

### 898. *Some 2,5-Dialkoxyphenols.*

By C. A. BARTRAM, D. A. BATTYE, and C. R. WORTHING.

A convenient preparation of 2,5-dialkoxyphenols is described.

OTHER work required a number of 2,5-dialkoxyphenols, and in particular large quantities of 2,5-dimethoxyphenol. 2,5-Dimethoxyphenol has been obtained<sup>1-4</sup> by the diazotisation of 2,5-dimethoxyaniline, but in our hands under a variety of conditions the yields were low (10—25%) and variable, and the method was unsuitable for large-scale work.<sup>4</sup> We obtained 2,5-dimethoxyphenol in 50% yield from 2,5-dimethoxyphenylmagnesium bromide by using Hawthorne's general method,<sup>5</sup> but this route was only convenient for small quantities.

We have found that 2,5-dimethoxyphenol can conveniently be prepared in an overall yield of 50—60% by Friedel-Crafts acetylation of *p*-dimethoxybenzene, followed by Baeyer-Villiger oxidation<sup>6</sup> with peracetic acid and hydrolysis of the resulting 2,5-dimethoxyphenyl acetate. We obtained maximum yields by using an excess of acetyl chloride as solvent<sup>7</sup> in the Friedel-Crafts reaction. Ballio and Almirante<sup>8</sup> reported yields of 54—90% for the oxidation of a series of methoxyacetophenones to the corresponding methoxyphenyl acetates by peracetic acid. Using their conditions we obtained a yield of 45—48% for this step; by modifying the process yields of 67—77% were practicable.

A number of 2,5-dialkoxyphenols (Table 2) were prepared from the corresponding 2,5-dialkoxyacetophenones (Table 1) by the above technique. The yields quoted are probably not optimum. 2,5-Dibutoxyphenol was insoluble in 2*N*-aqueous sodium or potassium hydroxide. The structure was confirmed, however, by the presence of an infrared absorption band at 3530 cm.<sup>-1</sup> and by the formation of ethers. The structure of 4-chloro-2,5-dimethoxyacetophenone followed from its conversion into the known 4-chloro-2,5-dimethoxyphenol.<sup>9</sup>

#### EXPERIMENTAL

*2,5-Dimethoxyacetophenone.*<sup>7</sup>—Powdered anhydrous aluminium chloride (579 g.) was added in portions during 3—4 hr. to a stirred solution of *p*-dimethoxybenzene (500 g.) in acetyl chloride (650 ml.) at -10°. The mixture was stirred between 0° and -10° for a further 3 hr.; further quantities of acetyl chloride were added, if necessary, to facilitate stirring. The mixture was added to ice (4 kg.) and hydrochloric acid (400 ml.; *d* 1.19) and stirred overnight. The oil was separated and combined with chloroform extracts (3 × 250 ml.) of the aqueous layer. The chloroform solution was washed with water (2 × 1 l.), 2*N*-aqueous sodium hydroxide (3 × 500 ml.), and water (1 × 2 l.), and dried (MgSO<sub>4</sub>). The solvent was evaporated, and the residual oil distilled *in vacuo* to give, after a forerun of *p*-dimethoxybenzene, 2,5-dimethoxyacetophenone (520—565 g.), b. p. 156—158°/15 mm. (lit.<sup>10</sup> 156—158°/15 mm.), *n*<sub>D</sub><sup>24</sup> 1.5422.

<sup>1</sup> Süs, *Annalen*, 1947, **557**, 237; Astill, Fassett, and Roudabush, *Biochem. J.*, 1959, **72**, 451.

<sup>2</sup> Burger and Fitchett, *J. Amer. Chem. Soc.*, 1953, **75**, 1359.

<sup>3</sup> Ungnade and Hein, *J. Org. Chem.*, 1949, **14**, 911.

<sup>4</sup> Austin, personal communication.

<sup>5</sup> Hawthorne, *J. Org. Chem.*, 1957, **22**, 1001; Yarboro and Karr, *ibid.*, 1959, **24**, 1141.

<sup>6</sup> Hassall, *Org. Reactions*, 1957, **9**, 73.

<sup>7</sup> Kuroda and Matsukama, *Sci. Papers Inst. Phys. Chem. Res., Tokyo*, 1932, **18**, 51.

<sup>8</sup> Ballio and Almirante, *Ann. Chim. appl.*, 1951, **41**, 421.

<sup>9</sup> Castelfranchi, Oliverio, and Scrocco, *Gazzetta*, 1956, **86**, 371.

<sup>10</sup> Klages, *Ber.*, 1904, **37**, 3987.

**2,5-Dimethoxyphenyl Acetate.**<sup>8</sup>—A solution of peracetic acid was prepared by adding commercial 36–40% peracetic acid (615 ml.; 2.79 moles) to a solution of anhydrous sodium acetate (10.29 g.) in acetic acid (100 ml.) in order to neutralise<sup>11</sup> the sulphuric acid (1% w/v) in Laporte peracetic acid. This solution was added dropwise to a stirred solution of 2,5-dimethoxyacetophenone (330 g., 1.89 moles) in acetic acid (300 ml.) at 40–42°, and the whole stirred overnight at this temperature. The solution was cooled to 20°, the excess of peracetic acid decomposed by 10% aqueous sodium hydrogen sulphite, and the mixture concentrated *in vacuo* on the steam-bath to about half its volume. The residue was poured into water (1 l.); the precipitated oil soon solidified. The solid was filtered off, washed with water, triturated with *n*-sodium carbonate (600 ml.), filtered off, washed with water, and dried *in vacuo* at 50°. The product was boiled with light petroleum (1:2 l.; b. p. 60–80°), then filtered, and carbon tetrachloride (100 ml.) was added to the filtrate. On cooling, 2,5-dimethoxyphenyl acetate (245–280 g.) separated in prisms, m. p. 68–69° (lit., 63–64°,<sup>8</sup> 68°<sup>12</sup>) (Found: C, 61.5; H, 6.1. Calc. for C<sub>10</sub>H<sub>12</sub>O<sub>4</sub>: C, 61.2; H, 6.2%). The petroleum-insoluble material was recrystallised from acetic acid to give 2,5-dimethoxy-1,4-benzoquinone<sup>8</sup> (8 g.) in yellow needles, decomp. >260° (lit.,<sup>13</sup> decomp. >260°) (Found: C, 57.6; H, 4.55. Calc. for C<sub>8</sub>H<sub>8</sub>O<sub>4</sub>: C, 57.1; H, 4.8%).

**2,5-Dimethoxyphenol.**—(a) A mixture of the acetate (196 g.), potassium hydroxide (268 g.), ethanol (120 ml.), and water (1340 ml.) was refluxed for 3 hr. The solution was cooled, washed with chloroform (2 × 250 ml.), and acidified with hydrochloric acid (250 ml.; *d* 1.19) which precipitated a red oil. The oil was separated and combined with carbon tetrachloride extracts (3 × 250 ml.) of the aqueous layer. The organic solution was washed with water (200 ml.), dried (MgSO<sub>4</sub>), and evaporated, and the residual oil distilled *in vacuo* to give 2,5-dimethoxyphenol (132–147 g.), b. p. 124–126°/7 mm., *n*<sub>D</sub><sup>25</sup> 1.5434 (lit.,<sup>2</sup> 1.5430).

TABLE 1.

## 2,5-Dialkoxyacetophenones.

Acetophenone	B. p./mm.	Properties	Found (%)			Reqd. (%)		Yield (%)	Note
			C	H	Formula	C	H		
2-EtO-5-MeO ...	100—106°/0.25	M. p. 40—42°	68.2	7.3	C <sub>11</sub> H <sub>14</sub> O <sub>3</sub>	68.0	7.3	57	1
5-EtO-2-MeO ...	92/0.25	<i>n</i> <sub>D</sub> <sup>18</sup> 1.5368	67.5	7.1	C <sub>11</sub> H <sub>14</sub> O <sub>3</sub>	68.0	7.3	73	2
2,5-(EtO) <sub>2</sub> .....	106/0.3	M. p. 40—41.5	69.2	7.8	C <sub>12</sub> H <sub>16</sub> O <sub>3</sub>	69.2	7.7	83	3, 4
2,5-(BuO) <sub>2</sub> ...	130/0.04	<i>n</i> <sub>D</sub> <sup>22</sup> 1.5110	73.0	9.1	C <sub>16</sub> H <sub>24</sub> O <sub>3</sub>	72.7	9.15	72	4, 5
4-Cl-2,5-(MeO) <sub>2</sub>	—	M. p. 100—102.5	55.9	5.0	C <sub>10</sub> H <sub>11</sub> ClO <sub>3</sub>	55.9	5.2	86	4, 6

(1) Prisms (from aqueous ethanol); ethylation of 2-hydroxy-5-methoxyacetophenone (Vyas and Shah, *Org. Synth.*, 1951, **31**, 90). (2) Methylation of 5-ethoxy-2-hydroxyacetophenone (Patel and Shah, *J. Indian Chem. Soc.*, 1954, **31**, 867). (3) Bost and Howe (*J. Amer. Chem. Soc.*, 1952, **74**, 257) give b. p. 129°/13 mm., m. p. 41°. (4) Friedel-Crafts acetylation as for 2,5-dimethoxyacetophenone. (5) Bost and Howe (*ibid.*) give b. p. 159°/2 mm., m. p. 26°; *semicarbazone*, needles (from ethanol), m. p. 175–177° (Found: C, 63.4; H, 8.5; N, 13.5. C<sub>17</sub>H<sub>27</sub>N<sub>3</sub>O<sub>3</sub> requires C, 63.5; H, 8.5; N, 13.1%). (6) Needles (from ethanol).

TABLE 2.

## 2,5-Dialkoxyphenols.

Phenol	B. p./mm.	Properties	Found (%)			Reqd. (%)		Yield*	Note
			C	H	Formula	C	H		
2-EtO-5-MeO .....	82°/0.20	<i>n</i> <sub>D</sub> <sup>22</sup> 1.5338	64.45	6.9	C <sub>9</sub> H <sub>12</sub> O <sub>3</sub>	64.3	7.2	43	—
5-EtO-2-MeO .....	82/0.40	M. p. 39—41.5°	64.4	7.1	C <sub>9</sub> H <sub>12</sub> O <sub>3</sub>	64.3	7.2	23	1
2,5-(EtO) <sub>2</sub> .....	82/0.06	M. p. 42—44	65.9	7.6	C <sub>10</sub> H <sub>14</sub> O <sub>3</sub>	65.9	7.7	45	2
2,5-(BuO) <sub>2</sub> .....	114/0.15	<i>n</i> <sub>D</sub> <sup>22</sup> 1.5048	70.8	9.2	C <sub>14</sub> H <sub>22</sub> O <sub>3</sub>	70.55	9.3	50	3
4-Cl-2,5-(MeO) <sub>2</sub> ...	—	M. p. 93—95	51.0	4.6	C <sub>8</sub> H <sub>9</sub> ClO <sub>3</sub>	51.0	4.8	44	4

\* From the acetophenone (acetate not isolated). (1) Needles [from light petroleum (b. p. 40–60°)]. (2) Needles (from water). (3) Insoluble in alkali, recovered from chloroform solution. (4) Prisms (from benzene); lit.,<sup>9</sup> m. p. 96–97°; acetate, needles (from aqueous ethanol), m. p. 79–82° (lit.,<sup>9</sup> m. p. 81°) (Found: C, 52.2; H, 4.7; Cl, 15.2. Calc. for C<sub>10</sub>H<sub>11</sub>ClO<sub>4</sub>: C, 52.05; H, 4.8; Cl, 15.4%); *p*-nitrobenzoate, yellow needles (from ethanol), m. p. 153–156° (lit.,<sup>9</sup> m. p. 154–155°) (Found: C, 53.6; H, 3.9; Cl, 10.0; N, 4.3. Calc. for C<sub>15</sub>H<sub>12</sub>ClNO<sub>6</sub>: C, 53.4; H, 3.6; Cl, 10.5; N, 4.15%). Oxidation carried out at 60°.

<sup>11</sup> Meltzer and Doczi, *J. Amer. Chem. Soc.*, 1950, **72**, 4986.

<sup>12</sup> Ciamician and Silber, *Ber.*, 1891, **24**, 2608.

<sup>13</sup> Fabinyi and Széki, *Ber.*, 1911, **44**, 2293.

(b) 2-Bromoquinol<sup>14</sup> was methylated with dimethyl sulphate, to give 1-bromo-2,5-dimethoxybenzene, b. p. 142—143°/17 mm. (lit.,<sup>3</sup> 140—144°/16 mm.),  $n_D^{22}$  1.5702 (Found: Br, 36.5. Calc. for  $C_8H_9BrO_2$ : Br, 36.8%). The remaining stages were carried out under an atmosphere of nitrogen. 2,5-Dimethoxyphenylmagnesium bromide was prepared by boiling magnesium (2.5 g.) and the bromo-ether (21.9 g.) in tetrahydrofuran (150 ml.) for 2 hr. The solution was added slowly to a stirred solution of tributyl borate<sup>15</sup> (30 ml.) in tetrahydrofuran (100 ml.) at  $\gamma$  -60°. Stirring was continued overnight as the reaction mixture was allowed to reach room temperature. After removal of the tetrahydrofuran at 40° *in vacuo*, benzene (100 ml.) was added, and the mixture cooled in ice, treated with *N*-hydrochloric acid (100 ml.), and stirred for 5 min. The organic layer was separated, washed with water, and refluxed for 3 hr. with 28% hydrogen peroxide (30 ml.). The benzene solution was washed successively with water, acidified ferrous sulphate solution, water, and 2*N*-sodium hydroxide. The alkali washings were acidified, and the oil was extracted into benzene, which was evaporated. The residue was distilled to give 2,5-dimethoxyphenol (8 g.), b. p. 104—108°/0.13—0.18 mm.,  $n_D^{23}$  1.5430. The benzoate, needles (from aqueous ethanol), m. p. 73—75° (lit.,<sup>16</sup> 73—75°) (Found: C, 69.7; H, 5.6. Calc. for  $C_{15}H_{14}O_4$ : C, 69.75; H, 5.5%), was identical (mixed m. p.) with the derivative prepared from the authentic phenol.<sup>4</sup>

The authors thank W. C. Austin for permission to quote his results and P. R. Wood for microanalyses.

PFIZER LIMITED, SANDWICH, KENT.

[Received, April 19th, 1963.]

<sup>14</sup> Terent'ev, Grivev, and Terent'ev, *Zhur. obshchei Khim.*, 1954, **24**, 1433.

<sup>15</sup> Johnson and Tompkins, *Org. Synth.*, Coll. Vol. II, p. 106.

<sup>16</sup> Gilman and Van Ess, *J. Amer. Chem. Soc.*, 1939, **61**, 1365.