SYNTHESIS OF DIQUINONES IN THE DIPHENYL- AND DINAPHTHYLMETHANE SERIES

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p-Quinones and hydroquinones [1] possess high antiviral activity in vitro in relation to group-A viruses (strain PR-8). In this connection the synthesis and study of the biological activity of diquinones of the diphenyl- and dinaphthylmethane series is of interest. These compounds are virtually inaccessible [2-4]. Dihydroxy derivatives of the diphenyl- and dinaphthylmethane series could serve as the most suitable starting compounds for their synthesis. However, it is not possible to obtain these compounds by this method because of the tendency of benzo- and naphthohydroquinones to form polymers upon reaction with aldehydes [5]. In this connection we chose monomethyl ethers of benzo- and naphthohydroquinones as the starting compounds for synthesis of quinones of the diphenyl- and dinaphthylmethane series. Monomethyl ethers of hydroquinones are accessible. We used monomethyl ethers of 2,3-dichlorohydroquinone (I), 2,5-dichlorohydroquinone (II), 5,8-dihydronaphthohydroquinone (III), and naphthohydroquinone (IV) for reaction. One of them (IV) was described earlier [6]; the three others (I-III) were obtained upon methylation of the corresponding hydroquinones. Compounds (I), (III) and (IV) upon reaction with formaldehyde in the presence of concentrated hydrochloric or sulfuric acid were transformed into the dimethyl ethers of 2,2',5,5'-tetrahydroxy-3,3',4'-tetrachlorodiphenylmethane (V), 1,1',4,4'-tetrahydroxy-5,5',8,8'-tetrahydro-2,2',-dinaphthylmethane (VI), and 1,1',4,4'-tetrahydroxy-2,2'-dinaphthylmethane (VII). Compound (II) does not react under analogous conditions. Upon heating it with formaldehyde in the presence of hydrochloric acid in acetic acid solution we isolated, instead of the expected dimethyl ether of 2,2',5,5'-tetrahydroxy-3,3',6,6'-tetrachlorodiphenylmethane, 5,8-dichloro-6-methoxybenzodioxane-1,3 (VIII), the structure of which was confirmed by the IR spectrum: the absorption band of the hydroxy group was absent. Upon oxidation with nitric acid (V-VII) were transformed into the corresponding diquinones: 2,2',5,5'-tetraoxo-3,3',4,4'-tetrachlorodiphenylmethane (IX), 1,1', 4,4'-tetraoxo-5,5',8,8'-tetrahydro-2,2'-dinaphthylmethane (X), and 1,1', 4,4'-tetraoxo-2,2'-dinaphthylmethane (XI). Bromination of 2,2', 5,5'-tetrahydroxy-4,4'-dimethyldiphenylmethane [3] forms a compound of the quinhydrone type, which was oxidized with nitric acid into 2,2',5,5'-tetraoxo-3,3',6,6'-tetrabromo-4,4'-dimethyldiphenylmethane (XII).

It was shown as a result of biological investigations that of the synthesized compounds only (V) in vitro possesses weak antiviral activity: in a dilution of 1:1000 it neutralizes the effect of 10 LD_{100} of group-A virus (strain PR-8).

EXPERIMENTAL

Monomethyl Ether of 2,3-Dichlorohydroquinone (I). To a solution of 23 g of 2,3-dichlorohydroquinone in 64 ml of 20% sodium hydroxide solution with stirring and a temperature of 56°C was added in drops 12.2 ml of dimethyl sulfate. The reaction mixture was maintained at the same temperature for 1 h, and then cooled and filtered from the admixture of the dimethyl ether of 2,3-dichlorohydroquinone. The filtrate was acidified with acetic acid and the precipitate was separated and recrystallized from water. Yield was 28%, mp 57-59°. Found, %: C 43.35; H 3.06; Cl 37.06. $C_7H_6Cl_2O_2$. Calculated, %: C 43.55; H 3.13; Cl 36.73.

Compound (II) was obtained analogously. Yield 72%, mp 94-95° (from 30% acetic acid). Found, %: C 43.39; H 3.11; Cl 36.66. $C_7H_6Cl_2O_2$. Calculated, %: C 43.55; H 3.13; Cl 36.73. Compound (III) was obtained the same as were (I) and (II). Yield 52%, mp 130° (from 55% acetic acid). Found, %: C 75.00; H 6.93. $C_{11}H_{12}O_2$. Calculated, %: C 74.98; H 6.86.

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Dimethyl Ether of 2,2',5,5'-Tetrahydroxy-3,3',4,4'-tetrachlorodiphenylmethane (V). A mixture of 3.18 g of (I), 2.5 ml of 34% formaldehyde solution, and 2.5 ml of hydrochloric acid (d 1.18) was mixed at 75-80° for 5 h and left for 24 h at room temperature. The reaction product was separated, washed with water, and recrystallized from a methanol–dioxane mixture. Yield 42%, mp 255° (decomp.). Found, %: C 45.30; H 3.16; Cl 35.27. $C_{15}H_{12}Cl_4O_4$. Calculated, %: C 45.26; H 3.04; Cl 35.62.

Dimethyl Ether of 1,1',4,4'-Tetrahydroxy-5,5',8,8'-tetrahydro-2,2'-dinaphthylmethane (VI). To a solution of 1.76 g of (III) in 20 ml of glacial acetic acid was added 3.7 ml of 34% formaldehyde solution and in drops with stirring at 5-10° was added 2.8 ml of sulfuric acid (d 1.83). The reaction mass was stirred an additional 2 h, and the residue was separated, washed with water, and recrystallized from benzene. Yield 56%, mp 187-188°. Found, %: C 75.1; H 6.74. $C_{23}H_{24}O_4$. Calculated, %: C 75.8; H 6.64.

Compound (VII) was obtained analogously. Yield 25%, mp 350° (from benzene). Found, %: C 76.7; H 5.4. $C_{23}H_{20}O_4$. Calculated, %: C 76.75; H 5.59.

5,8-Dichloro-6-methoxybenzodioxane-1,3 (VIII). A solution of 1.93 g of (II), 1.5 ml of 34% formaldehyde solution, and 1.5 ml of hydrochloric acid (d 1.18) in 10 ml of acetic acid was maintained at 75-80° for 6 h and the mixture was left at room temperature for 16 h. The precipitate was separated, washed with water, and recrystallized from alcohol. Yield 30%, mp 139.5-140°. Found, %: C 46.07; H 3.41; Cl 30.17. $C_8H_8Cl_2O_3$. Calculated, %: C 45.98; H 3.43; Cl 30.16.

2,2',5,5'-Tetraoxo-3,3',4,4'-tetrachlorodiphenylmethane (IX). To a solution of 1 g of (V) in 20 ml of acetone with intense stirring and at room temperature in drops was added 2.4 ml of nitric acid (d 1.4). At the end of addition stirring was continued an additional 1 h and the precipitate was separated and recrystallized from acetic acid. Yield 36%, mp 170°. Found, %: C 42.68; H 1.4; Cl 38.02. $C_{13}H_4Cl_4O_4$. Calculated, %: C 42.66; H 1.1; Cl 38.75.

Compound (X) was obtained analogously. Yield 49%, mp 155-156° (from alcohol). Found, %: C 76.19; H 4.82. $C_{21}H_{16}O_4$. Calculated, %: C 75.89; H 4.85. Compound (XI) was obtained as were (IX) and (X). Yield 37%, mp 150-155° (decomp., from alcohol). Found, %: C 76.67; H 3.66. $C_{21}H_{12}O_4$. Calculated, %: C 76.82; H 3.68.

2,2',5,5'-Tetraoxo-3,3',6,6'-tetrabromo-4,4'-dimethyldiphenylmethane (XII). To a suspension of 0.7 g of 2,2',5,5'-tetrahydroxy-4,4'-dimethyldiphenylmethane in 40 ml of chloroform with stirring in drops was added 1.6 g of bromine in 5 ml of chloroform. The next day the solvent was distilled, the residue was dissolved in dioxane, and with intense stirring to it was added 5 ml of nitric acid (d 1.4). The obtained pale-yellow solution was poured into water. The precipitate was separated and recrystallized from acetic acid. Yield 30%, mp 231-232°. Found, %: C 31.49; H 1.4; Br 55.72. $C_{15}H_8Br_4O_4$. Calculated, %: C 31.5; H 1.41; Br 55.9.

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