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MERCURATION OF SOME ALKYLPHENOLS AND ALKYLPHENOLALDEHYDES

BY

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CCCXXIII.—*Mercuration of Some Alkylphenols and Alkylphenolaldehydes.*

By Thomas Anderson Henry and Thomas Marvel Sharp.

In previous papers (J., 1922, **121**, 1055; 1924, **125**, 1049) the authors have described the mercuration of the hydroxybenzaldehydes and certain of their nitro-derivatives and have shown that the bactericidal action of the organo-mercury compounds formed is not entirely dependent on the number of mercury residues present, but is largely influenced by the configuration of the organic part of the molecule; thus, 2-hydroxymercuri-3-hydroxybenzaldehyde (Hg, 59·1%) is 2·5 times as toxic to *Bacillus typhosus* as 3 : 5-dihydroxymercuri-2-hydroxybenzaldehyde (Hg, 72·2%) (Henry, Sharp, and Brown, *Biochem. J.*, 1925, **19**, 513). The former is, in fact, a very active bactericidal agent and has also marked spirochæticidal properties, and solutions in oil of its acyloxy-derivatives are now being used successfully in India in the treatment of cases of leprosy complicated by syphilis.

It seemed desirable to ascertain whether the bactericidal action could be increased by the introduction of alkyl groups, since it is known that up to a certain point the *C*-alkylphenols show increasing bactericidal action with increasing weight of the substituent alkyl group.

We selected for investigation *p-tert.*-butyl- and *p-iso*amyl-phenols, carvacrol, and thymol, and one aldehyde derived from each of these.

Little has been done previously on the mercuration of alkylphenols and nothing on the mercuration of alkylphenolaldehydes. Dimroth has shown that *p*-cresol (*Ber.*, 1902, **35**, 2856) and thymol (*ibid.*, 2864) both yield mono- and di-mercurated derivatives, and other workers have investigated the same substances. *p-tert.*-Butyl- and *p-iso*amyl-phenols are now found to behave similarly, yielding both mono- and di-substituted mercury derivatives. The positions of the two mercuri-groups in the latter are shown to be in both cases ortho to the hydroxyl groups, since on treatment with cold nitric acid *o*-dinitro-compounds are formed. The constitution of the monomercuri-compounds of these two phenols follows from those of the disubstituted derivatives, and similarly the monomercuri-derivatives of the corresponding aldehydes are shown to be 2-hydroxy-3-acetoxymercuri-5-*tert.*-butylbenzaldehyde and 2-hydroxy-3-acetoxymercuri-5-*iso*amylbenzaldehyde, respectively.

Carvacrol would be expected to yield three products, *viz.*, the 4 : 6-diacetoxymercuri-, 4-acetoxymercuri-, and 6-acetoxymercuri-derivatives, since thymol yields the three analogous substances (Mameli and Mameli-Manessier, *Gazzetta*, 1922, **52**, 1), but we have only succeeded in obtaining a dimercuri- and one monomercuri-compound from carvacrol. The former is, no doubt, the expected 4 : 6-diacetoxymercuri-derivative, but the position of the mercury in the latter is difficult to determine, since coupling with benzenediazonium chloride yields a dibenzeneazocarvacrol, and treatment with bromine gives rise to polybrominated products which furnish no clue to the constitution, whilst nitric and nitrous acids give only tarry products from which no crystalline substance could be obtained. In thymol- and carvacrol-aldehydes there are only two positions available for the entry of the acetoxymercuri-residue, one meta and one ortho to the hydroxyl group. It is almost certain, therefore, that the mercury in these substances occupies the ortho-position, since meta-substituted mercuri-compounds are rarely formed, even when the directing group is one which normally causes meta-substitution (compare, however, Dimroth, *Annalen*, 1925, **446**, 148; Coffey, J., 1925, **127**, 1029; this vol., p. 637).

In the preparation of the four aldehydes used in the course of

this work a number of interesting by-products were obtained, which are being investigated.

The bactericidal action of the primary materials and of the mercury derivatives yielded by them have been kindly determined by Major Brown, C.I.E., M.B., B.Ch., bacteriologist to the Wellcome Bureau of Scientific Research. The results cannot be quoted in detail here. They indicate that the increase in bactericidal action, due to the introduction of alkyl groups into phenols, persists when the resulting alkylphenols are mercurated, and that the further introduction of an aldehyde group into the alkylphenols, as a rule, has very little influence on the bactericidal action of the final mercurated alkylphenolaldehyde.

Experimental.

Mercuration of Alkylphenols.

p-tert.-*Butylphenol.*—The *p-tert.*-butylphenol used was prepared by Liebmann's method (*Ber.*, 1882, **15**, 152, 1990); it had m. p. 99—100° and gave a crystalline benzoate, m. p. 80—81°. *p-tert.*-Butylphenol (6 g.), dissolved in alcohol (10 c.c.), and mercuric acetate (25·6 g.), dissolved in alcohol (160 c.c.) containing acetic acid (4 c.c.), were boiled together under reflux for an hour. A test portion diluted with water then dissolved completely in sodium hydroxide solution. After standing over-night, the liquid was filtered from a trace of mercurous acetate, concentrated to half-volume and then diluted with 200 c.c. of water; a white, sticky solid separated which on warming with alcohol became crystalline. After cooling, the solid was filtered off and dried to constant weight in a vacuum desiccator over sulphuric acid; it was pure 2 : 6-*diacetoxymercuri*-p-tert.-*butylphenol* (Found : C, 24·85; H, 2·7; Hg, 59·73. $C_{14}H_{18}O_5Hg_2$ requires C, 25·18; H, 2·72; Hg, 60·10%). Further quantities of this substance were obtained by concentration of the mother-liquors and repetition of the above treatment; yield 23·35 g. The substance melts at 224° (decomp.) and is readily soluble in ordinary organic solvents. The acetoxymercuri-groups were shown to be in the 2- and 6-positions by treating the product with ice-cold, concentrated nitric acid, whereupon there was formed in good yield 2 : 6-dinitro-*p-tert.*-butylphenol, m. p. 97—98° (Found : C, 50·05; H, 5·14. Calc. : C, 50·00; H, 5·04%). This m. p. was not depressed on admixture with a specimen prepared by the nitration of *p-tert.*-butylphenol (Studer, *Annalen*, 1882, **211**, 242). If the temperature is allowed to rise during this reaction the main product is picric acid.

To obtain a monomercurated product, *p-tert.*-butylphenol (6 g.; 2 mols.) and mercuric acetate (6·4 g.; 1 mol.), dissolved in 50% alcohol containing a little acetic acid, were mixed and left at room temperature for 20 hours; a test portion then dissolved in sodium hydroxide. After 3 days, a good crop of white needles had separated; this was filtered off and washed with alcohol and ether (yield 2·53 g.). It consisted of a mixture rich in the monomercurated substance. On concentrating the filtrate, some unchanged butylphenol passed over and a clear yellow oil separated which solidified on standing. This solid was steam-distilled to remove butylphenol and then dried on a porous tile (3·6 g.). It crystallised from ligroin, saturated with acetic acid, in beautiful, colourless, shining plates, m. p. 180° (Found: C, 35·1; H, 4·19; Hg, 49·2. $C_{12}H_{16}O_3Hg$ requires C, 35·25; H, 3·95; Hg, 49·1%). This substance is 2-*acetoxymercuri*-p-tert.-*butylphenol*, the constitution of which follows from that of the dimercuri-compound, since the 2- and 6-positions are identical.

p-iso*Amylphenol.*—*p-iso*Amylphenol, m. p. 95° (1 mol.), prepared by Liebmann's process (*loc. cit.*), and mercuric acetate (2 mols.) dissolved in the minimum amount of alcohol containing a little acetic acid, were boiled together under reflux for 2 hours. The solution was filtered from a little mercurous acetate, concentrated somewhat, and left to cool. A white, crystalline solid separated and more was obtained on further concentration, the yield being nearly quantitative. This substance is readily soluble in alcohol, acetic acid, ethyl acetate, or chloroform, and in benzene containing a little acetic acid. It crystallises from acetic acid in shining prisms, containing 1 mol. of the solvent; m. p. 123—125° (Found: C, 27·38, 27·33; H, 3·33, 3·27; Hg, 53·98. $C_{15}H_{20}O_5Hg_2,C_2H_4O_2$ requires C, 27·52; H, 3·26; Hg, 54·1%). On treatment with twice its weight of ice-cold, concentrated nitric acid, the mercury is removed with the formation of 2 : 6-dinitro-*p-iso*amylphenol, m. p. 64—66°, not depressed after admixture with a specimen prepared by the method of Anschütz and Rauff (*Annalen*, 1903, **327**, 211). The *potassium* salt forms red plates with a coppery lustre (Found: K, 13·27. Calc.: 13·38%). As in the case of *p-tert.*-butylphenol, picric acid is formed if the temperature is allowed to rise during this reaction. The mercury compound is therefore 2 : 6-*diacetoxymercuri*-p-iso*amylphenol.*

A monomercuri-compound was obtained by mixing cold 50% alcoholic solutions of *p-iso*amylphenol (2 mols.) and mercuric acetate (1 mol.). After 26 hours the reaction was complete; the alcohol was removed by distillation and the residual oil was steam-distilled;

during this operation the oil solidified, and when no more of the phenol passed over the solid was filtered off and crystallised, first from acetic acid and then from benzene containing about 1% of acetic acid. White, crystalline flakes of 2-*acetoxymercuri*-p-iso-*amylphenol*, m. p. 176—177° (decomp.), were thus obtained (Found : C, 36·7; H, 4·4; Hg, 47·64. $C_{13}H_{18}O_3Hg$ requires C, 36·9; H, 4·3; Hg, 47·44%). It is soluble in the common organic solvents. The constitution follows from that of the dimercuri-compound.

Carvacrol.—The carvacrol used was extracted from Cyprus origanum oil (Pickles, J., 1908, **93**, 862). Solutions of carvacrol (1 mol.) and mercuric acetate (2 mols.) in 50% alcohol were boiled together under reflux for 15 minutes; a test portion diluted with water then dissolved in sodium hydroxide. On cooling a colourless, crystalline substance was obtained. On concentrating the filtrate a pale yellow oil separated; the mother-liquors were poured off and the oil crystallised on warming with alcohol. The solid was filtered, the alcoholic filtrate added to the previous mother-liquors, and the above process repeated. In this way eight crops of crystals were obtained of which the fourth and sixth were identified as mercurous acetate. From 18 g. of carvacrol 61·3 g. of crude mercury compound were obtained. The first two crops (34 g.) were almost pure mono-acetoxymercuricarvacrol, whilst crops 3, 5 and 7 (21·8 g.) were nearly pure diacetoxymercuricarvacrol. Crop 8 (5·5 g.) consisted of a mixture of the two mercury compounds. One crystallisation of crops 1 and 2 from alcohol furnished pure *acetoxymercuricarvacrol* as short, highly refractive, colourless rods (decomp. at 196°) (Found : C, 34·96; H, 4·0; Hg, 49·08. $C_{12}H_{16}O_3Hg$ requires C, 35·25; H, 3·95; Hg, 49·1%). Similarly crops 3, 5 and 7 crystallised from alcohol and yielded pure *diacetoxymercuricarvacrol*, as colourless, well-formed prisms, which softened at 190° and decomposed at 215° (Found : C, 25·13; H, 2·89; Hg, 60·2. $C_{14}H_{18}O_5Hg_2$ requires C, 25·18; H, 2·7; Hg, 60·1%). For the orientation of these mercury compounds they were severally coupled with benzenediazonium chloride in alkaline solution, Dimroth (*Ber.*, 1902, **35**, 2853) having shown that when the mercuri-residue occupies the para-position to a hydroxyl group, the mercury is removed from the nucleus, its place being taken by a benzeneazo-group, whilst mercuri-residues in the ortho-position remain. Unfortunately, in this case both the mercuri-groups were removed and the product was *op*-di-benzeneazocarvacrol, which crystallised from alcohol in dark red-brown needles, m. p. 163° (corr.). The same product is obtained by coupling carvacrol with benzenediazonium chloride in alkaline solution (von Auwers and Michaelis, *Ber.*, 1914, **47**, 1295; these

authors give m. p. 158°). Since no case is known in which a mercuri-residue enters the benzene ring *meta* to a hydroxyl group, it is highly probable that the dimercurated product is 4 : 6-diacetoxymercuricarvacrol (HO in 1), which also makes it analogous with the 2 : 4-diacetoxymercurithymol : the monomercurated carvacrol may have the mercuri-residue in either the 4- or the 6-position.

Mercuration of Alkylphenolaldehydes.

2-*Hydroxy*-5-tert.-*butylbenzaldehyde.*—This substance has been prepared by the Reimer-Tiemann process (Dains and Rothrock, *Amer. Chem. J.*, 1894, **16**, 635) but we were only able to obtain minute yields by this method. For these experiments, it was prepared by condensing *p-tert.*-butylphenol with formaldehyde (B.P. 161679/1920), a process which usually furnishes substances with the aldehyde group in the para-position to the hydroxyl group. In this case, the para-position is occupied and the aldehyde group enters the ortho-position. The yield of pure aldehyde, b. p. 138—140°/12 mm., was 46% of the theoretical. It gave a phenylhydrazone, bright yellow plates, m. p. 184° (Found : C, 76·19; H, 7·5; N, 10·4. Calc. for $C_{17}H_{20}ON_2$: C, 76·1; H, 7·5; N, 10·4%).

2-Hydroxy-5-*tert.*-butylbenzaldehyde and mercuric acetate in molecular proportions, dissolved in alcohol containing acetic acid, were boiled under reflux for 15 minutes, a test portion then dissolving completely in sodium hydroxide. On cooling, mercuric acetate separated and on reheating the mercury compound was again formed at once. The hot solution was therefore poured into a large volume of water and the resulting white precipitate was filtered off at once. After drying in a vacuum desiccator, the substance was crystallised from alcohol containing a very little acetic acid; white, needle-shaped crystals separated, m. p. 220°, but from the crystallisation of 3·8 g. only 1·93 g. of the mercury compound could be obtained (Found : C, 35·6; H, 3·8; Hg, 45·84, 45·96. $C_{13}H_{16}O_4Hg$ requires C, 35·7; H, 3·7; Hg, 45·92%). This compound can only be 2-*hydroxy*-3-*acetoxymercuri*-5-tert.-*butylbenzaldehyde.* A yield of 73% of the theoretical can be obtained by heating together molecular proportions of the aldehyde and mercuric acetate on the water-bath for 2 hours without solvent. The liquid formed is then extracted with a hot mixture of benzene and ligroin containing acetic acid, filtered from mercurous acetate, and the filtrate set aside to cool, the mercuri-compound then separating.

2-*Hydroxy*-5-iso*amylbenzaldehyde.*—This substance has not been described previously. It was obtained by condensing *p-iso*amyl-

phenol with formaldehyde and is a liquid boiling at 165—168°/17 mm. The yield of pure aldehyde was 35% of the theoretical (Found: C, 74·6; H, 8·4. $C_{12}H_{16}O_2$ requires C, 74·96; H, 8·4%): *semicarbazone*, white needles from alcohol, m. p. 222° (Found: C, 62·3; H, 7·55; N, 17·1. $C_{13}H_{19}O_2N_3$ requires C, 62·55; H, 7·69; N, 16·89%). The *phenylhydrazone* crystallises from alcohol in white plates, which soon turn yellow, m. p. 177—178° (Found: C, 76·6; H, 8·0; N, 10·3. $C_{18}H_{22}ON_2$ requires C, 76·52; H, 7·85; N, 9·97%).

The mercuration of this aldehyde in alcoholic solution gave only a small yield of mercury compound, and the same phenomenon of demercuration was observed on cooling the alcoholic solution (see above). A much better yield was obtained by heating together equimolecular proportions of 2-hydroxy-5-*iso*amylbenzaldehyde and mercuric acetate on a water-bath in the absence of any solvent. After heating for 4 hours, a dark liquid was obtained which contained a trace of mercurous acetate but was otherwise completely soluble in sodium hydroxide. The liquid was extracted with ligroin, filtered from mercurous acetate, and the solution left to cool; bundles of white needles, m. p. 134—135°, were then obtained (yield 85% of theoretical) (Found: C, 37·27; H, 3·94; Hg, 44·6. $C_{14}H_{18}O_4Hg$ requires C, 37·27; H, 4·0; Hg, 44·5%). This compound must be 2-*hydroxy*-3-*acetoxymercuri*-5-iso*amylbenzaldehyde*.

4-*Hydroxy*-3-*methyl*-6-iso*propylbenzaldehyde* (p-*carvacrolaldehyde*). —Molecular proportions of *p*-carvacrolaldehyde, prepared by Adams and Montgomery's form of the Gattermann process (*J. Amer. Chem. Soc.*, 1924, **46**, 1519), and mercuric acetate, dissolved in alcohol containing acetic acid, were boiled under reflux for 1¼ hours; a test portion well diluted with water then dissolved completely in sodium hydroxide solution. The solution was filtered from a trace of mercurous acetate into excess of a 10% solution of sodium chloride. A pale cream-coloured precipitate formed (m. p. about 260°, decomp.); it was filtered, dried in a desiccator, crystallised from acetone containing one drop of hydrochloric acid, and thus obtained in small, four-sided plates, which soften and darken at about 209° and decompose indefinitely at about 260° (Found: C, 31·92; H, 3·17; Hg, 48·67. $C_{11}H_{13}O_2ClHg$ requires C, 31·95; H, 3·17; Hg, 48·54%). This substance is no doubt 4-*hydroxy*-5-*chloromercuri*-3-*methyl*-6-iso*propylbenzaldehyde*, since the only other possible position for the mercury is meta to the hydroxyl group. This compound is curiously unstable in solution; from 5·3 g. dissolved in acetone only 2·7 g. of the mercury compound could be recovered and the mother-liquors yielded unmercurated *p*-carvacrol-

aldehyde. Moreover, if the alcoholic solution of the mercuration product (which is completely soluble in sodium hydroxide) is allowed to cool before being poured into sodium chloride, mercuric acetate crystallises out. When this solution containing mercuric acetate is boiled again the whole becomes soluble in caustic alkalis (compare the mercury derivatives of the other alkylphenolaldehydes described in this paper).

A 50% yield of the corresponding 5-acetoxymercuri-derivative is obtained by heating together on a water-bath molecular proportions of *p*-carvacrolaldehyde and mercuric acetate for 1½ hours. The resulting yellow, viscous oil, containing some mercurous acetate, is extracted four times with hot ligroin to remove unchanged carvacrolaldehyde. The residue is dissolved in a small quantity of acetic acid and filtered from mercurous acetate. On cooling, colourless needles of 4-*hydroxy*-5-*acetoxymercuri*-3-*methyl*-6-iso*propyl*-*benzaldehyde* separate, m. p. 120°; they contain 1 mol. of acetic acid, which is not lost on drying in a vacuum desiccator (Found: C, 36·42; H, 4·17; Hg, 40·6. $C_{13}H_{16}O_4Hg,C_2H_4O_2$ requires C, 36·24; H, 4·06; Hg, 40·4%). On concentrating the acetic acid mother-liquors, demercuration takes place and mercuric acetate crystallises out.

On shaking the mercuri-compound with a solution of iodine in potassium iodide, an iodo-derivative, probably 5-*iodo*-4-*hydroxy*-3-*methyl*-6-iso*propylbenzaldehyde*, crystallising from alcohol in long, colourless needles, m. p. 157°, is obtained in good yield (Found: I, 42·18. $C_{11}H_{13}O_2I$ requires I, 41·75%).

4-*Hydroxy*-2-*methyl*-5-iso*propylbenzaldehyde* (p-*thymolaldehyde*).—Molecular proportions of thymolaldehyde, prepared by Adams and Montgomery's method (*loc. cit.*), and mercuric acetate, dissolved in alcohol containing a little acetic acid, were boiled under reflux for 15 minutes, filtered from a little mercurous acetate, and left to cool. A pale, cream-coloured, crystalline solid separated and more was obtained by concentrating the mother-liquors (yield of crude substance, 94% of theoretical). This is very impure (Hg, 50·6%). It crystallises well from acetone, containing a trace of acetic acid, in colourless, hard prisms, which decompose at 185° after sintering at 179°, but it is unstable in this solvent, some of the mercury being removed with re-formation of *p*-thymolaldehyde, which is recovered from the final mother-liquors (Found: C, 36·0; H, 3·9; Hg, 46·1. $C_{13}H_{16}O_4Hg$ requires C, 35·7; H, 3·7; Hg, 45·9%). The position of the mercury in this substance has not been proved, but there can be little doubt that the compound is 3-*acetoxymercuri*-4-*hydroxy*-2-*methyl*-5-iso*propylbenzaldehyde*, since the only other available position (6) is meta to the hydroxyl group. On treatment with a

solution of iodine in potassium iodide, the mercury is replaced by iodine with formation of an iodo-compound, which is probably 3-*iodo*-4-*hydroxy*-2-*methyl*-5-iso*propylbenzaldehyde*, crystallising from alcohol in pale yellow, octagonal prisms, m. p. 128—129° (Found : C, 43·8; H, 4·3; I, 41·8. $C_{11}H_{13}O_2I$ requires C, 43·4; H, 4·3; I, 41·75%).

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