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Synthesis of New Derivatives of Eugenol and Isoeugenol

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Six new derivatives of eugenol and isoeugenol, namely, 2-methoxy-4-(2,3-dichloropropyl)phenol (I), 2-methoxy-4-(1-bromoprop-2-enyl)phenol (II), 2-methoxy-4-(1-bromopropyl)phenol (III), 2-methoxy-4-(cyclopropylmethyl)phenyl acetate (IV), 2-methoxy-4-(2-chloroprop-1-enyl)phenol (V), and 2-methoxy-4-(1,2-dibromopropyl)phenol (VI) containing halogens (Cl or Br) and a cyclopropyl ring in the allylic side chain have been synthesized. The structures of these derivatives have been elucidated on the basis of IR, ^{1}H NMR, and mass-spectral data.

Introduction

Halogen derivatives of eugenol and isoeugenol have been reported in the literature (*1*, *2*). Earlier investigations on bromination indicated simultaneous substitution in the ring as well as in the allylic side chain (*1*).

We report here the synthesis of six new derivatives of eugenol and isoeugenol using halogen (Cl_2 or Br_2) and *N*-bromosuccinimide as halogenating reagents. A cyclopropane ring was introduced into the allylic side chain of eugenol by using the Simmons-Smith reaction (*3*, *4*). IR, NMR and mass-spectroscopic techniques were used to characterize these derivatives and elucidate their structures as shown in Figure 1.

Experimental Section

Melting points and boiling points are uncorrected. NMR spectra were recorded on a Varian T-60 spectrometer using Me_4Si as internal standard. Infrared spectra were run on a Perkin-Elmer Model 237B spectrometer. Mass spectra were recorded on an AEI mass spectrometer Model MS-30. Gas-chromatographic technique (GC) was used to monitor the reaction wherever possible. The yields in these reactions are based on isolated products.

Synthesis and Characterization of New Compounds

***2-Methoxy-4-(2,3-dichloropropyl)phenol* (*I*).** Dry chlorine gas was passed through a solution of 17 g (0.104 mol) of eugenol in 75 mL of carbon tetrachloride for 5 h at -5 to 2 °C. The solvent was removed under water suction. GC analysis of the reaction product indicated 65% of I. Fractional distillation under reduced pressure gave a forerun (4.4 g) at 73–75 °C (0.2 mm) consisting mainly of eugenol, and compound I (15.6 g, 64.6% yield) was collected at 133–135 °C (0.2 mm).

In the mass spectrum, the molecular ion peak appeared at *m/e* 234 (M^+) having a characteristic isotopic cluster for two chlorine atoms. Appearance of peaks at *m/e* 185 ($M^+ - CH_2Cl$) and 137 ($M^+ - CHClCH_2Cl$) indicated that two chlorine atoms have entered at the β and γ positions of the side chain and not in the phenyl nucleus. Absence of a C=C stretching band at 1640 cm^{-1} in the IR spectrum of I also showed that chlorine atoms were added at the β and γ positions of the side chain. ^{1}H NMR (CCl_4) δ 6.43–6.93 (m, 3 H, aryl), 5.6 (s, 1 H, OH), 3.8 (s, 3 H, OCH_3), 3.3–3.93 (m, 2 H, CH_2), 3.93–4.43 (m, 1 H, CHCl), and 2.82–3.33 (m, 2 H, CH_2Cl).

***2-Methoxy-4-(1-bromoprop-2-enyl)phenol* (*II*).** In a 250 mL round-bottomed flask fitted with a mechanical stirrer, a nitrogen inlet tube, a thermometer, and a reflux condenser with $CaCl_2$ guard tube, 33.8 g (0.206 mol) of eugenol, 24.1 g (0.12 mol) of *N*-bromosuccinimide (*5*) and 0.17 g of benzoyl peroxide in 130 mL of carbon tetrachloride were placed. The reaction mixture was refluxed for 6 h, and the precipitated succinimide was filtered and washed with carbon tetrachloride (2 × 15 mL). The filtrate, along with the washings, was washed with water (2 × 20 mL) and dried over anhydrous sodium sulfate. The residue after removal of the solvent was distilled under reduced pressure to give a forerun consisting mainly of eugenol. Compound II (24.1 g, 48.1% yield) was collected at 130–132 °C (0.3 mm).

In the mass spectrum the molecular ion peak appeared at *m/e* 242 (M^+), confirming an isotopic cluster for one bromine atom. The presence of a bromine atom at the α position to the phenyl nucleus was indicated by the peaks at *m/e* 215 ($M^+ - CH{=}CH_2$), 119/121 ($CHBrCH{=}CH_2$), and 163 (M^+ - Br). A band in the IR spectrum at 1185 cm^{-1} indicated allylic bromination (*6*), and the end methylene group was indicated by the appearance of characteristic bands at 2845 and 1423 cm^{-1} (*7*). Further, the characteristic C=C stretching (1642 cm^{-1}) and C-H out-of-plane bending vibrations (994 and 912 cm^{-1}) remained unchanged in the IR of the product. ^{1}H NMR (CCl_4) δ 6.40–6.77 (m, 3 H, aryl), 5.5 (br s, 1 H, OH), 3.71 (s, 3 H, OCH_3), 1.48 (d, 1 H, CHBr), 5.5–6.03 (m, 1 H, $C_\beta H{=}$), and 4.83–5.07 (br d, 2 H, $=CH_2$).

***2-Methoxy-4-(1-bromopropyl)phenol* (*III*).** Compound III was prepared by hydrogenation of 2-methoxy-4-(1-bromoprop-2-enyl)phenol in a Parr pressure reaction apparatus; 1 g (0.004 mol) of compound II, 20 mL of absolute ethanol, and 30 mg of palladized charcoal (10%) were taken in the hydrogenation flask. Hydrogenation was conducted at a hydrogen pressure of 20–25 psi for 5 h at room temperature. The catalyst was removed by filtration, and ethanol by distillation under reduced pressure. GC showed quantitative conversion to compound III.

In the mass spectrum the molecular ion peak appeared at *m/e* 244 (M^+) and also showed an isotopic cluster for one bromine atom. Important fragments supporting the structure are *m/e* 215 ($M^+ - CH_2CH_3$), 165 (M^+ - Br), and 121 ($M^+ - HCBrCH_2CH_3$). In the IR spectrum, the C=C stretching vibration at 1642 cm^{-1} was absent and the bromine atom at the benzylic position was indicated by the band at 1185 cm^{-1} (*6*). ^{1}H NMR (CCl_4) δ 6.45–6.77 (m, 3 H, aryl), 5.37 (br s, 1 H, OH), 3.73 (s, 3 H, OCH_3), 2.23–2.47 (t, 1 H, CHBr), 1.2–1.8 (m, 2 H, CH_2), and 0.7–0.93 (t, 3 H, $C_\gamma H_3$).

***2-Methoxy-4-(cyclopropylmethyl)phenyl acetate* (*IV*).** Compound IV was prepared by a carbene insertion reaction (*3*, *4*) to the olefinic double bond of eugenyl acetate using methylene iodide and a zinc–copper couple (Simmons-Smith reaction). Initially, eugenol was subjected to a methylene insertion reaction but the yields were not encouraging probably because of complex formation between phenolic hydroxyl and

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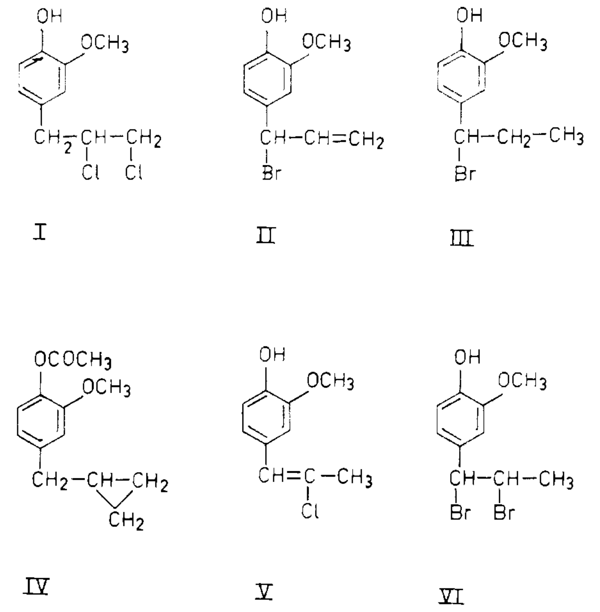

Figure 1. Derivatives of eugenol and isoeugenol.

reactant (*8*). Therefore, eugenyl acetate was used instead of eugenol. A mixture of 42% zinc-copper couple (*9*), 150 mL of absolute ether, and a few crystals of iodine were stirred until the brown color of iodine disappeared. To this was added a mixture of 26.6 g (0.13 mol) of eugenyl acetate and 39.6 g (0.15 mol) of methylene iodide. A mild exothermic reaction set in and continued for 30 min. Thereafter, the reaction mixture was refluxed gently at 37 °C. The reaction was monitored by GC. At the end of the reaction (40 h), the cold mixture was filtered and the filtrate was washed successively with 5% HCl, 5% $NaHCO_3$ solution, and water. The solution was dried over anhydrous $MgSO_4$. The residue obtained after removal of ether was distilled under reduced pressure. The product distilled at 100-102 °C (0.3 mm) gave 42% yield.

The mass spectrum exhibited significant peaks at *m/e* 220 (M^+), 178 ($M^+ - COCH_2$) and 137 (178 - c-Pr). The IR spectrum showed a characteristic band at 1010 cm^{-1} for the cyclopropyl ring (*7*). ^1H NMR (CCl_4) δ 6.23-6.76 (m, 3 H, aryl), 1.83 (s, 3 H, $COOCH_3$), 3.33 (s, 3 H, OCH_3), 2.07 (d, 2 H, $C_\alpha H_2$), 0.43-0.87 (m, 1 H, CH), 0.27-0.33 (br d, 4 H, CH_2CH_2).

***2-Methoxy-4-(2-chloroprop-1-enyl)phenol* (*V*).** Compound V was prepared by passing dry chlorine gas at the rate of 15-20 bubbles per minute through a solution of 73 g (0.45 mol) of isoeugenol in 175 mL of carbon tetrachloride for 10 h at -5 to 3 °C. The reaction mixture was washed with 10% $NaHCO_3$ (2 × 30 mL) and water (2 × 25 mL) and then dried over $MgSO_4$. Carbon tetrachloride was removed under water suction and the product (45 g) was distilled at 118-122 °C (0.4 mm). GC showed it to be a mixture of two compounds contributing 91% and 6% each along with 3% of the unreacted starting material. GC-MS study showed that the major compound has *m/e* 198 (M^+), which indicates that one hydrogen atom of isoeugenol has been substituted by chlorine. A minor compound gave a molecular ion peak at *m/e* 234 (M^+), indicating that two chlorine atoms have been added to the double bond. This compound could not, however, be isolated because of the low yield. *trans*-Isoeugenol has earlier been reported to undergo an addition reaction (*2*) with chlorine, but in the present case the reaction takes a different course leading to monosubstitution. To ascertain whether the chlorine atom has entered the side chain or the phenyl nucleus, we first dissolved compound V in 20% NaOH and then methylated it with dimethyl sulfate. The product was then subjected to potassium permagnate oxidation (*1*). Formation of veratric acid as the only product confirmed that the chlorine atom is in the side chain.

In the mass spectrum the molecular ion peak appeared at *m/e* 198 (M^+) showing one chlorine atom; other significant peaks were observed at *m/e* 183 ($M^+ - CH_3$), 167 ($M^+ - OCH_3$), and 136 ($M^+ - CClCH_3$). Appearance of a band at 1650 cm^{-1} in the IR spectrum showed the presence of a linear olefinic group (C=C) in the molecule. ^1H NMR (CCl_4) δ 6.27-7.17 (m, 3 H, aryl), 5.7 (s, 1 H, OH), 3.7 (d, 3 H, OCH_3), 6.15 (s, 1 H, $C_\alpha H$=), and 2.17 (s, 3 H, $C_\gamma H_3$).

***2-Methoxy-4-(1,2-dibromopropyl)phenol* (*VI*).** To a solution of 50 g (0.305 mol) of isoeugenol in 150 mL of carbon tetrachloride, a solution of 17 mL of bromine in 30 mL of carbon tetrachloride was added slowly under constant stirring for 3 h below 0 °C. The reaction was continued further for 2 h, and during this period a semisolid mass started appearing in the flask. The reaction mixture was allowed to stand for 12 h around 0 °C. The solid was filtered, washed with carbon tetrachloride (2 × 25 mL), and dried at room temperature. The compound melted at 91-93 °C and decomposed at 98 °C.

The molecular ion peak in the mass spectrum appeared at *m/e* 322 (M^+), having an isotopic cluster for two bromine atoms. Other significant peaks were observed at *m/e* 243 (M^+ - Br), 215 ($M^+ - CHBrCH_3$) and 199 ($CHBrCHBrCH_3$). The characteristic C=C stretching band at 1650 cm^{-1} was absent in the IR spectrum, indicating the addition of bromine across the double bond. ^1H NMR ($CDCl_3$) δ 6.66-7.03 (m, 3 H, aryl), 5.6 (br s, 1 H, OH), 3.93 (s, 3 H, OCH_3), 4.8-5.26 (m, 1 H, $C_\alpha HBr$), 4.3-4.8 (m, 1 H, $C_\beta HBr$), and 1.57-2.13 (dd, 3 H, $C_\gamma H_3$).

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