material was essentially that of diethyl carbonate; v.p.c. analysis confirmed the presence of diethyl carbonate by a peak of retention time 0.4 (13%) min. However the following peaks also were present, 1.5 (1%), 2.4 (11%), 3.3 (53%), 3.7 (1%), 4.7 (15%), 6.3 (1%), 7.3 (3%), and 8.0 (1%) min.

Sodium Borohydride Reduction of 2,2-Dicarbethoxycyclopentanone.[18]—2,2-Dicarbethoxycyclopentanone (8 g., 0.035 mole) was added dropwise with stirring to 2.6 g. (0.07 mole) of sodium borohydride in 250 ml. of absolute ethanol and the mixture was stirred for 24 hr. at room temperature. Dilute hydrochloric acid (1 l.) was added and the aqueous solution was extracted with ether. The ether extract was washed with sodium carbonate solution, dried over sodium sulfate, and the ether was distilled to yield 0.85 g. of product. The infrared spectrum of this material was not at all similar to diethyl carbonate and no peak in the v.p.c. corresponding in retention time to this compound was observed. Peaks of retention times of 4.5 (11%), 6.2 (10%), 7.9 (74%), and 8.3 (5%) min. were observed.

Attempted Thermal Rearrangement of the Acylation Products.—One-milliliter samples of the acylation products of 2-carbethoxycyclopentanone, 2-carbethoxycyclohexanone, and 2-carbethoxycycloheptanone were heated in sealed tubes at 200° for 30 min. V.p.c. and infrared analysis indicated no rearrangement took place.

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Highly Substituted Aromatics. The Synthesis and Nuclear Magnetic Resonance Spectrum of 2,4,6-Tri-*t*-butyl-3-fluorophenol[1]

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The low steric requirements of the fluoro substituent allow the insertion of a *t*-butyl group in the 2-position of 3-fluorophenol, as evidenced by the preparation of the title compound. The n.m.r. spectra of this material and some analogs were used for structure proof; long-range H–F spin–spin coupling between the protons of the 2- and 4-*t*-butyl groups and the adjacent fluorine was observed.

The large steric requirement of the *t*-butyl group has been the subject of a great deal of experimental and theoretical chemistry. The bulk effect of this substituent may be used to advantage or it may be the source of extreme synthetic difficulties. The latter are exemplified in the recent syntheses of *o*-di-*t*-butylbenzenes.[2] The strain energy involved in these systems, demonstrated by the apparent distortion of the benzene ring,[2a] supports Brown's earlier suggestion that these compounds are not to be expected from Friedel–Crafts type alkylation reactions.[3]

Extending the question of *ortho* steric effects of the *t*-butyl group, it is noted that innumerable compounds have been prepared by classical aromatic substitution methods which bear one substituent *ortho* to the bulky group.[4] In contrast, very few materials are known in which the *t*-butyl substituent is flanked by two groups other than hydrogen. Among these compounds are the "synthetic musks," in which both *ortho* groups are nitro.[5] Nitration appears generally to be less susceptible to bulk effects than many other electrophilic substitution reactions.[6] Kaeding[7] recently has prepared 4,6-dibromo-2-chloro-3-*t*-butylphenol. This compound, in which the *t*-butyl group is adjacent to bromine and chlorine, represents an extreme for halogenation.

In these examples the *ortho* groups were added after formation of a suitable *t*-butylbenzene derivative. The converse production of highly substituted aromatic *via* *t*-butylation was the object of the present study. The literature contains three reports of di-*ortho*-substituted *t*-butylbenzenes presumably prepared by direct alkylation. Katsui and Kuyama are quoted[8] as having examined the effect of 2,4-di-*t*-butylresorcinol on stabilization of vitamin A; the original literature indicates that the compound in question is the 4,6-derivative, instead, and that an error in translation is involved.

Dacre[9] has reported the preparation of 3,5-di-*t*-butyl-2,4-dihydroxytoluene from 2,4-dihydroxytoluene, but the only structure proof given was an acceptable carbon and hydrogen analysis. This, of course, would be identical for an isomeric O-butylated product, which is more likely the correct structure.[10]

Using the aluminum phenoxide-catalyzed alkylation reaction, which is noted for preferential *ortho* substitution,[11] Stroh, Seydel, and Hahn have reported the formation of 2,6-di-*t*-butyl-3-methylphenol from *m*-cresol.[12] However, it was subsequently shown that no substitution had taken place in the hindered *ortho* position and that the product was in reality 2,4-di-*t*-butyl-5-methylphenol.[13] Thus there are no clear-cut examples in the literature in which a *t*-butyl group has

(1) Work done in part at the University of California, Berkeley, Calif.

(2) (a) A. W. Burgstahler and M. O. Abdel-Rahman, *J. Am. Chem. Soc.*, **85**, 173 (1963); (b) L. R. C. Barclay, C. E. Milligan, and N. D. Hall, *Can. J. Chem.*, **40**, 1664 (1962); (c) E. M. Arnett, M. E. Strem and R. A. Friedel, *Tetrahedron Letters*, 658 (1961); (d) C. Hoogzand and W. Hübel, *ibid.*, 637 (1961).

(3) H. C. Brown and K. L. Nelson, *J. Am. Chem. Soc.*, **75**, 24 (1953).

(4) For a summary of the pertinent information, see G. S. Hammond and M. F. Hawthorne, "Steric Effects in Organic Chemistry," M. S. Newman, Ed., John Wiley and Sons, Inc., New York, N. Y., 1956, Chap. 3.

(5) R. J. W. LeFevre, *J. Chem. Soc.*, 977 (1933).

(6) (a) P. D. Bartlett, M. Roha, and R. M. Stiles, *J. Am. Chem. Soc.*, **76**, 2349 (1954); (b) W. Rundel, *Ber.*, **96**, 636 (1963); (c) K. Ley and E. Müller, *ibid.*, **89**, 1402 (1956).

(7) W. W. Kaeding, *J. Org. Chem.*, **26**, 4851 (1961).

(8) G. Katsui and H. Kuyama, *Vitamins* (Kyoto), **5**, 342 (1952); *Chem. Abstr.*, **47**, 8316.

(9) J. C. Dacre, *Biochem. J.*, **78**, 758 (1961).

(10) Resorcinol itself gives a complex mixture of products under these reaction conditions. Although these have not been completely identified, some are definitely ethereal (unpublished results).

(11) (a) A. J. Kolka, J. P. Napolitano, and G. G. Ecke, *J. Org. Chem.*, **21**, 712 (1956); (b) A. J. Kolka, J. P. Napolitano, A. H. Filbey, and G. G. Ecke, *ibid.*, **22**, 642 (1957).

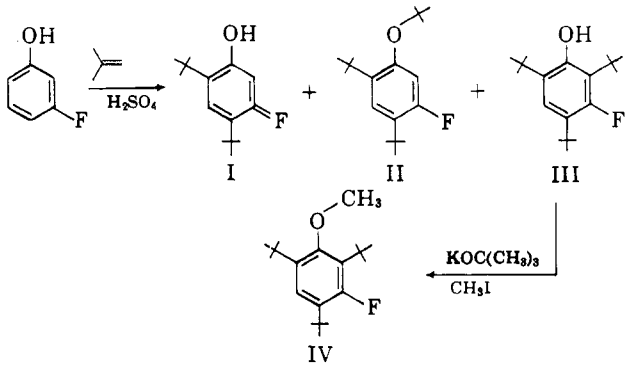
(12) R. Stroh, R. Seydel, and W. Hahn, *Angew. Chem.*, **69**, 699 (1957).

(13) R. Stroh, personal communication; see also R. Stroh, R. Seydel, and W. Hahn, "Neuer Methoden der Präparativen Organischen Chemie," Band II, Verlag Chemie, Weinheim, 1960, p. 231.

been directly substituted between two groups on an aromatic ring.[14]

A number of sources of the *t*-butyl group are available and have been used in Friedel–Crafts alkylation. Isobutylene undergoes a rapid reaction (acid-catalyzed) with phenol to give in high yield 2,4,6-tri-*t*-butylphenol.[15] Highly substituted phenols of this type have been explored extensively, mainly because of their effectiveness as antioxidants.[16,17] Bowman and Stevens[18] pointed up the large steric requirements of the butylation reaction when they observed the complete lack of reaction of 3,5-dimethylphenol.

In our hands, butylation failed to give reaction at the hindered *ortho* position (between hydroxyl and *meta* substituent) of *m*-cresol, *m*-chlorophenol, and 3,4-xylenol.[19] The small van der Waals radius of fluorine suggested that it might be suitable as a *meta* substituent,[20] and this was indeed found to be the case. *m*-Fluorophenol, as a neat liquid containing a small amount of concentrated sulfuric acid, undergoes vigorous reaction with isobutylene to yield principally the three products shown (I–III). Methylation gave the anisole derivative IV of the very hindered phenol III.[21]



A fourth product was obtained in small yield during the butylation procedure; this material could be made to predominate by prolonged treatment at higher temperatures. Its structure has not as yet been determined.[22]

Of primary interest from our standpoint is the formation of the highly substituted 2,4,6-tri-*t*-butyl-3-fluorophenol (III). The formation of this material adds a third class to the two already known in which the bulky alkyl group is flanked by two groups other than hydrogen, and further represents the first preparation of such a compound by direct *t*-butylation.[23] The yield of this material was quite sensitive to temperature changes; at 0° the rate of formation of III was prohibitively slow, while at 80° the equilibrium amount of this product was quite small. Optimum conditions were determined at approximately 45°, where the yield of 2,4,6-tri-*t*-butyl-3-fluorophenol increased steadily for approximately three hours, after which an equally steady decline was noted. The exact course of the reaction has not been determined, but it has been demonstrated that the over-all yield in terms of the four products noted previously is essentially quantitative. The decrease in III appears to be associated with the formation of the as yet unidentified fourth product.[22]

The *t*-butyl ether (II) of 2,4-di-*t*-butyl-5-fluorophenol is formed very rapidly and then decreases with increasing time. At the point where III is maximized, the yield of ether has been substantially diminished.[24] We have not as yet demonstrated whether I or II is the direct precursor of the tri-*t*-butylphenol (III), although it is tempting to speculate on an intramolecular rearrangement of the ether. The formation of products such as the *t*-butyl ether (II) appears to be possible only because the O-alkyl group is able to swing away from the bulky *ortho* substituent. Anisole itself, for instance, undergoes rapid *t*-butylation to give 2,4-di-*t*-butylanisole, with no evidence of the trialkylated product.[25]

The variation in the yield of 2,4,6-tri-*t*-butyl-3-fluorophenol stresses the fact that the *m*-fluoro group is indeed borderline between hydrogen (high yield by rapid reaction) and chlorine (no trialkylated product) for the butylation reaction. Under optimum conditions the yields obtained were I, 32%; II, 21%; and III, 25%.

The n.m.r. spectra of these materials, besides proving invaluable for structure determinations in this study, show interesting and clear-cut cases of long-range H–F spin–spin coupling. The data are shown in Table I. A number of examples of long-range hydrogen–fluorine nuclear magnetic interactions are found in the literature.[26] The mechanism of the transmission of these effects is still open to question. Spatial proximity[26b] and required bond geometry[26a] have both been stressed.

In the present case we note an essentially invariant H–F spin-coupling constant between 3-fluorine and the protons of the 4-*t*-butyl group (1 c.p.s.), irrespective of the other ring substituents. The 2-*t*-butyl group, in

(14) R. A. Benkeser, R. F. Grossman, and F. S. Clark [*J. Org. Chem.*, **27**, 3728 (1962)] have demonstrated that 2,3,5-trimethylphenol is not tritylated by triphenylcarbinol and sulfuric acid as reported previously by N. P. Buu-Hoi and R. Rips [*ibid.*, **22**, 666 (1957)]. This lack of reaction is in agreement with the available data in the literature and the results of the present study.

(15) G. H. Stillson, D. W. Sawyer, and C. K. Hunt, *J. Am. Chem. Soc.*, **67**, 303 (1945).

(16) For an excellent discussion, see G. Scott, *Chem. Ind.* (London), 271 (1963).

(17) The preferred catalyst for the butylation reaction is still an open question, and one which is being actively investigated by many workers. V. N. Ipatieff, H. Pines, and B. S. Friedman [*J. Am. Chem. Soc.*, **60**, 1495 (1938)] found phosphoric acid at 100° to give mainly 4-*t*-butyl- and 2,4-di-*t*-butylphenol. More recently, E. V. Alisova and S. V. Zavgorodnii [*Zh. Obshch. Khim.*, **32**, 3502 (1962)] have used mixed boron trifluoride–phosphoric acid in the alkylation reaction and found it to be an effective catalyst. In our hands, sulfuric acid gave quite reproducible results and was used exclusively in this study.

(18) R. S. Bowman and D. R. Stevens, *J. Org. Chem.*, **15**, 1172 (1950).

(19) Unpublished results with Denes Turcsanyi.

(20) F = 1.4 Å. (H = 1.2 Å., Cl = 1.8 Å.): E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, New York, N. Y., 1959, p. 51. As can be seen from the discussion in this reference, the van der Waals radius is not a particularly meaningful number for comparing bulk effects in a reaction such as aromatic substitution, since the electrophile comes nowhere near the distended cloud of the substituent. Hence these values are noted only as a point of departure.

(21) Methylation is the only satisfactory O-alkylation reaction that has been investigated for 2,6-di-*t*-butylphenols: see Experimental section and N. Kornblum and R. Seltzer, *J. Am. Chem. Soc.*, **83**, 3668 (1961).

(22) One interesting possibility which has been ruled out by n.m.r. is the *t*-butyl ether of III. Work is continuing to elucidate the nature of this material.

(23) One interesting exception is 2,4,6-tri-*t*-butylphenol-3-*d*, prepared by E. Muller, A. Rieker, and K. Scheffler, *Ann.*, **645**, 92 (1961), for e.p.r. studies.

(24) Acid-catalyzed and thermal decompositions and rearrangements of alkyl phenyl ethers are well known: (a) R. S. Bowman, D. R. Stevens, and W. E. Baldwin, *J. Am. Chem. Soc.*, **79**, 87 (1957); (b) R. A. Smith, *ibid.*, **54**, 1068 (1932); **53**, 272 (1931).

(25) Unpublished results with A. A. Thelen.

(26) (a) A. D. Cross and P. W. Landis, *J. Am. Chem. Soc.*, **84**, 3784 (1962); **84**, 1736 (1962); (b) M. Takahashi, D. R. Davis, and J. D. Roberts, *ibid.*, **84**, 2935 (1962).

TABLE I

NUCLEAR MAGNETIC RESONANCE DATA

Compound	Group position[a] and absorption, p.p.m.[b] 2-t-Butyl	4-t-Butyl	6-t-Butyl	O-Alkyl	2-Proton	6-Proton
I		1.35 (1.0)	1.40		6.35(13)	7.20 (9.5)
II		1.35 (~1)[c]	1.36	1.54	6.70(15)	7.18 (10)
III	1.58 (2.9)	1.37 (1.1)	1.42			7.10 (9)
IV	1.51 (1.5)	1.35 (1.0)	1.40	3.60		7.09 (10)
2,4,6-tri-t-butylanisole	1.45	1.31	1.45	3.69		7.27

[a] In each case the fluorine is assigned the 3-position for simplicity of comparison. [b] The internal standard was tetramethylsilane with deuteriochloroform as solvent. The figure in parentheses is the coupling constant between the proton(s) in question and the fluorine nucleus, c.p.s. [c] Half of this doublet appeared with the 6-t-butyl absorption.

which the protons are removed from fluorine by the same number of bonds and which possesses the same relative geometry to the fluorine nucleus as does the 4-t-butyl group, shows a different and somewhat higher coupling constant. Two possibilities are suggested to account for this behavior: (1) the hydroxyl (or methoxyl) group may be disturbing the aromatic ring current sufficiently to allow this difference, or (2) a buttressing effect of the hydroxyl group may be forcing the 2-t-butyl group relatively closer to the fluorine nucleus than the 4-alkyl group. This latter possibility seems to be negated by the observation that the conversion of hydroxyl to methoxyl causes a decrease in the coupling constant, rather than the anticipated increase.

The data in Table I are compatible only with the structures suggested; long-range coupling by two of the three t-butyl groups marks them as *ortho* to the fluorine. This information taken in conjunction with the magnitude of the aryl hydrogen–fluorine coupling constant[27] and the absence of aryl hydrogen–aryl hydrogen magnetic interactions fully designates the structures given for I–IV. The data for 2,4,6-tri-t-butylanisole are included for comparison. The added fluorine has only small effects on the resonance peak positions, but fortunately these shifts are sufficient to identify the t-butyl groups individually.

Experimental

m-Fluorophenol.—This material was prepared from m-fluoroanisole, which had in turn been synthesized from m-anisidine, by procedures which have been reported previously.[28]

t-Butylation of m-Fluorophenol.—The reaction vessel used for butylation was a flat-bottomed 35-mm. tube which contained a magnetic stirring bar. The top was sealed by a stopper containing an exit tube and an inlet capillary tube which extended to the bottom of the flask. The inlet was connected through a drying tube containing 4A Molecular Sieves to the isobutylene tank.[29]

m-Fluorophenol, 2.0 g. (0.018 mole), was placed in this vessel and the isobutylene flow started. The temperature was maintained at 45 ± 2° by a water bath held on combined hot plate–magnetic stirrer. After thermal equilibration sulfuric acid (0.17 g., 0.0017 mole), was added. A vigorous reaction ensued during which the volume of solution increased substantially. Small samples were withdrawn at intervals, shaken with pentane and water, and the pentane evaporated to give a residue which was examined by v.p.c. A 2-m. silicone column was used at 200°; retention times were I, 8 min.; II, 10 min.; and III, 12 min.

The yield of 2,4,6-tri-t-butyl-3-fluorophenol reached a maximum after approximately 2.5 hr. The solution was mulled with a few grams of activated alumina,[30] and the entire slurry was then added to a basic alumina column (Harshaw 90% alumina which had been activated by heating at 300° for 0.5 hr. and cooled in a desiccator was used).

t-Butyl 4,6-Di-t-butyl-3-fluorophenyl Ether.—Using pentane as eluting liquid, the t-butyl ether (II, 1.05 g., 21%) was obtained. Recrystallization from aqueous methanol gave material with m.p. 65–67°.

Anal.[31] Calcd. for $C_{18}H_{29}FO$: C, 77.1; H, 10.4. Found: C, 77.0; H, 10.4.

2,4,6-Tri-t-butyl-3-fluorophenol.—Gradual transition from pentane to ether as solvent caused the elution of 2,4,6-tri-t-butyl-3-fluorophenol, 1.25 g. (25%). After recrystallization from aqueous methanol, it had m.p. 147–148°; this white solid developed the blue tinge characteristic of 2,4,6-tri-t-butyl-phenol on standing.

Anal. Found: C, 77.2; H, 10 6.

4,6-Di-t-butyl-3-fluorophenol.—After the tri-t-butylated materials had been recovered, the chromatography column was stripped with methanol to give crude 4,6-di-t-butyl-3-fluorophenol, 1.3 g. (32%). A small sample was purified by collection from v.p.c.; it was obtained as a colorless liquid which rapidly developed a straw color on contact with air.

Anal. Calcd. for $C_{14}H_{21}FO$: C, 75.0; H, 9.4. Found: C, 74.7; H, 9.5.

Methyl 2,4,6-Tri-t-butyl-3-fluorophenyl Ether.—A sample of 2,4,6-tri-t-butyl-3-fluorophenol (0.27 g., 0.00095 mole) was dissolved in 5 ml. of tetrahydrofuran which had been dried and purified by distillation from lithium aluminum hydride. To this solution was added 0.46 g. (0.0041 mole) of potassium t-butoxide; after stirring 0.5 hr., 2 ml. of methyl iodide was added and the mixture stirred overnight.

Following a typical washing and extraction procedure, the residue was taken up in a small amount of pentane and subjected to column chromatography. Pentane elution gave 0.24 g. (87%) of the desired ether. The melting point was 126–127°, following recrystallization from aqueous methanol.

Anal. Calcd. for $C_{19}H_{31}FO$: C, 77.5; H, 10.6. Found: C, 77.3; H, 10.7.

Acknowledgment.—The authors wish to express their appreciation to Mr. Henry E. Gauthier of Varian Associates for his assistance both in obtaining and interpreting many of the n.m.r. spectra.

(27) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 86.

(28) C. M. Suter, E. J. Lawson, and P. G. Smith, *J. Am. Chem. Soc.*, **61**, 763 (1939).

(29) Phillips Petroleum 99% "Pure" grade isobutylene was used.

(30) This treatment prevented an exothermic initial reaction with the alumina chromatography column.

(31) Microanalysis by C. F. Geiger, 312 E. Yale St., Ontario, Calif.