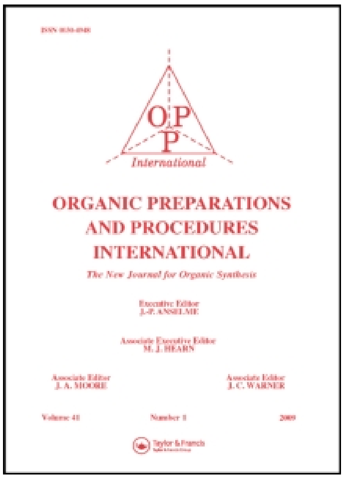

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REGIOSELECTIVE BROMINATION OF CARDANOL DERIVATIVES

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REGIOSELECTIVE BROMINATION OF CARDANOL DERIVATIVES

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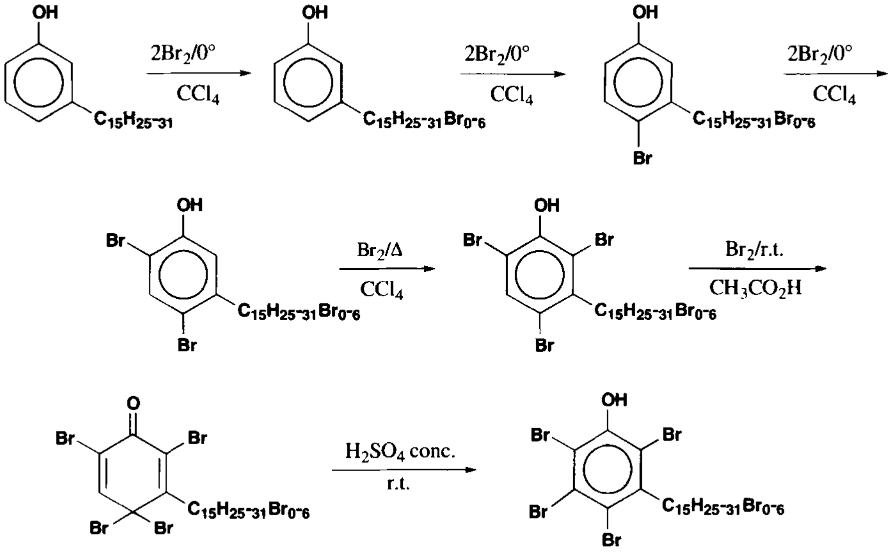
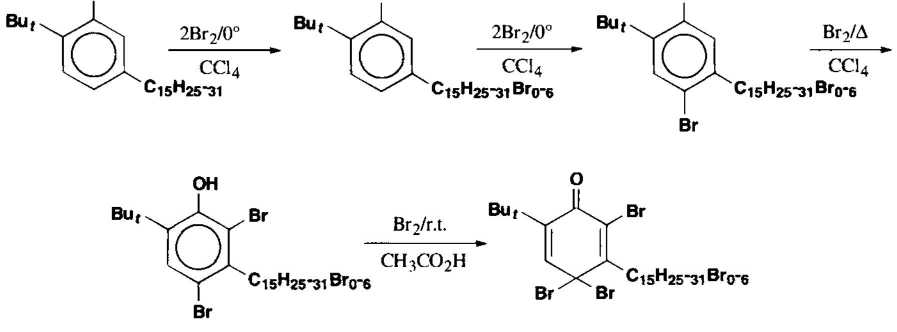
In continuation of our previous investigations,[1,2] we undertook the study of the selective bromination of some cardanol derivatives, in order to obtain products suitable as flame-retardant additives, capable of imparting a degree of ignition resistance to various polymeric materials. This investigation was also stimulated by recent market data relative to the increased demand for brominated flame retardants.[3,4]

Cardanol (side-chain $C_{15}H_{25-31}$) as a mixture of 3-*n*-pentadecylphenol, 3-*n*-pentadeca-8-enylphenol, 3-*n*-pentadeca-8,11-dienylphenol and 3-*n*-pentadeca-8,11,14-trienylphenol, undergoes addition of an average of four bromine atoms to the double bonds of the side-chain ($C_{15}H_{25-31}Br_{0-6}$) when at first treated with two equivalents of bromine in carbon tetrachloride at 0°. Under the same reaction conditions, the third equivalent of bromine selectively produces the first aromatic bromination in position 4 with respect to the phenolic hydroxy group. Due to the ambigous and difficult determination of the attack position (4 or 6 of the benzo ring) by means of the current spectroscopical methods (especially ^{1}H NMR), we subjected the compound obtained to aromatic *tert*-butylation, according to the method previously reported.[2f,g] The same product deriving from the first aromatic bromination of 6-*tert*-butylcardanol was obtained (see below). Likewise, the fourth equivalent of bromine, under the same reaction conditions, leads to the second regiospecific aromatic bromination in position 6. The third attack of the bromine atom in position 2 occurs with the same reagent under reflux, or in the presence of Lewis acid ($Br_2/CCl_4/ZnCl_2$), as well as with bromine in acetic acid at room temperature. The fourth bromine atom linkage on position 4 of the phenolic ring requires the treatment of the 2,4,6-tribromophenolic substrate in carbon tetrachloride, with a sixth bromine equivalent in acetic acid at room temperature. The result is 2,4,4,6-tetrabromo-3-*n*-(tetrabromo)pentadecylcyclohexa-2,5-dienone. An attempt to determine further attack of the bromine atom by ulterior addition to this 2,4,4,6-tetrabromocyclohexa-2,5-dienone derivative of a bromine equivalent in acetic acid under reflux failed, leading to the 2,4,6-tribromophenol derivative by a debromination process.



Scheme 1

The same result occurs when acetic acid or concentrated sulfuric acid are added to the 2,4,4,6-tetrabromocyclohexa-2,5-dienone derivative in various solvents and the reaction mixture is allowed to stand at room temperature. Lewis acids (i.e. $AlCl_3$, $FeCl_3$, $SnCl_4$), as such or in different solvents, determine the isomerization of this dienonic form in other similar species. Nevertheless, the treatment of the 2,4,4,6-tetrabromocyclohexa-2,5-dienone derivative with concentrated sulfuric acid and without solvent, produces the migration of a bromine atom from position 4 to position 5 of the benzo ring, furnishing 2,4,5,6-tetrabromo-3-*n*-(tetrabromo)pentadecylphenol.[5] The bromination reaction of 3-*n*-pentadecylphenol analogously proceeds on the benzo ring, obviously without the addition of the bromine atom in the side-chain, as shown in Scheme 1. The behavior of the regioselective bromination of cardanol and 3-*n*-pentadecylphenol is confirmed by the similar reaction on 6-*tert*-butylcardanol (side-chain $C_{15}H_{25\text{-}31}$) and 2-*tert*-butyl-5-*n*-pentadecylphenol, as depicted in Scheme 2.



Scheme 2

All these reactions afford the pertinent products in good to nearly-quantitative yields, with the exception of the conversion of 2,4,4,6-tetrabromo-3-*n*-(tetrabromo)pentadecylcyclohexa-2,5-dienone into 2,4,5,6-tetrabromo-3-*n*-(tetrabromo)pentadecylphenol, which gives a 40-50 % yield.

These findings are in agreement with a recent report describing the preparation of 2,4,5,6-tetrabromo-3-*n*-(tetrabromo)pentadecylphenol from cardanol able to impart flame retardancy properties to polyethylene and ethylene vinyl acetate based cable materials without adversely affecting the respective mechanical and other desired characteristics.[6,7] Although we worked under various reaction conditions and on different analogous substrates, we did not find the simple 2,4,5-tribromo-3-*n*-(tetrabromo)pentadecylphenol cited in that report.[6]

Clearly, the course of these reactions is also very important in order to correctly plan subsequent treatments (*i.e.* polymerization, phosphorylation, salification etc.),[6,7] further ring substitutions, as well as the bromine replacement reactions of these derivatives both in the aromatic ring and in the side-chain.

EXPERIMENTAL SECTION

Cardanol (with the registered trademark of Stabilcardo®) and 3-*n*-pentadecylphenol were kindly supplied by Oltremare SpA (Bologna, Italy) with physical and spectroscopic properties as previously reported.[2f] 6-*tert*-Butylcardanol and 2-*tert*-butyl-5-*n*-pentadecylphenol were synthesized according to the procedure described in a previous paper.[2f] Melting points were determined in open capillary tubes with a Büchi (Tottoli) apparatus and are uncorrected. The products often decompose at the melting point. IR spectra were obtained as liquid film or as Nujol mull with a Perkin-Elmer 298 spectrophotometer. IR-FT spectra were performed with a Nicolet Impact 400 spectrophotometer. MS spectra were made with a Hewlett Packard 5995 C spectrometer. Elemental analyses were performed with a Fisons EA 1108 instrument. ^{1}H NMR spectra at 60 MHz were recorded on Varian EM 360 L and at 200 MHz on Bruker AC 200 spectrometers and performed in CCl_4. Chemical shifts (δ) are reported in ppm downfield from internal TMS and coupling constants (J) in Hz. The abbreviations used are as follows: s, singlet; d, doublet, dd, doublet-doublet; t, triplet; q, quartet; m, multiplet; br, broad; D_2O ex, D_2O exchange. Densitometric analysis was made with a Scanning Densitometer Shimadzu CS-9000. Macherey-Nagel precoated silica gel SIL G-25UV$_{254}$ plates (0.25 mm) were employed for analytical thin layer chromatography (TLC) and Baker silica gel (0.063-0.200 mm) for column chromatography.

General Procedure for Bromination.- To a well stirred solution of cardanol or 6-*tert*-butylcardanol (1 mmol) dissolved in carbon tetrachloride (2 mL) was added dropwise a solution 1.0 M of bromine in carbon tetrachloride (2 mmol, 2 mL) and the mixture was magnetically stirred in ice bath for 15 min. Carbon tetrachloride (10 mL) was added to the reaction mixture, which was washed with saturated aqueous sodium carbonate (3x10 mL) and then with water (3x10 mL). The organic layer was dried over anhydrous sodium sulfate and after the evaporation of the reaction solvent the crude 3-*n*-(tetrabromo)pentadecylphenol and 2-*tert*-butyl-5-*n*-(tetrabromo)pentadecylphenol were obtained in good purity and in good yields. The subsequent aromatic bromination reactions of 3-*n*-(tetrabromo)pentadecylphenol and 2-*tert*-butyl-5-*n*-(tetrabromo)pentadecylphenol were realized by using equimolar amounts of bromine incrementally and by slightly varying the reaction conditions. The bromination treatment of 3-*n*-pentadecylphenol and 2-*tert*-butyl-5-*n*-pentadecylphenol was performed in an analogous way to cardanol and 6-*tert*-butylcardanol. The complete bromination reaction of all these substrates may be carried out in one flask. Crude 2,4,4,6-tetrabromo-3-*n*-(tetrabromo)pentadecylphenol or 2,4,4,6-tetrabromo-3-*n*-pentadecylphenol (1 mmol) were suspended in conc. sulfuric acid (96%) (4 mL) and the reaction mixture was stirred magnetically at room temperature for 3 hrs and then worked up as described.

3-*n*-(Tetrabromo)pentadecylphenol: oil; IR (neat): 3310, 1560, 780 cm^{-1}; ^{1}H NMR: δ 1.00 (s, CH_3), 1.13-2.25 (m, CH_2), 2.33-3.05 (m, CH_2Ph), 3.90-4.42 (m, CHBr), 6.05 (br s, OH, D_2O ex), 6.40-7.30 (m, Ph) ppm.

Anal. Calcd. for $C_{21}H_{32}Br_4O$: C, 40.68; H, 5.20; Br, 51.54. Found: C, 40.95; H, 5.38; Br, 51.29

4-Bromo-3-*n*-(tetrabromo)pentadecylphenol: oil; IR (neat): 3330, 1570, 780 cm^{-1}; ^{1}H NMR: δ 1.00 (s, CH_3), 1.13-2.30 (m, CH_2), 2.37-3.07 (m, CH_2Ph), 3.93-4.45 (m, CHBr), 5.43 (br s, OH, D_2O ex), 6.40 and 6.53 (dd, 6-H_{arom}, *J*= 3.0 Hz, *J*= 8.0 Hz), 6.62 (d, 2-H_{arom}, *J*= 3.0 Hz), 7.27 (d, 5-H_{arom}, *J*= 8.0 Hz) ppm.

Anal. Calcd. for $C_{21}H_{31}Br_5O$: C, 36.08; H, 4.47; Br, 57.16. Found: C, 36.35; H, 4.69; Br, 56.92

2,4-Dibromo-5-*n*-(tetrabromo)pentadecylphenol: oil; IR (neat): 3510, 1560, 780 cm^{-1}; ^{1}H NMR: δ 1.00 (s, CH_3), 1.15-2.30 (m, CH_2), 2.60-3.16 (m, CH_2Ph), 3.95-4.45 (m, CHBr), 5.63 (br s, OH, D_2O ex), 6.83 (s, 6-H_{arom}), 7.55 (s, 3-H_{arom}) ppm.

Anal. Calcd. for $C_{21}H_{30}Br_6O$: C, 32.42; H, 3.89; Br, 61.63. Found: C, 32.19; H, 3.66; Br, 61.90

2,4,6-Tribromo-3-*n*-(tetrabromo)pentadecylphenol: oil; IR (neat): 3510, 1560, 775, 690, 660 cm^{-1}; ^{1}H NMR: δ 1.00 (s, CH_3), 1.17-2.30 (m, CH_2), 2.63-3.23 (m, CH_2Ph), 3.95-4.47 (m, CHBr), 5.80 (br s, OH, D_2O ex), 7.67 (s, 5-H_{arom}) ppm.

Anal. Calcd. for $C_{21}H_{29}Br_7O$: C, 29.44; H, 3.41; Br, 65.28. Found: C, 29.21; H, 3.19; Br, 65.55

2,4,4,6-Tetrabromo-3-*n*-(tetrabromo)pentadecylcyclohexa-2,5-dienone: oil; IR (neat): 1680, 1585, 775, 670 cm^{-1}; ^{1}H NMR: δ 1.00 (s, CH_3),1.17-2.33 (m, CH_2), 2.62-3.30 (m, CH_2Ph), 3.95-4.50 (m, CHBr), 7.80 (s, 5-H_{arom}) ppm.

Anal. Calcd. for $C_{21}H_{28}Br_8O$: C, 26.96; H, 3.02; Br, 68.32. Found: C, 27.18; H, 3.29; Br, 68.18

2,4,5,6-Tetrabromo-3-*n*-(tetrabromo)pentadecylphenol: oil; IR (neat): 3450, 1560, 775, 690, 660 cm^{-1}; ^{1}H NMR: δ 1.00 (s, CH_3), 1.17-2.30 (m, CH_2), 2.63-3.23 (m, CH_2Ph), 3.95-4.47 (m, CHBr), 5.80 (br s, OH, D_2O ex) ppm.

Anal. Calcd. for $C_{21}H_{28}Br_8O$: C, 26.96; H, 3.02; Br, 68.32. Found: C, 26.69; H, 2.88; Br, 68.58

4-Bromo-3-*n*-pentadecylphenol: mp 56-58°; IR (nujol): 3330, 1570, 720 cm^{-1}; ^{1}H NMR: δ 1.00 (s, CH_3), 1.27 (m, CH_2), 2.60 (m, CH_2Ph), 6.03 (br s, OH, D_2O ex), 6.42 and 6.55 (dd, 6-H_{arom}, *J*= 3.0 Hz, *J*= 8.0 Hz), 6.67 (d, 2-H_{arom}, *J*= 3.0 Hz), 7.32 (d, 5-H_{arom}, *J*= 8.0 Hz) ppm.

Anal. Calcd. for $C_{21}H_{35}BrO$: C, 65.79; H, 9.20; Br, 20.84. Found: C, 65.86; H, 9.14; Br, 20.61

2,4-Dibromo-5-*n*-pentadecylphenol: mp 40-42°; IR (nujol): 3500 1560, 715 cm^{-1}; ^{1}H NMR: δ 1.00 (s, CH_3), 1.27 (m, CH_2), 2.60 (m, CH_2Ph), 5.55 (br s, OH, D_2O ex), 6.83 (s, 6-H_{arom}), 7.53 (s, 3-H_{arom}) ppm.

Anal. Calcd. for $C_{21}H_{34}Br_2O$: C, 54.56; H, 7.41; Br, 34.57. Found: C, 54.58; H, 7.49; Br, 34.81

2,4,6-Tribromo-3-*n*-pentadecylphenol: mp 52-54°; IR (nujol): 3510, 1560, 720 cm^{-1}; ^{1}H NMR: δ 1.00 (s, CH_3), 1.30 (m, CH_2), 2.98 (m, CH_2Ph), 5.80 (br s, OH, D_2O ex), 7.62 (s, 5-H_{arom}) ppm.

Anal. Calcd. for $C_{21}H_{33}Br_3O$: C, 46.61; H, 6.15; Br, 44.29. Found: C, 46.57; H, 6.21; Br, 44.01

2,4,4,6-Tetrabromo-3-*n*-pentadecylcyclohexa-2,5-dienone: mp 58-60°; IR (nujol): 1675, 1575, 770, 690, 660 cm^{-1}; ^{1}H NMR: δ 1.00 (s, CH_3), 1.30 (m, CH_2), 2.88 (m, CH_2Ph), 7.80 (s, 5-H_{arom}) ppm.

Anal. Calcd. for $C_{21}H_{32}Br_4O$: C, 40.68; H, 5.20; Br, 44.29. Found: C, 40.65; H, 5.27; Br, 44.51

2,4,5,6-Tetrabromo-3-*n*-pentadecylphenol: mp 59-61°; IR (nujol): 3440, 1560, 720 cm^{-1}; ^{1}H NMR: δ 1.00 (s, CH_3), 1.30 (m, CH_2), 2.98 (m, CH_2Ph), 5.80 (br s, OH, D_2O ex) ppm.

Anal. Calcd. for $C_{21}H_{32}Br_4O$: C, 40.68; H, 5.20; Br, 44.29. Found: C, 40.92; H, 5.45; Br, 44.44

2-*tert*-Butyl-5-*n*-(tetrabromo)pentadecylphenol: oil; IR (neat): 3450, 1580, 780 cm^{-1}; ^{1}H NMR: δ 1.00 (s, CH_3), 1.17-2.20 (m, CH_2 $C(CH_3)_3$), 2.27-2.67 (m, CH_2Ph), 3.97-4.37 (m, CHBr); 4.75 (br s, OH, D_2O ex), 6.37 (br s, 6-H_{arom}), 6.58 (br d, 4-H_{arom}, $J = 8.0$ Hz), 7.10 (d, 3-H_{arom}, $J = 8.0$ Hz), ppm.

Anal. Calcd. for $C_{25}H_{40}Br_4O$: C, 44.41; H, 5.96; Br, 47.27. Found: C, 44.17; H, 5.81; Br, 47.52

2-*tert*-Butyl-4-bromo-5-*n*-(tetrabromo)pentadecylphenol: oil; IR (neat): 3450, 1580, 780 cm^{-1}; ^{1}H NMR: δ 1.00 (s, CH_3), 1.17-2.20 (m, CH_2, $C(CH_3)_3$), 2.30-2.80 (m, CH_2Ph), 3.93-4.40 (m, CHBr); 4.90 (br s, OH, D_2O ex), 6.45 (s, 6-H_{arom}), 7.81 (s, 3-H_{arom}) ppm.

Anal. Calcd. for $C_{25}H_{39}Br_5O$: C, 39.77; H, 5.21; Br, 52.91. Found: C, 39.57; H, 5.48; Br, 53.18

2,4-Dibromo-6-*tert*-butyl-3-*n*-(tetrabromo)pentadecylphenol: oil; IR (neat): 3500, 1590, 780 cm^{-1}; ^{1}H NMR: δ 1.00 (s, CH_3), 1.17-2.20 (m, CH_2, $C(CH_3)_3$), 2.30-2.80 (m, CH_2Ph), 3.93-4.45 (m, CHBr); 5.88 (br s, OH, D_2O ex), 7.40 (s, 5-H_{arom}) ppm.

Anal. Calcd. for $C_{25}H_{38}Br_6O$: C, 36.00; H, 4.59; Br, 57.48. Found: C, 36.28; H, 4.88; Br, 57.71

2,4,4-Tribromo-6-*tert*-butyl-3-*n*-(tetrabromo)pentadecylcyclohexa-2,5-dienone: oil, IR (neat): 1665, 1585, 780, 760 cm^{-1}; ^{1}H NMR: δ 1.00 (s, CH_3), 1.17-2.20 (m, CH_2, $C(CH_3)_3$), 2.32-2.85 (m, CH_2Ph), 3.90-4.45 (m, CHBr), 7.33 (s, 5-H_{arom}) ppm.

Anal. Calcd. for $C_{25}H_{37}Br_7O$: C, 32.89; H, 4.09; Br, 61.27. Found: C, 32.68; H, 4.28; Br, 61.52

2-*tert*-Butyl-4-bromo-5-*n*-pentadecylphenol: mp 64-66°; IR (nujol): 3450, 1580, 720 cm^{-1}; ^{1}H NMR: δ 0.97 (s, CH_3), 1.27 (m, CH_2), 1.35 (s, $C(CH_3)_3$), 2.53 (m, CH_2Ph), 4.80 (br s, OH, D_2O ex), 6.38 (s, 6-H_{arom}), 7.27 (s, 3-H_{arom}) ppm.

Anal. Calcd. for $C_{25}H_{43}BrO$: C, 68.32; H, 9.86; Br, 18.18. Found: C, 68.37; H, 9.81; Br, 18.41

2,4-Dibromo-6-*tert*-butyl-3-*n*-pentadecylphenol: mp 56-58°; IR (nujol): 3500, 1590, 720 cm^{-1}; ^{1}H NMR: δ 1.00 (s, CH_3), 1.33 (m, CH_2), 1.43 (s, $C(CH_3)_3$), 2.90 (m, CH_2Ph), 5.80 (br s, OH, D_2O ex), 7.40 (s, 5-H_{arom}) ppm.

Anal. Calcd. for $C_{25}H_{42}Br_2O$: C, 57.92; H, 8.17; Br, 30.83. Found: C, 57.88; H, 8.19; Br, 31.11

2,4,4-Tribromo-6-*tert*-butyl-3-*n*-pentadecylcyclohexa-2,5-dienone: oil; IR (neat): 1665, 1585, 760, 670 cm^{-1}; ^{1}H NMR: δ 1.00 (s, CH_3), 1.30 (m, CH_2), 1.40 (s, $C(CH_3)_3$), 2.93 (m, CH_2Ph), 7.33 (s, 5-H_{arom}) ppm.

Anal. Calcd. for $C_{25}H_{41}Br_3O$: C, 50.27; H, 6.92; Br, 40.13. Found: C, 50.33; H, 6.89; Br, 40.41

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