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

FURTHER STUDIES IN THE ALKYLATION OF PHENOLS AND THIOPHENOLS

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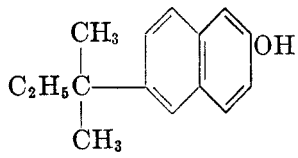
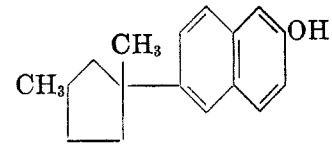
In previous papers of this series (1), the preparation and determination of the constitution of several alkylation products of β-naphthol have been discussed. The interesting anthelmintic, fungistatic, and antiseptic properties of certain alkylnaphthols thus obtained led us to investigate further alkylations.

In the naphthalene series, the phosphoric acid-catalyzed condensation of isoamyl alcohol with β-naphthol yielded as the main product a monoamyl compound; this, by analogy with the butylation and cyclohexylation of β-naphthol (1), is probably 6-*tert*-amyl-2-naphthol (I). In contrast to the *tert*-butylation reaction, no well-defined disubstitution-product could be separated.



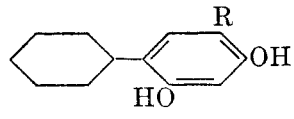
I



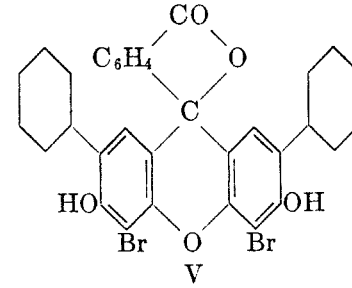
II

From β-naphthol and 1,3-dimethylcyclopentan-1-ol (prepared by the reaction of methylmagnesium iodide upon 3-methylcyclopentanone), an alkylation product, apparently 6-(1,3-dimethyl-1-cyclopentyl)-2-naphthol (II), was similarly obtained.

In the field of dihydric phenols, we found that phosphoric acid was also a very effective alkylation catalyst. Thus, from cyclohexanol and resorcinol, 4-cyclohexylresorcinol (III) was obtained in very satisfactory yield, whereas the method described in the literature gave but a 5% yield (2). In order to enhance the anthelmintic and antiseptic properties of 4-cyclohexylresorcinol by the introduction of halogen atoms into the molecule, we synthesized 6-chloro-4-cyclohexylresorcinol (IV) by treatment with sulfuryl chloride in the cold. Another interesting derivative of 4-cyclohexylresorcinol is 4,5-dibromo-2,7-dicyclohexyl-



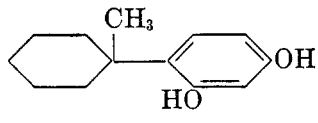
III R = H
IV R = Cl



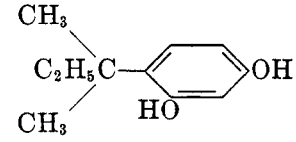
V

fluorescein (V), a dye easily obtained by bromination of the product from the zinc chloride-catalyzed condensation of 4-cyclohexylresorcinol with phthalic anhydride.

Whereas 4-cyclohexylresorcinol is a well-crystallized, rather high-melting compound, the product which we obtained by alkylating resorcinol with *o*-methylcyclohexanol in the presence of phosphoric acid was a non-crystalline viscous oil. The reason for this might well be that the normally expected (1, 3) rearrangement of the methylcyclohexyl group, which would yield 4-(1-methyl-1-cyclohexyl)resorcinol (VI), was not complete and therefore several isomers were present. The monoalkylation product from resorcinol and isoamyl alcohol, be-



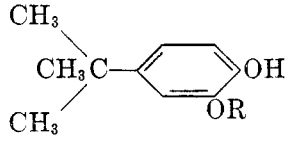
VI



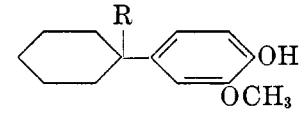
VII

lieved to be 4-*tert*-amylresorcinol (VII), was also an oil, although it gave a well-crystallized sodium derivative.

In the catechol series, 2-methoxy-4-*tert*-butylphenol (or 4-*tert*-butylguaiacol) (VIII) was obtained from *tert*-butyl alcohol or isobutylene and guaiacol. Similarly, alkylation of the latter with cyclohexanol and *o*-methylcyclohexanol gave 2-methoxy-4-cyclohexylphenol (X) and 2-methoxy-4-(1-methyl-1-cyclohexyl)-phenol (XI) respectively. The constitution given to all these alkylation products



VIII R = CH_3
IX R = H



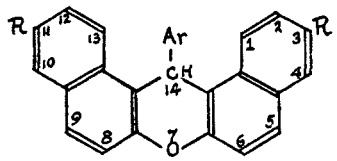
X R = H
XI R = CH_3

of guaiacol is assumed from the known fact that phosphoric acid-catalyzed alkylations of *ortho*-substituted phenols involve the position *para* to the phenol group (4). 4-*tert*-Butylguaiacol has proven of practical interest in replacing guaiacol and creosote as a less irritant antiseptic for the respiratory tract; sodium 4-*tert*-butylguaiacolsulfonate has also found pharmacological use as a substitute for sodium guaiacolsulfonate. Aside from these applications, 4-*tert*-butylguaiacol is a useful intermediate for the preparation of substituted catechols; thus, demethylation with pyridine hydrochloride gave 4-*tert*-butylcatechol (IX), and halogenation with sulfuryl chloride or bromine yielded an x-chloro- and an x-bromo-4-*tert*-butylguaiacol. In view of the complexity of substitution problems in the guaiacol molecule (5), the exact structure of these halogen derivatives must await further investigation.

A question of both theoretical and practical interest is whether thiohpenols can be alkylated in the same way as phenols. The answer as regards phosphoric

acid-catalyzed alkylations is in the negative, since we obtained from thiophenol or *p*-thiocresol with isoamyl alcohol none of the expected C-substituted products, but only the products of S-amylation (isoamyl phenyl sulfide and isoamyl *p*-cresyl sulfide); similarly, alkylation of the same thiophenols with technical methylcyclohexanol (a mixture of the *o*-, *m*-, and *p*-isomers) yielded the corresponding S-methylcyclohexyl derivatives. These results are in line with recent findings of Hansch and Robertson, who showed that neither thiophenol nor *p*-thiocresol undergo vapor phase C-alkylation with ethanol, the corresponding S-ethers being obtained instead (6). Another known fact which appears to be related to these conclusions is the difficulty with which allyl ethers of thiophenols undergo the Claisen rearrangement (7).

A reaction equivalent to alkylations and arylalkylations is the acid-catalyzed condensation of 2-naphthol (and its derivatives having their 1-position free) with aldehydes (1, 8) to 14-substituted 14*H*-Dibenzo[*a*, *j*]xanthenes. A series of new 14-aryl-14*H*-dibenzo[*a*, *j*]xanthenes (XII), most of them halogenated, has now been prepared for testing as potential plant-growth regulators, in view of



XII

the activity of the mother substance, 14-phenyl-14*H*-dibenzo[*a*, *j*]xanthene (9); they are listed in Table I. In antibacterial tests, this class of substances showed no appreciable *in vitro* activity against *Staphylococcus aureus* and *Escherichia coli*.

EXPERIMENTAL

6-tert-Amyl-2-naphthol (I). A mixture of 150 g. of β-naphthol, 100 g. of isoamyl alcohol, and 400 g. of phosphoric acid (*d.*, 1.85) was refluxed for 20 hours. After cooling, the reaction mixture was cautiously poured into water and extracted with benzene; the benzene layer was washed with a dilute aqueous solution of sodium bicarbonate, then with water, and dried over sodium sulfate. After removal of the solvent, the residue was vacuum-fractionated, giving 75 g. of a portion boiling at 210–230°/15 mm., which readily solidified. After several recrystallizations from ligroin, long colorless needles, m.p. 108°, with a faint naphthol odor, were obtained.

Anal. Calc'd for $C_{15}H_{18}O$: C, 84.1; H, 8.4.
Found: C, 84.0; H, 8.5.

In contrast to the *tert*-butylation of β-naphthol, very little higher-boiling material (10 g.) was obtained, and this did not yield any crystalline product.

6-(1,3-Dimethyl-1-cyclopentyl)-2-naphthol (II). A Grignard reagent was prepared from 74.5 g. of methyl iodide and 13 g. of magnesium in 500 ml. of anhydrous ether. To this ice-cooled solution, 3-methylcyclopentanone (10) was added dropwise with stirring. The reaction mixture was subsequently refluxed for ten minutes, and decomposed after cooling with an ice-cold aqueous solution of ammonium chloride. After the usual treatment, 30 g. of *1,3-dimethylcyclopentan-1-ol* was obtained in the form of a colorless oil with a campho-

raceous odor, boiling at 143–145° (11). The forerun (15 g.) consisted mainly of a 1,3-dimethylcyclopentene of unknown constitution.

A mixture of 45 g. of 1,3-dimethylcyclopentan-1-ol, 58 g. of β-naphthol, and 100 g. of phosphoric acid was refluxed for 16 hours, and the reaction product was worked up in the usual way. On vacuum-distillation, 22 g. of a portion b.p. 235–270°/25 mm., which readily solidified, was obtained. After recrystallization from ligroin, long colorless needles, m.p. 82°, were obtained.

Anal. Calc'd for $C_{17}H_{20}O$: C, 85.0; H, 8.3.

Found: C, 85.1; H, 8.3.

Condensation of β-naphthol with menthol. An attempt to alkylate β-naphthol with menthol resulted in a 60% yield of an oily product, b.p. 245–255°/16 mm., and a small quantity of a crystalline substance, m.p. 127°. The constitution of these products has not yet been elucidated.

Preparation of 4-cyclohexylresorcinol (III). A mixture of 160 g. of resorcinol, 140 g. of cyclohexanol, and 200 g. of phosphoric acid (*d.*, 1.85) was refluxed for 16 hours. After cooling, 200 ml. of water was carefully added, the mixture was extracted with benzene, and the benzene layer was treated in the usual way. Vacuum-distillation of the reaction product gave 167 g. of a portion, b.p. 215–240°/22 mm., which crystallized partially on standing with benzene. After recrystallization from benzene, 98 g. of 4-cyclohexylresorcinol was obtained in the form of long colorless needles; m.p. 124°, b.p. 220–222°/22 mm. The higher-boiling portion (52 g., b.p. 240–280°/22 mm.) yielded an additional 10 g. of the same product on prolonged standing with benzene.

Anal. Calc'd for $C_{12}H_{16}O_2$: C, 75.0; H, 8.3.

Found: C, 74.9; H, 8.4.

4-Cyclohexylresorcinol dimethyl ether. This was prepared in the usual way from compound III and methyl sulfate; it formed a colorless oil boiling at 189°/20 mm., and having an aromatic odor.

Anal. Calc'd for $C_{14}H_{20}O_2$: C, 76.3; H, 9.0.

Found: C, 76.4; H, 9.0.

6-Chloro-4-cyclohexylresorcinol (IV). A cooled solution of 19.2 g. of 4-cyclohexylresorcinol in 150 ml. of chloroform was treated dropwise with 13.5 g. of sulfuryl chloride. The reaction product was taken up in benzene, washed with an aqueous solution of sodium bicarbonate, then with water, dried over sodium sulfate, and vacuum-distilled after removal of the solvent. 6-Chloro-4-cyclohexylresorcinol formed fine colorless prisms, m.p. 91°, from benzene or chloroform.

Anal. Calc'd for $C_{12}H_{15}ClO_2$: C, 63.5; H, 6.6.

Found: C, 63.3; H, 6.6.

4,5-Dibromo-2,7-dicyclohexylfluorescein (V). To an intimate mixture of 25 g. of 4-cyclohexylresorcinol and 10.5 g. of phthalic anhydride kept at 180° in an oil-bath, 4.5 g. of powdered fused zinc chloride was added in small portions with continuous stirring. The mixture was heated for 30 minutes at 210°; the solid mass obtained was ground and purified by solution in a 5% potassium hydroxide solution and precipitation with dilute hydrochloric acid. The crude *2,7-dicyclohexylfluorescein* was obtained in almost quantitative yield as a yellow powder giving orange alkaline solutions with a strong green fluorescence. It was suspended in ethanol and treated with bromine in slight excess. The solid thus obtained formed a microcrystalline yellow powder, m.p. 290° from *o*-dichlorobenzene, giving cherry-red alkaline solutions which have a strong orange-green fluorescence.

Anal. Calc'd for $C_{32}H_{30}Br_2O$: C, 58.7; H, 4.6.

Found: C, 58.5; H, 4.7.

The corresponding *ammonium salt* formed shiny, water-soluble red needles.

2,7-Dicyclohexylfluorescein gave also a substitution product with iodine in an alkaline medium.

4-Methylcyclohexylresorcinol. The alkylation of 110 g. of resorcinol by 115 g. of *o*-methylcyclohexanol in the presence of 200 g. of phosphoric acid, performed as for cyclohexanol,

yielded after careful vacuum-fractionation, 108 g. of a pale yellow viscous oil, b.p. 235°/20 mm., which did not crystallize even after prolonged standing. This product was soluble in alkaline solutions, and remained unchanged after an attempted dealkylation with boiling pyridine hydrochloride.

Anal. Calc'd for $C_{13}H_{18}O_2$: C, 75.7; H, 8.7.
Found: C, 75.5; H, 8.7.

4-tert-Amylresorcinol (VII). A mixture of 110 g. of resorcinol, 88 g. of isoamyl alcohol, and 100 g. of phosphoric acid was refluxed for 20 hours. After the usual treatment, vacuum-fractionation of the reaction product yielded 81 g. of a pale yellow viscous oil, $n_D^{18.5}$ 1.5410, b.p. 173–174°/22 mm., which did not crystallize even after purification through its *sodium salt*, which formed long colorless needles from water.

Anal. Calc'd for $C_{11}H_{16}O_2$: C, 73.3; H, 8.8.
Found: C, 73.2; H, 9.0.

4-tert-Butylguaiacol (VIII) was readily obtained from guaiacol with either *tert*-butyl alcohol and phosphoric acid at normal pressure in the usual way, or with isobutylene and phosphoric acid under pressure. The reaction product was a fluid colorless oil, b.p. 253°, n_D^{18} 1.5241, with a pleasant aromatic odor; yield, 70–75%.

Anal. Calc'd for $C_{11}H_{16}O_2$: C, 73.3; H, 8.8.
Found: C, 73.4; H, 9.0.

4-tert-Butylcatechol (IX). A mixture of 18 g. of the preceding compound and 90 g. of redistilled pyridine hydrochloride was gently refluxed for 15 minutes. After cooling, 100 ml. of water was added, and the solid was purified by vacuum-distillation. 4-*tert*-Butylcatechol formed silky, lustrous needles, m.p. 75°, b.p. 265°, from anhydrous benzene.

Anal. Calc'd for $C_{10}H_{14}O_2$: C, 72.3; H, 8.4.
Found: C, 72.0; H, 8.2.

x-Chloro-4-tert-butylguaiacol. To a water-cooled solution of 18 g. of 4-*tert*-butylguaiacol in 50 ml. of chloroform, 13.5 g. of sulfuryl chloride was added dropwise with stirring. After an hour's standing at room temperature, the chloroform solution was washed with an aqueous solution of sodium bicarbonate and with water, and dried over sodium sulfate. After removal of the chloroform, the residue was vacuum-fractionated, yielding a pale yellow oil, b.p. 157°/20 mm., $n_D^{18.5}$ 1.5415, with a slight aromatic odor.

Anal. Calc'd for $C_{11}H_{15}ClO_2$: C, 61.5; H, 6.9.
Found: C, 61.6; H, 7.0.

Demethylation of this compound with pyridine hydrochloride gave an *x-chloro-4-tert-butylcatechol* crystallizing from anhydrous benzene in fine colorless needles, m.p. 89°.

Anal. Calc'd for $C_{10}H_{13}ClO_2$: C, 59.8; H, 6.5.
Found: C, 59.4; H, 6.5.

x-Bromo-4-tert-butylguaiacol. A water-cooled solution of 18 g. of 4-*tert*-butylguaiacol in 75 ml. of chloroform was treated dropwise with 16 g. of bromine in 25 ml. of chloroform. After an hour's standing, the chloroform solution was treated as above, yielding the brominated product in the form of a pale yellow oil, b.p. 170–172°/22 mm., $n_D^{18.5}$ 1.5585.

Anal. Calc'd for $C_{11}H_{15}BrO_2$: C, 50.9; H, 5.8.
Found: C, 51.3; H, 6.0.

2-Methoxy-4-cyclohexylphenol (X). A mixture of 40 g. of guaiacol, 32 g. of cyclohexanol, and 75 g. of phosphoric acid was refluxed for 20 hours. The reaction product was worked up in the usual way, yielding 42 g. of 4-cyclohexylguaiacol as a pale yellow, almost odorless oil, b.p. 175–180°/22 mm., $n_D^{18.5}$ 1.5458, which did not crystallize.

Anal. Calc'd for $C_{13}H_{18}O_2$: C, 75.7; H, 8.7.
Found: C, 75.6; H, 8.6.

2-Methoxy-4-(1-methylcyclohexyl)phenol (XI). From 50 g. of guaiacol, 46 g. of *o*-methylcyclohexanol, and 80 g. of phosphoric acid. Yield, 54 g. of a pale yellow, odorless, viscous oil, b.p. 190–193°/20 mm., $n_D^{18.5}$ 1.5491.

Anal. Calc'd for $C_{14}H_{20}O_2$: C, 76.3; H, 9.1.
Found: C, 76.1; H, 9.1.

S-Alkylations of thiophenol. (*a*) *With isoamyl alcohol.* A mixture of 22 g. of thiophenol, 22 g. of technical isoamyl alcohol, and 50 g. of phosphoric acid (*d.*, 1.85) was refluxed for 20 hours. After cooling, the reaction product was poured onto ice and extracted several times with ether; the ether solution was washed with a 12% sodium hydroxide solution, then with water, and dried over sodium sulfate. After evaporation of the solvent, the residue was vacuum-fractionated, giving 10 g. of *thiophenol S-isoamyl ether* as a fluid colorless oil with a slight garlic odor, b.p. 240–242°. No active hydrogen could be detected by the Tschugaeff-Zerewitinoff method, either with this ether or with the following ones.

Anal. Calc'd for $C_{11}H_{16}S$: C, 73.3; H, 8.9.

Found: C, 73.0; H, 9.0.

The alkali-soluble fraction on acidification yielded 4 g. of unreacted thiophenol.

(*b*) *With technical methylcyclohexanol.* A mixture of 22 g. of thiophenol, 30 g. of "methylcyclohexanol", and 50 g. of phosphoric acid was refluxed for 18 hours, and the reaction

TABLE I

14-ARYL-14*H*-DIBENZO[*a*, *j*]XANTHENES (XII)

Ar	R	FORMULA	M.P., °C.	ANALYSES			
				Calc'd		Found	
				C	H	C	H
3-Nitrophenyl	*tert*-Amyl	$C_{37}H_{37}NO_3$	244	81.7	6.8	81.6	6.8
4-Chlorophenyl	*tert*-Amyl	$C_{37}H_{37}ClO$	252	83.3	6.9	83.1	7.0
3,4-Dichlorophenyl	*tert*-Amyl	$C_{37}H_{36}Cl_2O$	262	78.2	6.2	78.0	6.5
2-Chlorophenyl	H	$C_{27}H_{17}ClO$	215	82.5	4.3	82.4	4.5
3,4-Dichlorophenyl	H	$C_{27}H_{16}Cl_2O$	226	75.9	3.7	75.6	3.7
2,4-Dichlorophenyl	H	$C_{27}H_{16}Cl_2O$	251	75.9	3.7	75.7	3.8
2-Chlorophenyl	Br	$C_{27}H_{15}Br_2ClO$	193	58.9	2.7	58.6	2.8
3,4-Dichlorophenyl	Br	$C_{27}H_{14}Br_2Cl_2O$	260	55.4	2.4	55.1	2.6
2,4-Dichlorophenyl	Br	$C_{27}H_{14}Br_2Cl_2O$	273	55.4	2.4	55.2	2.6

product worked up as above. Yield, 2 g. of unreacted thiophenol and 35 g. of *thiophenol S-methylcyclohexyl ether*, a fluid colorless oil, b.p. 150°/17 mm., $n_D^{17.5}$ 1.5626, with an aromatic odor.

Anal. Calc'd for $C_{12}H_{18}S$: C, 75.7; H, 8.7.

Found: C, 75.4; H, 8.8.

S-Alkylations of p-thiocresol. (*a*) *With isoamyl alcohol.* The reaction between 28 g. of *p*-thiocresol, 35 g. of isoamyl alcohol, and 100 g. of phosphoric acid yielded 20 g. of *p-thiocresol S-isoamyl ether* as a fluid colorless oil, b.p. 253°, 120°/17 mm., with an aromatic odor.

Anal. Calc'd for $C_{12}H_{18}S$: C, 74.2; H, 9.3.

Found: C, 74.4; H, 9.4.

(*b*) *With methylcyclohexanol.* The reaction of 28 g. of *p*-thiocresol, 30 g. of technical methylcyclohexanol, and 100 g. of phosphoric acid yielded 38 g. of *p-thiocresol S-methylcyclohexyl ether* as a fluid colorless oil, b.p. 168–170°/17 mm., n_D^{17} 1.5570.

Anal. Calc'd for $C_{14}H_{20}S$: C, 76.4; H, 9.1.

Found: C, 76.7; H, 9.4.

Other thiophenols such as *m*-thiocresol, *p*-chlorothiophenol, and β-thionaphthol could also be S-alkylated in the same way.

Preparation of 14-aryl-14H-dibenzo [a, j] xanthenes. A solution of the naphthol (2 moles) and the required aromatic aldehyde (1 mole) in the minimum amount of acetic acid was boiled with several ml. of hydrochloric acid until there was complete precipitation of an

oil. The oil solidified on cooling and was recrystallized several times from acetic acid or ethanol. The naphthols used were: β-naphthol, 6-bromo-2-naphthol, and 6-*tert*-amyl-2-naphthol. The aldehydes were: *o*-chloro-, *p*-chloro-, *m*-nitro-, 2,4-dichloro-, and 3,4-dichloro-benzaldehyde. All the dibenzoxanthenes thus obtained formed shiny colorless flat prisms; they showed a remarkable facility for crystallization, and might be useful for characterization purposes.

SUMMARY

1. In continuation of earlier work, further alkylations of β-naphthol are described.

2. Similar alkylations of resorcinol and guaiacol have been effected, leading to compounds of biological interest.

3. Phosphoric acid-catalyzed alkylations of thiophenols are shown to result in stable S-ethers.

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REFERENCES

(1) BUU-HOÏ, LE BIHAN, BINON, AND RAYET, *J. Org. Chem.*, **15**, 1060 (1950); BUU-HOÏ, LE BIHAN, AND BINON, *J. Org. Chem.*, **16**, 185 (1951).
(2) BARTLETT AND GARLAND, *J. Am. Chem. Soc.*, **49**, 2099 (1927).
(3) PINES, STREHLAU, AND IPATIEFF, *J. Am. Chem. Soc.*, **72**, 1564 (1950); IPATIEFF, MEISINGER, AND PINES, *J. Am. Chem. Soc.*, **72**, 2772 (1950).
(4) HART AND HAGLUND, *J. Org. Chem.*, **15**, 396 (1950).
(5) JONES AND ROBINSON, *J. Chem. Soc.*, **111**, 903 (1917); BUREŠ AND SUČEK, *Chem. Zentr.*, **100, I**, 1099 (1929).
(6) HANSCH AND ROBERTSON, *J. Am. Chem. Soc.*, **72**, 4810 (1950).
(7) HURD AND GREENGARD, *J. Am. Chem. Soc.*, **52**, 3356 (1930).
(8) CLAISEN, *Ann.*, **237**, 265 (1887).
(9) THOMPSON, SWANSON, AND NORMAN, *Botan. Gaz.*, **107**, 476 (1946).
(10) ZELINSKY, *Ber.*, **35**, 2489 (1902).
(11) ZELINSKY, *Ber.*, **34**, 3950 (1901).