

anhydrous calcium sulfate and 5 g. of the hydrazone of 2,4,6-triisopropylphenylglyoxal was covered with 75 cc. of dry ether and stirred for twelve hours at room temperature. The ether was decanted through a filter paper and the black residue washed by decantation with a total of 100 cc. of dry ether. Removal of the ether left the diazo compound as a yellow powder, which decomposed explosively at 125°. After recrystallization from methanol it was found to decompose at 104°; yield 4.5 g.

It was covered with water and a pinch of silver oxide was added. The mixture was boiled for thirty minutes. Eight grams of potassium hydroxide pellets was added and the boiling continued for fifteen minutes. A solid was removed by filtration and recrystallized from ether. It formed pale yellow crystals melting at 204–205°. This substance was not identified. When the filtrate was acidified the 2,4,6-triisopropylphenylacetic acid was precipitated. It was recrystallized from 75% acetic acid and then from ligroin; m. p. 146–146.5°. A mixture with an authentic specimen of the acid (see below) showed no depression in melting point.

(b)<sup>13</sup> The hydrolysis of 2,4,6-triisopropylbenzyl cyanide could not be effected satisfactorily with 50–80% sulfuric acid. The method of Redemann and Lucas<sup>14</sup> for the saponification of esters, however, was found to be suitable. A mixture of 67 g. of the pure nitrile, 500 cc. of diethylene glycol, 100 g. of potassium hydroxide and 20 cc. of water was heated under reflux for twelve hours and poured into water. The 2,4,6-triisopropylphenylacetic acid, precipitated by acidification of the mixture, was recrystallized from aqueous ethanol; m. p. 144–145°; yield 85%.

*Anal.* Calcd. for C<sub>17</sub>H<sub>26</sub>O<sub>2</sub>: C, 77.80; H, 9.99. Found: C, 78.08; H, 9.67.

Hydrolysis of the nitrile with potassium hydroxide and

(13) This preparation was carried out by Dr. M. L. Ward.

(14) Redemann and Lucas, *Ind. Eng. Chem., Anal. Ed.*, **9**, 521 (1937).

ethanol produced 2,4,6-triisopropylphenylacetamide. It was recrystallized from ethanol; m. p. 170–171°.

*Anal.* Calcd. for C<sub>17</sub>H<sub>27</sub>NO: C, 78.11; H, 10.41. Found: C, 78.15; H, 10.57.

**2,4,6-Triisopropylbenzyl Cyanide.**<sup>11</sup>—2,4,6-Triisopropylbenzyl chloride, prepared by the chloromethylation of 1,3,5-triisopropylbenzene,<sup>18</sup> was converted to the corresponding cyanide by treatment with cuprous cyanide. A mixture of 149 g. of the chloride, 57.8 g. of cuprous cyanide and 60 cc. of dry pyridine was heated at 210–220° for ninety minutes. When the mixture had cooled to 150° it was poured into a mixture of 500 g. of ice and 200 cc. of ammonium hydroxide. The mixture was allowed to stand overnight, and the crude nitrile was collected on a filter and distilled, b. p. 129–130° (4 mm.); m. p. 81–82°; yield 64%.

*Anal.* Calcd. for C<sub>17</sub>H<sub>26</sub>N: C, 83.89; H, 10.35. Found: C, 83.40; H, 10.26.

### Summary

Methods of synthesis of hindered aldoketenes have been studied.

The *cis* and *trans* enol benzoates of desoxymesitoin have been prepared. Hydrolysis was found to convert them to desoxymesitoin, showing that the *cis* and *trans* enols of desoxymesitoin were unstable and ketonized rapidly. The corresponding *cis* and *trans* acetates were also prepared. These results confirm the conclusion reached earlier that the dehydration product of hydromesitoin or isohydromesitoin is 1,1-dimesitylvinyl alcohol.

(15) Fuson, Horning, Ward, Rowland and Marsh, *This Journal*, **64**, 30 (1942).

URBANA, ILLINOIS

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## The Relation of Estrogenic Activity to Structure in Some 4,4'-Dihydroxydiphenylmethanes<sup>1</sup>

BY E. EMMET REID AND EDITH WILSON<sup>2</sup>

Estrogenic activity has been noted by Dodds and Lawson<sup>3</sup> in some 4,4'-dihydroxydiphenylmethanes, (HOC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>CRR'. It seemed worthwhile to prepare a number of these to see how the estrogenic activity varies with the size and character of the groups R and R'. Two series have now been made: one, in which R is methyl and R' varies from methyl to hexyl, and the other, in which R and R' are identical and vary from methyl to amyl. Besides these several compounds of different types, including the double one, (HOC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>C(CH<sub>3</sub>)CH<sub>2</sub>CH<sub>2</sub>C(CH<sub>3</sub>)-(C<sub>6</sub>H<sub>4</sub>OH)<sub>2</sub>, from acetonyl-acetone have been studied. In order to have comparable estrogenic data, the known compounds have been prepared and tested along with the new. For better chemical characterization the benzoates of all of them have been prepared. The results are in Table I. The activities of the members

(1) Original manuscript received October 20, 1942.

(2) Present address: Biochemical Research Foundation, Newark, Del.

(3) Dodds and Lawson, *Proc. Roy. Soc. (London)*, **B125**, 222 (1938).

of the second series are plotted in Fig. 1. When our work was nearly completed, an article by Campbell<sup>4</sup> covering part of the same ground appeared.

The activity reaches a peak in the first series with the methyl-propyl and in the second series a much higher peak at the propyl-propyl, which is ten times as potent as any of the others. The activities for ethyl-propyl and for propyl-butyl are borrowed from Campbell. For comparison the data for the corresponding *trans*-4,4'-dihydroxy- $\alpha,\beta$ -dialkylstilbenes<sup>5</sup> are plotted in Fig. 1, but they are in rat units per milligram while ours are in the same units per gram. The ethylene derivatives are around a thousand times as active as the methane derivatives, yet the shapes of the two curves are strikingly alike except that the maximum is at the ethyl-ethyl in the one and at the propyl-propyl in the other. The rise is gradual through the methyl-ethyl in the one and through the ethyl-propyl in the other. In both

(4) N. R. Campbell, *ibid.*, **B129**, 528 (1940).

(5) Dodds, Goldberg, Lawson and Robinson, *ibid.*, (London), **B127**, 140 (1939).

TABLE I  
MELTING POINTS AND ACTIVITIES

R	R'	M. p., °C.	Rat u./g.	Benzoate m. p., °C.
Methyl	Methyl <sup>8,6,7,8</sup>	155	28	161
Methyl ethyl	<sup>6,8,9,10,11</sup>	124	80	143
Methyl	Propyl <sup>6,8,10,11,12</sup>	149	200	120
Methyl	Butyl <sup>7</sup>	Liq	40 <sup>2</sup>	72
Methyl	Amyl	101	35	118
Methyl	Hexyl	88	50	114
Methyl	<i>i</i> -Propyl	194	50	204
Methyl	<i>i</i> -Butyl <sup>6,11</sup>	153	200	116
Ethyl	Ethyl <sup>6,10,12</sup>	204	200	163
Propyl	Propyl <sup>6,12</sup>	154	2000	142
Butyl	Butyl <sup>6</sup>	170.5	20	129.5
Amyl	Amyl	148.5	10	94
<i>c</i> -Pentanone <sup>6,8,11</sup>		157	766	205
<i>c</i> -Hexanone <sup>6,11,13,14</sup>		184	50	198
4-Me-Hexanone <sup>6,10,11,13</sup>		179	200	149.5
Methyl	Phenyl <sup>6,11,14,15</sup>	188	0	150.5
Methyl	<i>p</i> -MeO phenyl	245	55	221
Benzyl	Benzyl <sup>16</sup>	193	0	223
(CH <sub>3</sub> C-CH <sub>2</sub> ) <sub>2</sub> <sup>17</sup>		302 d	200	247

the activities drop off sharply as soon as the maxima are passed. Symmetry seems to play

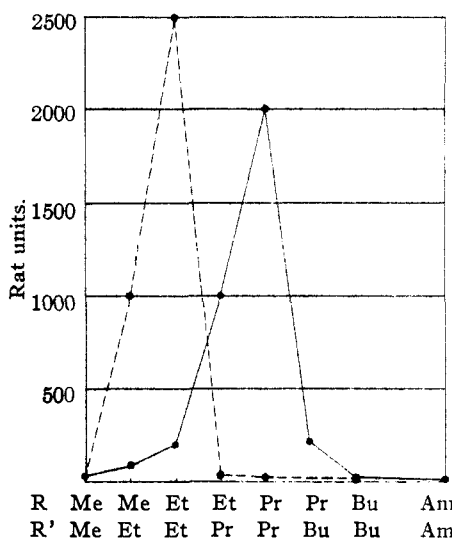


Fig. 1.—Estrogenic activity related to sizes of R and R':  
—●—●—, rat u./g. (HOC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>CRR'; —●—●—, rat u./mg. HOC<sub>6</sub>H<sub>4</sub>CR:CR'C<sub>6</sub>H<sub>4</sub>OH.

- (6) Campbell gives m. p. of Bu-Bu 165°.  
 (7) Zincke, *Ann.*, **343**, 85 (1905).  
 (8) v. Braun, *ibid.*, **472**, 1 (1929).  
 (9) Zincke, *ibid.*, **362**, 205 (1908).  
 (10) Easson, Harrison, McSwiney and Pyman, *Quart. J. and Year Book of Pharmacy*, **7**, 509 (1934).  
 (11) McGreal, Niederl and Niederl, *THIS JOURNAL*, **61**, 345 (1930).  
 (12) Dianin, *J. Russ. Phys.-Chem. Soc.*, **28**, 488, 523, 601 (1891).  
 (13) Schmidlin and Lang, *Ber.*, **43**, 2806 (1910).  
 (14) I. G. Farbenind., German patent 467,728 (1927); [*Chem. Abs.*, **23**, 1729 (1929).]  
 (15) I. G. Farbenind., German patent 604,406 (1932); [*Chem. Abs.*, **29**, 855 (1936).]  
 (16) Zincke, *Ann.*, **363**, 255, 280 (1908).  
 (17) Amann and Ponrobert, U. S. patent 1,614,172 (1927); [*Chem. Abs.*, **21**, 805 (1927).]

an important part; the maxima are at ethyl-ethyl and propyl-propyl. So far as the same compounds are concerned our results agree well with those of Campbell except that our value for propyl-propyl is much higher.

The methyl-*i*-butyl is considerably more active than the methyl-*n*-butyl. A methyl group in the 4-position in the cyclohexanone derivative raises its activity, so does the *p*-methoxy group in the methyl-*p*-methoxyphenyl. The double compound from acetyl-acetone shows as much activity as any except the propyl-propyl. This is remarkable considering its high molecular weight and low solubility.

The estrogenic activities were determined by Dr. Geschickter and Dr. Byrne by the standard method.

The melting points of the compounds of the two series show alternation, as do those of their benzoates.

### Experimental

The method of preparation was the same for all. The ketone and three equivalents of phenol were put into a glass-stoppered bottle and concentrated hydrochloric acid equal to about one-fifth of the phenol added. The mixture stood, with occasional shaking, until the reaction seemed to be complete, which took from a day or two for the simpler ketones up to twenty weeks for some others. Hydrogen chloride was passed into the slow ones from time to time. The condensations went much faster if, instead of using aqueous hydrochloric acid, the ketone-phenol mixture was saturated with hydrogen chloride, but the products so obtained were harder to purify. The mixtures turned red in any case, but the purified compounds were colorless. The reaction product was poured into hot water, the unused reactants driven off with steam, and the residue filtered off or collected in ether according to its physical state. The yields were high, 90% or better, even with the higher ketones if they were given time enough. Acetic acid, chloroform, acetone and toluene were used as solvents. The low melting compounds were hard to purify as they tended to separate from solvents as liquids. Some could be obtained pure only by saponification of the recrystallized benzoates. The benzoates were made by the Schotten-Baumann method. All melting points were determined with the aid of a thermometer calibrated for 3-inch immersion. The analyses of new compounds are in Table II.

TABLE II  
ANALYSES

R	R'	Carbon, %		Hydrogen, %	
		Calcd.	Found	Calcd.	Found
Methyl	amyl	80.28	79.41	8.45	8.51
Methyl	hexyl <sup>a</sup>	80.54	78.50	8.72	8.64
Benzoate		80.61	79.91	6.77	6.53
Amyl	amyl	81.17	80.98	9.41	9.50
Methyl	<i>i</i> -propyl	79.69	79.53	7.81	7.99
4-Methyl- <i>c</i> -hexanone		81.13	81.10	7.47	8.02
Methyl	<i>p</i> -MeO-phenyl	78.75	78.39	6.25	6.45
Benzyl	benzyl	85.26	85.70	6.31	6.34
(CH <sub>3</sub> CCH <sub>2</sub> ) <sub>2</sub>		79.19	79.30	6.60	6.79

<sup>a</sup> The low carbon is probably due to adsorbed water. On account of the low m. p. the compound was difficult to dry. The benzoate gave satisfactory figures.

### Summary

A number of 4,4'-dihydroxy-diphenylmethanes, (HOC<sub>6</sub>H<sub>4</sub>)<sub>2</sub>CRR', have been prepared and their

estrogenic activities determined in order to relate their activities to the size and character of the groups R and R'.

For characterization their benzoates have been made.

BALTIMORE, MD.

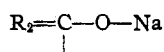
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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MISSOURI]

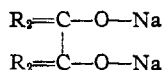
## Single Bond Energies. V. The Association of Ketyl

BY H. E. BENT AND A. J. HARRISON<sup>1</sup>

The compound formed by the addition of an alkali metal to an aromatic ketone is highly colored and by some investigators<sup>1a</sup> has been assigned the formula



although evidence has been advanced<sup>2</sup> to show that the compound should not be considered to be a free radical but is associated and should be represented as a pinacolate



We have attacked this problem by the method used in studying hexaphenylethane and triphenylmethyl reported by Ziegler and Ewald.<sup>3</sup> They found that on diluting a solution of hexaphenylethane the deviations from Beer's law could be explained satisfactorily by assuming an equilibrium between the ethane and the free radical and also assuming only the free radical to be colored.

Benzophenone was chosen as the first compound to be studied since it is the simplest aromatic ketone. Fluorenone was chosen as the second compound due to the presence of a five-membered ring. Peculiarities in five-membered rings have been found in the acidity of very weak acids,<sup>4,5</sup> the dissociation of free radicals<sup>6</sup> and the addition of sodium to single bonds.<sup>7</sup>

A solution of the ketyl is prepared by shaking the ketone in ether solution with 0.6% sodium amalgam. A portion of this solution is used to rinse the apparatus, removing adsorbed water. Fresh solution is then poured into the cell in which the optical density is to be determined. In order to avoid the errors inherent in an analysis one sample is used for a whole series of measurements, dilution being accomplished by means of the apparatus shown in Fig. 1. This device is

carefully calibrated to determine the amount of hold up in the annular space when a solution is poured through it. The total volume of ether is determined at the beginning of the experiment. This permits one to pour a known fraction of the solution through the dilution device and then to distill the ether back, condensing it in the solution which had been retained in the annular space, thus diluting the solution by a known fraction. Two or three dilutions may be carried out with one cell before the solution becomes too dilute to measure with precision. Another sample of the solution is removed and the sodium determined analytically.

Measurements of the optical density were carried out with a spectrophotometer, previously described,<sup>8</sup> which illuminates the cell with monochromatic light and gives high precision. All cells were of Pyrex glass with fused plane glass windows mounted in Dewars.

The experimental results from the study of fluorenone indicate that it gives rise to a ketyl which obeys Beer's law within the accuracy of our experimental measurements. A series of measurements at room temperature gave ratios for the optical densities which agreed very closely with the values for the dilution ratio. In order to find evidence for association if possible at lower temperatures a series of dilutions were carried out, measurements being made at  $-112^\circ$ , using solid carbon disulfide as the cooling agent. These measurements also showed close agreement with Beer's law. Since one would expect a temperature coefficient for the process of dissociation which would greatly increase the frac-

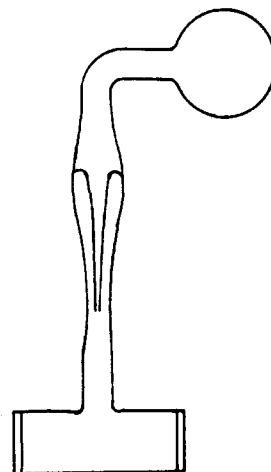


Fig. 1.—Dilution device. The solution is diluted without exposing to air by inverting the whole apparatus. A certain fraction of the liquid is retained in the annular space around the capillary. The apparatus is then returned to its original position without pouring solution back from the flask. On cooling the cell solvent distills from the flask back into the cell.

(1) Submitted in partial fulfillment of the requirements of the degree of Doctor of Philosophy at the University of Missouri. This paper was presented at the spring meeting of the American Chemical Society at Detroit in 1943.

(1a) Schlenk, *et al.*, *Ber.*, **44**, 1183 (1911); **46**, 2840 (1913); **47**, 473 (1914).

(2) Bachmann, *THIS JOURNAL*, **55**, 1179 (1933).

(3) Ziegler and Ewald, *Ann.*, **473**, 163 (1929).

(4) Conant and Wheland, *THIS JOURNAL*, **54**, 1212 (1932).

(5) McEwen, *ibid.*, **58**, 1124 (1936).

(6) Conant, *J. Chem. Phys.*, **1**, 427 (1933).

(7) Bent and Keevil, *THIS JOURNAL*, **58**, 1367 (1936).

(8) Jacobsohn, Bent and Harrison, *Rev. Sci. Instr.*, **11**, 220 (1940).