SYNTHESIS OF POLYBROMINATED DIPHENYL ETHERS OF MARINE ORIGIN

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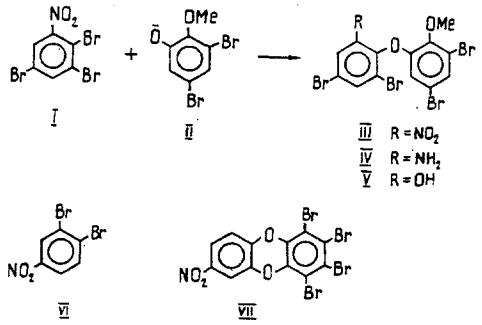
Polybrominated diphenyl ethers — antimicrobial metabolites of the marine sponge Dysidea fragilis *— have been obtained by the reaction of 2,3,5-tribromonitrobenzene with 3,5-dibromo-2-methoxyphenol and the reaction of brominated diphenyliodonium salts with brominated phenols.*

We have previously reported the isolation of brominated diphenyl ethers from a marine sponge of the genus *Dysidea* [1]. To confirm the structures of the compounds established on the basis of spectral characteristic, we have now synthesized some of them.

For the synthesis of the ether (V) we used the method described in [2] (Scheme 1)

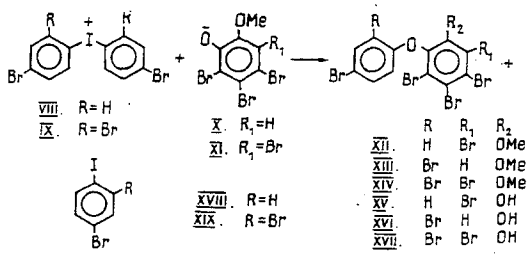
Scheme 1



The scheme for the synthesis of the desired diphenyl ether (V) included the following stages. The condensation of the tribromonitrobenzene (I) with the potassium salt of the dibromomethoxyphenol (II) in hexamethylphosphoramide, conducted by the procedure of [2], led to the nitrodiphenyl ether (III) with a yield of 40%. Reduction of the nitro group in (III) with sodium hydrogen sulfide according to [3] gave the amine (IV) with a yield of 59%. The desired ether (V) was obtained with a yield of 10% after the diazotization of the amine (IV) and hydrolysis of the diazonium salt in aqueous sulfuric acid [4]. The compound obtained was identical, according to its spectral characteristics, with the natural 4,6-dibromo-2-(4′,6′-dibromo-2′-hydroxyphenoxy)anisole [1].

Our attempts to use the condensation of 1,2-dibromo-4-nitrobenzene (VI) with the potassium salt of tetrabromoguaiacol (XVI) for the synthesis of the ether (XVII) by Scheme 1 led to the formation of the dioxin (VII). Therefore, for the synthesis of the ethers (XV)-(XVII) we used the reaction between symmetrical brominated diphenyliodonium salts and brominated guaiacol according to [5] (Scheme 2).

Scheme 2



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The diphenyliodonium salts (VIII) and (IX) were obtained by a modification of the method described in [5]. The bromination of guaiacol led to (X) and (XI). The coupling of the diphenyliodonium salts (VIII) and (IX) with the brominated guaiacols (X) and (XI), followed by demethylation of the methoxydiphenyl ethers (XII)-(XV) completed the synthesis of the required polybrominated diphenyl ethers (XV)-(XVII).

EXPERIMENTAL

NMR spectra were taken on a Bruker WM-250 instrument (δ scale, 0 — TMS) and mass spectra on a LKB-9000S instrument with direct introduction of the sample into the ion source at an ionizing energy of 70 eV, while melting points were determined on a Boëtius stage. The analyses of all the compounds corresponded to the calculated figures.

2,3,5-Tribromonitrobenzene (I) was obtained from 2,4-dibromo-6-nitroaniline by the method of Doyle et al. [6].

3,5-Dibromo-2-methoxyphenol (II) was obtained from salicylaldehyde by the method of Norte et al. [7].

4,6-Dibromo-2-(4′,6′-dibromo-2′-nitrophenoxy)anisole (III). In an atmosphere of nitrogen at 80°C, a solution of 0.9 g (0.0025 mole) of (I) in 2 ml of hexamethylphosphoramide was added to a solution of 0.8 g (0.0025 mole) of the potassium salt of the phenol (II) in 50 ml of dry hexamethylphosphoramide. The reaction mixture was stirred for 3 h. After cooling, it was poured into water, and the precipitate was filtered off and was crystallized from chloroform. This gave 0.56 g (40%) of compound (III) in the form of yellow prisms with mp 147-149°C. PMR spectrum (ppm, DMSO-d_6): 8.50 (1H, d, J = 2 Hz), 8.44 (1H, d, J = 2 Hz), 7.62 (1H, d, J = 2 Hz), 6.99 (1H, d, J = 2 Hz), 3.85 (3H, s, OMe); *m/z*: 565, 563, 561, 559, 557 (M^+, 100%).

3,5-Dibromo-2-(3′,5′-dibromo-2′-methoxyphenoxy)aniline (IV). A solution of 0.51 g (0.0009 mole) of (III) in 20 ml of a 1:1 mixture of benzene and methanol was boiled with an excess of a methanolic solution of sodium hydrogen sulfide (14 ml, 0.01 mole) for 7 h. The course of the reaction was followed on Silufol plates with chloroform as eluent. After the completion of the reaction, the mixture was extracted with methylene chloride (4 × 10 ml). The combined extracts were dried with Na_2SO_4 and evaporated, and the orange residue was chromatographed [SiO_2, hexane—chloroform (1:5)]. This gave 0.28 g (59%) of compound (IV) in the form of an amorphous powder. PMR spectrum ($CDCl_3$): 6.60 (1H, d, J = 2,2 Hz), 6.91 (1H, d, J = 2.2 Hz), 7.14 (1H, d, J = 2.2 Hz), 7.39 (1H, d, J = 2.2 Hz), 4.02 (3H, s, OMe), 3.95 (2H, br.s, NH_2); *m/z*: 535, 533, 531, 529, 527 (M^+, 100%).

4,6-Dibromo-2-(4′,6′-dibromo-2′-hydroxyphenoxy)anisole (V). A cooled solution of 0.034 g (0.0005 mole) of $NaNO_2$ was added to a solution of 0.26 g (0.0005 mole) of (IV) in 5 ml of dilute (1:3) sulfuric acid cooled to 0°C and then a urea solution was added and the mixture was boiled on the water bath for 30 min. After cooling, the mixture was extracted with methylene chloride (4 × 10 ml) and evaporated, and the residue was chromatographed [SiO_2, hexane—chloroform (1:5)]. This gave 0.026 g (10%) of compound (V), mp 143-145°C ($CHCl_3$). The melting point and the PMR and mass spectra corresponded to those of the natural compound [1].

1,2,3,4-Tetrabromo-7-nitrobenzo[b,e][1,4]dioxin (VII). The condensation of 0.7 g (0.0025 mole) of (VI) with 1.1 g (0.0025 mole) of the potassium salt of the phenol (XI) in hexamethylphosphoramide at 76°C according to [2] gave 0.6 g (45%) of compound (VII) in the form of yellow needles with mp above 250°C. PMR spectrum ($CDCl_3$): 7.30 (1H, d, J = 9 Hz), 7.94 (1H, d, J = 2 Hz), 8.00 (1H, dd, J = 2 Hz, 9 Hz); *m/z*: 549, 547, 545, 543, 541 (M^+, 100%).

3,4,5-Tribromoguaiacol (X) was obtained by brominating guaiacol as described in [4].

Tetrabromoguaiacol (XI). With continuous stirring, 12.8 g (0.08 mole) of bromine was added to 1.24 g (0.01 mole) of guaiacol that had been carefully stirred with 4 g (0.04 mole) of $CaCO_3$. After 30 min, the excess of bromine was driven out with a current of air, the free-flowing residue was transferred to a filter and was washed with chloroform, and the chloroform extract was evaporated. This gave 4.27 g (97%) of compound (XI), mp 162-162.5°C.

3,4,5,6-Tetrabromo-2-(2′,4′-dibromophenoxy)anisole (XIV). A solution of 0.63 g (0.0014 mole) of (XI) in 100 ml of water containing 0.5 g of NaOH was treated with 1 g (0.0014 mole) of the salt (IX), and the mixture was boiled until the solution had clarified and an oil had collected on the bottom (2 h). Then the compound (XIX) was distilled off with steam, the residual reaction mixture was extracted with methylene chloride (4 × 20 ml), and the combined extracts were evaporated and chromatographed (SiO_2, hexane). This gave 1.25 g (67%) of compound (XIV), mp 119-120°C (hexane) (literature: 118-120°C [1]). Its PMR and mass spectra corresponded to those given in [1].

3,4,5-Tribromo-2-(2′,4′-dibromophenoxy)anisole (XIII). The condensation of the phenol (X) and the salt (IX) under similar conditions gave compound (XIII) with a yield of 52%. Needles, mp 158-159°C (hexane) (literature: 157.5-159°C [2]). Its PMR and mass spectra corresponded to those given in the literature [2].

3,4,5,6-Tetrabromo-2-(4′-bromophenoxy)anisole (XII). Condensation of the phenol (XI) and the salt (VIII) under conditions similar to those for the synthesis of (XIV) gave compound (XII) with a yield of 45%. Needles, mp 147-149°C (acetone—hexane). PMR spectrum ($CDCl_3$): 7.40 (2H, d, J = 9 Hz), 6.73 (2H, J = 9 Hz), 3.80 (3H, s, OMe); *m/z*: 600, 598, 596, 594, 592, 590 (M^+, 100%).

3,4,5,6-Tetrabromo-2-(4′-bromophenoxy)phenol (XV). A solution of 0.6 g (0.001 mole) of compound (XII) in 5 ml of dry methylene chloride was kept with 20 drops of BBr_3 at room temperature until the reaction was complete. Then the mixture was distributed between water and ether, the organic layer was dried with Na_2SO_4 and evaporated, and the residue was chromatographed [SiO_2, hexane—chloroform (2:1)]. This gave 0.53 g (90%) of compound (XV), needles, mp 162-163.5°C (hexane). PMR spectrum ($CDCl_3$): 7.42 (2H, d, J = 9 Hz), 6.77 (2H, d, J = 9 Hz), 5.90 (1H, br.s, OH); *m/z*: 586, 584, 582, 580, 578, 576 (M^+, 100%).

3,4,5-Tribromo-2-(2′,4′-dibromophenoxy)phenol (XVI) was obtained similarly from compound (XIII), mp 199-200°C (hexane) (literature: 198-199°C [1]; 200-201°C [2]). Its spectral characteristics corresponded to those given in the literature [1, 2].

3,4,5,6-Tetrabromo-2-(2′,4′-dibromophenoxy)phenol (XVII) was obtained similarly from compound (XIV); needles, mp 161-163°C (hexane) (literature: 151-153°C [1]). Its spectral characteristics were identical with those of the natural ether [1].

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