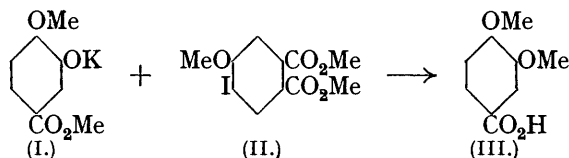


### 256. Phthalic Esters as Alkylating Agents.

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A new method is described for the alkylation of phenols in good yield. It consists in heating, to 190—200°, a salt of the phenol, preferably the potassium salt, with a molecular proportion of an alkyl phthalate.

In synthetic experiments on the preparation of certain complex diphenyl ethers by, for instance, condensation of the potassium derivative of methyl *isovanillate* (I) with methyl 5-iodo-4-methoxyphthalate (II) in presence of copper, the formation of a considerable proportion of veratric acid (III) was observed (this vol., p. 1158). Since this reaction was

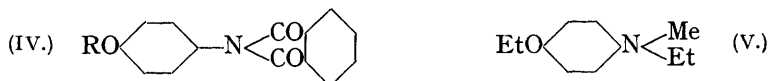


accompanied by a loss of phthalic esters in the neutral fraction from the condensation, it seemed that the methylation had been effected at the expense of the phthalic ester groups. It was thought that this might be an example of a more general reaction, and since many phthalic esters are cheap commercial products and those not available commercially are readily made, it was possible that phthalic esters might serve as alkylating agents for phenolic groups.

After preliminary experiments, it was found in general, that when the potassium salts of phenol and guaiacol were heated to 190—200° with a molecular proportion of methyl, ethyl or butyl phthalate, 70—85% yields of the corresponding phenol and guaiacol ethers were obtained. In each case the reaction proceeded better with potassium than with sodium. It was also essential, in preparing the potassium salt of the phenolic substances, to use as solvent for the potassium the same alcohol as is being introduced as a radical through the phthalic ester. In many of these reactions the yield of unused alkyl phthalate recovered by distillation was greater than would be expected if only one ester group per molecule of alkyl phthalate had been used in alkylating the phenol, showing that both ester groups of a proportion of the molecules were utilised. This was supported by the observation that methyl benzoate, used in the same way, gave a 63% yield of anisole and a 57% yield of veratrole. The possibility that the method might be extended to aromatic esters and that phenyl esters, for instance, of phthalic acid might be used with phenols for synthesising diphenyl ethers was not realised.

An extension of the reaction to nitrogenous substances was tried with *p*-methylamino-phenol. When the potassium salt of this phenol was heated with methyl phthalate, the only products identified were *p*-dimethylaminoanisole and *phthalo-4'-methoxyphenylimide* (IV, R = Me), methylation in the former case having occurred on oxygen and nitrogen. With ethyl phthalate, however, the product was mainly *p*-methylaminophenetole with a

small proportion of *p*-methylethylaminophenetole (V), characterised as its *picrate*, and *phthalo-4'-ethoxyphenylimide* (IV, R = Et). With butyl phthalate the main product was *p*-butoxymethylaniline. As the homologous series of esters is ascended, the amount of *N*-alkylation thus rapidly falls off, but *O*-alkylation proceeds normally.



The use of dry alkali-metal salts of acids and phenols in methylation experiments with methyl sulphate, a reagent which may be compared with alkyl phthalates, is not new; *e.g.*, Ullmann and Wenner (*Ber.*, 1900, **33**, 2477; compare Ullmann, *Annalen*, 1903, **327**, 104) converted sulphonic acids into methyl esters by heating the dry sodium salts with methyl sulphate. Graebe also (*Annalen*, 1905, **340**, 245) found that many organic acids in the form of their dry potassium salts gave good yields of methyl esters on heating with methyl sulphate. Among phenolic substances Graebe and Aders (*Annalen*, 1901, **318**, 365) methylated the dry sodium salt of euxanthone monomethyl ether and of alizarin, and Graebe (*ibid.*, 1905, **340**, 248) found that potassium chloranilate could be methylated by heating with methyl sulphate but not by methyl iodide or by methyl sulphate in presence of water. The higher alkyl sulphates are much less reactive than methyl sulphate, but this diminished reactivity could probably be overcome by heating the dry potassium salt of the substance to be alkylated with the alkyl sulphate, as is done in the present communication with alkyl phthalates. Ethyl and propyl sulphate are commercial products and higher alkyl sulphates might be made, following Smyth's lead (P., 1914, **30**, 14), from sulphuryl chloride and alcohols.

#### EXPERIMENTAL.

*Preparation of Anisole.*—Potassium (3.91 g.) was allowed to react with ice-cold methyl alcohol (30 c.c.) and then phenol (9.4 g.) and methyl phthalate (19.4 g.) were added. The excess of methyl alcohol was removed by warming under diminished pressure and the syrupy residue was heated, in a flask fitted with an air-condenser, in an oil-bath at 190—200° for 3 hours. When cold, the partly solid mass was dissolved in water and ether and the ether-soluble portion was washed with 2*N*-sodium hydroxide and fractionally distilled. The fraction, b. p. 150—200°, was redistilled, the anisole then boiling between 152° and 156°; yield, 8.1 g. (75%).

In a repetition of this experiment, after 7 hours' heating, the yield of anisole was 74% and 9.0 g. of unchanged methyl phthalate were recovered. The theoretical amount to be recovered, if only one methyl group from each methyl phthalate molecule is used, should be 5.1 g.

In an exactly similar manner the reaction was carried through with phenol and guaiacol as substrates, and methyl, ethyl, and butyl phthalates as alkylating agents, the potassium in each case being dissolved in the alcohol corresponding to the radical being introduced. The results are summarised in the following table:

Phenol.	Alkylating agent.	Product.	Yield, %.
Phenol	Methyl phthalate	Anisole	75
"	Ethyl "	Phenetole	66
"	Butyl "	Phenyl butyl ether	76
Guaiacol	Methyl "	Veratrole	78
"	Ethyl "	<i>O</i> -Ethylguaiacol	84
"	Butyl "	<i>O</i> -Butylguaiacol	80

*O*-Butylguaiacol is described by Allan and Robinson (J., 1926, 382) as a colourless oil, b. p. 236—239°, and by Hirao (*J. Chem. Soc. Japan*, 1932, **53**, 488) as a liquid, b. p. 178°/132 mm. We find a boiling point in agreement with Allan and Robinson, but we also find that the product readily solidifies to a solid, crystallising in long needles, m. p. 17—18° (Found: C, 73.3; H, 9.0. Calc.: C, 73.4; H, 9.1%).

*Preparation of Anisole and Veratrole by Means of Methyl Benzoate.*—When the methyl phthalate was replaced by a molecular equivalent of methyl benzoate, the yield of anisole was 63% and that of recovered methyl benzoate 16%.

In the case of guaiacol the products of the reaction had to be saponified to facilitate separation, the yield of crystalline veratrole being 57%.

*Alkylation of a Phenol with a Reactive Basic Centre.*—*p*-Methylaminophenol and methyl

*phthalate*. Potassium (3.91 g.) in methyl alcohol (30 c.c.), *p*-methylaminophenol (12.3 g.), and methyl phthalate (19.4 g.) were mixed, the excess of methyl alcohol removed, and the residue heated for 3 hours in an oil-bath at 200—210°. The product was dissolved in water and ether and the separated ethereal extracts were washed first with 2*N*-sodium hydroxide to remove phenols and then extracted three times with 3*N*-hydrochloric acid to remove the non-phenolic bases. The acid extract was basified, the bases extracted with ether, and the solvent removed. The residue (4.9 g.) crystallised readily and on recrystallisation from 50% aqueous ethyl alcohol gave pearly scales of *p*-dimethylaminoanisole, m. p. 46—47° (Found: C, 71.6; H, 8.6. Calc.: C, 71.5; H, 8.7%), agreeing in properties with the description given by Griess (*Ber.*, 1880, 13, 249). On keeping, the ethereal solution, which had been extracted with alkali and with acid, deposited flat rods, m. p. 162°, which were unchanged in m. p. on crystallisation from alcohol, but separated in needles. These proved to be *phthalo-4'-methoxyphenylimide* (IV, R = Me) (Found: C, 71.1; H, 4.4; N, 5.5; MeO, 12.2. C<sub>15</sub>H<sub>11</sub>O<sub>3</sub>N requires C, 70.7; H, 4.3; N, 5.2; MeO, 12.0%).

*p*-Methylaminophenol and ethyl *phthalate*. This reaction was carried out with molecular proportions of the components as described in the preceding example. The original ether-extracted aqueous liquor and the ethereal solution which had been extracted with alkali and with acid both deposited a sparingly soluble, crystalline solid (0.53 g. in all), which crystallised from 120 vols. of boiling alcohol in needles, m. p. 204—205°. These proved to be *phthalo-4'-ethoxyphenylimide* (IV, R = Et) (Found: C, 72.1, 72.0; H, 4.7, 4.8. C<sub>16</sub>H<sub>13</sub>O<sub>3</sub>N requires C, 71.9; H, 4.9%).

The acid extract of the ethereal solution, on basification and extraction with ether, gave, on removal of the solvent, an oil, 6.45 g. of which distilled at 130°/14 mm. This distillate, in 3*N*-hydrochloric acid (33 c.c.), was cooled to 0° and treated dropwise with sodium nitrite (10% solution) until there was a permanent reaction with starch-iodide paper. The crystalline *p*-nitrosomethylaminophenetole (3.93 g.) was collected; a portion crystallised from low-boiling petroleum had m. p. 46°. Brunner and Moser (*Monatsh.*, 1932, 61, 15) give m. p. 49°. The aqueous filtrate, whilst still acid, was extracted with ether, which removed a trace of nitroso-compound; it was then made alkaline and re-extracted with ether. On removal of the solvent a brown oil (1.25 g.) was left, which formed a hygroscopic crystalline hydrochloride. This readily gave *p*-methylethylaminophenetole *picrate*, m. p. 125°, in large elongated tablets from 10 vols. of boiling alcohol (Found: C, 50.0; H, 4.9. C<sub>11</sub>H<sub>17</sub>ON, C<sub>6</sub>H<sub>3</sub>O<sub>7</sub>N<sub>3</sub> requires C, 50.6; H, 5.2%).

*p*-Methylaminophenol and butyl *phthalate*. The yield of non-phenolic bases in this reaction was 9.1 g. This was treated with nitrous acid as in the previous experiment, and gave a crystalline nitroso-compound, which was not further examined. The tertiary base which was left unattacked was only 0.5 g.

On this basis the preparation of non-phenolic bases was repeated and the product distilled (b. p. 154—155°/16 mm.) without conversion into the nitroso-derivative. This proved to be *p*-butoxymethylaniline (Found: C, 73.7; 9.6. C<sub>11</sub>H<sub>17</sub>ON requires C, 73.3; H, 9.7%). It was characterised as its *picrate*, which was sparingly soluble in boiling water and crystallised in long silky needles, m. p. 98° (Found: C, 50.0; H, 5.0; N, 13.7. C<sub>11</sub>H<sub>17</sub>ON, C<sub>6</sub>H<sub>3</sub>O<sub>7</sub>N<sub>3</sub> requires C, 49.5; H, 5.2; N, 13.6%).