ability of the rat to incorporate DS into the liver tissue as was originally hoped might be true. Accordingly, another group of rats was fed DS for a period of six weeks and after this time interval blood-free liver homogenates were prepared for analysis of the dye. This time interval (six weeks) was chosen since the Wisconsin group has shown that both carcinogenic and non-carcinogenic azo dyes appear in the liver tissue in about equal amounts after this length of time.[4] Thus whether DS is or is not a carcinogen should have little effect on the amount of dye found in the liver after six weeks of feeding. Analysis of the liver preparations according to the method of Miller and Miller[11] failed to show the presence of dye. From this it was concluded that DS was either not incorporated into the rat liver, or that if it was then it was destroyed too rapidly to accumulate.

It was thought desirable to determine the intestinal absorption of DS since this factor has contributed to the low carcinogenicity of certain azo dyes.[12] Analysis of the feces from rats fed DS showed that approximately 15–25% of the dye ingested is excreted in the feces within a 48-hour period after ingestion.

Lastly, it was noted that the rats fed the DS ration gained weight much more rapidly than either of the other two groups of rats. This observation may not have any significance, however, since the rats were not limited in their intake and also since it was noted that the rats fed the DS ration consistently ate more than the other rats. In fact, at the end of 1.5 months of feeding the rats which were fed the DS ration had eaten all of the ration which had originally been calculated to be adequate for three or four months of feeding. The factor responsible for this observation was not determined.

[11] E. C. Miller and J. A. Miller, *Can. Res.*, **7**, 468 (1947).

[12] J. A. Miller, R. W. Sapp and E. C. Miller, *ibid.*, **9**, 652 (1949)

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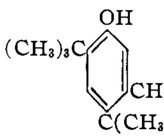
Reactions of 3,4,6-Trialkylphenols. I. Halogen Derivatives of 3-Methyl-4,6-di-*t*-butylphenol

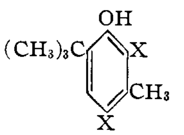
BY LAWRENCE E. FORMAN AND WILLIAM C. SEARS

RECEIVED AUGUST 13, 1953

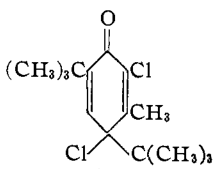
Chlorination of 3-methyl-4,6-di-*t*-butylphenol (I) yields 2-chloro-3-methyl-4,6-di-*t*-butylphenol (II) as the initial product. Further chlorination in carbon tetrachloride solution gives two products—a new compound (IV) containing two atoms of chlorine, and the partially dealkylated dichlorophenol IIIa. Compound IV is insoluble in sodium hydroxide solutions. The infrared spectrum shows that the hydroxyl band (3554 cm.$^{-1}$)[1] of a partially hindered phenol present in II and III has disappeared, while a new band attributable to a carbonyl group has appeared at 1659 cm.$^{-1}$. Similarly, the ultraviolet absorption spectrum, λ_{max}, has undergone a hypsochromic shift indicating a loss of benzenoid character as shown by a maximum at 284 mμ displacing to 246 mμ with a large increase in log *E*. Fisher–Hershberger–Taylor models indicate considerable steric hindrance to *para* substitution by chlorine at position 5, but admit the possibilities of substitution at positions 2 or 4 to give "ketohalogenides" similar to the compounds described by von Auwers[2] and Zincke.[3] This leads us to believe that further chlorination of II proceeds by the absorption of a positive chlorine atom at position 4 and the elimination of a proton from the hydroxyl group. Coppinger and Campbell[4] have indicated that a similar situation exists for the attack of bromine on 2,6-di-*t*-butyl-4-methylphenol.



I

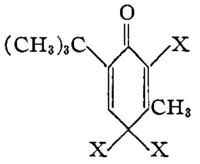


IIIa, X = Cl
IIIb, X = Br

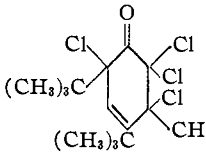


IV

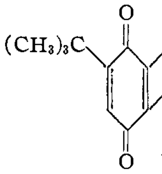
Further chlorination causes elimination of the 4-*t*-butyl group and the formation of a mixture of IIIa and Va.



Va, X = Cl
Vb, X = Br



VI



VIIIa
VIIIb

Chlorination of I in acetic acid in the presence of pyridine at 12°, gives rise to a tetrachloro addition product. The infrared spectrum indicates that this product is a non-conjugated cyclohexenone and therefore structure VI has been assigned.

The trichloro derivative Va may be prepared also by the addition of chlorine to 3-methyl-6-*t*-butylphenol (VII) in cold acetic acid.

Bromine reacts with I in carbon tetrachloride solution in the presence of iron to give the dibromo analog of III, 2,4-dibromo-3-methyl-6-*t*-butylphenol (IIIb). This compound may be prepared more readily by the addition of bromine to 3-methyl-6-*t*-butylphenol dissolved in acetic acid. No bromo derivative corresponding to IV was isolated. The bromo analog of V may be prepared by treating VII with sufficient bromine in cold acetic acid followed by refrigeration. This tribromo derivative, 2,4,4-tribromo-3-methyl-6-*t*-butylphenol (Vb) is unstable and loses bromine on standing in air at room temperature.

Oxidation of III or V, either by nitric or chromic acids in acetic acid, gives rise to the corresponding *p*-quinone, 2-halogeno-3-methyl-6-*t*-butylquinone-

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[1] L. J. Kitchen and W. C. Sears, THIS JOURNAL, **71**, 4110 (1949).

[2] K. von Auwers, *Ann.*, **301**, 203 (1898); *Ber.*, **32**, 2987 (1899).

[3] Th. Zincke, *Ann.*, **328**, 282 (1903).

[4] G. M. Coppinger and T. W. Campbell, THIS JOURNAL, **75**, 735 (1952).

TABLE I

INFRARED SPECTRUM, 2 TO 7μ

IIa		IIb		IIIb		IV		Va	
μ	Transmission, %	μ	Transmission, %	μ	Transmission, %	μ	Transmission, %	μ	Transmission, %
2.81	48	2.83	58	2.80	60				
3.38	7	3.37	4	3.36	30	3.41	10	3.36	34
								5.96	16
6.07	68					6.03	8	6.08	52
6.24	59	6.25	82	6.26	72	6.29	20	6.21	32
				6.46	75	[illegible]			
6.78	9	6.79	8	6.80	20	6.78	12	6.74	37
6.86[a]	16	6.87[a]	20	6.88	27	6.85	8	6.84	32
7.15	10	7.16	10						
7.20	10	7.21	10						

[a] Shoulder.

1,4 (VIII). Hydrolysis of V with aqueous ethanol[5] likewise brings about the formation of the *p*-quinone VIII.

Experimental[6]

3-Methyl-4,6-di-*t*-butylphenol (I).—Technical grade material from Koppers Co. was recrystallized from petroleum ether (25–65°). After two recrystallizations and drying on porous plate, a white crystalline product was obtained, m.p. 60.5–62.5° (reported[7] 62.1°).

2-Chloro-3-methyl-4,6-di-*t*-butylphenol (IIa).—One hundred thirty-eight grams (0.62 mole) of I dissolved in 400 ml. of CCl_4 was cooled to 5°. Sulfuryl chloride, 85 g. (0.63 mole), was added dropwise to the solution with cooling. The reaction mixture was heated to boiling on the steam-bath to complete the reaction and to expel gases. The solution was poured into a large excess of water in a separatory funnel and washed. The organic layer was separated and dried over anhydrous sodium sulfate. The dried solution was distilled from a Claisen flask to remove solvent, and finally *in vacuo* to give an oil distilling at 97–99.5° at 0.4 mm., $n^{20}D$ 1.5271. Redistillation through an 18-inch column packed with stainless steel helices gave a major product distilling at 113–116° (1.4 mm.), $n^{20}D$ 1.5266, $d^{25}{}_{25}$ 1.041, Y 37.8 dynes/cm., yield 51.5 g. (89.0%).

Anal. Calcd. for $C_{15}H_{23}ClO$: Cl, 13.91; mol. wt., 254.8. Found: Cl, 14.2, 14.5; mol. wt., 232.

Solution of the distillate in glacial acetic acid gave, after standing, white crystals, m.p. 53.0–53.8°. Infrared absorption data are given in Table I.

2,4-Dichloro-3-methyl-4,6-di-*t*-butylphenol (IV).—One mole (71 g.) of Cl_2 was slowly bubbled into a solution of 110 g. (0.5 mole) of I in 250 ml. of CCl_4 at 0°. After partial evaporation of the solvent and cooling the remainder, crystallization was induced by scratching the vessel walls. There was obtained 63.3 g. (43.8%) greenish tinted crystals melting at 76–77°. Crystallization from petroleum ether (25–65°) gave white plates, m.p. 78°.

Anal. Calcd. for $C_{15}H_{22}Cl_2O$: Cl, 24.52; C, 62.28; H, 7.67; mol. wt., 289.24. Found: Cl, 24.90; C, 62.37; H, 7.78; mol. wt., 274.

Oxidation of IV to 2-Chloro-3-methyl-6-*t*-butylquinone-1,4 (VIIIa).—IV (3.0 g.) was dissolved in 50 ml. of warm glacial acetic acid and heated to 50°. To this solution was added a solution of 1.0 g. of chromium trioxide in 25 ml. of acetic acid and 10 ml. of water. The mixture was held at 50° for 3 hours followed by dilution with water to 250 ml. The crude precipitate was filtered, washed with water and dried; yield 2.2 g. (100%), m.p. 86–90°. Crystallization of the crude product from petroleum ether followed by two crystallizations from aqueous alcohol gave yellow plates, m.p. 94–95° VIIIa, identical with that obtained below.

2,4,4-Trichloro-3-methyl-6-di-*t*-butyl-3,5-cyclohexadien-1-one (V).—A solution of 110 g. (0.5 mole) of I dissolved in 225 ml. of CCl_4 was treated with Cl_2 to a gain in weight of 42.5 g. The resulting solution was evaporated to about half its original volume and chilled. Crystals formed in the amount of 18.7 g., light greenish-yellow plates, m.p. 111.5–113°.

Anal. Calcd. for $C_{11}H_{13}Cl_3O$: mol. wt., 267.6; C, 49.37; H, 4.90; Cl, 39.75. Found: mol. wt., 268; C, 49.43, 49.58; H, 5.10, 5.15; Cl, 39.58, 39.60.

The non-crystalline portion (filtrate) was evaporated and distilled. Three fractions were collected, (a) 80–116° (5 mm.), $n^{20}D$ 1.5155, 3.5 g.; (b) 116–125.5° (5 mm.), $n^{20}D$ 1.5612, 32.1 g.; (c) 125–128° (5 mm.), $n^{20}D$ 1.5538, 32.8 g., the major portion of which is probably 2,4-dichloro-6-*t*-butylphenol.

Hydrolysis of Va to 2-chloro-3-methyl-6-*t*-butylquinone-1,4 (VIIIa), by the method of Thomson with 4 g. of Va gently refluxed in a solution of 75 ml. of alcohol and 25 ml. of water for two hours gave 0.6 g. yellow crystals. Melting point after crystallization from alcohol, 94–95°, is identical with the product obtained from chromic acid oxidation of Va (see below).

Oxidation of Va to 2-chloro-3-methyl-6-*t*-butylquinone-1,4 (VIIIa).—To 3.1 g. of Va dissolved in 50 ml. of warm glacial acetic acid was added a solution of 1 g. of chromium trioxide dissolved in a solution of 25 ml. of acetic acid plus 5 ml. of water. Dilution of the reaction solution with water gave a precipitate in nearly quantitative yield. Several recrystallizations from aqueous alcohol gave yellow plates, m.p. 94–95°, VIIIa. Mixed m.p. with the oxidation product of IV was 93.5–95°.

Anal. Calcd. for $C_{11}H_{13}ClO_2$: Cl, 16.69; C, 62.12; H, 6.16. Found: Cl, 16.65; C, 62.03; H, 6.44.

2,2,3,4-Tetrachloro-3-methyl,4,6-di-*t*-butyl-5-cyclohexen-1-one (VI).—Twenty-two grams (0.1 mole) of I dissolved in 100 ml. of glacial acetic acid and 40 ml. of dry pyridine was cooled in ice-water and slowly treated with chlorine until 20.6 g. (0.29 mole) had been absorbed. A crystalline precipitate which formed was removed by filtration and washed, m.p. 136–139°. The filtrate was diluted with water causing a further precipitation. The combined precipitates were crystallized from gasoline giving white cubic crystals, m.p. 135–139°. Two recrystallizations from gasoline gave fine white crystals, m.p. 140.5–141.0°.

Anal. Calcd. for $C_{15}H_{22}Cl_4O$: Cl, 39.38; mol. wt., 360.16. Found: Cl, 39.40, 39.20; mol. wt. 367, 372.

Hydrolysis of VI.—Three grams of VI was refluxed in a solution of 75 ml. of alcohol and 25 ml. of water for 4 hours. The solution was evaporated leaving a mixture of yellow crystals and a reddish oil. The yellow crystals were crystallized from petroleum ether giving bright yellow needles, m.p. 102–103°, mixed m.p. with VIIIa 68–72°. This compound was not further characterized.

2-Bromo-3-methyl-4,6-di-*t*-butylphenol (IIb).—This compound was prepared as described in paper II of this series; infrared spectrum is given in Table I.

2,4-Dibromo-3-methyl-6-*t*-butylphenol (IIIb). Method A.—A solution of 220 g. (1.0 mole) of I dissolved in 440 ml. of CCl_4 was cooled to 0° and was treated with 320 g. (2.0 moles) of bromine. The first mole of bromine was absorbed readily with the evolution of hydrogen bromide. There was no evidence of further reaction on addition of more bromine until 5.6 g. (0.1 mole) of iron filings was added. The mixture was allowed to warm up to room temperature and stand 4 days. The dark solution was filtered and washed successively with four portions of 125 ml. of water. The washed organic layer was allowed to stand 1.5 hours over calcium carbonate, filtered and concentrated to yield 215.7

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(5) R. H. Thomson, *J. Org. Chem.*, **13**, 373 (1948).

(6) All melting points and boiling points are uncorrected.

(7) W. A. Pardee and W. Weinrich, *Ind. Eng. Chem.*, **36**, 595 (1944).

g. (67%) of residual sirup. Crystallization from petroleum ether gave colorless needles, m.p. 51–52°.

Anal. Calcd. for $C_{11}H_{14}Br_2O$: Br, 49.63; C, 41.02; H, 4.38; OH, 5.28. Found: Br, 48.8, 49.1; C, 41.09, 41.31; H, 4.53, 4.51; OH, 5.37, 5.27 (Ac_2O–Py). The infrared absorption spectrum in the region of the –OH band for this compound is given in Table I.

Method B.—A more convenient method for the preparation of IIIb consists in treating VII[6,8] in acetic acid with bromine. VII (20 g., 0.122 mole, b.p. 129–130° (20 mm.)) in 100 ml. of acetic acid was treated with 39.2 g. (0.245 mole) of bromine dropwise with swirling and cooling. The bromine was decolorized rapidly and hydrogen bromide was evolved. After standing several hours, the mixture was diluted to 500 ml. with cold water. A solid precipitated which was filtered with suction and crystallized from gasoline; white needles, m.p. 51.5–52.0°, were obtained. The yield of dry crude product melting at 48–50° was 38.2 g. (97.5%); mixed m.p. with preparation of method A 51–52°.

Benzoate of IIIb.—To 1.1 g. of IIIb dissolved in 10 ml. of pyridine was added 1.0 g. of benzoyl chloride. The mixture was heated at 70° overnight and then was cooled and poured into dilute sulfuric acid, from which was isolated 1.2 g. of white powder, m.p. 103–105°. This was recrystallized from alcohol giving colorless crystals, m.p. 105–106°.

Anal. Calcd. for $C_{18}H_{18}O_2Br_2$: Br, 37.51; mol. wt., 426.15. Found: Br, 37.60, 37.20; mol. wt., 410, 426.

2,4,4-Tribromo-3-methyl-6-*t*-butyl-2,5-cyclohexadienone (Vb).—To a solution of IIIb (32.2 g., 0.1 mole) in 100 ml. of cold glacial acetic acid was added 17.6 g. (0.11 mole) of bromine followed by refrigeration for 4 days. The frozen mixture was diluted with water and again chilled. A heavy reddish oil resulting was washed with dilute sodium sulfite solution and then with water. On chilling again in refrigerator overnight a crystalline product formed. This product, after crystallization from alcohol and again from *n*-hexane, gave lemon-yellow crystals, m.p. 129.5–130.5° dec., yield 6.3 g.

Anal. Calcd. for $C_{11}H_{13}OBr_3$: Br, 59.80. Found: Br, 59.86, 59.77.

2-Bromo-3-methyl-6-*t*-butylquinone (VIIIb). Method A.—A solution of 230 ml. of glacial acetic acid and 32.2 g. (0.1 mole) of IIIb was treated with a solution of 10 g. of sodium dichromate dihydrate in 25 ml. of water, in several portions with swirling. The solution was heated to 50° and allowed to stand several hours. After cooling, the solution was diluted with 100 ml. of water causing an orange solid to precipitate in nearly theoretical yield. The product, crystallized from petroleum ether and then from *n*-heptane, consisted of orange plates, m.p. 105–106°.

Anal. Calcd. for $C_{11}H_{13}BrO_2$: Br, 31.08. Found: Br, 31.10, 31.25.

Method B.—VIIIb may be obtained from IIIb by the method of Zincke and Wugk.[9] To 1.0 g. of IIIb dissolved in 10 ml. of glacial acetic acid was added 1 ml. of concentrated nitric acid. After standing one hour, water was added to incipient precipitation followed by cooling; bright yellow plates, m.p. 104–105°, precipitated; mixed m.p. with product from method A showed no depression.

Infrared Measurements.—It has been shown that the OH band of a given *ortho*-substituted phenol has nearly the same frequency in the melt and in concentrated CCl_4 solution. Therefore, all compounds were measured as concentrated solutions in CCl_4 except IIa which was examined as a super-cooled liquid. The sample thickness was 0.002 inch for all compounds. The infrared curves were corrected for the absorption due to the solvent. The infrared bands were measured with an automatic recording spectrometer having a large NaCl prism, designed and constructed in this Laboratory.

Infrared Interpretation.—In all of the compounds, the C–H band was observed at about 3.39 μ. The spectra of IIa, IIb and IIIa exhibit bands very close to 2.82 μ, which is consistent with the structure of a phenolic OH adjacent to an *ortho* *t*-butyl group (Table I). The spectra of compounds IV and Va show no bands in the OH region. The bands observed in the spectra for IV and Va at 6.03 and 6.08 μ, respectively, are believed to be due to conjugated ketone groups. Both benzoquinone and 2,5-di-*t*-butylquinone were found to have a band at 6.03 μ, attributable to the conjugated carbonyl structure. This is further supported by the report of Rasmussen, Tunnicliff and Brattain[10] that the conjugation of a ketone group with a C=C group, as in acetophenone and isophorone, shifts the C=O band to the region of 5.90 to 6.00. The C=C band was observed in IIa, IIb, IIIb, IV and Va at 6.24, 6.25, 6.26, 6.29 and 6.21 μ, respectively.

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[8] A. E. Tchitchibabine, *Compt. rend.*, **198**, 1239 (1934).

[9] Th. Zincke and E. Wugk, *Ann.*, **363**, 296 (1908).

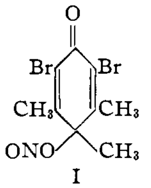
[10] R. S. Rasmussen, D. D. Tunnicliff and R. R. Brattain, THIS JOURNAL, **71**, 1068 (1949).

Reactions of 3,4,6-Trialkylphenols. II. Nitric Acid Reaction Products and their Decomposition

BY HARRY E. ALBERT AND WILLIAM C. SEARS

RECEIVED AUGUST 13, 1953

It has been shown, particularly by Auwers,[1-3] Fries[4-7] and Zincke,[8-10] that both in the naphthalene and benzene series, highly substituted phenolic compounds react with nitric acid to form quinoid compounds referred to as "chinetrols." These compounds were also obtained, but less readily,[6] when nitrous acid or nitrous oxide was used as the reagent. Although Auwers[3] in one of his later publications gave a nitrite ester structure (I) for such a reaction product from 2,6-dibromo-3,4,5-trimethylphenol and nitric acid, Fries[6] has shown a similar compound II not to have the nitrite ester group. All of the above-mentioned investigators have shown that one of the more common reactions of compounds having structures similar to II was the conversion to "chinols" where the nitro group is replaced by hydroxyl.



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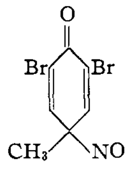

II

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[1] K. Auwers and H. Burrows, *Ber.*, **32**, 3034 (1899).

[2] K. Auwers, *ibid.*, **35**, 455 (1902).

[3] K. Auwers and K. Saurwein, *ibid.*, **55**, 2372 (1922).

[4] K. Fries and E. Hübner, *ibid.*, **39**, 435 (1906).

[5] K. Fries, *Ann.*, **389**, 305 (1912).

[6] K. Fries and G. Oehmke, *ibid.*, **462**, 1 (1928).

[7] K. Fries and A. Kuster, *ibid.*, **470**, 20 (1929).

[8] Th. Zincke, *ibid.*, **328**, 261 (1903).

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[10] Th. Zincke and M. Buff, *ibid.*, **341**, 318 (1905).