, m.p. 115–116°.

Anal. Calcd. for $C_{22}H_{28}O_4$: C, 74.13; H, 7.92. Found: C, 74.20; H, 7.91.

Reduction of VIc using Raney nickel catalyst resulted in a similar mixture of isomeric hexanols.

1-Diazo-3,4-bis-(*p*-methoxyphenyl)-2-hexanone.—A mixture of α,β-bis-(*p*-methoxyphenyl)-valeryl chloride (prepared from 3.14 g. of the acid) and 100 ml. of anhydrous ether was added slowly to a cold well-stirred dried ethereal solution of diazomethane (prepared from 15 g. of nitrosomethylurea[20]). The solid diazo ketone which separated was collected on a filter and dried; weight 1.5 g. (46% yield), m.p. 125–127°. No attempt was made to recrystallize or analyze the substance; it was used immediately.

1-Bromo-3,4-bis-(*p*-methoxyphenyl)-2-hexanone.—To a well-stirred suspension of 1.5 g. of 1-diazo-3,4-bis-(*p*-methoxyphenyl)-2-hexanone in 150 ml. of ether, 10 ml. of 48% hydrobromic acid was added slowly. The ether layer was separated and the solvent removed. The light orange colored solid which remained was recrystallized from alcohol to give 1.5 g. (88% yield) of desired bromide, m.p. 123–123.5°.

Anal. Calcd. for $C_{20}H_{23}BrO_3$: C, 61.39; H, 5.92. Found: C, 61.93; H, 6.16.

1-Hydroxy-3,4-bis-(*p*-methoxyphenyl)-2-hexanone.—A mixture of 0.63 g. of 1-diazo-3,4-bis-(*p*-methoxyphenyl)-2-hexanone, 15 ml. of dioxane and 10 ml. of 2 *N* sulfuric acid was warmed at 60–65° for a half-hour. After the addition of 60 ml. of water, the mixture was allowed to stand overnight. The solid which separated was isolated and recrystallized from dilute alcohol to give 0.5 g. (82% yield) of ketol, m.p. 143–144°. Further recrystallization failed to elevate the melting point, but analysis indicated the presence of an impurity.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 72.35; H, 7.51.

An acetate, prepared from the ketol by means of acetic anhydride and sodium acetate, was recrystallized from dilute alcohol, m.p. 79–80°.

Anal. Calcd. for $C_{22}H_{26}O_5$: C, 71.33; H, 7.07. Found: C, 71.22; H, 7.20.

Infrared Absorption Spectra.—The measurements and interpretations were made by Mr. Bruce Scott, Parke, Davis and Co., Detroit, Mich. The instrument used was Beckman IR-2 spectrophotometer on which was mounted a homemade, automatic slit-control device for maintaining a

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(16) A six-hour period of reduction led to a white viscous oil which was almost entirely alkali-soluble. Acidification of the alkali extract gave a white viscous oil which, when treated with absolute alcohol, resulted in the fortuitous separation of about 0.3 g. of phenolic white crystalline solid which is probably either VII or VIII. Recrystallized from alcohol, it melted at 257.5–259.5°. *Anal.* Calcd. for $C_{18}H_{28}O_3$: C, 73.94; H, 9.65. Found: C, 73.71; H, 9.18.

(17) By Mr. Peter H. Jackson.

(18) By the Huang-Minlon modification of the Wolff–Kishner reduction, THIS JOURNAL, **68** 2487 (1946).

(19) R. F. Nystrom and W. G. Brown, *ibid.*, **69**, 1197 (1947).

(20) F. Arndt in "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 165.

fairly constant radiation baseline. The samples were mulled to a paste with nujol mineral oil which was spread in a thin film between two rock salt plates

Certain corrections were made in the curves to give them a more polished appearance. Minor bands due to atmospheric carbon dioxide and water have been eliminated. The bands marked with asterisks are made up in good part of nujol absorption.

LAWRENCE, KANSAS RECEIVED JUNE 26, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY AND THE DEPARTMENT OF CHEMISTRY OF PURDUE UNIVERSITY]

The Action of the Catalyst Couple Aluminum Chloride–Hydrogen Chloride on Toluene at Low Temperatures; the Nature of Friedel–Crafts Complexes[1,2]

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In the absence of hydrogen chloride and at low temperatures (−80°), purified aluminum chloride neither interacts with nor dissolves appreciably in toluene. In the presence of excess hydrogen chloride, the aluminum chloride dissolves in the toluene to give a clear solution, a brilliant green in color. From the decrease in pressure of the hydrogen chloride, it appears that one mole of the gas is taken up per mole of $AlCl_3$ which goes into solution. The reaction is reversible; that is, removal of the hydrogen chloride precipitates the aluminum chloride and the toluene is recovered unchanged. The reaction is believed to involve the formation of a carbonium ion salt of the hypothetical acid, $HAlCl_4$: $CH_3C_6H_5 + HCl + {}^1/_2Al_2Cl_6 = [CH_3C_6H_6]^+[AlCl_4]^-$. At −45.4° one mole of hydrogen chloride is taken up for each two moles of $AlCl_3$: $CH_3C_6H_5 + HCl + Al_2Cl_6 = [CH_3C_6H_6]^+[Al_2Cl_7]^-$. The complexes which form in the course of Friedel–Crafts reactions are believed to be carbonium ion salts of this kind. It is proposed that the high solubility of aluminum halides in these Friedel–Crafts complexes is due to the formation of a series of higher complexes of this kind, with the general formula $R^+[AlX_4 \cdot nAlX_3]^-$. It is further proposed that these complexes play an important role in most Friedel–Crafts reactions by furnishing a highly polar medium in which the ionic intermediates may form and react.

Introduction

The alkylation of aromatic hydrocarbons, catalyzed by aluminum chloride and similar Friedel–Crafts catalysts, is ordinarily accompanied by the formation of deeply colored oily liquids of high density. In spite of considerable study, the precise nature and function of these "Friedel–Crafts complexes" are not well understood.[5] In the hope of throwing some light on the composition of these materials, a study was undertaken of the interaction of toluene, aluminum chloride, and hydrogen chloride at low temperatures, utilizing techniques which permitted following the pressure of hydrogen chloride as a function of composition.

Results

In the absence of hydrogen chloride, no reaction was observed between purified aluminum chloride and toluene. Five ml. of toluene was placed over 0.35 g. of aluminum chloride. In 22 hours at −80°, no change was observed. At −45° no color was noticed in 1 hour, and only a slight yellow coloration appeared after several additional hours. Finally, the sample was maintained at 0° for 20 hours. Again only a faint yellow color was observed. The toluene, removed from the sample, gave values for the vapor pressure (6.8 mm. at 0°) and refractive index (n^{25}D 1.4938) identical with the original sample of toluene.

Traces of water markedly altered the results. Thus, repetition of the experiment utilizing 0.35 g. of aluminum chloride to which had been added 6.6 mg. of water led to the development of marked colors. In 1 hour at −45° the aluminum chloride, pure white at the start, had become definitely colored, varying in spots from a light yellow to an intense canary yellow.

The action of hydrogen chloride was particularly interesting. At −80° aluminum chloride is not noticeably soluble in toluene, but subsequent addition of hydrogen chloride causes the aluminum chloride to dissolve. At the same time the toluene solution becomes a brilliant green in color. The reaction is reversible. Removal of the hydrogen chloride by distillation precipitates solid aluminum chloride. Re-addition of hydrogen chloride causes the aluminum chloride to redissolve, again giving the green solution. The cycle has been repeated as many as four times without evidence of irreversible changes. All of the components can be recovered quantitatively by distillation of the hydrogen chloride and toluene from the less volatile aluminum chloride.

The solution of the aluminum chloride was accompanied by a decrease in the hydrogen chloride pressure, and it was of interest to establish a quantitative relationship here. Unfortunately we encountered experimental difficulties which greatly affected the precision of the results. In addition to the usual difficulties involved in introducing small accurately weighed samples of anhydrous aluminum chloride into the vacuum apparatus, we discovered that equilibrium in these reactions is attained very slowly, frequently requiring days or even weeks. The devices we adopted for maintaining a constant temperature at −80° for extended periods of time did not prove very satisfactory. As a result, the precision we attained leaves much to be desired. However, the data do indicate, albeit only roughly, the ratio of aluminum chloride to hydrogen chloride in the green solution.

In a typical experiment 0.36 mmole of aluminum

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(1) The Catalytic Halides. II.

(2) Presented before the Division of Physical and Inorganic Chemistry at the New York Meeting of the American Chemical Society, September, 1947.

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(5) A summary of earlier work is contained in C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," A. C. S. Monograph No. 87, Reinhold Publishing Corp., New York, N. Y., 1941, pp. 48–54.