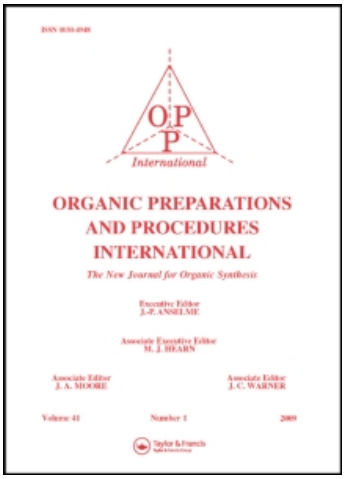

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SYNTHESIS OF POLYMETHOXY-1-TETRALONES[1]

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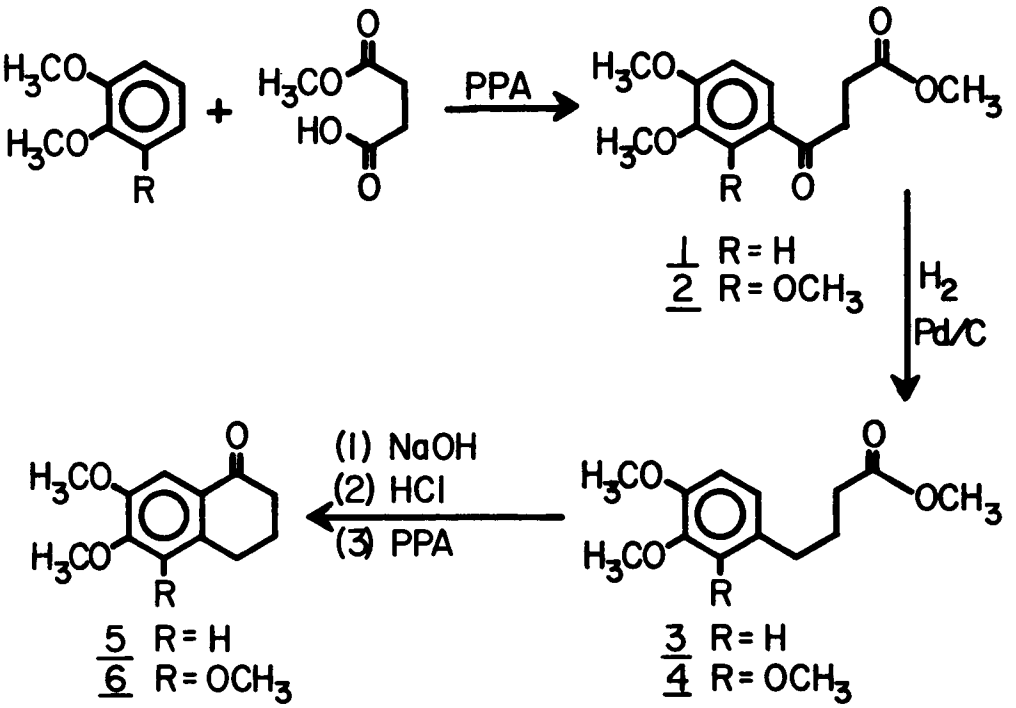
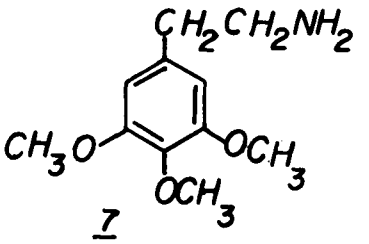
Due to symmetry, predicted solubility properties and similarity to biologically active compounds of natural and synthetic nature, tetralones with polymethoxy functionalities have been of interest to many medicinal chemists.[4] The possible significance of these functionalities in biological



activity is clearly illustrated via their incorporation in such compounds as mescaline (7), apomorphine (8), and many narcotics such as morphine and codeine.



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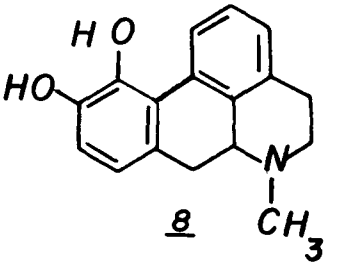

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Often utilized, but difficultly obtained starting substances for the laboratory preparation of many of these compounds, are the polymethoxy substituted tetralones. We have developed a simple, high-yield reaction sequence from readily available starting materials. Herein, is reported an investigation of the synthesis of 6,7-dimethoxy-3,4-dihydro-1[2*H*]-naphthalenone (5) and 5,6,7-trimethoxy-3,4-dihydro-1[2*H*]-naphthalenone (6).

While the classical methods of Haworth, i.e., Friedel-Crafts succinoylation and Clemmensen reduction followed by cyclization, have been applied successfully by many workers to the preparation of both 5[5,6] and 6,[7-9] these routes are fraught with difficulty. The overall yield of 5 and 6 (from the methoxybenzene) is low, 7-10% for 5[5,6] and 21-54% for the 5-hydroxy derivative of 6[7-9] which must then be methylated. Furthermore, isolation, purification and characterization of the intermediate chemicals are complicated because of many well recognized side reactions. For example methoxyl cleavage (usually at the ortho position,[7-12] but not exclusively,[13]) is a common problem of Friedel-Crafts reactions involving these types of compounds. A possible explanation of the specificity of this cleavage is proposed by Horton and Rossiter.[12] The use of 3-carbomethoxypropanoic acid[14] and PPA under succinoylation conditions[15] circumvents this problem

and provides the necessary intermediate (crystalline 1 or 2) in good yield with minimal experimental problems. Hence a mixture of methylated and partially methylated products is avoided. Also, the problem of remethylation, curiously difficult in this sytstem, does not arise.

Hydrogenolysis of aryl-substituted ketones over Pd/C is a well known and extremely efficient method for reduction to the corresponding hydrocarbons.[16-18] Yields of 3 and 4 are nearly quantitative via this technique and the vigorous conditions of the Clemmensen or Wolff-Kishner procedures are avoided.[17] Steric hindrance due to ortho substitution was not observed and does not seem to be a problem in this type of system.[4] Moreover, methoxyl cleavage was not detected making this a widely applicable general procedure.

The use of PPA as a cyclizing agent is well documented.[19,20] However, methoxyl cleavage has been reported in the type of derivatives herein discussed.[21] By utilizing lower reaction temperatures and longer reaction times, we have apparently minimized this problem.

Due to the efficiency of each step, the reaction sequence of reduction, saponification and cyclization to the final product may be carried out in an overall yield of 80-85% for 6 (based on 2) without the isolation and purification of any intermediates. This compares to a yield of 60-70% of demethylated 6 from the keto acid via the more classical methods of Haworth alluded to previously. The hydrogenolysis of ester 1 though much slower than that of 2 (2.5 hr as compared to 30 min) or even of the free acid, 4-(3,4-dimethoxyphenyl)-4-oxo-butanoic acid (20 min) was, nevertheless, nearly quantitative as was that of the corresponding acid. However, for efficiency is is recommended that 1 be saponified before reduction. The yield of 5 was 79% based on 1.

EXPERIMENTAL

Methyl 4-(3,4-dimethoxyphenyl)-4-oxo-butanoate (1).-

Method A.-1,2-Dimethoxybenzene (27.6 g, 0.2 mole) was stirred with 3-carbomethoxypropanoic acid[22] (40 g, 0.3 mole) in 220 g of 115% PPA at 45-50° for one hour and left overnight at room temperature. The dark brown reaction mixture was then poured onto 600 g of ice water. The yellowish product obtained solidified upon standing in ice water for several hours with occassional stirring. The crude product was filtered, washed with cold water followed by 5% $NaHCO_3$ and finally was air dried. The dry product was recrystallized from aqueous ethanol (1:1 vol.) to give pure (1); mp 94-95°, lit.[23] mp 95° (35.0 g, 64.5% yield); ir (KBr) μ: 5.88 (C=O); pmr ($DCCl_3$), δ 2.75 (t, 2, J_{HCCH} = 4 Hz, $CH_2\underline{CH}_2$), 3.30 (t, 2, J_{HCCH} = 4 Hz, $\underline{CH}_2CH_2$), 3.70 (s, 3, $CO_2\underline{CH}_3$) 3.91, 3.93 (s, 6, $Ar(O\underline{CH}_3)_2$), 6.90 (d, 1, J_{HCCH} = 5 Hz, Ar$\underline{H}$), and 7.60 (m, 2, J_{HCCH} = 2 Hz, Ar$\underline{H}$).

Method (B).-A solution of 13.8 g (0.1 mole) of 1,2-dimethoxybenzene and 31.0 g (0.2 mole) of 3-carbomethoxypropanoyl chloride[22] was added in portions with stirring to 230 g of 115% PPA pre-warmed to 40°. Stirring continued for 30 min and the reaction mixture was left for 2 hr until HCl ceased to evolve. It was then poured onto 400 g of ice water and worked up as in method (a) to give 19.9 g (79.6%) 1.

Methyl 4-(3,4-Dimethoxyphenyl)butanoate (3).-A solution of 10 g of 1 (0.038 mole) in 150 ml of glacial acetic acid was hydrogenated at about 60° with 2 g of 10% palladium on charcoal catalyst at 40 lbs pressure. The reaction mixture was cooled and filtered through a filter cake of filter aid; solvent was removed to give crude 3 (9.1 g, 96%) as a light yellow oil. An analytical sample was obtained by distillation; b.p. 152-153°/12μ; ir(film) μ: 5.86 (C=O); pmr ($DCCl_3$), δ 1.95 (quint., 2, J_{HCCH} = 4 Hz, $CH_2\underline{CH}_2CH_2$), 2.35 (t, 2, J_{HCCH} = 3.5 Hz, $CH_2CH_2\underline{CH}_2$), 2.61 (t, 2, J_{HCCH} = 3.5 Hz, $\underline{CH}_2CH_2CH_2$), 3.65 (s, 3, $CO_2\underline{CH}_3$), 3.85, 3.86 [s, 5, $Ar(O\underline{CH}_3)_2$], and 6.74 (m, 3, J_{HCCH} = 2 Hz, Ar$\underline{H}$).

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 65.54; H, 7.56.

Found: C, 65.36; H, 7.60.

6,7-Dimethoxy-3,4-dihydro-1[2*H*]-naphthalenone (5).-Ester 3 (23.8 g, 0.1 mole) was boiled with 250 ml of 10% KOH for 6 hr. The cold hydrolyzate was extracted with ether (2x100 ml). The aqueous layer was cooled in ice and acidified with dil HCl. Ether extraction (3x100 ml) gave a solution which evaporated to yield (13.7 g, 61%) 4-(3',4'-dimethoxyphenyl)butanoic acid, mp 60-61° (from hexane), lit. mp 61°; [24] ir (KBr) μ: 5.95 (C=O), 2.92 (OH); pmr ($DCCl_3$), δ 1.95 (q, 2, J_{HCCH} = 3.5 Hz, $CH_2CH_2\underline{CH}_2$), 3.81, 3.82 [s, 6, $Ar(O\underline{CH}_3)_2$], 6.75 (m, 3, J_{HCCH} = 2 Hz, Ar$\underline{H}$), and 8.55 (s, 1, $CO_2\underline{H}$).

To 4 g (0.018 mole) of 4-(3',4'-dimethoxyphenyl)butanoic acid was added 20 g of 115% PPA, and the mixture was stirred by a thermometer at 70-75° for 5 min. An additional 10 g of PPA were added and the mixture was stirred for another 5 min while warming at 70-75°. The dark brown viscous mixture was cooled, poured onto 250 ml of ice water and stirred to solidify. The product was filtered, washed with water and then with 5% $NaHCO_3$ and finally dried to give crude 5. Crystallization from n-heptane gave 3.65 g (83%) of 5, mp 99-100°, lit.[25] mp 99-100°; [26] ir (KBr) μ: 6.05 (C=O); pmr ($DCCl_3$) δ 2.15 (q, 2, J_{HCCH} = 4 Hz, $Ar\overset{O}{\overset{\|}{C}}CH_2\underline{CH}_2CH_2$) 2.55 (t, 2, J_{HCCH} = 4 Hz, $Ar\overset{O}{\overset{\|}{C}}CH_2CH_2\underline{CH}_2$), 2.90 (t, 2, J_{HCCH} = 4 Hz, $Ar\overset{O}{\overset{\|}{C}}\underline{CH}_2CH_2CH_2$) 3.90, 3.91 [s, 6, $Ar(O\underline{CH}_3)_2$], 6.65 (s, 1, Ar$\underline{H}$ at C-5), and 7.50 (s, 1, Ar$\underline{H}$ at C-8).

Methyl 4-(2',3',4'-Trimethoxyphenyl)-4-oxobutanoate (2).-In a modification of the procedure of Gardner,[15] 1,2,3-trimethoxybenzene (16.8 g, 0.1 mole) and 3-carbomethoxypropanoic acid (20 g, 0.15 mole) were stirred for 2.5 hr in 230 g of 115% PPA, the temperature being maintained at 45°. The mixture was then poured with stirring into 500 ml of ice and water. The granular product was removed by filtration, washed with H_2O and 5% $NaHCO_3$, and dissolved in 100 ml of diethyl ether. The ethereal solution of 2 was dried ($MgSO_4$) and then evaporated to an oil which crystallized upon

standing (25.2 g, 0.082 mole, 86% crude). Recrystallization from hot hexane gave pure 2, mp 48-49°, lit.[15] mp 48-49° (20.4 g, 0.072 ml, 72%); ir (KBr) μ: 5.77 (C=O), 6.02 (C=O); pmr ($DCCl_3$), δ 2.71 (t, 2, J_{HCCH} = 6 Hz, $C\underline{H}_2CH_2$), 3.69 (s, 3, $CO_2C\underline{H}_3$), 3.87, 3.90, and 3.99 (s, 9, $Ar(OC\underline{H}_3)_3$), 6.71 and 7.53 [d (AB pattern), 2, J_{HCCH} = 4.5 Hz, Ar$\underline{H}$].

Methyl 4-(2',3',4'-trimethoxyphenyl)butanoate (4).-A sample of 2 (9.5 g, 0.032 mole), glacial acetic acid (60 ml), and palladium on charcoal (10%, 4 g) were shaken under a H_2 atmosphere (30-40 psi) in a Parr hydrogenation apparatus. The reaction temperature was maintained at ca 60°. Hydrogen uptake ceased after ca 30 min (theoretical amount). The reaction mixture was cooled and filtered through a filter cake of filter aid. Solvent was removed to give crude 4 (8.6 g, quantitative) as a pale yellow oil. An analytical sample was obtained by distillation, bp 113-114/20-30 μ; ir(film) μ: 3.40 (C-H), 5.75 (C=O), 6.25 (Ar), 9.05 (OCH_3); pmr ($DCCl_3$), δ 1.85 (m, 3, $CH_2C\underline{H}_2CH_2$), 2.34 (t, 2, J_{HCCH} = 6 Hz, $C\underline{H}_2CH_2CH_2$), 2.60 (t, 2, J_{HCCH} = 7 Hz, $CH_2CH_2C\underline{H}_2$), 2.65 (s, 3, $CO_2C\underline{H}_3$), 3.81, 3.84 and 3.87 [s, 9, $Ar(OC\underline{H}_3)_3$], 6.59 and 6.81 [d (AB pattern), 2, J = 8 Hz, Ar$\underline{H}$].

Anal. Calcd. for $C_{14}H_{20}O_5$: C, 62.69; H, 7.46.
Found: C, 62.92; H, 7.57.

6,7,8-Trimethoxy-3,4-dihydro-1[2*H*]-naphthalenone (6).-Saponification of 4 (8.6 g, 0.032 mole) was achieved by boiling 4 in 100 ml of 5% NaOH for 5 hr. The cooled basic solution was extracted with ether (2x50 ml) and the extracts were discarded. The aqueous portion was acidified with HCl (6N) and extracted with ether (2x50 ml). The etheral extracts were dried ($MgSO_4$) and evaporated to give 4-(2',3',4'-trimethoxyphenyl)butanoic acid (8.0 g, quantitative) as a clear oil; ir(film) μ: 2.9 (OH), 5.85 (C=O), 9.06 (OCH_3), 6.25 (Ar); pmr ($DCCl_3$), δ 1.95 (m, 2, $CH_2C\underline{H}_2CH_2$),[27] 2.40 (t, 2, J_{HCCH} = 7 Hz, $C\underline{H}_2$-COH). 2.63 (t, 2, J_{HCCH} = 7 Hz, $ArC\underline{H}_2$) 3.82, 3.86, and 3.88 [s, 9, $ArOC\underline{H}_3$] 6.58 and 6.82 [d (AB pattern), 2, J_{HCCH} = 8 Hz, Ar$\underline{H}$], and 10.98

(s, 1, $CO_2\underline{H}$). The crude trimethoxyphenylbutanoic acid (8.0 g, 0.032 mole) without further purification was treated with 115% PPA (80 g) and the heated mixture was stirred for 45 min at 65-70°. The dark mixture was cooled to room temperature and poured into 200 ml of ice water (1:1). After the mixture was thoroughly hydrolyzed, the product was removed by filtration, washed (2% $NaHCO_3$) and dried to give crude 6. Sublimation (72-76°/0.0009mm) gave pure 6 (6.4 g, mp 74.5-76°, lit.[8] mp 74-74.5, 84%); ir (KBr) μ: 6.0 (C=O), 6.29 (Ar) 9.05 (OCH_3); pmr ($DCCl_3$) δ 2.07 (m, 2, $CH_2\underline{CH_2}CH_2$), 2.59 (t, 2, J_{HCCH} = 6.3 Hz, $\underline{CH_2}\overset{O}{\overset{\|}{C}}-$), 2.87 (t, 2, J_{HCCH} = 6 Hz, $Ar\underline{CH_2}$),[22] 3.85, 3.88, 3.93 [s, 9, $Ar(O\underline{CH_3})_3$], and 7.75 (s, 1, $Ar\underline{H}$).

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3. Predoctoral candidate 1972 - present.

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27. Assignment of methylene protons signals for 4, the crude substituted butanoic acid, and 6 are based, in part, on comparision with signals for similar protons in 3-phenylpropanoic acid (Sadtler Standard Spectra, spectra number 299 M).

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