

XXXVI.—*Syntheses of Antiseptic Derivatives of Indan-1 : 3-dione. Part I. Interaction of Malonyl Chloride and of Alkylmalonyl Chlorides with the Methyl Ethers of Resorcinol and  $\beta$ -Naphthol.*

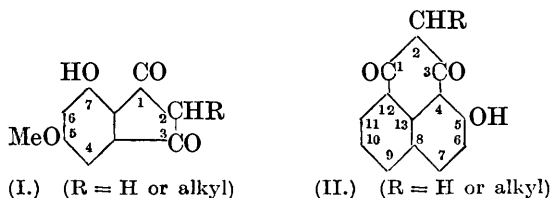
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MORGAN and COOPER (*Biochem. J.*, 1921, **15**, 587) first directed attention to the weak germicidal properties of aliphatic 1 : 3-diketones, and later they prepared and studied tellurium derivatives of a number of these substances, many of which were found to possess intense bactericidal potency (Morgan and Drew, *J.*, 1920, **117**, 1463; 1922, **121**, 922; Morgan, Cooper, and Burt, *Biochem J.*, 1923, **17**, 30; Morgan, Cooper, and Corby, *J. Soc. Chem. Ind.*, 1924, **43**, 304T). The alkyl derivatives of 1 : 3-diketones, particularly those of cyclic structure, are also of interest in this connexion and, during a recent examination of the antiseptic properties of certain substances of this type, results were obtained which suggested to one of us that it might prove possible to synthesise compounds of high antiseptic potency by attachment of the system  $\cdot\text{CO}\cdot\text{CHR}\cdot\text{CO}\cdot$  (R = alkyl) to the nuclei of phenols.

The action of diethylmalonyl chloride on aromatic hydrocarbons in the presence of aluminium chloride has been studied in detail by Freund, Fleischer, and co-workers (*Annalen*, 1910, **373**, 291; 1913, **399**, 182; 1913, **402**, 51; 1916, **411**, 14; 1918, **414**, 1; 1921, **422**, 231; *Ber.*, 1920, **53**, 1255, 1847), who prepared by this means numerous derivatives of indan-1 : 3-dione, but they did not investigate the corresponding condensations with phenols or their derivatives, apart solely from observing (*Annalen*, 1915, **409**, 268) that phenols of the indan-1 : 3-dione series may be obtained by the interaction of diethylmalonyl chloride and the respective dimethyl ethers of pyrocatechol and quinol.

In order to test the above suggestion as to the probable antiseptic properties of such compounds the Friedel-Crafts reaction has now been extended to the coupling of malonyl chloride and various monoalkylmalonyl chlorides with the methyl ethers of resorcinol and  $\beta$ -naphthol, respectively, and examination of the biochemical properties of the products upholds this forecast.

The work of Freund and Fleischer (*loc. cit.*) has shown that phenol ethers may also give rise to lactones in this type of condensation, and Auger (*Ann. Chim. Phys.*, 1891, 22, 351) obtained dibenzoylmethane derivatives from aromatic hydrocarbons and excess of the acid chloride. The compounds prepared by us from resorcinol dimethyl ether have the indandione structure (I), however, since they do not behave as lactones and their empirical formulæ and molecular weights are not in harmony with those required by dibenzoylmethane derivatives.



During the condensation with resorcinol dimethyl ether demethylation of one methoxy-group occurred readily, but the other methoxy-group was unaffected even when the temperature was raised or the time of heating with aluminium chloride prolonged. In view of the observation of Auwers and Rietz (*Ber.*, 1907, 40, 3514) that a methoxy-group can be demethylated with ease when in the *o*-position, but is strongly resistant to demethylation when in the *p*-position, to a substituent ketonic group, the methoxy-group is assigned position 5 in the nucleus of the new compounds. Similar behaviour was noted by Johnson and Hinegardner (*J. Amer. Chem. Soc.*, 1929, 51, 1503), who found that in the molecule of resorcinol dimethyl ether the methoxy-group in the *p*-position to the entering chaulmoogryl group could not be demethylated without complete breakdown of the product.

The compounds obtained by the interaction of various malonyl chlorides and  $\beta$ -naphthyl methyl ether each contain only one naphthol residue and this has its hydroxyl group free. These facts, considered in conjunction with the observation of Fries and Schimmelschmidt (*Ber.*, 1925, 58, 2835) that acetyl chloride in the presence of aluminium chloride attacks  $\beta$ -naphthyl methyl ether in the 1-position, indicate that the new compounds are 5-hydroxy-2-alkylperinaphthindandiones (II), and the stability of their

dione ring to boiling hydrochloric acid and to caustic alkali at 200° is in accord with this structure.

*Antiseptic Properties of Hydroxyindan-1:3-diones.*—The new substances exerted no action on *B. coli communis* when tested by the Rideal-Walker technique, and they were also without effect on the proliferation of organisms of the *B. pyocyaneus* group. In other cases, notably when tested against a strain of *Staphylococcus pyogenes albus* and against a number of Gram-positive bacilli, including *B. subtilis*, *B. megatherium*, and *B. mycoides*, very definite inhibition of growth was observed, the effect varying in intensity with the differences in the structures of the several compounds. Slow germicidal action was also noted in certain cases, and these will be examined in more detail.

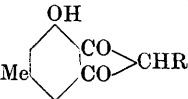
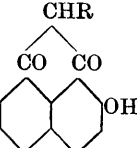
Compounds of these series are to be regarded, therefore, as possessing selective antiseptic properties distinct from the general disinfectant properties of the phenols from which they are derived.

The behaviour of a number of different bacteria was examined with a view to the selection of an organism which could be most suitably employed to obtain a comparison of the antiseptic activities of the substances. *Bacterium C* (National Collection of Type Cultures, Lister Institute) was finally chosen, since a comparison of the antiseptic activities of phenol and *p*-cresol, obtained by tests against it, gave relative values similar to those found for these compounds by the Rideal-Walker method using *B. coli communis*. The resistance shown by *Bacterium C* to the action of the substances under examination was found, moreover, to be approximately equal to the respective resistances exhibited by the Gram-positive bacilli tested; hence determinations carried out with *Bacterium C* may be considered to be of a definitely representative nature. *Bacterium C* was isolated originally by Chaston Chapman, who employed it in estimating the antiseptic activity of certain constituents of hop-resin (*J. Inst. Brewing*, 1925, **31**, 13; 1929, **35**, 363), and our best thanks are due to him for the gift of a culture.

The tests were carried out by the turbidity method in ordinary Lemco-peptone broth of  $p_H$  6.1, and the weights (in milligrams) of the different substances which were found to be necessary to inhibit growth in 10 c.c. of such broth for 48 hours at 37° were regarded as the inhibitory doses for purposes of comparison. Addition of the various doses to the broth tubes was made in solution in 0.2 c.c. of ethyl alcohol in every case, preliminary tests having shown that the presence of 2% of alcohol in the medium was without noticeable effect upon the development of the bacterium. The use of this procedure gave definite results and it was found possible to determine the end-point with a high degree of accuracy. All tests were

repeated several times and, simultaneously, control experiments were performed in which pure phenol was used as a standard antiseptic.

In the following table are shown (a) the inhibitory concentrations expressed as 1 g. per  $x$  c.c. and (b) the "equimolecular phenol coefficients of bacteriostatic power." The latter values express the activities of the molecules of the several substances in terms of that of the phenol molecule and, as Morgan, Cooper, and Burt (loc. cit.) have pointed out, this is a more accurate mode of expression than that usually followed in stating phenol coefficients.

	R =	H	CH <sub>3</sub>	C <sub>2</sub> H <sub>5</sub>	<i>n</i> -C <sub>3</sub> H <sub>7</sub>	<i>n</i> -C <sub>4</sub> H <sub>9</sub>
	(a)	1 in 22,000	1 in 10,000	1 in 8,300	1 in 12,500	1 in 20,000
	(b)	68	33	29	46	79
						
	(a)	1 in 16,600		1 in 66,400	1 in 166,000	1 in 277,000
	(b)	56		255	675	1187

The doses of phenol, *p*-cresol, resorcinol, and  $\beta$ -naphthol required to inhibit *Bacterium C* under the same conditions were 1 in 660, 1 in 1580, 1 in 1450, and 1 in 6250, respectively. The introduction of an alkyl substituent into the 2-position of the dione ring in the parent resorcinol derivative results in a lowering of the antiseptic power, but this depressing effect is counterbalanced to an increasing degree as the length of the substituent alkyl chain is increased. On the other hand, such a lowering effect is absent in the alkylated indan-diones derived from  $\beta$ -naphthol. Increase in antiseptic potency with increase in length of the chain of alkyl substituents has been observed in other classes of compounds, notably in the series of alkyl resorcinols studied by Johnson and Lane (*J. Amer. Chem. Soc.*, 1921, **43**, 348) and Dohme, Cox, and Miller (*ibid.*, 1926, **48**, 1688), and in the alkyl derivatives of phenol and of the cresols described by Coulthard, Marshall, and Pyman (*J.*, 1930, 280).

#### EXPERIMENTAL.

Preliminary experiments with carbon disulphide as the condensation medium on the lines of Freund and Fleischer's work gave poor results, and it was then found that higher yields could generally be obtained by the use of nitrobenzene. The latter has the advantage that it dissolves the whole reaction-complex, giving a homogeneous solution in which the reaction proceeds smoothly, without danger of local heating and undue tar formation.

*7-Hydroxy-5-methoxyindan-1 : 3-dione* (I ; R = H).—Attempts to prepare malonyl chloride by the use of thionyl chloride (Staudinger and Bereza, *Ber.*, 1908, **41**, 4463) resulted only in tar formation, although rigid adherence to the details of these authors was maintained. The following method was then tried with reasonably good results. Malonic acid (50 g.; 1 mol.) and phosphorus pentachloride (200 g.; 2 mols.) were mixed, with exclusion of atmospheric moisture. When brisk evolution of hydrogen chloride ceased, the mixture was cautiously warmed at 55° for 30 minutes. The liquid was then thoroughly cooled, filtered from the excess of phosphorus pentachloride, and fractionated at low pressure, 24 g. of the acid chloride (b. p. 47°/15 mm., 57°/28 mm.) being obtained (yield, 36%). The product was brown and fluorescent owing to slight decomposition.

Finely powdered, anhydrous aluminium chloride (13.5 g.) was added in small portions, during 20 minutes, to a mixture of resorcinol dimethyl ether (7 g.) and malonyl chloride (7 g.) in dry nitrobenzene (60 c.c.). After each addition the mixture was shaken to prevent local heating. The temperature rose to about 40°, and the reaction was completed by gradually warming the mixture to 70° during 1 hour, moisture being excluded. The reaction mixture was then poured on ice and treated with sufficient hydrochloric acid to bring the aluminium into solution, and the nitrobenzene was expelled in steam. The residue was shaken with ether and the ethereal extract was washed with water and exhaustively extracted with a 5% aqueous solution of sodium hydroxide. The alkaline extract on acidification and extraction with ether yielded 2.8 g. of brown resin. The first ethereal solution was washed with water and dried, and the ether removed, leaving 0.1 g. of a neutral resin (undemethylated product). The alkali-soluble resin solidified in a desiccator; after several crystallisations from acetone and finally from methyl alcohol, it formed lemon-yellow prisms, m. p. 217° (yield 30%) [Found, by micro-analysis: C, 62.2; H, 4.3.  $C_9H_4O_2(OH) \cdot OMe$  requires C, 62.5; H, 4.2.  $C_9H_4O_2(OH)_2$  requires C, 60.7; H, 3.4%].

*7-Hydroxy-5-methoxy-2-methylindan-1 : 3-dione*.—(This preparation was kindly carried out for us by Mr. F. A. Robinson.)  $\alpha$ -Cyanopropionic acid was prepared by condensation of potassium cyanide with potassium  $\alpha$ -bromopropionate and, on hydrolysis by boiling 20% aqueous potassium hydroxide for 16 hours and subsequent acidification, afforded methylmalonic acid (9 g. from 175 g. of  $\alpha$ -bromopropionic acid).

Methylmalonic acid (9 g.; 1 mol.) was treated with phosphorus pentachloride (34 g.; 2.1 mols.) under conditions similar to those adopted for the preparation of malonyl chloride. When the

product was fractionated under reduced pressure, 7 g. of methylmalonyl chloride (b. p. 45—50°/23 mm.) were obtained (yield, 60%).

Resorcinol dimethyl ether (2.6 g.; 1 mol.) and methylmalonyl chloride (3 g.; 1 mol.) in nitrobenzene (25 c.c.) were treated with powdered aluminium chloride (6 g.; 2.2 mols.) under the conditions employed when operating with malonyl chloride. The reaction mixture was poured on ice, treated with hydrochloric acid, and steam-distilled. The pitch-like residue, which was only partly soluble in ether, dissolved for the most part when triturated with acetone (100 c.c.). Addition of ether (500 c.c.) to the filtered solution precipitated a grey amorphous powder, which was removed. The acetone-ether filtrate was shaken several times with water, whereby the required product was obtained in ethereal solution free from acetone and the amorphous by-product. Extraction of this ethereal solution with a 5% solution of sodium hydroxide, followed by acidification, gave a resin (0.5 g.) which quickly solidified; a trace of undemethylated indandione derivative remained in the ether. The product separated from acetone in colourless needles, m. p. 225—226° [Found, by micro-analysis: C, 64.5; H, 5.1.  $C_{10}H_6O_2(OH) \cdot OMe$  requires C, 64.1; H, 4.85.  $C_{10}H_6O_2(OH)_2$  requires C, 62.5; H, 4.2%].

*7-Hydroxy-5-methoxy-2-ethylindan-1:3-dione* was prepared from resorcinol dimethyl ether (11.5 g.) and ethylmalonyl chloride (15 g.) in nitrobenzene (70 c.c.) by gradual addition of aluminium chloride (23.5 g.) and subsequent heating at 75° for 1 hour. The principal product (11 g., 62%), which was accompanied by 0.4 g. of undemethylated condensation product and 3.5 g. of amorphous matter insoluble in ether, was separated by the means adopted for the isolation of 7-hydroxy-5-methoxy-2-methylindan-1:3-dione (above). Crystallised several times from acetone and finally from methyl alcohol, it formed pale fawn-coloured cubes, m. p. 192.5°, sparingly soluble in acetone and in methyl alcohol in the cold, but readily soluble in the hot solvents [Found: C, 65.35; H, 5.2; *M*, 215, 223.  $C_{11}H_8O_2(OH) \cdot OMe$  requires C, 65.5; H, 5.45%; *M*, 220.  $C_{11}H_8O_2(OH)_2$  requires C, 64.1; H, 4.85%; *M*, 206].

*7-Hydroxy-5-methoxy-2-n-propylindan-1:3-dione* was prepared by the same general reaction, 6 g. of resorcinol dimethyl ether and 8 g. of *n*-propylmalonyl chloride yielding 8 g. (84% yield) of monodemethylated and 0.5 g. of undemethylated condensation product. The former, crystallised from methyl alcohol and then from acetone, formed minute, pale fawn leaves, m. p. 190.5°, moderately easily soluble in the cold in methyl alcohol, ethyl alcohol, and acetone [Found: C, 66.3; H, 5.95; *M*, 241, 253.  $C_{12}H_{10}O_2(OH) \cdot OMe$

requires C, 66.7; H, 6.0%; *M*, 234.  $C_{12}H_{10}O_2(OH)_2$  requires C, 65.5; H, 5.45%; *M*, 220].

The condensation of *n*-butylmalonyl chloride with resorcinol dimethyl ether was effected by the general method and afforded a 62% yield of the required product. This could not be obtained crystalline, and for purposes of the biological tests it was purified by conversion into its acetyl compound, which was then deacetylated, washed, and dried, a clear viscous resin being obtained.

*5-Hydroxyperinaphthindan-1:3-dione* (II; R = H) was prepared by addition of aluminium chloride (10.5 g.) to a mixture of  $\beta$ -naphthyl methyl ether (6 g.) and malonyl chloride (5.5 g.) in nitrobenzene (50 c.c.). The yield was poor (2.5 g.; 31%), probably in consequence of the instability of the acid chloride. The substance was practically insoluble in benzene and in light petroleum, and was but sparingly soluble in acetone, methyl alcohol, and ethyl alcohol, even at the boiling point. It was purified by slow evaporation of its solutions in acetone and in ethyl alcohol; it then formed a dull yellow, micro-crystalline powder, m. p. 276—280° (Found, by micro-analysis: C, 73.2; H, 4.0.  $C_{13}H_8O_3$  requires C, 73.6; H, 3.8%).

*5-Hydroxy-2-ethylperinaphthindan-1:3-dione* was obtained by the general method as a yellowish-brown powder (yield, 50%), together with a black amorphous substance (yield, 20%) which was insoluble in organic solvents and in aqueous caustic soda and was not further examined. Crystallisation of the dione from methyl alcohol and then from acetone afforded clusters of long golden-brown needles, m. p. 215°, sparingly soluble in methyl alcohol and acetone in the cold, more readily in the hot solvents (Found: C, 74.7; H, 4.8.  $C_{15}H_{12}O_3$  requires C, 75.0; H, 5.0%).

*5-Hydroxy-2-n-propylperinaphthindan-1:3-dione*.— $\beta$ -Naphthyl methyl ether (6 g.) and *n*-propylmalonyl chloride (7 g.) in nitrobenzene (50 c.c.) gave, on addition of aluminium chloride (10 g.) and subsequent heating at 80°, a 95% yield of a brown resin which solidified in a vacuum. On successive recrystallisations from hot acetone and methyl alcohol it formed a bright canary-yellow powder, m. p. 181°, difficultly soluble in methyl and ethyl alcohol and in acetone (Found: C, 75.5; H, 5.25.  $C_{16}H_{14}O_3$  requires C, 75.6; H, 5.5%). Acetone solutions of the substance were brilliant yellow, and when the solid material was moistened with acetone and exposed to the air it darkened superficially until it was almost black; it regained its normal appearance on drying. Other compounds of this series exhibited this behaviour in lesser degree.

*5-Hydroxy-2-n-butylperinaphthindan-1:3-dione* was obtained as a resin in 75% yield from  $\beta$ -naphthyl methyl ether (12 g.) and *n*-butylmalonyl chloride (15 g.). It solidified after several days and

was crystallised from methyl alcohol and then from acetone, forming minute, rich yellow leaflets, m. p.  $185^{\circ}$  (Found: C, 75.65; H, 5.65.  $C_{17}H_{16}O_3$  requires C, 76.1; H, 6.0%). It is fairly readily soluble in both of these solvents when cold and more readily when hot.

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