

[CONTRIBUTION FROM THE RESEARCH LABORATORIES, VETERANS ADMINISTRATION HOSPITAL, HOUSTON, TEXAS]

## Orientation in Aromatic Substitution. I. 1,2-Dimethoxy-3-isopropylbenzene and 3,5-Dimethylanisole

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Some anomalous orientations found in a study of electrophilic substitution reactions of 1,2-dimethoxy-3-isopropylbenzene and 3,5-dimethylanisole are presented. Apparently, the difference in electron availability at various positions in these aromatic systems is small and steric hindrance can become the dominating factor with the orientation being determined by the size and the shape of the entering group.

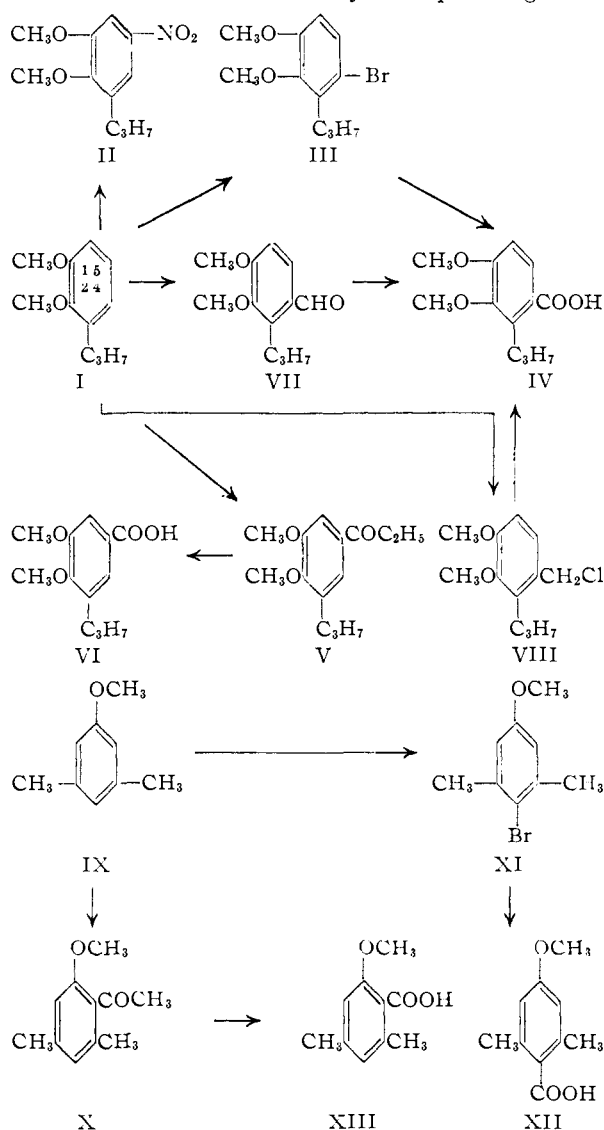
In continuation of certain studies,<sup>1,2</sup> some anomalous orientations were encountered in 1,2-dimethoxy-3-isopropylbenzene (I). It has been shown conclusively that nitration of I gives 1,2-dimethoxy-3-isopropyl-5-nitrobenzene (II).<sup>3,4</sup> The bromination of I has now been studied. A good yield of 1,2-dimethoxy-3-isopropyl-4-bromobenzene (III) was formed and shown to be identical with that prepared by an unequivocal synthesis<sup>4</sup> from 1-methoxy-2-acetoxy-3-isopropylbenzene. Compound III was converted by the published procedure<sup>4</sup> to 3,4-dimethoxy-2-isopropylbenzoic acid (IV). Acylation of I with propionyl chloride gave 3,4-dimethoxy-5-isopropylpropiophenone (V), oxidation yielding 3,4-dimethoxy-5-isopropylbenzoic acid (VI) which was identical with the acid prepared from 3-methoxy-4-hydroxy-5-isopropylacetophenone.<sup>5</sup> No cleavage of the 2-methoxyl group, migration of the isopropyl group, or isomerization occurred in the Friedel-Crafts reaction when anhydrous ferric chloride was used as the catalyst.

Formylation of I by the Gattermann reaction gave 3,4-dimethoxy-2-isopropylbenzaldehyde (VII). Oxidation of VII gave the acid IV. It is of interest to note that, whereas 3,4-dimethoxy-2-methylbenzaldehyde forms a sodium bisulfite addition product,<sup>6</sup> the aldehyde VII under the same conditions does not. This can be explained on the basis of steric effects. Chloromethylation of I gave 3,4-dimethoxy-2-isopropylbenzyl chloride (VIII) since the acid IV was obtained on permanganate oxidation.

In a recent publication,<sup>7</sup> attention was called to the "somewhat unexpected" orientation found in the acylation<sup>8,9</sup> of 3,5-dimethylanisole (IX). The product (80-90%) was formulated as 2,4-dimethyl-6-methoxyacetophenone (X). The structure of this ketone was not conclusively demonstrated.<sup>7-10</sup> For this reason X was subjected to the haloform reaction and gave a high yield (96%) of 2,4-dimethyl-6-methoxybenzoic acid (XIII). It was identical with the acid prepared from 2,4-dimethyl-

6-hydroxybenzaldehyde<sup>11</sup> by permanganate oxidation of the corresponding methyl ether.<sup>12</sup>

In view of the results on I, it was of interest to determine the orientation in IX on bromination. The bromo compound obtained (92%) gave 4-methoxy-2,6-dimethylbenzoic acid (XII) on carbonation of the Grignard reagent. It was identical with the acid<sup>12</sup> obtained by the permanganate



(1) J. D. Edwards, Jr., and J. L. Cashaw, *THIS JOURNAL*, **76**, 6141, 6188 (1954).

(2) J. D. Edwards, Jr., and J. L. Cashaw, *J. Org. Chem.*, **20**, 847 (1955).

(3) R. Adams, M. Hunt and R. C. Morris, *THIS JOURNAL*, **60**, 2972 (1938).

(4) R. Adams and B. R. Baker, *ibid.*, **61**, 1138 (1939).

(5) R. Adams, M. Hunt and B. R. Baker, *ibid.*, **61**, 1134 (1939).

(6) R. I. T. Cromartie and J. Harley Mason, *J. Chem. Soc.*, 1052 (1952).

(7) J. C. Roberts, *ibid.*, 2989 (1955).

(8) K. von Auwers and E. Borsche, *Ber.*, **48**, 1698 (1915).

(9) T. Posternak, *Helv. Chim. Acta*, **23**, 1046 (1940).

(10) D. Gardner, J. F. Grove and D. Ismay, *J. Chem. Soc.*, 1817 (1954).

(11) A. L. Wilds and C. Djerassi, *THIS JOURNAL*, **68**, 1862 (1946).

(12) S. R. Finn, G. J. Lewis and M. G. L. Megson, *J. Soc. Chem. Ind. (London)*, **69**, 129 (1950).

oxidation of 4-methoxy-2,6-dimethylbenzaldehyde.<sup>11,12</sup> The bromination product is therefore 4-bromo-3,5-dimethylanisole (XI). The acid XII was also shown to be identical with that derived from the bromination product<sup>13</sup> of 3,5-dimethylphenol.

From the experimental results on the bromination, formylation and chloromethylation reactions, it appears that in I position 4 supplies the highest electron density or has the smallest "reactivity number."<sup>14</sup> However, it is probable that its advantage over position 5 is small and may be easily masked by steric hindrance. From a consideration of models, the preferred conformation of the isopropyl group is that in which one methyl group lies above the plane of the ring and the other below. The geometry of the transition states involved in the *ortho* nitration and bromination of toluene, discussed recently by De La Mare and Harvey,<sup>15</sup> can be extended to the electrophilic substitutions reported in this paper. On this basis, steric hindrance between the bulky nitro or propionyl<sup>16</sup> group and the isopropyl substituent in the 3-position is regarded as sufficiently large to direct substitution into the 5- rather than into the adjacent 4-position.

Since it is known that when the acyl halide is not fully engaged by the catalyst in the Friedel-Crafts reaction,<sup>17</sup> a decrease in reactivity and an increase in bulk causes resistance of attack in aromatic compounds at the sterically more hindered

but preferred positions, the propionylation of I was carried out by first forming the soluble propionyl chloride-aluminum chloride complex in methylene chloride. Even under these conditions the ketone V resulted.

Steric hindrance would also explain why IX is brominated in the 4-position but acetylated at the 2-position. In like manner, one can explain why the Fries rearrangement<sup>10</sup> of 3,5-dimethylphenylacetate even at 0° gives only the *o*-hydroxy ketone and no *p*-hydroxy ketone.

Consideration of the projection diagrams of the uniplanar structures shows (Fig. 1) that there is only slight steric overlap when the acetyl group is in the 2-position of IX whereas the interference is considerable if the acetyl group is in the 4-position. In Fig. 2, the projection diagram of the bromo derivative XI does not show any steric hindrance.

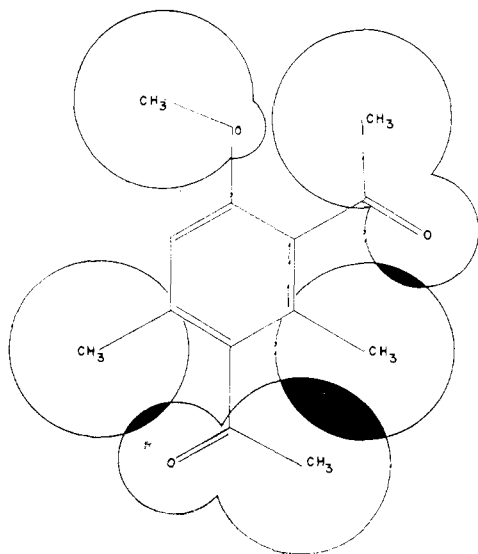


Figure 1.

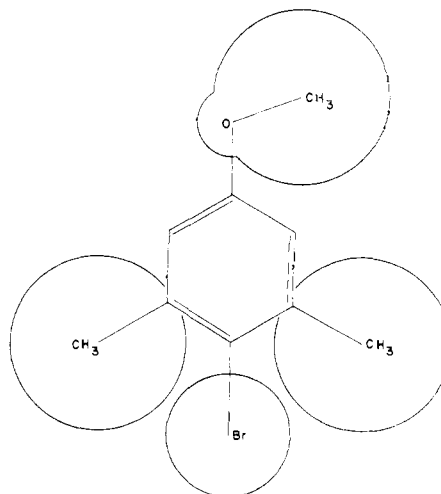


Figure 2.

The ultraviolet spectra of the acids IV and VI (Fig. 3) show that steric interference in the IV acid occurs between the aromatic and carboxyl groups. Both bands of the IV acid are shifted to shorter wave lengths with a decrease in intensity. The infrared spectrum of a chloroform solution of the acid XIII had absorption bands at 1692  $\text{cm}^{-1}$  (s) and 1720  $\text{cm}^{-1}$  (s). These bands are probably due to the presence of monomeric and dimeric forms since the spectrum in dioxane exhibited only one band at 1718  $\text{cm}^{-1}$  (s). It is known<sup>18</sup> that solutions in dioxane appear to be monomeric.

It was found that the substituted aromatic ketones reported in this paper as well as some others, gave a limited reaction, if any, to yield the acids in the haloform reaction under the usual conditions.<sup>19-21</sup> However, if the calculated amount<sup>20</sup> of potassium hydroxide and bromine was used and the aqueous dioxane mixture refluxed, good yields of the acids were obtained.

**Acknowledgment.**—The authors are greatly indebted to Professor R. B. Turner for his fruitful

(13) R. C. Fuson, J. Corse and P. B. Weldon, *THIS JOURNAL*, **63**, 2645 (1941).

(14) P. M. G. Bavin and M. J. S. Dewar, *J. Chem. Soc.*, 164 (1956).

(15) P. B. D. De La Mare and J. T. Harvey, *ibid.*, 39 (1956).

(16) As has been pointed out,<sup>14</sup> the Friedel-Crafts reaction is probably reversible and any valid test should be based on reactions which are irreversible such as bromination and nitration. Since isomerization of aromatic ketones in the Friedel-Crafts reaction is known (G. Baddeley, *Quart. Revs. (London)*, **8**, 372 (1954)), the propionylation reaction reported here may occur by an intermediate cation, formed by attack at the 4-position, which could isomerize to give V by a complex in which the propionyl group is shared by ring carbon atoms 4 and 5. This isomerization is patterned after that published (D. A. McCaulay and A. P. Lien, *THIS JOURNAL*, **74**, 6249 (1954)) for the methylbenzenes.

(17) G. Baddeley, *Quart. Revs. (London)*, **8**, 369 (1954).

(18) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954, p. 141.

(19) M. W. Farrar and R. Levine, *THIS JOURNAL*, **71**, 1496 (1949).

(20) R. Levine and J. R. Stephens, *ibid.*, **72**, 1642 (1950).

(21) D. J. Craun and N. L. Allinger, *ibid.*, **77**, 6292 (1955).

counsel, encouragement, and interest during the study.

### Experimental<sup>22</sup>

**1,2-Dimethoxy-3-isopropyl-4-bromobenzene (III).**—To a solution of 32.9 g. of I<sup>2,3</sup> in 60 ml. of anhydrous carbon tetrachloride, there was added dropwise over a period of one hour, with good stirring at 0–5°, a solution of 29.3 g. of bromine in 40 ml. of carbon tetrachloride. After removal of the solvent, the product was distilled to give 42.7 g. (90%), b.p. 106° (1.2 mm.),  $n_D^{20}$  1.5440. The index of refraction and the infrared spectrum of the pure liquid was identical with the product prepared from 1-methoxy-2-acetoxy-3-isopropylbenzene.<sup>4</sup> It was necessary to fractionally distill the product synthesized by Adams procedure<sup>4</sup> [ $n_D^{20}$  found was 1.5414, reported<sup>4</sup> 1.5413] since the infrared spectrum had hydroxyl group absorption.

Carbonation of the Grignard reagent<sup>4</sup> of III gave 3,4-dimethoxy-2-isopropylbenzoic acid (IV),<sup>23</sup> m.p. 121–123° (reported<sup>4</sup> 119–121°).

**3,4-Dimethoxy-2-isopropylpropiophenone (V).** (a).—To 15.1 g. of finely divided anhydrous ferric chloride, covered with 150 ml. of anhydrous carbon disulfide, there was added dropwise over a period of one hour, with stirring, a mixture of 25 g. of I and 14.3 g. of propionyl chloride in 25 ml. of carbon disulfide. After the addition, the mixture was refluxed for 18 minutes, cooled, poured with stirring into ice-water, and extracted with ether. The ethereal extract was washed with aqueous sodium bicarbonate followed by water. After drying over anhydrous sodium sulfate, the ether was removed over a steam-bath and the residue distilled to give 4.3 g. of I and 15.3 g. of product, b.p. 113–116° (0.04 mm.),  $n_D^{20}$  1.5257. The yield, considering recovery of starting material, was 56%. The semicarbazone was prepared<sup>24</sup> and recrystallized from methanol, m.p. 163–165°.

*Anal.* Calcd. for C<sub>15</sub>H<sub>23</sub>N<sub>3</sub>O<sub>3</sub>: C, 61.40; H, 7.92. Found: C, 61.42; H, 7.82.

Oxidation of the aldehyde with neutral permanganate gave 3,4-dimethoxy-2-isopropylbenzoic acid (VI). This was shown by infrared analysis<sup>23</sup> and a mixed melting point with a sample prepared from 3-methoxy-4-hydroxy-5-isopropylacetophenone.<sup>5</sup>

(b).—A solution of 12.1 ml. of propionyl chloride in 30 ml. of anhydrous dichloromethane was added dropwise with stirring at room temperature to a suspension of 18.5 g. of aluminum chloride in 40 ml. of dichloromethane. The resulting solution was added dropwise to 25 g. of I in 50 ml. of dichloromethane at –5°. The addition required 40 minutes, after which the ice-bath was removed and the stirring continued for 50 minutes. The color changed slowly from bright to deep red. After cooling, the mixture was decomposed with cold dilute hydrochloric acid and extracted with ether. The ethereal extract was washed twice with 5% sodium hydroxide followed by water. After drying over anhydrous sodium sulfate, the ether and dichloromethane was removed over a steam-bath. Distillation gave 8.7 g. of I and 15.1 g. of material, b.p. 108–116° (0.10 mm.). The infrared spectrum of the pure liquid showed a small percentage of acetoxyl group absorption. Apparently some cleavage of the 2-methoxyl group occurred

(22) All melting points are uncorrected and were made on a Fisher-Johns melting point apparatus. The analyses were done by the Huffman Microanalytical Laboratories, Wheatridge, Colo. The infrared determinations were made on a Perkin-Elmer model 21 spectrophotometer. The pure liquids were determined in a 0.013-mm. cell and the solutions (3–5%) in matched (0.1-mm.) cells. All ultraviolet spectra were determined in methanol (Spectrograde) on a Beckman DR spectrophotometer.

(23) The two acids IV and VI were prepared by the published procedures<sup>4,5</sup> and both were found to sublime at 120° (0.05 mm.). In all of the experimental work reported, where determination of structure was ascertained by conversion to the acid, the crude reaction products were air-dried and sublimed. By examination of the infrared spectra of the chloroform solutions, it was possible to determine whether the material was a single acid or a mixture. None of the cases reported in this paper gave a mixture. The IV acid had bands at 2550, 2650, 1682, 1590, 1568, 1050 and 1020 cm.<sup>-1</sup>. The VI acid had bands at 2620, 1685, 1582, 1062 and 1003 cm.<sup>-1</sup>.

(24) F. Wild, "Characterization of Organic Compounds," Cambridge University Press, London, 1948, p. 122.

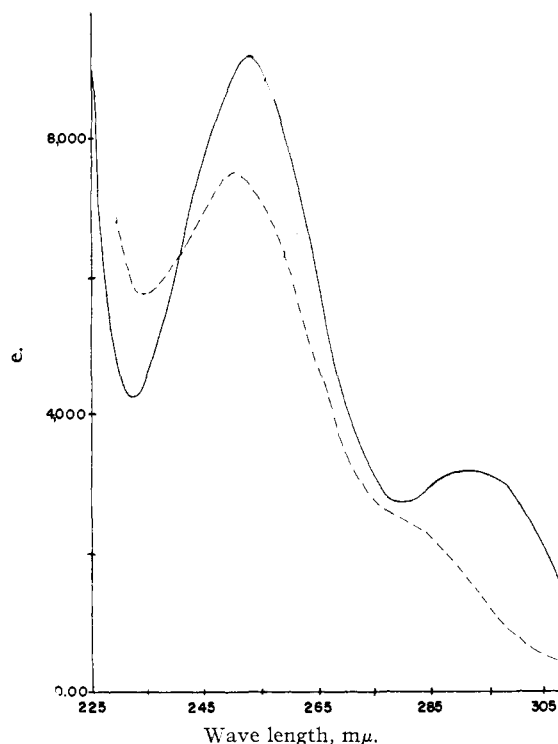


Fig. 3.———, 3,4-Dimethoxy-5-isopropylbenzoic acid (VI); ----, 3,4-dimethoxy-2-isopropylbenzoic acid (IV).

with subsequent esterification. No attempt was made to purify this fraction.

A solution of 4.7 g. of the above ketone in 110 ml. of pure dioxane<sup>25</sup> was added with good stirring to a solution prepared from 9.6 g. of bromine and 10.3 g. of potassium hydroxide (assay 86%) in 50 ml. of water at 0–10°. After stirring at room temperature for 30 minutes, the solution was refluxed for 15 minutes. On cooling, 25 ml. of 4% potassium hydroxide solution was added and the mixture was extracted three times with large volumes of ether. To the aqueous phase, 0.5 g. of sodium bisulfite was added and, on completion of solution, an excess of concd. hydrochloric acid was added. In two hours the precipitate was filtered, dried, sublimed<sup>23</sup> and recrystallized from ether-petroleum ether (30–60°), m.p. 113–115°, yield 2.5 g. The infrared spectrum and a mixed melting point showed the product to be the VI acid.

When the Friedel-Crafts reaction was carried out in the conventional manner, but using a threefold excess of aluminum chloride, apparently a variety of irreversible changes occurred. The acid obtained from the product by the haloform reaction was not identified. It was recrystallized from ether-petroleum ether (30–60°), m.p. 128–129°. Found: C, 68.95; H, 5.70.

**3,4-Dimethoxy-2-isopropylbenzaldehyde (VII).**—To a mixture of 71 g. of aluminum chloride and 400 ml. of anhydrous benzene, immersed in an ice-bath, there was added dropwise with stirring 75 g. of I. To this mixture there was added a solution of 65 ml. of anhydrous hydrogen cyanide in 100 ml. of benzene. A slow stream of anhydrous hydrogen chloride was passed through the mixture with stirring at room temperature for 8 hours. It was then cooled in an ice-bath and decomposed by the addition of an excess of crushed ice-hydrochloric acid. The resulting mixture was boiled for a few minutes to remove the excess hydrogen cyanide and, after cooling, extracted with ether. The ethereal extract was washed with 300 ml. of 5% sodium hydroxide followed by water. After drying over anhydrous sodium sulfate, the ether and benzene were removed over the steam-bath. Distillation gave 35.7 g. of I and 24 g. of aldehyde, b.p. 98–102° (0.13 mm.),  $n_D^{20}$  1.5485. The yield was 52%, considering recovered starting material.

(25) L. F. Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., Boston, Mass., 1955, p. 285.

The 2,4-dinitrophenylhydrazone was prepared<sup>26</sup> and crystallized from methanol, m.p. 190–192°.

*Anal.* Calcd. for  $C_{18}H_{20}N_4O_6$ : C, 55.66; H, 5.20. Found: C, 55.79; H, 5.58.

Oxidation of 2 g. of the above aldehyde in the usual manner using permanganate and purified acetone<sup>27</sup> gave after sublimation<sup>28</sup> and crystallization from ether–petroleum ether (30–60°), 1 g. of the IV acid, m.p. 121–122°. Structure was established by infrared analysis and a mixed melting point.

**Chloromethylation of I.**—To a solution of 5 g. of I in 8 ml. of glacial acetic acid, there was added with good stirring 4.5 g. of freshly distilled monochloromethyl ether.<sup>28</sup> The mixture was stirred at room temperature for 16 hours, poured into cold water and extracted with ether. The ethereal extract was washed 3 times with water and dried over anhydrous sodium sulfate. After evaporation of the ether, 150 ml. of water, 6 g. of sodium carbonate and 6 g. of potassium permanganate was added to the residue. The mixture was heated on the steam-bath with occasional stirring for 3 hours. After filtration an excess of hydrochloric acid was added. On standing for 4 hours in an ice-bath, the crystalline material was filtered, dried and sublimed<sup>29</sup> to give 0.5 g. of acid. The product was recrystallized from ether–petroleum ether (30–60°), m.p. 121–122°. A mixed melting point and infrared analysis showed it to be the IV acid.

**2,4-Dimethyl-6-methoxyacetophenone (X).**—In view of the results of Posternak<sup>9</sup> in attempting to repeat the work of von Auwers,<sup>3</sup> the Friedel-Crafts reaction was carried out in the following manner: To a suspension of 26.7 g. (0.2 mole) of aluminum chloride and 150 ml. of benzene (distilled from sodium hydride) there was added dropwise with stirring at 5–7°, 27.2 g. (0.2 mole) of 3,5-dimethylanisole,<sup>29</sup> followed by the dropwise addition of 15.7 g. (0.2 mole) of acetyl chloride in 50 ml. of dry benzene. After the addition was complete, the ice-bath was removed and the mixture stirred at room temperature for 2 hours. The final temperature was 23°. It was then poured with good stirring into an excess of concd. hydrochloric acid–crushed ice. After standing for 24 hours, the product was extracted with ether and washed with dilute sodium hydroxide. Acidification

of the alkaline extract gave only a negligible amount of precipitate. The original ethereal extract was washed with water and dried over anhydrous sodium sulfate. Evaporation of the ether and benzene gave a residue which was taken up in 100 ml. of petroleum ether (30–60°) by warming. After filtration and cooling at –20°, 27.4 g. of colorless crystals were obtained. The filtrate was concentrated to 35 ml. and cooled to give 4 g. more of the product; total yield 31.4 g. (88%), m.p. 48° (reported<sup>9</sup> 48°).

**2,4-Dimethyl-6-methoxybenzoic Acid (XIII).**—To a solution of 12.9 g. of potassium hydroxide in 50 ml. of water at 3–7°, there was added dropwise with good stirring 12.2 g. of bromine.

This solution was added with good stirring to 4.45 g. of IX in 110 ml. of pure dioxane<sup>29</sup> and allowed to stir at room temperature for one hour. It was then refluxed with stirring for one hour. After cooling, 1 g. of sodium bisulfite was added followed by 25 ml. of 8% potassium hydroxide. The mixture was extracted three times with large volumes of ether. To the aqueous phase there was added an excess of concd. hydrochloric acid. After cooling for 30 minutes at 10° the product was filtered and air-dried; yield 4.3 g. (95%), m.p. 156–158°. After two recrystallizations from benzene the m.p. was 177–178° (Found: C, 66.89; H, 6.62) and did not change on further recrystallizations. Literature<sup>12,30</sup> reports 167° and 167.5–168°. This acid was shown by mixed melting point and infrared analysis to be identical with the acid prepared from 2,4-dimethyl-6-hydroxybenzaldehyde<sup>11,12</sup> by methylation and oxidation.

**4-Bromo-3,5-dimethylanisole (XI).**—To 54.4 g. (0.4 mole) of IX dissolved in 1.5 l. of anhydrous carbon tetrachloride at 0–3°, there was added dropwise over a period of 6 hours, with good stirring, a solution of 64 g. (0.4 mole) of bromine in 250 ml. of carbon tetrachloride. The resulting solution was washed with 2 l. of 3% sodium hydroxide. After the extract was washed with water and dried over anhydrous sodium sulfate, the carbon tetrachloride was removed over the steam-bath. Distillation at 98.5° (2.75 mm.) gave 79.5 g. (92%),  $n_D^{20}$  1.5606, of product. The structure of this compound was established to be 4-bromo-3,5-dimethylanisole by carbonation of the Grignard reagent in the usual manner<sup>3</sup> (72%). The resulting acid (XII), m.p. 146°, was identical with that prepared by the permanganate oxidation of 2,6-dimethyl-4-methoxybenzaldehyde.<sup>11,12</sup> It was also identical with the acid prepared from the bromination product of 3,5-dimethylphenol.<sup>13,31</sup>

(26) Reference 24, p. 115.

(27) Reference 25, p. 281.

(28) "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1947, p. 377.

(29) D. A. Shirley, "Preparation of Organic Intermediates," John Wiley and Sons, Inc., New York, N. Y., 1951, p. 126.

(30) K. von Auwers and K. Sauerwein, *Ber.*, **55**, 2380 (1922).

(31) Sample kindly supplied by Professor R. C. Fuson.

HOUSTON, TEXAS