[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE WASHINGTON SQUARE COLLEGE OF NEW YORK UNIVERSITY]

The Synthesis of Diisobutyl Mono-, Di- and Tri-hydroxyphenols[1]

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Theoretical Part

The synthesis of long chain substituted phenols still occupies an important place in organic chemical research on account of the high antiseptic value and low toxic action of such products. Their present day methods of preparation involve the condensations of alcohols, alkyl halides, aldehydes, acids or acid chlorides with the phenolic compound[2] and intramolecular rearrangement of phenyl ethers to the isomeric phenols, with Scichilone, Claisen, Hurd, Van Alphen and others,[3] using unsaturated alkyl phenyl and aryl phenyl ethers, while Niederl and co-worker[4] demonstrated, contrary to the general conceptions,[5] that the rearrangement of saturated alkyl phenyl ethers is quite general, a fact that subsequently has been experimentally verified by other workers.[6] Isolated cases of addition of phenols to unsaturated carbocyclics, acetylenic and polyethylenic compounds have been reported in the literature,[7] with Koenigs[8] reporting a case of addition of phenols to a mono olefinic hydrocarbon (isoamylene). But it remained for the authors to show that the addition of

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(1) From the thesis presented by Emile McK. Beekman to the Faculty of the Graduate School, of New York University in partial fulfilment of the requirements for the degree of Master of Science, 1933.

(2) Read and Miller, THIS JOURNAL, **54**, 1195 (1932); Hinegardner and Johnson, *ibid.*, **51**, 1503 (1929); Twiss, *ibid.*, **48**, 2206 (1926); Dohme, Cox and Miller, *ibid.*, **48**, 1688 (1926); Klarmann, *ibid.*, **48**, 791, 2308 (1926); Johnson and Lane, *ibid.*, **43**, 348 (1921); Johnson and Hodge, *ibid.*, **35**, 1014 (1913); Phillips, U. S. Patent 1,650,036 (1928); Wuyts, U. S. Patent 1,469,705 (1923); Leonard, U. S. Patent 1,771,895 (1930); Schaffer, U. S. Patent 1,745,507–8 (1930); Hirzel, U. S. Patent 1,717,105 (1929); Davis, U. S. Patent 1,213,465 (1917); Liebmann, *Ber.*, **14**, 1842 (1881); **15**, 150 (1882); Anschütz and Beckerhoff, *ibid.*, **28**, 407 (1895); Senkowski, *ibid.*, **24**, 2974 (1891); Baeyer, *ibid.*, **5**, 25, 280, 1096 (1872); Danckwortt, *ibid.*, **42**, 4163 (1909); Jaeger, ter Meer, Fabinyi and Steiner, *ibid.*, **7**, 281, 1197, (1874); **11**, 283, 287 (1878); Akt. Ges. f. Anilinfabrikation, *ibid.*, **16**, 2514 (1883); German Patent 23,775 (1883); Merck, German Patent 78,882 (1887); Dohme, Canadian Patent 272,351 (1927); 264,841–2, 265,025 (1926); British Patent 219,922 (1923); Kailan and Antrop, *Monatsh.*, **52**, 297 (1929); Schubert and Richter, *Centr. Bakt. Parasitenk.*, **66**, **11** (1925); Taylor and Austin, *J. Exp. Med.*, **27**, 635 (1917); Frobisher, *J. Bact.*, **13**, 163 (1927); Mazzara, *Gazz. chim. ital.*, **12**, 505 (1883); *Ber.*, **16**, 792 (1883); Dobrzycki, *J. prakt. Chem.*, [2] **36**, 390 (1887).

(3) Scichilone, *Gazz. chim. ital.*, **12**, 449 (1882); Claisen and co-workers, *Ann.*, **237**, 261 (1887); **401**, 21 (1924); **418**, 69 (1919); **442**, 210 (1925); *Ber.*, **45**, 3157 (1912); **58**, 275 (1925); **59**, 2344 (1926); *Z. angew. Chem.*, **36**, 478 (1923); Hurd and co-workers, THIS JOURNAL, **53**, 1917, 1068 (1931); **54**, 1648 (1932); Van Alphen, *Rec. trav. chim.*, **46**, 799 (1927); Heller, *Ber.*, **45**, 418 (1912); Niederl and Storch, THIS JOURNAL, **55**, 284 (1933).

(4) Niederl and Natelson, THIS JOURNAL, **53**, 272, 1928 (1931); **54**, 1063 (1932).

(5) Houben, "Die Methoden der organischen Chemie," Verlag Georg Thieme, Leipzig, 1930, Vol. III, p. 181; Claisen and Eisleb, *Ann.*, **401**, 21 (1913).

(6) Sowa, Hinton and Nieuwland, THIS JOURNAL, **54**, 2019 (1932); Smith, *ibid.*, **55**, 849 (1933); Rheinische Kampfer Fabrik, Swiss Patent 144,207 (1931); Schoeller, U. S. Patent 1,835,344 (1931).

(7) Liebermann and Hartmann, *Ber.*, **24**, 2582 (1891); **25**, 957 (1892); Schrauth and Quasebarth, *ibid.*, **57**, 854 (1924); Wenzke and Nieuwland, THIS JOURNAL, **46**, 177 (1924); Aquinas and Nieuwland, *ibid.*, **50**, 2566 (1928); Claisen, German Patent 374,142 (1923).

(8) Koenigs, *Ber.*, **23**, 3146 (1890); Koenigs and Carl, *ibid.*, **24**, 179, 3889 (1891); Koenigs and Mai, *ibid.*, **25**, 2650 (1892).

phenols to mono ethylenic compounds is a general reaction and that such condensations involve, first, the addition of the cationoid catalyzer to the double bond, in accordance with the postulations of Robinson–Wreschner,(9) and then go through primary ether formation and subsequent rearrangement of the intermediate ether thus formed,(10) a fact that has been recently verified experimentally by other investigators.(11)

In the present communication, report is being given on the addition of mono-, di- and tri-hydroxyphenols to such a longer chain mono ethylenic hydrocarbon as to warrant the production of phenols of desired physiological properties. The hydrocarbon chosen for study was one which is readily available. Because of its mode of preparation from isobutyl and tertiary butyl alcohols diisobutylene(12) is potentially available in large quantities at relatively low cost. Diisobutylene is a mixture of two isomers.(13)

$$\underset{\text{Trimethyl-2,4,4-pentene-2}}{CH_3C(CH_3)_2CH{=}C(CH_3)_2} \quad \text{and} \quad \underset{\text{Trimethyl-2,4,4-pentene-1}}{CH_3C(CH_3)_2CH_2C(CH_3){=}CH_2}$$

From the above formula it is evident that an addition of sulfuric acid to the double bond produces the same sulfate, from either structure

$$CH_3C(CH_3)_2CH_2C(CH_3)_2OSO_3H$$

It is therefore reasonable to assume that the same substituted phenol would be produced from either isomer.

The process involves the solution of diisobutylene in a suitable solvent, glacial acetic acid, and the addition of a mixture of sulfuric acid and acetic acids at low temperatures. The mixture formed, which is largely diisobutyl sulfate, is added to the cold solution of the phenol in glacial acetic acid and allowed to stand. This process is varied dependent upon the ease of substitution in the phenol employed.

Representative members of the mono-, di-, and tri-hydroxyphenols were chosen for study. Diisobutyl-(tri-methopentyl)-phenol, *o*-cresol, catechol, resorcinol, hydroquinone, guaiacol and pyrogallol were prepared. Preliminary bacteriological work on some of these products has shown them to possess comparatively high phenol coefficients.

The advantages of this method of preparation of substituted phenols are as follows. First, the method of preparation involves the use of unsaturated hydrocarbons which are usually more easily obtained than the

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(9) Robinson-Wreschner, "Versuch einer Elektronentheorie organisch-chemischer Reaktionen," Ferdinand Enke, Stuttgart, 1932, pp. 14–17.

(10) Niederl, THIS JOURNAL, **50**, 2230 (1928); **51**, 2426 (1929); *Z. angew. Chem.*, **44**, 467 (1931); *Monatsh.*, **60**, 150 (1932); Niederl and Natelson, THIS JOURNAL, **53**, 272 (1931); Smith and Niederl, *ibid.*, **53**, 806 (1931); Niederl, Smith and McGreal, *ibid.*, **53**, 3390 (1931); Niederl and Storch, *ibid.*, **55**, 284 (1933); Niederl and Casty, *Monatsh.*, **51**, 1038 (1929).

(11) Sowa, Hinton and Nieuwland, THIS JOURNAL, **54**, 3694 (1932).

(12) Prileshajew, *Chem. Centr.*, II, 2032 (1907); Butlerow, *Ann.*, **189**, 48 (1877); Addo, *Gazz. chim. ital.*, **31**, I, 326 (1901); Malbot and Gentil, *Compt. rend.*, **108**, 957 (1889); Kondakow, *J. prakt. Chem.*, [2] **54**, 453 (1896).

(13) Whitmore and Wrenn, THIS JOURNAL, **53**, 3136 (1931).

corresponding acids or alcohols. Second, the process is simple in operation and does not necessitate the use of complex apparatus or procedure. Third, the yields obtained are comparable with those obtained by other methods and finally the products obtained show high antiseptic value. Fourth, because of the nature of the procedure, this process will give rise most often to either secondary or tertiary alkyl substituted phenols, hence this method supplements well the method using aliphatic acids which can give rise to only primary substituted phenols.

As to the reaction mechanism the more recent postulations by Niederl and Storch[14] are applicable without reservations or further modifications. Of special interest and significance in these reactions is the fact that practically no intermediate ethers were isolated in the cases of the di- (catechol, resorcinol, hydroquinone) and tri-hydroxyphenols (pyrogallol).

Such intramolecular rearrangements involve the transformation from the ether to a quinoid configuration with a lower inner energy potential as shown in a previous publication and since such quinoid compounds form with greater ease from di- and tri-hydroxyphenols, the non-isolability of the intermediate ether in the experiments described herein even strengthens the reaction mechanism advanced.

It is self-evident that considerations of the repulsion energies involved in these intramolecular transitions[15] also hold for the cases cited in this communication. The fact that these longer chain ethers rearrange more readily may be further explained on the basis of well-known kinetic reaction principles or by certain electron displacement considerations.[16]

With the accomplished synthesis of various amyl and substituted amyl phenols (both mono- and polyhydroxylic) either by intramolecular rearrangement of the isomeric ether[17] or by the direct addition of the corresponding phenol to an unsaturated compound, the production of such phenols can be carried out with the greatest ease, as shown in this communication and elsewhere,[18] and in view of the fact that tetrahydrotubanol, one of the skeletal substances of rotenone is an isoamyldihydroxyphenol[19] and hence structurally related to the substances given in the experimental part (trimethoamyl mono-, di- and tri-hydroxyphenols), the importance of the method set forth herein appears to be enhanced.

Experimental Part

Preparation of Substituted Di- and Tri-hydroxyphenols.—One-half mole (56 g.) of diisobutylene was dissolved in 75 g. of glacial acetic acid and cooled to 15°. To this

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(14) Niederl and Storch, THIS JOURNAL, **55**, 284 (1933).

(15) Niederl and co-workers, *ibid.*, **53**, 1928 (1931); **54**, 1063 (1932); **55**, 284 (1933); Latimer, *ibid.*, **51**, 3185 (1929).

(16) Eyring, *ibid.*, **54**, 3203 (1932).

(17) Ethylthymol (*sec*-amyl-*m*-cresol), Niederl and Natelson, *ibid.*, **54**, 1069 (1932); Siegel, M.Sc. Thesis, New York University, 1933.

(18) *Sec*-amylresorcinol (m. p. 93°), Gospodinoff, M.Sc. Thesis, New York University, 1933.

(19) Haller, THIS JOURNAL, **54**, 4755 (1932).

solution was added, with constant stirring with a mechanical stirrer, one-half mole (49 g.) of concd. sulfuric acid (sp. gr. 1.84) dissolved in 50 g. of glacial acetic acid and cooled to 15°. On adding the sulfuric acid solution to the solution of the hydrocarbon care is taken that the temperature does not rise above 15°. This mixture separates into an oily, light brown liquid covered with a layer of colorless acetic acid and was then added to a solution of excess of one-half mole of the di-hydroxyphenol (60 g.) or tri-hydroxyphenol (70 g.) dissolved in 150 g. of glacial acetic acid, cooled to 15°. Vigorous stirring is applied to the phenol solution by means of an efficient mechanical stirrer during the addition, the temperature being kept constant at about 15°. The addition should take about twenty minutes. Stirring is continued for about ninety minutes more, allowing the ice to melt in the ice-bath. If any phenol has separated out, due to the lowered temperature, stirring is continued further at room temperature until all the separated material has redissolved. The mixture is then allowed to stand for four days at room temperature.

The condensation mixture is then poured into two liters of cold water and allowed to stand overnight, when the substituted phenol separates as an oily or crystalline mass. The water is removed by means of a siphon, the oily mass is taken up in ether, the ether is evaporated off and the product distilled in vacuum. The distillate is recrystallized from petroleum ether or ligroin (b. p. 90–110°).

Preparation of Substituted Monohydroxyphenols.—In this series the following procedure was found to give good yields. One-half mole of the diisobutylene was mixed directly with a slight excess of one-half mole of the phenol. The mixture was cooled to 0° and one-half mole of concentrated sulfuric acid was added drop by drop stirring constantly with a mechanical stirrer, not allowing the temperature to rise above 5°. The mixture was allowed to come to room temperature and allowed to stand for seven days. The mixture was then heated on a steam-bath for one hour and poured into a liter of crushed ice. The sulfuric acid was neutralized with 5% alkali and the phenol was taken up in ether and transferred to a distilling flask, where the ether was evaporated and the phenol distilled at atmospheric pressure. The distillate which comes above 230° is collected and then fractionated.

Table I

	Substance, diisobutyl	Formula	Yield, %	M. p., °C.	B. p., °C.
I	Pyrogallol	$(CH_3)_3CCH_2C(CH_3)_2C_6H_2(OH)_3$	40	103	......
II	Catechol	$(CH_3)_3CCH_2C(CH_3)_2C_6H_3(OH)_2$	54	109	......
III	Resorcinol	$(CH_3)_3CCH_2C(CH_3)_2C_6H_3(OH)_2$	40	101–102	219 (23 mm.)
IV	Hydroquinone	$(CH_3)_3CCH_2C(CH_3)_2C_6H_3(OH)_2$	52	142	210–225 (7 mm.)
V	Guaiacol	$(CH_3)_3CCH_2C(CH_3)_2C_6H_3(OH)OCH_3$	70	.....	295–298 (760 mm.) 138–144 (4 mm.)
VI	Phenol	$(CH_3)_3CCH_2C(CH_3)_2C_6H_4OH$	25	83	......
VII	o-Cresol	$(CH_3)_3CCH_2C(CH_3)_2C_6H_3(CH_3)OH$	35	49–50	......

	Empirical formula	Analyses, % Calcd. C	Calcd. H	Found C	Found H
I	$C_{14}H_{22}O_3$	70.59	9.24	71.00	9.24
II	$C_{14}H_{22}O_2$	75.67	9.90	75.54	9.91
III	$C_{14}H_{22}O_2$	75.67	9.90	75.74	9.66
IV	$C_{14}H_{22}O_2$	75.67	9.90	75.95	9.95
V	$C_{15}H_{24}O_2$	76.27	10.17	76.57	9.97
VI	$C_{14}H_{22}O$	81.55	10.68	81.83	10.28
VII	$C_{15}H_{24}O$	81.82	10.91	82.17	10.37

Remarks

I.—On pouring the condensation mixture into water a heavy, darkly colored tar separated. The tar was transferred to a steam distilling flask and steam distilled to remove the last traces of diisobutylene and acetic acid. The residue was taken up in ether and dried over sodium sulfate (anhyd.). The ether was evaporated and the deeply colored residue was heated for several hours on a steam-bath to remove traces of ether. The mass was extracted with 75 cc. of hot toluene, 35 cc. of warm petroleum ether was added and the mixture allowed to crystallize.

II.—This product came out crystalline from the condensation mixture, was poured into water and recryst. from ligroin, in which solvent it was very soluble in the hot and difficultly soluble in the cold.

III.—On pouring the condensation mixture into water this compound came out as an oil at the bottom of the beaker and was vacuum distilled after evaporating occluded water.

IV.—Hydroquinone is not very soluble in acetic acid and 250 g. of glacial acetic acid was used with warming to dissolve 60 g. of hydroquinone. This mixture had to be stirred vigorously for several hours to prevent separation into two layers. The product came out as a mixture of crystals and oil and the whole was vacuum distilled.

V.—n_D^{20} 1.5132; sp. gr. 0.983. Light yellow oil with coumarin-like odor.

VI.—The light colored oil was cooled in an ice-bath for several hours when long needles separated out. These were pressed out on a porous plate and recryst. from petroleum ether.

VII.—The heavy oil obtained after distillation solidified to a viscous mass in an ice-bath and then crystallized in rosets. It was then recrystallized from petroleum ether in which it was rather soluble in the cold.

The three diisobutyl dihydroxyphenols were placed on a microscope slide in such a fashion that each of the substances occupied the corner of a triangle, small enough to be still covered by an ordinary cover glass. The compounds were melted simultaneously and allowed to come into contact with each other. By microscopic examination under crossed Nicols (convergent polarized light) the following observations were made: all three substances were crystalline, bi-refringent and lit up on rotating either the microscope stage or one of the Nicol prisms. In the zone of contact (eutectic) of diisobutyl catechol and diisobutyl hydroquinone, the formation of optically mono-axial, mixed crystals took place, each showing the "polarization cross," whereas no crystallization whatsoever took place at the zones of contact of diisobutyl resorcinol with any one of the foregoing. This would clearly indicate and afford visual observation that the *o*- and *p*-substituted benzenes are more closely related chemically, than the *m*- and *o*- or *p*- products, respectively. However, until more such cases have been examined no generalization can be made at present.

Summary

Diisobutyl-(tri-methopentyl)-phenol, *o*-cresol, guaiacol, catechol, resorcinol, hydroquinone and pyrogallol were prepared by the addition of the respective phenol to diisobutylene by means of sulfuric acid, using glacial acetic acid as the solvent. These compounds have been shown to possess high phenol coefficients in a preliminary investigation which will be reported in detail later.

Further work is being carried on in the amylene, hexylene, heptylene and octylene series.

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