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THE EVALUATION OF A BIOGENETICALLY BASED APPROACH TO THE SYNTHESIS OF OCTAHYDRO-1H-BENZOFURO[3,2-e]ISOQUINOLINES

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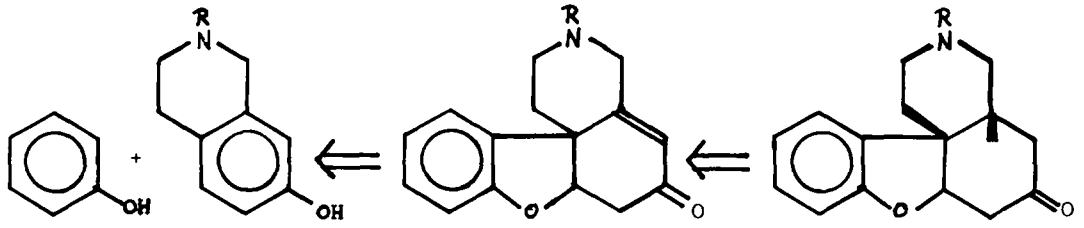
Abstract- A potential synthetic route to octahydro-1H-benzofuro [3,2-e]isoquinoline derivatives by intermolecular oxidative phenolic coupling has been studied. A variety of successful coupling reactions have been effected between 2-naphthol or 4-t-butylphenol and p-cresol, 2-(p-hydroxyphenyl)ethanol, 3,4-dimethylphenol, 5-indanol and 6-hydroxytetralin, but 2-acetyl-7-hydroxytetrahydroisoquinoline failed to participate in such reactions.

The synthesis of molecules possessing elements of the structure of morphine has been an important point of departure in the continuing search for improved analgesics[1]. A surprisingly late addition to the range of structural variants investigated were derivatives of octahydro-1H-benzofuro[3,2-e]isoquinoline which have been found to be potent analgesics[2]. Analogy with the established biosynthesis of morphine by intramolecular oxidative phenolic coupling of 1-benzyl-1,2,3,4-tetrahydroquinolines suggested the synthetic approach indicated in Scheme 1, in which the desired skeleton is assembled by the oxidative coupling of the phenolic units (1) and (2). Subsequent reduction of the double bond of (3) should then provide (4) with the trans fused piperidine ring as in morphine.

Despite occasional references in the literature to unsuccessful attempts[3] to effect the oxidative coupling of dissimilar phenols the only established examples at the inception of this investigation were provided by the minor products of the oxidation of p-cresol.[4a] Subsequently the successful coupling of p-cresol with 2,4-dimethylphenol and 2,4,6-trimethylphenol, and of 2-naphthol with 6-bromo-2-naphthol were reported[4b]. These oxidation reactions are believed to proceed by coupling of phenoxyl radicals formed by electron abstraction from the corresponding phenoxide anions[5]. In order for satisfactory cross-coupling to occur it is obviously essential that the phenoxyl radicals be generated at comparablerates from each of the substrates so that the phenols must have closely similar oxidation potentials.

+A preliminary report on part of this work has already appeared: C. W. Bird and Y.-P. S. Chauhan, Tetrahedron Letters, 1978, 24, 2133.

SCHEME 1



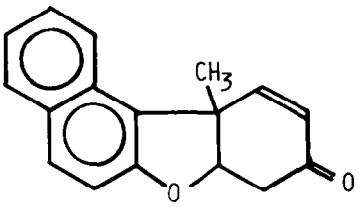
(1) (2) (3) (4)

As there is a quantitative relationship between the oxidation potential of phenols and their acidity[6] comparable concentrations of the anions of selected pairs of phenols should be present in solution. Since the required product of coupling in the present case results from ortho-para bonding it would be possible in principle to obtain two products of cross-coupling as well as the two products of co-coupling. This situation may be avoided by selecting as one of the substrates a phenol that is only capable of undergoing ortho coupling and employing it in substantial excess over its partner so as to minimise self-coupling by the latter. As the product of self-coupling of the excess phenol will be the diphenol resulting from ortho-ortho coupling separation from the neutral product of cross-coupling will be facilitated.

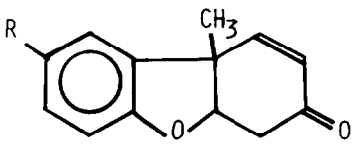
Initial experiments were conducted by oxidising p-cresol in the presence of a threefold molar excess of 2-naphthol with potassium ferricyanide in sodium carbonate solution, and yielded the desired product of crosscoupling (5). The structure of (5) was fully established by its spectroscopic properties. Apart from the anticipated carbonyl and olefinic stretching vibrations at 1670 and 1615 $cm.^{-1}$ in the infrared spectrum, the ^{1}H nmr spectrum showed a singlet at 1.88ppm. for the protons of the angular methyl group, two double doublets at 2.81(J=17.5, 3.9 Hz) and 3.08(J=17.5,3.2Hz)ppm. assigned to the C8 methylene protons and a multiplet at 4.72-4.88ppm. for the adjacent C7a methine proton. the C9 olefinic proton appeared as a doublet at 5.93(J=10.5Hz)ppm. and vicinal C11 proton as a double doublet at 6.87(J=10.3,2.0Hz) with the smaller coupling resulting from long range interaction with the C7a methine proton. The remaining aromatic protons appeared as a multiplet between 7.05 and 8.13ppm. Similar oxidation of a 1:1 molar ratio of p-cresol and 2-naphthol yielded an inseparable mixture of (5) and Pummerer's ketone (6). Silver carbonate on celite has been found to be a far superior reagent for the oxidative co-coupling of phenols[4b] but failed to effect the present cross-coupling reaction yielding only (6). This failure was tentatively attributed to differing ease of adsorption of the phenols on celite. However, although both phenols had similar mobilities on silica gel with acetonitrile as eluant, oxidation of a mixture of the phenols in acetonitrile with silver carbonate on silica gel gave solely Pummerer's ketone.

The coupling of p-cresol with phenols bearing bulky para substituents potentially capable of subsequent replacement was also examined. Oxidative coupling with 4-t-butylphenol gave (7), and with p-benzylphenol the ketone (8), but in much lower yields than obtained with 2-naphthol hence the latter phenol was used in much of the ensuing work. As a methoxyl substituent at position 9 of (4) was a desirable feature, *pace* morphine, attempts were made unsuccessfully to effect the coupling of p-cresol with 2-methoxy-4-cyanophenol. The latter compound is known to undergo self-coupling at C6[7] and was expected on the basis of structure-oxidation potential relationships to have a comparable oxidation potential to p-cresol. A possible reason for failure in this case may arise from a preponderance

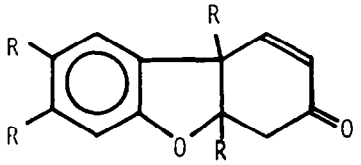
of electron density being associated with the cyano nitrogen rather than the ortho carbon-6.



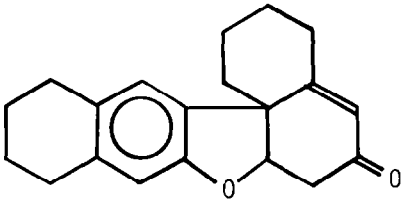
(5)



(6) R = CH_3
(7) R = t-C_4H_9
(8) R = $C_6H_5CH_2$



(9) RR = $(CH_2)_4$
(10) RR = $(CH_2)_3$



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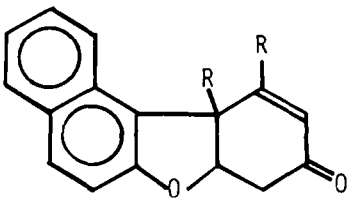
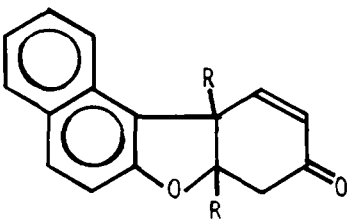


(12) RR = $(CH_2)_4$
(13) RR = $(CH_2)_3$
(14) R = CH_3



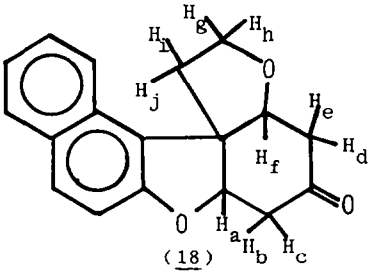
(15) RR = $(CH_2)_4$
(16) RR = $(CH_2)_3$
(17) R = CH_3

Attention was then turned to coupling reactions with 6-hydroxytetralin, a readily available surrogate for the projected 7-hydroxytetrahydroisoquinoline. Oxidative self-coupling of this phenol gave a mixture of ketones (9) and (11), with the latter predominating. The two isomers were readily differentiated by their ^1H nmr spectra. Ketone (9) exhibited doublets at 5.85 and 6.33(J=10Hz) for the olefinic protons, whereas (11) showed only a single olefinic proton at 5.85 (J=1.5Hz)ppm. in addition to a triplet at 4.57(J=4.6Hz)ppm. for the C-7a methine proton. The aromatic protons in both compounds gave rise to singlets, at 6.56 and 6.84ppm. for (9) and at 6.54 and 7.26 in the case of (11), confirming that coupling had occurred at C7 rather than C5 of the hydroxytetralin. In contrast co-oxidation of 6-hydroxytetralin with 2-naphthol yielded only a single product whose ^1H nmr spectrum with olefinic proton doublets at 5.99 and 6.88(J=10.1Hz)ppm. indicated it to have the structure (15) rather than (12). Inspection of molecular models indicates that the tetramethylene chain in (12) would be in close proximity to the peri hydrogen of the naphthalene ring, whereas no such repulsion is present in (15). At this point a satisfactory synthetic route to 2-acetyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline had been established[8] and its coupling with firstly 2-naphthol and then4-t-butylphenol attempted. In each case the only neutral product isolated under a variety of conditions was the dimer resulting

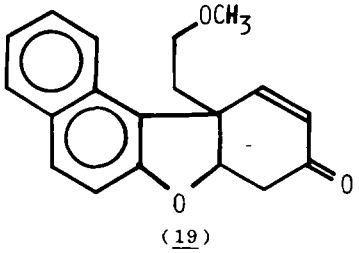
from self-coupling of the isoquinoline substrate. No obvious explanation for this failure to undergo oxidative co-coupling is apparent.

Two alternative strategies remained for achieving our objective. The first was to carry out coupling with an appropriately substituted 5-indanol and then convert the five-membered carbocyclic ring into a piperidine ring. However, it appeared highly likely that steric restraints would lead to the formation of (16) rather than (13) and experiment confirmed this conclusion. This result could not be merely attributed to the factor which led to the formation of (15) in preference to (12) as self-coupling of 5-indanol gave solely the ketone (10). The second strategy entailed closure of the piperidine ring subsequent to coupling.

Oxidative coupling of 2-(p-hydroxyphenyl)ethanol with 2-naphthol gave a good yield of a ketone to which the structure (18) was assigned. The infrared spectrum indicated the presence of an unconjugated carbonyl group (1720cm.$^{-1}$) and the absence of a hydroxyl group. Analysis of the ^{1}H nmr spectrum, aided by spin decoupling, fully suported the assignment. In particular H_d and H_e were observed as double doublets at 2.32(J=18.0,2.7Hz) and 2.72(J=17.9,3.5Hz)ppm. coupled to the methine proton H_f which with H_g and H_h formed a multiplet at 4.2-4.4ppm. Similarly the methine proton H_a appears as a double doublet at 4.88(J=2.8,2.0Hz) coupled to signals centered on 2.97ppm, but partially obscured by neighbouring ones, attributable to H_b and H_c. Attempts to open the tetrahydrofuran ring with iodotrimethylsilane or boron tribromide were unsatisfactory and prompted us to attempt coupling of 2-(hydroxyphenyl)ethyl iodide with 2-naphthol. However, only trace amounts of the desired ketone were formed, but a modest yield of (19) resulted



(18)



(19)

from coupling 2-(p-hydroxyphenyl)ethyl methyl ether with 2-naphthol. As Michael additions to (19) will occur from the less hindered direction namely cis to the methoxyethyl group which would eventually lead to a cis-fused rather than a trans-fused piperidine ring it will be necessary to incorporate an appropriately functionalised carbon into the original phenol. In view of the preferred formation of (15) in the cross-coupling of 6-hydroxytetralin, and a mixture of (9) and (11) in its self-coupling there appeared to be some doubt as to the likely course of couplings with 3,4-disubstituted phenols. These doubts were allayed when it was established that oxidative coupling of 3,4-dimethylphenol with 2-naphthol gave solely the ketone (14). Thus we now appear to have delineated a potential route to the octahydro-1H-benzofuro[3,2-e]isoquinoline ring system.

EXPERIMENTAL

All melting points are uncorrected. Infrared spectra were recorded for nujol mulls on a Pye-Unicam SP200 or Perkin-Elmer 157 spectrophotometer. Nmr spectra were recorded at 90 MHz on a Perkin-Elmer R90 spectrometer and at 200MHz on a Nicolet NT200 spectrometer for $CDCl_3$ solutions with internal TMS. Mass spectra were obtained by the ULIRS Mass Spectrometry Service at QEC (MS25).

Oxidative Coupling of Phenols with Potassium Ferricyanide

An aqueous solution(400ml) of potassium ferricyanide(98.7g,0.3mole) was added dropwise over 1 hour to a mechanically stirred solution of phenols(0.2mole) and sodium carbonate(0.4mole,42.4g) in water(2l) maintained at 0-10°. In some cases sufficient

ethanol was added to ensure a clear solution of the phenols at the start of the reaction. Stirring was continued for a further 3 hours and the sticky brownish yellow precipitate filtered off. It was diiolved in ether and washed with 5% aqueous sodium hydroxide solution and water. The dried (Na_2SO_4) ether extract was evaporated to give the crude ketonic product, which was dissolved in acetic acid (2ml/g) and ethanol(10ml/g) and heated under reflux for 1 hour with an equal weight of Girard reagent P. The cooled solution was diluted with aqueous sodium chloride solution and then extracted several times with ether to remove udesirable organic material. The aqueous layer was then treated with conc. hydrochloric acid (20ml) and heated briefly on the steambath to complete the hydrolysis of the Girard derivative. The cooled solution was then extracted with ether and the dried extracts(Na_2SO_4) evaporated to give the purified ketone(s). The results in individual cases were as follows:-

(a) 2-Naphthol(17.5g) and p-cresol(2.5g) yielded 7a.11a-dihydro-11a-methylbenzo[b] naphtho[1,2-d]furan-9(8H)-one (20%) mp.108-110°(Found:C,81.65;H,5.67.Calc. for $C_{17}H_{14}O_2$:C,81.59;H,5.63%); IR 1670,1615cm^{-1};Nmr 1.88(s,3H,CH_3),2.81(dd,1H,H-8a, J=17.2.3.9Hz),3.08(dd,1H,H-8b,J=3.2,17.5Hz),4.72-4.88(m,1H,H-7a),5.93(d,1H,H-10 J=10.5Hz),6.87(dd,1H,H-11,J=10.3,2.0Hz),7.05-8.13(m,6H,ArH)ppm.; MS m/e 250(59) 235(100),207(22),178(20),165(15),152(22).

(b) 4-t-Butylphenol(14.5g) and p-cresol(2.5g) gave 2-t-butyl-9a-methyl-5a,9a-dihydrodibenzofuran-7(6H)-one (10%) mp.137-139°(Found:C,79.61;H,7.85.Calc. for $C_{17}H_{20}O_2$:C,79.54;H,7.63%); IR 1655,1616cm^{-1};Nmr 1.64(s,3H,CH_3),2.05(s,9H,3xCH_3) 2.81-3.0(m,2H,H-6),4.61-4.75(m,1H,H-5a),5.94(d,1H,H-8,J=10.1Hz),6.48(dd,1H,H-9, J=10.1,2.0Hz),6.73(d,1H,H-4,J=9.2Hz),7.13(d,1H,H-1,J=2.0Hz),7.29(dd,1H,H-3,J= 9.0,2.0Hz)ppm.; MS m/e 256(36),241(100),214(8),199(5),177(7).

(c) 2-Naphthol(15.5g) and 3,4-dimethylphenol(2.5g) provided 7a,11a-dihydro-11,11a-dimethylbenzo[b]naphtho[1,2-d]furan-9(8H)-one (8%) mp.174-176°(Found:C81.80; H,6.35.Calc. for $C_{18}H_{16}O_2$:C,81.82;H,6.33%); IR 1660,1605cm^{-1};Nmr 1.81(s,6H,2x CH_3),2.41(dd,1H,H-8a,J=18.5,3.7Hz),3.03(dd,1H,H-8b,J=18.5,2.5Hz),4.62(m,1H,H-7a),5.83(d,1H,H-10,J=1.1Hz),7.03-8.01(m,6H,ArH);MS m/e 264(43),249(35),242(100) 195(52),152(35).

(d) 2-Naphthol(15.5g) and 5-indanol(2.5g) gave an inseparable mixture of the ketones (16) and (10). The mass spectrum of the mixture showed peaks at m/e 276,234 and 165 which could be assigned to (16) in addition to those characteristic of (10). Similarly the ^{1}H nmr spectrum contained signals unambiguously assignable to (16): 1.81-2.32(m,6H,3xCH_2),2.92(s,2H,CH_2),5.92(d, 1H,H-2,J=10.1Hz),6.98(d,1H,H-1,J=10.1Hz),7.03-7.95(m,6H,ArH).

(e) 2-Naphthol(15.5g) and 6-hydroxytetralin(2.5g) yielded 4a,11c-butanobenzo[b] naphtho[1,2-d]furan-3(4H)-one mp.128-130°(Found:C,82.75;H,6.21.Calc. for $C_{20}H_{18}O_2$:C,82.75;H,6.21%);IR 1665,1610cm^{-1};Nmr 1.45-1.81(m,8H,4xCH_2),2.84(s,2H, CH_2),5.99(d,1H,H-2,J=10.1Hz),6.88(d,1H,H-1,J=10.1Hz),7.01-8.10(m,6H,ArH); MS m/e 290(100),248(42),234(22),205(30),194(35),165(32),152(18).

(f) 2-Naphthol(15g) and 2-(p-hydroxyphenyl)ethanol(2.5g) provided 1,2,3a,4,5,6,6a, 13c-octahydrobenzofurano[4,3a-b]naphtho[1,2-d]furan-5-one(15%) mp.157-159° (Found:C,77.15;H,5.75.Calc. for $C_{18}H_{16}O_3$:C,77.23;H,5.73%);IR 1720cm^{-1};Nmr 2.12(dt,1H,H_i,J=14.0,9.0,9.0Hz),2.32(dd,1H,H_d,J=18,2.7Hz),2.72(dd,1H,H_e,J=17.9, 3.3Hz),2.97(dd,2H,H_b and H_c,J=3.1,1.3Hz remainder of signals obscured),3.39(ddd 1H,H_j,J=14,7.9,3.5Hz),4.2-4.4(m,3H,H_f+H_g+H_h),4.88(dd,1H,H_a,J=2.0,2.8Hz),7.10-7.88(m,6H,ArH);MS m/e 280(100),252(20),238(10),223(8),219(20),195(33),182(60), 165(40).

(g) 2-Naphthol and 2-(p-hydroxyphenyl)ethyl methyl ether(2.5g) yielded 7a,11a-dihydro-11a-(2'-methoxyethyl)benzo[b]naphtho[1,2-d]furan-9(8H)-one(5%) as an oil (Found:C,77.60;H,6.13.Calc. for $C_{19}H_{18}O_3$:C,77.55;H,6.12%); IR 1670,1610cm^{-1} Nmr 2.54(t,2H,CH_2,J=6.4Hz),2.87(dd,2H,H-8,J=3.4,4.1Hz),3.22(s,3H,CH_3),3.56(t, 2H,CH_2,J=6.4Hz),5.15(m,1H,H-7a),5.92(d,1H,H-10,J=10.3Hz),6.89(d,1H,H-11,J=10.3 Hz),7.14-7.98(m,6H,ArH).

(h) 6-Hydroxytetralin gave a mixture of ketones (9) and (11) with R_f's of 0.6 and 0.53 respectively on silica gel in chloroform, which were separated by fractional crystalisation from methanol. The less soluble compound was 7,8,9,10-tetrahydro-4a,11b-butanobenzo[b]naphtho[2,3-d]furan-3(4H)-one (2%) mp.149-151°(Found:C,81.63;H,7.58.Calc. for $C_{20}H_{22}O_2$;C,81.63;H,7.48%);IR 1670, 1620cm^{-1}; Nmr 1.43-1.87(m,12H,6xCH_2),2.35-2.78(m,4H,2xCH_2),2.80(s,2H,H-4), 5.85(d,1H,H-2,J=9.9Hz),6.33(d,1H,H-1,J=10.1Hz),6.50(s,1H,H-11),6.84(s,1H,H-6); MS m/e 294(100),266(20),252(20),238(13),237(15),148(10),92(30),77(20).
The more soluble product(8%) was 1,2,3,4,7,7a,10,11,12,13-decahydro-6H-dinaphtho[1,2-b:2',3'-d]furan-6-one mp.157-159°(Found:C,81.59;H,7.49%); IR 1675,1630cm^{-1}; Nmr 1.51-2.03(m,10H,5xCH_2),2.37-2.84(m,8H,4xCH_2),4.57(t,1H,H-7a, J=4.6Hz),5.86(d,1H,H-5,J=1.5Hz),6.54(s,1H,H-14),7.26(s,1H,H-9); MS m/e 294(100) 281(21),266(16),252(55),238(20),237(32),224(10).

(i) 5-Indanol formed 4a,10b-propanobenzo[b]indanolo[5,6-d]furan-3(4H)-one (20%) mp. 80-83°(Found:C,81.16;H,6.78.Calc. for $C_{18}H_{18}O_2$:C,81.20;H,6.76%); IR 1695, 1620cm^{-1};Nmr 1.56-2.38(m,6H,3xCH_2),2.72(s,2H,CH_2),2.83-2.94(m,6H,3xCH_2),5.93 (d,1H,H-2,J=10.1Hz),6.63(s,1H,H-10),6.98(d,1H,H-1,J=10.1Hz),7.0(s,1H,H-6); MS m/e 266(63),238(12),224(100),209(12),165(15),133(20).

Preparation of 2-(p-hydroxyphenyl)ethyl methyl ether

Finely powdered potassium hydroxide(15.2g) wasadded to a solution of benzyl chloride (22.5ml) and 2-(p-hydroxyphenyl)ethanol (24.7g) in ethanol(300ml),and the mixture

refluxed and stirred for 9 hours. The precipitated potassium chloride was filtered off and the ethanolic solution evaporated in vacuo. The residue was taken up in chloroform and washed with potassium hydroxide solution and water prior to drying (Na_2SO_4) and evaporation. The 2-(p-benzyloxyphenyl)ethanol had mp.68-70° from ethyl acetate (Found:C,78.98;H,7.04.Calc. for $C_{15}H_{16}O_2$:C,78.93;H,7.08%); IR 3300cm^{-1} Nmr 1.55(br.s,1H,OH),2.78(t,2H,CH_2,J=6.4Hz),3.79(t,2H,CH_2,J=6.5Hz),5.03(s,2H,OCH_2-Ph),6.89(d,2H,ArH,J=9.0Hz),7.15(d,2H,ArH,J=9.0Hz),7.37(s,5H,C_6H_5)ppm.

A solution of 2-(benzyloxyphenyl)ethanol (18.3g) in tetrahydrofuran (50ml)was added dropwise to a suspension of sodium hydride (6.0g) in tetrahydrofuran and the mixture subsequently refluxed for 30 minutes. Then methyl iodide (18ml) was added slowly and the reaction mixture heated under reflux for a further 6 hours.Water was then added cautiously to the cooled mixture to destroy any unreacted sodium hydride. The 2-(p-benzyloxyphenyl)ethyl methyl ether was isolated by ether extraction and crystallised from ethanol,mp. 58-60°(Found:C,79.43;H,7.48.Calc. for $C_{16}H_{18}O_2$:C,79.34;H,7.44%);Nmr 2.82(t,2H,CH_2,J=6.8Hz),3.35(s,3H,OCH_3),3.56(t,2H,CH_2 J=6.5Hz),5.03(s,2H,OCH_2Ph),6.87(d,2H,ArH,J=8.8Hz),7.15(d,2H,ArH,J=8.8Hz),7.37(s, 5H,C_6H_5).

This material (15g) was dissolved in ethanol(200ml) and shaken with hydrogen at 60 p.s.i. and room temperature for 24 hours in the presence of 10%palladium on charcoal catalyst (0.5g). Evaporation of the filtered solution gave 2-(p-hydroxy-phenyl)ethyl methyl ether as an oil which could be crystallised from ethyl acetate mp. 27-29°(Found:C,71.18;H,7.83.Calc. for $C_9H_{12}O_2$:C,71.15;H,7.89%);IR 3350cm^{-1}; Nmr 2.82(t,2H,CH_2,J=7.0Hz),3.45(s,3H,OCH_3),3.50(t,2H,CH_2,J=7.0Hz),5.35(br.s,1H,OH), 6.65(d,2H,ArH,J=9.0Hz),7.05(d,2H,ArH,J=9.0Hz)ppm.

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