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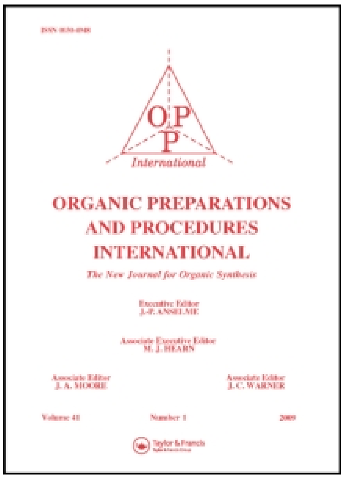

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AN IMPROVED PREPARATION OF 2,3,4-TRIMETHOXYBENZSUBER-6-ONE

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AN IMPROVED PREPARATION OF 2,3,4-TRIMETHOXYBENZSUBER-6-ONE

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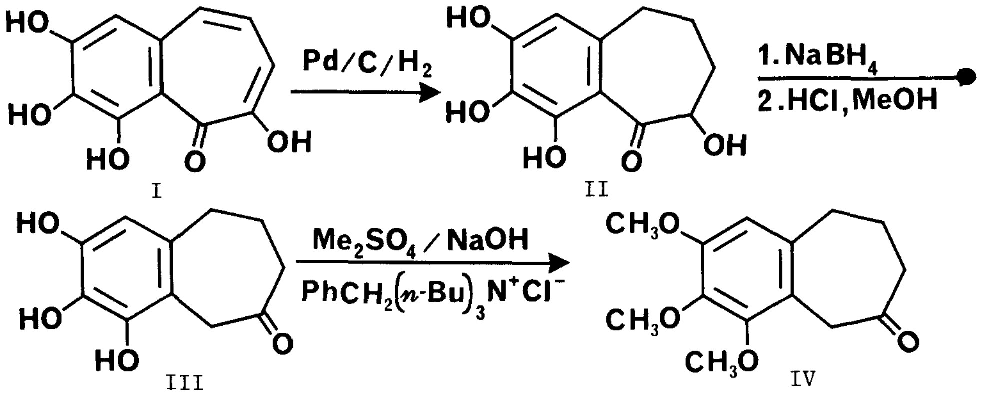
The literature reveals several preparations for the title benzsuberone derivative, 2,3,4-trimethoxybenzcyclohepten-6-one (IV) starting material, inter alia, in a total synthesis for colchicine.[1] The seven-membered ring of IV has been constructed from appropriately substituted benzene derivatives,[2,3] while other approaches involve functional group manipulation of purpurogallin I.[4-6] Generally, these multi-step routes are tedious and laborious and the reproducibility of some of the results has been questioned.[3,7] We now report a facile conversion of commercially available purpurogallin I into IV in preparative yield.



Treatment of tetrahydropurpurogallin II with aqueous sodium borohydride[8] and dehydration of the diol reduction product with methanolic hydrogen chloride afforded the phenolic benzsuberone III in good yield. This was converted in good yield into its trimethyl ether IV by treatment with dimethyl sulfate under phase transfer catalysis conditions.[9] The 2,3,4-trimethyl ether of purpurogallin I has been prepared using diazomethane.[10]

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Some workers (e.g., ref. 5) have experienced considerable difficulty and attained only low yields in conversion of tetrahydropurpurogallin II into its 2,3,4-trimethyl ether, using diazomethane. Attempted methylation of the phenolic groups of II with dimethyl sulfate-potassium hydroxide gave very poor yields of the trimethyl ether.[5]

EXPERIMENTAL

Melting points were determined in open glass capillaries and are uncorrected. NMR spectra were recorded on a Varian Associates T-60 instrument, using tetramethylsilane as the internal standard. IR spectra were recorded with a Beckman 4240 instrument. Mass spectra were obtained using a Finnigan 3200 instrument. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

Tetrahydropurpurogallin (II).- This was prepared in 70% yield by hydrogenation of purpurogallin I by the procedure of Walker.[5] An analytical sample was recrystallized from ethyl acetate, mp. 227-229° (dec.), lit.[5] mp. 230-232° (dec.). NMR (DMSO-d_6-D_2O): δ 1.2-2.3 (m, 4H, $C\underline{H}_2C\underline{H}_2CHOH$), 2.6-3.0 (m, 2H, $ArC\underline{H}_2$), 4.4-4.7 (m, 1H, $C\underline{H}OH$), 6.25 (s, 1H, $Ar\underline{H}$); IR (KBr) 3470, 3180 (OH), 1630 cm^{-1} (C=O); MS: m/e 206 ($M^+ - H_2O$).

2,3,4-Trihydroxybenzcyclohepten-6-one (III).- $NaBH_4$ (1.65 g, 43.6 mmol) in 65 mL of 0.2 N NaOH was added in one portion to 6.5 g (29 mmol) of II under N_2 and the reaction mixture was stirred at room temperature for 2 hr. Excess $NaBH_4$ was destroyed by dropwise addition of 50% H_2SO_4, and the reaction mixture was poured into 650 mL of acetone. The resulting mixture was filtered and the filtrate was taken to dryness under reduced pressure. The solid residue[11] was taken up in 130 mL of methanol saturated with anhydrous HCl, and this mixture was heated under reflux under N_2 for 3 hr. The solvents were evaporated under reduced pressure and the solid residue was purified by the fractional elution method:[12,13] the crude solid was loosely packed into a glass column, 15 cm x 0.7 cm, surrounded by a water-cooling jacket in which the circulating water was held at 20°. From a constant addition funnel, 95% ethanol was added dropwise to the top of the column

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at a rate slow enough that no liquid collected at the top. Approximately 1.5 hr after the first drop of dark liquid dripped from the bottom, the product in the column was light pink. It was recrystallized from ethyl acetate-petroleum ether (bp. 37-57°) to afford 4.35 g (73%) of III, mp. 190-191° (dec.). NMR (DMSO-d_6): δ 1.5-2.1 (m, 2H, $C\underline{H}_2$), 2.2-2.9 (m, 4H, $ArC\underline{H}_2CH_2C\underline{H}_2C{=}O$), 3.58 (s, 2H, $ArC\underline{H}_2C{=}O$), 6.1 (s, 1H, $Ar\underline{H}$), 8.3 (br s, 3H, $ArO\underline{H}$); IR (KBr): 3390, 3320 (OH), 1670 cm^{-1} (C=O); MS: m/e 208 (M^+).

Anal. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81.

Found: C, 63.12; H, 5.55

The semicarbazone of III was recrystallized from ethanol, mp. 209-210°.

Anal. Calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84.

Found: C, 54.48; H, 5.80; N, 15.77.

2,3,4-Trimethoxybenzcyclohepten-6-one (IV).- Compound III (1.5 g, 7.2 mmol) was stirred for 3 hr under N_2 at room temperature with 0.45 g (1.44 mmol) of benzyl tri-n-butylammonium chloride, 0.43 g (10.8 mmol) of NaOH, and 3.4 mL (36 mmol) of dimethyl sulfate in 25 mL of H_2O and 35 mL of methylene chloride. A solution of 1.3 g (32.5 mmol) of NaOH in 10 mL of H_2O was then added dropwise to the reaction mixture over 15 min, and stirring was continued for an additional 20 hr. The aqueous layer was separated and was extracted with three 50 mL portions of methylene chloride. The combined organic layer and extracts were evaporated under reduced pressure. The residue was taken up in 100 mL of ether and was washed successively with three portions of 15% NH_4OH, two 50 mL portions of 5% NaOH, and saturated NaCl solution, and dried ($MgSO_4$). Evaporation of the ether and distillation of the residue in a short path apparatus gave 1.3 g (72%) of an oil, bp. 137° (0.1 mm), lit[2] bp. 144° (0.4 mm). The product solidified on standing, and it was recrystallized from ether-petroleum ether (bp. 37-57°) to give an analytical sample, mp. 46-47°, lit[2] mp 46-46.5°. NMR ($CDCl_3$) δ 1.7-2.3 (m, 2H, $C\underline{H}_2$),

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2.4-3.1 (m, 4H, $ArC\underline{H}_2CH_2C\underline{H}_2C{=}O$), 3.75 (s, 2H, $ArC\underline{H}_2C{=}O$), 3.88 (s, 9H, $OC\underline{H}_3$), 6.5 (s, 1H, $Ar\underline{H}$); IR (KBr) 1700 cm^{-1} (C=O); MS: m/e 250 (M^+).

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