PREPARATION AND POLAROGRAPHIC HALF-WAVE POTENTIALS OF NEOPENTYLHYDROQUINONES

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2-Neopentyl-, 2-tert-butyl-5-neopentyl- and 2,5-dineopentylhydroquinones were obtained by demethylation and reduction of the corresponding pivaloyl derivatives of hydroquinone dimethyl ether. Polarographic measurements allowed to formulate conclusions about the effect of the alkyl structure upon the half-wave potentials of alkylhydroquinones.

While investigating the properties of the inhibitors of oxidation and their transformations during the stabilization process, we also studied the effects of substitution upon the polarographic half-wave potentials of the hydroquinone derivatives[1], as well as the connections which exist between the half-wave potentials and antioxidative activity[2]. To discuss the antioxidative properties of the (2-alkoxyalkyl)hydroquinone[3] series, it was necessary to prepare 2-neopentyl- and 2,5-dineopentylhydroquinones which yielded the data on the influence of the alkoxyl group. At the same time, the latter compounds helped to obtain a more complete and comprehensive picture of the effects of the alkyl structure upon the polarographic half-wave potentials of alkylated hydroquinones. The preparation of 2-neopentylhydroquinone was based on 2-pivaloylhydroquinone dimethyl ether (*I*) which was obtained in a mixture with a small amount of 2-pivaloyl-5-tert-butylhydroquinone dimethyl ether (*II*) by acylation of hydroquinone dimethyl ether with pivaloyl chloride in the presence of aluminium chloride. The tert-butylated derivative is formed in a by-reaction of pivaloyl chloride which undergoes a partial decarbonylation in the presence of $AlCl_3$[4,5]; the tert-butyl carbonium ion thus obtained is an alkylating agent. The ratio of the products of the simultaneously occurring acylation and alkylation reactions is affected by the reactivity of the aromatic component[6]; both methoxyl groups present in the benzene ring led in the first place to acylation. 2,5-Dipivaloylhydroquinone dimethyl ether (*III*) was the starting compound for the preparation of 2,5-dineopentylhydroquinone; it was obtained by a modification of the synthesis of 2,5-dipropionylhydroquinone dimethyl ether as described by Noland and Baude[7]. The starting compound was 2,5-dibromohydroquinone dimethyl ether, which was transformed into 2,5-dicyano derivative; the latter, after a reaction with tert-butylmagnesium chloride and hydrolysis of the reaction mixture with hydrochloric acid, yielded the dipivaloyl derivative. Pivaloylhydroquinones *IV* and *VI* were obtained by the cleavage of pivaloylhydroquinone dimethyl ethers *I* and *III* with hydrobromic acid. The preparation of 2-pivaloyl-5-tert-butylhydroquinone (*V*) was carried out by demethylation of dimethyl ether *II* with pyridine hydrochloride[8]. This procedure restricted the possibility of the cleavage of the tert-butyl group from the aromatic ring. The neopentylhydroquinones *VII*—*IX* were obtained by the reduction of pivaloylhydroquinones *IV*—*VI* with hydrazine hydrate using Huang-Minlon's modification[9] of Wolff–Kizhner's reaction. Column chromatography on silicagel was used in the purification of all reaction products.

The structure of the compounds obtained was checked by the IR and NMR spectra. It was found that all the pivaloyl derivatives, *IV* to *VI*, obtained as described above, exhibited a pronounced decrease in the stretching frequency of the carbonyl group in the IR spectra ($\nu_{C=O} = 1640\ cm^{-1}$) compared to the value usual with arylalkyl ketones ($1690\ cm^{-1}$). The decrease in $\nu_{C=O}$ can be explained by the formation of an intramolecular hydrogen bond between the carbonyl group and the hydrogen atom of the hydroxyl group. The same phenomenon has also been observed with hydroxy- and dihydroxyacetophenones[10,11] where the $\nu_{C=O}$ values vary within the range $1629-1655\ cm^{-1}$. Hydroxypivalophenones *IV* and *V* exhibit the formation of one intramolecular hydrogen bond only; the IR spectra show stretching frequencies of the free hydroxyl group at $3610-3615\ cm^{-1}$. In the case of dipivaloylhydroquinone (*VI*) the O—H bond is reflected only in a little intensive wide band near $3000\ cm^{-1}$; there is an overlap with the C—H bond frequencies.

The polarographic behaviour of the compounds described here is similar to that of the alkylated hydroquinone derivatives which have been studied earlier[1]. To allow a comparison of the results, the half-wave potentials were measured in the same medium as in the earlier work. Their values (mV, against a standard hydrogen electrode) recalculated for pH = O are as follows: 2-n-butylhydroquinone: 663, 2-sec-butylhydroquinone: 661, 2-neopentylhydroquinone: 660, 2,5-dineopentylhydroquinone: 603, and 2-neopentyl-5-tert-butylhydroquinone: 580.

The measurements were extended to comprise n-butyl and sec-butylhydroquinones. The comparison of the half-wave potentials with the $E_{1/2}$ values for the other alkylated hydroquinones[1] leads to the following conclusions: Substitution of hydroquinone with alkyl groups leads in all the cases investigated to a shift of the half-wave potential to more negative values with respect to the unsubstituted hydroquinone $\Delta E_{1/2} = (E_{1/2})_X - (E_{1/2})_H$. For normal C_1—C_4 alkyl groups, the $\Delta E_{1/2}$ value is the same within the limits of experimental error; consequently, an extension of the n-alkyl chain does not affect the shift. A similar finding has been made for the half-wave potentials of the 4-alkylpyrocatechols[12] investigated earlier, in accordance with the results obtained for further members of the pyrocatechols series[13] ($E_{1/2}$ mV: 4-n-propylpyrocatechol: 777, 4-n-butylpyrocatechol: 780, 4-n-pentylpyrocatechol: 782, 4-n-octylpyrocatechol: 781). The half-wave potential of sec-butylhydroquinone does not differ from the $E_{1/2}$ values for n-alkylhydroquinones and isopropylhydroquinones. This seems to show that a branching of the chain of alkyl groups having one hydrogen atom on the α-carbon atom affects the change in $\Delta E_{1/2}$ but little, and that even an extension of the branched chain leaves the shift unaffected. The branching of the substituent chain on the α-carbon atom has a significant effect only with the tert-alkyl groups. It can be seen from $E_{1/2}$ of the neopentyl derivative that the separation of the tert-alkyl group from the site of substitution with the methylene group is sufficient to abolish the effect of the tert-alkyl group upon the increase in the shift of the half-wave potential; $E_{1/2}$ has the same value as the half-wave potentials of the n-alkyl

derivatives. A similar case is represented by the potential of 2-(1,1,3,3-tetramethylbutyl)hydroquinone (tert-octylhydroquinone)[1], where the alkyl group can be regarded as a tert-butyl group substituted on the second carbon atom with a further tert-butyl group; this substitution, if compared to 2-tert-butylhydroquinone, does not lead to an increase in the shift of $\Delta E_{1/2}$ which would be proportional to the increase in the steric requirements of the whole substituent. Finally, and in agreement with the knowledge available so far[1], the $E_{1/2}$ values of 2,5-disubstituted hydroquinone derivatives containing neopentyl group confirm the validity of the additivity of the substituent effects upon the changes in the polarographic half-wave potential in the case of substitution in these positions. The $E_{1/2}$ values obtained by calculations based on additivity ($E_{1/2}$ of 2,5-dineopentylhydroquinone: 603 mV, of 2-neopentyl-5-tert-butylhydroquinone: 584 mV) agree very well with the experimental data.

EXPERIMENTAL

The melting points were determined on a Boetius block. The samples used for analysis were dried at 2 Torr over P_2O_5. The NMR spectra were recorded in deuterated chloroform on a JEOL-JNM-3-60 spectrometer, using hexamethyldisiloxane as an internal standard (τ=9·95). The IR spectra were recorded on a Perkin-Elmer type 457 apparatus in tetrachloromethane and in the KBr pellets. The mass spectrum was obtained on an AEI MS 902 spectrometer.

2-Pivaloylhydroquinone Dimethyl Ether (*I*)

66 g (0·5 mol) of anhydrous aluminium chloride was added during 4 h to 50 g (0·36 mol) of hydroquinone dimethyl ether and 57 g (0·47 mol) of pivaloyl chloride in a mixture of 18 ml of nitrobenzene and 72 ml sym-tetrachloroethane; the temperature was kept at approx. −10°C for 4 days. The reaction mixture was decomposed with ice and HCl; the solvent was removed by distillation with water vapour. The remaining water fraction was extracted with ether, the ether layer washed with water, dried with magnesium sulphate, and the ether removed by distillation. A viscous oil containing two compounds was thus obtained; it was fractionated on a chromatographic column (silicagel, gradual elution with benzene and ether) into two fractions. The second fraction was recrystallized from methanol, yielding 17 g (21·1%) of white crystals, m.p. 46·5–48·5°C. IR:

TABLE I

R_F Values of the Alkyl and Acyl Derivatives of Hydroquinone

Compound	*I*[a]	*II*[a]	*III*[a]
2-Neopentylhydroquinone	0·12	0·31	—
2-Pivaloylhydroquinone	0·48	0·52	—
2,5-Dineopentylhydroquinone	0·82	0·96	0·80
2-Neopentyl-5-tert-butylhydroquinone	0·84	0·94	0·78
2-Pivaloyl-5-tert-butylhydroquinone	0·92	0·98	—
2,5-Dipivaloylhydroquinone	0·95	0·96	1·00

[a] *Cf.* Experimental.

$\nu_{C=O}$ = 1700 cm^{-1}. For $C_{13}H_{18}O_3$ (222·3), calculated: 70·24% C, 8·16% H; found: 70·19% C, 8·17% H.

2-Pivaloyl-5-tert-butylhydroquinone Dimethyl Ether (*II*)

The first fraction obtained during the preparation of compound *I* yielded by crystallization from methanol 6 g (6%) of white crystals, m.p. 62·5—63·5°C. IR: $\nu_{C=O}$ 1695 cm^{-1}; NMR: confirms the substitution at positions 2 and 5. For $C_{17}H_{26}O_3$ (278·4), calculated: 73·35% C, 9·41% H; found: 73·44% C, 9·45% H.

2,5-Dipivaloylhydroquinone Dimethyl Ether (*III*)

To a solution of tert-butylmagnesium chloride (prepared after ref.[14] from 9·8 g (0·41 g-atom) magnesium and 44 ml (0·41 mol) tert-butyl chloride) in 250 ml of anhydrous ether, a suspension of 11·5 g (0·061 mol) of 2,5-dicyanohydroquinone dimethyl ether[7] in 770 ml anhydrous benzene was added. After ether had been removed by distillation, the reaction mixture was refluxed 30 h and on cooling poured into a mixture of 700 g of ice and 460 ml of concentrated HCl. The ketimine hydrochloride present in the aqueous layer was hydrolyzed by refluxing the mixture during 10 h. The reaction mixture was extracted with ether, the ether layer washed with water, dried with magnesium sulphate, and the solvent removed by distillation. The raw brown-red product was twice crystallized from methanol; the yield was 2·3 g (12·5%) of yellowish crystals, m.p. 195 to 199°C. IR: $\nu_{C=O}$ 1690 cm^{-1}. For $C_{18}H_{26}O_4$ (306·4) calculated: 70·56% C, 8·55% H; found: 70·84% C, 8·53% H.

2-Pivaloylhydroquinone (*IV*)

A mixture of 3 g (0·0135 mol) of 2-pivaloylhydroquinone dimethyl ether, 33 ml of 48% hydrobromic acid and 165 ml acetic acid was refluxed 3 h and on cooling diluted with 500 ml of water. The ether extract was washed with water and dried with magnesium sulphate. The viscous oil that remained after the ether had been removed by distillation was purified on a chromatographic column (silicagel, formamide as the stationary phase, benzene as the mobile phase). Crystallization from cyclohexane yielded 1·3 g (49·5%) of yellow crystals, m.p. 95—98°C. IR: $\nu_{C=O}$ 1640 cm^{-1}, ν_{O-H} 3610 cm^{-1}. For $C_{11}H_{14}O_3$ (194·2) calculated: 68·02% C, 7·27% H; found: 68·01% C, 7·21% H.

2-Pivaloyl-5-tert-butylhydroquinone (*V*)

10 ml of conc. HCl was added with stirring to 9 ml of pyridine and the mixture was heated to 210°C to distill off water; on cooling to 140°C, 3 g (0·0108 mol) of 2-pivaloyl-5-tert-butylhydroquinone dimethyl ether was added to the mixture which was then refluxed 2 h, diluted with 75 ml of water and extracted with ether. The ether solution was shaken with water and dried with magnesium sulphate. The removal of ether by distillation yielded viscous oil which was treated on a chromatographic column (silicagel impregnated with formamide, elution with benzene). Crystallization from cyclohexane yielded 1·7 g (63%) of yellow crystals, m.p. 185—186°C. IR: $\nu_{C=O}$ 1640 cm^{-1}, ν_{O-H} 3615 cm^{-1}. For $C_{15}H_{22}O_3$ (250·3) calculated: 71·97% C, 8·86% H; found: 72·06% C, 8·99% H.

2,5-Dipivaloylhydroquinone (*VI*)

A mixture of 5·5 g (0·018 mol) 2,5-dipivaloylhydroquinone dimethyl ether, 44 ml (0·4 mol) 48% HBr and 220 ml (3·8 mol) of acetic acid was refluxed 24 h. The reaction mixture was then poured

into 1000 ml water and the suspension was stirred 5 h while cooled with water; the solid substance that precipitated was removed by filtration and after washing with water and drying was recrystallized from petroleum ether. A further fraction was obtained by extracting the aqueous filtrate with ether. The oil left after the solvent had been removed by distillation was purified chromatographically on a column filled with silicagel impregnated with formamide; elution with hexane. 1·6 g (32%) of yellow needles was obtained, m.p. 180—181°C. IR: $\nu_{C=O}$ 1640 cm^{-1}; NMR: $C(CH_3)_3$ 8·57, H arom. 2·37, OH···C=O —1·32; m.s.: molecular peak 278. For $C_{16}H_{22}O_4$ (278·4) calculated: 69·04% C, 7·97% H; found: 69·18% C, 8·18% H.

2-Neopentylhydroquinone (*VII*)

A mixture of 1·4 g (0·006 mol) of 2-pivaloylhydroquinone with 1 ml 85% hydrazine hydrate and 1 g KOH in 10 ml of triethylene glycol was refluxed 1·5 h, water removed by distillation, the temperature of the reaction mixture increased to 190°C, and the mixture was further refluxed for 3 h. On cooling, the reaction mixture was diluted with 4 ml water, acidified with HCl and extracted with ether. The ether fraction was washed with water and dried with magnesium sulphate. The raw product obtained by removing the solvent by distillation was purified on a chromatographic column (silicagel, benzene : ether = 2 : 1 as the mobile phase). A double crystallization from cyclohexane yielded 0·6 g (46%) of white substance, m.p. 142—144°C. IR: ν_{O-H} 3615 cm^{-1}; NMR: $C(CH_3)_3$ 9·1, CH_2 7·6, OH 6·5, H arom. 3·45; m.s.: molecular peak 180. For $C_{11}H_{16}O_2$ (180·3) calculated: 73·30% C, 8·95% H; found: 73·70% C, 9·00% H.

2-Neopentyl-5-tert-butylhydroquinone (*VIII*)

The conditions of the reaction of 1·7 g (0·0068 mol) of 2-pivaloyl-5-tert-butylhydroquinone with 1·2 ml of hydrazine hydrate and 1·2 g of KOH in 11·5 ml of triethylene glycol, as well as the treatment of the reaction mixture were the same as in the synthesis of 2- neopentylhydroquinone. The raw product was purified on a chromatographic column (silicagel, elution with benzene). Crystallization from cyclohexane yielded 0·5 g (31·2%) of a white substance, m.p. 136—137°C. IR: ν_{O-H} 3 615 cm^{-1}, NMR: $C(CH_3)_3$ (in neopentyl) 9·12, $C(CH_3)_3$ 8·68, CH_2 7·66, OH 5·83, H_{arom} 3·68, H_{arom} 3·35; m.s.: molecular peak 236. For $C_{15}H_{24}O_2$ (236·4) calculated: 76·23% C, 10·24% H; found: 76·35% C, 10·32% H.

2,5-Dineopentylhydroquinone (*IX*)

The conditions of the reaction of 2·5 g (0·0087 mol) 2,5-dipivaloylhydroquinone, 2 ml of 85% hydrazine hydrate, 2·75 g KOH and 20 ml triethylene glycol and the treatment of the reaction mixture were the same as in the synthesis of 2-neopentylhydroquinone. The raw product obtained by distilling off the solvent was purified on a chromatographic column (silicagel, elution with benzene). The yield was 0·6 g (26·7%) of white crystals, m.p. 170·5—171°C. IR: ν_{O-H} 3615 cm^{-1}; NMR: $C(CH_3)_3$ 9·1, CH_2 7·6, OH 6·25, H arom 3·55; m.s.: molecular peak 250. For $C_{16}H_{26}O_2$ (250·4) calculated: 76·75% C, 10·47% H; found: 76·83% C, 10·43% H.

Chromatography and Polarography

The composition of the reaction mixtures, the process of isolation of the compounds during preparative chromatography and their purity were checked on Silufol UV 254 plates, a Kavalier product (developing systems benzene and the mixture benzene–ether 2 : 1) and on the Whatman No 1 paper impregnated with a 20% formamide solution in methanol. The R_F values of pure

compounds obtained by paper chromatography with the following mobile phases: benzene (*I*), isopropyl ether : heptane = 1 : 2 (*II*) and benzene : heptane = 1 : 1 (*III*) are given in Table I. Polarographic measurements were carried out in a water-jacketed cell with a three-electrode system. The curves were recorded on an LP 60 polarograph with an EZ recorder (Laboratorní přístroje, Prague), using a compensator of the potential gradient, *iR*. The rate of polarization was 100 mV/min, chart speed was 4 cm/min, basic sensitivity of the recorder was $3 \cdot 6 \cdot 10^{-10}$ A/mm. The drop time of the vertical mercury dropping electrode at the open circuit in distilled water with the height of the mercury reservoir 40 cm was 3·1 s, the mean outflow velocity was 2·4 mg s^{-1}. A platinum wire was used as the working reference electrode. The third electrode consisted of a saturated calomel electrode connected with the solution under investigation by a salt bridge containing the supporting electrolyte. The acetate buffer solutions in the pH range 4·4—5·6 prepared from 0·2M acetic acid and 0·2M sodium acetate and used for measuring the half-wave potentials were diluted with the same volume of ethanol; the final "pH" values were measured with a hydrogen electrode on a compensation pH-meter (Development Workshops ČSAV, Brno). The half-wave potentials were measured in a nitrogen atmosphere with $1 \cdot 10^{-3}$M hydroquinone solutions in the above buffer solutions with ethanol in the presence of fuchsine for suppressing maxima at a temperature 25 ± 0·1°C with an accuracy of ±3 mV.

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