LXIX.—*Syntheses of Antiseptic Derivatives of Indan-1 : 3-dione. Part II. Interaction of Alkylmalonyl Chlorides with* p-*Tolyl Methyl Ether.*

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IN Part I (this vol., p. 272) it was shown that the action of an alkylmalonyl chloride on the dimethyl ether of resorcinol and on the methyl ether of β-naphthol, under prescribed conditions, results in the formation of hydroxy-derivatives of indan-1 : 3-dione which possess antiseptic activity.

This general reaction has now been applied to the dimethyl ether of quinol and to the methyl ethers of thymol and *p*-cresol. The products from the first-named were obtained in low yields and proved to be so sparingly soluble in the ordinary organic media that their further examination was abandoned; the thymol ether derivatives were uncrystallisable resins. *p*-Tolyl methyl ether, however, afforded high yields of crystalline derivatives, and a series of these has been studied in detail.

During the course of the preparation of the latter the general reaction was found to be amenable to considerable variations in procedure, some of which simplify the preparation of these indandiones. For instance, it is possible to conduct the condensations in such diverse media as *n*-hexane, decahydronaphthalene, carbon

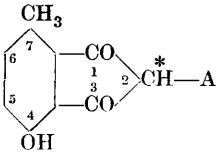
tetrachloride, anhydrous ether, and, in certain cases, in the absence of a solvent, and the substitution of ferric chloride for aluminium chloride gives equally high yields. Moreover, *p*-tolyl acetate may be used in place of the methyl ether and, when operating in nitrobenzene, the free phenol may be employed. Preparation of the alkylmalonyl chloride *in situ* constitutes a final simplification which has proved successful in the cases tried. On the other hand, condensations of alkylmalonyl chlorides with resorcinol yielded only uncrystallisable resins, and resorcinol diacetate gave rise to crystalline products which have not yet been identified.

Antiseptic Properties of Hydroxyindan-1 : 3-*diones*.—The behaviour of the new compounds was found to be similar to that of the indan-1 : 3-diones obtained from the methyl ethers of resorcinol and β-naphthol (*loc. cit.*). For instance, although they were without effect on the proliferation of several strains of *B. coli communis* and *B. pyocyaneus* in bacteriological broth or under the conditions of the Rideal–Walker method, they inhibited the development of *Staphylococcus pyogenes albus* and of a number of Gram-positive bacilli, including *B. subtilis*, *B. megatherium*, and *B. mycoides*. The compounds were also found to exert pronounced inhibitory action on the proliferation of two strains of *B. phlei* which were employed as representatives of the acid-fast group. Moreover, the inhibitory effects may be followed by germicidal action, since *S. pyogenes albus*, *B. mycoides*, and *B. phlei* were killed in less than 48 hours when exposed in broth at 37° to the influence of 4-*hydroxy*-7-*methyl*-2-n-*heptylindan*-1 : 3-*dione* (VIII) at concentrations only slightly greater than those which had been found necessary to prevent growth in the respective cases. A more detailed study of this germicidal activity is now in progress.

The series of new indandiones was graded in order of antiseptic power on the results of determinations carried out with an organism designated *Bacterium C* (National Collection of Type Cultures, Lister Institute). This has been found to be highly suitable for such a purpose, since it develops very rapidly and maintains a remarkably uniform standard of virility over long periods of time; moreover, the respective concentrations of the various new substances necessary to prevent its proliferation were found to be of much the same order as those required to inhibit *S. pyogenes albus*, *B. subtilis*, *B. megatherium*, and *B. mycoides*. The bacteriostatic concentrations as determined by employment of *Bacterium C* in broth (p_H 6·1) for 48 hours at 37° are shown in the second column of Table I. In the third column the ' equimolecular phenol coefficients of bacteriostatic power ' are given. The latter figures indicate the respective values of the molecules of the various substances as inhibitors of

growth, expressed in terms of that of the phenol molecule. The concentrations of phenol and *p*-cresol required to inhibit *Bacterium C*, under the same experimental conditions as those adopted in testing the indandiones, were 1 in 660 and 1 in 1580, respectively.

TABLE I.



Group substituted for A.	Bacteriostatic concentration, expressed as 1 g. of substance in *x* c.c. of medium.	Equimolecular phenol coefficient of bacteriostatic power.
(I) H	1 in 22,700	64
(II) CH_3	1 in 10,000	30
(III) C_2H_5	1 in 11,300	37
(IV) *n*-C_3H_7	1 in 18,200	64
(V) *n*-C_4H_9	1 in 45,400	170
(VI) *n*-C_5H_{11}	1 in 111,000	440
(VII) *n*-C_6H_{13}	1 in 333,000	1395
(VIII) *n*-C_7H_{15}	1 in 333,000	1470
(IX) *iso*-C_3H_7	1 in 30,300	106
(X) *iso*-C_4H_9	1 in 35,700	133
(XI) *iso*-C_5H_{11}	1 in 90,900	360
(XII) C_2H_5 substituted for both H* and A ...	1 in 23,800	89

The concentrations of compound (V) required to inhibit *S. pyogenes albus*, *B. subtilis*, and *B. phlei* for 48 hours at 37° were 1 in 25,000, 1 in 25,000, and 1 in 33,000, respectively, and the same organisms were inhibited under the same conditions by compound (VIII) in respective concentrations of 1 in 500,000, 1 in 333,000, and 1 in 500,000.

Reference to the table shows that attachment of one of the lower alkyl groups, in place of a hydrogen atom, to the carbon atom in the medial position with respect to the two carbonyl groups results in a diminution of antiseptic potency [compare compound (I) with compounds (II), (III), and (IV)]. As the length of the alkyl chain is increased, this effect becomes neutralised, groups higher than *n*-propyl giving rise to considerably enhanced activities, the progressive increase of which appears to have reached its limit with the introduction of the *n*-heptyl radical. Similar differences in antiseptic values were noted in a homologous series of indan-1 : 3-diones derived from resorcinol dimethyl ether (*loc. cit.*), and in a series of 4-alkyl derivatives of 1-phenyl*cyclo*hexane-3 : 5-dione prepared by Mr. I. H. S. Matar in these laboratories. On comparing compounds (IV) and (IX) it is of interest to note the superiority of *iso*propyl to *n*-propyl in enhancing antiseptic activity in this single case examined, whereas in the next two pairs of higher homologues

the respective influences of the *iso*butyl and *iso*amyl radicals are somewhat less than those of the corresponding normal alkyl groups [compare (V) and (VI) with (X) and (XI)]. Hence, from the point of view of the present investigations the further employment of *iso*alkylmalonyl chlorides would not appear to be of interest; nor would that of dialkylmalonyl chlorides, judging from the relative values of (V) and (XII).

In continuation of this work hydroxylated indandiones substituted in the aromatic nucleus by *n*-alkyl chains of varying length have been prepared, and examination of their antiseptic properties is in progress.

EXPERIMENTAL.

In all the following preparations molecular quantities of the two components were employed; the reactions were promoted by addition of anhydrous aluminium chloride (approx. 2 mols.), and completed at temperatures varying from 60° to 100° according to the particular case.

4-Hydroxy-7-methylindan-1 : 3-dione (I).—*p*-Tolyl methyl ether (5 g.) and malonyl chloride (5·8 g.) in nitrobenzene (50 g.) were treated with aluminium chloride (11·5 g.), added gradually, with shaking, during 30 minutes. The reaction was completed by warming at 60° for 45 minutes. The mass was stirred with ice, sufficient hydrochloric acid was added to bring the aluminium into solution, and the nitrobenzene and unchanged *p*-tolyl methyl ether were removed in steam. The tarry residue was shaken with ether, a small amount of amorphous material remaining undissolved. The ethereal extract was washed with water and extracted thoroughly with 5% sodium hydroxide solution. This left in the ether 0·2 g. of undemethylated condensation product, which was isolated as a crystalline solid but was not further examined. Acidification of the alkaline extract yielded the required phenolic product, which was taken up in ether and dried over sodium sulphate (4 g., 50% yield). On repeated crystallisation from acetone and then from ethyl alcohol the *substance* formed lemon-yellow needles, m. p. 258° (Found, by microanalysis: C, 68·7; H, 4·8; *M*, 180, 187. $C_{10}H_8O_3$ requires C, 68·2; H, 4·5%; *M*, 176).

4-Hydroxy-2 : 7-dimethylindan-1 : 3-dione (II).—*p*-Cresol (2·4 g.) and methylmalonyl chloride (3·4 g.) in nitrobenzene (20 g.) were treated with aluminium chloride (6·0 g.) and the mixture was warmed at 60—65° for 30 minutes. Subsequent treatment as in the case of the preparation of compound (I) gave an alkaline extract from which the product was isolated in the usual manner. It solidified (3·0 g.) in a vacuum and proved to be a mixture of methylmalonic acid (0·8 g.) and *4-hydroxy-2 : 7-dimethylindan-1 : 3-dione*.

The latter was very sparingly soluble in hot acetone and in cold methyl alcohol, separating in small compact prisms (0·8 g.) and leaflets respectively. After three recrystallisations the m. p. was 253° (sintering at 243°) (Found, by micro-analysis: C, 69·8; H, 5·6. $C_{11}H_{10}O_3$ requires C, 69·5; H, 5·3%).

4-*Hydroxy*-7-*methyl*-2-*ethylindan*-1 : 3-*dione* (III) was prepared by gradual addition of aluminium chloride (23 g.) to a solution of *p*-tolyl methyl ether (10 g.) and ethylmalonyl chloride (13·7 g.) in carbon disulphide (50 c.c.) and subsequent heating at 80° for 1 hour. The reaction mixture was stirred with ice, treated with hydrochloric acid, shaken with ether, and extracted with a 5% solution of sodium hydroxide, thus giving a neutral residue (A), which consisted largely of undemethylated condensation product, and an acidic portion (B). Traces of unchanged *p*-tolyl methyl ether were expelled from (A) by steam. The residual 4-methoxy-7-methyl-2-ethylindan-1 : 3-dione was a light brown resin which did not crystallise. The alkaline extract of (B) on acidification gave a 20% yield of the required hydroxylated *indandione*, which was considerably augmented by demethylation of its methoxy-derivative (A) by means of aluminium chloride in nitrobenzene at 100°. Crystallisation from boiling ethyl alcohol afforded colourless prisms, m. p. 197° (Found: C, 70·4; H, 5·8. $C_{12}H_{12}O_3$ requires C, 70·6; H, 5·9%).

4-*Hydroxy*-7-*methyl*-2 : 2-*diethylindan*-1 : 3-*dione* (XII).—*p*-Tolyl methyl ether (10·4 g.) and diethylmalonyl chloride (16·7 g.) in nitrobenzene (100 g.) were treated with aluminium chloride (23 g.) and heated at 70° for 45 minutes. The resulting demethylated *dione* was isolated in the usual manner, dried, freed from resin by cautious washing with light petroleum (b. p. 35—40°), and crystallised from methyl alcohol, forming colourless prisms (0·8 g.), m. p. 199—200° (Found: C, 72·35; H, 6·6. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%).

When this preparation was carried out in carbon disulphide solution the main product was 4-*methoxy*-7-*methyl*-2 : 2-*diethylindan*-1 : 3-*dione*, which was obtained in good yield as an oil. An attempt to convert this substance into (XII) by heating it with aluminium chloride (3 mols.) in toluene at 100° during 3 hours resulted in replacement of one of the two ethyl groups by hydrogen and demethylation at position 4, whereby a high yield of (III) (m. p. and mixed m. p. 197°) was obtained.

4-*Hydroxy*-7-*methyl*-2-n-*propylindan*-1 : 3-*dione* (IV) was obtained by treating a mixture of *p*-tolyl methyl ether (5 g.) and *n*-propylmalonyl chloride (7·5 g.) in nitrobenzene (50 g.) with aluminium chloride (11·5 g.) and subsequent heating at 80° for 45 minutes. The yield (9 g.) was quantitative. On crystallisation from methyl alcohol and then from acetone the *dione* formed colourless needles,

m. p. 187°, fairly readily soluble in methyl alcohol, ethyl alcohol and acetone in the cold, very readily in the hot solvents (Found : C, 71·5; H, 6·2. $C_{13}H_{14}O_3$ requires C, 71·6; H, 6·4%). The same substance was also obtained in quantitative yield when *p*-tolyl acetate (6 g.) and *n*-propylmalonyl chloride (7·5 g.) were condensed under similar conditions.

4-*Hydroxy*-7-*methyl*-2-n-*butylindan*-1 : 3-*dione* (V).—(a) *p*-Tolyl methyl ether (6 g.) and *n*-butylmalonyl chloride (10 g.) in *n*-hexane (60 c.c.) were treated with aluminium chloride (13·5 g.) and subsequently raised to and maintained at 70°, under reflux, for 1 hour. The hexane was then distilled off and the residue was treated with hydrochloric acid and shaken with ether. From this extract the *product* was obtained in theoretical yield. It crystallised well from methyl alcohol, benzene, ethyl alcohol and acetone. On slow evaporation of solutions in the latter solvent it separated in very large, transparent prisms, m. p. 165° (Found : C, 72·4; H, 7·0. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%).

The following details are given as examples of further modifications which may be adopted in a number of these condensations.

(b) *p*-Tolyl methyl ether and finely powdered aluminium chloride were stirred together and butylmalonyl chloride was then added in small portions and with thorough mixing. The whole was heated at 95° for 1 hour and the clear resinous mass was then cooled and treated with hydrochloric acid. The separated product was extracted with ether and obtained in quantitative yield.

(c) *p*-Cresol (5 g.) and butylmalonyl chloride (10 g.) in nitrobenzene (50 g.) were treated with aluminium chloride (13·5 g.) and heated at 95° for 45 minutes (yield, 85%). Use of anhydrous ferric chloride (16·5 g.) gave an equal yield, but the product was discoloured by traces of iron compounds, difficult to remove.

(d) Phosphorus trichloride (5 g.), *p*-tolyl acetate (10 g.), and *n*-butylmalonic acid (10·6 g.) in nitrobenzene (75 g.) were heated at 100° for 30 minutes. The mixture was cooled, treated with aluminium chloride (17·6 g.), and again heated at 100° for 30 minutes. The product was isolated in the usual manner and the yield was quantitative.

In the present series of preparations the highest yields of indandiones were those obtained from condensations in which *n*-propylmalonyl chloride and *n*-butylmalonyl chloride were employed. With further increase in length of the alkyl chain there appeared to be more tendency to resin formation, especially when the condensations were completed at temperatures above 80°. On the other hand, when the reactants were heated at temperatures below 70° the condensations in some cases were incomplete, as shown by the

amounts of alkylmalonic acids recovered. Compounds VI, VII, VIII, IX, X, and XI were all prepared by the condensation of *p*-cresol with the appropriate alkylmalonyl chloride according to method (c) as described above for the preparation of (V), with the sole difference that the reactions were completed at temperatures between 70° and 80°.

4-*Hydroxy*-7-*methyl*-2-n-*amylindan*-1 : 3-*dione* (VI), small colourless plates, m. p. 146°, from acetone (yield, 29%) (Found, by micro-analysis : C, 73·0; H, 7·0; *M*, 253. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%; *M*, 246).

4-*Hydroxy*-7-*methyl*-2-n-*hexylindan*-1 : 3-*dione* (VII), colourless leaflets, m. p. 136°, from ethyl alcohol (yield, 31%) (Found, by micro-analysis : C, 74·2; H, 7·8. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7%).

4-*Hydroxy*-7-*methyl*-2-n-*heptylindan*-1 : 3-*dione* (VIII), colourless prisms, m. p. 124°, from methyl alcohol and from acetone (yield, 50%) (Found : C, 74·2; H, 8·2. $C_{17}H_{22}O_3$ requires C, 74·45; H, 8·0%).

4-*Hydroxy*-7-*methyl*-2-iso*propylindan*-1 : 3-*dione* (IX), colourless needles, m. p. 224°, from acetone (yield, 16%) (Found, by micro-analysis : C, 71·1; H, 6·5. $C_{13}H_{14}O_3$ requires C, 71·6; H, 6·4%).

4-*Hydroxy*-7-*methyl*-2-iso*butylindan*-1 : 3-*dione* (X), large colourless laminæ, m. p. 152·5°, from acetone (yield, 47%) (Found, by micro-analysis : C, 72·2; H, 7·0. $C_{14}H_{16}O_3$ requires C, 72·4; H, 6·9%).

4-*Hydroxy*-7-*methyl*-2-iso*amylindan*-1 : 3-*dione* (XI), colourless needles, m. p. 142°, from acetone (yield, 44%) (Found : C, 72·7; H, 7·5. $C_{15}H_{18}O_3$ requires C, 73·2; H, 7·3%).

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