

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY, UNIVERSITY OF MISSOURI]

Orientation Effects in the Alkylation of *m*-Xylene by Various Procedures and Reagents

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Investigations of the alkylation of substituted aromatic hydrocarbons by an alcohol and 70-85% sulfuric acid^{1,2} have led to the belief, but apparently without definite proof in some cases, that the normal orientation effects of alkyl groups are always exerted when this procedure is used. Thus, *i*-propylbenzene has been reported to yield 1,2,4-trisopropylbenzene, and the dialkylbenzenes obtained from benzene or toluene have been reported to be the *o*- and *p*-isomers. In their investigation of the action of aluminum chloride on the 1,3-dimethyl-4-butylbenzenes, Nightingale and Smith³ assumed that the products obtained from *m*-xylene and *t*-butyl alcohol by the sulfuric acid procedure had the 1,3,4 orientation, although it was observed that the trinitro derivatives of the 1,3-dimethyl-4-*t*-butyl- and -5-*t*-butylbenzene melted at 112 and 113°, respectively, and gave only small depressions in melting points when mixed.

During further work with these compounds, the similarity in melting points and the small depressions in the mixed melting points of other derivatives of the two hydrocarbons led to the conviction either that the 1,3,4-hydrocarbon did not have this orientation, but was mainly the 1,3,5-isomer, or that a rearrangement of the 1,3,4- to the 1,3,5-isomer occurred during the preparation of the derivatives. In order to decide between these alternatives we have reinvestigated the nature of the products obtained when *m*-xylene is alkylated by *t*-butyl alcohol and 85% sulfuric acid, and it has been found that the previous work³ was in error in that the trialkylbenzene from this reaction is a mixture consisting of approximately two parts of 1,3-dimethyl-5-*t*-butylbenzene and one part of the 1,3,4-isomer.

The study has been extended to include the trialkylbenzenes formed from *m*-xylene by alkylation with other butyl compounds in the presence of boron trifluoride or ferric chloride as catalysts. The results showed that the abnormally oriented trialkylbenzene (1,3,5) was obtained not only from 75 and 85% sulfuric acid, but with boron tri-

fluoride and with ferric chloride, when *t*-butyl compounds were used. The abnormally oriented product with boron fluoride was unexpected, for 1,2,4-trisopropylbenzene is reported from benzene, *i*-propyl alcohol and this catalyst.⁴ The normally oriented trialkylbenzene (1,3,4) was obtained from *m*-xylene, *s*-butyl alcohol and either 85% sulfuric acid or boron trifluoride as the catalyst.

The structures of the hydrocarbons were established by oxidation rather than by conversion to the trinitro derivatives in order to avoid any chance that a rearrangement might occur during the preparation of the derivatives. The oxidation product of 1,3-dimethyl-5-*t*-butylbenzene (Friedel-Crafts) proved to be 5-*t*-butyl-isophthalic acid, m. p. 343°, rather than trimesic acid, and the trialkylbenzene from *m*-xylene, *t*-butyl alcohol and 85% sulfuric acid yielded a mixture of 4-*t*-butyl-isophthalic acid and 5-*t*-butyl isophthalic acid. The 4-*t*-butylisophthalic acid is soluble in the aqueous pyridine solution in which the oxidation was carried out, whereas the 5-isomer is only slightly soluble, and this fact made it possible to separate the mixture of acids.

To establish the identity of the 5-*t*-butylisophthalic acid, the compound was synthesized by the method of Doebner⁵ from pyruvic acid, trimethylacetaldehyde and barium hydroxide. The acid so obtained melted at 343° and did not depress the melting point of the acid formed by oxidation.

The 1,3-dimethyl-4-*t*-butylbenzene was synthesized by coupling the Grignard reagent from 1,3-dimethyl-4-iodobenzene with *t*-butyl chloride.⁶ Oxidation of this hydrocarbon with potassium permanganate in aqueous pyridine yielded 4-*t*-butylisophthalic acid.

The stability of the tertiary radical toward potassium permanganate is surprising. In one experiment, more than enough permanganate was used to oxidize the *t*-butyl group and the two methyl groups of the 1,3,5-hydrocarbon and the mixture was refluxed gently. The product was

(1) Meyer and Bernhauer, *Monatsh.*, **53**, 721 (1929).(2) Kirmann and Graves, *Bull. soc. chim.*, (5) **1**, 1494 (1934).(3) Nightingale and Smith, *THIS JOURNAL*, **61**, 101 (1939).(4) McKenna and Sowa, *ibid.*, **59**, 470 (1937).(5) Doebner, *Ber.*, **24**, 1748 (1891).(6) Smith and Perry, *THIS JOURNAL*, **61**, 1411 (1939).

nearly pure 5-*t*-butylisophthalic acid in almost quantitative yield. Oxidation of *p*-*t*-butyltoluene with excess permanganate likewise yielded only *p*-*t*-butylbenzoic acid.

These results do not invalidate the work of Nightingale and Smith,³ for both 1,3-dimethyl-4-*t*-butyl- and 4-*s*-butylbenzene synthesized through the Grignard route are converted to the 5-*t*-butyl isomer by the action of aluminum chloride.

The abnormal orientation of these trialkylbenzenes made it desirable to verify the structure of the trialkylbenzene from *m*-xylene, *s*-butyl alcohol and 85% sulfuric acid or boron trifluoride. The 1,3-dimethyl-4-*s*-butylbenzene was synthesized through 2,4-dimethylacetophenone and ethylmagnesium bromide. The carbinol was dehydrated to the olefin, which was reduced with hydrogen and Raney nickel under pressure. The trialkylbenzenes were identical. This hydrocarbon could be oxidized to 4-*s*-butylisophthalic acid, but the 5-*s*-butyl isomer yielded trimesic acid.

It may or may not be significant that three of the condensing agents which lead to abnormally oriented trialkylbenzenes, sulfuric acid, aluminum chloride and ferric chloride, can also cleave a *t*-butyl group from the benzene ring.⁷

Results from the alkylation of *m*-xylene with *t*-amyl alcohol and either 85% sulfuric acid or boron trifluoride are not so clean-cut. Analyses and neutral equivalents of the acids obtained by oxidation of the trialkylbenzene fraction correspond to a *t*-amylisophthalic acid, as do their methyl esters. The fact that these compounds melt higher than 5-*t*-amylisophthalic acid and its methyl ester is difficult to explain. Mixtures of the acids with 5-*t*-amylisophthalic acid melt between the two, as do mixtures of the methyl esters. The reaction products from *t*-amyl alcohol are undoubtedly more complicated mixtures than in the case of the butyl compounds. By analogy with the reaction products from *t*-butyl alcohol the trialkylbenzenes should have the 1,3,5 orientation. *t*-Amylbenzene was unaffected by potassium permanganate in aqueous pyridine solution.

Oxidation of 1,3-dimethyl-5-*t*-amylbenzene (Friedel-Crafts) yielded 5-*t*-amylisophthalic acid, identical with 5-*t*-amylisophthalic acid synthesized by Doebner's method. Unfortunately the Grignard reagent from 1,3-dimethyl-4-iodobenzene would not couple with *t*-amyl chloride and a

Fittig synthesis was likewise unsuccessful, so 4-*t*-amylisophthalic acid could not be made to complete the series.

In an effort to find solid derivatives of these alkylbenzenes which would avoid the use of nitric or sulfuric acid, the hydrocarbons were chloromethylated. The substituted benzyl chlorides were converted to the corresponding acetamides by heating with acetamide, and to the benzyl alcohols.

The reactions were useful only with 1,3-dimethyl-5-*t*-butylbenzene. The 2,4-dimethyl-6-*t*-butylbenzylacetamide separated readily as a solid, and 2,4-dimethyl-6-*t*-butylbenzyl alcohol is a solid. The other amides were viscous and would not crystallize readily. The other benzyl alcohols were liquids. Careful oxidation of 2,4-dimethyl-6-*t*-butylbenzyl alcohol to the corresponding known monocarboxylic acid⁸ served to establish the location of the —CH₂Cl group as between the methyl and *t*-butyl radicals rather than between the two methyl groups.

Experimental⁹

Most of the trialkylbenzenes were prepared by procedures previously described.³ The preparation of 1,3-dimethyl-4-*s*-butylbenzene has been improved by increasing the amount of *s*-butyl alcohol to 100 cc., and reducing the reaction time to seven hours. The hydrocarbons were vacuum distilled through columns packed with single turn glass helices.

The diacetamino derivative of 1,3-dimethyl-4-*t*-butylbenzene, not previously described, melts at 331°.

Anal. Calcd. for C₁₆H₂₄O₂N₂: N, 10.14. Found: N, 10.00.

Preparation of 1,3-Dimethyl-5-*t*-butylbenzene. (a) **With Ferric Chloride as Catalyst.**—*m*-Xylene (144 g.) and anhydrous ferric chloride (12.2 g.) were placed in a 3-necked flask cooled with an ice-salt mixture and fitted with a sealed stirrer and dropping funnel. *t*-Butyl chloride (25 g.) was added at such a rate that the temperature of the reaction mixture did not rise above -4.5°. Stirring was continued an additional four hours. The reaction mixture was decomposed as for a Friedel-Crafts reaction; yield, 29.6 g.; b. p. 88° (14 mm.).

(b) **With Boron Fluoride as Catalyst.**—*m*-Xylene (106 g.) was alkylated with *t*-butyl alcohol (74 g.) and boron fluoride (41 g.) by the method of McKenna and Sowa⁴ using a 3-necked conical flask. The boron fluoride was admitted into the reaction mixture during six hours. The flask was cooled with water at the beginning of the reaction. The hydrocarbon layer was separated, washed and dried; yield, 27.5 g.; b. p. 78-79° (8 mm.).

(c) **With 75% Sulfuric Acid as Catalyst.**—The experimental conditions were those of Meyer and Bernhauer.¹

(8) Bauer, *Ber.*, **33**, 2562 (1900).

(9) Semimicro analyses by D. R. Smith and E. Milberger.

(7) Ipatieff and Corson, *THIS JOURNAL*, **59**, 1417 (1937).

The *m*-xylene (184 g.) and *t*-butyl alcohol (123 g.) were placed in a 3-necked flask in a water-bath at 65–70°. A solution of concentrated sulfuric acid (1060 cc.) and water (540 cc.) was added during an hour while the reaction mixture was stirred mechanically. The hydrocarbon layer was washed, dried and distilled. The following fractions were obtained at 13 mm. after removal of *m*-xylene: (I) 24 g. up to 85°; (II) 3 g. 85–89°; (III) 8.2 g. 89–92°; (IV) 5 g. 92–97°. Fraction (III) is the trialkylbenzene.

Oxidation of 1,3-Dimethyl-5-*t*-butylbenzene.—The hydrocarbon (5 g.) from *t*-butyl chloride and aluminum chloride was dissolved in pyridine (40 cc.) and water (20 cc.) in a 3-necked flask. Finely powdered potassium permanganate (21.5 g.) was added in small portions during two hours with the temperature maintained around 80°. The mixture was heated until the purple color disappeared. The mixture was stirred mechanically during the entire period.

The manganese dioxide was separated by filtration and the filtrate acidified strongly with hydrochloric acid. The 5-*t*-butylisophthalic acid precipitated. A small amount of acid was extracted from the manganese dioxide. The combined acids (6.5 g.) were recrystallized from glacial acetic acid; m. p. 343°. Since the acid begins to sublime below the melting point, the sample was packed into the tube and the tube sealed.

Anal. Calcd. for C₁₂H₁₄O₄: C, 64.84; H, 6.30; neut. eq., 111. Found: C, 64.73; H, 6.49; neut. eq., 110.

The methyl ester was prepared with diazomethane, m. p. 97°.

Anal. Calcd. for C₁₄H₁₈O₄: C, 67.20; H, 7.20. Found: C, 67.08; H, 7.29.

Only 5-*t*-butylisophthalic acid was obtained by the oxidation of the hydrocarbons from the three alkylations described above.

Oxidation of 1,3-Dimethyl-4-*t*-butylbenzene.—A 7-g. sample of the hydrocarbon (Grignard synthesis⁶) was oxidized in aqueous pyridine solution. After separation of the manganese dioxide, most of the pyridine was distilled from the solution before acidifying; yield, 5 g.; m. p. 230°.

Anal. Calcd. for C₁₂H₁₄O₄: C, 64.84; H, 6.30; neut. eq., 111. Found: C, 64.77; H, 6.39; neut. eq., 112.5.

Oxidation of the Trialkylbenzene from *m*-Xylene, *t*-Butyl Alcohol and 85% Sulfuric Acid.—The hydrocarbon (10.8 g.) was oxidized with excess permanganate. The 5-*t*-butylisophthalic acid (9.7 g.) separated when the solution was acidified after removal of the manganese dioxide. The filtrate was made basic and most of the pyridine distilled off. The solution in the distilling flask was again acidified and the 4-*t*-butylisophthalic acid (5.2 g.) separated. The purified acids melted at 343° and 230°, respectively, and did not depress the melting points of authentic samples.

Synthesis of 5-*t*-Butylisophthalic Acid.—Trimethylacetaldehyde¹⁰ (23.7 g.), pyruvic acid (50 g.), barium hydroxide (120 g.) and 1000 cc. of water were refluxed gently for one hundred hours.⁵ To free the crude 5-*t*-butylisophthalic acid from oxalic acid, the solid was suspended in a little water and potassium permanganate solution added in the cold until the purple color persisted.

Hydrochloric acid was added and the manganese dioxide removed with sulfur dioxide; yield, 4.1 g.; m. p. 343°.

Anal. Calcd. for C₁₃H₁₆O₄: C, 64.86; H, 6.30; neut. eq., 111. Found: C, 64.63; H, 6.54; neut. eq., 112.5.

Preparation of 1,3-Dimethyl-4-*s*-butylbenzene. (a) **Through the Grignard Reaction.**—A solution of 2,4-dimethylacetophenone (155 g.) in ether was added to the Grignard reagent from 86 g. of ethyl bromide. The complex was decomposed in the usual manner.

The crude carbinol was added to 250 g. of acetic anhydride containing ten drops of concentrated sulfuric acid. The anhydride was distilled off at a somewhat reduced pressure and the residue fractionated. The olefin distilled at 102° (1 mm.). To purify the olefin, it was heated with sodium, vacuum distilled, and again vacuum distilled from Raney nickel.

The olefin (45 g.) was reduced in methyl alcohol solution with Raney nickel at 80–90° (2000 lb.). After removal of the solvent and catalyst, the hydrocarbon was heated with sodium and fractionated; yield, 38 g.; b. p. 82° (1 mm.).

The diacetamino derivative of this hydrocarbon melted at 270° and did not depress the melting point of diacetamino-1,3-dimethyl-4-*s*-butylbenzene prepared by the sulfuric acid procedure.

(b) **With Boron Fluoride as the Catalyst.**—*m*-Xylene (106 g.) was alkylated with *s*-butyl alcohol and boron fluoride (49 g.); yield, 30 g.; b. p. 91–93° (13 mm.).

The diacetamino derivative of this hydrocarbon melted at 270° and did not depress the melting point of the derivative of the hydrocarbon from the Grignard reaction. Careful oxidation of 1,3-dimethyl-4-*s*-butylbenzene (10 g.) at 70° yielded 2 g. of 4-*s*-butylisophthalic acid; m. p. 188°.

Anal. Calcd. for C₁₂H₁₄O₄: C, 64.86; H, 6.30; neut. eq., 111. Found: C, 64.81; H, 6.30; neut. eq., 111.7.

Synthesis of 5-*t*-Amylisophthalic Acid.—The 2,2-dimethylbutyraldehyde was prepared by adding the Grignard reagent from 425 cc. of *t*-amyl chloride to 460 cc. of methyl formate.¹⁰ The reaction temperature was maintained at –50° to –55°; yield, 53.7 g. (26%).

A mixture of pyruvic acid (45 g.), 2,2-dimethylbutyraldehyde (24.5 g.), barium hydroxide (106 g.) and 900 cc. of water was refluxed for one hundred hours. The acid was purified as described above; yield, 7.5 g.; m. p. 307°.

Anal. Calcd. for C₁₃H₁₆O₄: C, 66.10; H, 6.78; neut. eq., 118. Found: C, 66.19; H, 6.67; neut. eq., 115.

The methyl ester melted at 81°.

Anal. Calcd. for C₁₅H₂₀O₄: C, 68.18; H, 7.20. Found: C, 68.34; H, 7.51.

Oxidation of 4 g. of 1,3-dimethyl-5-*t*-amylbenzene (Friedel-Crafts) yielded 5-*t*-amylisophthalic acid; m. p. 307°; yield, 5 g.

The methyl ester melted at 78°.

Anal. Calcd. for C₁₃H₁₆O₄: C, 66.10; H, 6.78; neut. eq., 118. Found: C, 66.10; H, 7.11; neut. eq., 123.

Alkylation of *m*-Xylene with *t*-Amyl Alcohol. (a) **With Boron Fluoride as Catalyst.**—*m*-Xylene (200 cc.) was alkylated with *t*-amyl alcohol (200 cc.) and 30–50 g. of boron fluoride as described above. The reaction mixture was stirred for four hours. The following fractions were obtained at 16 mm. after removal of *m*-xylene: (I) 4.5

(10) Campbell, *THIS JOURNAL*, **59**, 1980 (1937).

TABLE I
 CHLOROMETHYL DERIVATIVES AND BENZYL ALCOHOLS

Alkylbenzene, 1,3-dimethyl-	Chloromethyl derivative ^a				Benzyl alcohol ^b					
	°C.	B. p.	Mm.	C. %	H. %	°C.	B. p.	Mm.	C. %	H. %
5- <i>s</i> -Butyl	115		1	74.25	9.36	158-162		14	81.20	10.15
5- <i>t</i> -Butyl	111-116		6	74.14	9.59	m. p. 99			81.18	10.12
4- <i>n</i> -Butyl	103-108		1	74.66	9.40	135-140			81.13	10.10
4- <i>s</i> -Butyl	100-106		4	74.25	9.32	145-150		10	81.16	10.40

^a Calcd. for C₁₃H₁₉Cl: C, 74.28; H, 9.04. ^b Calcd. for C₁₃H₂₀O: C, 81.25; H, 10.41.

g. 91-94°; (II) 15 g. 94-96°; (III) 15 g. 96-104°; (IV) 29 g. 100-135°; residue 15 g.

Oxidation of 4 g. of the trialkylbenzene (II) yielded 6 g. of a dicarboxylic acid, m. p. 330°, corresponding to a *t*-amylisophthalic acid.

Anal. Calcd. for C₁₈H₁₆O₄: C, 66.10; H, 6.78; neut. eq., 118. Found: C, 65.85; H, 6.99; neut. eq., 113.

(b) **With 85% Sulfuric Acid as Catalyst.**—This alkylation was carried out as previously described.¹¹ The dibenzamino derivative of the trialkylbenzene from this reaction melted at 305°. A mixture of this derivative and the dibenzamino derivative (m. p. 303°) of 1,3-dimethyl-5-*t*-amylbenzene (Friedel-Crafts) melted at 298°.

Oxidation of this hydrocarbon yielded an acid melting at 320-325°, which, mixed with the acid (m. p. 330°) from the trialkylbenzene prepared with boron fluoride, melted at 319°. The neutral equivalent was 116.

The method of oxidation of alkylbenzenes such as durene containing only methyl radicals or methyl radicals and *t*-alkyl radicals with potassium permanganate in aqueous pyridine solution has been generally successful with other compounds such as 4-methyl-2'-methoxydiphenyl ether. Yields are much higher than in aqueous solution. Bumping is avoided, for it is not necessary to boil the mixture and in some cases the temperature must be kept at 80° or lower. *t*-Butylbenzene and *t*-amylbenzene were unaffected even after long heating with excess permanganate. The ethylbenzenes gave indefinite oxidation products.

Chloromethyl Compounds and Derivatives.—The hydrocarbons were chloromethylated by the method of v. Braun and Nelles.¹² Boiling points and analytical data are summarized in Table I. Derivatives were prepared from 2,4-dimethyl-6-*t*-butylbenzyl chloride as follows:

The acetate was prepared by refluxing 4.2 g. of the chloride, 2.5 cc. of acetic anhydride, 7.5 cc. of acetic acid and 2.5 g. of potassium acetate. The mixture was poured onto ice, washed, and dried over sodium sulfate. The ether was distilled leaving the crude ester.

The crude ester (2.5 g.) was refluxed three hours with potassium hydroxide (6.6 g.) in alcohol (25 cc.) and water (35 cc.). The oily top layer solidified on cooling. The carbinol was separated by filtration and recrystallized from 28-30° petroleum ether; yield, 2.25 g.; m. p. 99°.

(11) Nightingale and Shanholtzer, *J. Org. Chem.*, **6**, 6 (1942).

(12) v. Braun and Nelles, *Ber.*, **67**, 1094 (1934).

The carbinol was oxidized to the corresponding monocarboxylic acid with potassium permanganate at 0 to 20°. The 2,4-dimethyl-6-*t*-butylbenzoic acid melted at 168°, the recorded value.⁸

2,4-Dimethyl-6-*t*-butylbenzylacetamide was prepared by heating a mixture of the chloride (2.1 g.) and acetamide (1.2 g.) in an oil-bath at 210° for thirty-five minutes. The solid was boiled with water to remove acetamide and recrystallized from a mixture of chloroform and petroleum ether; yield, 2.2 g.; m. p. 197°.

Anal. Calcd. for C₁₅H₂₃NO: N, 6.00. Found: N, 6.25.

Nitrations.—All efforts in this Laboratory to prepare the trinitro derivatives, by the use of the nitrating mixture previously described,³ have been fruitless. A nitrating mixture in the ratio of 15 g. of nitric acid sp. gr. 1.5 and 30 g. of 15% fuming sulfuric acid has been satisfactory, although this mixture is not as smooth a nitrating agent as the mixture originally used. We can give no explanation for this difference.

Summary

Abnormally oriented trialkylbenzenes (1,3,5 rather than 1,3,4) are formed when *m*-xylene is alkylated with *t*-butyl alcohol in the presence of 75-85% sulfuric acid or boron trifluoride, and with *t*-butyl chloride and anhydrous ferric chloride as the catalyst.

The normally oriented trialkylbenzene (1,3,4) is formed when *m*-xylene is alkylated with *s*-butyl alcohol and either 85% sulfuric acid or boron trifluoride.

Abnormally oriented trialkylbenzenes are formed from *m*-xylene and *t*-amyl alcohol and *t*-amyl chloride under the same conditions as for the *t*-butyl compounds.

The 1,3-dimethyl-4-*t*-butyl, 5-*t*-butyl and 5-*t*-amylbenzenes can be oxidized in aqueous pyridine solution to the corresponding *t*-butyl and *t*-amyl isophthalic acids.