Quinones. Part 10.[1] Side-chain Methylthiolation of Methylbenzoquinones
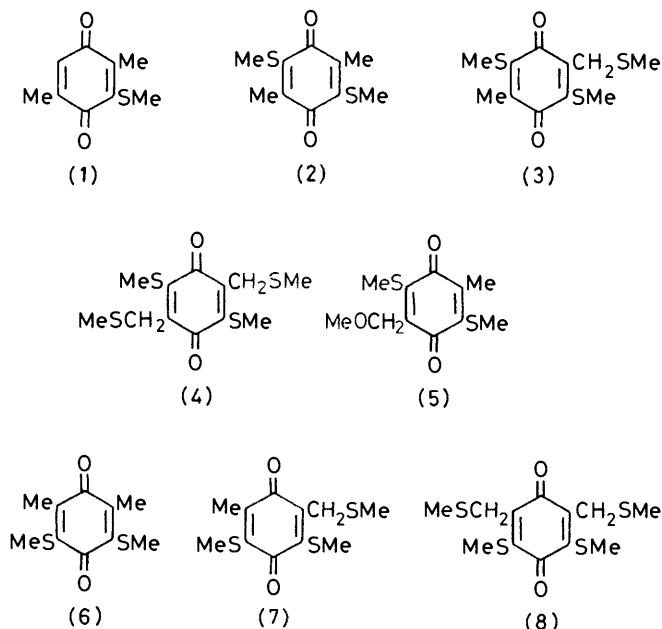
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2,3,5,6-Tetramethylbenzoquinone undergoes side-chain reaction with excess of sodium methanethiolate to form mono-, di-, and tri-methylthiomethyl derivatives in low yields. 2,5- and 2,6-Dimethylbenzoquinones react first on the nucleus to give dimethyl(dimethylthio)quinones followed by limited side-chain methylthiolation. The side-chain reaction is restricted by a competing redox reaction. The presence of semiquinone radical anions can be detected by selective line-broadening in the n.m.r. spectra of quinone–thiolate solutions.

RESULTS

In the preceding paper [1] it was shown that methyl-1,4-naphthoquinones can undergo side-chain alkylthiolation by reaction with an alkylthiolate. In this paper we examine the behaviour of methylbenzoquinones with sodium methanethiolate.

2,5-Dimethylbenzoquinone reacts at room temperature with 2 mol of sodium methanethiolate to give a mixture of the mono- and di-nuclear methylthiolated quinones (1) and (2) respectively, and the corresponding quinols. No other products were evident indicating the absence of attack on the side chains. Side-chain reaction occurred using a large excess of thiolate, the same results being obtained starting either with the dimethylquinone or with (2). It was more convenient to use (2) as the starting material. Using 20 mol equiv. of sodium methanethiolate in benzene–methanol, after a prolonged (< 20 h) induction period, reaction occurred relatively rapidly to form several coloured products in very small amounts, some of which eventually reacted further.

very small amounts of the methylthiomethylquinones (7) and (8). The use of less reagent did not significantly affect the yields of side-chain thiomethylated products.

The reaction of 2,3,5,6-tetramethylbenzoquinone (duroquinone) with 2 mol of sodium methanethiolate for two hours afforded the dimer, diduroquinone (9),[2] the mono(methylthiomethyl)quinone (10) (9%), and traces of higher methyl-

Yields of the methylthiomethylquinones (3) and (4) never exceeded 5%. A very minor product was the quinone (5) resulting from side-chain methoxylation. The isomer (6) of (2) behaved similarly; reaction with a large excess of sodium methanethiolate gave, after a long induction period,
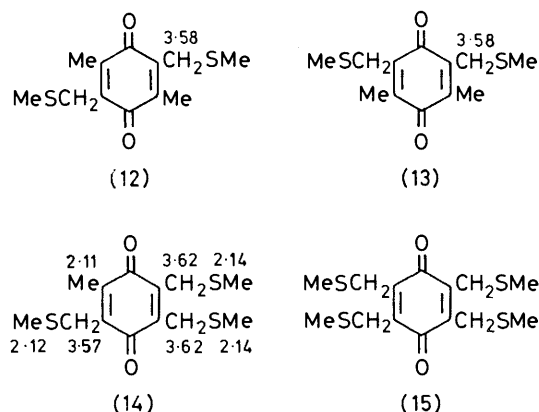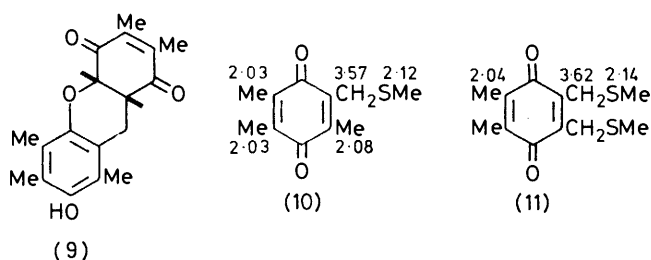
thiolated products. The yield of (10) could be increased to >30% using a large excess (20 mol) of thiolate and a longer reaction time, while with 40 mol of thiolate and a reaction time of 75 h compounds (11)—(14) could be isolated in yields ranging from 36% for (11) to 3% for the tris(methylthiomethyl)quinone (14). The ultimate compound (15) was not found although in several experiments products containing methoxy-groups were detected in small amounts.

The structure of the 2,3-bis(methylthiomethyl)quinone (11) is deduced from its n.m.r. spectrum. As can be seen from formulae (10)—(14) neighbouring quinone methyl groups resonate at δ 2.03—2.04, but at 2.08—2.11 when adjacent to a methylthiomethyl substituent. The methylene signals of adjacent methylthiomethyl groups resonate at δ 3.62, but appear at δ 3.57—3.58 when adjacent to a methyl group. The quinones (12) and (13) were obtained as an inseparable mixture; the methylene protons all resonated at

δ 3.58 but the methyl groups appeared as three singlets (total 12 H) at δ 2.13, 2.11, and 2.10.

DISCUSSION

These methylthiolation reactions proceed by addition of thiolate anions to a quinone methide (or its anion) as in the side-chain alkylthiolation[1] of methylnaphthoquinones. Evidence for intermediate quinone methide formation comes from the reaction of duroquinone with 2 mol of thiolate which yielded mainly the dimer (9)[2] as well as the mono-methylthiolated quinone (10); however normally a substantial excess of reagent was used suggesting that the addition step probably involves the quinone methide anion (Scheme 1 for duroquinone). Further side-chain reaction of duroquinone could only be effected with a large excess of thiolate and the yield of the tris(methylthiomethyl)quinone (14) did not exceed 3%. It should be possible to improve on this, and indeed to obtain the tetrasubstituted compound (15) by starting from the quinone (11). Progressive methylthiolation is

SCHEME 1
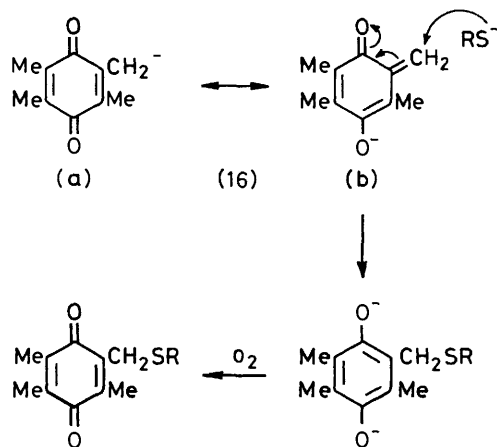
self-inhibiting because each side-chain substitution will raise the redox potential of the preceding quinone making the oxidation step, in the presence of an excess of thiolate, increasingly difficult. The importance of aerial oxidation was quickly apparent upon stoppering the reaction flask when the reaction ceased.

Of the di-methylthiolated quinones, the 2,3-isomer (11) predominates. In the side-chain amination of duroquinone with piperidine the only diamino-product is (17), the formation of which was attributed[3] to initiation of the second amination by intramolecular proton abstraction (18). A similar mechanism for di-methylthiolation is possible but would be expected to be less effective as sulphides are very weakly basic.

The formation of (5) in very small amounts, and of traces of methoxy-compounds in the duroquinone reactions, is not surprising as low concentrations of methoxide ion will be present (MeS⁻ + MeOH ⇌ MeSH + MeO⁻) in the reaction mixtures. Hence (5) could arise from (3) by direct replacement of the side-chain methylthio-group or by nucleophilic addition to the
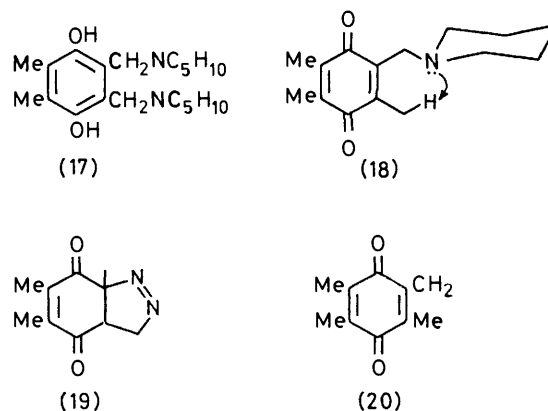
quinone-methide derived from (2). Methoxide ion is a stronger base than methanethiolate but a weaker nucleophile, and in the original preparation[2] of diduroquinone (9) was obtained from duroquinone in 94% yield by addition of a catalytic amount of ethanolic potassium hydroxide.

It is apparent from these few examples that side-chain methylthiolation is a limited reaction with benzoquinones, and probably with any methylquinone of relatively high redox potential. Side-chain amination is not restricted to the same extent, as amines are less readily oxidised. An alternative method, at least for the preparation of mono-methylthiomethylbenzoquinones, would be the generation of quinone methides by Dean's
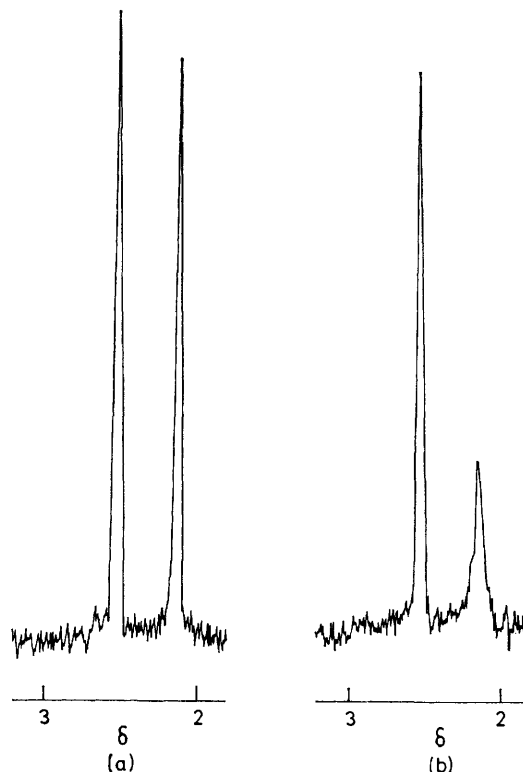
100-MHz ^{1}H N.m.r. spectra of 2,6-dimethyl-3,5-dimethylthiobenzoquinone in (a) deuteriomethanol and (b) deuteriomethanol containing sodium methanethiolate (10^{-3}M)

procedure.[4] Thus treatment of the diazomethane adduct (19) of trimethylbenzoquinone with two mol of sodium methanethiolate should produce (16) followed by addition and oxidation to give (10) (Scheme 1).

The reduction of quinones by methanethiolate can be conveniently demonstrated by n.m.r. spectroscopy. Addition of sodium methanethiolate (10^{-3}M) to duroquinone in deuteriomethanol broadens the methyl signal. The effect is more obvious with 2,6-dimethyl-3,5-dimethylthiobenzoquinone (2) (see Figure) where the C-methyl signal has partially collapsed but the S-methyl singlet is unaffected. At higher methanethiolate concentrations there was complete collapse of the C-methyl signal, but the original spectrum was restored on quenching with deuterioacetic acid. The same phenomena were observed with methylnaphthoquinones, the spectrum obtained with 2-methyl-1,4-naphthoquinone being precisely the same as that published by Sanders [5] from the interaction of the quinone with t-butylamine, showing the virtual disappearance of the methyl and 3-H signals and partial collapse of the aromatic resonances. These observations can be ascribed to the presence of semi-quinone radical anions undergoing rapid electron exchange with quinone molecules.[5,6] This was confirmed by the strong semiquinone e.s.r. spectra observed for solutions of duroquinone and 2,3-dimethylnaphthoquinone in deuteriomethanol to which sodium methanethiolate had been added. Spectra corresponding to benzylic radicals [e.g. (20)] formed by oxidation of quinone anions [e.g. (16a)] could not be detected.

EXPERIMENTAL

U.v. and n.m.r. spectra were measured for solutions in ethanol and deuteriochloroform respectively. Unless stated otherwise light petroleum refers to the fraction of b.p. 60—80°.

2,5-Dimethyl-3-methylthio- (1) and 2,5-Dimethyl-3,6-dimethylthio-benzoquinone (2).—2,5-Dimethylbenzoquinone [7] (1.94 g) in benzene (30 ml) was stirred with sodium methanethiolate (4.04 g, 2 mol) in methanol (40 ml) for 4 h. The mixture was poured into ether–water and the ether layer was dried and evaporated. The residue was passed down a dry column of silica gel in benzene to give 2,5-dimethyl-3,6-dimethylthioquinol (0.71 g) [ν_{CO} absent, δ 5.89 (2 OH), 2.46 (2 SMe), and 2.20 (2 ArMe)] which was stirred in ether with silver oxide for 0.5 h to yield the quinone (0.68 g) which was identical with the second compound eluted from the column, 2,5-dimethyl-3,6-dimethylthiobenzoquinone (2), red needles, m.p. 106.5—107° (from light petroleum) (Found: C, 52.8; H, 5.3; S, 28.4%; M^+, 228.027 8. $C_{10}H_{12}O_2S_2$ requires C, 52.6; H, 5.3; S, 28.1%; M, 228.027 9); $\lambda_{max.}$ 247, 271sh, and 380 nm (log ε 4.17, 3.64, and 3.72); δ 2.55 (6 H, s, SMe) and 2.19 (6 H, s, Q–Me). Further elution gave 2,5-dimethyl-3-methylthiobenzoquinone (1) (0.40 g) as orange-red needles, m.p. 113° (from light petroleum) (Found: C, 59.4; H, 5.7; S, 17.9%; M^+, 182.040 0. $C_9H_{10}O_2S$ requires C, 59.3; H, 5.5; S, 17.6%; M, 182.040 1); $\lambda_{max.}$ 246, 257sh, 291sh, and 437 nm (log ε 4.03, 3.95, 3.34, and 3.19); δ 6.55 (1 H, q, J 1.5 Hz, H-6), 2.55 (3 H, s, SMe), 2.16 [3 H, s. C(2)-Me], and 2.06 [3 H, d, J 1.5 Hz, C(5)-Me]; and 2,5-dimethyl-3-methylthioquinol.

2,6-Dimethyl-3,5-dimethylthiobenzoquinone (6).—Methanethiol was bubbled through a solution of 2,6-dimethylbenzoquinone [7] (3.87 g) in methanol (80 ml) for 30 min. Evaporation of the pale yellow solution left a mixture of quinols which was taken into ether and shaken with aqueous ferric chloride. T.l.c. showed the presence of two orange quinones, but no starting material. The ether was removed, and methanethiol was again passed through a methanolic solution of the residue for 40 min. Evaporation followed by re-oxidation of the residue, in ether, with aqueous ferric chloride gave a single product, 2,6-dimethyl-3,5-dimethylthiobenzoquinone as red needles, m.p. 111—112° (from ethanol) (1.24 g) (Found: C, 52.6; H, 5.3; S, 27.8%; M^+, 228.027 8. $C_{10}H_{12}O_2S_2$ requires C, 52.6; H, 5.3; S, 28.1%; M, 228.027 9); $\lambda_{max.}$ 247, 267sh, 375, and 456sh nm (log ε 3.99, 3.61, 3.57, and 3.03); δ 2.52 (6 H, s, SMe) and 2.16 (6 H, s, Q–Me).

Reaction of 2,5-Dimethyl-3,6-dimethylthiobenzoquinone with Sodium Methanethiolate.—2,5-Dimethyl-3,6-dimethylthiobenzoquinone (0.484 g) in benzene (10 ml) was stirred with sodium methanethiolate (2.99 g, 10 mol) in methanol (30 ml) for 20 h. The mixture was poured into ether–10% aqueous potassium dihydrogen phosphate, the dried ether layer was evaporated, and the residue separated by preparative t.l.c. on silica gel in ether–light petroleum (1 : 9) to give 2-methyl-3,6-dimethylthio-5-(methylthiomethyl)benzoquinone (3) (37 mg) as orange-red needles, m.p. 32.5—33° (from light petroleum, b.p. 40—60°) (Found: M^+, 274.015 7. $C_{11}H_{14}O_2S_3$ requires M, 274.015 5); $\lambda_{max.}$ 247.5, 274sh, and 382 nm (log ε 4.44, 3.58, and 3.63); δ 3.77 (2 H, s, Q–CH$_2$–S), 2.55 (6 H, s, Q–SMe), 2.18 (3 H, s, –CH$_2$SMe), and 2.14 (3 H, s, Q–Me); m/e 274 (M^+, 12%), 259 (100), 244 (11), 231 (22), 229 (9), 228 (56), 227 (45), 226 (79), 213 (20), 211 (22), 199 (32), 185 (11), 180 (32), 179 (63), 123 (11), 99 (16), 86 (95), and 85 (45); and 2,5-dimethylthio-3,6-bis(methylthiomethyl)benzoquinone (4) (42 mg), as red needles, m.p. 62.5° (from light petroleum, b.p. 40—60°) (Found: M^+, 320.003 5. $C_{12}H_{16}O_2S_4$ requires M, 320.003 3); $\lambda_{max.}$ 250 and 388 nm (log ε 4.20 and 3.68); δ 3.77 (4 H, s, Q–CH$_2$–S), 2.55 (6 H, s, Q–SMe), and 2.16 (6 H, s, CH$_2$SMe); m/e 320 (M^+, 33%), 275 (14), 274 (100), 273 (26), 272 (47), 259 (15), 257 (23), 229 (16), 227 (12), 226 (33), 225 (21), 224 (9), 183 (23), 179 (13), and 85 (47). A third orange band on further preparative t.l.c. in ethyl acetate–toluene (1 : 49) gave 2-methyl-3,6-dimethylthio-5-methoxymethylbenzoquinone (5) (5 mg) as red needles, m.p. 74° (from light petroleum) (Found: M^+, 258.038 2. $C_{11}H_{14}O_3S_2$ requires M, 258.038 4); $\lambda_{max.}$ 248 and 384 nm (log ε 4.00 and 3.61); δ 4.46 (2 H, s, Q–CH$_2$–O), 3.37 (3 H, s, OMe), 2.56 (6 H, s, SMe), and 2.17 (3 H, s, Q–Me); m/e 258 (M^+, 100%), 243 (17), 228 (32) 227 (28), 226 (71), 225 (18), 215 (26), 213 (13), 211 (13), 193 (16), 185 (12), 183 (18), 101 (13), 99 (26), 88 (22), and 86 (12).

Reaction of 2,6-Dimethyl-3,5-dimethylthiobenzoquinone with Sodium Methanethiolate.—2,6-Dimethyl-3,5-dimethylthiobenzoquinone (0.604 g) was treated with sodium methanethiolate (3.73 g, 20 mol) as in the preceding experiment. Work-up as before by preparative t.l.c. on silica gel in ether–light petroleum (1 : 9) gave some starting quinone and 2-methyl-3,5-dimethylthio-6-methylthiomethylbenzoquinone (7) (36 mg) as red needles, m.p. 65.5—66° (from light petroleum, b.p. 40—60°) (Found: C, 48.3; H, 5.2; S, 34.8%; M^+, 274.015 9. $C_{11}H_{14}O_2S_2$ requires C, 48.1; H, 5.1; S, 35.1%; M, 274.015 4); $\lambda_{max.}$ 246.5, 276sh, and 380 nm (log ε 4.18,

3.59, 3.41, and 3.63); δ 3.74 (2 H, s, Q–CH₂–S), 2.53 (6 H, s, Q–SMe), 2.17 (3 H, s, CH₂S*Me*), and 2.14 (3 H, s, Q–Me); *m/e* 274 (M^+, 17%), 259 (84), 244 (105), 241 (11), 231 (21), 228 (37), 227 (40), 226 (100), 216 (13), 213 (10), 211 (23), 199 (18), 183 (10), 181 (11), 180 (37), 179 (89), 171 (30), 99 (21), 85 (60), 71 (32), 70 (30), and 69 (19). A red band of lower R_{F} was re-run in butan-2-one–light petroleum (1 : 19) to yield 3,5-*dimethylthio*-2,6-*bis*(*methylthiomethyl*)*benzo-quinone* (8) (21 mg) as an orange-red oil (Found: M^+, 320.003 5. $C_{12}H_{16}O_2S_4$ requires *M*, 320.003 3); λ_max. 247 and 387 nm (log ε 4.05 and 3.52); δ 3.74 (4 H, s, Q–CH₂–S), 2.55 (6 H, s, Q–SMe), and 2.13 (6 H, s, CH₂–S*Me*); *m/e* 320 (M^+, 3.5%), 274 (16), 273 (18), 272 (71), 257 (35), 245 (10), 244 (100), 229 (40), 227 (20), 226 (11), 225 (12), 211 (11), and 85 (32).

Reaction of Duroquinone with Sodium Methanethiolate.— (*a*) To a solution of duroquinone (0.5 g) in benzene (5 ml) and methanol (8 ml) was added sodium methanethiolate (0.43 g, 2 mol). The mixture was stirred for 2 h under a drying tube and then poured into water (25 ml) and benzene (30 ml). The organic phase was washed with dilute hydrochloric acid and water, dried (MgSO₄), evaporated, and separated by preparative t.l.c. on silica gel in chloroform to give un-changed duroquinone, diduroquinone (9) as light orange leaflets (from ethanol), m.p. 208—209° (lit.,[2] 207.5—208°) (160 mg), and 3,5,6-*trimethyl*-2-(*methylthiomethyl*)*benzoquin-one* (10) as orange crystals, m.p. <15° (56 mg) (from light petroleum, b.p. 40—60°) (Found: M^+, 210.071 7. $C_{11}H_{14}$-O_2S requires *M*, 210.071 4); λ_max. 265 and 350 nm (log ε 4.20 and 2.85); δ 3.57 (2 H, s, Q–CH₂–S), 2.12 (3 H, s, SMe), 2.08 [3 H, s, C(3)-Me], and 2.03 [6 H, s, C(5) and C(6)-Me]; *m/e* 210 (M^+, 100%), 195 (45), 180 (10), 167 (22), 164 (26), 136 (16), and 91 (11).

(*b*) Sodium methanethiolate (4.28 g, 20 mol) was added to duroquinone (0.5 g) in benzene (20 ml) and methanol (35 ml), and the mixture was stirred under a drying tube for 15 h and then poured into benzene (30 ml) and 10% potassium dihydrogen phosphate (50 ml). The organic phase was dried (MgSO₄) and evaporated, and chromato-graphed on silica to give 3,5,6-trimethyl-2-(methylthio-methyl)benzoquinone (0.25 g) with minor amounts of duro-quinone and di- and tri-methylthiolated products.

(*c*) Duroquinone (0.497 g) in benzene (30 ml) was stirred with sodium methanethiolate (8.65 g, 40 mol) in methanol (58 ml) for 75 h. Work up as in (*b*) and chromatography in ethyl acetate–light petroleum (7 : 193) gave 9 fractions. Fraction 1 was duroquinone (9 mg), and fraction 2 contained

3,5,6-trimethyl-2-methylthiomethylbenzoquinone (10) (32 mg), identical with that described in (*b*). Fractions 4 and 6 were combined and crystallised from ethanol to afford 5,6-*dimethyl*-2,3-*bis*(*methylthiomethyl*)*benzoquinone* (11) (283 mg) as orange plates, m.p. 66.5° (from ethanol) (Found: C, 56.4; H, 6.2; S, 24.9%; M^+, 256.059 6. $C_{12}H_{16}O_2S_2$ requires C, 56.2; H, 6.3; S, 25.0%; *M*, 256.059 2); λ_max. 264sh, 270, and 364 nm (log ε 4.20, 4.21, and 3.05); δ 3.62 (4 H, s, Q–CH₂–S), 2.14 (6 H, s, SMe), and 2.04 (6 H, s, QMe); *m/e* 256 (M^+, 6%), 209 (16), 208 (47), 194 (22), 193 (100), and 111 (9). Preparative t.l.c. of fractions 7 and 8 in toluene gave an inseparable mixture (60 mg) of 3,6-*dimethyl*-2,5-*bis*(*methylthiomethyl*)- (12) and 3,5-*dimethyl*-2,6-*bis*(*methylthiomethyl*)-*benzoquinone* (13) as yellow needles, m.p. 65—66° (from light petroleum, b.p. 40—60°) (Found: M^+, 256.059 4. $C_{12}H_{16}O_2S_2$ requires *M*, 256.059 2); λ_max. 264sh, 271, and 365 nm (log ε 4.13, 4.14, and 2.94); δ 3.58 (4 H, s, Q–CH₂–S) and 2.13, 2.11, and 2.10 (total 12 H, overlapping s, QMe and SMe); *m/e* 256 (M^+, 3%), 241 (10), 210 (100), 195 (9), 194 (10), and 91 (10). Fraction 9, after preparative t.l.c. in benzene yielded 2-*methyl*-3,5,6-*tris*-(*methylthiomethyl*)*benzoquinone* (14) as a yellow oil (30 mg) (Found: M^+, 302.046 8. $C_{13}H_{18}O_2S_3$ requires *M*, 302.046 8); λ_max. 271 and 376 nm (log ε 4.05 and 3.04); δ 3.62 [4 H, s, C(5)–CH₂–S and C(6)–CH₂–S], 3.57 [2 H, s, C(3)–CH₂–S], 2.14 [6 H, s, C(5)–CH₂S*Me* and C(6)–CH₂SMe], 2.12 [3 H, s, C(3)–CH₂SMe], and 2.11 (3 H, s, QMe); *m/e* 302 (M^+, 15%), 256 (14), 255 (23), 254 (100), 239 (32), 209 (16), 208 (50), 207 (40), 194 (13), 193 (89), 192 (18), 191 (53), 179 (17), 165 (13), 111 (56), 103 (10), 91 (25), and 77 (22).

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