115. *Synthesis and Anti-bacterial Properties of Alkyl and Alkenyl Derivatives of 2 : 6-Dimethoxybenzoquinone.*

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A number of 3-alkyl, 3-alkenyl, and 3 : 5-dialkyl derivatives of 2 : 6-dimethoxybenzoquinone (I) have been prepared by the action of appropriate diacyl peroxides on (I), and the anti-bacterial powers of these quinones against *Staphylococcus aureus* have been compared.

Fieser and Oxford (*J. Amer. Chem. Soc.*, 1942, **64**, in the press) prepared a number of alkyl- and alkenyl-substituted benzo- and naphtha-quinones by the reaction RH(quinone) + Alk·CO·O·O·CO·Alk = R·Alk + Alk·CO_2H + CO_2, the yields varying from a trace up to 60%. It has recently been discovered that 2 : 6-dimethoxybenzoquinone and 4 : 6-dimethoxytoluquinone are powerful inhibitors of the growth of *Staphylococcus aureus in vitro* (Oxford, *Chem. and Ind.*, 1942, **61**, 189), and it became of interest to prepare other alkyl derivatives of 2 : 6-dimethoxybenzoquinone with two side chains, and also with side chains longer than methyl, in order that their anti-bacterial action might be compared with that of the simpler quinones. This has now been accomplished by an application of the above reaction on the readily accessible 2 : 6-dimethoxybenzoquinone (see Baker, J., 1941, 665). An excess of this quinone was used if only one side chain was to be introduced, but for the introduction of two side chains a little more than the theoretical amount of the peroxide was found to be suitable. The following have thus been prepared with ease : 3-ethyl-, 3-*n*-propyl-, 3-propenyl-, 3-*iso*butyl-, and 3 : 5-dimethyl-2 : 6-dimethoxybenzoquinone. An attempt to prepare the 3 : 5-diethyl derivative yielded an uncrystallisable oil, undoubtedly containing this substance, which could not easily be further purified. The reaction failed with di*iso*butyryl and disuccinyl peroxides.

Although the yields in this application of the above reaction are small (15% or less), the separation of the alkylquinone from the water-soluble fatty acid and from unchanged 2 : 6-dimethoxybenzoquinone is readily accomplished by extraction of the aqueous acetic acid reaction mixture with cold light petroleum, in which the last-named quinone, unlike its homologues, is insoluble. None of the new quinones is markedly more active against *Staph. aureus* than 4 : 6-dimethoxytoluquinone; indeed the 3-propenyl derivative is considerably less active.

Experimental.

Diacetyl, dipropionyl, and di-*n*-butyryl peroxides were prepared from the corresponding acid anhydrides by the method of Gambarjan (*Ber.*, 1909, **42**, 4010), light petroleum (b. p. 40—60°) being used as the diluent in the last instance in place of ether. Di*iso*butyryl, dicrotonyl, and di*iso*valeryl peroxides were prepared from the corresponding acid chlorides essentially by the method of Price, Kell, and Krebs (*J. Amer. Chem. Soc.*, 1942, **64**, 1103) save that light petroleum (b. p. 40—60°) was used as diluent in place of benzene. In all instances the diluent was allowed to evaporate spontaneously at room temperature immediately before use of the peroxide. Dicrotonyl peroxide, thus prepared, melts at about 34°; Clover and Richmond (*Amer. Chem. J.*, 1903, **29**, 194) record m. p. 41°.

The following description of the preparation of 2 : 6-dimethoxy-3-ethylbenzoquinone is typical of the method used for the introduction of one side chain. To a solution of dipropionyl peroxide (1·0 g.) in glacial acetic acid (60 ml.) was added 2 : 6-dimethoxybenzoquinone (1·25 g.; 9% excess), and the whole slowly heated with stirring (in a water-bath) until the temperature had reached 80° and the quinone had dissolved. The temperature of the bath was then raised to 100° and maintained until the addition of a piece of porous pot to the glacial acetic acid solution showed that effervescence had ceased (15—30 minutes). The cooled solution was diluted with water (300 ml.) and extracted twice with light petroleum (once only for the higher homologues and four times for the propenyl derivative). The unchanged 2 : 6-dimethoxybenzoquinone may then be recovered by filtration of the aqueous layer. The extract was dried over anhydrous

sodium sulphate and concentrated to small volume, and the remainder of the solvent allowed to evaporate spontaneously. The slightly gummy, crystalline residue was pressed on a porous plate and recrystallised from a little light petroleum (b. p. 80—100°); yield, 0·12 g. The higher homologues, being readily soluble in cold light petroleum, were crystallised from aqueous methanol. The propenyl derivative was repeatedly crystallised from light petroleum at 0°.

For the preparation of 2 : 6-dimethoxy-3 : 5-dimethylbenzoquinone the quantities were: 2 : 6-dimethoxybenzoquinone (2·0 g.), diacetyl peroxide (3·0 g.; 7% excess), and glacial acetic acid (100 ml.). A corresponding experiment with dipropionyl peroxide yielded a completely oily product which resisted all attempts at crystallisation. It had considerable anti-bacterial activity (see table) and, like 2 : 6-dimethoxy-3 : 5-dimethylbenzoquinone, gave a deep blue colour with concentrated sulphuric acid. The monosubstituted alkyl-quinones gave a blue colour with a marked violet tinge with this reagent, but the propenyl derivative gave merely a brown colour. The last-named, which was much more intensely coloured than the other quinones, gave also a much bluer colour with dilute caustic soda solution on warming.

The physical and anti-bacterial properties of this series of quinones are summarised in the table. For the tests against *Staph. aureus*, sterile aqueous solutions containing usually 30—100 parts per million were made up and added to sterile heart broth and 2% glucose broth as described by Oxford (*Chem. and Ind.*, 1942, **61**, 48). The test organisms were three strains of *Staph. aureus* numbered 3095, 3750, and 3761 in the National Collection of Type Cultures (Lister Institute), and the inoculum given to each tube was always 500—1000 viable bacteria per ml. Dilute aqueous solutions of these quinones, which are only very sparingly soluble in water, seem perfectly stable for long periods at room temperature in diffuse daylight.

TABLE.

Derivative of 2 : 6-dimethoxybenzoquinone.	Crystalline appearance and m. p.	Analytical data: Found, % (micro-analyses by Drs. Weiler and Strauss, Oxford).	Analytical data: Calc., %.	μg. per ml. completely inhibiting *Staphylococcus aureus*: N.C.T.C. No. 3095 in glucose broth for 1 day (A) and 2 days (B) at 37°.	N.C.T.C. No. 3750 in glucose broth for 1 day (A) and 2 days (B) at 37°.	N.C.T.C. No. 3761 in standard heart broth for 1 day (A) and 2 days (B) at 37°.
Unsubstituted	Yellow needles, 255°	Graebe and Hess, *Annalen*, 1905, **340**, 237.		2·5 (A) 12·5 (B)	3·7 (A) 21·0 (B)	12·5 (A) 21·0 (B)
3-Methyl- (*i.e.*, 4 : 6-dimethoxytoluquinone)	Yellow needles, 125°	Anslow, Ashley, and Raistrick, J., 1938, 439; see also Fieser and Oxford, *loc. cit.*		1·7 (A) 3·3 (B)	1·7 (A) 3·3 (B)	3·3 (A) 10·0 (B)
3-*Ethyl*-, $C_{10}H_{12}O_4$	Small yellow plates, 59°	C, 61·1 H, 6·2	C, 61·2 H, 6·2	1·8 (A) 3·6 (B)	1·8 (A) 1·8 (B)	1·8 (A) 9·1 (B)
3-n-*Propyl*-, $C_{11}H_{14}O_4$	Yellow plates and needles, 20°	C, 63·6 H, 7·1	C, 62·8 H, 6·7	2·9 (A) 5·9 (B)	2·9 (A) 2·9 (B)	5·9 (A) 9·8 (B)
3-iso*Butyl*-, $C_{12}H_{16}O_4$	Yellow needles, 50—51°	C, 64·4 H, 7·1	C, 64·3 H, 7·2	2·0 (A) 4·0 (B)	4·0 (A) 4·0 (B)	4·0 (A) 4·0 (B)
3-*Propenyl*-, $C_{11}H_{12}O_4$	Orange-red needles, 84°	C, 63·4 H, 5·7 OMe, 30·1	C, 63·4 H, 5·8 OMe, 29·8	7·1 (A) 24·0 (B)	7·1 (A) 24·0 (B)	7·1 (A) 24·0 (B)
3 : 5-*Dimethyl*-, $C_{10}H_{12}O_4$	Orange-yellow plates, 134°	C, 61·4 H, 6·4	C, 61·2 H, 6·2	3·2 (A) 3·2 (B)	1·6 (A) 3·2 (B)	3·2 (A) 3·2 (B)
3 : 5-*Diethyl*-	Yellow oil	Not obtained pure		9·1 (A)	9·1 (A) 9·1 (B)	9·1 (A)

The unexpected failure of the reaction with di*iso*butyryl peroxide was at first thought to be due to the greater stability of this peroxide, which, when heated in a narrow tube, decomposes vigorously at 110—120°, *i.e.*, 20° higher than the corresponding decomposition point for di-*n*-butyryl peroxide. No trace of quinone soluble in light petroleum was obtained, however, when the reaction with 2 : 6-dimethoxybenzoquinone was carried out at the b. p. of glacial acetic acid instead of 100°. This peroxide differs from the rest in having substituents attached to the α-carbon atoms. No trace of quinone soluble in sodium bicarbonate solution was formed when disuccinyl peroxide (Clover and Houghton, *Amer. Chem. J.*, 1904, **32**, 55) was caused to react in glacial acetic acid solution at 100° with 2 : 6-dimethoxybenzoquinone.

The work is being continued, particularly in the direction of the introduction of other unsaturated side chains, and also of the finding of the optimum conditions for the alkylation of quinones by this method.

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