[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NEW YORK UNIVERSITY]

Steric Hindrance in Ketone–Phenol Condensations. The Synthesis of Cyclo-alkylene Phenols and Cyclo-alkyl Coumaranes[1]

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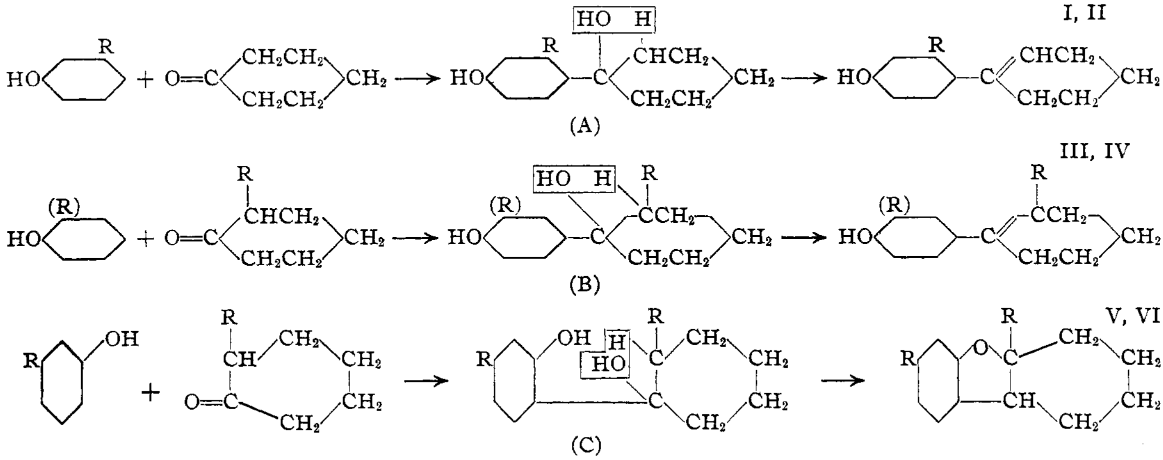
In a previous publication[2] it was asserted that in the condensation of ketones with phenols "the nature of the end-product is influenced not only by the type of carbonyl compound employed, but also by the type of phenol used" and that "this influence exerts itself particularly through the position of the second substituent in the benzene ring, *i. e.*, whether it is ortho, meta or para to the hydroxyl group." As shown in this communication, this hypothesis now has been substantiated fully.

In the following it has been established that meta alkylated phenols react differently than ortho alkylated phenolic compounds; the latter yield alkylidene-diphenols,[3] while the former yield unsaturated compounds in these condensations. The representative types of *m*-alkyl phenols chosen were *m*-cresol and *m*-ethylphenol. These two *m*-alkylated phenols were condensed with cyclohexanone. In each instance the respective cyclohexenyl phenol, the 1-(4′-hydroxy-2′-methyl)-phenylcyclohexene-1 (I) and the 1-(4′-hydroxy-2′-ethyl)-phenylcyclohexene-1 (II) was obtained. In both cases, the alkyl radical in the final condensation product is adjacent to the carbon carrying the cyclohexenyl radical. It appears, then, that such an arrangement in the molecule of the final condensation product inhibits the introduction of a second phenolic radical, which would be the normal course of the reaction (A).

If this hypothesis is correct, then a similar effect should be exerted when a cyclic ketone is chosen for condensation, which would give a condensation product with an alkyl radical adjacent to the carbon carrying the phenolic group. Condensation experiments with *o*-methylcyclohexanone verified this postulation. Thus when *o*-methylcyclohexanone was condensed with phenol itself and with *o*-cresol, compounds which ordinarily yield the respective cyclohexylidene-diphenol, also the unsaturated, monophenolic compound, namely, the 2-methyl-1-(4′-hydroxy)-phenylcyclohexene-1 (III) and the 2-methyl-1-(4′-hydroxy-3′-methyl)-phenylcyclohexene-1 (IV) was obtained, a fact which clearly indicates steric hindrance (B).



Since both the meta-alkylated phenols and the ortho-alkylated cyclohexanones gave rise separately to steric hindrance phenomena, it was then thought to try the extreme case, namely, the condensation of both the above mentioned reactants. The condensation was slow, but positive, but no unsaturated phenolic condensation product was obtained, instead, only coumaranes, the 2,6-dimethyl-2,3-cyclohexyl-coumarane (V), and the 2-methyl-6-ethyl-2,3-cyclohexyl-coumarane

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[1] Three of the key substances (I, III, IV) presented in this paper were found by Victor Niederl in pursuance of his thesis researches. The other material presented in this paper is taken from the theses presented by J. Charney, J. Rodgeville and A. Ziering to the Graduate School of New York University in partial fulfilment of the requirements for the degree of Master of Science, June, 1939.

[2] J. B. Niederl and V. Niederl, THIS JOURNAL, **61**, 348 (1939).

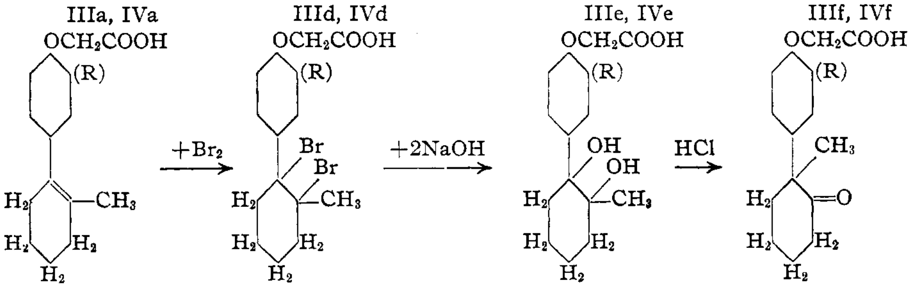
[3] M. E. McGreal, V. Niederl and J. B. Niederl, *ibid.*, **61**, 345 (1939).

(VI) resulted. This would indicate that when steric hindrance becomes too great, ortho alkylation takes place (C).

The formation of all three types of condensation products may be formulated as shown.

Of the four crystalline phenolic key substances (I, II, III, IV), all of which exhibit feeble oestrogenic properties (0.2 mg. = 1 rat unit), the following crystalline derivatives were prepared: aryloxyacetic acids (Ia, IIa, IIIa, IVa), phenylurethans (Ib, IIb, IIIb, IVb), acetates (Ic, IIc, IIIc, IVc) and benzoates (IIIh, IVh). For the unsaturation tests the aryloxyacetic acids (Ia, IIa, IIIa, IVa) were chosen. Baeyer's permanganate test[4] was positive in all cases. In addition to this, the aryloxyacetic acids (Ia, IIa, IIIa, IVa) were brominated and the resulting crystalline bromine derivatives isolated (Id, IId, IIId, IVd). Titration of the dibromides (IIId, IVd) with either 0.1 or 0.01 *N* sodium hydroxide solution gave a neutralization equivalent of a tribasic acid, proving that in these titrations both bromine atoms were hydrolyzed, a behavior which is typical of bromine atoms attached to tertiary carbon atoms. Thus it could be shown that the ethylenic linkage is between the carbon atom carrying the phenyl radical and the carbon atom carrying the methyl group. To substantiate this further, dibromides IIId and IVd were hydrolyzed to the respective glycols (IIIe, IVe) and these in turn were subjected to pinacolone rearrangement. The resulting ketones (IIIf, IVf) were identified through their 2,4-dinitrophenylhydrazones (IIIg, IVg).

(β')



Experimental

Condensation Method

1-(4'-Hydroxy-2'-methyl)-phenylcyclohexene-1 (I).—Half molar quantities of *m*-cresol and cyclohexanone were dissolved in 100 cc. of glacial acetic acid and the mixture placed in a 1-liter, triple-necked, round-bottomed flask which was provided with a reflux condenser, a thermometer and a gas inlet tube extending to the bottom of the vessel. A vigorous stream of dry hydrogen chloride gas was passed into the system for six hours at room temperature, then the flask stoppered and left standing at room temperature for two to three weeks. After this time the reaction mixture was dissolved in 200 cc. of benzene, this solution washed several times with an equal volume of water and then extracted with 150 cc. of Claisen solution. The Claisen solution extract was acidified with dilute hydrochloric acid; the oil which precipitated out was taken up in 100 cc. of benzene, washed with water and dried with calcium chloride. The benzene was distilled off and the residue distilled under diminished pressure. The fraction boiling between 120 and 140° was collected and redistilled in vacuum; b. p. 130–133° at 4 mm.; n^{25}_{D} 1.5413. After several weeks the substance crystallized; yield 12 to 15%.

1-(4'-Hydroxy-2'-ethyl)-phenylcyclohexene-1 (II).—Half molar mixtures of *m*-ethylphenol and cyclohexanone were condensed exactly as described above and worked up in a similar manner. The pure product boiled at 145–148° and 5 mm.; n^{25}_{D} 1.5421. It also crystallized after several weeks; yield, about 15%.

2-Methyl-1-(4'-hydroxy-phenylcyclohexene-1 (III).—Half molar quantities of phenol and *o*-methylcyclohexanone were condensed as described above, except that no glacial acetic acid was used, and left standing for ten days, by which time the reaction mixture had solidified. The crystalline mass was treated with hot water, filtered off on a sintered glass filter and recrystallized from diisobutylene; yield, 55–60%.

2-Methyl-1-(4'-hydroxy-3'-methyl)-phenylcyclohexene-1 (IV).—Half molar mixtures of *o*-cresol and *o*-methylcyclohexanone were condensed in exactly the same manner as compound III. The reaction mixture, even upon prolonged standing, did not crystallize and after standing for fourteen days it was dissolved in 200 cc. of benzene and worked up as described for compound I. The product was finally distilled in vacuum and the fraction boiling between 155–160° at 12 mm. crystallized in the receiver. It was recrystallized from diisobutylene; yield, 45–50%.

Aryloxyacetic Acid Derivatives (Ia, IIa, IIIa, IVa).—These derivatives were prepared by dissolving the respective compound in 30% sodium hydroxide solution to which sufficient methyl alcohol was added to effect solution. The calculated amount of chloroacetic acid was added, the reaction mixture gently refluxed for two hours, and worked up according to the directions given in Shriner and Fuson.[5]

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(4) Mulliken, "A Method for the Identification of Pure Organic Compounds," J. Wiley and Sons, Inc., New York, N. Y., 1904, p. 79.

(5) Shriner and Fuson, "The Systematic Identification of Organic Compounds," J. Wiley and Sons, Inc., New York, N. Y., 1935, pp. 148–149.

Phenylurethans (Ib, IIb, IIIb, IVb).—One gram of substance was dissolved in 1 cc. of phenyl isocyanate in a test-tube which was sealed and placed in a beaker containing boiling water. The test-tube was opened when its content had solidified and the crystalline material placed in a porous tile to dry. It was recrystallized from diisobutylene.

Acetates (Ic, IIc, IIIc, IVc).—Ten grams of the respective phenol was dissolved in 30 cc. of acetic anhydride and the mixture refluxed for four hours in a ground-glass joint apparatus. The acetic anhydride and acetic acid was distilled off and the residual oil distilled in vacuum; b. p.: (Ic) 155–157° (12 mm.), (IIc) 169–174° (12 mm.), (IIIc) 161° (10 mm.), (IVc) 172–174° (12 mm.).

Benzoates (IIIh, IVh).—These two benzoates were prepared by dissolving 0.5 g. of substance in 5 cc. of benzoyl chloride in a test-tube and refluxing the mixture for thirty minutes. Then the solution was poured into 25 cc. of 10% sodium carbonate solution and stirred thoroughly for five minutes. The oil which separated was taken up in 30 cc. of ether and the ethereal solution washed with 1% sodium hydroxide solution and then with water until neutral. The ether solution was dried with calcium chloride and then permitted to evaporate at room temperature. The crystalline residue was twice recrystallized from 80% ethyl alcohol.

Bromine Derivatives of Aryloxyacetic Acids (Id, IId, IIId, IVd).—To a suspension of the respective aryloxyacetic acid derivatives in carbon tetrachloride a solution of bromine in the same solvent (0.3 g. per cc.) was added slowly until the calculated amount of bromine had been introduced. The bromo derivative which precipitated was washed with ether to remove any unreacted acid and the ether insoluble bromine derivative was filtered off and dried on a porous tile. It was recrystallized from ethyl alcohol.

Glycols of Aryloxyacetic Acids (IIIe, IVe).—One gram of the respective aryloxyacetic acid dibromide (IIId, IVd) was dissolved in 30 cc. of 1 *N* aqueous sodium hydroxide solution and the solution was allowed to stand at room temperature for three hours. After this time, the solution was acidified with hydrochloric acid. This caused the separation of a water insoluble oil, which was taken up with ether. The ether extract was washed twice with distilled water and then allowed to evaporate at room temperature. The crystalline residue was twice recrystallized from diisobutylene. One gram of the glycol (IIIe, IVe) was added to 30 cc. of a mixture consisting of two parts of alcohol, one part of cond. hydrochloric acid and eight parts of distilled water. This mixture was refluxed for three hours. It was then diluted with an equal amount of water and twice extracted with 30 cc. of ether. The combined ether extracts were washed once with distilled water and then allowed to evaporate at room temperature. The residue (IIIf, IVf) was dissolved in 30 cc. of alcohol. To this

TABLE I

COMPOUNDS, FORMULAS AND ANALYSES

				Analyses, %											
				Carbon		Hydrogen		Nitrogen		Bromine		Mol. wt.		Neut. equiv.	
No.	Formula or derivative	M. p., °C.	Empirical formula	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Fd.	Calcd.	Fd.
1-(4′-Hydroxy-2′-methyl)-phenyl-cyclohexene-1															
I	$C_6H_3(OH)(CH_3)C_6H_9$	65	$C_{13}H_{16}O$	82.99	83.16	8.50	8.41	...	...	...	...	188	184	...	...
Ia	Aryloxyacetic ac.	160	$C_{15}H_{18}O_3$	73.18	73.06	7.31	7.25	...	...	...	...	...	...	246	251
Ib	Phenylurethan	114	$C_{20}H_{21}O_2N$	78.19	78.03	6.84	6.68	4.56	4.51	...	...	...	...	...	...
Ic	Acetate	...	$C_{15}H_{18}O_2$	78.65	78.92	7.82	7.70	...	...	...	...	...	...	...	...
Id	Bromine deriv. of Ia	150	$C_{15}H_{17}O_3Br$	55.38	55.12	5.23	5.46	...	...	24.61	23.79	...	...	...	...
1-(4′-Hydroxy-2′-ethyl)-phenyl-cyclohexene-1															
II	$C_6H_3(OH)(C_2H_5)C_6H_9$	55	$C_{14}H_{18}O$	83.18	83.02	8.91	8.60	...	...	...	...	202	208	...	...
IIa	Aryloxyacetic ac.	117	$C_{16}H_{20}O_3$	73.86	73.51	7.69	7.86	...	...	...	...	...	...	260	264
IIb	Phenylurethan	134	$C_{21}H_{23}O_2N$	78.52	78.52	7.16	7.46	4.36	4.25	...	...	...	...	...	...
IIc	Acetate	...	$C_{16}H_{20}O_2$	78.69	78.56	8.19	7.98	...	...	...	...	...	...	...	...
IId	Bromine deriv. of IIa	146	$C_{16}H_{19}O_3Br$	56.63	56.30	5.60	6.05	...	...	23.60	23.10	...	...	...	...
2-Methyl-1-(4′-hydroxy)-phenyl-cyclohexene-1															
III	$C_6H_4(OH)C_6H_8(CH_3)$	144	$C_{13}H_{16}O$	82.99	82.78	8.68	8.46	...	...	...	...	188	184	...	...
IIIa	Aryloxyacetic ac.	136	$C_{15}H_{18}O_3$	73.17	72.97	7.32	7.39	...	...	...	...	...	...	246	245
IIIb	Phenylurethan	160	$C_{20}H_{21}O_2N$	78.19	78.24	6.84	6.59	4.56	4.43	...	...	...	...	...	...
IIIc	Acetate	...	$C_{15}H_{18}O_2$	78.65	78.51	7.82	7.88	...	...	...	...	...	...	...	...
IIId	Bromine deriv. of IVa	104	$C_{15}H_{18}O_3Br_2$	44.12	43.89	4.66	4.63	...	...	39.41	39.34	...	...	...	...
IIIe	Glycol of IIIa	130	$C_{15}H_{20}O_5$	64.28	63.88	7.14	7.03	...	...	...	...	280	279	...	...
IIIh	Benzoate	72	$C_{19}H_{20}O_2$	82.19	82.14	6.85	6.73	...	...	...	...	...	...	...	...
2-Methyl-1-(4′-hydroxy-3′-methyl)-phenyl-cyclohexene-1															
IV	$C_6H_3(OH)(CH_3)C_6H_8(CH_3)$	86	$C_{14}H_{18}O$	83.18	83.04	8.91	8.74	...	...	...	...	202	198	...	...
IVa	Aryloxyacetic ac.	113	$C_{16}H_{20}O_3$	73.84	73.69	7.69	7.58	...	...	...	...	...	...	260	263
IVb	Phenylurethan	134	$C_{21}H_{23}O_2N$	78.52	78.38	7.16	7.23	4.36	4.32	...	...	...	...	...	...
IVc	Acetate	...	$C_{16}H_{20}O_2$	78.69	78.51	8.18	8.17	...	...	...	...	...	...	...	...
IVd	Bromine deriv. of IVa	107	$C_{16}H_{20}O_3Br_2$	45.75	45.89	4.76	4.99	...	...	38.08	38.14	...	...	...	...
IVe	Glycol of IVa	140	$C_{16}H_{22}O_5$	65.31	65.06	7.48	7.22	...	...	...	...	294	307	...	...
IVg	Phenylhydrazone of IVf (2,4-dinitro)	87	$C_{22}H_{24}O_7N_4$	57.89	57.68	5.26	5.43	12.28	12.00	...	...	...	...	...	...
IVh	Benzoate	69	$C_{21}H_{22}O_2$	82.03	82.10	7.19	6.89	...	...	...	...	...	..	...	...
2,6-Dimethyl-2,3-cyclohexyl-coumarane															
V	$C_6H_3O(CH_3)C_6H_9(CH_3)$	...	$C_{14}H_{18}O$	83.18	83.08	8.91	8.95	...	...	...	...	202	204	...	...
2-Methyl-6-ethyl-2,3-cyclohexylcoumarane															
VI	$C_6H_3O(C_2H_5)(C_6H_9(CH_3)$	...	$C_{15}H_{20}O$	83.33	83.12	9.26	9.15	...	...	...	...	216	213	...	...

solution 0.75 g. of 2,4-dinitrophenylhydrazine was added and the mixture refluxed for five minutes. Upon cooling the 2,4-dinitrophenylhydrazone separated out (IIIg, IVg), which was recrystallized from alcohol.

2,6-Dimethyl-2,3-cyclohexylcoumarane (V) and 2-Methyl-6-ethyl-2,3-cyclohexylcoumarane (VI).—Half molar quantities of the respective meta-alkylated phenol and *o*-methylcyclohexanone were dissolved in 100 cc. of glacial acetic acid and condensed as described for compound I, except that the reaction was carried out while the reactants were heated on a water-bath to about 80°. The condensation mixture was left standing for fourteen days, but during this time it was resaturated with hydrogen chloride several times. The reaction product was then dissolved in 200 cc. of benzene, this solution washed several times with water and then extracted with 250 cc. of Claisen solution. Upon acidification of the Claisen solution extract only the unreacted *m*-alkylated phenol (*m*-cresol, or *m*-ethylphenol) was recovered. The benzene solution was then subjected to fractional distillation. Compound V boiled at 139–141° and 12 mm.; $n^{25}\text{D}$ 1.5338; sp. gr.^{25}, 1.0252; yield, about 40%. Compound VI boiled at 146–148° and 12 mm.; $n^{25}\text{D}$ 1.5302; sp. gr.^{25}, 1.0218; yield, about 30%.

The authors desire to express their appreciation to Reed and Carnrick, Jersey City, N. J., for the physiological tests performed.

Summary

Steric hindrance phenomena encountered in certain types of ketone–phenol condensation systems were studied.

Cycloalkylene phenols and cycloalkyl coumaranes were isolated in such condensation systems. Of the cycloalkylene phenols which represent new types of unsaturated phenols, numerous derivatives were prepared.

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The Reaction between Hexabromobenzene and Phenylmagnesium Bromide

By T. A. Geissman and R. C. Mallatt

The formation of hexamethyl- and hexaphenylbenzenes in the reaction between hexabromobenzene and methylmagnesium and phenylmagnesium halides was reported by Durand.[1] The identity of the hexamethylbenzene was established by comparison with an authentic sample, but the "hexaphenylbenzene" was later shown to be 1,2,4,5-tetraphenylbenzene by Dilthey,[2] who prepared this compound by an unambiguous method.

A tentative mechanism for the formation of 1,2,4,5-tetraphenylbenzene was suggested by Dilthey,[2] which involved first a replacement of four of the six bromine atoms by phenyl groups, followed by a "reduction," yielding 1,4-dimagnesiumbromide-2,3,5,6-tetraphenylbenzene which on hydrolysis would yield the tetraphenylbenzene actually obtained. No experimental evidence was offered to support this proposal other than the observation that metallic magnesium is without action on hexabromobenzene, showing that a simple removal of two bromine atoms, possibly through a free radical intermediate, did not take place.

Since other mechanisms for the formation of 1,2,4,5-tetraphenylbenzene are conceivable it was considered of interest to reëxamine the reaction between hexabromobenzene and phenylmagnesium bromide and to isolate (a) intermediates and (b) other products than those mentioned, and to attempt to formulate the reaction upon a factual basis.

The reaction was carried out in ether, as described by Durand, and a few runs were made in benzene. The chief product of the reaction in either solvent was a dark resinous tar from which the products mentioned below were isolated only with difficulty and in small yields. 1,2,4,5-Tetraphenylbenzene and 1,2,4,5-tetrabromobenzene were obtained by hydrolysis of the reaction mixture, while carbonation led to the formation of 1,2,4,5-tetraphenylbenzene-3,6-dicarboxylic acid (IV). Attempts to show the derivation of the tetrabromobenzene from the postulated intermediate (I) failed to yield tetrabromoterephthalic acid. Similar results were obtained when the solutions of the Grignard reagent were filtered before addition of the hexabromobenzene. This observation, coupled with the fact that an ether–benzene solution of the magnesium–magnesium iodide complex was without effect on hexabromobenzene, leads to the conclusion that reaction be-

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[1] Durand, *Compt. rend.*, **191**, 1460 (1930)

[2] Dilthey, *Ber.*, **67**, 2004 (1934).