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The Synthesis and Assay of Radiolabelled Benzene Derivatives

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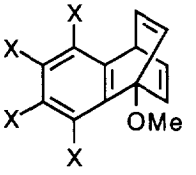
Abstract: *Several new syntheses of 1- and 4-[^{14}C]anisole have been investigated and routes from [^{14}C]cyanide and from 2-[^{14}C]acetone are described which are better than those previously reported. The key step in one of the syntheses was catalytic dehydrogenation of 1-[^{14}C]cyclohexanone to 1-[^{14}C]phenol. Degradation of 5,6,7,8-tetrachloro-3,4-dihydro-1,4-etheno-[^{14}C]naphthalen-2(1H)-one (**10**) prepared from [^{14}C]anisole and tetrachlorobenzyne has shown that the key step had proceeded without scrambling of the label.*

Introduction

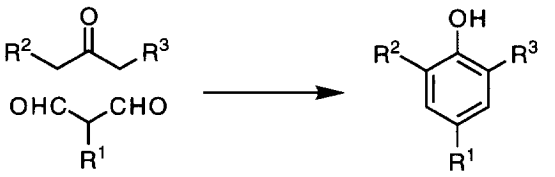
We have previously discussed our need to prepare specifically radiolabelled derivatives of 1-methoxybenzobarrelene (**1**) (1,4-dihydro-1-methoxy-1,4-ethenonaphthalene) and its tetrachloro- (**2**) and tetrafluoro- (**3**) derivatives.[1] As there is little practical alternative to preparing these compounds *via* the cycloadditions of tetrahalogenobenzyne to the appropriate arenes,[2] the problem reduced in this case to the preparation of 1- and 4-[^{14}C]anisole. It was important that we should know either by unambiguous synthesis or by degradation just how specifically the label had been located.



(**1**) X = H
(**2**) X = Cl
(**3**) X = F

There are several published syntheses of anisole or phenol labelled *ipso*[3-5] or *para*[4c] with heavy isotopes of carbon. Two distinct approaches to the construction of such specifically labelled aromatic compounds may be discerned. One method involves the condensation of two three-carbon fragments to produce the aromatic ring in one step[4,6] (***Equation*** [1]). The instability and inaccessibility of most malondialdehyde derivatives and the need for this component to act as an electrophile have restricted the choice of one component to sodium nitromalondialdehyde. This component is not easily labelled and it is the other component which is used to introduce the heavy isotope. In practice the choice of this second component is usually restricted to acetone, labelled forms of which are readily available. The key intermediate in syntheses by this route is 4-nitrophenol.

We have now developed this method into both the most convenient synthesis of 1-[^{14}C]anisole currently available[7] and a modified synthesis of 4-[^{14}C]anisole that we have found to be shorter and more convenient than the previously published method.



[1]

The second method[3,5a-i] has two major variants differing in the nature of the first cyclic product. In one variant cyclohexanone may be formed either from labelled carbon dioxide and the bis-Grignard reagent from 1,5-dibromopentane or by pyrolysis of the barium salt of pimelic acid, itself derived from labelled cyanide and 1,5-dibromopentane. In the other variant the first cyclic product is 1-methylcyclohexene, formed from labelled acetate and the bis-Grignard reagent from 1,5-dibromopentane. In both variants the ring is synthesised from a one- and a five-carbon fragment that could be modified before ring formation to introduce a predeterminned substitution pattern. The key intermediate in these syntheses is 1-methylcyclohexene, the compound at which these variants all converge.

There are several points to note. Firstly, one may choose to enter the synthetic scheme at any of several positions, even as late as 1-[^{14}C]phenol which is now commercially available, and the overall yield will vary accordingly. Secondly, the loss of half of the label as carbon dioxide in the pyrolysis of the barium salt of pimelic acid or the low yield observed in the reaction between carbon dioxide and the bis-Grignard reagent from 1,5-dibromopentane give syntheses through cyclohexanone a poor start. Thirdly, cyclohexanone and phenol differ only in their levels of oxidation but in spite of this structural closeness they are, in most published schemes, synthetically remote. Fourthly, the use of a methyl group to protect the positional integrity of the the label during the aromatisation step generates a large number of additional steps devoted to introducing and removing this group. Low radiochemical yields have no doubt discouraged syntheses using cyclohexanone; perversely enough, most syntheses by this route then proceed on to 1-methylcyclohexene and so on. Attempts to oxidise cyclohexanone to phenol are rare but the conversions of 3,5-dimethyl-1-[^{14}C]cyclohexanone[5a] and 1-[^{13}C]cyclohexanone[3b] into the corresponding phenols by catalytic dehydrogenation have been reported, suggesting that synthesis through cyclohexanone could be considerably improved. This suggestion has been confirmed and we have developed a one-step conversion of cyclohexanone to phenol and a different two-step conversion of cyclohexanone to anisole as alternatives to the earlier five- and six-step conversions.[7]

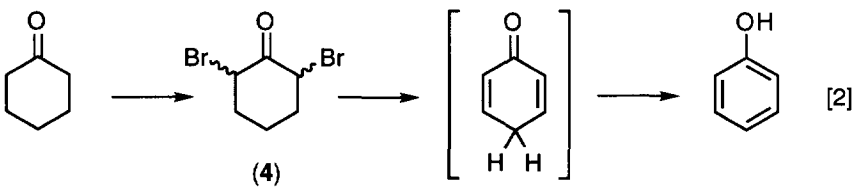
Results and Discussion

There are three distinct objectives on the synthetic pathway to isotopically labelled phenol and anisole. The label must be introduced, the ring system and substitution pattern must be constructed, and the oxidation level must be adjusted. Of these only the last may be performed before the label is introduced but it might be possible to construct the ring and introduce the label in one step. All other reactions must be regarded as potentially superfluous even if possibly justified either by an improvement in yield relative to more direct syntheses or by the very probably temporary absence of reactions suitable for shorter syntheses. The reactions

chosen must be such that the positional integrity of the label is established and maintained. The choice of syntheses with isotopically enriched reagents is as much directed by the availability of reagents as by the desire to conserve the enriched isotope. In our case the initially available source of ^{14}C was sodium [^{14}C]cyanide suggesting that the successful synthesis would proceed through pimelonitrile, cyclohexanone and phenol. Sodium cyanide was converted to pimelonitrile, pimelic acid, and cyclohexanone. Dehydration and decarboxylation of pimelic acid by acetic anhydride during distillation have been reported[8] but appear to offer no advantage. In an attempt to to form the ring system in higher yield pimelonitrile was subjected to Thorpe-Ziegler cyclisation.[9] The product was obtained in near quantitative yield, but the i.r. spectrum differed from that previously reported: the bands previously observed at 2219, 3419, and 3509 cm^{-1} were observed at 2180, 3360, and 3450 cm^{-1}. The concordance of melting points,[9b] and other i.r. bands (previously 1616 and 1647 cm^{-1} now 1610 and 1647 cm^{-1} and the mass and ^1H nmr spectra leave little doubt that the structure of the product is correctly assigned. Attempts to hydrolyse the product to cyclohexanone were unsuccessful; the reasons for this are not clear but previous attempts have also failed[9c] to produce useful yields and the synthesis of cyclohexanone by cyclisation of pimelonitrile was abandoned.

One other synthesis of cyclohexanone that is based on cyanide commends itself: the formation of ketones by rearrangement under the influence of electrophiles of trialkylcyanoborates has been reported in full detail.[10] The method should become that of choice for the preparation of 1-[^{14}C]cyclohexanone and many of its derivatives but we did not have the foresight to develop the method in advance of its discoverers.

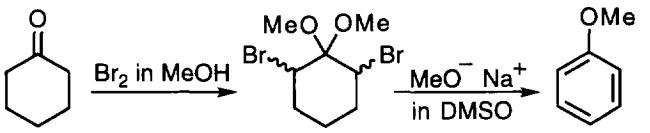
The conversion of cyclohexanone to phenol was considered next. The sequence dibromination-bisdehydro-bromination - spontaneous aromatisation seemed attractive (Equation [2]). Bromination of cyclohexanone with pyridinium tribromide[11] in acetic acid gave a lachrymatory oil in 86% yield, characterised by i.r. spectroscopy as a mixture (**4**) of *cis*- and *trans*-2,6-dibromocyclohexanone. Bromine itself was a less satisfactory reagent for this bromination.[12] Attempts to dehydrobrominate the mixture of dibromides under a variety of conditions[13] gave disappointing yields of phenol (estimated as benzoate). We considered that a good deal of the difficulty that we found with this step could be attributed to the other base catalysed reactions of α-bromoketones[14] so this approach was modified.



(**4**) [2]

Bromination of cyclohexanones in methanol or ethylene glycol has been reported to give α-bromoacetals.[15] Use of two equivalents of bromine results in α,α'-dibromoacetal formation. When cyclohexanone in methanol was treated with two equivalents of bromine a mixture of *cis*- and *trans*-2,6-dibromo-1,1-dimethoxycyclohexane (**5**) was obtained in 86% yield. This product was aromatised with sodium methoxide or sodium *t*-butoxide in dimethylsulphoxide to give anisole in overall yields from cyclohexanone of 27 and 52% respectively (Equation [3]). This constitutes a two-step conversion of cyclohexanone into anisole that would be a satisfactory solution to part of our requirements. It is interesting to note that although phenol is

not an intermediate in this reaction it is nonetheless a potentially very versatile route to aryl alkyl ethers. A route passing through phenol would be even more attractive.

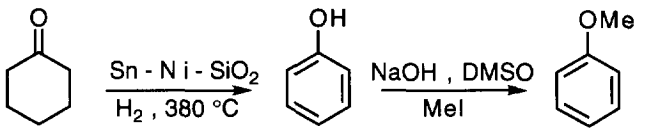


[3]

(5)

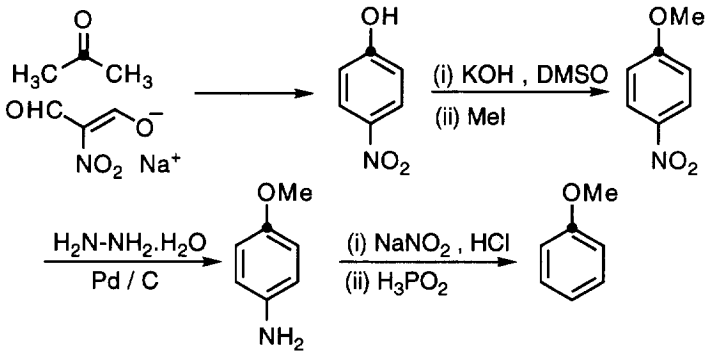
The catalytic dehydrogenation of cyclohexanone to phenol has been reported[3b,5a,16a-e]. The yields and conversions quoted are excellent, but the conditions are more suited to a continuous flow process than to batch production. The method of Swift[16a] was investigated. Passage of cyclohexanone vapour in a hydrogen carrier-gas over a tin-nickel catalyst, supported on silica-gel, and heated to 380° at such a rate that the catalyst temperature was maintained gave a 60% yield of phenol, estimated as the benzoate. This yield is not as good as those reported by Swift but compares favourably with other methods.[16b-e]

The problems of conducting successful batch flow-dehydrogenations without specialised equipment should not be underestimated. Difficulties in accurately measuring the reaction parameters lend some hit or miss character: the range of conditions under which dehydrogenation occurs is not great and in a small batch-process the time available for fine tuning is limited. Nonetheless, careful work will yield reasonable results. The 1-[^{14}C]phenol obtained by this route was methylated[17] using methyl iodide and sodium hydroxide in dimethylsulphoxide (90%) and the product was diluted with anisole as required for subsequent work (Equation 4). This sequence constitutes the two-step conversion of cyclohexanone into phenol that we had been seeking. In it we had dispensed with the use of a methyl group to label the position of the heavy isotope during aromatisation and had used the *C-O* bond itself for this purpose.



[4]

When later we were freed from the constraint of using [^{14}C]NaCN as the source of radiolabel we investigated one other synthesis of 1-[^{14}C]anisole, shown in *Scheme 1*. Condensation of sodium nitromalondialdehyde with 2-[^{14}C]acetone gave 4-nitro-1-[^{14}C]phenol.[4c] This reaction meets most of the objectives set out earlier but in doing so it introduces an unwanted nitro-group. 4-Nitrophenol was methylated[17] with methyl iodide and potassium hydroxide in dimethylsulphoxide (99%) to give 4-nitroanisole that was reduced to 4-aminoanisole (94%) with hydrazine hydrate and palladised charcoal.[18] The removal of the unwanted nitro-group was completed by reductive deamination. Several more or less convincing ways of deaminating 4-aminoanisole have been reported.[19] When 4-aminoanisole was diazotised at 0° with pentylnitrite-trifluoroacetic acid in tetrahydrofuran and the product was treated sequentially with urea - to destroy the excess of pentylnitrite[20] - and hydroquinone[19e,f] gas evolution commenced at once but only 55 ± 3% (by g.l.c.) of anisole could be detected in the product.



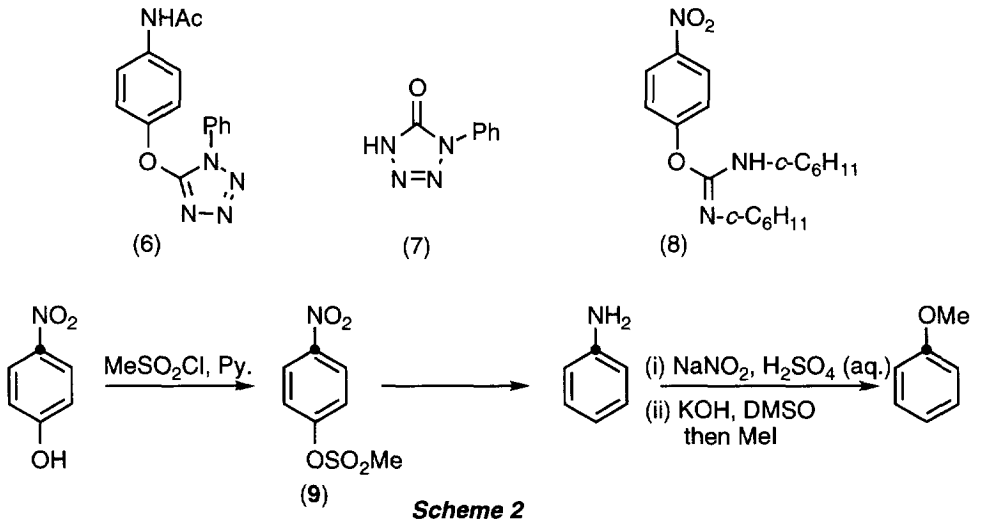
Scheme 1

The deamination was greatly improved by diazotisation of the 4-aminoanisole with sodium nitrite in dilute hydrochloric acid followed by reduction of the diazonium salt using a two-phase mixture of aqueous hypophosphorous acid[19a] and pentane to give anisole in 90 ± 5% (g.l.c.; 88% isolated) yield. This two-phase variant of a venerable old reaction gave a very clean product. Parry[4d] has also followed a similar route, as far as the diazotisation, in a synthesis of 4-hydroxy-4-[^{14}C]arenes. The overall yield of 1-[^{14}C]anisole of over 50% that is available by this method combines with the simplicity and convenience of the procedure to make this synthesis of 1-[^{14}C]anisole the most attractive currently available.

The synthesis of 4-[^{14}C]anisole posed fewer problems as there was already a reasonably short published synthesis (*Scheme 2*) based on the ready availability of 4-nitro-1-[^{14}C]phenol,[4c] which we had already utilised. Although we made minor changes to the published procedure for our convenience we encountered no difficulties before the key step: reductive deoxygenation. At this point we were unable to reduce 1-phenyl-(4-acetamidophenoxy)tetrazole (**6**) to acetanilide and 1-phenyltetrazolone (**7**) reproducibly and could obtain no better than about 60% conversion. We were unwilling to commit labelled material to so apparently capricious a procedure and so alternatives to this key step were sought. The published procedure[4c] employs five steps to bring about a transformation that might reasonably be carried out in two: appropriate *O*-derivatisation followed by reduction[4h] to aniline. One problem is that the ease of hydrogenolysis of the phenoxy *C-O* bond will depend on the nature of the *para*-substituent with reduction of the nitro-group to an amino-group retarding any subsequent hydrogenolysis.[21] A shorter route would need a hydrogenolytic cleavage so efficient that it would proceed either before or despite reduction of the *para*-nitro-group. Attempts to deoxygenate 4-nitrophenol by hydrogenolysis[22] of the isourea (**8**) formed with dicyclohexylcarbodiimide gave 4-aminophenol rather than aniline. It seems likely that the nitro-group adversely affects the stability of the isourea (**8**), which breaks down before hydrogenolysis occurs.

Sulphonate esters should be more stable in this respect. 4-Nitrophenol was quantitatively converted to the mesylate (**9**) by a standard method[23b] and then hydrogenated[23] at atmospheric pressure over palladised charcoal in the presence of triethylamine to give aniline, the desired intermediate, in 65% yield. 4-[^{14}C]Aniline prepared by this method was diazotised with one equivalent of sodium nitrite and converted by hydrolysis with dilute sulphuric acid into 4-[^{14}C]phenol, which was methylated as previously described[4c] (*Scheme 2*). Use of more than one equivalent of sodium nitrite in the diazotisation is a poor but interesting method, which we mention in

passing, but which we will not further describe, of completing the conversion of 4-nitro-1-[^{14}C]phenol by way of 4-[^{14}C]aniline into 4-nitro-4-[^{14}C]phenol.[24] We have found the published method modified in this way to be a short and satisfactory route to 4-[^{14}C]anisole. Although developed as a route to 4-[^{14}C]anisole this route is also a quick and convenient synthesis of 4-[^{14}C]aniline (in three steps) and 4-[^{14}C]phenol (in four steps).

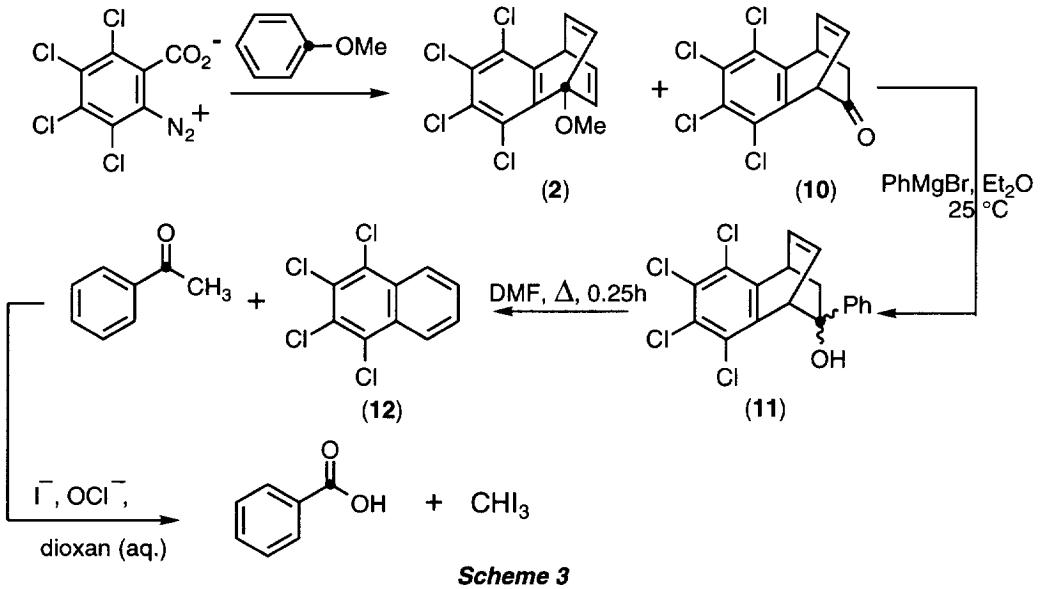


Scheme 2

The majority of routes discussed above leave no doubt about the position of the radiolabel. Catalytic dehydrogenation of 1-methyl-1-[^{13}C]cyclohexene to 1-[^{13}C]toluene has been reported[5i] to proceed with some scrambling of the label. Such scrambling is relatively easy to detect with [^{13}C] labelling but would be more difficult to estimate using a [^{14}C]label. The problem is serious because this dehydrogenation has often been used[3a,d,5f-i] in the conversion of cyclohexanone to phenol. One of the roles of the methyl group is to protect the positional integrity of the radiolabel during aromatisation and in this it clearly fails. This scrambling emphasises the importance of the wet-chemical routes to 1-[^{14}C]anisole described above but raises a question about whether or not any scrambling had occurred in the direct dehydrogenation of 1-[^{14}C]cyclohexanone to [^{14}C]phenol. [^{14}C]Anisole prepared from 1-[^{14}C]cyclohexanone by direct dehydrogenation to [^{14}C]phenol would be expected to bear the label at *C*1; any scrambled label would be found mostly at *C*2 (= *C*6). We have previously reported[7,25] some novel chemical degradations of arenes. We selected a method designed specifically to separate and isolate *C*1 and *C*2 (= *C*6) of an arene and applied it to the [^{14}C]anisole prepared by catalytic dehydrogenation.

[^{14}C]Anisole was reacted with tetrachlorobenzyne to give[2b,26] 5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1,4-etheno[^{14}C]naphthalene (1-methoxy-[^{14}C]-tetrachlorobenzobarrelene) (**2**) and 5,6,7,8-tetrachloro-3,4-dihydro-1,4-etheno-[^{14}C]naphthalen-2(1*H*)-one ([^{14}C]tetrachlorobenzobarrelenone) (**10**). The ketone (**10**) was treated at room temperature with phenylmagnesium bromide to give a carbinol (**11**) (100%) that was pyrolysed in dimethylformamide to give tetrachloronaphthalene (**12**) (88%) and acetophenone (**13**). The acetophenone was degraded[27] to iodoform and benzoic acid (*Scheme 3*). The radioactivity present in the original anisole appeared entirely in the benzoic acid fragment whereas the tetrachloronaphthalene (**12**) and

iodoform exhibited only background levels of radioactivity (*Table*). It follows that the [^{14}C]anisole prepared from 1-[^{14}C]cyclohexanone through [^{14}C]phenol was exclusively 1-[^{14}C]anisole. As no scrambling had occurred in the catalytic dehydrogenation the positional integrity of the label had been preserved by the *C-O* bond. It seems that not only does the methyl group fail to correctly locate the label but also the job that it does inadequately need not be separately undertaken at all. The successful development of unambiguous syntheses of 1- and 4-[^{14}C]-anisole completes the preparatory work required for our [^{14}C]-tracer study of the acid catalysed rearrangement of 1-methoxybenzobarrelene, which will be reported separately.



Scheme 3

Table

Distribution of radioactivity among degradation fragments of [^{14}C]anisole

Fragment	Atoms in anisole	Activity ± SE dpm/mol x 10^{-6}	Relative Activity
Iodoform	C-2 = C-6	background‡	(0)
1,2,3,4-Tetrachloro-naphthalene	C-2 = C-6; C-3 = C-5 C-4	1.048 ± 2.89	0.002
Benzoic acid	C-1	474.3 ± 2.89	100

‡ Not isolated in aa pure enough form for an accurate determination of the specific activity.

Acknowledgements.

We thank the S.R.C. for research studentships to N.J.H., J.H.H., and S.V.L.

Experimental

General Methods

Reactions involving Grignard reagents and organolithium compounds were carried out under dry, oxygen-free nitrogen, in apparatus dried overnight at 120 °C. Light petroleum refers to the fraction of boiling range 60-80 °C unless otherwise specified. Solvents were dried by conventional methods and solutions of products were dried over anhydrous magnesium sulphate. Analytical t.l.c. was carried out using silica-gel (Merck GF254) for layers 0.25 mm thick, and preparative layer chromatography (p.l.c.) was carried out using silica-gel (Merck PF254) for layers 0.75 mm thick. Analytical g.l.c. was carried out using a Pye 104 series chromatograph (5ft column of 10% SE30 on firebrick unless otherwise stated; flame ionisation detection).

I.r. spectra were determined for potassium bromide discs (solids) or thin films (liquids) unless otherwise stated using a Perkin-Elmer 257 spectrophotometer. U.v. spectra were determined using Unicam SP800 or SP8000 spectrophotometers. N.m.r. spectra were determined using Perkin-Elmer R10 and R32 spectrometers with tetramethylsilane (for ^{1}H) or trichlorofluoromethane (for ^{19}F) as internal standards in *ca.* 20% w/v solutions. Mass spectra were determined at 70eV on an A.E.I. MS12 spectrometer. Melting points were determined on a Kofler hot-stage apparatus and are uncorrected.

Radioactivities were determined for dilute solutions of the sample (*ca.* 1 mg) in DMF (0.2 mL) and scintillator (5 mL) using a Beckman Instruments CPM-100 liquid scintillation spectrometer. The scintillator was a solution of 2,5-diphenyloxazole (0.38%) and 1,4-bis- 2-(4-methyl-5-phenyloxazolyl)benzene (0.02%) in toluene. The efficiency of the scintillator was determined using [^{14}C]hexadecane of known specific activity (obtained from the then Radiochemical Centre, Amersham) as standard.

Preparations that are closely analogous to published procedures are briefly summarised at the end of this section.

2-Amino-1-cyanocyclohexene

(a) Using lithium *N*-ethylanilide[9d]

A solution of pimelonitrile (7.32 g, 60 mmol) in ether (250 mL) was added dropwise during 96h to the condensate from an ethereal solution of lithium *N*-ethylanilide [from *n*-butyllithium in hexane (60 mmol) and *N*-ethylaniline (7.26 g, 60 mmol) in ether (250 mL)] being heated under reflux. The turbid reaction mixture was treated with water (1.19 g, 65 mmol), maintained at room temperature for 3h, and filtered. The filtrate was dried ($MgSO_4$) and evaporated to give 2-amino-1-cyanocyclohexene, pale yellow crystals (7.27 g, 98%), m.p. 92 °C (lit.,[9b] m.p. 94-95 °C); *m/z* 122 (M+) ν_{max}(KBr) 3 450, 3 360, 3 060, 2 960, 2 940, 2 900, 2 850, 2 180, 1 650, 1 610, 1 425, 1 405, 1 210, and 1 150 cm^{-1} (lit.[9g] 3 484, 3 389, 2 188, 1 644, and 1 615cm-1); δ_H(60 MHz; $CDCl_3$) 4.43 (2H, br.s), 2.15 (4H, m), and 1.61 (4H, m).

(b) Using lithium diethylamide[9a]

A solution of pimelonitrile (1.22 g, 10 mmol) in ether (100 mL) was added dropwise during 10h to the condensate from an ethereal solution of lithium diethylamide [from *n*-butyllithium in hexane (11 mmol) and

diethylamine (0.80 g, 11 mmol) in ether (500 mL)] being heated under reflux. The reaction mixture was maintained at room temperature for 48h. A solution of water (0.19 g, 11 mmol) in THF (10 mL) was added. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure to give 2-amino-1-cyanocyclohexene, pale yellow crystals (1.08 g, 88%), spectroscopically indistinguishable from the previous sample.

On the route to 1-[^{14}C]anisole - From cyclohexanone *via* catalytic dehydrogenation

(a) Phenol

A sample of catalyst[16a] (20 g, 8.3 wt% Ni and 3.7 wt% Sn supported on t.l.c. grade silica-gel), firmly packed into a horizontal pyrex tube and held in place by glass wool plugs, was reduced at 400 °C for 4hr in a stream of hydrogen. The catalyst temperature was lowered to 380±5 °C and cyclohexanone (9.00 g, 92 mmol) was passed through the catalyst in a stream of hydrogen at such a rate that the catalyst temperature remained within bounds; about 30min was required. The exhaust gases were trapped at -78 °C. The condensate was dissolved in ether and extracted with aqueous sodium hydroxide (2*N*; 4x25 mL). The ethereal phase gave no reaction with acidified ethanolic 2,4-dinitrophenylhydrazine and was discarded. The combined basic extracts were acidified (conc. HCl) and extracted with ether (4x25 mL). The combined ethereal extracts were dried ($MgSO_4$) and evaporated to give phenol (5.25 g, 60%), characterised as its benzoate,[27] m.p. 71-74 °C (lit.[27] m.p. 69 °C).

(b) Anisole. A solution of phenol (0.94 g, 10 mmol) and sodium hydroxide (1.60 g, 40 mmol) in DMSO (20 mL) was treated with methyl iodide (2.48 g, 20 mmol) and maintained at room temperature for 30 min. The reaction mixture was diluted with water (20 mL) and extracted with light petroleum [(b.p. 40-60 °C) 3x25 mL]. The combined petroleum extracts were washed with aqueous sodium hydroxide (2*N*; 3x25 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure to give anisole, a clear oil (0.98 g, 90%), spectroscopically identical with an authentic sample.

From cyclohexanone *via* sequential bromination-dehydrobromination

(a) 2,6-Dibromo-1,1-dimethoxycyclohexane (5)

A solution of cyclohexanone (9.80 g, 100 mmol) in methanol (120 mL) was treated with bromine (*ca.* 1 g). When the initial brown colour of the solution had nearly faded the remaining bromine (total 32.00 g, 200 mmol) was added at such a rate that the colour of the bromine remained just visible; the reaction mixture became warmer and eventually boiled gently. Solvent was removed under reduced pressure to leave a mixture (45:55) of *cis*- and *trans*- 2,6-dibromo-1,1-dimethoxycyclohexane (**5**),[15] a light orange oil (26.10 g, crude yield 86%), ν_{max} (film): no carbonyl stretching band; δ(60 MHz; $CDCl_3$) 4.55 and 4.30 2H, [(dd, *J*6 and 4 Hz, *cis*) and (m, *trans*)], 3.80, 3.53, and 3.34 [6H, (s, *cis*), (s, *trans*), and (s, *cis*)], and 2.5-1.6 (6H, m).

(b) Anisole

(i) using sodium methoxide.

A solution of 2,6-dibromo-1,1-dimethoxycyclohexane (**5**) (26.00 g, 86 mmol) in DMSO (120 mL) was treated with sodium methoxide (11.30 g, 210 mmol). The reaction was maintained at room temperature for 24h. The solution was diluted with brine (100 mL) and extracted with light petroleum [(b.p. 40-45 °C)

3x24 mL]. The combined extracts were washed with water (2x10 mL) then brine (10 mL) and dried ($MgSO_4$). Solvent was removed by distillation to leave a dark oil (14.69 g) that was shown (g.l.c.; 10% SE30 on Celite, 130 °C; 1,4-dichlorobenzene and authentic anisole as standards) to contain anisole (31%; 27% from cyclohexanone). A portion (5.00 g) of this product was purified by chromatography on alumina (50 g). Light petroleum (b.p. 40-45 °C) eluted anisole (0.83 g, 27%; 24% from cyclohexanone), spectroscopically identical with an authentic sample. (ii) using potassium *t*-butoxide. 2,6-Dibromo-1,1-dimethoxycyclohexane (**5**) [from cyclohexanone (0.98 g, 10 mmol) and bromine (3.20 g, 20 mmol) in methanol as described above] was added dropwise during 5min to a solution of potassium *t*-butoxide [from potassium (1.17 g, 30 mg-atoms) and *t*-butanol (10 mL); excess of *t*-butanol removed under reduced pressure] in DMSO (40 mL). The reaction was maintained at room temperature for 24h, diluted with brine (400 mL) and extracted with ether (3x30 mL). The combined ether extracts were washed with water (3x20 mL) and dried ($MgSO_4$). The solvent was removed by distillation to leave a pale yellow oil that was shown (g.l.c.; conditions as in (i) above) to consist of anisole (52% from cyclohexanone).

From 4-nitrophenol.

(a) 4-Nitroanisole. A stirred solution of 4- nitrophenol (12.9 g, 100 mmol) and potassium hydroxide (22.4 g, 400 mmol) in DMSO (100 mL) was treated at room temperature with methyl iodide (56.8 g, 400 mmol) in one portion. The reaction was stirred at room temperature for 2h then diluted with water (400 mL) and extracted with ether (4x50 mL). The combined ether extracts were washed with water (3x50 mL) and dried ($MgSO_4$). The solvent was evaporated to give 4-nitroanisole, lemon yellow needles (15.2 g, 99%) m.p. and mixed m.p. 52-54 °C (lit.[28] m.p. 54 °C).

(b) 4-Aminoanisole.

A warm (*ca.* 60 °C) solution of 4-nitroanisole (7.61 g, 50 mmol) in ethanol (95%; 50 mL) was treated sequentially with palladised charcoal (10% Pd; 0.05 g) and hydrazine hydrate (10 mL, *ca* 100 mmol; added dropwise). The reaction mixture was boiled for 2h then cooled to room temperature and filtered. The filtrate was diluted with ether (150 mL), washed with water (4x25 mL) and dried (Na_2SO_4). Solvent was evaporated to leave 4-aminoanisole, clear crystals with a blue-green lustre (5.77 g, 94%), spectroscopically identical with an authentic sample. A portion (0.62 g, 5 mmol) of this product was treated with acetic anhydride in pyridine (1*M*; 6 mL, 6 mmol) to give 4-methoxyacetanilide (0.63 g, 77%), m.p. 128-129 °C (lit.[28] m.p.130-132 °C).

(c) Anisole (i) by diazotisation in the presence of hydroquinone.

A stirred solution of 4-aminoanisole (12.30 g, 100 mmol) and trifluoroacetic acid (0.1 mL) in THF (100 mL) maintained at 5 °C was treated with pent-2-ylnitrite (14.04 g, 120 mmol) dropwise during 5 min. The solution was stirred at 5 °C for 1h, treated with urea (0.60 g, 10 mmol) and allowed to warm to 15 °C. Hydroquinone (11.0 g, 100 mmol) was added. External cooling was applied to keep the reaction temperature below 25 °C until a vigorous gas evolution had subsided. The mixture was warmed to ca. 40 °C for 1h. THF was removed by distillation and the residual dark oil was absorbed onto sufficient alumina to produce a dry, free-running powder. The absorbed product was applied to a short (5 cm), wide (10 cm) column of alumina and eluted with light petroleum (b.p. 40-60 °C) to give anisole, a clear, colourless oil (5.95 g, 55%), pure by g.l.c. (10% SE30 on Celite, 120°C) and spectroscopically identical to an authentic sample.

(ii) By diazotisation followed by reduction with hypophosphorous acid.

A stirred solution of 4-aminoanisole (6.15 g, 50 mmol) in hydrochloric acid (conc.; 11 mL) and water (75 mL) was treated at 10 °C dropwise during 10min with a solution of sodium nitrite (3.50 g, 50 mmol) in water (7 mL). The red solution was stirred at 5-10 °C for 10min, filtered, and added to cool (*ca.* 10 °C) hypophosphorous acid (30% aqueous solution; 54 mL, 300 mmol). The resultant yellow, gently effervescent solution was covered with light petroleum [(b.p. 40-45 °C) 25 mL] and stirred at room temperature for 64h, by which time gas evolution had ceased. The phases were separated, the aqueous phase was extracted with light petroleum [(b.p. 40-45 °C) 3x24 mL], and the combined petroleum phases were washed with brine (2x10 mL). One tenth of the extract was found (g.l.c. 10% PEGA on Celite, 120°C; 1,4-dichlorobenzene and authentic anisole as standards) to contain anisole (90±5%). The remaining extract was dried ($MgSO_4$) and distilled to give anisole, a clear colourless oil (3.90 g, 80%), b.p. 150-156 °C (lit.[29] b.p. 155 °C), pure by g.l.c. (conditions as above).

On the route to 4-[^{14}C]anisole

(a) 4-Nitrophenyl methanesulphonate (9)

A solution of 4-nitrophenol (4.37 g, 31.44 mol) in pyridine was treated at *ca.* 5 °C with methanesulphonyl chloride (5 mL; 7.4 g, 64.6 mmol) and the mixture was stirred at room temperature for 30min. The mixture was diluted with ether (200mL), washed with dilute hydrochloric acid (2*N*; 2x50 mL), dried ($MgSO_4$), and evaporated to dryness to leave 4-nitrophenyl methanesulphonate **(9)** (6.2 g, 91%), m.p. 92-94 °C (lit.[23b] m.p. 93-94 °C).

(b) Aniline

A suspension of palladised charcoal (10% Pd; *ca.* 1 g) in a solution of 4-nitrophenyl methanesulphonate **(9)** (4.3 g, 19.8 mmol) in methanol (*ca.* 100 mL) and triethylamine (*ca.* 2 g, 20 mmol) was stirred at 25-40°C under one atmosphere of hydrogen until absorption of hydrogen was complete. The reaction was filtered. The filtrate was basified with dilute aqueous sodium hydroxide and extracted with ether. The ether was removed by distillation to give aniline (1.2 g, 65%).

Reactions to show the specificity of 1-[^{14}C]anisole labelling. 5,6,7,8-Tetrachloro-1,4-dihydro-9-hydroxy-9-phenyl-1,4-ethanonaphthalene (11)

A stirred solution of phenylmagnesium bromide [from magnesium (0.122 g, 5 mg-atoms) and bromobenzene (just sufficient to completely react with the magnesium) in ether (*ca.* 50 mL)] maintained at 10°C was treated with a solution of 5,6,7,8-tetrachloro-3,4-dihydro-1,4-ethenonaphthalen-2(1*H*)-one[2b,26] **(10)** (0.120 g, 0.390 mmol) in ether (25 mL). The reaction mixture was stirred at room temperature for 4h then poured into aqueous ammonium chloride (saturated; *ca.* 50 mL) and extracted with ether (3x25 mL). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure. The residue was purified by chromatography on silica-gel to give *5,6,7,8-tetrachloro-1,4-dihydro-9-hydroxy-9-phenyl-1,4-ethanonaphthalene* **(11)** (0.152 g, 100%) m.p. *ca.* 145 °C(dec) (from EtOH) (*Found*: C,55.9; H,3.0. $C_{18}H_{12}Cl_4O$ *requires* C,55.9; H,3.1%); ν_{max} (KBr) 3 550, 3 450(broad); δ(90MHz; $CDCl_3$) 1.91 (1H, dd, *J* 3Hz and *J* 16Hz), 2.15 (1H, br s), 2.41 (1H, dd, *J* 3.5Hz and *J* 16Hz), 4.45-4.75 (2H, m), 6.6-7.2 (7H, m).

Pyrolysis of alcohol (11). A solution of 5,6,7,8-tetrachloro-1,4-dihydro-9-hydroxy-9-phenyl-1,4-ethanonaphthalene **(11)** (0.344 g, 0.891 mmol) in dry DMF (25 mL) was heated under reflux for 30min. The cool reaction mixture was poured into water (50 mL) and extracted with carbon tetrachloride (5x25 mL). The combined extracts were washed with water, dried ($MgSO_4$) and concentrated. The residue was purified by preparative t.l.c.(silica-gel) to give 1,2,3,4-tetrachloronaphthalene **(12)** (0.208 g, 88%) identified by spectroscopic and chromatographic comparison with an authentic sample,[26] and a solution containing acetophenone, characterised as its 2,4-dinitrophenylhydrazone, m.p. 229-235 °C (lit.[27] m.p. 237 °C). **Oxidation of acetophenone with potassium iodide and sodium hypochlorite.** A stirred solution of acetophenone (0.16 g, 1.37 mmol) and potassium iodide (0.50 g, 3.0 mmol) in water (10 mL) and carefully purified dioxan (10 mL) maintained at room temperature was treated with aqueous sodium hypochlorite (5%; 3 mmol). Another portion of potassium iodide (0.30 g, 1.8 mmol) was added and the mixture was treated with another portion of sodium hypochlorite (5%, 1.8 mmol). The reaction mixture was filtered to give iodoform, yellow feathery crystals (0.304 g, 57%) m.p. 112-120 °C (lit.[27] m.p.119 °C). The filtrate was treated with sodium thiosulphate (*ca.* 3 g), acidified, and extracted with ether (3x25 mL). The combined extracts were dried ($MgSO_4$) and evaporated under reduced pressure to give benzoic acid (0.166 g, 67%), m.p. 119-121 °C (from hexane) (lit.[27] m.p. 121 °C).

Miscellaneous procedures.

Product; yield (crude yield) and characterisation; starting material and method:

Pimelonitrile: 80% (97%), b.p. 120 °C/0.9 mmHg, (lit.[30] 149 °C/1 mm Hg); from 1,5-dibromopentane (57.5 g, 250 mmol) in aqueous ethanol.[5e,27]. from 1,5-dibromopentane (2.30 g, 10 mmol) in DMSO[9f,30] (96%), b.p. 118 °C/0.3mm Hg, (lit.[30] b.p. 149 °C/1 mmHg).

Pimelic acid: 83%, m.p.102-105 °C, (lit.[28] m.p.104-105 °C); from pimelonitrile and conc. HCl.[5e,27]

Cyclohexanone: 73% as the 2,4-dinitrophenylhydrazone, m.p. 157-160 °C, (lit.[27] 162 °C); from pimelic acid by dry distillation;[5e,27] pimelic acid (17%, m.p. 102-103 °C) sublimed from the mixture and was recovered.

2,6-Dibromocyclohexanone (4): (65%), ν_{max}(film) 1 750, 1 732 and 1 713cm,$^{-1}$ (lit.[12] 1 750(*cis*) and 1 732 (*trans*) cm^{-1}); the weak band at 1 713cm^{-1} indicates incomplete bromination; from cyclohexanone (37.0 g, 385 mmole) and bromine.[12] **2,6-dibromocyclohexanone(4)**: (69%), b.p. 80-85°C/0.3 mmHg, ν_{max} (film) 1 750, 1 735, and 1 729cm^{-1} (lit.[12] as above); from cyclohexanone (2.94 g 30 mmole) and pyridinium tribromide.[11]

Phenol: <5% as the 3,5-dinitrobenzoate[27]; from 2,6-dibromocyclohexanone **(4)** in boiling collidine.[13b] **Phenol**: 25% as the benzoate;[27] from 2,6-dibromocyclohexanone **(4)** in boiling pyridine.[13c] **Phenol**: 24% as the benzoate;[27] from 2,6-dibromocyclohexanone **(4)** and lithium chloride in boiling DMF.[13d] **Phenol**: 67%, b.p. 85-95°C/15 mmHg, (lit.[29] b.p. 182 °C); by diazotisation of aniline (0.90 g, 9.7 mmole) in dilute sulphuric acid.[4c]

4-Nitrophenol: (63%), m.p. 112-114 °C, (lit.[29] m.p. 115-116 °C); from acetone (2.9 g, 50 mmole) and sodium nitromalondialdehyde.[4c]

4-Aminophenol: 97%, m.p. 187-191 °C,(lit.[29] m.p. 186-187 °C); from 4-nitrophenol (2.23 g, 16 mmole) by catalytic transfer hydrogenation using hydrazine hydrate.[18]

1-Phenyl-5-(4'-aminophenoxy)tetrazole (**6**): 58%, m.p. 173-175 °C, (lit.[31] m.p. 171-173 °C); from 4-aminophenol (1.69 g, 16 mmole).[4c]

1-Phenyl-5-(4'-acetamidophenoxy)tetrazole: 86%, m.p. 158-160°C, (lit.[4c] m.p. 159-161 °C); by acetylation of 1-phenyl-5-(4'-aminophenoxy)tetrazole (**6**) (1.74 g, 6.9 mmole).[4c]

Acetanilide: 64%, m.p.112-114 °C, (lit.[29] m.p. 114 °C); by hydrogenolysis of 1-phenyl-5-(4'-acetamidophenoxy)tetrazole (1.72 g, 5.8 mmole);[4c] the yield quoted is the best that we obtained: there were many much worse than this.

5,6,7,8-Tetrachloro-3,4-dihydro-1,4-ethenonaphthalen-2(1*H*)-one (**10**): 2%, ^{1}H-n.m.r. comparison with our[26] authentic sample; from anisole (2.05 g, 19.0 mmole) and 2-carboxy-tetrachlorobenzenediazonium chloride (4.0 g, 12.4 mmole). **CAUTION: 2-carboxytetrachlorobenzenediazonium chloride can explode unpredictably when dry and should not be handled without protective screens);**[2b] the yield quoted is based on anisole and the major product is 5,6,7,8-tetrachloro-1,4-dihydro-1-methoxy-1,4-ethenonaphthalene (**2**) (26%).

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