Gas–Liquid Phase-transfer Synthesis of Phenyl Ethers and Sulphides with Carbonate as Base and Carbowax as Catalyst

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When a mixture of a phenol (or thiol) and an alkyl halide is passed, in the gaseous state, through a solid bed of potassium carbonate (or sodium hydrogencarbonate) and catalytic amounts of Carbowax 6000, contained in a glass column at 170 °C, the corresponding ethers (or sulphides) may be collected at the outlet. The Carbowax acts in a similar manner to the crown ethers used in solid–liquid phase-transfer catalysis. The potassium carbonate–Carbowax combination allows the generation of anions up to a pK_a of ca. 12. The catalysis mechanism is discussed and the synthesis of several ethers and thioethers is reported, some of which are obtained only with difficulty by normal liquid–liquid phase-transfer catalysis.

SINCE the versatility of phase-transfer catalysis (p.t.c.) has been shown in the development of a wide and interesting range of organic reactions, there has been a considerable effort to optimize catalysis conditions, catalyst selection, and generation of the reactive nucleophile.[1]

In this regard, liquid–liquid p.t.c. (l.l.p.t.c.) between the aqueous phase of the nucleophile and the organic phase of the substrate, and solid–liquid p.t.c. (s.l.p.t.c.) between the solid phase of the nucleophile and the organic phase of the substrate, have been well established.

More recently, we have developed a method [gas–liquid p.t.c. (g.l.p.t.c.)] for using a column containing the solid salt of the nucleophile and the catalyst, in which the reagent and product are in the gas phase.[2]

In general, with regard to the type of catalyst, crown ethers and cryptands catalyse anion-promoted reactions under s.l.p.t.c. conditions and, when a long alkyl chain is present to make these catalysts liposoluble, they catalyse reactions conducted under l.l.p.t.c. conditions as well.[3] On the other hand, quaternary ammonium and phosphonium salts are catalysts for reactions carried out in l.l.-, s.l.-[4] and g.l.-[5] p.t.c. conditions. Although their ability to complex alkaline cations is not negligible, acyclic polyethers have not been reported to be phase-transfer catalysts of comparable activity, except for a few limited examples.[6] They are generally shown to be catalysts when present in large concentrations and, since they are very soluble in water, only under s.l. conditions.

Finally, the reagent anion may be placed in the reaction as such, or may be generated by another base. For example, with potassium carbonate and sodium hydrogencarbonate in polar, aprotic solvents,[7] or under phase-transfer conditions,[8] it has recently been proved possible to prepare a wide choice of nucleophiles, which give high yields of substitution product.
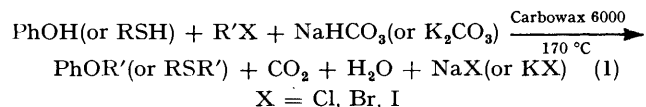
We describe herein a new procedure for the preparation of phenolic ethers and sulphides which generates the reagent anion in a column by exchange with carbonate or hydrogencarbonate, promoted by polyethylene glycol (Carbowax 6000), which constitutes the solid bed. The reaction is run under continuous flow conditions and the reaction products are collected by cooling at the outlet of the column.

A detailed report has previously been published of the synthesis of alkyl iodides and esters from alkyl halides using this method, with a phosphonium salt as the catalyst.[2]

RESULTS

Potassium hydrogencarbonate and sodium carbonate could not be used because of the poorly porous form in which they are commercially available. In fact, the solid bed should be as porous as possible in order to disperse the catalyst over a sufficiently wide surface area.

The phenyl ethers and sulphides were prepared, according to equation (1), in a column filled with solid, anhydrous

$$\text{PhOH(or RSH)} + \text{R}'\text{X} + \text{NaHCO}_3\text{(or K}_2\text{CO}_3) \xrightarrow[\text{170 °C}]{\text{Carbowax 6000}}$$
$$\text{PhOR}'\text{(or RSR}') + \text{CO}_2 + \text{H}_2\text{O} + \text{NaX(or KX)} \quad (1)$$
$$\text{X} = \text{Cl, Br, I}$$

potassium carbonate or sodium hydrogencarbonate on which the catalyst had previously been adsorbed. The column (40 cm × 2 cm) was heated to 170 °C. The liquid mixture of the phenol (or the thiophenol) (0.55—0.11 mol) and the alkylating agent (procedure A, Experimental section) was introduced using a peristaltic pump (flow rate, 40 ml/h). The gaseous state of both reagents and products was carefully maintained inside the column.

The ethers begin to collect 1—2 min after the entrance of the reagents; the average contact time between the gas-phase reagents and the solid bed may be considered to be of the same duration and shows the presence of important diffusion and partition processes between the gaseous phase and the molten catalyst. The process may be considered as that of normal partition gas chromatography, in which both products and reagents obey the laws of partition and diffusion. However, the high temperature permitted inside the column with this method leads to a more rapid reaction rate.*

* It might appear that at the high temperatures employed different solid supports could easily allow the phenol ether synthesis. The results reported in this note indicate that not all the basic supports are efficient in the test reaction of PhOH with BuBr carried out under the same conditions as in Table 1 (the conversion into PhOBu is given in brackets and was determined by [1]H n.m.r. spectroscopy). (*a*) Basic Al$_2$O$_3$ (Merck Art. No. 1061) (<1%). (*b*) Basic Al$_2$O$_3$ + MeONa (1.5 mol equiv. with respect to PhOH) (9.5%). (*c*) Basic Al$_2$O$_3$ + MeONa + Carbowax 6 000 (5% by weight with respect to the basic support) (17.0%). (*d*) MgO (C. Erba Cod. 459586) (<1%). (*e*) MgO + Carbowax 6 000 (5% by weight with respect to the basic support) (<1%).

TABLE 1

Alkylation of phenol with 1-bromobutane,[a] as a function of the base and of the catalyst

Base (mol equiv. with respect to the phenol)	Catalyst (%) [b]	Conversion (%) [c]	C-Alkylation (%) [d]
K$_2$CO$_3$ (1.5)	—	3	12
K$_2$CO$_3$ (1.0)	Carbowax (2)	66	0
K$_2$CO$_3$ (1.0)	Carbowax (5)	86 (57) [e]	0
K$_2$CO$_3$ (2.0)	Carbowax (5)	94	0
K$_2$CO$_3$ (1.0)	Brij [f] (5)	68	0
K$_2$CO$_3$ (1.0)	NaLS [g] (5)	20	13
NaHCO$_3$ (3.0)	—	68	13
NaHCO$_3$ (3.0)	Carbowax (5)	65	0

[a] Phenol, 0.55 mol, 52 g; 1-bromobutane, 0.71 mol, 97 g; T, 170 °C; flow rate, 40 ml/h. [b] By weight with respect to the base. [c] By [1]H n.m.r. spectroscopy based on the initial phenol. [d] By g.l.c. (SE 30 5% on Varaport, T, 190 °C) based on the initial phenol; only 2-n-butylphenol was detected. [e] Flow rate, 120 ml/h. [f] C$_{12}$H$_{25}$[OCH$_2$CH$_2$]$_{23}$OH. [g] C$_{12}$H$_{25}$SO$_4$Na.

peristaltic pump, the solid phenol (0.2—0.06 mol) was placed in the column mixed with the catalytic bed and the halide was allowed to flow through (procedure B, Experimental section).

The reaction products were purified by distillation or crystallization. No attempt was made to optimize the reported yields, since conversions increase when the reaction is run with higher quantities of reagents in a larger column in which the reagents remain in the gas phase for a longer period.*

DISCUSSION

Generation of the Anion.—In accordance with a series of observations that bases which are weak in aqueous solution change strength by several orders of magnitude in the absence of interaction with polar protic solvents,[9] potassium carbonate and sodium hydrogencarbonate were able to generate phenoxide and phenylthio ions in the absence of water, enabling substitution reactions with alkyl halides.

However, when the reaction is run in two phases (liquid–liquid, solid–liquid) or, as in this case, three phases (solid–liquid–gas), a catalyst is necessary if the solvent used cannot solubilize the nucleophile and does

TABLE 2

Synthesis of phenyl ethers and sulphides with K$_2$CO$_3$ and NaHCO$_3$ as bases and Carbowax 6000 as phase-transfer catalyst [a]

Expt. No.	Starting compounds ArOH (RSH)	RX	Base	Molar ratio ArOH(RSH) : RX : Base	Procedure [b]	Ether (sulphide) (b.p. [°C/mm Hg]; m.p. [°C]; ref.)	Conversion [c] (%)	Yield [d] (%)
1	PhOH	EtBr	K$_2$CO$_3$	1 : 1.3 : 1	A [e]	PhOEt (72—73/34; —; 12)	81	67
2	PhOH	BuBr	K$_2$CO$_3$	1 : 1.3 : 1	A [e]	PhOBu (89—91/18; —; 13)	86	77
3	PhOH	Me[CH$_2$]$_7$Cl	K$_2$CO$_3$	1 : 1.3 : 4.5	A [f]	PhO[CH$_2$]$_7$Me (153/15; —; 14)	72	61
4	PhOH	PhCH$_2$Cl	NaHCO$_3$	1 : 1.3 : 2.5	A [f]	PhOCH$_2$Ph (105—107/0.3; 38—40; 15)	91 [g]	57
5	4-ClC$_6$H$_4$OH	BuBr	NaHCO$_3$	1 : 1.5 : 3	A [e]	4-ClC$_6$H$_4$OBu (120/15; —; 16)	98	64
6	3,5-Me$_2$C$_6$H$_3$OH	BuBr	K$_2$CO$_3$	1 : 1.6 : 2	A [e]	3,5-Me$_2$C$_6$H$_3$OBu (128/14; —; h)	91	64
7	4-OHC$_6$H$_4$OH	BuBr	K$_2$CO$_3$	1 : 3 : 3	B [e]	4-HOC$_6$H$_4$OBu (—; 66—67; 12) / 4-BuOC$_6$H$_4$OBu (—; 43—44; 17)	85 [i]	24 / 54
8	2-OHNp [j]	MeI	K$_2$CO$_3$	1 : 4 : 2	B [e]	2-NpOMe [j] (—; 71—72; 18)	89 [k]	72
9	2-HONp [j]	EtBr	NaHCO$_3$	1 : 8 : 3.3	B [e]	2-NpOEt [j] (—; 37—38; 19)	92 [l]	83
10	2-AcC$_6$H$_4$OH	BuBr	K$_2$CO$_3$	1 : 2 : 3.3	A [f]	2-AcC$_6$H$_4$OBu (106/0.2; —; 20)	96	92
11	4-EtCOC$_6$H$_4$OH	BuBr	K$_2$CO$_3$	1 : 1.5 : 2	B [f]	2-EtCOC$_6$H$_4$OBu (115/0.25; 30—31; 21)	98	71
12	PhSH	BuBr	NaHCO$_3$	1 : 1.3 : 2	A [e]	PhSBu (107/15; —; 22)	95	71
13	PhSH	Me[CH$_2$]$_7$Cl	K$_2$CO$_3$	1 : 1.3 : 4.5	A [f]	PhS[CH$_2$]$_7$Me (108/0.25; —; 22)	92	87
14	Me[CH$_2$]$_{11}$SH	BuBr	K$_2$CO$_3$	1 : 1.5 : 2	A [f]	Me[CH$_2$]$_{11}$SBu (117/0.2; —; 24)	86 [i]	79
15	HSCH$_2$CH$_2$OH	BuBr	K$_2$CO$_3$	1 : 1.5 : 2	A [e]	HOCH$_2$CH$_2$SBu (102—103/15; —; 25)	85 [i]	70

[a] T, 170 °C; catalyst 5% by weight with respect to the base; flow rate, 40 ml/h. [b] Procedure A: liquid solutions of the phenols (or thiophenols), 0.11—0.55 mol, and of the alkylating agents, passed through the column. Procedure B: the phenols (0.06—0.22 mol) in the first two-thirds of the column, the alkylating agents passed through the column. [c] By [1]H n.m.r. spectroscopy, based on the initial phenol (or thiophenol). [d] Isolated product (distillation or crystallization: see Experimental section). [e] At 20 mmHg. [f] At 1.0 mmHg. [g] 3% of C-alkylation (g.l.c.). [h] [1]H N.m.r. δ (CCl$_4$) 6.40 (s, 3 H), 3.86 (t, 2 H), 2.25 (s, 6 H), and 2.0—0.8 (m, 7 H). [i] By g.l.c. analysis. [j] Np = naphthyl. [k] 14% of C-alkylation (n.m.r.). [l] 7% of C-alkylation (n.m.r.).

Table 1 gives the results for reaction (2) and shows the optimum reaction conditions and catalyst selection.

$$\text{PhOH} + \text{BuBr} \xrightarrow[\text{NaHCO}_3 \text{ (or K}_2\text{CO}_3\text{)}]{\text{cat.}} \text{PhOBu} + \text{CO}_2 + \text{H}_2\text{O} + \text{NaBr} \quad (2)$$
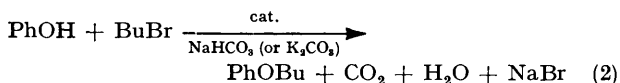
Table 2 gives the results of reactions of various phenols and thiols with alkyl halides (the catalyst was Carbowax 6000, m.p. 55—62 °C, molecular weight, *ca.* 6 000, used 5% by weight with respect to the base). When the phenol and the halide were not sufficiently miscible to give a liquid solution which could be introduced into the column with the

not promote exchange between this anion and the anion produced in the reaction.

* It is worth noting that the reaction of phenol and butyl bromide carried out under established phase-transfer conditions (A. McKillop, J. C. Fiaud, and R. P. Hug, *Tetrahedron*, 1974, **30**, 1379) gave no significant conversions if potassium carbonate was used instead of sodium hydroxide: after 15 h of stirring at room temperature, the tetrabutylphosphonium bromide catalyst gave 20% conversion into PhOBu (compared with 85% reported with sodium hydroxide). Under these conditions, when Carbowax was used as a catalyst (0.8 mol of polymer units of ethylene oxide per mol of phenol) in the presence of water (l.l.p.t.c.), a 2% conversion was achieved. In the absence of water (s.l.p.t.c.) a 10% conversion was observed.
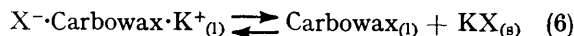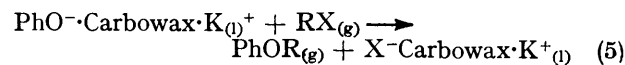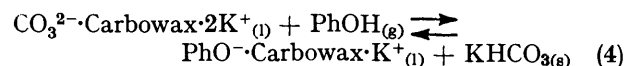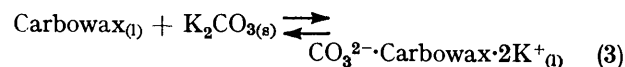
This is shown by the results given in Table 1: potassium carbonate alone is only able to promote a low conversion. That which does occur may be attributed essentially to surface imperfections of the crystals which, with their higher potential energy, are more readily attacked by phenol.

On the other hand, sodium hydrogencarbonate seems able, surprisingly, to promote the reaction even in the absence of a catalyst. It should be noted, however, that $NaHCO_3$ is not stable at the reaction temperature used, and decomposes into Na_2CO_3, CO_2, and H_2O. This probably gives rise to smaller, more imperfect, and reactive crystals. In any case, the higher percentage of C-alkylation observed in the absence of a catalyst shows that the reaction occurs in a polar medium (the surface of the solid salt). In the presence of a catalyst, no C-alkylation is observed.*

Catalyst Selection.—It is of prime importance that the catalyst does not decompose under the reaction conditions: this not only guarantees that catalysis is constant, but also prevents the formation of contaminating by-products. In this regard, the phosphonium salts are known to be stable at high temperature,[26] but not the strong bases, while ammonium salts are stable in the presence of bases, but decompose at high temperature.[10]

Therefore, the best catalysts in p.t.c. are crown ethers and cryptands, as they are not very susceptible to side reactions with the medium. However, their major disadvantage is their cost. In addition to offering the advantage of low cost, chemically stable Carbowax effectively simulates the functions of crown ethers and cryptands, and is a p.t.c. catalyst for several soft anions, in the absence of water.

Disregarding the partition equilibria of the reagents and of the products between the gaseous and the liquid phase, reactions (3)—(6) may be occurring.

$$Carbowax_{(l)} + K_2CO_{3(s)} \rightleftharpoons \\ CO_3^{2-} \cdot Carbowax \cdot 2K^+{}_{(l)} \quad (3)$$

$$CO_3^{2-} \cdot Carbowax \cdot 2K^+{}_{(l)} + PhOH_{(g)} \rightleftharpoons \\ PhO^- \cdot Carbowax \cdot K^+{}_{(l)} + KHCO_{3(s)} \quad (4)$$

$$PhO^- \cdot Carbowax \cdot K_{(l)}{}^+ + RX_{(g)} \longrightarrow \\ PhOR_{(g)} + X^- Carbowax \cdot K^+{}_{(l)} \quad (5)$$

$$X^- \cdot Carbowax \cdot K^+{}_{(l)} \rightleftharpoons Carbowax_{(l)} + KX_{(s)} \quad (6)$$

The importance of equilibria (3), (4), and (6) was not studied. In any case, the high rate of reaction (5)

justifies the assumption that equilibria are fast and, although they do not decidedly shift in a useful direction, they have little influence on the reaction rate.

Since it is possible to employ the Carbowax in catalytic quantities, equation (3) must be more right-shifted than equation (6) is left-shifted, otherwise the catalyst would be poisoned by the anion produced in the reaction.†

The reaction occurs in the liquid film made up by the phenoxide–catalyst complex which covers the inorganic salt crystals. It is here that the gaseous alkyl halide disperses and reacts. The X^- anion generated by the reaction and initially bonded in a complex with the catalyst is then exchanged by the latter with carbonate [equations (6) and (3)].
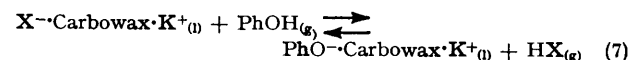
There are several phase-transfer processes (gas–liquid and solid–liquid) in the above scheme, promoted by diffusion, partition, and exchange [equations (4) and (5)], which occur without the aid of a catalyst. In order that the equilibrium shown in equations (3) and (6) may occur, a catalyst is required and Carbowax shows a behaviour similar to that of the classical phase-transfer catalyst. One can make a comparison with s.l.p.t.c.: in this case the liquid phase comprises the molten catalyst and a fraction of the organic substrate and product, both in equilibrium with their gaseous phases.

There appear (Table 1) to be no differences between Carbowax and Brij with regard to reaction rate (yield) or the nature of the reactive microenvironment (C- or O-alkylation). Probably the fact that Brij is a poorer complexing agent (23 oxyethylene groups) than Carbowax (140 oxyethylene groups on average) is compensated for by the presence of alkyl chains. These latter may play an important role in the salt exchange, 'softening' the salt, and may affect the absolute reaction rate (less polar medium).

As in l.l.- and s.l.-p.t.c., under the conditions described herein the anionic sodium lauryl sulphate is not an effective catalyst (see also the synthesis of alkyl iodides [2b]), since the low conversion percentages are always accompanied by C-alkylation products. It does not promote exchange between the anions (the real function of the phase-transfer catalyst), and the reaction proceeds in an environment which is not different from that of the inorganic salt.

Synthetic Applications.—The potassium carbonate–Carbowax combination allows the generation of anions up to a pK_a of $ca.$ 12. Since alkoxides cannot be generated in $situ$, complete selectivity is observed towards the

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* These results are in agreement with observations (G. Bram, N. Geraghty, G. Nee, and J. Seyden-Penne, *J. Chem. Soc., Chem. Commun.*, 1980, 325) on the alkylation of ambident anions by alkyl halides carried out with the reagents adsorbed on insoluble supports: acetoacetate anions gave C-alkylation products when adsorbed on alumina, while O-alkylation predominates on polystyrene resin-supported hexamethylphosphoric triamide. See also the behavior of phase-transfer catalysts supported on silica gel (P. Tundo and P. Venturello, *J. Am. Chem. Soc.*, 1979, **101**, 6606) and on polystyrene (M. Molinari, F. Montanari, S. Quici, and P. Tundo, *J. Am. Chem. Soc.*, 1979, **101**, 3920).

† It may be also supposed that PhOH exchanges with $X^- \cdot$ Carbowax·$K_{(l)}$ [equation (7)] and consequently reaction (8) occurs. We have shown that equation (7) does not occur either

$$X^- \cdot Carbowax \cdot K^+{}_{(l)} + PhOH_{(g)} \rightleftharpoons \\ PhO^- \cdot Carbowax \cdot K^+{}_{(l)} + HX_{(g)} \quad (7)$$

$$HX_{(g)} + K_2CO_{3(s)} \longrightarrow KX_{(s)} + KHCO_{3(s)} \quad (8)$$

with PhOH or with stronger acids like AcOH; when such acids were allowed to flow in the gaseous state through finely ground KBr coated with catalyst (Carbowax 6000 or $Bu_4P^+Br^-$) no generation of HBr was detected.

sulphur in 2-mercaptoethanol, with the exclusive formation of the S-alkylation product.

The pK_a of 2-acetylphenol is higher than that of other phenols since this compound is stabilized by a hydrogen bond with the carbonyl group.[11] However, under the conditions described here, the anion generated is sufficiently reactive and gives the O-alkylation product. We have observed no etherification reaction with alkyl halides with l.l.p.t.c. procedures.

This new method affords some selectivity for suitable substrates and offers the possibility of preparing compounds which are obtainable only with difficulty by normal l.l.p.t.c. Moreover, it offers many advantages not readily achieved with classical synthetic methods: no organic or aqueous solvents are used and if there are no side products, this leads to a high degree of purity for the reaction product.

EXPERIMENTAL

^{1}H N.m.r. spectra were recorded on a Hitachi–Perkin-Elmer R-24B 60 MHz spectrometer using tetramethylsilane as the internal standard. A Varian series 1440 gas chromatograph and a Masterflex, model No. 7013 peristaltic pump were used. All organic and inorganic reagents were ACS grade and were used without further purification. Catalysts were supplied by C. Erba (sodium lauryl sulphate), Fluka (Brij 35), and Merck (Carbowax 6000).

Preparation of Catalytic Bed.—In each case, the catalyst (10.0 g) was dissolved in methanol (300 ml) and potassium carbonate or sodium hydrogencarbonate (190 g) was added. The solvent was removed under reduced pressure and the resulting powder was oven-dried at 130 °C for 15 h.

Ether Synthesis.—Procedure A. The column was filled with a weighed quantity of prepared catalytic bed while held horizontally in a protective sheath which contained liquid paraffin thermostatted at 170 °C. The final traces of solvent were removed under reduced pressure.

Working always under reduced pressure, the liquid mixture of the phenol (or thiophenol) and alkyl halide was passed along the column, using a peristaltic pump, at a rate of 40 ml/h. Reaction products were collected at the outlet of the condensation column and the crude final product was analysed with ^{1}H n.m.r. spectroscopy and g.l.c. (in comparison with authentic samples) to determine the composition and degree of conversion. Conversions into the ether from phenol were established by integration of the singlet, triplet, or quartet corresponding to CH_2O (or CH_2S) in comparison with the aromatic protons common to both the phenol and the phenolic ether. For Expts. 14 and 15 (Table 2) the degree of conversion was established by g.l.c. No undescribed by-products were observed. The collected mixture was washed with 5% sodium hydroxide and water, dried, and distilled to give the pure product. For example, the mixture of thiophenol (0.33 mol, 36 g) and 1-bromobutane (0.44 mol, 60 g) was allowed to flow (40 ml/h) through the solid bed at 170 °C, which comprised sodium hydrogencarbonate (0.66 mol) and Carbowax (59 g) at 20 mmHg. G.l.c. analysis showed the formation of butyl phenyl sulphide, and ^{1}H n.m.r. spectroscopy showed a conversion of 95% [integration of triplet at δ (CCl$_4$) 2.86 corresponding to CH_2S *versus* aromatic signals]. After the normal procedure the product was distilled to give 39 g, yield 71%, b.p. 107 °C (15 mmHg), n_D^{20} 1.5476.

Procedure B. For phenols which were solid and insoluble in the alkyl halide, the phenol was weighed and mechanically mixed with a known quantity of catalytic bed and then placed in the first two-thirds of the column. The final third of the column was then filled with catalytic bed containing no phenol. The alkyl halide was then passed through and the products were collected at the outlet, using the method described in procedure A. For example, hydroquinone (0.10 mol, 11 g), was mechanically mixed with potassium carbonate (0.2 mol) which contained Carbowax and placed in two-thirds of the column, and the other third was filled only with potassium carbonate (0.1 mol) and Carbowax. 1-Bromobutane (0.3 mol, 41 g) was passed through (40 ml/h) at 170 °C, under reduced pressure (1 mmHg). The products were solidified by cooling at the outlet. G.l.c. showed a conversion of 85% with respect to the initial hydroquinone. Treatment of the reaction mixture with 10% sodium hydroxide separated the mono- from the di-butyl derivative. Usual procedures gave 4-n-butoxyphenol, 4.0 g, crystallized from light petroleum, m.p. 66—67 °C (yield 24%) and 1,4-di-n-butoxybenzene, 12.0 g, crystallized from pentane, m.p. 43—44 °C (yield 54%).

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