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THE STRUCTURE OF DI-*tert*-BUTYLNAPHTHALENESULPHONIC ACIDS[1]

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ABSTRACT

Commercial sodium di-*tert*-butylnaphthalenesulphonate has been resolved into its isomers, which were shown to be sodium 2,6- and 2,7-di-*tert*-butylnaphthalene-4-sulphonates.

Sodium di-*tert*-butylnaphthalenesulphonate is known as an effective central inhibitor of the cough reflex (1). Although some authors (1) refer to this antitussive drug as sodium 2,6-di-*tert*-butylnaphthalenesulphonate, its mode of preparation suggests that it is a mixture of at least two different isomers. It is prepared (2) by a Friedel–Crafts alkylation of naphthalene with 2 moles of *tert*-butyl chloride followed by sulphonation of the butylation product. Since several workers (3) have shown that *tert*-butylation of naphthalene gives a mixture containing about equal parts of 2,6- and 2,7-di-*tert*-butylnaphthalene, the commercial product can be inferred to consist of approximately equal quantities of the corresponding sulphonates. The purpose of this work was to isolate the isomers of sodium di-*tert*-butylnaphthalenesulphonate and to determine their structure.

Reaction of commercial sodium di-*tert*-butylnaphthalenesulphonate with thionyl chloride according to a procedure recently developed by Bosshard *et al.* (4) gave a mixture from which two isomeric sulphonyl chlorides could be isolated by fractional crystallization: one melting at 167–169°, insoluble in cold ligroin; the second melting at 117–118°, moderately soluble in ligroin. Hydrolysis of these sulphonyl chlorides with sodium hydroxide regenerated the pure sulphonates. The sulphonate obtained from the higher-melting isomer was shown to be sodium 2,7-di-*tert*-butylnaphthalenesulphonate by conversion to 2,7-di-*tert*-butylnaphthalene (3) with 60% sulphuric acid. In the same way the sulphonate obtained from the lower-melting sulphonyl chloride was related to 2,6-di-*tert*-butylnaphthalene.

In order to determine the position of the sulphonic acid group of these compounds, sulphonation of 2,6- and 2,7-di-*tert*-butylnaphthalene under conditions which usually bring about α-sulphonation of naphthalene and naphthalene derivatives (5) was carried out. Reaction of these sulphonic acids with thionyl chloride gave the same sulphonyl chlorides as those isolated from the commercial product. On the other hand alkaline fusion of the sulphonates yielded naphthols which readily coupled with phenyldiazonium chloride to give orange-red azo dyes; these were easily reduced by stannous chloride to aminonaphthols, which in turn gave yellow quinones on oxidation. The quinone obtained from the 2,6-di-*tert*-butylnaphthol was found to be identical with the quinone obtained by Fieser and Price (6) from a chromic acid oxidation of 2,6-di-*tert*-butylnaphthalene.

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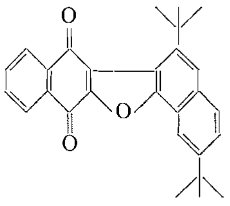
This quinone was later shown by Crawford and Glesmann (3) to be 2,6-di-*tert*-butyl-1,4-naphthoquinone. Chromic acid oxidation of 2,7-di-*tert*-butylnaphthalene under similar conditions also gave a quinone, identical with that resulting from the coupling reaction of the 2,7-di-*tert*-butylnaphthol, reduction of the azo dye, and oxidation of the aminonaphthol. Furthermore, we found that the disubstitution product obtained by Buu-Hoi and Demerseman (7) from the alkylation of α-naphthol with *tert*-butyl bromide, which they suggest may be a 4,*x*-di-*tert*-butyl-1-naphthol, was identical with the naphthol obtained from the alkaline fusion of 2,6-di-*tert*-butylnaphthalenesulphonate. Thus the sulphonic acid group of the starting sulphonates can only be in the 1 or 4 positions.

Of the two possible α-positions, position 4 seemed more probable: sulphonation of 2,6- and 2,7-dimethylnaphthalene occurs preferentially in position 4 (8) and furthermore position 1 is subjected to the steric effect of the tertiary butyl group. Position 1 was finally eliminated by the fact that yellow di-*tert*-butyldinaphthofuranquinones, I and II, giving an intense blue color with sulphuric acid, could be isolated from the reaction of 2,6- and 2,7-di-*tert*-butylnaphthols with 2,3-dichloro-1,4-naphthoquinone. This cyclization reaction was shown by Buu-Hoi and Demerseman (7) to be characteristic of naphthols having an unsubstituted position adjacent to the OH group, which holds only if the hydroxyl group of the 2,6- and 2,7-di-*tert*-butylnaphthol occupies position 4. Consequently the sulphonic acid group in the starting sulphonates must occupy position 4.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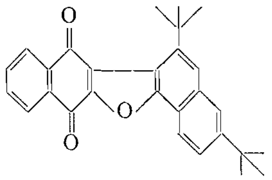
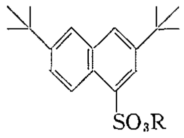

II

Reaction of 2,7-di-*tert*-butylnaphthalene-4-sulphonyl chloride with alcohols in pyridine solution afforded a series of esters which are reported in Table I. The methyl and ethyl ester of 2,6-di-*tert*-butylnaphthalene-4-sulphonic acid were prepared by reaction of the acid with diazomethane and diazoethane in ether solution.

TABLE I



R	M.p. (solvent)	Analysis % C, calc.	% H, calc.	% C, found	% H, found
Ethyl	138–139° (EtOH)	68.93	8.10	69.32	8.20
n-Propyl	109–110° (EtOH)	69.57	8.35	69.57	8.36
n-Butyl	74–75° (EtOH)	70.17	8.57	70.54	8.49
n-Hexyl	77–78° (EtOH)	71.24	8.97	71.28	8.99
Cyclohexyl	124° (EtOH)	71.60	8.51	71.77	8.48
Phenyl	78–79° (EtOH)	72.69	7.12	72.86	7.12
Glycolyl	85–87° (CCl_4 – pet. ether)	65.90	7.74	66.93	8.31
Glyceryl	135–136° (CCl_4 – pet. ether)	63.93	7.67	64.47	7.72

EXPERIMENTAL

2,6- and 2,7-Di-tert-butylnaphthalene-4-sulphonyl Chloride

The commercial mixture of sodium di-*tert*-butylnaphthalenesulphonate (34.6 g, 0.1 mole), thionyl chloride (25 ml), and dimethylformamide (0.8 ml) were heated for 1 hour on the steam bath. The excess of thionyl chloride was evaporated under reduced pressure and the residue was triturated with 100 ml of cold water, filtered, and dried over sulphuric acid. The dried mixture of sulphonyl chlorides (36.2 g) was recrystallized in 100 ml of ligroin, with the aid of 3 g of decolorizing charcoal; there was so obtained 12.3 g (36%) of 2,7-di-*tert*-butylnaphthalene-4-sulphonyl chloride, m.p. 163–165°. The analytical sample, recrystallized from ligroin, had a melting point of 167–169°. Calc. for $C_{18}H_{23}O_2SCl$: C, 63.79; H, 6.84%. Found: C, 63.97; H, 7.01%.

Concentration of the mother liquors and repeated recrystallization of the residue from isopropanol gave 8.2 g (24.3%) of 2,6-di-*tert*-butylnaphthalene-4-sulphonyl chloride, m.p. 117–118°. Calc. for $C_{18}H_{23}O_2SCl$: C, 63.79; H, 6.84%. Found: C, 64.03; H, 6.97%.

Sodium 2,7-Di-tert-butylnaphthalene-4-sulphonate

To a boiling solution of 5 g of 2,7-di-*tert*-butylnaphthalene-4-sulphonyl chloride in 20 ml of ethanol there was slowly added a solution of 1.2 g of sodium hydroxide in 40 ml of water. The mixture was refluxed for 4 hours, the solvents removed, and the residue recrystallized from water to give 4.8 g (85%) of colorless waxy plates. Calc. for $C_{18}H_{23}O_3SNa.2H_2O$: C, 57.15; H, 7.20; S, 8.47%. Found: C, 57.44; H, 7.12; S, 7.49%.

Sodium 2,6-Di-tert-butylnaphthalene-4-sulphonate

Hydrolysis of 2,6-di-*tert*-butylnaphthalene-4-sulphonyl chloride with sodium hydroxide gave 90% of colorless needles from nitromethane, m.p. >360°. Calc. for $C_{18}H_{23}O_3SNa.2H_2O$: C, 57.15; H, 7.20; S, 8.47%. Found: C, 57.51; H, 7.09; S, 8.08%.

2,7-Di-tert-butylnaphthalene

A mixture of 8 g of sodium 2,7-di-*tert*-butylnaphthalene-4-sulphonate and 100 ml of a 60% solution of sulphuric acid was stirred and heated at 150–160° for 5 hours, cooled, poured into 1 liter of cold water, and extracted with ether. The ether extracts were washed with water, dried, and concentrated. After recrystallization from ethanol the residue yielded 2.8 g of colorless needles, m.p. 103–104°; these gave no depression of melting point when mixed with a sample prepared according to Price *et al.* (3).

2,6-Di-tert-butylnaphthalene

Hydrolysis of 5 g of sodium 2,6-di-*tert*-butylnaphthalene-4-sulphonate in 60% sulphuric acid gave 1.7 g of flat needles, m.p. 145–146°. Identity of this material with pure 2,6-di-*tert*-butylnaphthalene (3) was confirmed by a mixed melting point.

2,6-Di-tert-butylnaphthalene-4-sulphonic Acid

Chlorosulphonic acid (56 g, 0.48 mole) was slowly added, with stirring and cooling, to a solution of 116 g (0.48 mole) of pure 2,6-di-*tert*-butylnaphthalene in 240 ml of dichloroethane. The reaction mixture was allowed to stand for 2 hours at 0–5° and the solvent was removed at room temperature under reduced pressure. The residue, a heavy oil, started to crystallize upon the addition of 0.5 mole of water; recrystallization from dichloroethane gave 155 g (95%) of the hydrate of 2,6-di-*tert*-butylnaphthalene-4-sulphonic acid as colorless plates, m.p. 158°. Calc. for $C_{18}H_{24}O_3S.H_2O$: C, 63.87; H, 7.74%; M.W., 338.5. Found: C, 63.45; H, 7.76%; N.E., 339.3.

2,7-Di-tert-butylnaphthalene-4-sulphonic Acid

2,7-Di-*tert*-butylnaphthalene (3.3 g) dissolved in 7 ml of dichloroethane and treated, as described for the 2,6-isomer, with 1.8 g of chlorosulphonic acid gave 2.6 g (55%) of the hydrate of 2,7-di-*tert*-butylnaphthalene-4-sulphonic acid, m.p. 140–142° (chloroform – petroleum ether). Calc. for $C_{18}H_{24}O_3S.H_2O$: C, 63.87; H, 7.74%; M.W., 338.5. Found: C, 62.54; H, 7.82%; N.E., 339.4.

2,6-Di-tert-butylnaphthalene-4-sulphonyl Chloride

The anhydrous residue obtained from the reaction of 56 g of chlorosulphonic acid and 116 g of 2,6-di-*tert*-butylnaphthalene as described above was mixed, in a distillation apparatus, with 91 ml of thionyl chloride and 3 ml of dimethylformamide. The mixture was stirred and heated on the steam bath until it became homogeneous ($\frac{1}{2}$ hour). During that time most of the excess of thionyl chloride had distilled over; the remainder was removed under reduced pressure. The residue was triturated with cold water and extracted with ether. The combined ether extracts were dried and concentrated; the solid residue, recrystallized from alcohol, gave 133.5 g (86%) of colorless prisms, m.p. 117–118°. These gave no depression of melting point when mixed with a sample of the sulphonyl chloride obtained from the commercial mixture of sulphonates.

The amide was prepared by passing dry ammonia through a solution of the chloride in tetrahydrofuran, removing the solvent, triturating the residue with water, and recrystallizing the dried solid from ligroin: m.p. 160–161°. Calc. for $C_{18}H_{25}O_2NS$: C, 67.67; H, 7.89; N, 4.38%. Found: C, 67.70; H, 7.89; N, 4.37%.

2,7-Di-tert-butylnaphthalene-4-sulphonyl Chloride

The anhydrous 2,7-di-*tert*-butylnaphthalene-4-sulphonic acid, treated as described above with thionyl chloride and dimethylformamide, gave 90% of colorless prisms, m.p. 167–169°; this melting point was not depressed by mixing with the 2,7-di-*tert*-butylnaphthalene-4-sulphonylchloride obtained from the commercial mixture of sulphonates.

The amide was prepared as above, m.p. 165°. Calc. for $C_{18}H_{25}O_2NS$: C, 67.67; H, 7.89; N, 4.38%. Found: C, 67.17; H, 8.06; N, 4.59%.

2,7-Di-tert-butyl-4-naphthol

Potassium 2,7-di-*tert*-butylnaphthalene-4-sulphonate (30 g), 100 g of potassium hydroxide, and 30 ml of water were heated slowly in an iron crucible until the mixture melted and the potassium salt of the naphthol floated on the surface of the melt as a dark-brown oil. The mixture was cooled, dissolved in water, acidified with hydrochloric acid, and extracted three times with ether. The combined ether extracts were washed with water, dried, and concentrated. The residue, a heavy black oil, was distilled under reduced pressure and yielded 14.2 g of a yellow oil, b.p. 170–180°/4 mm. Crystallization of this oil in ligroin afforded 8 g (41%) of colorless needles, m.p. 125–126°. The analytical sample, recrystallized from ligroin, had a melting point of 127–128°. Calc. for $C_{18}H_{24}O$: C, 84.32; H, 9.44%. Found: C, 84.47; H, 9.43%.

2,6-Di-tert-butyl-4-naphthol

Alkaline fusion of potassium 2,6-di-*tert*-butylnaphthalene-4-sulphonate carried out as described above for the 2,7-isomer, gave 63% of a reddish oil, b.p. 190°/3 mm, which afforded 25% of colorless crystals, m.p. 142°. The identity of this compound with the one obtained by Buu-Hoi and Demerseman (7) from *tert*-butylation of α-naphthol was confirmed by a mixed melting point.

2,7-Di-tert-butyl-1-phenylazo-4-naphthol

Aniline (3.4 g), dissolved in 11 ml of concentrated hydrochloric acid and 11 ml of water, was diazotized with a solution of 2.8 g of sodium nitrite in 14 ml of water. The resultant solution of phenyldiazonium chloride was added dropwise to a well-stirred mixture of 8 g of 2,7-di-*tert*-butyl-4-naphthol, 30 ml of 10% sodium hydroxide solution, and 20 ml of tetrahydrofuran cooled to 5°. The mixture was then stirred for 30 minutes at 5° and allowed to stand overnight. Most of the tetrahydrofuran was removed under reduced pressure and the water was decanted from the heavy dark oil, which was then boiled with 40 ml of glacial acetic acid and filtered hot. After cooling and filtering, the crude precipitate was recrystallized from 200 ml of acetic acid to yield 2.6 g (28%) of red crystals, m.p. 229–239°. Calc. for $C_{24}H_{28}ON_2$: C, 79.96; H, 7.83; N, 7.77%. Found: C, 79.91; H, 7.88%; N, 7.74%.

2,6-Di-tert-butyl-phenylazo-4-naphthol

The coupling reaction of 4 g of 2,6-di-*tert*-butyl-4-naphthol with phenyldiazonium chloride was carried out as described above for the 2,7-isomer. After removal of the tetrahydrofuran, a solid was obtained which was filtered and recrystallized from acetic acid to give 2.2 g of the orange-red azo compound, m.p. 204–206°. Calc. for $C_{24}H_{28}ON_2$: C, 79.96; H, 7.83; N, 7.77%. Found: C, 79.80%; H, 7.80%; N, 7.42%.

2,7-Di-tert-butyl-1,4-naphthoquinone

(a) From 2,7-Di-tert-butylnaphthalene

A solution of 2.6 g of chromium trioxide in 4.4 ml of acetic acid and 2.9 ml of water was added dropwise to a stirred slurry of 2.0 g of 2,7-di-*tert*-butylnaphthalene in 11 ml of acetic acid maintained at 60°. After the addition was complete, the mixture was stirred for ½ hour at 60°, poured into 150 ml of cold water and extracted with ether. The ether extracts were washed with water, dried, and concentrated; the residue crystallized from dilute alcohol and yielded 2.0 g (89%) of yellow needles, m.p. 72°. Calc. for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20%. Found: C, 79.71%; H, 7.92%.

Reaction of the quinone with 2,4-dinitrophenylhydrazine gave a compound which crystallized from acetic acid as orange-red needles, m.p. 250–251°. Calc. for $C_{24}H_{26}O_5N_4$: C, 63.98; H, 5.82; N, 12.44%. Found: C, 63.79; H, 5.90; N, 12.41%.

(b) From 2,7-Di-tert-butyl-1-phenylazo-4-naphthol

A solution of 8 g of stannous chloride in 24 ml of concentrated hydrochloric acid was added to a boiling slurry of 1.9 g of 2,7-di-*tert*-butyl-1-phenylazo-4-naphthol in 80 ml of methanol; the azo compound slowly dissolved and after 1½ hours the solution was colorless. It was concentrated to a volume of approximately 30 ml and cooled. The crystalline 2,7-di-*tert*-butyl-1-amino-4-naphthol hydrochloride was filtered and slurried in a solution of 0.6 ml of sulphuric acid in 12 ml of water. A solution of 0.4 g of potassium dichromate in 6 ml of water was added to the resultant mixture and the whole was heated at steam-bath temperature for 5 minutes, cooled, diluted with water, and extracted with ether. The ether extracts were washed with water, dried, and concentrated. Upon reaction with 2,4-dinitrophenylhydrazine the liquid residue gave an orange-red compound, m.p. 250–251°, found by a mixed melting point determination to be identical with the addition compound obtained as under (*a*).

2,6-Di-tert-butyl-1,4-naphthoquinone

(a) From 2,6-Di-tert-butylnaphthalene

Oxidation of 13.8 g of 2,6-di-*tert*-butylnaphthalene with 18 g of chromium trioxide as described above for the 2,7-isomer yielded a solid compound after the reaction mixture was poured into water. Recrystallization of this solid from ethanol gave 7.4 g (48%) of yellow needles, m.p. 85–86° (lit. (6) m.p. 83.5–84.5°).

(b) From 2,6-Di-tert-butyl-1-phenylazo-4-naphthol

Reduction of this azo compound (0.23 g) with stannous chloride and oxidation of the aminonaphthol with potassium dichromate gave 0.1 g (60%) of yellow needles, m.p. 85–86°, not depressed when mixed with a sample prepared according to (*a*).

Esters of 2,7-Di-tert-butylnaphthalene-4-sulphonic Acid

A solution of 0.15 mole of the appropriate alcohol in 80 ml of anhydrous pyridine was cooled to $-10°$; 0.08 mole of powdered 2,7-di-*tert*-butylnaphthalene-4-sulphonyl chloride was added at such a rate that the temperature would not exceed $-5°$; the resultant mixture was stirred for 2 hours at 0–5° and poured into water (500 ml). In those cases where a solid ester was obtained it was separated by filtration and recrystallized from the appropriate solvent; when an oil was obtained, the ester was extracted with ether and isolated by the usual procedure. Physical data for the esters involved are included in Table I.

Esters of 2,6-Di-tert-butylnaphthalene-4-sulphonic Acid

A slight excess of an ethereal solution of the appropriate diazoalkane was added to a cooled solution of the monohydrate of 2,6-di-*tert*-butylnaphthalene-4-sulphonic acid in ether. After standing overnight the solvent was removed and the ester isolated. The methyl ester was obtained as a solid which crystallized from methanol as colorless prisms, m.p. 123–124°. Calc. for $C_{19}H_{26}O_3S$: C, 68.22; H, 7.84; S, 9.58%. Found: C, 68.58; H, 7.95; S, 9.94%.

The ethyl ester was obtained as a colorless oil, b.p. 180–185/1 mm. Calc. for $C_{20}H_{28}O_3S$: C, 68.93; H, 8.10%. Found: C, 68.92%; H, 8.26%.

3′,7′-Di-tert-butyldinaphtho(1′,2′-2,3)(2″,3″-4,5)furan-1″,4″-quinone

A solution of 2.6 g of 2,6-di-*tert*-butyl-4-naphthol and 2.3 g of 2,3-dichloro-1,4-naphthoquinone in 15 ml of anhydrous pyridine was stirred and refluxed for 18 hours. After cooling, the mixture was diluted with methanol and filtered. Recrystallization of the filter cake from toluene gave 0.52 g (13%) of yellow needles, m.p. 354–355°. Calc. for $C_{28}H_{26}O_3$: C, 81.92; H, 6.38%. Found: C, 81.78; H, 6.53%.

3′,6′-Di-tert-butyldinaphtho(1′,2′-2,3)(2″,3″-4,5)furan-1″,4″-quinone

A solution of 4.6 g of 2,3-dichloro-1,4-naphthoquinone and 5.2 g of 2,7-di-*tert*-butyl-4-naphthol in 30 ml of pyridine was stirred and refluxed for 18 hours. After cooling, the mixture was filtered and the filtrate concentrated to a volume of approximately 10 ml. The pyridine solution was then diluted with methanol and allowed to stand overnight. Filtration and recrystallization of the filter cake in toluene–methanol afforded 1.1 g (15%) of orange-yellow needles, m.p. 217–218.° Calc. for $C_{28}H_{26}O_3$: C, 81.92; H, 6.38%. Found: C, 82.21; H, 6.57%.

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