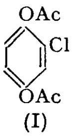
137. *Acylation Reactions Catalysed by Strong Acids. Part VI.* A Comparison of Zinc Chloride and Perchloric Acid as Catalysts for the Thiele Acetylation of Quinones.*

By H. Burton and P. F. G. Praill.

Zinc chloride is not an effective catalyst for the general reaction named in the title; mixtures of the normal triacetates and chlorodiacetates are usually produced. Tolu-2 : 5-quinone gives mainly an abnormal chlorotoluquinol diacetate. The simpler quinones react rapidly with acetic anhydride in the presence of a little 72% perchloric acid. 2-Methyl-1 : 4-naphthaquinone also undergoes the reaction under suitable conditions; a synthesis of phthiocol is thus available.

In their initial work on the reaction which is now generally known as " the Thiele acetylation of quinones," Thiele and Winter (*Annalen*, 1900, **311**, 341) used, for the most part, a solution of the quinone in an excess of acetic anhydride containing a little concentrated sulphuric acid. It has been pointed out by us (*J.*, 1950, 1203), and confirmed by Gillespie (*J.*, 1950, 2997), that acetylium ions would be produced from the acetic anhydride–sulphuric acid mixture. Thiele and Winter also used, to a limited extent, a mixture of zinc chloride † and acetic anhydride but obtained chloroquinol diacetate (I) from benzoquinone, and 1 : 2 : 4-triacetoxynaphthalene from either 1 : 2- or 1 : 4-naphthaquinone. We have also shown (*J.*, 1951, 726) that mixtures of zinc chloride and an excess of acetic anhydride are sources of acetylium ions, and the above result with benzoquinone might appear to be anomalous, since the formation of (I) involves, in the first instance, the addition of acetyl chloride (not necessarily as such). It has long been stated (Schulz, *Ber.*, 1882, **15**, 652) that benzoquinone and acetyl chloride react in the absence of any catalyst to give a mixture of quinol diacetate (I) and 2 : 5-dichloroquinol diacetate, but no yields of these products were given.



(I)

We have reinvestigated the reaction between benzoquinone and acetic anhydride–zinc chloride and find that when mixtures containing more than 2 mols. of the anhydride

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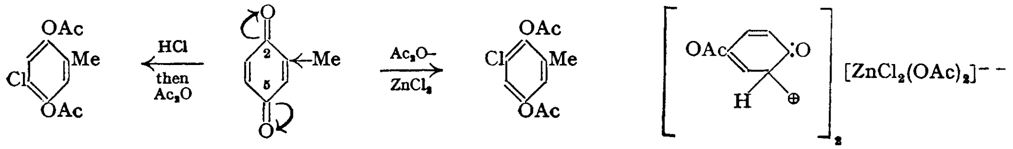
* Part V, *J.*, 1951, 726.

† Although zinc chloride is usually referred to as a catalyst for the Thiele acetylation, it is actually used in approximately the same molecular amount as the quinone.

are heated an exothermic reaction occurs; after a short time zinc acetate crystallises from the reaction mixture but in no case was there any evolution of hydrogen chloride. In all the experiments we carried out we had no difficulty in isolating some 1 : 2 : 4-triacetoxybenzene in addition to (I); the amount varied according to the experimental conditions.

Thiele and Winter (*loc. cit.*) showed that tolu-2 : 5-quinone (II) gave a high yield of



(IV) (II) (III) (V)

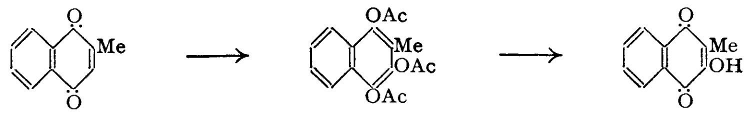
2 : 4 : 5-triacetoxytoluene with acetic anhydride–sulphuric acid. With acetic anhydride–zinc chloride we have found that a little of the triacetate, and a relatively large amount of 3-chlorotolu-2 : 5-quinol diacetate (III), m. p. 65°, are produced. The production of (III) appeared to us to be abnormal since the electronic displacements in (II) suggest that the normally orientated chlorotoluquinol diacetate should be the 4-chloro-isomer (IV). As with benzoquinone, we found that zinc acetate separated from the hot reaction mixture and that no volatile product was evolved.

The structure of (III) follows from its hydrolysis to 3-chlorotolu-2 : 5-quinol, m. p. 113—114°, the constitution of which was established by Angeletti and Oliverio (*Gazzetta*, 1940, **70**, 342). 4-Chlorotolu-2 : 5-quinol, m. p. 175°, has been prepared by the addition of hydrogen chloride to (II) (Schniter, *Ber.*, 1887, **20**, 2285; Clark, *J. Amer. Chem. Soc.*, 1892, **14**, 574; Raiford, *Amer. Chem. J.*, 1911, **46**, 450) and its constitution was established by Raiford. We find that its diacetate (IV) has m. p. 112—113°.

The reaction (II) ⟶ (III) would appear to necessitate the addition of an acetylium ion to the $C_{(5)}$:O of (II) with the intermediate production of the complex (V) and in this sense the reaction can be considered to be abnormal. It is known (Part V, *J.*, 1951, 726) that acetylium ions are produced from mixtures of zinc chloride and an excess of acetic anhydride; since no hydrogen chloride is evolved during the reaction, we must presume that the complex (V) decomposes to zinc acetate and the necessary chloro-acetoxy-intermediate. We are of the opinion that complexes of type (V), which are in fact ternary, are probably more important in reactions involving Friedel–Crafts catalysts than has hitherto been generally realised.

We have also reinvestigated the reaction of 1 : 4-naphthaquinone with zinc chloride–acetic anhydride and find, in agreement with Thiele and Winter (*loc. cit.*), that 1 : 2 : 4-triacetoxynaphthalene is the major product; we have however been able to show that a little of a chlorine-containing compound—presumably 1 : 4-diacetoxy-2-chloronaphthalene—is also produced.

Anderson and Newman (*J. Biol. Chem.*, 1933, **103**, 405) showed that sulphuric acid was ineffective as a catalyst for the Thiele acetylation of 2-methyl-1 : 4-naphthaquinone (VI).



(VI) (VII) (VIII)

We have shown that (VI) is equally resistant to the action of zinc chloride–acetic anhydride : in the experiments we have carried out, provided that extensive decomposition did not occur, we recovered a very high proportion of unchanged quinone. In analogous experiments using nitromethane as the solvent we were able to isolate a very small amount of a chlorine-containing substance which we believe to be 1 : 4-diacetoxy-3-chloro-2-methylnaphthalene and which must be formed by a mechanism similar to that discussed above.

The kinetic study by Mackenzie and Winter (*Trans. Faraday Soc.*, 1948, **44**, 171, 243) of the perchloric acid-catalysed Thiele acetylation of benzo- and tolu-quinones shows clearly that this acid is a very effective catalyst. Our results (*J.*, 1950, 1203) on the *C*-acetylation of anisole with acetic anhydride–perchloric acid, in conjunction with those of Mackenzie and Winter, indicate that if acetylium ions alone are the " driving force " for the Thiele acetylation process then it should be possible to effect the reaction (VI) ⟶ (VII); at the same time it must be emphasised that an excess of acetic anhydride is a necessary factor. We have found, as briefly reported earlier (*Chem. and Ind.*, 1950, 92), that, provided that a relatively large amount of perchloric acid is used, (VII) can be obtained in yields of 43—54% after 20 hours at room temperature. In marked contrast to this result, we find that 1 : 4-naphthaquinone and benzo- and tolu-quinone (cf. Mackenzie and Winter, *locc. cit.*) are rapidly converted by a little 72% perchloric acid and an excess of acetic anhydride into almost quantitative yields of the appropriate triacetoxy-derivatives.

There appears little doubt that for preparative purposes perchloric acid is probably the most efficient catalyst for the Thiele acetylation. It would seem however from the work of Fieser (*J. Amer. Chem. Soc.*, 1948, **70**, 3165) and Cram (*ibid.*, 1949, **71**, 3953) that boron trifluoride is also an efficient catalyst, presumably because of the facile reaction $Ac_2O + BF_3 \longrightarrow Ac^+ + [BF_3{\cdot}OAc]^-$.

Alkaline hydrolysis of (VII) with free access to air gave as expected a high yield of 3-hydroxy-2-methyl-1 : 4-naphthaquinone (phthiocol) (VIII) thus affording a simple synthesis of this important compound (Anderson and Newman, *J. Biol. Chem.*, 1933, **101**, 773).

EXPERIMENTAL

Reactions with acetic anhydride and zinc chloride.

Benzoquinone.—(*a*) The quinone (10·2 g.) rapidly dissolved on addition to a solution of zinc chloride (16·2 g.) in acetic anhydride (24·0 g.); the mixture was then heated on a steam-bath, whereupon a slight exothermic reaction occurred and the internal temperature rose to 100°. Gentle heating was continued for 1 hour and during the latter half of this period a considerable amount of zinc acetate separated. The cooled mixture was poured into water and after several hours the semi-solid product was filtered off and dissolved immediately in hot methanol. The first crop of crystalline material obtained was almost pure chloroquinol diacetate (8·8 g.), pale orange rhombic prisms (from benzene–light petroleum), m. p. 72°. A further crop of crystalline material (1·2 g.) gave colourless needles, m. p. 96—97°, from alcohol, which did not depress the m. p. of 1 : 2 :4-triacetoxybenzene.

A considerable amount of non-crystallisable gummy material was isolated from the mother-liquors.

(*b*) A solution of benzoquinone (0·08 g.-mol.) and zinc chloride (0·01 g.-mol.) in acetic anhydride (0·40 g.-mol.) was heated on a boiling water-bath for 6 hours. During this period the mixture darkened and separation of zinc acetate occurred. The cooled mixture was poured into water, and the product was worked up as in (*a*), giving chloroquinol diacetate (0·007 g.-mol.) and 1 : 2 : 4-triacetoxybenzene (0·004 g.-mol.). An ethereal extract of the aqueous liquor yielded some tar.

(*c*) The same mixture as for (*b*) was boiled for 30 minutes. Fractional crystallisation of the product gave chloroquinol diacetate (0·005 g.-mol.) and 1 : 2 : 4-triacetoxybenzene (0·005 g.-mol.) together with a dark brown gum (4·6 g.).

*Tolu-*2 : 5-*quinone.*—A solution of the quinone (0·1 g.-mol.) and zinc chloride (0·12 g.-mol.) in acetic anhydride (0·25 g.-mol.) was heated on a boiling-water-bath, the internal temperature rising to *ca.* 120°. The mixture was shaken without further heating for 10—15 minutes, by which time much solid had separated and the temperature had fallen to 95°. The mixture was then heated at 90—95° for a further 30 minutes, cooled, and poured into ice-water (*ca.* 250 c.c.). After several hours the rather waxy solid was filtered off and dissolved in the minimum amount of hot alcohol. The cooled solution deposited almost colourless needles (11·0 g.), m. p. 61°, which consisted mainly of 2 : 5-*diacetoxy*-3-*chlorotoluene*, colourless prisms (from benzene), m. p. 65° (Found: C, 54·3; H, 4·5; Cl, 15·1. $C_{11}H_{11}O_4Cl$ requires C, 54·4; H, 4·5; Cl, 14·6%), together with a little 2 : 5-diacetoxy-4-chlorotoluene, m. p. and mixed m. p. 112—113° (see below).

The residue (*ca.* 11 g.) obtained by evaporation of the alcoholic mother-liquors was a viscous brown syrup from which further crops of crystalline material were obtained with considerable difficulty. One crop was slightly impure 2 : 5-diacetoxy-3-chlorotoluene and a further crop (3·3 g.), m. p. 54—55°, on crystallisation from benzene–light petroleum deposited hard nodules (0·6 g.), m. p. 111°, which depressed the m. p. of 2 : 5-diacetoxy-4-chlorotoluene to 90°, but admixed with 2 : 4 : 5-triacetoxytoluene had m. p. 112°.

1 : 4-*Naphthaquinone.*—(*a*) A solution of the quinone (0·02 g.-mol.) and zinc chloride (0·02 g.-mol.) in acetic anhydride (0·12 g.-mol.) was heated to 50°. At first the heat of reaction was sufficient to keep the temperature at 50° but later further heating was necessary. After 30 minutes the cooled, green reaction mixture was poured into cold water, and the precipitated yellow solid filtered off and recrystallised from methanol without drying. The crystalline material (4·3 g.) was fractionally crystallised from benzene and was shown to be a mixture of 1 : 2 : 4-triacetoxynaphthalene (1·9 g.), m. p. and mixed m. p. 130—131°, and unchanged 1 : 4-naphthaquinone.

(*b*) A similar experiment was carried out at 90° for 4 hours and here the initial dark green reaction mixture turned brown but no separation of solid material was observed. The crude product was fractionally crystallised from methanol, giving (i) light brown needles (3·0 g.), m. p. and mixed m. p. 131—132° after recrystallising from alcohol, and (ii) a mixture (2·1 g.) containing dark brown prisms, m. p. 130° (separated by hand-picking), which depressed the m. p. of 1 : 2 : 4-triacetoxynaphthalene to *ca.* 110°. These prisms which contained chlorine were dissolved in hot benzene and light petroleum (b. p. 60—80°) was added; the resulting precipitate of amorphous material was filtered off and the solution was concentrated; on cooling, hemispherical clusters of needles separated. Recrystallised from light petroleum containing a little benzene, almost colourless needles, m. p. 134—135° (Found: C, 60·2; H, 4·2; Cl, 12·8. $C_{14}H_{11}O_4Cl$ requires C, 60·3; H, 3·9; Cl, 12·7%), of presumably 1 : 4-*diacetoxy-*2-*chloronaphthalene* were obtained.

(*c*) In another experiment a similar mixture in nitromethane (24·4 g.) was heated at 85° for 2 hours. After decomposition of the reaction mixture with water the product was extracted with ether. The ethereal extract was washed with water, dried (Na_2SO_4), and evaporated in a vacuum. Fractional crystallisation of the residue gave 1 : 2 : 4-triacetoxynaphthalene (3·3 g.), m. p. and mixed m. p. 135° after recrystallisation from alcohol, and gummy material (1·8 g.).

2-*Methyl-*1 : 4-*naphthaquinone.*—(*a*) A mixture of the quinone (0·05 g.-mol.), zinc chloride (0·05 g.-mol.), and acetic anhydride (0·3 g.-mol.) was heated on a steam-bath until all the zinc chloride had dissolved (*ca.* 15 minutes) and then for a further 30 minutes. The dark mixture was cooled rapidly and decomposed with ice, whereby a light brown solid product separated. Crystallisation of this from methanol gave unchanged quinone (m. p. and mixed m. p.).

(*b*) When the above mixture was boiled under reflux for 1¾ hours, hydrogen chloride was evolved but acetyl chloride could not be detected. The reaction product was a black tar.

(*c*) A mixture of 2-methyl-1 : 4-naphthaquinone (0·05 g.-mol.), zinc chloride (0·05 g.-mol.), acetic anhydride (0·15 g.-mol.), and nitromethane (30·6 g.) was heated on the steam-bath for 8 hours; no evolution of hydrogen chloride occurred. The residue left after removal of volatile products by evaporation in a vacuum was mixed with powdered ice, and the crude solid crystallised from methanol. The first (main) crop consisted (m. p. and mixed m. p.) of unchanged quinone, but the more soluble fraction had m. p. *ca.* 95°. Recrystallisation of this from 2 : 1 benzene–light petroleum gave pale brown needles (0·1 g.), m. p. 194° after sintering at 185°. Recrystallisation from ethyl alcohol then gave colourless needles, m. p. 196—197°, of 1 : 4-diacetoxy-3-chloro-2-methylnaphthalene (Found: C, 61·9; H, 4·8; Cl, 11·8. Calc. for $C_{15}H_{13}O_4Cl$: C, 61·5; H, 4·4; Cl, 12·1%). Fries and Lohmann (*Ber.*, 1921, **54**, 2921) give m. p. 194°.

Reactions with acetic anhydride and 72% perchloric acid.

Benzoquinone.—72% Perchloric acid (0·5 c.c., 0·006 g.-mol. of $HClO_4$) was slowly added to a solution of benzoquinone (0·05 g.-mol.) in acetic anhydride (50 c.c.). The temperature rose rapidly to *ca.* 55°, and after being cooled to below 20° the mixture was left at room temperature for 30 minutes before being poured into ice-water. The slightly impure 1 : 2 : 4-triacetoxybenzene (0·048 g.-mol.), m. p. 94°, separated from methanol in colourless needles, m. p. 97·5°.

1 : 4-*Naphthaquinone.*—72% Perchloric acid (0·6 g.) was added to a solution of 1 : 4-naphthaquinone (5 g.) in acetic anhydride (30 c.c.) at room temperature. After 30 minutes the mixture was decomposed by ice-water, and the resulting solid (yield 95%), m. p. 133·5—134·5°, crystallised

from alcohol. The triacetate, m. p. 135°, was identical (m. p. and mixed m. p.) with that prepared by reductive acetylation of 2-hydroxy-1 : 4-naphthaquinone (lawsone).

2-*Methyl*-1 : 4-*naphthaquinone*.—72% Perchloric acid (0·01 g.-mol.) was added dropwise to a solution of 2-methyl-1 : 4-naphthaquinone (0·02 g.-mol.) in acetic anhydride (34·4 c.c.), and the mixture kept for 20 hours at room temperature. The resulting deep red-brown solution was poured cautiously on crushed ice (*ca.* 250 g.), and the resulting light-coloured solid product was collected and dissolved in the minimum amount of hot methanol. The solid which separated on cooling, when recrystallised from benzene–light petroleum (2 : 1), separated in clusters of colourless prisms (*ca.* 54%), m. p. 158—159° (Found : C, 64·3; H, 5·1. Calc. for $C_{17}H_{16}O_6$: C, 64·6; H, 5·1%). Anderson and Newman (*J. Biol. Chem.*, 1933, **103**, 197) give m. p. 158—159° after fusing (? sintering) at 148°, for 1 : 3 : 4-triacetoxy-2-methylnaphthalene.

With a ratio of quinone to perchloric acid of 3 : 1 the yield of pure triacetate, under otherwise identical conditions, was 43%.

3-*Hydroxy*-2-*methyl*-1 : 4-*naphthaquinone* (*Phthiocol*).—Hydrolysis of the above triacetate with hot 2N-sodium hydroxide and free access to air gave 80% of crude 3-hydroxy-2-methyl-1 : 4-naphthaquinone. Crystallisation from methanol gave bright yellow needles, m. p. 173° (Found : C, 70·1; H, 4·4. Calc. for $C_{11}H_8O_3$: C, 70·0; H, 4·3%). Anderson and Newman (*ibid.*, 1933, **101**, 773) give m. p. 173—174° for the natural product.

3-*Chlorotolu*-2 : 5-*quinol*.—A mixture of the diacetate (2 g.), N-sulphuric acid (5 c.c.), and alcohol (7 c.c.) was boiled for 9—10 hours; the ethyl acetate formed was allowed to evaporate from time to time, being replaced by sufficient acid–alcohol to maintain a clear solution. On cooling, colourless needles (1·0 g.), m. p. 112°, separated (Found : C, 53·1; H, 4·6; Cl, 21·9. Calc. for $C_7H_7O_2Cl$: C, 53·0; H, 4·5, Cl, 22·4%).

The quinol was readily oxidised by acid–dichromate to the quinone, which crystallised from alcohol in bright yellow needles, m. p. 90°.

4-*Chlorotolu*-2 : 5-*quinol*.—Dry hydrogen chloride was passed slowly into a solution of tolu-2 : 5-quinone (0·1 g.-mol.) in chloroform (100 c.c.) at room temperature (water-cooling) for 1 hour during which solid material separated. After the mixture had been kept for a further hour the solid (*A*) was filtered off and crystallised first from benzene–ethyl acetate (5 : 1) and then from chloroform–ethyl acetate, giving colourless prisms (0·08 g.-mol.), m. p. 175° (Found : C, 53·7; H, 4·6; Cl, 21·7. Calc. for $C_7H_7O_2Cl$: C, 53·0; H, 4·5; Cl, 22·4%).

A suspension of the chlorotoluquinol (3·6 g.) in acetic anhydride (5·1 g.) and acetic acid (5·4 g.) was treated with 72% perchloric acid (1 drop); the temperature rose rapidly to 55° and complete dissolution occurred. After *ca.* 1 minute the mixture was decomposed with ice, and the resulting solid crystallised first from alcohol and then from benzene–light petroleum. 4-*Chlorotolu*-2 : 5-*quinol diacetate* (2 : 5-*diacetoxy*-4-*chlorotoluene*) separated in colourless needles, m. p. 112—113° (Found : C, 54·3; H, 4·6; Cl, 14·9. $C_{11}H_{11}O_4Cl$ requires C, 54·4; H, 4·5; Cl, 14·6%).

Evaporation of the original chloroform solution after filtration of (*A*) gave a brown solid (2 g.), m. p. 105—107°, which crystallised from benzene in light brown needles, m. p. 113—116°. With acetic anhydride–acetic acid (1 : 1) and a trace of 72% perchloric acid this gave (?) 2 : 5-*diacetoxy*-3 : 4-*dichlorotoluene*, colourless needles (from methanol), m. p. 124° (Found : C, 47·6; H, 3·8; Cl, 25·6. $C_{11}H_{10}O_4Cl_2$ requires C, 47·7; H, 3·6; Cl, 25·6%).

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