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PHASE TRANSFER MEDIATED SYNTHESIS OF RADIOLABELLED ALKYL ARYL ETHERS AND SULPHIDES

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SUMMARY

Tritium- or ^{14}C-labelled methyl iodide and ethyl iodide were used for alkylations of phenols and thiols. The reactions were performed in a two-phase system with phase transfer catalysis at room temperature. Products of high specific activity were isolated in isotope yields ranging from 38% to 100%.

Key Words: ^{14}C-methyl iodide, ^{3}H-methyl iodide, methyl aryl sulphide, trichloroguajacol, polychlorobenzene, PCB, PTC.

INTRODUCTION

Access to O- and S-methyl- or ethyl-substituted phenols and thiols, respectively, labelled with ^{3}H or ^{14}C in the alkyl group has proved to be quite valuable in connection with toxicological studies of such compounds. An improved method for synthesis of labelled methyl and ethyl sulphides or ethers is presented. The sulphides and the corresponding sulphones were synthesized in order to make possible autoradiographic studies concerning uptake, distribution and elimination. Other studies concerning the metabolism of these compounds have also been initiated.

Similarily, ^{14}C- and ^{3}H-methyl-labelled trichloroguajacols as well as the corresponding veratrols have been prepared from 3,4,5-trichlorocatechol to facilitate metabolic studies in fish of 4,5,6-trichloroguajacol. This and related phenols are important components in effluents from chlorine bleaching of pulp (1). Such effluents also contain certain chlorinated dimethylsulphones (2). An intermediate in the synthesis of ^{14}C-labelled 1,1-dichlorodimethyl

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sulphone, 2'-[^{14}C]methylthio-4-bromoacetophenone, has now been prepared by the same method.

The procedure described was based on conventional phase transfer catalysis (PTC) of the phenolic compounds or phenylthiols (3). It is shown that it is possible to perform the reaction on a micro-scale with high specific activity alkyl iodides.

RESULTS AND DISCUSSION

The compounds synthesized are shown in Table 1. With a few exceptions the general molar ratio of the chemicals used in the PTC alkylations of hydroxy and thiol groups were: alkyl iodide (1 mol), substrate (2 mol), tetrabutylammonium hydrogen sulphate (4 mol) and base (6 mol). Even though higher isotope yields may be obtained with a larger excess of nucleophile at micro-scale preparations more complex product mixtures were found to be formed in pilot experiments. With twice as much nucleophile to alkyl iodide optimal conditions for the reaction and separation of pure products were met. Only catalytical amounts of the ammonium salt (TBA) were insufficient for high yields of alkylated products. It is essential that only a molar amount of base is used compared to the acidic protons present in the reaction mixture. Under certain circumstances it was not possible to use an excess of nucleophile, viz. when both thiol groups should be methylated in the biphenyldithiol (c.f. Table 1). This may partly explain the lower isotope yield in that reaction. Alkylations with tritium instead of carbon-14 labelled iodides were performed at much higher specific activity and that may explain the comparably lower yields obtained in these reactions.

The transfer procedure of the labelled alkyl iodide is reproducible and reliable with a minimum risk of radioactive losses. The amounts of radioactivity in the trap-flask (IV), Figure 1, should be checked. More than 0.5% of the activity was never found there. The total activity recovered in the reactions was measured and in agreement with the amounts used. The PTC alkylation is performed at room-temperature - an advantage compared to reactions performed under reflux, especially with small volumes of solvent.

EXPERIMENTAL

[^{3}H]Methyl iodide, [^{14}C]methyl iodide and [1-^{14}C]ethyl iodide (for their specific activities see Table 1) were purchased from Amersham International plc. 2,5-Dichlorobenzenethiol, 2,6-dichlorobenzenethiol, 2,4,5-trichlorophenyl disulphide and pentachlorobenzenethiol were obtained from Aldrich.

TABLE 1. Reaction conditions for phase transfer catalysed preparation of methylated or ethylated phenols ond thiols.

SUBSTRATE (umol)	ALKYL IODIDE (mCi;mCi/mmol)	AMMONIUM SALT (umol)	BASE (umol)	ORGANIC SOLVENT (ml)	WATER (ml)	REACTION TIME (h)	PRODUCTS* yield (%)
3,4,5-Trichloro-catechol (2000)	^{14}C-MeI 1;2.4	TBA 4000	NaOH 8000	$PhCH_3$ 5.0	5.0	2	3,4,5-trichloroguajacol (55%) 4,5,6-trichloroguajacol (34%) 3,4,5-trichloroveratrol (4.3%)
3,4,5-Trichloro-catechol (400)	^{3}H-MeI 25;200	TBA 400	NaOH 1200	PhCH3 1.0	1.0	2	3,4,5-trichloroguajacol (31%) 4,5,6-trichloroguajacol (25%) 3,4,5-trichloroveratrol (4%)
2,5-Dichloro-benzenethiol (12.8)	^{14}C-MeI 0.5;58.5	TBA 25.7	NaOH 38.5	CH_2Cl_2 2.0	2.0	2	methylthio-2,5-dichlorobenzene (57%)
2,6-Dichloro-benzenethiol (34)	^{14}C-MeI 1.0;59	TBA 68	NaOH 102	CH_2Cl_2 2.0	2.0	2	methylthio-2,6-dichlorobenzene (70%)
2,4,5-Trichloro-benzenethiol (27.6)	^{14}C-MeI 1.0;59	TBA 52	NaOH 79.6	CH_2Cl_2 2.0	2.0	2	methylthio-2,4,5-trichlorobenzene (95%)
Pentachloro-benzenethiol (34.7)	^{14}C-MeI 1.0;57.6	TBA 69.4	NaOH 104	CH_2Cl_2 4.0	4.0	18	methylthio-pentachlorobenzene (100%)
Pentachloro-benzenethiol (4.2)	^{3}H-MeI 25.0;11.8**	TBA 8.5	NaOH 12.7	CH_2Cl_2 2.0	2.0	18	methylthio-pentachlorobenzene (47%)
2,2',5,5'-Tetrachloro-4-biphenylthiol (100)	^{14}C-MeI 1.0;10^3	TBA 200	NaOH 300	CH_2Cl_2 2.5	2.5	18	4-methylthio-2,2',5,5'-tetra-chlorobiphenyl (76%)
2,2',5,5'-Tetrachloro-4-biphenylthiol (5)	(1-^{14}C)-EtI 0.25;51	TBA 20	NaOH 25	CH_2Cl_2 0.5	0.5	2	4-ethylthio-2,2',5,5'-tetra-chlorobiphenyl (66%)
2,2',5,5'-Tetrachloro-4,4-biphenyldithiol(3.2)	^{14}C-MeI 25;7.8**	TBA 12.8	NaOH 19.2	CH_2Cl_2 2.0	2.0	2	4,4'-bis(methylthio)-2,2',5,5'-tetrachlorobiphenyl (38%)
4-Bromophenacyl-thiol (65)	^{14}C-MeI 1.0;59	TBA 130	NaOH 160	CH_2Cl_2 2.0	2.0	- 1	2'-methylthio-4-bromo-acetophenone (65%)

* For purification see Experimental.
** The specific activity are in these cases in Ci/mmol.

3,4,5-Trichlorocatechol was synthesized from 4,5,6-trichloroguajacol (4) by demethylation with hydrogen bromide in boiling acetic acid.

2,2',5,5'-Tetrachloro-4,4'-biphenyldithiol was synthesized as described (5) and similarily 2,2',5,5'-tetrachloro-4-biphenylthiol. 4-Bromphenacyl thiol was prepared in low yield from 2',4-dibromoacetophenone (Sigma Chemical Co.) and sodium hydrogen sulphide under conditions given for the synthesis of phenacylthiol (6). Tetrabutylammonium hydrogen sulphate (Labkemi AB, Stockholm) and analytical grade solvents were used.

The identity of the labelled compounds was confirmed by comparison with authentic unlabelled references. The labelled alkylated compounds were purified by preparative thin layer chromatography on silica gel (Kieselgel 60 F-254, 0.25 mm, Merck) and/or reversed phase TLC plates (RP-18 F254S, 0.25 mm, Merck). A Packard Tri-carb 460C liquid scintillation counter was used for quantitative calculations of radioactivity with the appropriate [^{14}C]toluene or [^{3}H]toluene as internal standard. Toluene PPO/POPOP was used as scintillation fluid.

The reactions were carried out under the conditions given in Table 1. The reactions were all performed by use of the apparatus shown in Figure 1 and under the following general procedure: A magnet and the appropriate amount of phenol or thiol is placed in a pear-shaped flask (III). The flask is closed with a screw-cap containing a septum. Nitrogen is introduced into the flask and the vessel containing the labelled alkyl iodide (II) before the ampoule is opened. The alkyl iodide is frozen at the bottom of the ampoule by use of liquid nitrogen. The adequate amounts of tetrabutylammonium hydrogen sulphate and sodium hydroxide in water is added to the reaction flask (III), thereafter the glass seal of the ampoule is broken with a "magnetic hammer". The transfer needle (B) to the reaction flask is connected to the ampoule as well as the needle (A) to the solvent containing tube (I). The liquid nitrogen is removed and the solvent (2/3 of the final volume) is transferred to the ampoule by means of a nitrogen stream via A. The alkyl iodide solution is transferred to the reaction flask in the same manner and the procedure is repeated once with 1/3 of the final organic solvent volume. The needles are removed from the flask and washed with a solution of potassium ethyl xanthate in acetone. Needle B is first washed and the glass vessel II is half filled with the xanthate solution. The other half of II is filled when needle A is washed. Finally needle C is washed. As soon as the needles are removed from the reaction flask the two-phase system is vigorously stirred by a magnet bar at ambient temperature (20-25°C).

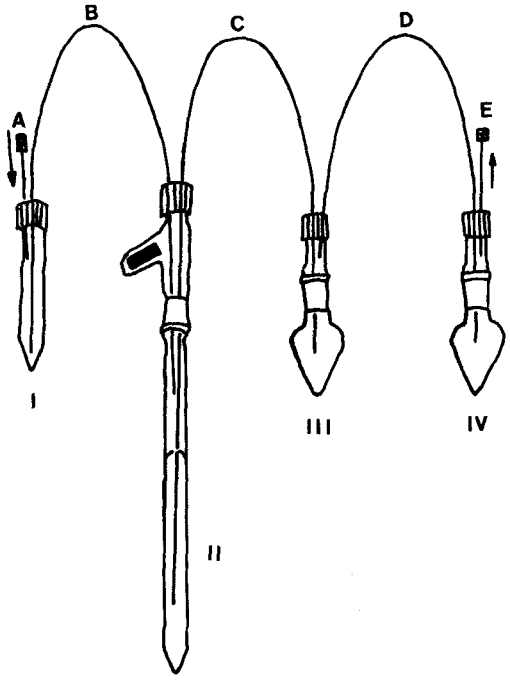

Figure 1.
Apparatus set up for alkylations with labelled alkyl iodides. Tube containing organic solvent (I), ampoule with adaptor(II), reaction flask (III) and saftey flask (IV). Gas inlet needle (A), transfer needles (B,C,D) and outlet (E).

At the end of the reaction time the two phases are allowed to separate. The organic layer is transferred by help of needles and a stream of nitrogen to a separate flask. The water phase is extracted with the organic solvent used in the reaction and the solvent transferred as above. The flask containing the extract is chilled before a sample is taken out for radioactivity measurements. The solvent is evaporated and the residue is dissolved in a small volume of dichloromethane. The solution is put on a silica gel TLC plate and the product(s) are isolated. The purity of the product is checked on both straight phase silica gel and RP-18 TLC plates by autoradiography and in case of low purity a preparative purification is performed on a RP-18 TLC plate.

The two isomeric trichloroguajacols and the trichloroveratrol were separated by liquid chromatography on silica gel with dichloromethane as mobile phase. These products were identified by comparison with authentic references (7).

All the methylthiopolychlorobenzenes were isolated after TLC on silica gel with hexane:ethyl acetate (4:1) as eluent. The two alkylthiotetrachlorobiphenyls and the bis(methylthio)-tetrachlorobiphenyl were isolated after TLC on silica gel with hexane:chloroform (4:1) and hexane:ethyl acetate (2:1), respectively. The purity of all alkyl aryl sulphides was

checked by reversed phase TLC (RP-18; methanol). Finally the 2'-methylthio-4-bromoacetophenone was purified on silica gel TLC with hexane:ethyl acetate (4:1) as mobile phase. The identity of the labelled sulphides was also confirmed by GC comparison with authentic reference compounds.

A portion of the labelled alkyl aryl sulphides synthesized was oxidized to the corresponding sulphones by use of hydrogen peroxide in acetic acid (5). The sulphones obtained were: [^{14}C]methylsulphonyl-2,5-dichlorobenzene, [^{14}C]methylsulphonyl-2,6-dichlorobenzene, [^{14}C]methylsulphonyl-2,4,5-trichlorobenzene, [^{3}H]- and [^{14}C]methylsulphonyl-pentachlorobenzene, 4-[^{14}C]methyl- and 4-[1-^{14}C]ethylsulphonyl-2,2',5,5'-tetrachlorobiphenyl and 4,4'-bis-[^{3}H]methylsulphonyl-2,2',5,5'-tetrachlorobiphenyl.

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