The method of preparation, the occurrence of a secondary nitro grouping, and the successful execution of exactly the same reactions with the similar allyl (XV, XVI, XVII) and crotyl (XI, XVIII, XIX) compounds leave no doubt as to the structures of the *n*-butyl and *s*-butyl compounds (V and IX).

**Preparation of the Sodium Salts (VI and X) of the Nitroacetates (V and IX).**—By dissolving 0.50 g. (0.0026 mole) of V in absolute ethyl alcohol and adding 0.0026 mole of sodium ethoxide (in absolute ethyl alcohol) at room temperature, the alcohol-insoluble sodium ethyl α-nitrocaproate (VI) was precipitated. The salt was separated by centrifugation and washed several times with dry ether to give 0.38 g. (70% yield) of VI; m.p. 212–214° dec.

In exactly the same manner, 0.28 g. (0.0015 mole) of IX gave 0.21 g. (66% yield) of sodium α-nitro-β-methylvalerate (X); m.p. 231–233° dec.

**Hydrogenation of XI.**—The hydrogenation of 7.5 g. (0.029 mole) of XI dissolved in 100 ml. of acetic anhydride was conducted for three hours at room temperature and three atmospheres pressure in the presence of platinum oxide as a catalyst. Only one molar equivalent of hydrogen was absorbed under these conditions, and this was complete in less than one-half hour. The catalyst was removed by filtration, and the acetic anhydride was removed under reduced pressure. Distillation of the residue gave 5.0 g. (64% yield) of ethyl *n*-butylnitromalonate (XII); b.p. 100–104° (1 mm.), $n^{17}D$ 1.4429.

**The decarbethoxylation of XII** to ethyl α-nitrocaproate XIII was conducted in the manner previously described for the conversion of IV to V. The yield of XIII was 22%; $n^{23}D$ 1.432, $d^{23}_4$ 1.062.

When XIII was treated with sodium ethoxide as described for the conversion of V to VI, a 59% yield was obtained of sodium salt, XIV, m.p. 209–211° dec. Mixtures of XIV and VI displayed no depression of the melting point, 212–214° dec. Mixtures of XIV and X, and of VI and X, melted over the same range of 205–215°.

**Acknowledgments.**—Ethyl *n*-butylmalonate was obtained through the courtesy of Professor R. T. Morrison. The analyses were done in the Microchemical Laboratory of New York University by Dr. W. C. Woodland and Dr. T. S. Ma, who supervised the laboratory, and by their assistants, Dr. E. V. Piel, Dr. H. J. Stolten, Mr. J. D. McKinley, Jr., Mr. R. H. Hansen and Mr. Paul Pemsler.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE RESEARCH AND DEVELOPMENT LABORATORIES, UNIVERSAL OIL PRODUCTS COMPANY]

# The Butylation of Guaiacol

BY R. H. ROSENWALD

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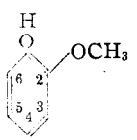
This paper establishes the course of the reaction in the butylation of guaiacol with *t*-butyl alcohol in the presence of 85% phosphoric acid as to the positions occupied by the entering *t*-butyl group. From the *t*-butylguaiacols thus obtained, three of the possible four position isomers were isolated and identified. The reaction product consists of equal amounts of 4- and 5-*t*-butylguaiacol with about 10 mole per cent. of 6-*t*-butylguaiacol. In this case, the directive influences of the hydroxy and methoxy functions are of equal strength in regard to substitution in the para positions.

In the course of preparation of alkylphenols to be evaluated as antioxidants, a procedure often employed is the butylation of a selected phenol to give a derivative with the butyl group in a position ortho or para to the hydroxyl group. The ease of alkylation and the orientation of the entering substituent can be considered as due to the activating effects of the hydroxyl group. The inability to place a *t*-butyl group in a position meta to the hydroxyl by direct alkylation[1] can be considered as evidence of this strong directive effect.

It is of interest to examine the alkylation product in the case of guaiacol, for in this compound the strong directive effect of the methoxy group competes with the directive effect of the hydroxyl group.[2–4] Regardless which one of the four available positions is occupied by the entering butyl group, the alkylation reaction must involve substitution meta to either the hydroxy or methoxy group.




This paper establishes the course of reaction in the butylation of guaiacol as to the positions occupied by the entering groups. As shown in the first two runs of Table I, guaiacol was alkylated with *t*-butyl alcohol in the presence of 85% phosphoric acid to give, in good yield, a mixture of *t*-butylguaiacols. From the mixture thus obtained, three individual compounds of the possible four were identified in amounts as indicated in Table I. The alkylation product consists of approximately equal quantities of 4- and 5-*t*-butylguaiacol with about 10 mole per cent. of 6-*t*-butylguaiacol. These results indicate that the directive influences of the hydroxy and methoxy functions are of equal strength in regard to substitution in the para position. The lack of substitution in the 3-position, ortho to the methoxy group, can be attributed to the more pronounced steric effect of this group in comparison to the steric effect of the hydroxyl group. The bulk of the methoxy group is sufficient to hinder the attack on the adjacent position by a large *t*-butyl cation.

This observation as to the comparable directive effects of the hydroxy and methoxy functions was not entirely expected. It is generally considered that the hydroxy group possesses a more powerful directive effect than methoxy.[5] This fact is evident in the nitration[6] and in the bromination of guaiacol[7] in which cases substitution in the 4- and 6-positions is realized. However, in the sulfonation of guaiacol, a mixture containing about equal amounts of the 4- and 5-sulfonic acids is obtained.[8] On the basis of strong directive effect of the hydroxy

(1) R. S. Bowman and D. Stevens, *J. Org. Chem.*, **15**, 1172 (1950).
(2) R. Q. Brewster and H. Choguill, THIS JOURNAL, **61**, 2702 (1939).
(3) T. Lea and R. Robinson, *J. Chem. Soc.*, 411 (1926).
(4) P. B. D. de la Mare and C. A. Vernon, *ibid.*, 1764 (1951).
(5) R. C. Fuson, "Advanced Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 282.
(6) A. Klemenc, *Monatsh.*, **33**, 701 (1912).
(7) P. Robertson, *J. Chem. Soc.*, **93**, 788 (1908).
(8) A. Rising, *Ber.*, **39**, 3685 (1906).

TABLE I

| Reaction conditions: Temp., °C. | Time of alcohol addition, min. | Time of stirring min. | Charge, wt. g.: Guaiacol | t-Butyl alcohol | Phosphoric acid | Concn. of acid wt. % $H_3PO_4$ | Wt. crude product, g. | Composition of product, mole %: Guaiacol | 4-t-Butylguaiacol | 5-t-Butylguaiacol | 6-t-Butylguaiacol |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 68–72 | 45 | 15 | 372 | 246 | 1500 | 85 | 497 | 4 | 46 | 41 | 9 |
| 73–76 | 40 | 15 | 248 | 163 | 1000 | 85 | 358 | .. | 46.5 | 43 | 10.5 |
| 42–43 | 11 | 15 | 31 | 18.5 | 250 | 85 | 41.0 | 24 | 31 | 33 | 12 |
| 72 | 13 | 13 | 31 | 18.5 | 250 | 70 | 30 | 77.5 | 10 | 8.5 | 4 |
| 74–75 | 4 | 5 | 31 | 18.5 | 200 | 100 | 32.6 | 60 | 19 | 20 | 1 |

TABLE II

| Compound | M.p., °C. | B.p., °C. | Mm. | Formula | Analyses, wt. %: Calcd. C | Calcd. H | Found C | Found H |
|---|---|---|---|---|---|---|---|---|
| 4-t-Butylguaiacol | 50–51 | 123–125 | 12 | $C_{11}H_{16}O_2$ | 73.30 | 8.95 | 73.34 | 8.92 |
| 5-t-Butylguaiacol | 22–23 | 91 | 0.9 | $C_{11}H_{16}O_2$ | 73.30 | 8.95 | 73.30 | 9.02 |
| 6-t-Butylguaiacol | 31–32 | 115 | 10 | $C_{11}H_{16}O_2$ | 73.30 | 8.95 | 73.61 | 9.07 |
| 3-t-Butylveratrole | −15 | 90 | 5 | $C_{12}H_{18}O_2$ | 74.19 | 9.34 | 74.47 | 9.42 |
| 4-t-Butylveratrole | 36–37 | ..... | .. | $C_{12}H_{18}O_2$ | 74.19 | 9.34 | 74.04 | 9.30 |
| 4-Bromo-6-t-butylguaiacol | 42–43 | ..... | .. | $C_{11}H_{15}O_2Br$ | 50.98 | 5.83 | 51.02 | 6.04 |
| 2-Methoxy-4-t-butylphenyl benzyl ether | 33–34 | ..... | .. | $C_{18}H_{22}O_2$ | 79.96 | 8.20 | 79.94 | 7.93 |
| Phenylurethan derivative of -guaiacol | 158–158.5[b] | ..... | .. | $C_{14}H_{13}O_3N$ | 69.12 | 5.39 | 69.62 | 5.42 |
| 4-t-Butyl- | 138–138.5[a] | ..... | .. | $C_{18}H_{21}O_3N$ | 72.21 | 7.07 | 72.60 | 7.06 |
| 5-t-Butyl- | 127.5–128[a] | ..... | .. | $C_{18}H_{21}O_3N$ | 72.21 | 7.07 | 72.66 | 6.95 |
| 6-t-Butyl- | 181–183[b] | ..... | .. | $C_{18}H_{21}O_3N$ | 72.21 | 7.07 | 72.60 | 7.04 |

[a] Crystallized from benzene–ligroin. [b] Crystallized from methanol.

group, the butylation of guaiacol has been considered as involving only the 4-position.[9]

These observations indicate a variance under certain conditions as to the comparative directive effects of the two functions under consideration. Of fundamental difference in these two functions is the ability of the hydroxy group to ionize and form a phenate anion, which is indeed a reactive species as to attack by electrophilic reagents. However, in acid media, such as sulfuric acid or phosphoric acid, formation of the phenate ion is repressed, and the activating influences are those of the hydroxy and methoxy groups which are similar in character. The structure of the product is dependent to a large extent on the electronic effects of the substituents, not only in the positions ortho and para to each substituent, but also on the meta positions.[10]

The results as obtained in runs 1 and 2 are not the result of some peculiarity of the reaction conditions. As shown in the last three runs in Table I, such factors as lowering reaction temperature to 42–43°, reducing acid concentration to 70%, or increasing acid concentration to 100%, did not fundamentally alter the course of the reaction. The extent of alkylation was greatly varied, but the relative amounts of the 4 and 5 butyl isomers were unchanged. The relative amounts of 6-t-butylguaiacol formed did vary noticeably; low acid concentration favored its formation; high acid concentration repressed its formation.

The results obtained cannot be ascribed to any rearrangement of the butyl group in the presence of 85% phosphoric acid. It was found that 4-, 5- and 6-t-butylguaiacol at 75° did not rearrange in the presence of the acid. The isomers as isolated are the result of a substitution process and not a rearrangement.

The structures of these three butyl isomers were established by independent syntheses as shown.

The presence of each of these three compounds in the alkylation product was established by isolation of the compound or its derivative and comparison with synthetic samples. Quantitative analyses of the reaction products were carried out by infrared spectroscopic procedures. For reference purposes spectra of guaiacol and its t-butyl derivatives are given in Figs. 1 to 4.

## Experimental[11]

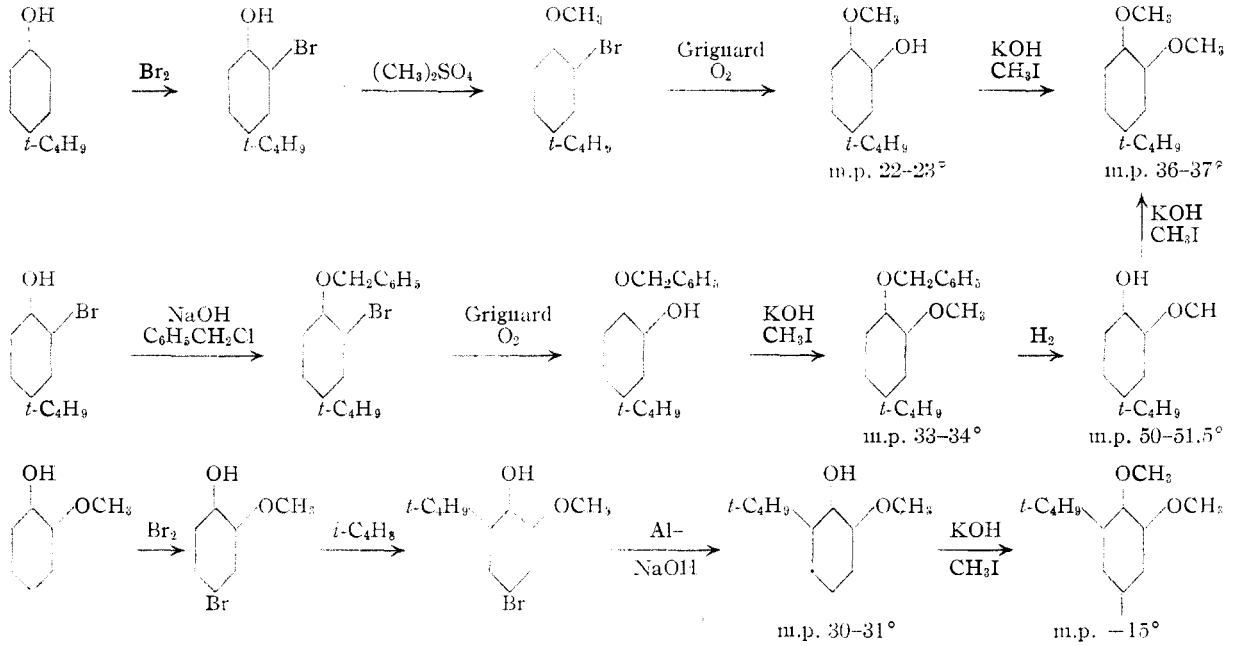
Guaiacol was obtained from Cliffs Dow Chemical Company, Marquette, Michigan.

**Alkylation of Guaiacol. A. Large-Sized Run.**—To a well-stirred emulsion of guaiacol (372 g.) and 85% phosphoric acid (1500 g.) in a 3-liter flask, 246 g. of t-butyl alcohol was added under conditions as listed in the first run of Table I. The reaction product was dissolved in one liter of petroleum ether and the following extractions were made to effect partial separation of the products. (a) The petroleum ether solution was successively extracted with a 3% solution of sodium hydroxide (400 and 1200 ml.). A heavy precipitate formed from which was obtained, after acidification, 148.6 g. of distillable product (b.p. 123–125° (12 mm.)). This material was composed of 4-t-butylguaiacol (96%) and 5-t-butylguaiacol (4%). Crystallization from pentane gave pure 4-t-butylguaiacol, m.p. 50–51.5°. The oil obtained upon acidification of the aqueous caustic solution was distilled to yield a crude mixture of guaiacol, 4- and 5-t-butylguaiacol (271.0 g., b.p. 88–125°) (10 mm.)). (b) The petroleum ether solution was extracted with 400 ml. of a 10% solution of sodium hydroxide to give 5.3 g. of phenolic material. (c) The petroleum ether solution was extracted four times with 100 ml. of Claisen solution (1 part of potassium hydroxide, 1 part of water, 2 parts of methanol). Distillation of the caustic soluble material which separated on acidification gave 50.5 g. of product, b.p. 114–117° (10 mm.), essentially all at 115°. This material, m.p. 30–31° after crystallization from pentane, is the 6-t-butylguaiacol isomer which possesses a de-

(9) Ng. Ph. Buu-Hoï, H. Le Bihan, F. Binon and Ng. Xuong, *J. Org. Chem.*, **16**, 988 (1951).

(10) C. Ingold and F. Shaw, *J. Chem. Soc.*, 2918 (1927).

(11) All melting and boiling points are uncorrected.




creased solubility in aqueous caustic due to the steric effect of the *t*-butyl group adjacent to the hydroxy function.

Infrared inspection of the phenolic materials from (a) and (c) determined the amounts of guaiacol and the three butyl isomers present, the values for which are presented in the first run of Table I. The preparation of phenylurethan derivatives likewise established the presence of the various isomers.

B. **Small-Sized Runs.**—The product from the small-sized runs (31 g. of guaiacol) was isolated by extraction with petroleum ether, followed by inspection as to composition by infrared.

**Attempted Rearrangement.**—Three grams of 4-, 5- or 6-*t*-butylguaiacol was contacted with vigorous stirring with 15 g. of 85% phosphoric acid for a period of one hour at a temperature of 75°. In each case, the recovered material was identified by infrared, and by melting point whenever possible, as unchanged starting material.

**Synthesis of 5-*t*-Butylguaiacol.**[12]—To a stirred solution of *p*-*t*-butylphenol (150 g.) in chloroform (250 ml.) and carbon tetrachloride (250 ml.) was added, at a temperature of 3 ± 2°, 160 g. of bromine dissolved in 200 ml. of chloroform. After evaporation of the solvent, the product was distilled over sodium carbonate to give 214 g. (97%) of 2-bromo-4-*t*-butylphenol, b.p. 113° (9 mm.).

*Anal.* Calcd. for $C_{10}H_{13}OBr$: Br, 34.86. Found: Br, 34.7.

The above phenol (76 g.) was methylated in aqueous solution with dimethyl sulfate to give 63.9 g. (66% yield) of 2-bromo-4-*t*-butylanisole, b.p. 101–103° (1 mm.).

*Anal.* Calcd. for $C_{11}H_{15}OBr$: Br, 32.87. Found: Br, 32.3.

The above bromide was converted to the corresponding phenol by the oxidation of the Grignard solution in the presence of isopropylmagnesium bromide.[13] This oxidation gave a 42% yield of 5-*t*-butylguaiacol, b.p. 91° (0.9 mm.). Crystallization from pentane at low temperature gave a solid of melting point 22–23°. This compound was characterized by infrared inspection, and by preparation of phenylurethan derivative which was found identical to that isolated from (a) as described in the alkylation experiment.

**Synthesis of 4-*t*-Butylguaiacol.**—Benzyl chloride (76 g.) was added to a stirred mixture, boiling under reflux, of 2-bromo-4-*t*-butylphenol (115 g.), 250 ml. of ethyl alcohol and a solution of sodium hydroxide (35 g. in 100 g. of water). The benzyl chloride was added over a period of 20 minutes, followed by 3 hours of stirring. The caustic insoluble product gave 125.9 g. (80%) of 2-bromo-4-*t*-butylphenyl benzyl ether, b.p. 160–162° (0.6 mm.).

*Anal.* Calcd. for $C_{17}H_{19}OBr$: Br, 25.03. Found: Br, 24.3.

This bromo compound was converted to the corresponding phenol by oxidation of the Grignard reagent. The product from 55.3 g. of 2-bromo-4-*t*-butylphenyl benzyl ether gave, upon extraction with Claisen solution, 57 g. (64%) of an insoluble potassium salt. The potassium salt was methylated with methyl iodide in methanol to give 41.8 g. of 2-methoxy-4-*t*-butylphenyl benzyl ether, m.p. 33–34° after crystallization from pentane.

2-Methoxy-4-*t*-butylphenyl benzyl ether (27 g.) was hydrogenated in pentane for two hours in the presence of 3 g. of nickel-on-kieselguhr catalyst at 20° and 35 atmospheres of hydrogen pressure. Upon contacting the pentane solution with a 10% solution of sodium hydroxide, an insoluble sodium salt formed from which was obtained 6.5 g. of 4-*t*-butylguaiacol, m.p. 50–51°. This product was identical on basis of melting point, infrared spectra and phenylmethane derivative with the compound isolated from (a) in the alkylation experiment.

**Synthesis of 6-*t*-Butylguaiacol.**—4-Bromoguaiacol (b.p. 133° (16 mm.), m.p. 36–37°[14]) was obtained by the bromination of guaiacol. 4-Bromoguaiacol (119 g.) was butylated at 60° with 2-methylpropene in the presence of boron trifluoride etherate (118 g.). Extraction of the reaction product in pentane with a 10% solution of sodium hydroxide removed unreacted bromoguaiacol, and extraction with Claisen solution gave 28.4 g. of 4-bromo-6-*t*-butylphenol. Crystallization from pentane gave 21.4 g. of pure product, m.p. 41–43°. The same compound was prepared by the bromination of 6-*t*-butylguaiacol as obtained in the butylation of guaiacol (fraction c).

Using the method of Hart, 4-bromo-6-*t*-butylguaiacol was debrominated with Al–Ni alloy in the presence of caustic.[15] The 6-*t*-butylguaiacol thus obtained in 70% yield possessed a melting point of 31–32° and was found identical in all respects to the product isolated from the alkylation of guaiacol.

**4-*t*-Butylveratrole.**—The identity of 4- and 5-*t*-butylguaiacol was further verified by methylation with methyl iodide to 4-*t*-butylveratrole, m.p. 36–37°. Methylation of the butylguaiacols obtained in fraction (a) of the alkylation experiment gave uncontaminated 4-*t*-butylveratrole, thereby indicating the absence of 3-*t*-butylguaiacol in the reaction mixture.

**3-*t*-Butylveratrole.**—The methylation of 6-*t*-butylguaiacol with methyl iodide gave a 61% yield of 3-*t*-butylveratrole, b.p. 90° (5 mm.), m.p. −15°.

(12) In spite of a number of attempts, 5-*t*-butylguaiacol could not be prepared by the diazotization of 2-amino-4-*t*-butylanisole and replacement of the diazo function by a hydroxyl group.

(13) M. Kharasch and W. Reynolds, THIS JOURNAL, **65**, 501 (1943).

(14) Literature reports a value of 45–46°: F. Hoffman-La Roche and Cie. Basel German Patent 105,052; *Chem. Zentr.*, **70**, 1079 (1899).

(15) H. Hart, THIS JOURNAL, **71**, 1966 (1949).

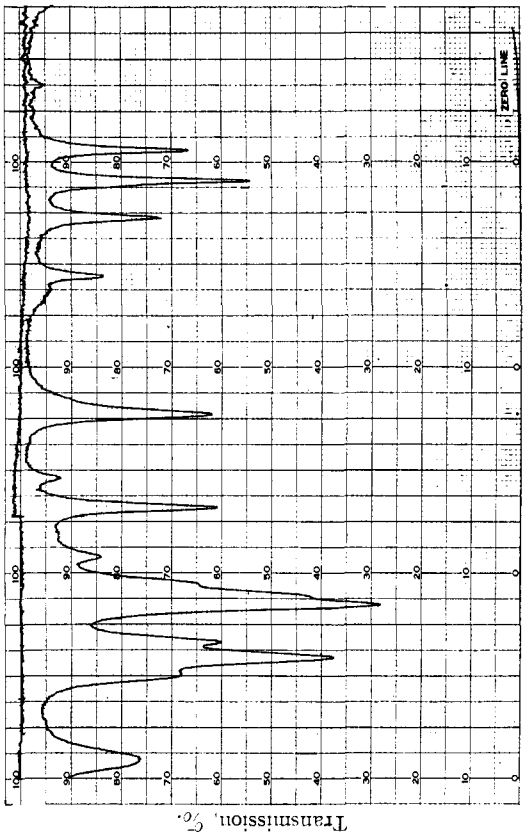



Fig. 2.—4-*t*-Butylguaiacol, 10.04 g./l. in $CS_2$, 0.213 mm.: 100% line, $CS_2$, 0.213 mm.; ref. beam, $CS_2$, 0.210 mm.

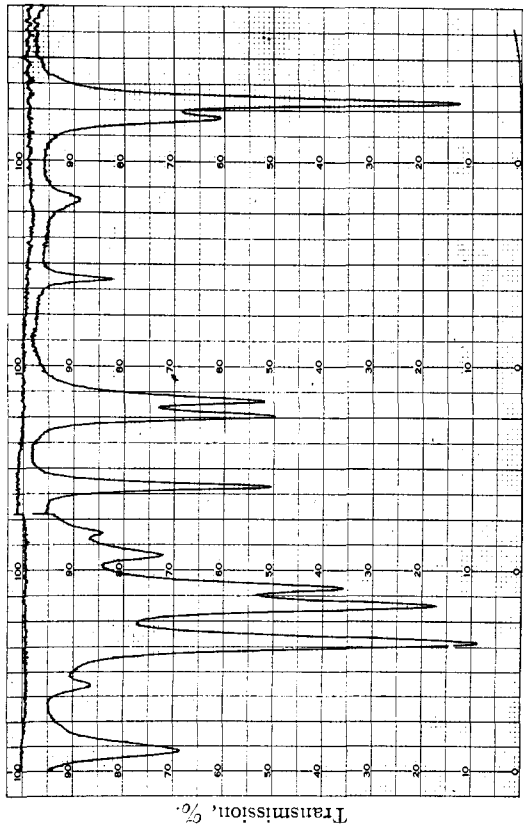



Fig. 1.—Guaiacol, 10.43 g./l. in $CS_2$, 0.213 mm.: 100% line, $CS_2$, 0.213 mm.; ref. beam, $CS_2$, 0.210 mm.

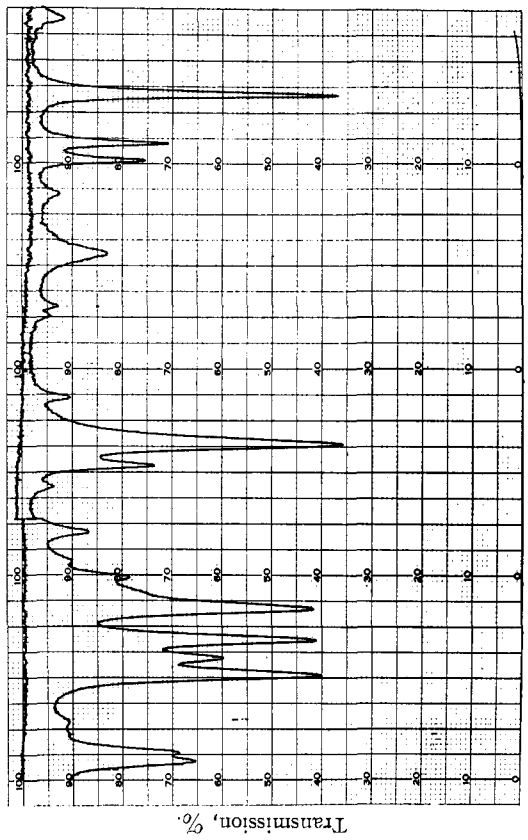



Fig. 4.—6-*t*-Butylguaiacol, 10.52 g./l. in $CS_2$, 0.213 mm.: 100% line, $CS_2$, 0.213 mm.; ref. beam, $CS_2$, 0.210 mm.

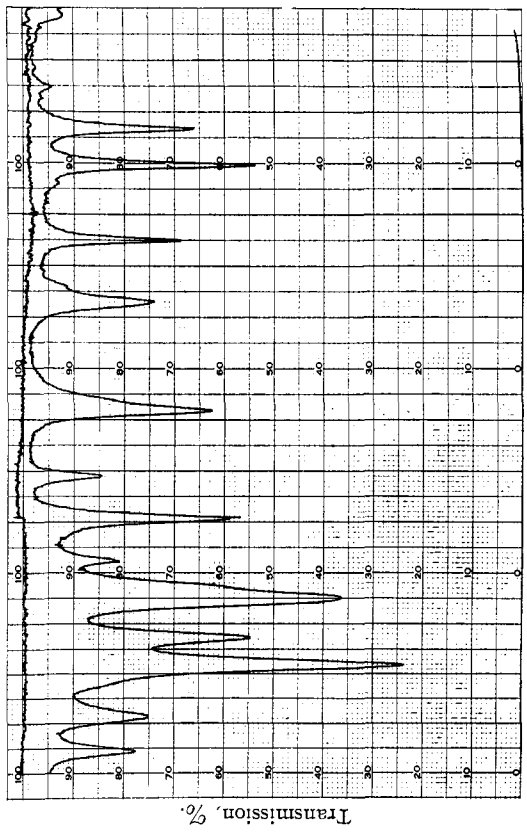



Fig. 3.—5-*t*-Butylguaiacol, 10.09 g./l. in $CS_2$, 0.213 mm.: 100% line, $CS_2$, 0.213 mm.; ref. beam, $CS_2$, 0.210 mm.

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