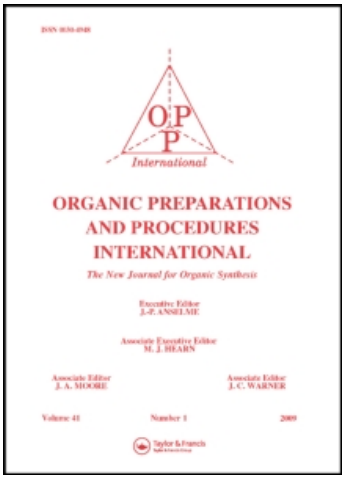

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A SYNTHESIS OF 2,3-DIMETHOXY-6-(3,4-DIMETHOXYPHENYLACETYL)TOLUENE

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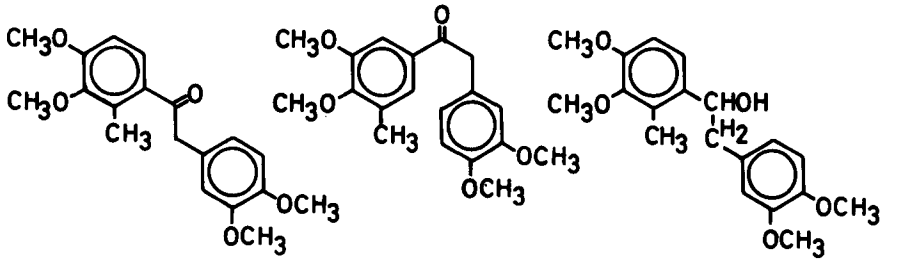
2,3-Dimethoxy-6-(3,4-dimethoxyphenylacetyl)toluene (I) might be an interesting starting material for the preparation[1] of, among others, substituted 1-benzyl-8-methylisoquinolines. For this purpose, we investigated reactions starting from 2,3-dimethoxytoluene and homoveratric acid (3,4-dimethoxyphenylacetic acid). Introduction of the 3,4-dimethoxyphenylacetyl group under Friedel-Crafts conditions did not appear attractive[1]. We found that the condensation of 3,4-dimethoxyphenylacetic acid with 2,3-dimethoxytoluene proceeds under mild conditions in polyphosphoric acid to give the desired product in good yield. 2,3-Dimethoxy-5-(3,4-dimethoxyphenylacetyl)toluene (II), was isolated in 5% yield from the mother liquor.



I II III

In analogous reactions it had been found that electrophilic substitutions of 2,3-dimethoxytoluene take place in positions 5 and 6. The fact

that position 6 is more activated than position 5 can be attributed to the inductive effect of the methyl group. Edwards et al.[2] suggest that the 3-methoxy group exerts a considerable directive effect while mesomerism of the 2-methoxy group is sterically hindered by the two ortho substituents. By chemical means it was shown that formylation[3], chloromethylation[4], chloroacetylation[4], bromination and other acylations[2] invariably take place predominantly in position 6.

In view of the above we assume that little, if any substitution occurs in position 4. The nmr spectra of the two isomers isolated confirm the structures. 2,3-Dimethoxy-6-(3,4-dimethoxyphenylacetyl)toluene (I) exhibited two doublets for the two aromatic protons (δ 7.47, 7.63 ppm and δ 6.70, 6.83 ppm; J = 8.5 Hz), while the isomer II showed a broadened singlet for two aromatic protons (δ 7.45 ppm). The three protons of the methyl group are found for the ortho substituted isomer (I) at a lower field (δ 2.39 ppm) than for the meta substituted isomer (II) (δ 2.28 ppm), which is to be expected on account of the deshielding effect of the carbonyl group.[5]

Compound I was easily reduced with lithium aluminium hydride to give 2-(3,4-dimethoxyphenyl)-1-(2,3-dimethoxy-6-tolyl)ethanol (III).

EXPERIMENTAL[6]

2,3-Dimethoxy-6-(3,4-dimethoxyphenylacetyl)toluene (I). - 3,4-Dimethoxyphenylacetic acid (19.6 g; 0.10 mole) and 2,3-dimethoxytoluene (Fluka; 45g; 0.30 mole) were well mixed with polyphosphoric acid (150 g) and heated at 45-50° during 2 hrs, with stirring. The warm reaction mixture was poured into a mixture of ice (100g) and chloroform (400 ml) to which water was added to dissolve all the solid material. After separation of the chloroform layer, the aqueous solution was extracted with two 100 ml portions of

chloroform. The combined chloroform layers were washed with 10 % NaOH (3 portions of 100 ml) and with water (2 portions of 50 ml), respectively, and dried over $MgSO_4$. The solvent and the excess of 2,3-dimethoxytoluene (25 g) were distilled in vacuo. The residue (30 g) was recrystallized once from 1:1 EtOH/pet ether (bp. 80-100°) and twice from 1:1 EtOH/water to give 20.0 g I (61 %), mp. 113-117°. An analytical sample mp. 115-117° was purified by recrystallization from 1:1 EtOH/water.

Anal. Calcd. for $C_{19}H_{22}O_5$: C, 69.1; H, 6.7. Found: C, 68.9, H, 6.7 %.
Mass spectrum m/e 330 (M^+), 179 (M−151), and 151 (M−179).

2,3-Dimethoxy-5-(3,4-dimethoxyphenylacetyl)toluene (II). - In one experiment, 250 mg of the isomer, 2,3-dimethoxy-5-(3,4-dimethoxyphenylacetyl)toluene (II), was isolated from the mother liquor. Nmr analyses showed the total amount of this isomer formed to be 1.5 g (5 %). The product was recrystallized from 1:2 EtOH/pet ether (bp. 80-100°) to give an analytical sample, mp. 119-120°.

Anal. Calcd. for $C_{19}H_{22}O_5$: C, 69.1; H, 6.7. Found: C, 69.0; H, 6.9 %.
Mass spectrum m/e 330 (M^+), 179 (M−151), and 151 (M−179).

2-(3,4-Dimethoxyphenyl)-1-(2,3-dimethoxy-6-tolyl)ethanol (III). - To a solution of 2,3-dimethoxy-6-(3,4-dimethoxyphenylacetyl)toluene (3.30 g; 10 mmoles) in THF (100 ml), lithium aluminium hydride (1.14 g; 30 mmoles) was added at 0°. After having been stirred at room temperature for 4 hrs, the reaction mixture was cooled to 0° and water was added. THF was removed by distillation in vacuo and the residue was extracted with two 50-ml portions of chloroform. After drying over $MgSO_4$, the solvent was removed in

vacuo to yield a colorless oil, which crystallized after treatment with a 1:3 mixture of EtOH and pet ether (bp. 40-60°). Recrystallization from this solvent mixture (1:3) gave 1.35 g III (41 %), mp. 85-86°.

Anal. Calcd. for $C_{19}H_{24}O_5$: C, 68.7; H, 7.3. Found: C, 68.7; H, 7.3 %.

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