Dimethoxy Aromatic Compounds. VIII.[1] Degenerate Dealkylation–Realkylation Reaction of 1-Bis(2,4-dimethoxyphenyl)-2-methylpropane

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The condensation reaction under acid condition of the benzylic alcohols 1, 2 and 3 with the hexadeutero dimethoxybenzenes 4, 5 and 6 leads to the expected hexadeutero bis(dimethoxyphenyl)-2-methylpropanes 7, 8 and 9, respectively. However, the presence of both dodecadeutero and unlabelled 1-bis(2,4-dimethoxyphenyl)-2-methylpropanes 10 and 11 indicates that 9 undergoes a rapid degenerate dealkylation–alkylation reaction.

Keywords dimethoxyaromatic compound; 1,1-bis(2,4-dimethoxyphenyl)-2-methylpropane; ^{2}H-labeled compound; dealkylation reaction; Friedel–Crafts alkylation

Dimethoxy aromatic moieties occur frequently in compounds of biological importance. We have examined their spectroscopic[1–5] and chemical behavior.[5–9] In particular, the stereochemistry[10] as well as the bromination[7] and nitration[9] reactions under various experimental conditions of bis(dimethoxyphenyl)ethanes have been extensively studied. Extending our investigations to the study of the electron impact-induced fragmentations, we found an interesting rearrangement process[1] and, to elucidate the mechanism, we required several deuterium-labelled compounds bearing trideutero methoxy groups.

The condensation reaction under acid conditions of the benzylic alcohols **1**,[11] **2**[7] and **3** with the hexadeutero dimethoxybenzenes **4**,[12] **5**[12] and **6**,[12] respectively, seemed a suitable synthetic route (Chart 1).

Although the reaction of **1** with **4** or of **2** with **5** afforded the expected hexadeutero tetramethoxydiphenylethanes **7** and **8** respectively, the same reaction with **3** and **6** afforded a mixture of the hexadeutero derivative **9**, dodecadeutero derivative **10** and unlabelled derivative **11**. In fact, its ^{1}H-NMR spectrum at 60 MHz in $CDCl_3$ shows a ratio of the integrated areas of the isopropyl methyls and methoxy groups of about 3:1, which roughly indicates a composition of **9**:**10**=1:2.

The presence of the unlabelled compound **11** was revealed by the 75 eV electron-impact mass spectrum of the reaction product, which in the molecular ion region, as well as in the base peak region $[M-C_3H_7]^+$, shows a ratio of **11**:**9**:**10**=0.12:1:2.4.

This composition corresponds to the statistical combination (0.1:1:2.5) of labelled and unlabelled 1,3-dimethoxybenzene moieties in the reaction medium, when a ratio of **3**:**6**=1:5 was used, and equilibrium was reached within 30 min. In addition, the same equilibrium composition was obtained when the unlabelled compound **11** was treated with **6** in a ratio of **11**:**6**=1:10, whereas practically pure dodecadeutero compound **10** was obtained when **11** was treated with a large excess of **6** (**11**:**6**=1:60).

All these findings can be rationalized in terms of dealkylation of **9** by electrophilic attack of a proton on the strongly activated position 1 or 1′, followed by realkylation by the benzylic carbocation **12** on the 1,3-dimethoxybenzene labelled compound (**6**) or unlabelled

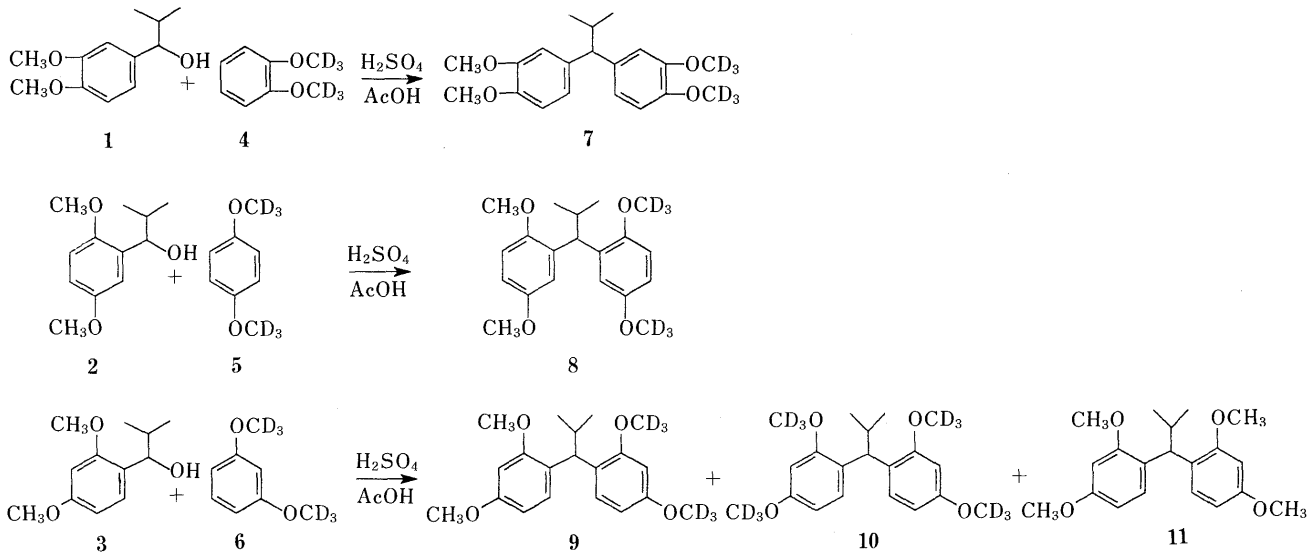
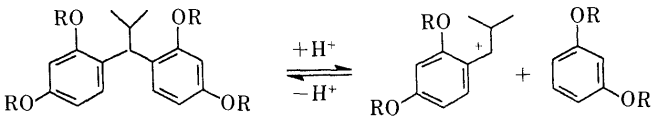


Chart 1



9–11 12 6, 13

R=CH_3 or CD_3

Chart 2

compound (**3**) (Chart 2).

Dealkylation processes of highly activated dimethoxy-aromatic substrates by electrophilic attack of a proton in bromination[7] or nitration[9] reactions have been reported. Under those conditions, however, bromine or nitronium ion constituted the main dealkylating agents.

In conclusion, the 2,4-dimethoxy derivatives undergo rapid dealkylation–alkylation reactions under the conditions normally used for the synthesis of these compounds. As the realkylation product is identical to the starting one, the occurrence of the equilibrium reaction shown in Chart 2 can be detected only by using labelled compounds.

^{13}C-NMR studies[9] have indicated a higher electron density on the C-1 carbon atom of the 2,4-dimethoxy compound **11** with respect to its 3,4- and 2,5-dimethoxy isomers, the chemical shift values being 126.16, 137.97 and 134.58 ppm, respectively. Hence, the occurrence of the degenerate dealkylation–realkylation reaction only for the 2,4-dimethoxy derivative is attributable to the fact that the 1-position is highly activated for electrophilic attack of a proton.

Experimental

Melting points were taken on a Kofler apparatus and are uncorrected. MS were run on a JEOL 01SG-2 instrument with an electron beam energy of 75 eV (ionizing current 100 mA) and accelerating voltage of 10 kV. ^{1}H-NMR spectra were recorded on a Varian EM-360A spectrometer using tetramethylsilane (TMS) as an internal standard and $CDCl_3$ as the solvent. The IR spectra (Nujol mull) were recorded on a Jasco 810 spectrometer.

1-(2,4-Dimethoxyphenyl)-2-methyl-1-propanol (3) This compound was obtained by Grignard reaction: 2,4-dimethoxybenzaldehyde (1.0 g) and isopropyl magnesium bromide (obtained from 1.0 g of magnesium and 4.2 g of isopropyl bromide) in anhydrous diethylether afforded **3** (1.1 g) as a colorless oil, bp 180 °C (6 mmHg). IR: 3470 cm^{-1} (OH). ^{1}H-NMR δ: 0.78 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 1.00 (3H, d, J=6.8 Hz, $CHC\underline{H}_3$), 1.90 (1H, oct., J=6.8 Hz, $C\underline{H}(CH_3)_2$), 2.48 (1H, s, exchangeable with D_2O, OH), 3.70 (6H, s, 2×OCH_3), 4.43 (1H, d, J=6.8 Hz, $C\underline{H}CH(CH_3)_2$), 6.35 (1H, d, J_m=2.5 Hz, 3-H), 6.38 (1H, dd, J_o=8.5, J_m=2.5 Hz, 5-H), 7.08 (1H, d, J_o=8.5 Hz, 6-H).

General Procedure of Condensation Reaction A solution of 0.0082 mol of the appropriate alcohol (**1**, **2** or **3**) was added dropwise to a stirred solution of 0.041 mol of dimethoxybenzene (**4**, **5** or **6**, respectively) in acetic acid (15 ml)/H_2SO_4 70% (10 ml) at between 6 and 10 °C. After standing for 24 h at room temperature, the mixture was poured onto crushed ice and extracted with $CHCl_3$. The solution was neutralized and concentrated under reduced pressure. The unreacted hexadeutero dimethoxybenzene was removed by steam distillation. Finally the residue was extracted with $CHCl_3$ and purified by flash column chromatography on silicagel using cyclohexane–ethyl acetate (9:1) as the eluent.

1-(3,4-Dimethoxyphenyl)-1-(3,4-[dimethoxy-$^2H_6$]phenyl)-2-methylpropane (7) White crystals from ethanol, mp 96 °C. ^{1}H-NMR δ: 0.88 (6H, d, J=6.8 Hz, $CH(C\underline{H}_3)_2$), 2.50 (1H, m, $C\underline{H}(CH_3)_2$), 3.30 (1H, d, J=11.0 Hz, $C\underline{H}CH(CH_3)_2$), 3.80 (3H, s, OCH_3), 3.82 (3H, s, OCH_3), 6.78 (6H, s, aromatic H). MS m/z: 336 (M^+).

1-(2,5-Dimethoxyphenyl)-1-(2,5-[dimethoxy-$^2H_6$]phenyl)-2-methylpropane (8) White crystals from ethanol, mp 83 °C. ^{1}H-NMR δ: 0.88 (6H, d, J=6.8 Hz, $CH(C\underline{H}_3)_2$), 2.50 (1H, m, $C\underline{H}(CH_3)_2$), 3.70 (6H, s, 2×OCH_3), 4.35 (1H, d, J=11.0 Hz, $C\underline{H}CH(CH_3)_2$), 6.63 (2H, d, J_m=2.5 Hz, 4, 4′-H), 6.66 (2H, s, 3, 3′-H), 6.93 (2H, d, J_m=2.5 Hz, 6, 6′-H). MS m/z: 336 (M^+).

Mixture of 9, 10, 11 White crystals from ethanol, mp 112 °C. ^{1}H-NMR δ(A=integrated areas): 0.88 (A=6, d, J=6.8 Hz, $CH(C\underline{H}_3)_2$), 2.50 (A=1, m, $C\underline{H}(CH_3)_2$), 3.70 (A=2, s, OCH_3), 4.30 (A=1, d, J=11.0 Hz, $C\underline{H}CH(CH_3)_2$), 6.40 (A=2, d, J_m=2.5 Hz, 3, 3′-H), 6.48 (A=2, dd, J_o=8.5, J_m=2.5 Hz, 5, 5′-H), 7.30 (A=2, d, J_o=8.5 Hz, 6,6′-H). MS m/z: 336 (M^+ **9**), 342 (M^+ **10**), 330 (M^+ **11**).

1,1-Bis(2,4-[dimethoxy-$^2H_6$]phenyl)-2-methylpropane (10) White crystals from ethanol, mp 112 °C. ^{1}H-NMR δ: 0.88 (6H, d, J=6.8 Hz, $CH(C\underline{H}_3)_2$), 2.50 (1H, m, $C\underline{H}(CH_3)_2$), 4.30 (1H, d, J=11.0 Hz, $C\underline{H}CH(CH_3)_2$), 6.40 (2H, d, J_m=2.5 Hz, 2×3-H), 6.48 (2H, dd, J_o=8.5, J_m=2.5 Hz, 2×5-H), 7.30 (2H, d, J_o=8.5 Hz, 2×6-H). MS m/z: 342 (M^+).

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