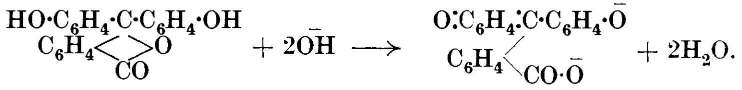
CCIV.—*The Constitution of Phenolphthalein. Part I. Preparation of Some Compounds of the Phthalein Type.*

By HAKON LUND.

THE constitutions of phenolphthalein and its coloured derivatives have been thoroughly discussed by many chemists and different theories have been put forward to explain the intense colour of the salts of phenolphthalein and similar compounds. Friedländer (*Ber.*, 1893, **26**, 173) was the first to suggest the usually accepted theory that one of the phenol groups is transformed into a quinonoid group when phenolphthalein reacts with one or two molecules of alkali :



$$\begin{array}{c}HO\cdot C_6H_4\cdot C\cdot C_6H_4\cdot OH\\ C_6H_4{<}\underset{CO}{\,}{>}O\end{array} + 2\bar{O}H \longrightarrow \begin{array}{c}O{:}C_6H_4{:}C\cdot C_6H_4\cdot\bar{O}\\ C_6H_4{<}\underset{CO\cdot\bar{O}}{\,}\end{array} + 2H_2O.$$

The discussion has, however, not yet led to any conclusive result. The latest work * dealing with the constitution of phenolphthalein and related substances is that of Birge and Acree (*J. Amer. Chem. Soc.*, 1919, **41**, 1031, where reference is given to a series of preceding papers), who have presented a " quinone phenolate " theory for the coloured compounds in the phthalein series. In this paper, they promise an extensive investigation which, unfortunately, seems to have been interrupted. Some of the experiments there suggested will be dealt with in the present investigation, although from another point of view.

The purpose of this investigation is to examine a series of phthalein compounds in regard to their physico-chemical properties. It is hoped that it will be possible to bring the halochromism of these

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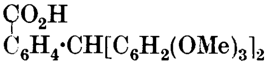
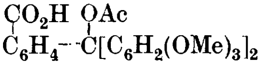
* When this communication was submitted for publication the author had no knowledge of the papers by Thiel and his co-workers (*Sitzungsber. Ges. Beförd. gesamt. Naturwiss. Marburg*, 1927, **62**, 471). Their results will be discussed in a future paper.

compounds into close relationship with that of the common triphenylcarbinol derivatives, some of which were studied a few years ago (*Dissert.*, Copenhagen, 1926. See also *J. Amer. Chem. Soc.*, 1927, **49**, 1346). The theoretical treatment of the subject will, however, be given in a subsequent paper. Here only the preparation of a number of new phthaleins and some of their purely chemical properties will be described.

In order to examine the influence of the carboxyl group 4-*carboxy-2′ : 4′ : 6′ : 2″ : 4″ : 6″-hexamethoxytriphenylcarbinyl acetate* (II) was prepared by condensing terephthalaldehydic acid (1 mol.) with phloroglucinol trimethyl ether (2 mols.) by means of hydrogen chloride and oxidising the product, 2′ : 4′ : 6′ : 2″ : 4″ : 6″-*hexamethoxytriphenylmethane*-4-*carboxylic acid* (I), in glacial acetic acid solution with lead tetra-acetate. The *perchlorate* also was prepared; the carbinol-acid itself and its anhydride were too unstable to be isolated.

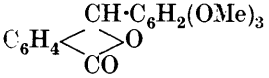
(I.) 

$\overset{CO_2H}{C_6H_4}\cdot CH[C_6H_2(OMe)_3]_2$

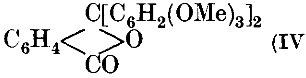
 (II.)

$\overset{CO_2H}{C_6H_4}-\overset{OAc}{C}[C_6H_2(OMe)_3]_2$

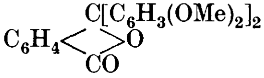
In the attempt to prepare the corresponding *o*-phthalic derivative in a similar way, 2′ : 4′ : 6′-*trimethoxyphenylphthalide* (III) was obtained, the condensation taking place between only one molecule each of phloroglucinol trimethyl ether and *o*-phthalaldehydic acid. *Phloroglucinolphthalein hexamethyl ether* (IV) had to be made from phthalyl chloride, anhydrous zinc chloride being used as a condensing agent; it is colourless in neutral solution, whereas (II) is strongly coloured even when it is neutralised with one molecule of sodium hydroxide.

(III.) 

$C_6H_4<\begin{matrix}CH\cdot C_6H_2(OMe)_3\\ CO\end{matrix}>O$

 (IV.)

$C_6H_4<\begin{matrix}C[C_6H_2(OMe)_3]_2\\ CO\end{matrix}>O$

Resorcinolphthalein tetramethyl ether,  $C_6H_4<\begin{matrix}C[C_6H_3(OMe)_2]_2\\ CO\end{matrix}>O$ (V), was prepared in order to compare it with phenolphthalein dimethyl ether and (IV) in regard to their behaviour towards bases and acids. Phenolphthalein dimethyl ether dissolved in alcoholic potassium hydroxide, forming the compound $C_6H_4(CO_2K)\cdot C(OH)(C_6H_4\cdot OMe)_2$; this remained in solution when water was added, provided that excess of alkali was present. Compound (V) also dissolved, forming an analogous salt; but on dilution with water this salt slowly split off potassium hydroxide and (V) was precipitated quantitatively. Compound (IV) did not react at all with potassium hydroxide : 1 mol. was boiled for an hour with 30 mols. of potassium hydroxide in the minimum quantity of alcohol necessary for dissolving the compound; on cooling, however, a portion of the original compound crystallised, and the remainder was immediately precipitated on dilution with water.

Towards acids the three compounds behave similarly to the non-carboxylated, methoxy-substituted triphenylcarbinols: with increasing number of methoxy-groups the tendency to form coloured salts with acids increases. For instance, phenolphthalein dimethyl ether is only slightly coloured in concentrated hydrochloric acid, whereas the hexamethoxy-compound (IV) is strongly coloured in 10% hydrochloric acid. The great difference in absolute "basicity" of similarly substituted compounds of the two classes will be discussed in a subsequent paper.

During the work with the polymethoxylated triphenylcarbinols, it was observed that compounds containing two phloroglucinol trimethyl ether groups were very unstable in the presence of acids. The same proved to be the case with the compound (IV). In order to check the constitution of this compound it was intended to reduce it to the corresponding phthalin. Usually the best reducing agent for the polymethoxylated triphenylcarbinols is a solution of hydrochloric acid in alcohol. The compound (IV) dissolved in this medium, forming a strongly coloured solution which gradually lost its colour exactly as was to be expected. But no odour of acetaldehyde could be detected, and the compound which crystallised was an acid with an equivalent weight of about 320 instead of 468. The reaction proved to be a splitting of the molecule:

$$(IV) + H_2O \longrightarrow CO_2H\cdot C_6H_4\cdot COR + RH,$$

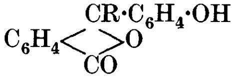
where R denotes 2 : 4 : 6-trimethoxyphenyl.

When the compound (IV) was heated for a short time with a mixture of glacial acetic acid and concentrated hydrochloric acid, the reaction proceeded still farther:

$$(IV) + 2H_2O \longrightarrow C_6H_4(CO_2H)_2 + 2RH.$$

The phloroglucinol trimethyl ether could be recovered practically quantitatively, and the phthalic acid was identified through the fluorescein test.

Finally, unsymmetrical phthaleins of the type



$$C_6H_4<\begin{array}{c}CR\cdot C_6H_4\cdot OH\\ \\ CO\end{array}>O \qquad (VI),$$

where R is 4-methoxyphenyl, 2 : 4-dimethoxyphenyl, or 2 : 4 : 6-trimethoxyphenyl, were prepared. 4′-Hydroxy-*o*-benzoylbenzoic acid was condensed with phenolic ethers by means of an agent which appears not to have been applied before, *viz.*, a solution of concentrated sulphuric acid in anhydrous ethyl ether. This mixture has to only a small extent the splitting effect upon these compounds which makes hydrogen chloride, aluminium chloride, and stannic chloride unsuitable for this condensation.

Phenolphthalein monomethyl ether (VI; R = 4-methoxyphenyl) was described by Meyer and Spengler (*Ber.*, 1905, **38**, 1328) as being intensely red in alkaline solution. Later Green and King (*Ber.*, 1907, **40**, 3729) showed that this colour was due to the presence of some phenolphthalein. They drew the conclusion that an alkaline solution of the pure monomethyl ether would be colourless, since the red colour became weaker and weaker by repeated crystallisations. Actually, however, it is yellow, and the colour fades slowly, as does that of all the phenolphthaleins, in the presence of a large excess of alkali.

A fact which has hitherto been overlooked is that this compound only crystallises with solvent of crystallisation, *e.g.*, one half molecule of toluene. After the solvent has been removed by heating, the molten mass solidifies to a glass-like substance which can be kept for months without crystallising. When, however, it is covered with a solvent such as alcohol, benzene, or toluene, crystallisation sets in after a few minutes and the whole mass is soon transformed into loose crystals. The different melting points reported in the literature, therefore, are of very limited value, because the temperature at which the compound becomes liquid depends on the solvent used and on the rate of heating.

Phenolphthalein monomethyl ether is insoluble in sodium carbonate solution, but gives a yellow solution in dilute aqueous sodium hydroxide—a fact which furnishes a method of purification. *Resorcinolphenolphthalein* 2′ : 4′-*dimethyl ether* (VI) forms a yellow solution in sodium carbonate; and *phloroglucinolphenolphthalein* 2′ : 4′ : 6′-*trimethyl ether* is soluble with an intense yellowish-brown colour in secondary sodium phosphate solution, where the hydroxyl-ion concentration is much smaller. This shows that the phenolic hydrogen becomes more acidic with increasing substitution of methoxy-groups in the other benzene ring. This phenomenon will be more thoroughly discussed in a future paper.

EXPERIMENTAL.

2′ : 4′ : 6′ : 2″ : 4″ : 6″-*Hexamethoxytriphenylmethane*-4-*carboxylic Acid* (I).—Into a solution of phloroglucinol trimethyl ether (2 g.) and terephthalaldehydic acid (0·9 g.) in absolute alcohol (35 c.c.) hydrogen chloride was passed until crystallisation began. After an hour the crystals were collected (2·25 g.; yield, 80%) and recrystallised from alcohol and from toluene; m. p. 258—260° (corr.) (Found: C, 66·4; H, 5·9; equiv., by titration, 470. $C_{26}H_{28}O_8$ requires C, 66·6;

H, 6·0%; equiv., 468). This colourless compound is soluble in acetone and acetic acid and slightly soluble in alcohol.

4-*Carboxy-2′ : 4′ : 6′ : 2″ : 4″ : 6″-hexamethoxytriphenylcarbinyl Acetate* (II).—The preceding compound (1 g.) and lead tetra-acetate (1 g.) were left in glacial acetic acid at 50° for 4 hours and at room temperature over-night. 4·63 C.c. of *N*-sulphuric acid in glacial acetic acid were then added and the filtered solution was evaporated under reduced pressure at about 45°. The residue was twice dissolved in chloroform and precipitated with anhydrous ether, yielding 0·45 g. of a violet-black powder with a bronze lustre (Found : C, 63·7; H, 5·8. $C_{28}H_{30}O_{10}$ requires C, 63·85; H, 5·75%). The acetate is soluble in acetone, acetic acid and chloroform and slightly soluble in ether and water. In all solvents except ether it dissolves with a very intense violet colour. When the colourless ethereal solution is shaken with water, this slowly becomes coloured.

The *perchlorate*, prepared from perchloric acid and the acetate in chloroform–ether solution, crystallises in violet leaflets with an intense metallic lustre. It decomposes violently when heated. For analysis the compound was oxidised with acid potassium permanganate, and the perchloric acid then reduced by means of titanous sulphate (Rothmund, *Z. anorg. Chem.*, 1909, **62**, 108) (Found : Cl, 6·1. $C_{26}H_{27}O_{12}Cl$ requires Cl, 6·3%).

2′ : 4′ : 6′-*Trimethoxyphenylphthalide* (III).—Hydrogen chloride was passed into a solution of phloroglucinol trimethyl ether (1·1 g.) and *o*-phthalaldehydic acid (0·5 g.) in absolute alcohol (15 c.c.); colourless crystals were soon deposited. The product (1·1 g.) was collected after 12 hours and recrystallised from alcohol and from toluene; m. p. 200° (corr.) (Found : C, 67·9; H, 5·4. $C_{17}H_{16}O_5$ requires C, 68·0; H, 5·4%). The production of the phthalide is in agreement with the facts that alcoholic hydrogen chloride splits off one molecule of phloroglucinol trimethyl ether from the compound (IV) and that benzhydrol-*o*-carboxylic acids very readily lose water, yielding phthalides.

Phloroglucinolphthalein Hexamethyl Ether (IV).—A solution of phthalyl chloride (2 g.) and phloroglucinol trimethyl ether (3·3 g.) in absolute ether containing freshly fused zinc chloride (about 8 g.) was shaken during 15 minutes. The slightly coloured ethereal layer was then poured off, the violet residue decomposed by water, and the solid separated. After being washed with water, ground with excess of potassium hydroxide solution, again washed, and dried (yield, 4·2 g.), it was recrystallised from alcohol and from toluene; it was then colourless and melted at 175—176° (corr.) (Found : C, 66·8; H, 5·7. $C_{26}H_{26}O_8$ requires C, 66·9; H, 5·6%). It forms a violet solution in dilute hydrochloric acid.

The phthalein (IV), dissolved in hot alcohol, was treated with concentrated hydrochloric acid, and when the violet colour had been discharged the solution was evaporated to a small volume, treated with an excess of aqueous potassium hydroxide to hydrolyse the ester formed, and acidified. • 2′ : 4′ : *6′-Trimethoxybenzoyl-*o*-benzoic acid* was precipitated; after recrystallisation from water and from toluene, it melted at 184—185° (corr.) (Found : C, 64·4; H, 5·0; equiv., 320. $C_{17}H_{16}O_6$ requires C, 64·5; H, 5·1%; equiv., 316).

The phthalein (0·5 g.), dissolved in 5 c.c. of glacial acetic acid, was boiled with 1 c.c. of hydrochloric acid for a few minutes until the violet colour had disappeared. Addition of water then precipitated phloroglucinol trimethyl ether (0·31 g.; calc., 0·36 g.). The filtrate contained phthalic acid.

Resorcinolphthalein Tetramethyl Ether (V).—This compound, which could not be prepared from phthalyl chloride and resorcinol dimethyl ether, was made in the following way : A solution of 2′ : 4′-dimethoxybenzoyl-*o*-benzoic acid (3 g.) in hot resorcinol dimethyl ether (3 g.) was cooled and treated with a cold solution of 10 c.c. of concentrated sulphuric acid in 20 c.c. of anhydrous ether. The mixture was poured into 300 c.c. of cold water, the ether expelled by heating on the steam-bath, and the water decanted from the viscous reaction product. This, after being freed from the excess of resorcinol dimethyl ether by steam-distillation, solidified on cooling (yield, 4·1 g.) and was then recrystallised from alcohol and from toluene; it crystallised very slowly (Found: C, 70·8; H, 5·4. $C_{24}H_{22}O_6$ requires C, 70·9; H, 5·5%). This colourless compound, m. p. 153° (corr.), is soluble without colour in acetone, acetic acid and hot alcohol. In 20% hydrochloric acid it dissolves with a reddish-violet colour.

Phenolphthalein Monomethyl Ether (VI; $R = C_6H_4{\cdot}OMe$).—(1) Phenolphthalein (1 mol.) was treated with methyl sulphate (1 mol.), and the crude product was dissolved in ether and repeatedly shaken with sodium carbonate solution, until this remained colourless (about 15 times). The monomethyl ether was now extracted from the ethereal solution by means of *N*-sodium hydroxide, recovered by acidification, and crystallised from benzene and from toluene.

(2) 4′-Methoxybenzoyl-*o*-benzoic acid (3 g.) and phenol (3 g.) were fused together and cooled, a solution of concentrated sulphuric acid (12 c.c.) in anhydrous ether (12 c.c.) added, and the mixture poured into cold water. The purification was as described above, but three washings with sodium carbonate were sufficient to remove unchanged acid and the trace of phenolphthalein formed. The yield of monomethyl ether was 3·1 g. (80%).

A specimen recrystallised from toluene, when dried at 130° in a current of air under diminished pressure, lost 12·2% in weight (calc. for $\frac{1}{2}$ molecule of toluene of crystallisation, 12·3%).

Resorcinolphenolphthalein 2′ : 4′-Dimethyl Ether [VI; R = $C_6H_3(OMe)_2$].—4′-Hydroxybenzoyl-*o*-benzoic acid (2 g.) was dissolved with cooling in 10 c.c. of concentrated sulphuric acid and added slowly to a solution of resorcinol dimethyl ether (1·5 g.) in 20 c.c. of anhydrous ether, and the whole was poured into water. The mixture was then extracted with ether. The ethereal solution was washed twice with potassium bicarbonate solution, whereby the unchanged acid, if any, was removed. Two extractions with 50 c.c. of *N*-sodium hydroxide brought the *phthalein* into aqueous solution. This was freed from ether by warming on the steam-bath, cooled, and acidified. After recrystallisation from alcohol the phthalein melted at 220° (corr.). For combustion it was recrystallised from toluene (Found: C, 73·2; H, 4·9. $C_{22}H_{18}O_5$ requires C, 72·9; H, 5·0%).

Phloroglucinolphenolphthalein 2′ : 4′ : 6′-Trimethyl Ether [VI; R = $C_6H_2(OMe)_3$].—This was prepared from 1·4 g. of phloroglucinol trimethyl ether and 2 g. of the ketonic acid in the same way as the previously described compound. Yield, 1·15 g.; m. p. 200° (corr.) (Found: C, 70·2; H, 5·2. $C_{23}H_{20}O_6$ requires C, 70·4; H, 5·1%).

In this case an equilibrium seems to be established, ketonic acid + phenolic ether $\rightleftharpoons$ phthalein + water, which is displaced towards the left side with increasing sulphuric acid concentration. A certain amount of acid, however, has to be present in order to bring about the condensation. After several experiments the proportion indicated (10 c.c. of acid to 20 c.c. of ether) was found to be the most advantageous in this case.

The phthalein is soluble in sodium carbonate and hydroxide solutions with an intense brownish-yellow colour which is much less readily discharged by excess of alkali than that of the two preceding compounds. The similar colour of a solution in secondary sodium phosphate, however, disappears when a little primary phosphate solution is added.

The author desires to express his gratitude to Professor Einar Biilmann for his kind interest in this work.

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