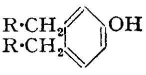
432. *Substitution in* 3 : 4-*Dialkylphenols.*

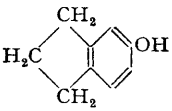
By G. D. Parkes.

The coupling of diazonium salts and some 3 : 4-dialkylphenols has been investigated and the proportions in which reaction takes place, in the 2- and 6-positions respectively, have been determined. The results seem to show that the variation in activation energies for reaction as either one of the Kekulé structures, shown by Sutton and Pauling to be theoretically possible as the result of valency deflexion brought about by fusion of saturated rings on to a benzene ring, can also occur as a consequence of steric hindrance between groups in the ortho-position to each other.

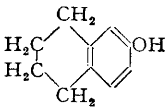
The proportions in which coupling between solutions of diazonium salts and *as-o*-xylenol (3 : 4-diethylphenol) takes place in the 2- and 6-positions respectively was investigated by Diepolder (*Ber.*, 1909, **42**, 2916) who found that coupling occurred to the extent of 83% in the 6-position and 17% in the 2-position. Mills and Nixon (*J.*, 1930, 2510) investigated the coupling of diazonium salts with 5-hydroxyindane (which reacted almost entirely in the 6-position) and with tetrahydro-β-naphthol where reaction was almost exclusively in the 1-position. These results were interpreted by Mills and Nixon as indicating a high degree of " fixation " of the double bonds of the Kekulé formula for benzene; that in a 1 : 2-dialkyl-4-phenol the more stable arrangement of bonds is that represented by (I) and that in the light of Diepolder's results the arrangement of the bond system postulated for 5-hydroxyindane (II) is the normal arrangement whereas that in tetrahydro-β-naphthol (III) is an abnormal arrangement brought about through the attachment to the benzene nucleus of the tetramethylene chain.



(I.)



(II.)



(III.)

The last statement seemed, at first, to contradict some of the other stereochemical considerations brought forward by Mills and Nixon and it was thought more probable that as the alkyl groups in the dialkylphenol became larger the steric effects of these groups on each other would tend to change the stable arrangements of the bonds from one form to the other. Later work (compare Fieser and Lothrop, *J. Amer. Chem. Soc.*, 1936, **58**, 2050; 1937, **59**, 945; Sidgwick and Springall, *J.*, 1936, 1532; Placzek, *Leipziger Vorträge*, 1931, 71; Ingold, *et al.*, *J.*, 1936, 966) and, in particular, the development of the theory of resonance, has made it impossible to uphold the idea that benzene can, under any conditions, be represented by one single Kekulé structure. Nevertheless, these results are interesting as indicating the existence of a type of directed reactivity in the benzene ring not previously contemplated.

Sutton and Pauling (*Trans. Faraday Soc.*, 1935, **31**, 939) examined the problem from the point of view of wave mechanics and concluded that the effect of saturated side rings upon the ratio of the coefficients of the wave functions of the two Kekulé structures is relatively small (about 6%) and that the benzene ring retains the greater part of its stabilising resonance energy. Nevertheless, making the reasonable assumption that the ratio of the activation energies, for reaction as either one of the Kekulé structures, depends upon the square of the ratio of the coefficients, it is possible to account for the experimental facts described by Mills and Nixon. (Compare also Longuet-Higgins and Coulson, *Trans. Faraday Soc.*, 1946, **42**, 756).

Since, therefore, the distortion of the ortho-valencies of benzene, by 5-atom or 6-atom saturated rings fused on to the nucleus, can bring about the variation in the ratio of the activation energies described, it was thought of interest to investigate the possibility of a similar distortion being caused by the steric hindrance of two ortho-substituents not forming part of a ring. The reactivity of 3 : 4-dialkylphenols towards diazotised amines furnishes one method for testing this point since, if the above conclusions are sound, diazotised amines would be expected to show an increasing tendency to couple at position 2 as compared with position 6 as the sizes of the alkyl groups increased.

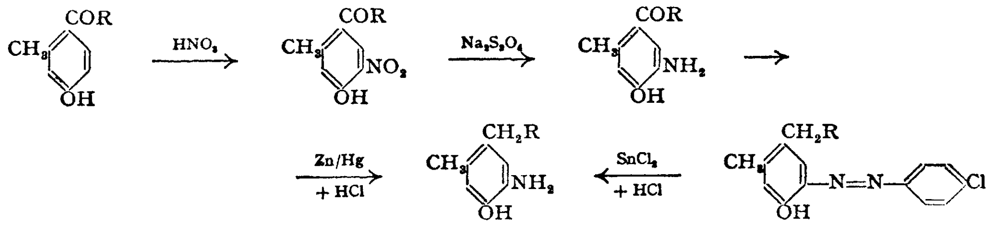
3-Methyl-4-ethylphenol was obtained from 4-acetyl-3-methylphenol (compare Skraup and Poller, *Ber.*, 1924, **57**, 2033) by Clemmensen reduction. 3-Methyl-4-propylphenol was obtained similarly from 4-propionyl-3-methylphenol. The preparation of 3-methyl-4-*iso*propyl- and 3-methyl-4-*iso*butyl-phenol was attempted similarly, as also of 4-methyl-3-ethylphenol, by several methods, but without success.

3:4-Diethylphenol was obtained by way of a Grignard reaction with *m*-methoxybenzaldehyde and methyl iodide, the resulting secondary alcohol being esterified with hydrogen chloride and reduced with hydrogen in presence of palladium forming, by removal of the ether-methyl group, *m*-ethylphenol. This was then treated with acetyl chloride in the presence of zinc chloride and the 4-acetyl-3-ethylphenol, so formed, reduced by Clemmensen's method. This method was used since a Friedel–Crafts reaction with acetyl chloride and *m*-methoxyethylbenzene resulted in the formation of the 6-acetyl instead of the desired 4-acetyl compound.

For the coupling reactions *p*-chlorobenzenediazonium chloride was used as it was found that some of the benzeneazo-compounds of the higher phenols are too low melting for easy separation by recrystallisation. Diepolder's experiments were repeated, using benzenediazonium chloride as well as the *p*-chloro-compound, for comparison.

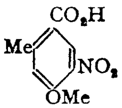
The isomers were separated by fractional crystallisation and the proportions in which each occurred determined. The result was also checked in further experiments by comparing the melting point of the washed and dried " crude " product with the melting-point curve of mixtures of the pure components.

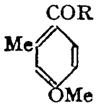
Diepolder (*loc. cit.*) established the orientation of his higher-melting isomer by reducing it to an amino-phenol identical with that obtained from a mononitroxylenol, which he converted into a known nitro-*o*-xylene. This method could not be applied to the present work since nitration of the dialkylphenols concerned gave a mixture of liquid products. The problem was solved by nitrating 4-acetyl-3-methylphenol and 4-propionyl-3-methylphenol, establishing the constitution of the nitro-compounds and then reducing them in stages to the aminomethylalkylphenols and comparing them with the products obtained by fission of the azo-compounds :



The constitution of the mononitro-compounds was established by heating their methyl ethers for a long time with excess of dilute neutral potassium permanganate solution. This gave the same toluic acid (hitherto of uncertain constitution) as was obtained from 5-nitro-*o*-4-xylenol by Cain and Simonsen (*J.*, 1914, 162). This acid must have the structure (IV), since a toluic acid obtained from (V) must have the methyl and methoxyl groups in the meta-position to one another.

(IV.)





(V.)

The results of these experiments are shown in the following table :

Phenol.	Percentage of coupling in 2-position.	Percentage of coupling in 6-position.
3 : 4-Dimethylphenol	20	80
3-Methyl-4-ethylphenol	33	67
3-Methyl-4-*n*-propylphenol	55	45
3 : 4-Diethylphenol	45	55

These results seem to show that steric hindrance between the groups in the ortho-position does take place and results in the same kind of variation in the ratio of the activation energies for reaction as one or other of the Kekulé structures as is brought about by the fusion of saturated rings of different sizes on to the benzene nucleus.

EXPERIMENTAL.

Phenols and Derivatives.—4-Acetyl-3-methylphenol (10 g.) (Skraup and Poller, *loc. cit.*) was mixed with hydrochloric acid (200 c.c.) (1 vol. of acid ; 2 vols. of water) and amalgamated zinc [made by standing zinc (40 g.) in saturated mercuric chloride (100 c.c.) for 10 minutes], heated under reflux until reaction started, and finally refluxed for several hours. The colourless oil obtained by steam distillation was extracted with ether and dried (Na_2SO_4), the solvent removed, and the product distilled. The 3-methyl-4-ethylphenol, a colourless oil, b. p. 235°, set to a white crystalline solid on scratching in a freezing mixture. Yield, 4 g.

4-Propionyl-3-methylphenol (22 g.), obtained similarly (but compare v. Auwers, *Annalen*, 1924, **439**, 174), was converted into 3-methyl-4-*n*-propylphenol (88 g. of amalgamated zinc; 125 c.c. of conc. hydrochloric acid ; 250 c.c. of water). It was a colourless oil, b. p. 252°/759 mm. Yield, 10 g. 3-*Methyl-4-*n*-propylphenoxyacetic acid*, obtained from 2 g. of the phenol, 1 g. of potassium hydroxide in 15 c.c. of water, and 2 g. of chloroacetic acid in 10 c.c. of water, crystallised as small flat rectangular prisms, m. p. 121°, from benzene (Found : C, 69·35 ; H, 7·66. $C_{12}H_{16}O_2$ requires C, 69·2 ; H, 7·69%).

m-Methoxyphenylmethylcarbinol was prepared by the method described by Klages and Allendorf (*Ber.*, 1898, **31**, 1003), using 133 g. of *m*-methoxybenzaldehyde and 144 g. of methyl iodide. Yield, 110 g. of a colourless viscous oil, b. p. 110°/10 mm. This was converted by the method used by Klages (*Ber.*, 1903, **36**, 3584) for the ortho-compound into 1-chloro-1-*m*-methoxyphenylethane (50 g. from 55 g. of carbinol). The following were prepared similarly : *m*-methoxyphenylethylcarbinol, a colourless viscous oil, b. p. 130°/8 mm., *phenylurethane*, colourless needles, m. p. 47° (Found : N, 5·27. $C_{17}H_{19}O_3N$ requires N, 5·20%) ; 1-chloro-1-*m*-methoxyphenylpropane, a colourless oil.

m-Methoxyethylbenzene was obtained by reduction of 1-chloro-1-*m*-methoxyphenylethane (40 g.) in methyl alcohol (200 c.c.) by hydrogen in presence of 2% palladium on strontium carbonate and calcium carbonate (45 g.). After filtration of the solution, methyl alcohol was removed by evaporation, and the crude product separated from calcium chloride by adding ether and filtering, evaporating, and distilling the ether solution under reduced pressure. The product was a colourless, mobile liquid, b. p. 74°/10 mm. Yield, 18·5 g. *m*-Methoxypropylbenzene was prepared similarly as a colourless mobile liquid, b. p. 92°/11 mm. Yield, 17·5 g. (Found : C, 80·12 ; H, 9·29. $C_{10}H_{14}O$ requires C, 80·0 ; H, 9·3%).

m-Methoxyethylbenzene (10 g.) was demethylated by boiling for 8 hours with acetic acid (15 c.c.) and hydriodic acid (10 g.). Iodine was removed by means of sodium hydrogen sulphite and the *m*-ethylphenol extracted with ether, dried (Na_2SO_4), and distilled under reduced pressure. It was a colourless oil, b. p. 95°/10 mm. Yield, 7 g.

Acetyl chloride (18 g.) was added, dropwise, to *m*-ethylphenol (15 g.) and finely powdered zinc chloride (18 g.) and the mixture kept for 3 days. The solid which separated was filtered off and reduced to 3 : 4-diethylphenol, without further purification, by Clemmensen's method [using 80 g. of zinc, 200 c.c. of concentrated mercuric chloride solution, and 400 c.c. of hydrochloric acid (1 vol. of conc. HCl : 2 vols. of water)], extracted with ether, dried (Na_2SO_4), and distilled under reduced pressure. It was a colourless oil, b. p. 125°/10 mm. Yield, 2 g.

Coupling Reactions.—Diepolder's experiment (*loc. cit.*) was repeated using *as*-*o*-xylenol and *p*-chlorobenzenediazonium chloride for comparison purposes. Coupling was effected with 3-methyl-4-ethylphenol, 3-methyl-4-propylphenol, and 3 : 4-diethylphenol, using 2 g. of phenol in 30 c.c. of 5% sodium hydroxide and 1·7 g. of *p*-chloroaniline in a mixture of sulphuric acid (2 g.) and water (30 c.c.), diazotized with sodium nitrite (1·2 g.) in water (10 c.c.). The products were filtered off, washed with distilled water, and dried in a vacuum desiccator.

Separation of the Isomers.—When dry, the melting point of the mixture of azo-compounds obtained as above was determined and the mixture was then dissolved in the smallest quantity of alcohol warmed to 30—40°. The solution was allowed to cool slowly to 0°. The crystals which separated were filtered off and recrystallised again from warm alcohol. This process was repeated and the melting point determined after each recrystallisation until the melting point had reached a maximum.

The mother liquor from the first crystallisation was diluted with water (double the volume of alcohol used) and the precipitate filtered off. The subsequent mother liquors from the recrystallisation of the less soluble isomer were treated similarly and all the precipitates combined, dissolved in just enough alcohol, warmed to 20° and the solution allowed to cool to room temperature. Some of the less soluble isomer separated and was discarded. The more soluble substance was precipitated with water and the melting point taken. The process was repeated until the melting point reached a maximum. Melting-point curves were then compiled for known mixtures of each pair of isomers and from them the composition of the initial mixtures of isomers was deduced.

The following substances were isolated: 6-(p-*chlorobenzeneazo*)-3 : 4-*dimethylphenol*, m. p. 156°, (Found: Cl, 13·6. $C_{14}H_{13}ON_2Cl$ requires Cl, 13·6%); 2-(p-*chlorobenzeneazo*)-3 : 4-*dimethylphenol*, m. p. 109° (Found: Cl, 13·6%); 6-*benzeneazo*-3-*methyl*-4-*ethylphenol*, bright red needles, m. p. 69° (Found: N, 11·6. $C_{15}H_{16}ON_2$ requires N, 11·7%); 2-*benzeneazo*-3-*methyl*-4-*ethylphenol*, light brown microcrystalline powder, m. p. 41° (Found: N, 11·5%); 6-(p-*chlorobenzeneazo*)-3-*methyl*-4-*ethylphenol*, golden brown prisms, m. p. 122° (Found: Cl, 13·0. $C_{15}H_{15}ON_2Cl$ requires Cl, 13·0%); 2-(p-*chlorobenzeneazo*)-3-*methyl*-4-*ethylphenol*, dark brown prisms, m. p. 73·4° (Found: Cl, 13·0%); 6-(p-*chlorobenzeneazo*)-3-*methyl*-4-n-*propylphenol*, brick-red powder, m. p. 115° (Found: Cl, 12·4. $C_{16}H_{17}ON_2Cl$ requires Cl, 12·3%); 2-(p-*chlorobenzeneazo*)-3-*methyl*-4-n-*propylphenol*, orange-red powder, m. p. 90° (Found: Cl, 12·4%); 6-(p-*chlorobenzeneazo*)-3 : 4-*diethylphenol*, m. p. 130° (Found: Cl, 12·2. $C_{16}H_{17}ON_2Cl$ requires Cl, 12·3%); 2-(p-*chlorobenzeneazo*)-3 : 4-*diethylphenol*, m. p. 95° (Found: Cl, 12·4%).

Orientation of the Azo-compounds.—The azo-compound (1 g.) was dissolved in the least quantity of boiling alcohol, and modified Witt's solution (Mills and Nixon, *loc. cit.*) added until the colour was discharged. The solution was diluted to about 400 c.c. with water, saturated when hot with hydrogen sulphide, boiled, filtered immediately, evaporated to small bulk (water-bath), made alkaline with sodium hydroxide, and the *p*-chloroaniline distilled off in steam. The residue was filtered, acidified with dilute acetic acid, and the precipitate filtered off, washed with water, dried, and recrystallised. The 6-*p*-chlorobenzeneazo-3 : 4-dimethylphenol, m. p. 156°, gave 6-amino-3 : 4-dimethylphenol, m. p. 174—175° (decomp.), identical with an authentic specimen prepared by reduction of 6-nitro-3 : 4-dimethylphenol with sodium hydrogen sulphide (compare, Diepolder, *loc. cit.*). The benzeneazo-3-methyl-4-ethylphenol, m. p. 69°, when treated similarly gave 6-amino-3-methyl-4-ethylphenol, m. p. 160° (decomp.), identical with an authentic specimen prepared as described below. The *p*-chlorobenzeneazo-3-methyl-4-ethylphenol, m. p. 122°, gave the same product. The *p*-chlorobenzeneazo-3-methyl-4-*n*-propylphenol, m. p. 115°, gave 6-amino-3-methyl-4-*n*-propylphenol, m. p. 145°, identical with an authentic specimen prepared as described below. The *p*-chlorobenzeneazo-3 : 4-diethylphenol, m. p. 130°, gave 6-amino-3 : 4-diethylphenol, m. p. 146°.

Synthesis of the Necessary Reference Substances.—*Nitration of* 4-*acetyl*-3-*methylphenol.* The phenol (7 g.) was suspended in 45 c.c. of glacial acetic acid and 2·5 c.c. of concentrated nitric acid (*d* 1·42) in 2·5 c.c. of glacial acetic acid were added slowly with cooling and shaking. The mixture, warmed on a water-bath, became hot and deep red. It was poured on ice, the precipitate of *nitro*-4-*acetyl*-3-*methylphenol* washed, dried, and recrystallised; it formed long, slender, pale brownish-yellow prisms from alcohol, m. p. 129° (Found: N, 7·34. $C_9H_9O_4N$ requires N, 7·2%).

Nitro-4-acetyl-3-methylphenol (3 g.) was added with stirring to sodium hydroxide (0·7 g.) in a little water and heated (water-bath). The bright orange sodium salt was powdered and heated with toluene (1 c.c.) and methyl sulphate (3 c.c.) in an oil-bath (110—120°; 30 minutes). The colourless liquid, diluted with water, was boiled, made alkaline, and cooled. The *methyl ether* formed very pale yellow needles from alcohol, m. p. 98·5° (Found: N, 6·8. $C_{10}H_{11}O_4N$ requires N, 6·7%).

5-*Nitro*-4-*methoxy*-2-*methylbenzoic acid.* The methyl ether (1 g.) was refluxed with potassium permanganate (4 g.) in water (150 c.c.) for several hours, and excess of potassium permanganate reduced by a few drops of alcohol. The liquid was filtered hot, cooled, and acidified with hydrochloric acid. The white flocculent precipitate, recrystallised from water, gave clusters of microscopic needles, m. p. 235° (decomp.), identical with the substituted toluic acid of hitherto uncertain constitution obtained by Cain and Simonsen (*loc. cit.*) from 6-nitro-3 : 4-dimethylanisole. The toluic acid must have the –Me meta to the –OMe since this is the only acid which could be formed from a mononitro-4-acetyl-3-methylphenol. Cain and Simonsen's acid is therefore 5-nitro-4-methoxy-2-methylbenzoic acid, and the nitration product of 4-acetyl-3-methylphenol has the nitro-group in the 6-position.

6-*Amino*-4-*acetyl*-3-*methylphenol.* This was obtained by reduction of the nitro-compound (1·8 g.) in boiling alkaline solution with sodium dithionite (hydrosulphite). On neutralisation (with dilute acetic acid) 1 g. of *base* was obtained, in pale yellow prisms, m. p. 116° from alcohol (Found: N, 8·63. $C_9H_{11}O_2N$ requires N, 8·5%).

6-*Amino*-3-*methyl*-4-*ethylphenol.* The aminoacetylphenol (0·6 g.) was refluxed (2 hrs.) with amalgamated zinc (1·5 g.) and hydrochloric acid (10 c.c.; 1 : 1) with further additions of acid from time to time. The liquid was cooled, filtered, neutralised with ammonia, and extracted with ether. The ether extract was dried (Na_2SO_4) and the ether removed, yielding 6-*amino*-3-*methyl*-4-*ethylphenol* as a white, crystalline powder, m. p. 160° (decomp.) (Found: N, 9·2. $C_9H_{13}ON$ requires N, 9·3%).

The following were prepared similarly: 6-*nitro*-4-*propionyl*-3-*methylphenol*, pale greenish-yellow prisms from alcohol, m. p. 95° (Found: N, 6·7. $C_{10}H_{11}O_4N$ requires N, 6·7%); 6-*nitro*-3-*methyl*-4-*propylphenyl methyl ether*, white rectangular prisms from alcohol, m. p. 137° (Found: N, 6·33. $C_{11}H_{13}O_4N$ requires N, 6·3%); 6-*amino*-4-*propionyl*-3-*methylphenol*, pale brown prisms with domed ends, m. p. 135° (Found: N, 7·4. $C_{10}H_{13}O_2N$ requires N, 7·8%); 6-*amino*-3-*methyl*-4-n-*propylphenol*, white crystalline powder, m. p. 145° (decomp.) (Found: N, 8·1. $C_{10}H_{15}ON$ requires N, 8·5%).

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