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Synthesis of homogentisic acid by carbonylation

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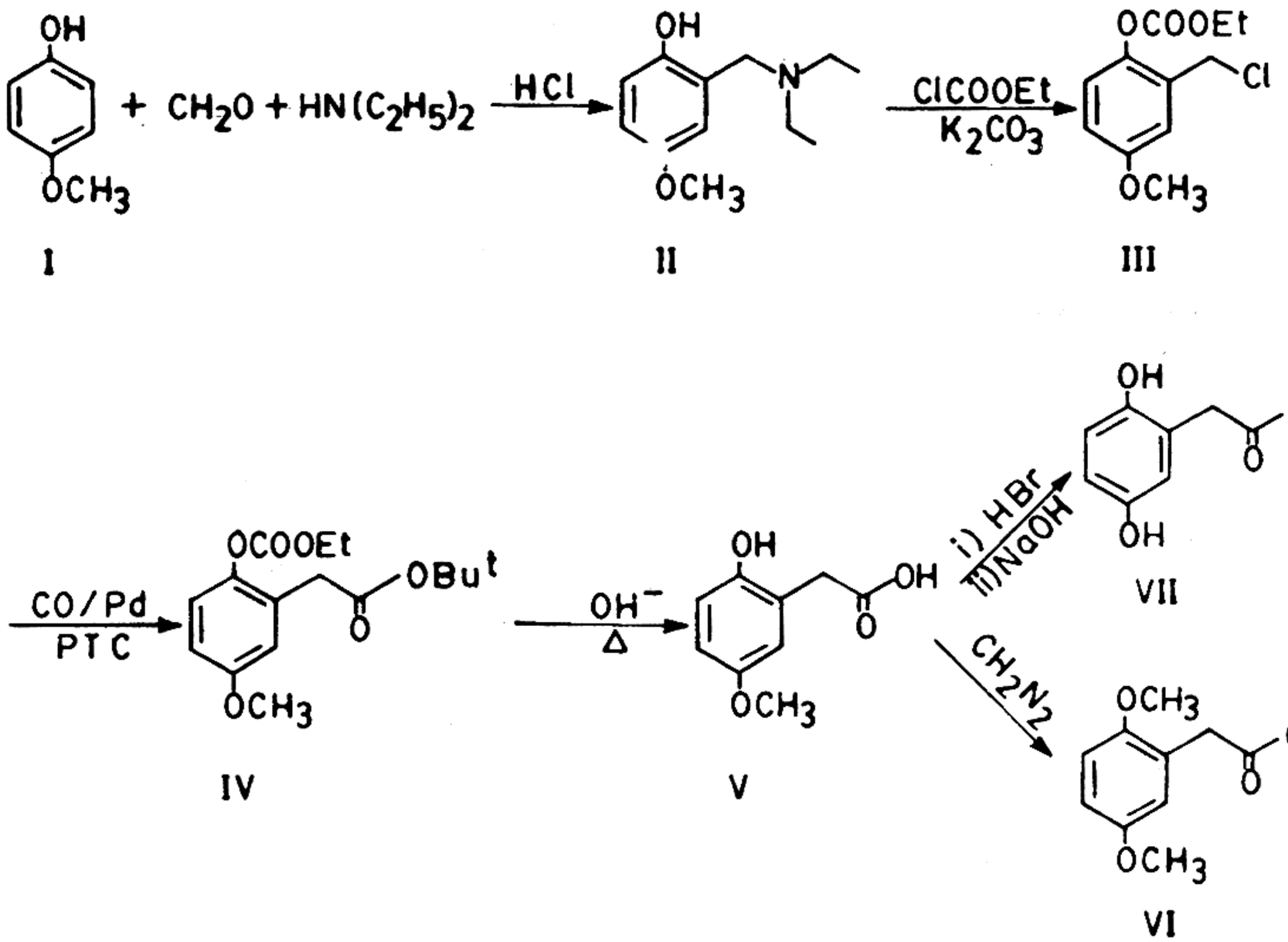
The synthesis of homogentisic acid by carbonylation of 2,5-dihydroxybenzyl chloride derivative followed by hydrolysis is discussed.

Homogentisic acid is an important intermediate in the overall catabolic process of phenylalanine and tyrosine[1], responsible for the formation of pigment melanin. Several reports, on the synthesis of homogentisic acid, have appeared by virtue of its biological importance. All involve a multistep sequence starting either from *p*-benzoquinone or its derivatives[2-4]. Its synthesis by carbonylation appears not to have been described so far. In this note we report its synthesis via the preparation of 2,5-dihydroxybenzyl chloride derivative from hydroquinone monomethyl ether followed by carbonylation and hydrolysis. A Mannich reaction using formaldehyde and diethyl amine on hydroquinone mono methyl ether (I) results in the formation of the derivative (II), which on treatment with cathyl chloride (ethyl chloroformate) leads to 2-O-carboethoxy-5-methoxybenzyl chloride (III) which on carbonylation under mild conditions using PTC-PdL_2Cl_2 as catalyst[5] forms the corresponding *t*-butyl phenyl acetate derivative (IV). IV on hydrolysis under reflux with NaOH results in the formation of 2-hydroxy-5-methoxyphenylacetic acid (V). Demethylation and methylation of V gives homogentisic acid (VII) and its methyl ester dimethyl ether (VI) respectively (Scheme 1).

Melting points and boiling points were determined on Mettler FP 51/5 (probe) Monitor and are uncorrected. IR spectra were recorded on Perkin-Elmer-283B spectrometer; ^1H NMR spectra on Varian FT-80A and Jeol FX 90QFT NMR spectrometers using TMS as internal reference. Liquid samples were purified by bulb to bulb distillation at reduced pressure. Satisfactory micro analysis was obtained, C $\pm$ 0.30; H $\pm$ 0.15.



Scheme 1

2-Hydroxy-5-methoxy-N,N-diethylbenzylamine (II)

To a mixture of *p*-methoxyphenol (32 g; 30 mmole) and diethyl amine (130 ml; 125 mmole) under nitrogen atmosphere at 70°C was added paraformaldehyde (6 g) while stirring and the mixture refluxed for 6 hr. The mixture was cooled to 50°C and diethyl amine removed on a rotary evaporator. The mixture was cooled to room temperature and 10% aq HCl added to make the solution acidic. The solution was extracted with ether to remove unreacted starting material. The aq HCl portion was basified with 10% liquor ammonia and extracted with dichloromethane. The combined dichloromethane phase was dried (K_2CO_3) and dichloromethane removed on a rotary evaporator. The resulting product was subjected to Kugel Rohr distillation to give 2,5-dihydroxyphenyl derivative (II), yield 52 g (85%); b.p. 90°C/5mm (Found: C, 68.7; H, 9.0. $C_{12}H_{19}O_2$ requires C, 68.9; H, 9.1%). MS: m/z (1%) 209 M^+ (31), 137 (29), 58 (100); IR (Neat): 2880, 2800, 1500, 1400, 1260, 1220, 1150, 1040 and 820 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.125 (t, 6H, 2N-CH_2-CH_3); 2.5 (q, 4H, 2 NCH_2-); 3.75 [s, 2H, Ar-CH_2-N $(C_2H_5)_2$]; 3.75 (s, 3H, $-OCH_3$); 6.5 (s, 1H, Ar-H at C_3); 6.69 (bs, 2H, Ar-H at C_5 and C_6).

2-Oxo-carboethoxy-5-methoxybenzyl chloride (III)

To a solution of benzylamine (II) (42 g, 20 mmole) in chloroform (50 ml) was added anhyd. potassium carbonate (12.5 g; 90 mmole) and treated slowly with ethyl chloroformate (20 ml, 19 mmole acid free) in 2 hr at 0°C while stirring. The mixture was stirred at 0°C for another 2 hr and diluted with $CHCl_3$/water (1:1, 100 ml). The combined organic phase was washed with 1% HCl (2 × 25 ml) followed by water (4 × 5 ml) and dried ($CaCl_2$). The solvent was evaporated and the residue purified by bulb to bulb distillation to give III, yield 39 g (80%), b.p. 85°C/2 mm (Found: C, 54.2; H, 5.2. $C_{11}H_{13}ClO_4$ requires C, 54.0; H, 5.3%), MS: m/z 244 M^+ (40), 246 (13), 136 (100); IR (Neat): 2950, 2910, 2820, 1770, 1610, 1510, 1500, 1470, 1370, 1250, 1200, 1040, 1000, 900 and 780 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.39 (t, 3H, $-CH_2CH_3$); 3.75 (s, 3H, $-OCH_3$); 4.26 (q, 2H, $-COOCH_2$-); 4.48 (s, 2H, Ar-CH_2Cl); 6.76 to 7.60 (m, 3H, Ar-H).

2-Oxo-carboethoxy-5-methoxy-t-butyl phenyl acetate (IV)

Compound IV was prepared by carbonylation of III (4.5 g, 20 mmole) by the literature method[5] and purified by bulb to bulb distillation IV; yield 2.5 g (40%); b.p. 78°/2 mm (Found: C, 65.4; H, 7.4. $C_{13}H_{18}O_4$ requires C, 65.5; H, 7.6%), MS: m/z (1%) 310 M^+ (5), 136 (100); IR (Neat): 2940, 1810, 1500, 1425, 1312, 1250 and 1035 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.40 (t, 3H, $-COO-CH_2CH_3$); 1.46 [s, 9H, $C(CH_3)_3$]; 3.57 (s, 2H, Ar-CH_2CO); 4.14 (s, 3H, OCH_3); 4.27 (q, 2H, $COOCH_2$); 6.80-7.20 (m, 3H, Ar-H).

2-Hydroxy-5-methoxyphenylacetic acid (V)

To a solution of compound IV (3.1 g, 10 mmole) in ethanol (30 ml), aq. sodium hydroxide (0.5 N, 30 ml) was added and the mixture refluxed for 6 hr. The mixture was cooled, diluted with water (60 ml) and extracted with ether (3 × 50 ml). The aq. portion was cooled, acidified with conc. HCl and extracted with ether (3 × 50 ml) and dried (Na_2SO_4). Evaporation of the solvent gave the crude product which was crystallised from petroleum ether (40-60°) gave pure V, yield 0.55 g (30%), m.p. 82° (Found: C, 59.0; H, 5.4. $C_9H_{10}O_4$ requires C, 59.3; H, 5.5%); MS: m/z (1%) 182 (24), 136 (100), IR(KBr): 3380, 1720, 1610, 1510, 1470, 1430, 1350, 1260, 1200, 1160, 1020 and 810 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.69 (s, 2H, Ar-CH_2); 3.79 (s, 3H, OCH_3); 6.63-6.79 (m, 2H, Ar-H C_3 & C_4); 7.25 (s, 1H, Ar-H, C_6).

Methyl ester dimethyl ether of homogentisic acid (VI)

To a solution of V (91 mg, .05 mmole) in ether, distilled diazomethane was added while stirring at 0-5°. The mixture was stirred for 2 hr at 0-5° and the solvent removed in rotary evaporator to give the crude ester which was purified by recrystallisation from pet. ether (40-60°) to give VI; yield 60 mg (60%), m.p. 43° (lit.[4] m.p. 45°C); MS: (70 eV) m/z (1%) 210 M^+ (14), 136 (100); IR (KBr): 2990, 2840, 1730, 1600, 1590, 1500, 1460, 1430, 1330, 1300, 1280, 1220, 1150, 1020, 800 and 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 3.6 (s, 2H, Ar-CH_2-COO); 3.70 (s, 3H, $-OCH_3$ at C_5); 3.75 (s, 3H, $-OCH_3$); 3.81 (s, 3H, $COOCH_3$); 6.81 (s, 3H, Ar-H).

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