ml. of dry ether. A crystal of iodine was added, followed by 1 ml. of ethyl bromide. As soon as the reaction had started, the stirrer was turned on, a slow stream of dry nitrogen was passed through the flask and 60 g. (0.4 mole) of 1-diethylamino-3-chloropropane, dissolved in 100 ml. of dry ether, was added over a period of ten minutes. Another ml. of ethyl bromide was added, the flask was heated in a water-bath kept at 45-50° for five minutes and then 27.2 g. (0.2 mole) of anisaldehyde, dissolved in 160 ml. of dry ether,[9] was added over a period of ninety minutes. The stirring, heating and nitrogen flow were continued during the addition and for twelve hours after the addition was complete. A white precipitate formed.[10] After standing overnight the reaction mixture was hydrolyzed by a solution of 75 g. of ammonium chloride in 200 ml. of water. The two layers were separated, the aqueous phase was extracted once with ether and the combined ether solutions were extracted with three 100-ml. portions of cold 2 *N* hydrochloric acid. The acid solutions were made alkaline with excess potassium carbonate and extracted with ether. The ether extract was dried over anhydrous potassium carbonate, the ether distilled and the residue distilled through a 15-cm. Vigreux column, first at 20 mm. to recover the excess 1-diethylamino-3-chloropropane and then at 1 mm. The alcohols were obtained as pale yellow, viscous oils.

Oxidation of Alcohols to Ketones. 4-Diethylamino-1-*p*-methoxyphenylbutanone-1.—4-Diethylamino-1-*p*-methoxyphenylbutanol-1 (26.7 g., 0.11 mole) was dissolved in 125 ml. of glacial acetic acid contained in a 400-ml. beaker. The solution was heated to 60° on a steam-bath, the bath removed and a solution of chromic anhydride (prepared by dissolving 7.1 g. (0.071 mole) of the anhydride in 5 ml. of water and then adding 5 ml. of glacial acetic acid) was added with stirring at such a rate as to keep the temperature at 60-65°. The reaction mixture was heated for fifteen minutes on the steam-bath, chilled and poured into a cold solution of 150 g. of sodium hydroxide in 400 ml. of water. The ketone was immediately extracted with ether, since on standing chromium hydroxide precipitated. The ether solution was dried over anhydrous potassium carbonate, the ether distilled and the residue distilled through a 15-cm. Vigreux column.

Preparation of Diamines.—The ketones were converted to oximes as described previously,[2] the oximes being recrystallized from dilute alcohol. They were then reduced catalytically.[2]

Preparation of Quinacrine Analogs.—The couplings were carried out essentially as described before.[2] In general the hydrochlorides obtained were much less soluble than those prepared previously, some of them being quite insoluble even in hot water.

Summary

1. Quinacrine analogs (I) in which the group R in the α-position of the side chain is benzyl, phenyl, *p*-methoxyphenyl and 3,4-methylenedioxyphenyl have been synthesized.

2. 4 - Diethylamino - 1 - *p* - dimethylaminophenylbutanol-1 and 4-diethylamino-1-*p*-chlorophenylbutanone-1 have been prepared.

DURHAM, N. C. RECEIVED APRIL 20, 1945

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[9] In other cases more ether was needed to completely dissolve the aldehyde.

[10] When a colored precipitate or solution was obtained, the yield of alcohol was almost invariably poor. However, we have been unable to discover why this should happen occasionally.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SCHIEFFELIN & CO.]

Synthetic Estrogenic Compounds. II. Dialkyl Derivatives of 1,3-Di-(*p*-hydroxyphenyl)-propane

BY ALFRED H. STUART, ANTHONY J. SHUKIS AND RALPH C. TALLMAN

In the first paper of this series[1] we reported a number of compounds derived from 1,3-di-(*p*-hydroxyphenyl)-propane by substitution of an alkyl or aryl group in the propane chain. As a continuation of this study, relating structure to estrogenic activity, we have prepared several compounds in which the di-(*p*-hydroxyphenyl)-propane nucleus has been further modified by the introduction of alkyl groups on two of the carbon atoms of the propane chain, giving the two types of di-alkyl derivatives IV and VII. In this investigation the substituent groups have been limited to methyl, ethyl and *n*-propyl.

All of the six possible 1,3-di-alkyl compounds (IV) have been prepared, three of them only as mixtures of isomeric forms. Starting materials for this series were the 1,3-di-(*p*-methoxyphenyl)-ketones (I, R = CH_3, C_2H_5, C_3H_7) previously described.[1] These reacted smoothly with Grignard reagents in refluxing ether; the resulting carbinols were not isolated, but dehydrated on distillation. The position of the double bond thus introduced was dependent on the nature of the entering alkyl group. Using methylmagnesium iodide we obtained unsaturated compounds (II) which gave *p*-methoxyacetophenone and anisic acid on permanganate oxidation. Similar oxidation of the products from ethyl and propyl Grignard reagents, however, gave the original ketones (I), indicating a preponderance of the structure III.

Hydrogenation of these unsaturated compounds, followed by demethylation, gave the series of phenols IV. In the case of both the dimethyl and diethyl compounds only a single crystalline product was obtained. The phenol in which $R_1 = CH_3$ and $R_2 = C_3H_7$ was also obtained crystalline, but there was evidence of the presence of a second isomer in minor amounts. The remaining three derivatives were thick, clear resins. Preparation of the unsymmetrical compounds by alternating the order in which the alkyl groups were introduced had no appreciable effect on the physical or physiological properties of the products.

The α-alkyl-di-*p*-methoxychalcones described in the previous communication were used as starting materials for the synthesis of 1,2-dialkyl derivatives of 1,3-di-(*p*-hydroxyphenyl)-propane. Introduction of a second alkyl group was effected

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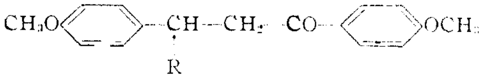
[1] Stuart and Tallman, THIS JOURNAL, **65**, 1579 (1943).

by 1,4-addition of Grignard reagents. This reaction was satisfactory for the preparation of ketones of the structure V when ethyl or propyl magnesium bromide was used and the two isomeric racemic mixtures expected in each case have been isolated. However, we have not been able to obtain compounds in which R_1 is methyl by this method. There is some analogy for this apparent anomaly. From the reaction of benzalpropiophenone with ethylmagnesium bromide, only the 1,4-addition product was obtained by Kohler[2] and also by Reynolds.[3] However, Smith and Hanson[4] found that methylmagnesium iodide reacted with benzalpropiophenone to give 75% yields of an indene and no detectable amount of any 1,4-addition product. From the reaction of our chalcones with methylmagnesium iodide we have obtained considerable amounts of crystalline compounds which appeared to have an indene structure. In addition, the desired ketones seemed to be present to some extent in the reaction mixtures, but we have been unable to isolate and identify the pure isomers. Investigation of these compounds is continuing.

After separation of the two isomeric forms of each of the other six ketones (V, $R_1 = C_2H_5$, C_3H_7, $R_2 = CH_3$, C_2H_5, C_3H_7), the individual racemates were hydrogenated to the ethers (VI) by means of copper–chromium oxide catalyst at 220–230°, and hydrolysis carried out in the usual manner.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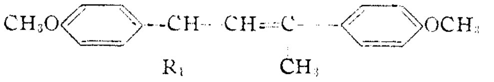
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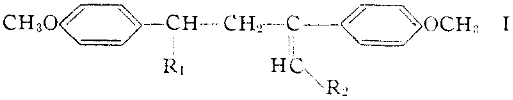
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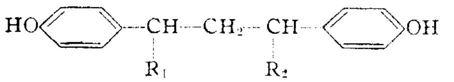
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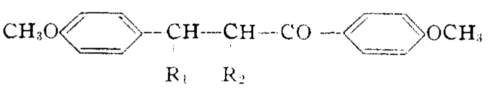
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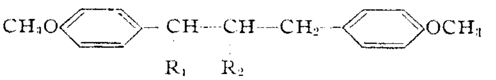
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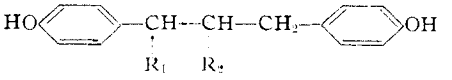
VII

One of the phenols of this group has previously been reported. Campbell, Dodds and Lawson[5] obtained a phenol, m. p. 127°, from di-anethole, by hydrogenating the double bond and hydrolyzing the ether groups. We have repeated this synthesis and find the product identical in m. p. and estrogenic activity with our isomer A of 1,3-di-(*p*-hydroxyphenyl)-2-methyl-pentane (VII, $R_1 = C_2H_5$, $R_2 = CH_3$).

The two series of phenols (IV and VII) have been assayed for estrogenic activity in this Laboratory by the Allen–Doisy technique and the results are expressed in rat units in the tables.[6] Unfortunately, the figures do not lend themselves to much generalization. Most of the compounds show a very low order of activity. The rather marked superiority of the 1-methyl-3-propyl derivative over the other members of the 1,3-series is worthy of note. Many of the 1,2-dialkyl derivatives also show little estrogenic effect and, in some cases, only a slight difference between isomers. In all cases where there was an appreciable difference in activity between the two isomeric forms, the phenol isomer B (*i. e.*, derived from the higher-melting form of the ketone V) was the more active. Five of the individual racemates gave positive estrus responses at levels below 1 mg., maximum activity being reached with the B isomers of the diethyl and the 1-ethyl-2-propyl derivatives. The results have been of value mostly in directing syntheses of the more active tri-substituted compounds which will be described in a future publication.

Experimental

Grignard Reactions on 1,3-Di-*p*-methoxyphenyl Ketones (I).—Saturated ethereal solutions of the butanone, pentanone or hexanone were added to ether solutions of two molecular equivalents of the proper Grignard reagents (methylmagnesium iodide, ethyl- or propylmagnesium bromide). Heat of the reaction was usually sufficient to initiate reflux, which was then maintained on a steam-bath for five hours. The reaction mixtures were decomposed and worked up in the usual manner. The oily products were heated to 150–200° under water-pump vacuum, whereupon water was evolved in most cases. Addition of one drop of concentrated hydrochloric acid was effective in ensuring rapid and complete splitting. The unsaturated ethers were purified by high vacuum distillation. Yields averaged 80–90%.

Structure of Di-*p*-methoxyphenylalkenes.—The unsaturated ethers listed in Table I are of two types, depending on the position of the double bond as shown by permanganate oxidations. The following is a typical oxidation: to a solution of 0.5 g. of 2,4-di-(*p*-methoxyphenyl)-pentene-2 in a mixture of 20 cc. of acetone and 8 cc. of water, was added 0.5 g. of sodium carbonate and 1 g. of potassium permanganate. After refluxing for one hour, the solution was filtered, the acetone evaporated from the filtrate and the oily precipitate separated into alkali-soluble and neutral fractions. The acidic fraction was anisic acid; the neutral oil gave a semicarbazone identical in m. p. and mixed m. p. with that of *p*-methoxyacetophenone. The analogous alkenes (II, $R_1 = C_2H_5$, C_3H_7) gave similar results.

Oxidation, by the same procedure, of 0.5 g. of 3,5-di-(*p*-methoxyphenyl)-heptene (III, $R_1 = C_2H_5$, $R_2 = CH_3$) gave no appreciable acidic product. The neutral fraction was taken up in ethanol from which 0.3 g. of 1,3-di-(*p*-

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(2) Kohler, *Am. Chem. J.*, **38**, 556 (1907).

(3) Reynolds, *ibid.*, **44**, 318 (1910).

(4) Smith and Hanson, This Journal, **57**, 1326 (1935).

(5) Campbell, Dodds and Lawson, *Proc. Roy. Soc.*, **B128**, 253 (1940).

(6) We define the rat unit as the minimum amount of material which will produce complete vaginal cornification in 80% of a group of castrate female rats following a single subcutaneous injection in sesame oil.

TABLE I

DI-*p*-METHOXYPHENYLALKENES

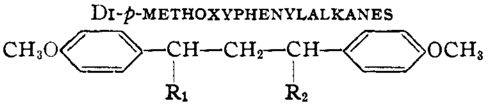
Type formula	R_1	R_2	M. p., °C.	B. p., °C. (2 mm.)	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found
II	CH_3			185	80.80	80.08	7.86	8.43
II	C_2H_5			190	81.03	80.95	8.17	8.40
II	C_3H_7			195	81.25	81.21	8.44	8.42
III	C_2H_5	CH_3	87		81.25	81.30	8.44	8.33
III	C_3H_7	CH_3		197	81.43	81.81	8.70	8.64
III	C_3H_7	C_2H_5		200	81.60	81.86	8.88	9.18

methoxyphenyl)-pentanone (m. p. 70°) crystallized. The other alkenes obtained with ethyl- or propylmagnesium bromides likewise were reconverted to the original ketones on oxidation.

Hydrogenation.—Each of the alkenes was readily hydrogenated at atmospheric pressure over Adams catalyst in glacial acetic acid solution. The saturated ethers distilled under oil-pump vacuum as colorless, oily liquids; yields were virtually quantitative. The compounds are listed in Table II.

TABLE II

DI-*p*-METHOXYPHENYLALKANES



R_1	R_2	B. p., °C. (2 mm.)	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found
CH_3	CH_3	180–182	80.23	80.14	8.51	8.48
CH_3	C_2H_5	181–182	80.48	79.90	8.79	8.73
CH_3	C_3H_7	170–171	80.73	80.63	9.03	9.12
C_2H_5	C_2H_5	180–181	80.73	80.90	9.03	9.12
C_2H_5	C_3H_7	189–190	80.92	81.30	9.27	9.57
C_3H_7	C_3H_7	190–191	81.11	80.93	9.48	9.34

Hydrolysis.—The above ethers were hydrolyzed to the corresponding phenols by means of hydriodic-acetic acid mixtures or with potassium hydroxide in ethanol at 200°. Both methods were described in the first paper of this series. The phenols were obtained as clear, glassy resins. Those which solidified were recrystallized from benzene or from cyclohexane. The phenols are listed in Table III.

TABLE III

DI-*p*-HYDROXYPHENYLALKANES (IV)

R_1	R_2	M. p., °C.	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	Rat unit in mg.[a]
CH_3	CH_3	144	79.64	79.62	7.87	8.05	10
CH_3	C_2H_5	Resin	79.95	79.84	8.21	8.36	5
CH_3	C_3H_7	116	80.24	80.28	8.51	8.51	0.2
C_2H_5	C_2H_5	86–88	80.24	79.80	8.51	8.59	1
C_2H_5	C_3H_7	Resin	80.48	80.79	8.79	8.79	1
C_3H_7	C_3H_7	Resin	80.71	80.21	9.25	9.96	5

[a] Assayed as obtained from reaction mixture without separation of isomers.

Grignard Reactions on α-Alkyl Chalcones.—Ether solutions of di-*p*-methoxy-α-methyl, -ethyl, or -propyl chalcones were added dropwise to ether solutions of three molecular equivalents of ethyl- or propylmagnesium bromide, the well-stirred reaction mixtures being maintained at about −10°. When addition was complete, the mixtures were allowed to warm to room temperature over a period of two to three hours, then decomposed and worked up in the usual manner. The oily reaction products were distilled under oil-pump vacuum and dissolved in ethanol and the two isomeric forms of each compound separated by rather laborious fractional crystallizations. In the two cases in which one solid and one liquid isomer were obtained, separation was relatively simple, consisting of cooling the alcohol solution until crystallization of the solid fraction was complete and then fractionally distilling the oily residue from the filtrates. Separation of the two isomeric forms of the other four compounds was effected by customary fractionation procedures. Higher melting isomers were obtained without undue difficulty in most cases. Isolation of pure samples of the lower-melting forms from the filtrates usually required considerable manipulation.

Yields of crude reaction products averaged about 80% and it seemed, in general, that the two isomers were present in roughly equivalent amounts in each case. However, because of the losses in fractionation, it is impossible to state accurate yields of pure individual racemic mixtures.

In spite of numerous attempts, we have never succeeded in obtaining ketone derivatives of any of these compounds.

Reduction.—In order to ensure complete reduction of the carbonyl group, each isomer was treated as follows: 15 to 20 g. of ketone in 100 cc. of ethanol was hydrogenated with 2 g. of copper–chromium oxide catalyst at 230° and 200–250 atm. for eighteen to twenty hours. The products were colorless, oily liquids which were purified by vacuum distillation. Properties of the 1,3-di-*p*-methoxyphenylalkanes (VI) are listed in Table V.

TABLE IV

1,3-DI-*p*-METHOXYPHENYL KETONES (V)

R_1	R_2	Isomer	M. p., °C.	B. p., °C. (2 mm.)	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found
C_2H_5	CH_3	A	52		76.89	76.99	7.74	7.64
		B	72		76.89	77.08	7.74	7.93
C_2H_5	C_2H_5	A		181–183	77.27	77.37	8.03	8.20
		B	82		77.27	77.32	8.03	8.20
C_2H_5	C_3H_7	A		183–185	77.61	77.41	8.29	8.47
		B	69		77.61	77.30	8.29	8.50
C_3H_7	CH_3	A	52		77.27	77.21	8.03	7.61
		B	78		77.27	77.44	8.03	8.21
C_3H_7	C_2H_5	A	62		77.61	77.33	8.29	8.35
		B	93		77.61	78.28	8.29	8.87
C_3H_7	C_3H_7	A	45–47		77.93	77.91	8.53	8.40
		B	60		77.93	77.88	8.53	8.47

TABLE V

1,3-DI-*p*-METHOXYPHENYLALKANES (VI)

R_1	R_2	Isomer	B. p., °C. (2 mm.)	$n^{26}D$	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found
C_2H_5	CH_3	A	188-192	1.5564	80.49	80.30	8.78	9.22
		B	190-192	1.5516	80.49	80.16	8.78	8.37
C_2H_5	C_2H_5	A	180-183	1.5460	80.73	80.55	9.03	9.15
		B	188	1.5492	80.73	80.62	9.03	8.83
C_2H_5	C_3H_7	A	195-200	1.5435	80.93	81.42	9.26	9.65
		B	183-185	1.5420	80.93	80.43	9.26	9.29
C_3H_7	CH_3	A	187-190	1.5461	80.73	80.53	9.03	9.05
		B	183-185	1.5461	80.73	80.52	9.03	9.00
C_3H_7	C_2H_5	A	193-194	1.5453	80.93	80.99	9.26	9.32
		B	188	1.5430	80.93	80.60	9.26	9.47
C_3H_7	C_3H_7	A	190-195	1.5400	81.13	80.70	9.47	9.53
		B	199-200	1.5401	81.13	80.60	9.47	8.88

TABLE VI

1,3-DI-*p*-HYDROXYPHENYLALKANES (VII)

R_1	R_2	Isomer	M. p., °C.	% Carbon Calcd.	% Carbon Found	% Hydrogen Calcd.	% Hydrogen Found	Rat unit in mg.
C_2H_5	CH_3	A	128[a]	79.96	79.99	8.20	7.89	2.5
		B	138	79.96	79.76	8.20	8.24	5
C_2H_5	C_2H_5	A	52	80.24	80.17	8.51	8.13	5
		B	109	80.24	80.12	8.51	8.56	0.04
C_2H_5	C_3H_7	A	Resin	80.49	80.14	8.78	9.08	0.25[b]
		B	Resin	80.49	81.37	8.78	8.82	0.03
C_3H_7	CH_3	A	84-86	80.24	79.93	8.51	8.15	7.5
		B	115	80.24	80.28	8.51	8.11	10
C_3H_7	C_2H_5	A	111	80.49	80.00	8.78	8.45	7.5
		B	91-93	80.49	80.42	8.78	8.89	0.2
C_3H_7	C_3H_7	A	57-59	80.73	80.10	9.03	9.44	10
		B	Resin	80.73	79.98	9.03	9.35	0.25

[a] Campbell, Dodds and Lawson,[5] reported m. p. 127° for a compound of this structure prepared from di-anethole. We repeated their synthesis and obtained a phenol which shows no depression in mixed m. p. with the above isomer. [b] Since none of the precursors of this phenol were obtained crystalline, it is probable that the material tested may contain some of the more active isomer and hence give an erroneously high assay value.

Hydrolysis.—Each of the phenol ethers was hydrolyzed by heating with 2 parts of potassium hydroxide and 4 parts of ethanol at 200° for eighteen hours. The phenols distilled as clear glasses, most of which eventually crystallized. The solids were purified by recrystallization from benzene or from ethylene dichloride.

Summary

A number of 1,2- and 1,3-dialkyl derivatives of 1,3-di-(*p*-hydroxyphenyl)-propane have been prepared and tested for estrogenic activity.

There is considerable variation in the estrogenic activity of the various compounds, a maximum being reached with the 1-ethyl-2-propyl derivative for which the rat unit is 30 micrograms.

NEW YORK, N. Y.

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