

THE ISOPROPYL CRESOLS

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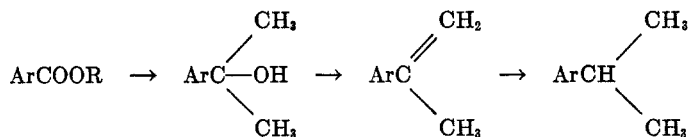
Received August 17, 1953

I. FROM *o*-CRESOL

The Friedel-Crafts reaction has been found to be well adapted to the synthesis of thymol (1). For this preparation *m*-cresol is alkylated with isopropyl chloride in the presence of aluminum chloride, using ethylene dichloride as solvent. When this procedure was applied to *o*-cresol there was obtained in good yield a product which, after crystallization, melted sharply at 36–36.5°. This material, which will be referred to as *pseudo*-carvacrol, gave several derivatives melting correctly for those of carvacrol; however, subsequent investigation showed that it is actually a difficultly separable mixture of carvacrol and 3-isopropyl-2-methylphenol. The latter compound, which has not previously been reported, was synthesized from 2-methyl-3-chloroaniline by two different routes, the most direct of which proceeded through 2-bromo-6-chlorotoluene and 2-isopropyl-6-chlorotoluene. Infrared analysis, using the bands at 12.34 and 12.82 μ , indicated that *pseudo*-carvacrol contains about 25% of 3-isopropyl-2-methylphenol and 75% of carvacrol. Absorption curves for the mixture and its two components are given in Fig. 1.

The other two isopropyl *o*-cresols have been reported: 6-isopropyl-2-methylphenol (2, 3) and 4-isopropyl-2-methylphenol (4), but it was considered desirable to prepare them anew and to characterize them more accurately.

6-Isopropyl-2-methylphenol was prepared by two methods. In the first, the Grignard reagent of 6-bromo-2-methylanisole was treated with isopropyl sulfate and the resulting 6-isopropyl-2-methylanisole was demethylated to the phenol. The second synthesis was an adaptation of the method first described by Behal and Tiffenau (3) in which an ester group is converted to an isopropyl group by the steps:



starting with the methyl ether of methyl *o*-cresotinate.

4-Isopropyl-2-methylphenol was prepared by two methods. In the first, 4-bromo-2-methylanisole was converted by way of the cyano compound to the methyl ether of the corresponding cresotinic acid methyl ester and the latter was treated by the Behal and Tiffenau procedure. In the second, the Grignard reagent of 4-isopropyl-2-bromoanisole was treated with methyl sulfate and the resulting ether was demethylated to the phenol.

The physical constants of the isopropyl *o*-cresols are listed in Table I.

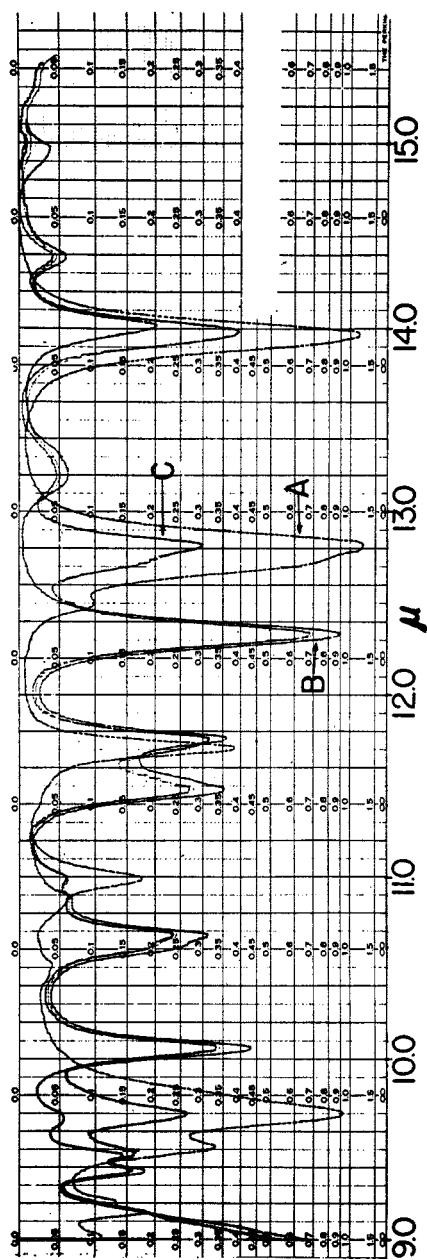


FIG. 1. INFRARED ABSORPTION SPECTRA, RANGE 9.0-15.5 μ , OF ISOPROPYL CRESOLS. A, 3-Isopropyl-2-methylphenol; B, Carvacrol; C, *pseudo*-Caryacrol.

TABLE I
 ISOPROPYL *o*-CRESOLS

Isomer	C.P., °C.	M.P., °C.	d_{25}^{25}	n_D^{20}	Oxyacetic acid M.P., °C.	<i>p</i> -Nitro- benzoate M.P., °C.
3-Isopropyl-2-methylphenol		82-83			131.5-132.5	113-114.5
4-Isopropyl-2-methylphenol	8.3	8.6				
	28.3	28.5	0.9793	1.5253	102-103	80-81
5-Isopropyl-2-methylphenol	3	3.5	.9751	1.5238	151-151.5	53-54
6-Isopropyl-2-methylphenol	-16.5	-14.5	.9782	1.5239	83-84	oil

It is interesting to note that the odors of the isomers become increasingly stronger as the isopropyl group moves from the 3- to the 6-position: the 3-isopropyl has a weak, phenolic odor; the 4-isopropyl has an odor similar to that of carvacrol, but somewhat milder and less pungent; the 6-isopropyl has a sharp, pungent phenolic odor.

II. FROM *m*-CRESOL

The four isomeric isopropyl *m*-cresols have been described: 2-isopropyl-3-methylphenol (*vic*-thymol), 4-isopropyl-*(p)*-thymol), 5-isopropyl-*(sym)*-thymol), and 6-isopropyl-(thymol).

When *m*-cresol is alkylated with isopropyl alcohol or isopropyl ether in the presence of mineral acids or acid clays all four isomers are formed. We have never observed the formation of *vic*-thymol when alkylating by the Friedel-Crafts method. The thermal stability of the isomers in the presence of acid catalysts is of the order: *sym*-thymol > thymol > *p*-thymol > *vic*-thymol. Thus if it is desired to isolate *vic*-thymol the alkylation must be interrupted at the earliest possible stage. The isomers may be separated without difficulty by fractionation *in vacuo*. The order of volatility is: *vic*-thymol > thymol > *sym*-thymol > *p*-thymol.

vic-Thymol has been described but briefly in the literature (5, 6). We have prepared a number of derivatives, including the *o*- and *p*-nitro, the dinitro, the *p*-nitroso, the oxyacetic acid, and the *p*-nitrobenzoate. According to Schwenk, *et al.* (7) compounds of the type represented by *p*-nitro-*vic*-thymol methyl ether undergo, upon treatment with Raney nickel alloy and sodium hydroxide, reduction of the nitro group to amino and loss of the methoxy group. In this case the resulting 2-amino-6-isopropyltoluene would have yielded, upon hydrolysis of the diazonium salt, 3-isopropyl-2-methylphenol (see Part I). However, the methoxy group was not eliminated and only the aminoanisole was obtained. Attempts to replace the hydroxyl group by amino by treating either *p*-nitro-*vic*-thymol or its methyl ether with ammonia were unsuccessful. Likewise, attempts to replace the hydroxyl by halogen by treating *p*-nitro-*vic*-thymol with phosphorus oxychloride or phosphorus pentachloride or with hydrogen bromide under pressure failed.

The chemistry of thymol itself has been well elaborated and no further work was done on that isomer.

TABLE II
 ISOPROPYL *m*-CRESOLS

Isomer	M.P., °C.	Oxyacetic Acid M.P., °C.	<i>p</i> -Nitrobenzoate M.P., °C.
2-Isopropyl-3-methylphenol (<i>vic</i> -Thymol) . . .	70-71	147.5-148.5	107.5-108.5
4-Isopropyl-3-methylphenol (<i>p</i> -Thymol)	112-113	128-129	143-144
5-Isopropyl-3-methylphenol (<i>sym</i> -Thymol) . .	50-50.5	87-88	87-88
6-Isopropyl-3-methylphenol (Thymol)	51.5	150	70

sym-Thymol was first described by Knoevenagel (8), who reported that it melted at 54° and formed a tribromide melting at 118°. Our preparation, from the alkylation of *m*-cresol, obtained by saponification of the *p*-nitrobenzoate, melted at 50-50.5° and formed a tribromo derivative melting at 138.5-139°. We have repeated Knoevenagel's synthesis and have found the melting point to be 50° and that of the tribromo derivative 138.5-139°. Horning (9), using Knoevenagel's procedure but with sulfur instead of bromine for dehydrogenation of the intermediate ketone found a melting point of 48-49°, and for the phenylurethan 112-113°. We were unable to prepare a nitroso derivative of *sym*-thymol.

p-Thymol has been characterized by several derivatives, including the nitration products.

The physical constants of the isopropyl *m*-cresols are listed in Table II.

Here also, as in the *o*-cresol series, the odors of the isomers become stronger as the isopropyl group moves toward the hydroxyl group. *p*-Thymol is practically odorless; *sym*-thymol has a weak odor somewhat reminiscent of thymol; *vic*-thymol has an odor intensity approximately equivalent to that of thymol but is somewhat more pungent and less aromatic than thymol.

III. FROM *p*-CRESOL

The two isomeric isopropyl *p*-cresols have been described. 2-Isopropyl-4-methylphenol was prepared by Guillaumin (2), using the Behal and Tiffenau procedure, who reported a m.p. of 36°. 3-Isopropyl-4-methylphenol is mentioned but once, in the patent literature (5) where it is reported to melt at 37°. We have repeated Schöllkopf's preparation and have obtained only the 2-isopropyl isomer. We have prepared this isomer by Guillaumin's procedure, starting from *p*-cresotinic acid, and by an independent method whereby the Grignard reagent from 2-bromo-4-methylanisole was reacted with isopropyl sulfate. Our product melted at 36-37°. The Grignard reagent from 3-bromo-4-methylanisole, when treated with isopropyl sulfate led, by an unexpected rearrangement, to the same product. However, when 3-bromo-4-methylanisole was converted by way of the 3-cyano derivative to the corresponding cresotinic acid ether and the Behal and Tiffenau sequence followed, 3-isopropyl-4-methylphenol was obtained. It melted at 39-40°.

The physical constants of the isopropyl *p*-cresols are listed in Table III.

As in the *o*- and *m*-cresol series, it is also the case in the *p*-cresol series that the closer the isopropyl group lies to the hydroxyl group the more intense is the odor.

TABLE III
 ISOPROPYL *p*-CRESOLS

Isomer	M.P., °C.	Oxyacetic Acid M.P., °C.	<i>p</i> -Nitrobenzoate M.P., °C.
2-Isopropyl-4-methylphenol.....	36-37	134-135.5	97-98
3-Isopropyl-4-methylphenol.....	39-40	151-151.5	109-110

3-Isopropyl-4-methylphenol has a mild cresylic odor while 2-isopropyl-4-methylphenol has a harsh, pungent, intensely cresylic odor which might almost be described as bitter.

EXPERIMENTAL

I. ISOPROPYL *o*-CRESOLS

Carvacrol. Spanish Origanum oil (Fritzsche Bros.) was extracted with 5% sodium hydroxide solution, the extract was washed three times with hexsol (a 65-85° petroleum ether), acidified, and the carvacrol converted to the phosphate which was recrystallized to constant m.p. (73.5-74.5°). Saponification of the latter yielded carvacrol having c.p. 3°, m.p. 3.5°, d_{25}^{25} 0.9751, n_D^{20} 1.5238.

pseudo-Carcacrol. To a mixture of 3,200 g. of aluminum chloride and 800 g. of ethylene dichloride there was added with agitation 1,728 g. of *o*-cresol (c.p. 30°), keeping the temperature at 0°. The resulting solution was cooled to -10° and 1,280 g. of isopropyl chloride was added during 1.5 hrs. at -10°. After quenching, washing and distilling there was collected a fraction (1,861 g.) boiling at 88-89°/2 mm. and having the characteristic odor of carvacrol, which could not be resolved by further fractionation into sharp-melting cuts. The semi-crystalline residue of 318 g. consisted principally of 2-methyl-3,5-d-isopropylphenol which has m.p. 74.5-75.5°. Crystallization of the above fraction from hexsol yielded 529 g. of *pseudo*-carvacrol as colorless, feathery needles of m.p. 36-36.5°.

Anal. Calc'd for C₁₆H₁₄O: C, 79.95; H, 9.39.

Found: C, 79.90; H, 9.50.

Carvacrol derivatives from carvacrol or pseudo-carcacrol. Starting from either carvacrol or *pseudo*-carvacrol, the following carvacrol derivatives were prepared: nitrosocarcacrol, m.p. 153°; thymoquinone, m.p. 44.5-45.5°; carvacroxyacetic acid, m.p. 151-151.5°; carvacryl phosphate, m.p. 73.5-74.5°; carvacryl oxalate, m.p. 63-64°; dichlorocarcacrol, m.p. 40-41°; 4-bromocarcacrol, m.p. 46°. In each case the yield was lower from *pseudo*-carvacrol.

3-Isopropyl-2-methylphenol. *A. From pseudo-carcacrol*. Upon treatment of *pseudo*-carvacrol with *p*-nitrobenzoyl chloride an oil was obtained which, after crystallizing once from ethanol and twice from hexsol yielded crystals of m.p. 113-114.5° (carvacryl *p*-nitrobenzoate prepared from carvacrol has m.p. 53-54°).

Anal. Calc'd for C₁₇H₁₇NO₄: C, 68.2; H, 5.73; N, 4.68.

Found: C, 67.8; H, 5.8; N, 4.9.

Saponification of the crystals, followed by recrystallization of the liberated phenol, yielded 3-isopropyl-2-methylphenol as colorless needles of m.p. 82-83°, having a mild phenolic odor. The oxyacetic acid derivative formed brilliant plates of m.p. 131.5-132.5°.

Although repeated crystallization of *pseudo*-carvacrol from hexsol invariably gave crystals of m.p. 36-36.5°, it was found that by inoculation of a solution with a seed of the 82-83° crystals a considerable quantity (about 13%) of the latter could be crystallized out provided the solution was allowed to crystallize statically. If the solution was agitated during cooling a heavy crop of *pseudo*-crystals precipitated out.

A comparison of the infrared absorption curves (Fig. 1) of carvacrol, 3-isopropyl-2-methylphenol, and *pseudo*-carvacrol indicated that the latter consisted of a mixture of about 75% carvacrol and 25% 3-isopropyl-2-methylphenol. A synthetic mixture in these proportions yielded, after one crystallization from hexsol, *pseudo*-carvacrol of m.p. 36-36.5°.

B. From 3-chloro-2-methylphenol. Hydrolysis of the diazonium salt of 3-chloro-2-methyl-aniline yielded 3-chloro-2-methylphenol, needles of m.p. 85–86° (from hexsol-benzene). The methyl ether, prepared in the usual manner, had m.p. –3°. Refluxing of the latter with cuprous cyanide in the presence of pyridine yielded 3-cyano-2-methylanisole, b.p. 86–87°/2.5 mm., m.p. 46–48°. Saponification of the nitrile yielded 2-methyl-3-methoxybenzoic acid, m.p. 153–155°. The methyl ester of the acid had b.p. 113°/5 mm., d_{25}^{25} 1.160, n_D^{20} 1.5300.

To a Grignard reagent prepared from 201 g. of methyl iodide, 34.5 g. of magnesium, and 400 ml. of ether there was added during 3 hrs. a solution of 102 g. of the above methyl ester in 200 ml. of ether. The reaction mixture was quenched on iced dilute hydrochloric acid, washed to neutrality, the ether was distilled off and the remainder was refluxed for 1 hr. with 220 g. of 20% alcoholic potassium hydroxide. The solution was diluted with 300 g. of water, the ethanol was distilled off, and the oil was taken up in benzene, washed to neutrality, and the solvent removed. The remaining 97 g. of crystals yielded, after crystallization from 200 g. of hexsol, 91 g. of dimethyl (2-methyl-3-methoxyphenyl)carbinol as odorless crystals of m.p. 100.5–102°.

It had been planned to dehydrate the carbinol with acetic anhydride according to the procedure of Guillaumin (2), followed by hydrogenation to the isopropyl derivative. Other work in connection with the present paper (see 4-isopropyl-2-methylphenol, A) performed previously to the present synthesis had indicated that in some cases the acetic anhydride treatment provoked a polymerization of the isopropenyl compound and that this difficulty could be avoided by direct hydrogenation of the *tert*-carbinol to the isopropylated compound. This procedure was adopted in the present case. A mixture of 90 g. of the carbinol, 200 g. of methanol, and 9 g. of copper chromite was hydrogenated in a rocking autoclave during 5 hrs. at 200° and 800 p.s.i. There was obtained on subsequent distillation 76 g. of 3-isopropyl-2-methylanisole of c.p. –1°, m.p. –0.5°, b.p. 67°/3 mm., d_{25}^{25} 0.9540, n_D^{20} 1.5148. Demethylation of the ether by refluxing in acetic acid–48% hydrobromic acid solution yielded 3-isopropyl-2-methylphenol which melted, after crystallization from hexsol, at 82–83° and was identical with the material previously isolated from *pseudo*-carvacrol.

C. From 2-bromo-6-chlorotoluene. Cuprous bromide prepared (10) from 390 g. of copper sulfate crystals was added to 265 g. of 48% hydrobromic acid. A mixture of 371 g. of 3-chloro-2-methylaniline and 2,035 g. of 26% hydrobromic acid was diazotized at 0° with 184 g. of sodium nitrite. The diazonium solution was added to the refluxing, agitated cuprous bromide solution and the whole was refluxed for 15 min. After cooling, the oil was washed with dilute sodium hydroxide and distilled to yield 457 g. of 2-bromo-6-chlorotoluene as an oil having b.p. 60°/3 mm., d_{25}^{25} 1.5720, n_D^{20} 1.5791.

Anal. Calc'd for C_7H_4BrCl : Br, 38.9; Cl, 17.3.

Found: Br, 38.9; Cl, 17.6.

This product is described definitively but once (11) and the only constant given is the b.p. (118–120°/40 mm.).

To the Grignard reagent prepared from 206 g. of 2-bromo-6-chlorotoluene was added an ether solution of 472 g. of isopropyl sulfate (12). After refluxing for 1 hr. the solution was quenched on iced dilute hydrochloric acid, the solvent was removed, and the remaining oil was refluxed for 1 hr. with 10% sodium hydroxide, steam-distilled and the oil was distilled *in vacuo*. There was collected, in addition to 43 g. of *o*-chlorotoluene, 90 g. of 2-isopropyl-6-chlorotoluene, b.p. 64°/3 mm., d_{25}^{25} 1.0210, n_D^{20} 1.5203.

A mixture of 17 g. of 2-isopropyl-6-chlorotoluene, 13.2 g. of sodium carbonate, 125 g. of water, and 0.5 g. of copper powder was heated in the copper liner of a rocking autoclave for 7 hrs. at 300–320°. From the alkaline extract of the oil there was obtained on acidification 2 g. of 3-isopropyl-2-methylphenol which, after crystallization from hexsol melted, either alone or in admixture with that prepared by the previously described procedures, at 82–83°. The alkali-insoluble portion yielded 8 g. of recovered 2-isopropyl-6-chlorotoluene.

6-Isopropyl-2-methylphenol. A. From 2-bromo-6-methylphenol. Prepared by the method of Huston and Neeley (13), 2-bromo-6-methylphenol had m.p. 16.5°. The methyl ether had

c.p. -39° , m.p. -36° , b.p. $62-63^{\circ}/3$ mm., d_{25}^{25} 1.4100, n_D^{20} 1.5472. Upon treatment of the Grignard reagent of the latter with isopropyl bromide, followed by hydrolysis, only *o*-cresol methyl ether was obtained. When isopropyl sulfate was used instead of the bromide and the previously described procedure was followed, there was obtained 6-isopropyl-2-methyl-anisole as an oil of sharp odor, b.p. $52^{\circ}/2.5$ mm., d_{25}^{25} 0.9427, n_D^{20} 1.4992. Demethylation in acetic-hydrobromic acid yielded 6-isopropyl-2-methylphenol as an oil of b.p. $76^{\circ}/3.5$ mm., d_{25}^{25} 0.9789, n_D^{20} 1.5227, having a pungent phenolic odor. Overnight heating was required to prepare the oxyacetic acid derivative, m.p. $83-84^{\circ}$. The *p*-nitrobenzoate was an oil which could not be induced to congeal.

B. From o-cresotinic acid. *o*-Cresotinic acid, m.p. $163-164^{\circ}$, was converted to the methyl ester, c.p. -1° , m.p. 0° , b.p. $79^{\circ}/2.5$ mm. The potassium salt of the ester, in methanol solution, was refluxed for 17 hrs. with an equivalent quantity of methyl iodide. The oil remaining after removal of solvent was twice washed by agitation for 1 hr. at $50-55^{\circ}$ with 5% sodium hydroxide. Subsequent distillation yielded the methyl ether of methyl *o*-cresotinate as a practically odorless oil of b.p. $86^{\circ}/2.5$ mm., d_{25}^{25} 1.1043, n_D^{20} 1.5162. An ether solution of 175 g. of the ether-ester was added to a solution of methylmagnesium iodide prepared from 345 g. of methyl iodide. Working up in the customary manner yielded 148 g. of dimethyl (3-methyl-2-methoxyphenyl)carbinol as a viscous oil of b.p. $89^{\circ}/2.5$ mm. Dehydration of the carbinol by refluxing for 16 hrs. with 296 g. of acetic anhydride yielded 124 g. of 3-isopropenyl-2-methoxytoluene, b.p. $52^{\circ}/2.5$ mm. Hydrogenation of the latter in methanol solution with Raney nickel catalyst at atmospheric pressure gave 123 g. of 6-isopropyl-2-methyl-anisole. The ether was demethylated as in *A*, and the crude phenol was taken up in Claisen's solution, washed with benzene, and the phenol was liberated and distilled to yield 97 g. of 6-isopropyl-2-methylphenol having c.p. -16.5° , m.p. -14.5° , b.p. $68^{\circ}/2.5$ mm., d_{25}^{25} 0.9782, n_D^{20} 1.5239.

4-Isopropyl-2-methylphenol. A. From 4-bromo-2-methylphenol. Methylation of 4-bromo-2-methylphenol (m.p. $63.5-64.5^{\circ}$) yielded 4-bromo-2-methylanisole of m.p. $67.5-68.5^{\circ}$ which, upon heating with cuprous cyanide and pyridine, was converted to 4-cyano-2-methylanisole, b.p. $99^{\circ}/3$ mm., m.p. $50-52^{\circ}$. Saponification of the nitrile yielded 3-methyl 4-methoxybenzoic acid, m.p. $196-197^{\circ}$, which was converted to the methyl ester, m.p. $67-68^{\circ}$. Treatment of the latter with methylmagnesium iodide yielded dimethyl (3-methyl-4-methoxyphenyl)carbinol, m.p. $41-42.5^{\circ}$, b.p. $113^{\circ}/3$ mm. Upon attempting to dehydrate the carbinol to the isopropenyl derivative an undistillable polymer was obtained. Upon hydrogenation of the carbinol (see 3-isopropyl-2-methylphenol, *B*) there was obtained 4-isopropyl-2-methylanisole, an oil having an odor reminding somewhat of safrole, b.p. $66^{\circ}/3$ mm., d_{25}^{25} 0.9377, n_D^{20} 1.5069. Demethylation in acetic-hydrobromic acid yielded 4-isopropyl-2-methylphenol as an oil having a mild, carvaerol-like odor, b.p. $83^{\circ}/3$ mm., d_{25}^{25} 0.9793, n_D^{20} 1.5253. The phenol exists in two crystalline forms: one having c.p. 8.3° , m.p. 8.6° and the other c.p. 28.3° , m.p. 28.5° . The oxyacetic acid derivative melted at $102-103^{\circ}$ and the *p*-nitrobenzoate at $80-81^{\circ}$.

B. From 2-bromo-4-isopropylphenol. *p*-Isopropylphenol (Dow Chemical Co.), m.p. $61-62.5^{\circ}$, was brominated in carbon tetrachloride solution to yield 2-bromo-4-isopropylphenol, b.p. $78-79^{\circ}/2.5$ mm., d_{25}^{25} 1.3803, n_D^{20} 1.5559. The methyl ether had b.p. $93-94^{\circ}/2.5$ mm., d_{25}^{25} 1.3204, n_D^{20} 1.5478. To the Grignard reagent prepared from 200 g. of the methyl ether and 21.7 g. of magnesium was added 270 g. of methyl sulfate. After standing overnight the mixture was quenched on iced dilute hydrochloric acid, the ether was removed, the oil was refluxed for 1 hr. with 10% sodium hydroxide, steam-distilled, and finally vacuum-distilled to yield 126 g. of 4-isopropyl-2-methylanisole, b.p. $66^{\circ}/3$ mm. Demethylation as in *A* yielded the phenol, b.p. $83^{\circ}/3$ mm., d_{25}^{25} 0.9813, n_D^{20} 1.5260, c.p. 12° , m.p. 18.5° . The *p*-nitrobenzoate melted, after successive crystallizations from hexsol and methanol, at $72.5-74^{\circ}$ and yielded after saponification phenol of c.p. 22.5° , m.p. 24° . The oxyacetic acid derivative prepared from the regenerated phenol melted at $98.5-100^{\circ}$. Thus the phenol prepared by this method was not as pure as that from Method *A*.

II. ISOPROPYL *m*-CRESOLS

vic-Thymol. This isomer may be crystallized without difficulty from the lowest-boiling fractions (about 84–87°/3.5 mm.) of the distillation of the crude alkylation product obtained by treating *m*-cresol with isopropyl ether in the presence of acid clays such as Tonsil or Filtrol at a temperature of 140–150°. It is reported (5, 6) to melt at 69°, but our material melted, after crystallization from hexsol, at 70–71°. The oxyacetic acid derivative has m.p. 147.5–148.5°. Because of its thermal instability in the presence of acids (it rearranges to a mixture of the other three isomeric isopropyl *m*-cresols) *vic*-thymol cannot be converted to the *p*-nitrobenzoate by heating with *p*-nitrobenzoyl chloride. The ester forms readily by use of the Schotten-Baumann method, and has m.p. 107.5–108.5°.

vic-Thymol nitro derivatives. To a solution of 21.4 g. of *vic*-thymol in 63 g. of acetic anhydride there was added, at –10°, a solution of 10 g. of 98% nitric acid in 30 g. of acetic acid. The 26 g. of crude crystals obtained upon quenching yielded, after crystallization from hexsol, 8 g. of 2-isopropyl-3-methyl-4-nitrophenol as brilliant yellow mica-like plates of m.p. 120–121°. From the mother liquor there was obtained, by crystallization from ethanol, 7 g. of 2-isopropyl-3-methyl-6-nitrophenol as brilliant yellow needles of m.p. 105–106°.

Anal. Calc'd for C₁₀H₁₃NO₂: C, 61.51; H, 6.70; N, 7.18.

Found (120–121°): C, 61.61; H, 6.72; N, 7.14.

Found (105–106°): C, 61.41; H, 6.75; N, 7.26.

Nitration of *vic*-thymol by addition to an excess of nitric acid in acetic acid-acetic anhydride, at 15°, yielded 2-isopropyl-3-methyl-4,6-dinitrophenol as yellow prisms of m.p. 81–82°.

Anal. Calc'd for C₁₀H₁₂N₂O₅: C, 49.98; H, 5.04; N, 11.62.

Found: C, 49.91; H, 4.99; N, 11.65.

vic-Thymol, dissolved in acetic-hydrochloric acid and treated at 0° with an aqueous sodium nitrite solution, yielded 2-isopropyl-3-methyl-4-nitrosophenol as flat yellow needles (from benzene) melting with decomposition at 176–177°.

Oxidation of the *p*-nitrosophenol by warming at 30–40° with 25% nitric acid yielded 2-isopropyl-3-methyl-4-nitrophenol of m.p. 120–121°, which confirms the structure assigned to the latter compound, since the nitroso group invariably goes to the position *para* to the phenolic hydroxyl. As a side product of the oxidation there was produced some of the dinitro derivative of m.p. 81–82°.

Treatment of the methyl ether of 2-isopropyl-3-methyl-4-nitrophenol, a yellow oil of b.p. 137°/3 mm., with Raney nickel-aluminum alloy and sodium hydroxide solution according to the procedure of Schwenk (7) gave, instead of the desired 2-methyl-3-isopropylaniline, 2-isopropyl-3-methyl-4-aminoanisole, an oil of b.p. 118°/4 mm.

Anal. Calc'd for C₁₁H₁₇NO: C, 73.70; H, 9.55; N, 7.81.

Found: C, 73.50; H, 9.35; N, 8.0.

The *N*-acetyl derivative melted at 137–138°.

Autoclaving of a mixture of 2-isopropyl-3-methyl-4-nitrophenol, 25% ammonia, and ethanol at 100° or 140° gave only unchanged starting material, while at 170° or 200° tar was produced. Treatment with phosphorus oxychloride and pyridine, or with phosphorus pentachloride gave tar. Autoclaving with 48% hydrobromic acid at 130° was ineffective, while at 190° tar was formed.

sym-Thymol. A. From 1-methyl-5-isopropyl-cyclohex-1-en-3-one. A repetition of Knoevenagel's synthesis (8) yielded *sym*-thymol of b.p. 102–103°/3.5 mm. which melted, after crystallization from hexsol, at 50°. Bromination in carbon tetrachloride solution yielded the tribromo derivative which crystallized from hexsol as small lemon-yellow prisms of m.p. 138–139° (Knoevenagel reported 118°).

Anal. Calc'd for C₁₀H₁₁Br₃O: Br, 61.9. Found: Br, 61.6.

B. From *m*-cresol. A fraction of b.p. 98–100°/2 mm. from the distillation of the crude alkylation product obtained by treating *m*-cresol with either isopropyl ether in the presence

of an acid clay or with isopropyl chloride in the presence of aluminum chloride yielded, after repeated crystallization from hexsol, *sym*-thymol as microscopic, felt-like needles of m.p. 49–50.5°. The *p*-nitrobenzoate crystallized from methanol as pale yellow plates of m.p. 87–88°. The phenol regenerated from the *p*-nitrobenzoate melted at 50–50.5°. The oxyacetic acid derivative formed pearly plates of m.p. 87–88°. The tribromo derivative melted, either alone or in admixture with that prepared according to method A, at 138.5–139°. Attempts to prepare a nitroso derivative in either acetic acid or ethanol solution gave only reddish tarry oils from which no crystals could be isolated.

p-Thymol. This isomer is readily obtained by crystallization of the residue remaining after *vic*-thymol, thymol, and *sym*-thymol have been distilled from the crude alkylated *m*-cresol mixture. Upon agitated crystallization from hexsol it forms compact, sand-like prisms, while upon static crystallization long multisided rods, frequently 10 cm. in length, are formed, m.p. 112–113°. Attempts to prepare a nitroso derivative failed, as was anticipated. The oxyacetic acid derivative melted at 128–129° and the *p*-nitrobenzoate, long pale yellow rods, at 143–144°. The methyl ether had b.p. 82°/3 mm., d_{25}^{25} 0.9477, n_D^{20} 1.5101.

Nitration of either the phenol or its methyl ether in acetic acid-acetic anhydride solution under conditions calculated to produce mononitro products led to oils which refused to congeal and which probably consisted of mixtures of the isomeric *ortho*-nitro derivatives. Nitration of the phenol with an excess of nitric acid yielded 2,6-dinitro-4-isopropyl-3-methylphenol, yellow prisms of m.p. 82–83°.

Anal. Calc'd for $C_{13}H_{12}N_2O_5$: C, 49.98; H, 5.04; N, 11.62.

Found: C, 50.16; H, 5.05; N, 11.7.

The methyl ether of the dinitrophenol, pale yellow plates, melted at 67–68°.

III. ISOPROPYL *p*-CRESOLS

2-Isopropyl-4-methylphenol. *A.* From *p*-cresotinic acid. *p*-Cresotinic acid prepared by the method of Zeltner and Landau (14), m.p. 151–152°, was converted to the methyl ester, c.p. 2°, m.p. 2.5° b.p. 83–84°/3 mm. The latter yielded, by the procedure of Guillaumin (15) methyl 2-methoxy-5-methylbenzoate, b.p. 104–105°/3 mm. Following the Behal and Tiffenau sequence the latter was converted to dimethyl (2-methoxy-5-methylphenyl)carbinol, b.p. 102°/3.5 mm., which was dehydrated to 2-isopropenyl-4-methylanisole, b.p. 78°/4 mm. Hydrogenation yielded 2-isopropyl-4-methylanisole, b.p. 62.5°/2.5 mm., and demethylation of the latter with hydrobromic acid gave 2-isopropyl-4-methylphenol, b.p. 82°/3 mm., having an intensely pungent, cresylic odor. After crystallization from hexsol it melted at 36–37°. The oxyacetic acid derivative had m.p. 134–135.5° and the *p*-nitrobenzoate m.p. 97–98°.

B. From 2-bromo-4-methylphenol. Bromination of *p*-cresol in carbon tetrachloride yielded 2-bromo-4-methylphenol, c.p. 20°, m.p. 20.5°, b.p. 67°/3 mm., which was converted to the methyl ether, c.p. 15°, m.p. 15.5°, b.p. 80°/2.5 mm. The Grignard reagent of the latter, treated with isopropyl sulfate, yielded 2-isopropyl-4-methylanisole and the latter upon demethylation gave the phenol, identical with that produced by method A.

C. By alkylation of *p*-cresol. A mixture of 540 g. of *p*-cresol, 32 g. of Tonsil, and 0.1 g. of 50% sulfuric acid was heated to 180° and, with vigorous agitation, 128 g. of isopropyl ether was added during 1.5 hrs. at 180–190°. The mixture was cooled, filtered, and distilled. The fraction boiling at 76°/2.5 mm. (120 g.) had c.p. 30°, m.p. 33°, and yielded, after crystallization from hexsol, 80 g. of 2-isopropyl-4-methylphenol of m.p. 36–37°. The oxyacetic acid derivative melted, either alone or in admixture with that from A, at 134–135°. The *p*-nitrobenzoate melted at 97–98°.

D. From *p*-nitrotoluene. 2-Bromo-4-nitrotoluene, m.p. 76–77°, from the bromination of *p*-nitrotoluene in the presence of iron, was reduced in a mixture of iron powder, water, ethanol, and hydrochloric acid to 3-bromo-4-methylaniline, c.p. 27.5°, m.p. 28°, b.p. 95°/3 mm. This procedure is simpler and better than that of Lucas and Scudder (16). Acid hydrolysis of the diazonium sulfate produced 3-bromo-4-methylphenol, feathery needles from

hexsol, m.p. 56–57°, b.p. 95°/3 mm., having a much milder odor than that of the isomeric 2-bromo-4-methylphenol. Methylation yielded 3-bromo-4-methylanisole, b.p. 75°/3 mm. Treatment of the Grignard reagent of the latter with isopropyl sulfate yielded an oil of b.p. 62–65°/2.5 mm. which, upon demethylation with hydrobromic acid, gave a phenol of c.p. 9°, m.p. 13°, b.p. 82–83°/3 mm., having the same pungent odor as the 2-isopropyl-4-methylphenol prepared by procedures A, B, or C. The oxyacetic acid derivative melted at 119–120.5°. The *p*-nitrobenzoate melted, after repeated crystallization, at 72–80°. The phenol obtained by saponification of the *p*-nitrobenzoate had c.p. 30.5°, m.p. 31.5°. Recrystallization from hexsol gave 2-isopropyl-4-methylphenol of m.p. 36–37°, unchanged upon admixture with material of the previous preparations. The oxyacetic acid derivative melted at 134–135.5°, either alone or upon admixture with previously prepared specimens. Thus an unexpected rearrangement had occurred during the Grignard reaction.

3-Isopropyl-4-methylphenol. The above-prepared 3-bromo-4-methylanisole yielded upon refluxing with cuprous cyanide in the presence of pyridine, 3-cyano-4-methylanisole, c.p. 29°, m.p. 29.5°, b.p. 97°/3 mm., d_{25}^{25} 1.0663, n_D^{20} 1.5368. Hydrolysis in 60% sulfuric acid yielded 2-methyl-5-methoxybenzoic acid, needles from benzene, m.p. 146–147°. The methyl ester was an oil of b.p. 92°/2 mm. By the Behal and Tiffenau procedure the ester was converted to dimethyl (2-methyl-5-methoxyphenyl)carbinol, a viscous oil of b.p. 118°/3.5 mm., d_{25}^{25} 1.0524, n_D^{20} 1.5337; the carbinol was dehydrated to 3-isopropenyl-4-methylanisole, b.p. 67.5°/2.5 mm., d_{25}^{25} 0.9598, n_D^{20} 1.5247, and the latter hydrogenated to 3-isopropyl-4-methylanisole, b.p. 65.5°/3 mm., d_{25}^{25} 0.9515, n_D^{20} 1.5156. Demethylation of the ether with hydrobromic acid yielded 3-isopropyl-4-methylphenol as powdery crystals (from hexsol) of m.p. 39–40°, having a very mild, cresylic odor. The oxyacetic acid derivative melted at 151–151.5° and the *p*-nitrobenzoate at 109–110°.

Acknowledgments. We are indebted to Dr. Harry Hausdorff of the Perkin-Elmer Corp. for the spectral analysis of *pseudo*-carvacrol, and to Mr. D. Johnston and the staff of the Analytical Laboratory for all other analyses.

SUMMARY

1. Of the ten possible isomeric isopropyl cresols, nine have been described in the literature. The unknown isomer, 3-isopropyl-2-methylphenol, has been synthesized and characterized.
2. The product *pseudo*-carvacrol, obtained by the Friedel-Crafts isopropylation of *o*-cresol, has been demonstrated to be a mixture of approximately 75 % of carvacrol and 25 % of 3-isopropyl-2-methylphenol.
3. One of the isomers, 3-isopropyl-4-methylphenol, which has been mentioned but once, in the patent literature and characterized only by melting point, has been synthesized and more adequately characterized.
4. The chemistry of several of the isomers has been elaborated to a limited extent.

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