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High-Performance Liquid Chromatographic Determination of the Oxidation Products of 4-Isopropylbiphenyl and 4,4'-Diisopropylbiphenyl

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4-Isopropylbiphenyl and 4,4'-diisopropylbiphenyl were oxidised with oxygen and the obtained oxidation products: hydroperoxides, alcohols, and ketones, as well as the unreacted raw material were analysed applying high-performance liquid chromatography on a Nova-Pak silica column under conditions of isocratic and gradient elution using hexane and 2-propanol as eluents.

Opracowano metodę analizy produktów utleniania tlenem 4-izopropylbifenylu i 4,4'-diizopropylbifenylu, zawierających odpowiednie wodoronadtlenki, alkohole, ketony oraz nieprze-reagowany surowiec. Oznaczenia wykonano metodą wysokosprawnej chromatografii cieczowej stosując kolumnę Nova-Pak Silica oraz elucję izokratyczną i gradientową mieszaniny heksanu i 2-propanolu.

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Oxidation of 4-isopropylbiphenyl (IBPh) [1] and 4,4'-diisopropylbiphenyl (DIBPh) [2] with oxygen to hydroperoxides is the first step in the synthesis of hydroxybiphenyls, analogically as it is in case of synthesis of phenol from isopropylbenzene (the Hock method) [3] (Fig. 1).

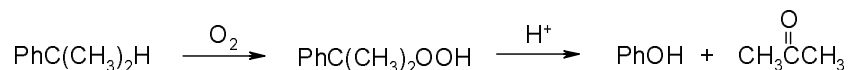


Figure 1. The scheme of phenol synthesis by the Hock method

4-Hydroxybiphenyl (HO-IBPh) and 4,4'-dihydroxybiphenyl are semiproducts in the synthesis of plant protection agents, emulsifiers, pharmaceuticals, and polymers [4–6]. So far, they have been obtained by sulfonation, which is toxic to the environment [7, 8]. 4,4'-Dihydroxybiphenyl can be also obtained from phenol in a multi-stage process comprising alkylation of phenol with isopropene, oxidative coupling, and dealkylation [9, 10]. The synthesis of HO-IBPh and 4,4'-dihydroxybiphenyl from IBPh and DIBPh, respectively, is environmentally-friendly and may displace in future the currently used sulfonation method if it proves to be economical. The products of oxidation of IBPh and DIBPh with oxygen include hydroperoxides, unreacted substrates, and such by-products as alcohols and small amounts of ketones (Figs. 2, 3).

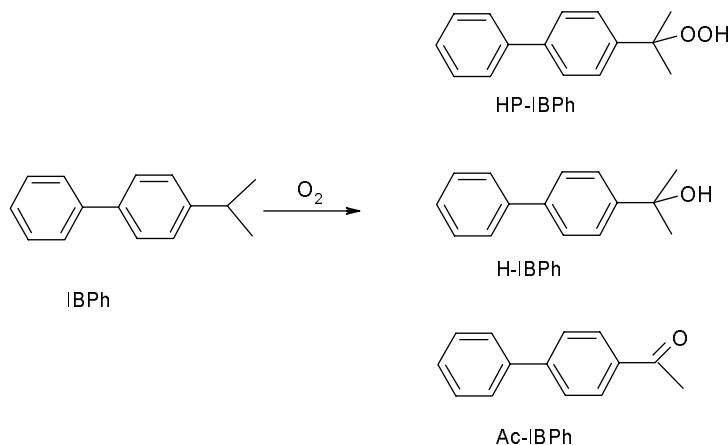


Figure 2. Oxidation products of IBPh

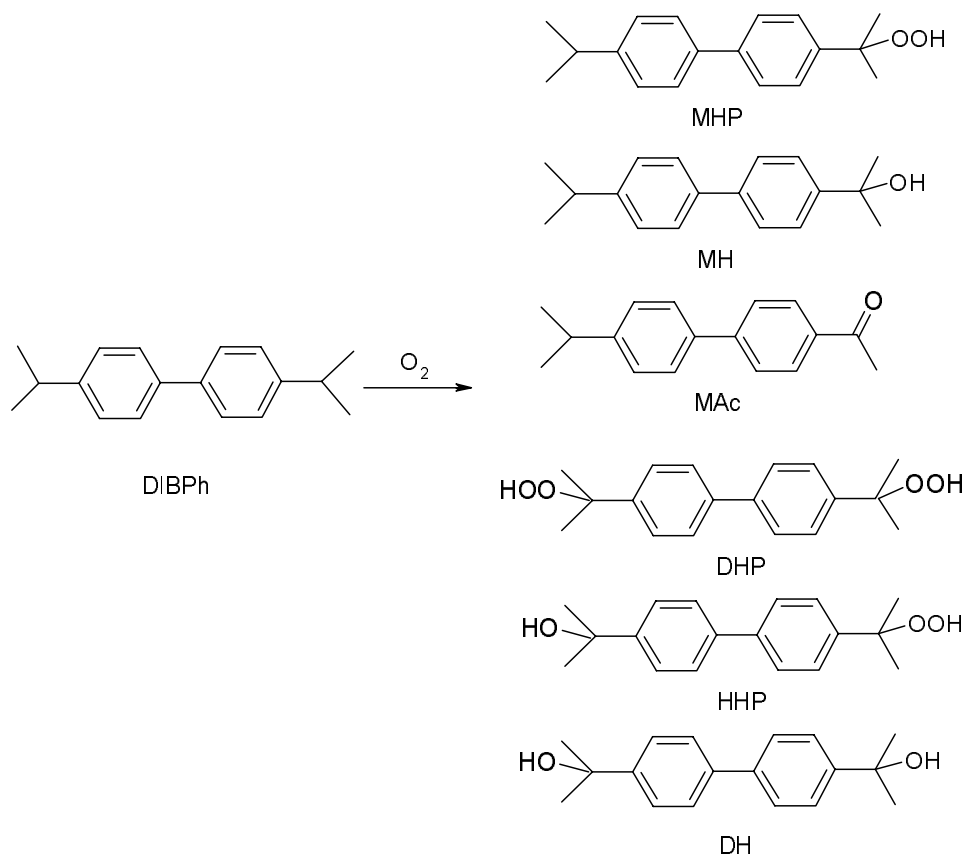


Figure 3. Oxidation products of DIBPh

Due to the presence of comparatively unstable and non-volatile hydroperoxides among the oxidation products of IBPh and DIBPh, only few analytical techniques can be applied for their determination. There are no literature data concerning determination of the oxidation products of isopropylbiphenyls. Oxidation products of other isopropylaromatics were determined by gas chromatography (GC). In GC analysis of the oxidation products of isopropylbenzene [11,12,13,14] decomposition of cumene hydroperoxide was not observed. When, however, GC was used to determine less volatile oxidation products of 2-isopropyl-naphthalene, hydroperoxide present in the mixture was completely decomposed to alcohol [15]. Heinze *et al.* [16] have determined oxidation products of 2-isopropyl-naphthalene by GC method, preceded by reduction of hydroperoxide to alcohol applying $LiAlH_4$.

High-performance liquid chromatography seems to be a particularly effective method for determination of the oxidation products of isopropylaromatics. HPLC

was successfully applied for determination of the oxidation products of isopropylbenzenes [17] and isopropyl-naphthalenes [18]. It has been proven [17, 19, 20] that peroxide compounds are not decomposed during the analysis.

The content of hydroperoxides among the oxidation products can be determined by iodometric method [21, 22]. In case of the oxidation product of DIBPh, however, only the total content of hydroperoxides: 4-(1-hydroperoxy-1-methylethyl)-4'-(1-methylethyl)biphenyl (MHP), 4-(1-hydroperoxy-1-methylethyl)-4'-(1-hydroxy-1-methylethyl)biphenyl (HHP), and 4,4'-bis(1-hydroperoxy-1-methylethyl)biphenyl (DHP) can be determined.

This paper describes a HPLC analysis of the oxidation products of IBPh and DIBPh, which follows the determination procedure of similar oxidation products of 2-isopropyl-naphthalene and 2,6-disopropyl-naphthalene [18].

EXPERIMENTAL

Materials

The solvents 2-propanol and hexane, both of HPLC grade, were supplied by Merck.

IBPh was provided by Rütgers Kureha Solvents GmbH, Duisburg, Germany; purity > 99%, mp 14–22°C, bp 293–303°C, n_D^{20} 1.5800, d_4^{15} 0.9880 g cm⁻³.

DIBPh was provided by Rütgers Kureha Solvents GmbH, Duisburg, Germany; purity > 99%, mp 66°C, bp 334°C.

Standards

4-(1-Hydroperoxy-1-methylethyl)biphenyl (HP-IBPh) was separated from the oxidation products of IBPh. 30 g of this product containing 34.5% of HP-IBPh (45.3 mmol HP-IBPh) was dissolved in 120 cm³ of toluene. HO-IBPh, occurring as a contaminant, was removed by extraction with 2% NaOH. Then, the solution was cooled down to 5°C, and at this temperature 11.1 cm³ of 20% NaOH (67.7 mmol NaOH) was dropped into the stirred solution for 0.5 h. Sodium salt of hydroperoxide was filtered off and rinsed with water (5 × 5 cm³) and hexane (5 × 5 cm³). Then, the sodium salt was placed in water and neutralized with 5% HCl solution. HP-IBPh was filtered off and rinsed with water (3 × 5 cm³). 7.18 g of HP-IBPh (purity 94%, yield 66%), contaminated by IBPh and HO-IBPh, were obtained. A sample of raw HP-IBPh was again washed using sodium salt and crystallized from toluene. Chemical identity of HP-IBPh was confirmed: m.p. 83.5–85°C; results of elemental analysis calculated for C₁₅H₁₆O₂: 78.92% C, 7.06% H, found, 78.93% C, 6.95% H, O_{active}: calculated 7.01, found, 6.80%. ¹H-NMR (CDCl₃/TMS) δ = 7.26–7.65 (m, 9H_{Ar} and 1H_{OOH}), 1.67 (s, 6H, C(CH₃)₂OOH). ¹³C-NMR 143.547, 140.651, 140.417 (C₁, C_{1'} or C₄), 128.771, 127.296, 127.082, 125.888 (C₂, C₃, C_{2'} or C_{3'}), 127.342 (C_{4'}), 83.901 (C(CH₃)₂OOH), 26.077 (C(CH₃)₂OOH).

4-Acetylbiphenyl (Ac-IBPh), 2-(biphenyl-4-yl)-2-propanol (H-IBPh) and 4-hydroxybiphenyl (HO-IBPh) were commercially available.

MHP, DHP, HHP, 4-(1-hydroxy-1-methylethyl)-4'-(1-methylethyl)biphenyl (MH), 4,4'-bis(2-hydroxy-1-methylethyl)biphenyl (DH) were obtained as previously described [23].

4-Isopropyl-4'-acetylbiiphenyl, 1-(4'-isopropyl-biphenyl-4-yl)-ethanone (MAc) were obtained as the products of catalytic oxidation of DIBPh. 40 g (168 mmol) of DIBPh were oxidized with oxygen at 90°C in the presence of $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ (0.287 g; 1.68 mmol) and tetrabutylammonium bromide (0.0108 g; 3.336×10^{-2} mmol) for 10 h, according to the method presented in reference [24]. The obtained product contained, among others, 13% of MAc. To 25 g of the obtained oxidation product, 110 cm³ of ethyl alcohol were added and the mixture was heated up to the boiling point. After cooling and filtration, 9 g of the precipitate (containing 63% of peroxide bis(methyl-1-(4'-isopropylbiphenyl-4-yl)ethyl)) and 16 g of the filtrate were obtained. The filtrate was separated on the chromatographic column (Kieselgel 60/Merck 0.063–0.200 mm), applying CH_2Cl_2 :acetone (20:1, v/v) as the eluent. From 2 g of the filtrate, 0.17 g of MAc was separated and crystallized from ethanol. Crystallization yield was 0.13 g MAc; m.p. 118–119.5°C (lit. 120–121°C – Beilstein Data; BRN 2449010); ¹H-NMR (CDCl_3/TMS) δ = 8.02 (d, 2H_{Ar}, J = 8.7 Hz), 7.68 (d, 2H_{Ar}, J = 8.7 Hz), 7.57 (d, 2H_{Ar}, J = 8.1 Hz), 7.34 (d, 2H_{Ar}, J = 8.1 Hz), 2.93–3.04 (m, 1H, C(CH₃)₂H), 2.64 (s, 3H, CH₃), 1.30 (d, 6H, J = 6.9 Hz, C(CH₃)₂H). ¹³C-NMR 197.764, 149.189, 145.738, 137.329, 137.607, 128.886, 127.197, 127.057, 126.990, 33.851, 26.623, 23.926.

Apparatus and chromatographic conditions

Chromatographic analysis was performed using an Alliance Waters 2690 high-performance liquid chromatograph (Waters, Millipore, MA, USA) consisting of a Waters 717 plus autosampler and a Waters 996 photodiode array detector. An analytical cartridge column Nova-Pak Silica 60 A 4 μm (150 mm \times 3.9 mm; Waters) was thermostated at 25°C. A mixture of 2-propanol and hexane at the flow rate of 1.0 cm³ min⁻¹ was used as a mobile phase. HP-IBPh and H-IBPh were detected at 251 nm, Ac-IBPh at 276 nm, HO-IBPh at 260 nm. MHP, MH, HHP, DHP, DH were detected at 254 nm, MAc at 285 nm. These wavelengths were close to the absorption maxima of the studied compounds. Calibration was carried out according to the external standardization method. 2–20 μL portions of the standard solution were used for single point calibration.

The following chromatographic conditions for gradient elution were applied:

- | | | |
|------------------------------------|-----------------------|-----------|
| – time | 0–3 min | 3–11 min. |
| – hexane–2-propanol (v/v) | 99:1 | 97:3 |
| – equilibration: hexane–2-propanol | 99:1 (v/v) for 3 min. | |

¹H and ¹³C NMR spectra in CDCl_3 were recorded on a Varian Unity Inova–300 spectrometer using tetramethylsilane as the internal standard. Melting points of the synthesized compounds were determined on SMP 3 (Stuart Scientific) apparatus using capillary tubes.

RESULTS AND DISCUSSION

Oxidation products of IBPH and DIBPh, including hydroperoxides, alcohols, ketones, as well as unreacted substrates, were separated and determined by HPLC using a Nova-Pak Silica 60 Å 4 μm (150 mm \times 3.9 mm) analytical column and a mixture of hexane and 2-propanol as a mobile phase in the analogous way as isopropyl-naphthalenes were determined [18].

4-Hydroxybiphenyl occurred merely among final oxidation products of IBPh and was formed during their storage, as a decomposition product of HP-IBPh. HO-IBPh

was selected for further studies. During the storage of the oxidation products of DIBPh, 2-isopropyl-naphthalene [18], and cumene under the same conditions such decomposition of hydroperoxides was not observed.

In order to determine the optimum eluent composition providing the best separation of the oxidation products of IBPh and DIBPh, the dependence of $\lg k$ (k – the retention factor) on $\lg x$ (x – the molar ratio of the eluent constituents) was constructed (Figs. 4 and 5).

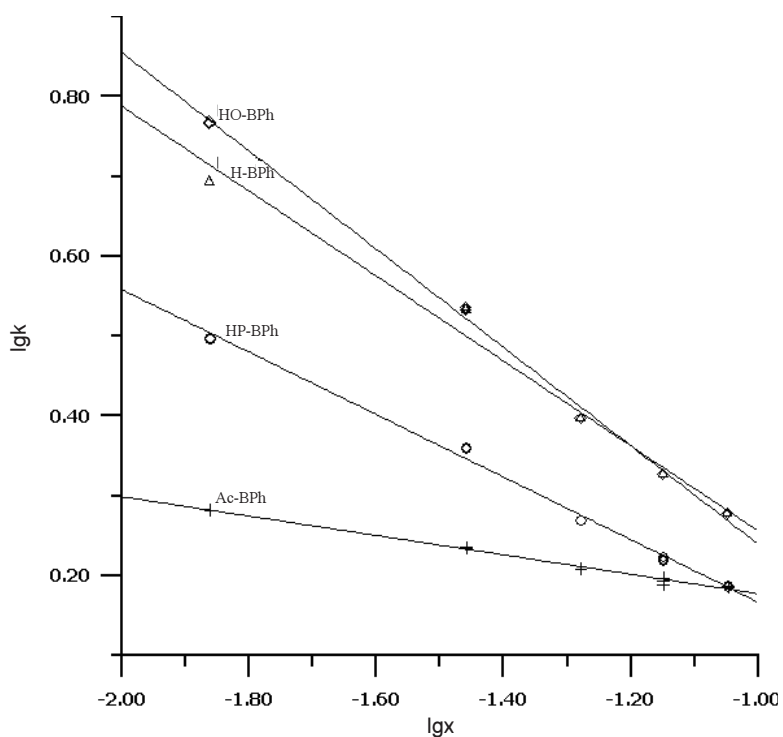


Figure 4. $\lg k$ vs $\lg x$ (x – 2-propanol-to-hexane molar ratio) dependence for the oxidation products of IBPh

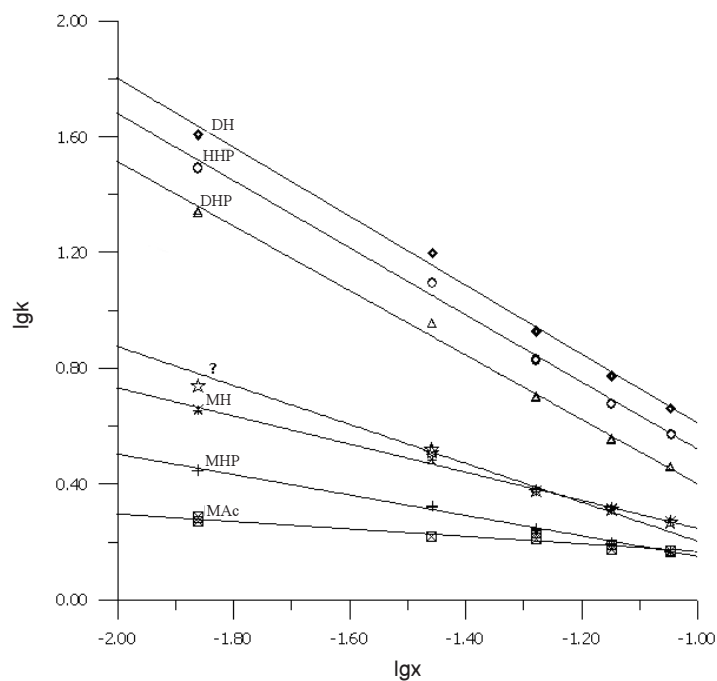


Figure 5. $\lg k$ vs $\lg x$ (x – 2-propanol-to-hexane molar ratio) dependence for the oxidation products of DIBPh

Typical chromatograms of IBPh and DIBPh oxidation products obtained for the eluent mixture hexane–2-propanol (99:1, v/v) are presented in Figs. 6 and 7.

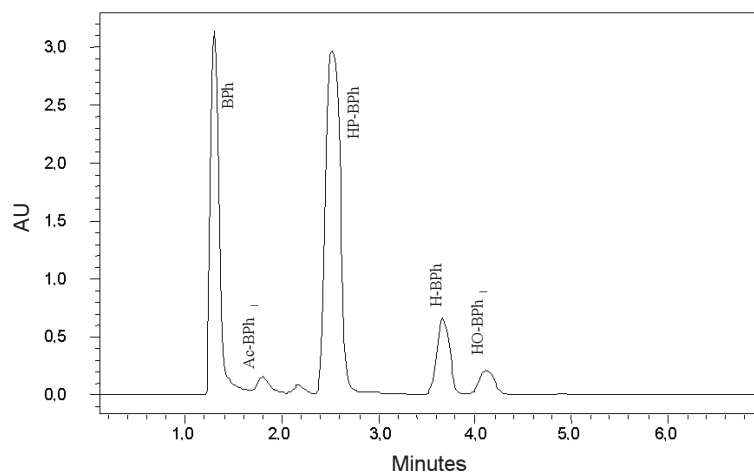


Figure 6. Chromatogram of the oxidation product of IBPh; hexane–2-propanol 99/1; $\lambda = 251$ nm

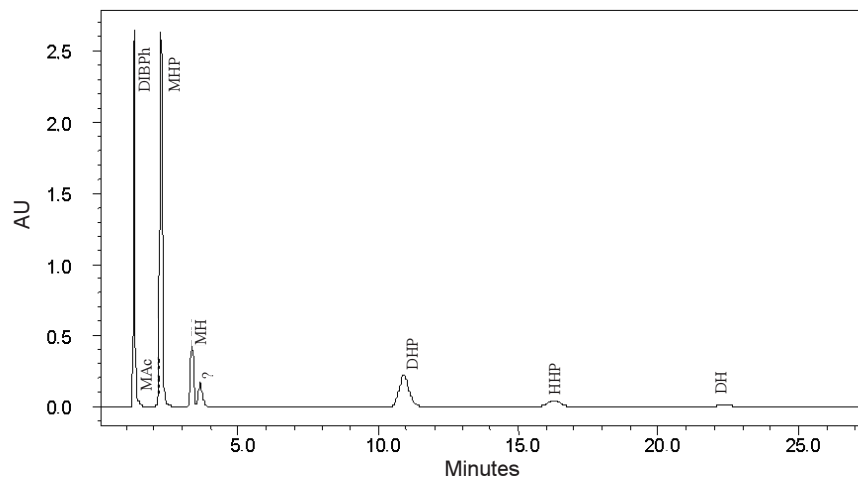


Figure 7. Chromatogram of the oxidation products of DIBPh; eluent: hexane–2-propanol (99:1); detection wavelength $\lambda = 254$ nm

Complete separation of all oxidation products of IBPh and DIBPh was obtained for 1% (vol) content of 2-propanol in the eluent mixture. Then, however, single analysis of DIBPh took 25 min. In order to shorten the separation time, gradient elution was applied, analogically as in the analysis of 2,6-diisopropylnaphthalene. Typical chromatogram of the oxidation products of DIBPh obtained under conditions of gradient elution is presented in Figure 8. The time of a single analysis, including column stabilization, was shortened to 14 min.

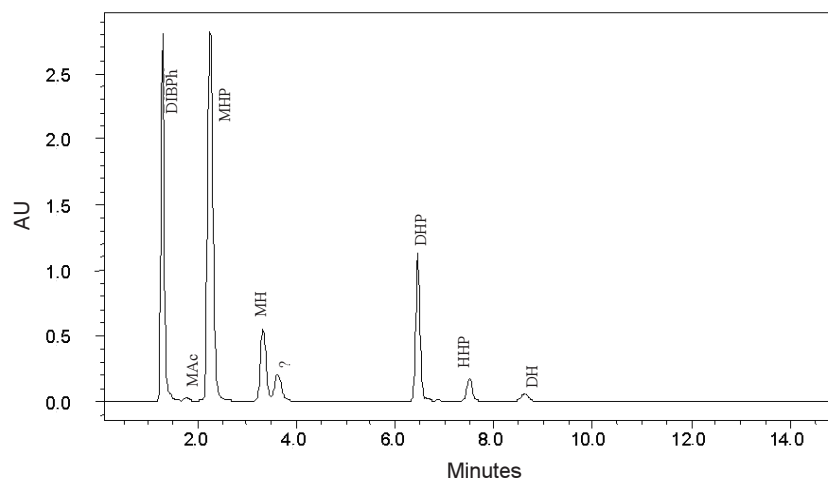


Figure 8. Chromatogram of the oxidation products of DIBPh; gradient elution with hexane–2-propanol mixture; detection wavelength $\lambda = 254$ nm

The chromatograms presented in Figs. 6–8 were analogical to the chromatograms of the oxidation products of isopropylthalenes obtained under similar conditions [18]. However, only in case of IBPh phenol was observed among the final products.

External standard calibration yielded a linear dependence between the peak areas and the contents of particular analytes. Linear regression parameters corresponding to the calibration plots of particular compounds are listed in Tables 1 and 2. Precision of the method was estimated as the relative standard deviation of replicate determinations (Tab. 3 and 4).

Table 1. The results of standard calibration for the oxidation products of 4-isopropylbiphenyl: linear regression parameters of the peak area vs the injection volume of the analyte dependence estimated by the least-squares method; number of points for each compound $n = 7$; number of injections $m = 3$

Compound	Range, μg	Slope, $a \times 10^6$	Intercept, $b \times 10^5$	Correlation coefficient, R
Ac-IBPh	0.2–2.0	6.168	–3.096	0.9964
HP-IBPh	0.5–5.0	4.500	–2.230	0.9986
H-IBPh	0.5–5.0	4.932	1.414	0.9984
HO-IBPh	0.5–5.0	5.995	–2.198	0.9982

Table 2. The results of standard calibration for the oxidation products of 4,4'-diisopropylbiphenyl: linear regression parameters of the peak area vs the injected mass of the analyte dependence estimated by the least-squares method; number of points for each compounds $n = 7$; number of each injection $m = 3$

Compound	Range, μg	Slope, $a \times 10^6$	Intercept, $b \times 10^5$	Correlation coefficient, R
MHP	0.2–3.0	4.765	–1.840	0.9989
MH	0.2–3.0	5.223	–1.074	0.9993
MAc	0.2–2.0	4.856	–3.198	0.9990
DHP	0.2–2.0	4.350	–0.763	0.9976
HHP	0.2–2.0	3.961	–0.203	0.9996
DH	0.2–2.0	4.365	0.195	0.9993

Table 3. Reproducibility of the standard method for determination of oxidation products of 4-isopropylbiphenyl; number of replicate determinations for each compound $m = 8$

Compound	Amount added, μg	Amount found, μg	SD, μg	RSD, %	Amount added, μg	Amount found, μg	SD, μg	RSD, %
Ac-IBPh	0.289	0.295	0.007	2.57	2.104	2.187	0.007	0.31
HP-IBPh	0.434	0.441	0.008	1.80	4.240	4.079	0.046	1.13
H-IBPh	0.481	0.423	0.007	1.60	4.812	4.702	0.012	0.25
HO-IBPh	0.438	0.448	0.007	1.57	4.384	4.372	0.014	0.32

Table 4. Reproducibility of the standard method for determination of oxidation products of 4,4'-diisopropylbiphenyl; number of replicate determinations for each compound $m = 8$

Compound	Amount added, μg	Amount found, μg	SD, μg	RSD, %	Amount added, μg	Amount found, μg	SD, μg	RSD, %
MHP	0.251	0.255	0.008	3.33	2.763	2.788	0.011	0.39
MH	0.227	0.259	0.004	1.61	2.791	2.766	0.012	0.43
MAc	0.202	0.186	0.004	2.05	2.244	2.264	0.020	0.88
DHP	0.214	0.218	0.002	1.00	2.040	2.000	0.014	0.70
HHP	0.216	0.220	0.008	3.52	2.030	2.022	0.013	0.66
DH	0.254	0.262	0.001	0.44	2.112	2.080	0.005	0.25

CONCLUSIONS

In this paper, we have proposed the HPLC method for quantitative analysis of the oxidation products of IBPh and DIBPh using a Nova-Pak Silica 60 Å 4 μm column and a mixture of hexane and 2-propanol as the eluent. Analogical methods have been already successfully applied for determination of the oxidation product of isopropyl-naphthalenes [18].

The obtained results demonstrate that the proposed analytical method allows precise and relatively fast determination of autooxidation products of IBPh and DIBPh.

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