[CONTRIBUTION FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS, AND THE RESEARCH LABORATORIES OF THE "SOCIETE BELGE DE L'AZOTE", LIÈGE]

CONDENSATION OF PHENOLS AND NAPHTHOLS WITH STYRENE

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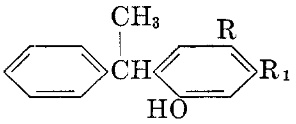
In the framework of our investigations into the fixation of alkyl, cycloalkyl, and arylalkyl groups upon phenols and naphthols to give compounds of potential practical interest (1), arylalkylations with styrene have come under consideration, in view of the ready availability of this intermediate.

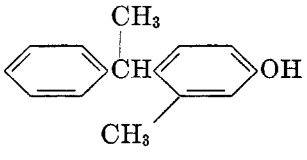
The condensation of styrene with phenol was first investigated by Koenigs (2), who used as catalyst sulfuric acid dissolved in acetic acid, and found the reaction to give a mixture of *o*- and *p*-(α-phenylethyl)phenol. Stoermer and Kippe (3) performed the same condensation with hydriodic acid, and recently, Frisch (4) made a more thorough study of the preparation and properties of *o*- and *p*-(α-phenylethyl)phenol; the latter substance was also isolated by McGreal and Niederl (5) in the arylalkylation of phenol with β-phenylethyl alcohol in the presence of zinc chloride. With respect to substituted phenols, Koenigs and Carl (6) prepared a liquid α-phenylethyl-*o*-cresol, and a solid α-phenylethyl-*m*-cresol (m.p. 124°); several patents (7) also refer to the synthesis of similar compounds by condensation of α-haloethylbenzenes with various phenols, but the liquid products thus obtained were insufficiently characterized, and were probably mixtures of several isomers.

The first step in the present research was the search for a suitable catalyst, and phosphoric acid, which had proved highly satisfactory for the alkylation of phenols, gave but poor results in the case of styrene. Sulfuric acid was more suitable, but high yields of condensation products were recorded only when styrene was diluted in an appropriate solvent such as toluene, so as to minimize polymerization.

This technique proved successful with a wide variety of monophenols, diphenols, and naphthols, and was used for the preparation, in excellent yields, of several new compounds in addition to ones already known. *p*-Cresol gave the liquid 4-methyl-2-(α-phenylethyl)phenol (I), and *o*-cresol also gave a liquid product, which might be a mixture of the two possible α-phenylethyl-*o*-cresols. The results obtained with *m*-cresol were more complex, as we isolated two substances (m.p. 50° and 125°) resulting from the addition of one molecule of styrene to one of *m*-cresol, the lower-melting isomer being apparently 3-methyl-6-(α-phenylethyl)phenol (II), and the higher-melting isomer being 3-methyl-4-(α-phenylethyl)phenol (III); in addition, a second compound melting at 125° was isolated

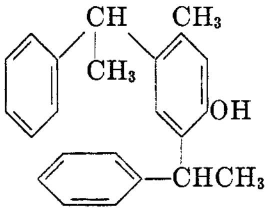


I $R = CH_3, R_1 = H$
II $R = H, R_1 = CH_3$

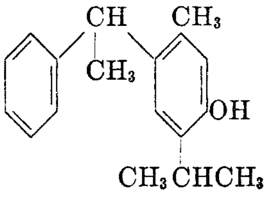


III

from the higher-boiling fraction, which proved to result from the addition of two molecules of styrene to one of *m*-cresol, and which was probably 3-methyl-4,6-bis-(α-phenylethyl)phenol (IV). In view of the fact that Koenigs and Carl (6) gave no boiling point for their product of m.p. 124°, it might be questioned whether it was compound III or IV.



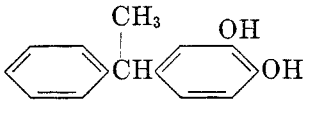
IV



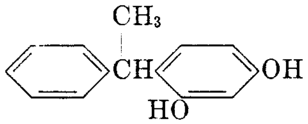
V

From thymol, the solid 3-methyl-4-(α-phenylethyl)-6-isopropylphenol (V) was obtained as the sole condensation product.

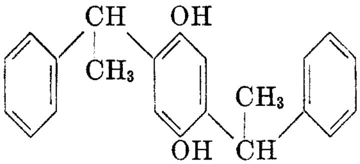
The reaction proved equally successful with diphenols and with their monoethers. Thus, from catechol and resorcinol, 4-(α-phenylethyl)catechol (VI) and 4-(α-phenylethyl)resorcinol (VII) were readily prepared. Guaiacol could be expected to react like *o*-cresol, and, in fact, a liquid (α-phenylethyl) guaiacol was obtained, which was probably a mixture of the two possible isomers. As in most of its previously known cases of substitution (8), hydroquinone gave a disubstituted product, 2,5-di-(α-phenylethyl)hydroquinone (VIII).



VI



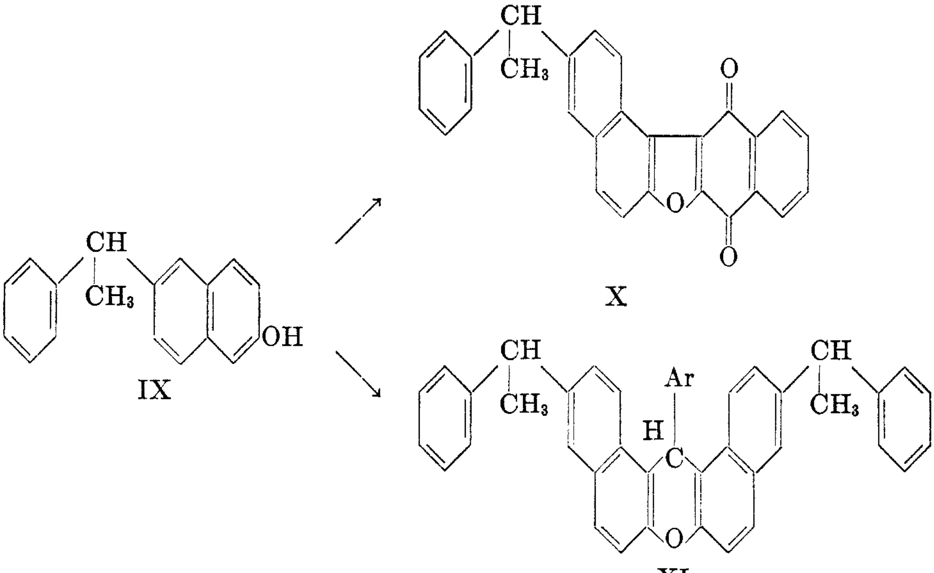
VII

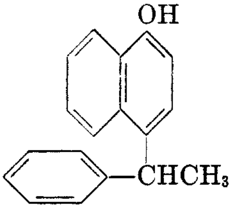


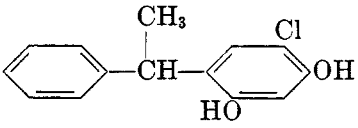
VIII

In the case of β-naphthol, a solid monosubstituted compound was obtained, for which the two possible sites of substitution to be considered are the 6- and the 1-position (1). This compound was shown to be 6-(α-phenylethyl)-2-naphthol (IX), since it gave with 2,3-dichloro-1,4-naphthoquinone a brazanquinone (X), a reaction characteristic of β-naphthols with their adjacent α-position free (1). A further proof of the correctness of formula IX was afforded by the easy formation of 14-aryl-14*H*-dibenzo[*a*,*j*]xanthenes (XI) under the influence of various aldehydes.

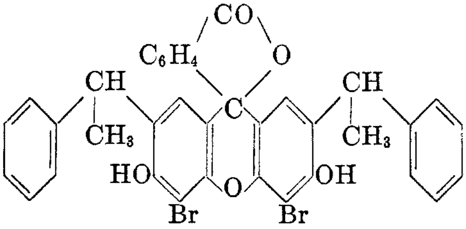
With α-naphthol, styrene also gave a condensation product, apparently 4-(α-phenylethyl)-1-naphthol (XII), a liquid whose homogeneity was however demonstrated by the preparation of a solid methyl ether.




XII


XIII

The α-phenylethylated phenols and naphthols obtained in the course of this work are of manifold practical interest as intermediates for the preparation of lipid-soluble germicides, fungicides, and dyes. For instance, 4-(α-phenylethyl)-resorcinol was converted by sulfuryl chloride into the bacteriostatic 1-chloro-2,4-dihydroxy-5-(α-phenylethyl)benzene (XIII); the same diphenol could also be converted into 4,5-dibromo-2,7-di-(α-phenylethyl)fluorescein (XIV) by conventional reactions. From naphthol IX, the tensio-active 6-(α-phenylethyl)-2-naphthoxyacetic acid was prepared for examination as a potential plant hormone.


XIV

EXPERIMENTAL[1]

α-Phenylethylation of phenol. (a) *With phosphoric acid.* To a mixture of 188 g. (2 moles) of phenol and 300 g. of concentrated phosphoric acid (*d.* 1.85) heated at about 100°, 145 g. (1.4 moles) of styrene was added in small portions with stirring. After 12 hours' refluxing, the mixture was cooled, washed with water, and extracted with benzene, 43 g. of polystyrene remaining undissolved. The benzene solution was washed with a dilute aqueous solution of sodium carbonate and dried over sodium sulfate, the solvent removed, and the residue vacuum-fractionated. The portion boiling at 160–210°/13 mm. consisted of a mixture of α-phenylethylphenols and distyrene, and separation was effected by alkali-extraction of the phenols and subsequent acidification. The total yield of α-phenylethylphenols was 72 g. (25%); it was substantially increased by diluting styrene in toluene, as in the following experiment.

(b) *With sulfuric acid.* To a mixture of 94 g. of phenol (1 mole) and 10 g. of concentrated sulfuric acid heated at about 100°, 52 g. (0.5 mole) of styrene in toluene (100 ml.) was added in small portions. After six hours' refluxing, the mixture was worked up as above; the yield of α-phenylethylphenols was 85–90%. *o*-(α-Phenylethyl)phenol condensed with phthalic anhydride and sulfuric acid into an amorphous phthalein, which gave frothy, violet, alkaline aqueous solutions.

4-Methyl-2-(α-phenylethyl)phenol. The condensation of 108 g. of *p*-cresol with 52 g. of styrene in toluene solution and in the presence of sulfuric acid (10 g.), gave an 80% yield of a monocondensation product as a pale yellow viscous oil, b.p. 175–177°/13 mm., which did not crystallize even after prolonged standing at −10°.

Anal. Calc'd for $C_{15}H_{16}O$: C, 84.9; H, 7.5.
Found: C, 85.0; H, 7.6.

The higher-boiling residue consisted of a viscous bis-(α-phenylethyl)-*p*-cresol, b.p. 250°/15 mm.

α-Phenylethylation of o-cresol. The mixture of the two possible (α-phenylethyl)-*o*-cresols, obtained in 85% yield, formed a viscous pale yellow oil, boiling at 179°/13 mm. After prolonged standing in the refrigerator, it solidified partly.

Anal. Calc'd for $C_{15}H_{16}O$: C, 84.9; H, 7.5.
Found: C, 84.8; H, 7.8.

α-Phenylethylation of m-cresol. From 108 g. of *m*-cresol and 52 g. of styrene there was obtained 92 g. of crude monocondensation product (86% yield), boiling at 180–210°/13 mm. This portion solidified partly on trituration with cyclohexane, yielding *3-methyl-4-(α-phenylethyl)phenol* (III), which recrystallized from cyclohexane in shiny, short, colorless prisms, m.p. 125°, b.p. 190–192°/13 mm.

Anal. Calc'd for $C_{15}H_{16}O$: C, 84.9; H, 7.5.
Found: C, 85.0; H, 7.6.

The mother-liquors were redistilled, giving *3-methyl-6-(α-phenylethyl)phenol* (II), b.p. 178–180°/13 mm., crystallizing from petroleum ether in shiny colorless prisms, m.p. 50°.

Anal. Calc'd for $C_{15}H_{16}O$: C, 84.9; H, 7.5.
Found: C, 85.0; H, 7.5.

The higher-boiling reaction product gave on fractionation 12 g. of *3-methyl-4,6-bis-(α-phenylethyl)phenol* (IV), which formed colorless needles from cyclohexane, m.p. 125°, b.p. 244–246°/13 mm. This substance was far more soluble in cyclohexane than compound III, and its melting-point was markedly depressed on admixture with this latter.

Anal. Calc'd for $C_{23}H_{24}O$: C, 87.3; H, 7.6.
Found: C, 87.0; H, 7.6.

3-Methyl-4-(α-phenylethyl)-6-isopropylphenol (V). This compound, obtained in 75% yield, boiled at 190–195°/13 mm., and crystallized from cyclohexane in fine colorless needles, m.p. 66°.

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[1] The yields quoted in this paper are calculated in relation to the amount of styrene used.

Anal. Calc'd for $C_{18}H_{21}O$: C, 85.4; H, 8.3.
Found: C, 85.2; H, 8.4.

4-(α-Phenylethyl)catechol (VI). Obtained in 62% yield, it formed fine colorless prisms from cyclohexane, m.p. 75°, boiling at 230–235°/13 mm. In this preparation, the duration of heating was reduced to two hours.

Anal. Calc'd for $C_{14}H_{14}O_2$: C, 78.5; H, 6.5.
Found: C, 78.0; H, 6.6.

(α-Phenylethyl)guaiacol, prepared by refluxing for one hour a mixture of 74 g. of guaiacol, 52 g. of styrene (dissolved in 100 ml. of toluene), and 10 g. of sulfuric acid, was a pale yellow, almost odorless oil, b.p. 217°/13 mm. Yield, 58 g.

Anal. Calc'd for $C_{15}H_{16}O_2$: C, 78.9; H, 7.0.
Found: C, 79.2; H, 7.1.

The bis-(α-phenylethyl)guaiacol fraction formed a pale yellow viscous oil, boiling at 263°/13 mm. Yield, 18 g.

Anal. Calc'd for $C_{22}H_{24}O_2$: C, 82.5; H, 7.5.
Found: C, 82.2; H, 7.6.

4-(α-Phenylethyl)resorcinol (VII). Obtained in 72% yield from 88 g. of resorcinol and 52 g. of styrene, it formed from a mixture of benzene and ligroin fine dull, colorless needles, m.p. 79°, b.p. 243–244°/12 mm.

Anal. Calc'd for $C_{14}H_{14}O_2$: C, 78.5; H, 6.5.
Found: C, 78.1; H, 6.3.

1-Chloro-2,4-dihydroxy-5-(α-phenylethyl)benzene (XIII). To an ice-cooled solution of 10.7 g. of the foregoing compound in dry chloroform, 8.1 g. of sulfuryl chloride was added dropwise with stirring. After removal of the solvent, the residue gave on recrystallization from a mixture of benzene and ligroin, fine colorless needles, m.p. 107°.

Anal. Calc'd for $C_{14}H_{13}ClO_2$: C, 67.6; H, 5.2.
Found: C, 67.9; H, 5.0.

4,5-Dibromo-2,7-di-(α-phenylethyl)fluorescein (XIV). An intimate mixture of 21.4 g. of 4-(α-phenylethyl)resorcinol and 8.9 g. of phthalic anhydride was heated at 180°, and 4.5 g. of freshly fused zinc chloride was added. The mixture was heated with stirring at 210° until solidification occurred; after cooling, the mass obtained was ground and dissolved in a dilute aqueous solution of potassium hydroxide. The filtered solution on acidification yielded 2,7-di-(α-phenylethyl)fluorescein as a yellow powder, which gave with aqueous alkalis dichroic solutions with an intense orange-green fluorescence. A solution of 15 g. of this product in 200 ml. of ethanol was treated with 9 g. of bromine; the precipitate obtained on dilution with water was dried *in vacuo*, and gave after recrystallization from benzene an orange-yellow microcrystalline powder, decomposing above 215°, and melting at 226°.

Anal. Calc'd for $C_{36}H_{26}Br_2O_5$: C, 61.8; H, 3.7.
Found: C, 61.0; H, 3.7.

2,5-Di-(α-phenylethyl)hydroquinone (VIII). To a hot suspension of 110 g. of hydroquinone in 200 ml. of toluene containing 10 g. of sulfuric acid, 104 g. of styrene in 100 ml. of toluene was added in small portions with stirring. After one hour's refluxing, the mixture was worked up in the usual way. The portion boiling at 230–285°/13 mm. (150 g.) crystallized from benzene in fine colorless needles, m.p. 162°.

Anal. Calc'd for $C_{22}H_{22}O_2$: C, 83.0; H, 6.9.
Found: C, 82.7; H, 7.1.

6-(α-Phenylethyl)-2-naphthol (IX). A solution of 288 g. of β-naphthol in 200 ml. of toluene containing 30 g. of sulfuric acid, was treated in small portions with 104 g. of styrene in 50 ml. of toluene. After three hours' refluxing, the mixture was worked up in the usual way, giving 230 g. (92% yield) of a monocondensation product, b.p. 240–270°/13 mm. This was redistilled (b.p. 248–250°/13 mm.), and recrystallized from acetic acid, giving fine colorless prisms, m.p. 86°, extremely soluble in the usual solvents.

Anal. Calc'd for $C_{18}H_{16}O$: C, 87.2; H, 6.4.
Found: C, 86.9; H, 6.5.

The *methyl ether* boiled at 234–236°/13 mm., and formed from ethanol shiny colorless leaflets, m.p. 70°.

Anal. Calc'd for $C_{19}H_{18}O$: C, 87.0; H, 6.8.

Found: C, 87.0; H, 6.9.

3-(α-Phenylethyl)dinaphtho [2, 1, 2′, 3′] furan-8,13-dione (X). A solution of 2 g. of IX and 2 g. of 2,3-dichloro-1,4-naphthoquinone in 10 ml. of dry pyridine was refluxed for one hour. After cooling, the reaction product was treated with dilute hydrochloric acid and the solid collected, dried, and recrystallized from benzene. A 90% yield of silky yellow needles, m.p. 230°, was obtained, giving a deep greenish-blue color with sulfuric acid.

Anal. Calc'd for $C_{28}H_{18}O_3$: C, 83.3; H, 4.5.

Found: C, 83.6; H, 4.7.

14-(3,4-Dichlorophenyl)-14H-dibenzo[a, j]xanthene. A solution of 2 g. of IX and 1 g. of 3,4-dichlorobenzaldehyde in 10 ml. of acetic acid was boiled with some drops of hydrochloric acid until turbidity took place. After cooling, the oily precipitate was decanted, and redissolved in hot acetic acid. The solid obtained on cooling was recrystallized from ethanol, giving fine colorless needles, m.p. 182°.

Anal. Calc'd for $C_{43}H_{31}Cl_2O$: C, 81.3; H, 4.9.

Found: C, 81.6; H, 5.0.

6-(α-Phenylethyl)-2-naphthoxyacetic acid. This was prepared in 70% yield from 24.8 g. of naphthol IX and 10 g. of chloroacetic acid in the presence of aqueous sodium hydroxide; it formed colorless prisms from benzene, m.p. 132°, giving frothy solutions in aqueous alkalis.

Anal. Calc'd for $C_{20}H_{20}O_3$: C, 77.9; H, 6.5.

Found: C, 78.2; H, 6.5.

4-(α-Phenylethyl)-1-naphthol (XII). Prepared in 80% yield in the same way as for the isomeric naphthol IX, it formed a pale yellow, very viscous oil, b.p. 248–250°/13 mm., which did not solidify on prolonged storage at −10°.

Anal. Calc'd for $C_{18}H_{16}O$: C, 87.2; H, 6.4.

Found: C, 87.0; H, 6.6.

The *methyl ether* boiled at 225–226°/13 mm., and crystallized from methanol in shiny colorless leaflets, m.p. 62°.

Anal. Calc'd for $C_{19}H_{18}O$: C, 87.0; H, 6.8.

Found: C, 86.7; H, 6.6.

SUMMARY

1. The condensation of styrene with various phenols, diphenols, and naphthols, in the presence of phosphoric or sulfuric acid, has been investigated.

2. The constitution of the phenylethylated products thus obtained is discussed, and several of their functional derivatives are described.

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