REACTIONS WITH THIOETHOXIDE ION IN DIMETHYLFORMAMIDE

I. SELECTIVE DEMETHYLATION OF ARYL METHYL ETHERS*

By G. I. Feutrill† and R. N. Mirrington†‡

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Abstract

Recent methods for demethylating aryl methyl ethers have been briefly reviewed, especially methods involving the use of nucleophilic reagents.

Sodium thioethoxide dissolved in *N*,*N*-dimethylformamide has been developed as a powerful new reagent for demethylating aryl methyl ethers cleanly and rapidly in high yield. The reaction conditions can be controlled so that aromatic bromo substituents or isolated olefinic bonds are unaffected.

Of special interest has been the selective monodemethylation of the methyl ethers of di- and tri-hydric phenols, exemplified by the isolation in high yield of orcinol monomethyl ether, *p*-methoxyphenol, guaiacol, and phloroglucinol dimethyl ether from the respective fully *O*-methylated compounds. An exception was pyrogallol trimethyl ether which afforded pyrogallol 1-monomethyl ether in high yield.

During multistage syntheses, a phenolic hydroxyl group is usually protected by conversion into the methyl ether, firstly because of the ease of preparation of anisoles in high yield and, secondly, because of the comparative inertness of these compounds to a wide variety of reagents and conditions. Because of their stability, however, aryl methyl ethers present some difficulty when regeneration of the parent phenol is desired. Although many reagents have been developed for this purpose, none is completely specific when sensitive functional groups are present elsewhere in the molecule.

The cleavage of ethers has been reviewed by Burwell[1] and synthetic applications of aryl methyl ethers and their subsequent cleavage have been discussed more recently by McOmie.[2] The methods available for the regeneration of phenols from aryl methyl ethers include cleavage by acidic reagents, or by organometallic compounds, by treatment with alkali metals, or by reaction with nucleophiles.

Cleavage by acidic reagents such as solutions of hydrochloric, hydrobromic, and hydriodic acids is one of the oldest yet still very common procedures. Amine salts, especially the pyridinium halides,[2,3] have also been used widely, but the reaction conditions required are harsh, and limit the use of such reagents.

Demethylations by Lewis acids, like the protic acids, are considered to proceed via oxonium ion intermediates, and the trichlorides and tribromides of aluminium

* A preliminary account of some of this work appeared in *Tetrahedron Lett.*, 1970, 1327.

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[1] Burwell, R. L., *Chem. Rev.*, 1954, **54**, 615.

[2] McOmie, J. F. W., *Adv. org. Chem.*, 1963, **3**, 228.

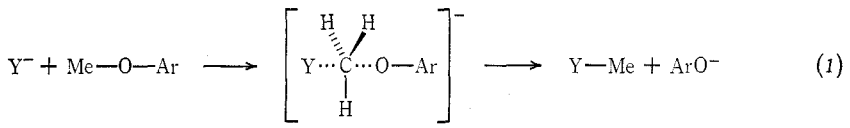
[3] Curphey, T. J., Hoffman, E. J., and McDonald, C., *Chemy Ind.*, 1967, 1138; Petrzilka, T., Haefliger, W., and Sikemeier, C., *Helv. chim. Acta*, 1969, **52**, 1102.

and boron appear to have been the most successful reagents of this type. The boron trihalides in particular have been used under relatively mild conditions.[4]

Of the organometallic reagents, methylmagnesium iodide, in the absence of solvent, has been used widely for the cleavage of anisoles, and has often been successful where acidic reagents have proved to be unsatisfactory.[5,6] Cleavage of ethers has also been achieved by treatment with alkali metal alkyls and, in particular, a solution of lithium biphenyl in tetrahydrofuran has been used to demethylate anisole in high yield.[7]

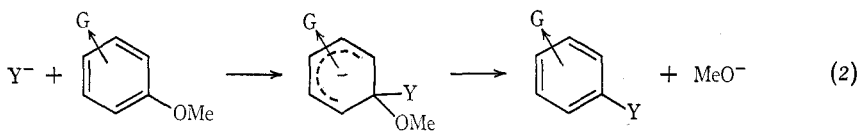
Solutions of alkali metals, usually sodium or lithium, in liquid ammonia, in the absence of a proton source, cleave aryl alkyl ethers to give good yields of the parent phenols.[8] In heterogeneous reactions, sodium has been shown to convert anisole into phenol, but elevated temperatures are required. Sodium–potassium alloy is far more reactive and achieves the same result at room temperature.[1,7,9]

Nucleophilic attack at the alkyl carbon of an anisole, with subsequent displacement of the aryloxide ion (eqn. (*1*)), has been investigated as a method of demethylation under basic conditions.



(*1*)

Cleavages with anions such as hydroxide,[1,10,11] methoxide,[12] ethoxide,[12] sulphite,[13] thioethoxide,[14] and thiophenoxide,[15,16] each in protic solvents, have required the use of high temperatures and long reaction times, mostly in sealed tubes or autoclaves. Despite these drastic conditions, in some cases only partial demethylation was achieved. Aryl methyl ethers which have a strong electron-withdrawing substituent (G) require milder conditions for cleaving the ether linkage, but these compounds are also likely to suffer substitution at the aromatic carbon atom with strong carbon nucleophiles (eqn (*2*)).[14]



(*2*)

[4] McOmie, J. F. W., Watts, M. L., and West, D. E., *Tetrahedron*, 1968, **24**, 2289; Dean, F. M., Goodchild, J., Houghton, L. E., Martin, J. A., Morton, R. B., Parton, B., Price, A. W., and Somvichien, N., *Tetrahedron Lett.*, 1966, 4153.

[5] Wilds, A. L., and McCormack, W. B., *J. Am. chem. Soc.*, 1948, **70**, 4127.

[6] Johnson, W. S., Rogier, E. R., and Ackerman, J., *J. Am. chem. Soc.*, 1956, **78**, 6322.

[7] Eisch, J. J., *J. org. Chem.*, 1963, **28**, 707.

[8] Birch, A. J., *J. chem. Soc.*, 1947, 102.

[9] Markiewitz, K. H., and Dawson, C. R., *J. org. Chem.*, 1965, **30**, 1610.

[10] Chesterfield, J. H., McOmie, J. F. W., and Tute, M. S., *J. chem. Soc.*, 1960, 4590.

[11] Cannon, J. R., and Metcalf, B. W., unpublished data.

[12] Wacek, A. v., and Morghen, I., *Ber. dt. chem. Ges.*, 1937, **70B**, 183.

[13] Gierer, J., and Koutek, B., *Acta chem. scand.*, 1969, **23**, 1343.

[14] Koutek, B., and Setinek, K., *Collн Czech. chem. Commun.*, 1968, **33**, 866.

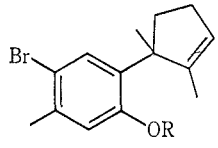
[15] Hughes, G. K., and Thompson, E. O. P., *Nature*, 1949, **164**, 365.

[16] Wildes, J. W., Martin, N. H., Pitt, C. G., and Wall, M. E., *J. org. Chem.*, 1971, **36**, 721.

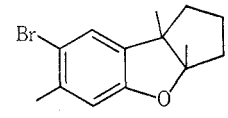
Halide ions have been shown to be powerful nucleophiles in some solvents.[17] Thus, lithium iodide in refluxing collidine successfully converted oestrone methyl ether into oestrone in 48 hr,[18] and lithium bromide in acetonitrile selectively demethylated lunasine perchlorate to lunacrine.[19] The selectivity and the mild conditions of the latter reaction may be ascribed to the electron-withdrawing effect of the quaternary nitrogen atom in the starting material.

Sodium amide in refluxing piperidine[20] has been reported to show great promise in the conversion of aryl ethers into the corresponding phenols under basic conditions. Anisole was converted into phenol in 82% yield after 12 hr by this method. Brotherton and Bunnett attributed the high nucleophilicity of the reagent to the formation of piperidide ions; this was supported by the isolation of *N*-alkyl piperidines in several cases.

The dealkylation of aryl alkyl ethers by diphenyl phosphide ion in tetrahydrofuran has been investigated by Mann and Pragnell.[21] The reagent was found to convert anisole into phenol in 83% yield with coincident formation of methyl diphenyl phosphine.



(1) R = H
(2) R = Me



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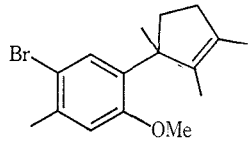

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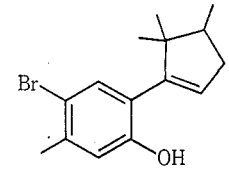


(5)

In our projected synthesis of laurinterol, the phenol (1) was a key intermediate. The corresponding methyl ether (2) was available from earlier work,[22] but it seemed that demethylation by acidic reagents would be complicated by conversion of the phenol into the cyclic ether (3), or other rearrangement products.* In addition, the presence of the aromatic bromo substituent made it seem unlikely that the use

* Yamada *et al.*[23] have since attempted to demethylate the closely related bromo anisole (4) with boron trichloride, but this reaction led to the rearranged product (5).

[17] Parker, A. J., *Adv. org. Chem.*, 1965, **5**, 1.
[18] Harrison, I. T., *Chem. Commun.*, 1969, 616.
[19] Goodwin, S., and Horning, E. C., *J. Am. chem. Soc.*, 1959, **81**, 1908.
[20] Brotherton, T. K., and Bunnett, J. F., *Chemy Ind.*, 1957, 80.
[21] Mann, F. G., and Pragnell, M. J., *J. chem. Soc.*, 1965, 4120.
[22] Mirrington, R. N., and Nichols, R. J., unpublished data.
[23] Yamada, K., Yazawa, H., Uemura, D., Toda, M., and Hirata, Y., *Tetrahedron*, 1969, **25**, 3509.

of organometallic reagents or alkali metals for the demethylation of (2) would be successful.

It was clear that in order to convert (2) into (1) it was necessary to obtain a demethylation procedure which could be carried out under basic conditions, and which was amenable, on the grounds of convenience and expense, to comparatively large-scale reactions. Further considerations in the choice of reagent were its ready preparation and the ease of recovery of the demethylated product.

None of the available nucleophilic reagents appeared to meet these criteria. Piperidide ions had been shown to react readily with aromatic bromides;[20,24] subsequently Yamada and coworkers[23] were unable to convert (2) into (1) using this reagent. Lithium halides appear to react very slowly even with unhindered methoxy groups.[18] The use of diphenylphosphide ion in tetrahydrofuran appeared unattractive for two reasons. Apart from the relative inaccessibility of the reagent, Mann and Pragnell experienced some difficulty in recovering the phenolic product from the reaction medium.[21]

Since demethylation of aryl methyl ethers by nucleophilic reagents proceeds by S_N2 displacement on the alkyl methyl group (eqn (*1*)), one is obliged, in seeking a more suitable reagent, to consider the enhancement of nucleophilicity of anions dissolved in dipolar aprotic solvents.[25] The factors determining the nucleophilic activity of an anion have also been widely discussed, and there is general agreement with the summary that nucleophilicity involves the reaction rate and is dependent on the polarizability and basicity of the anion.[26,27] Negative ions with the very polarizable sulphur atom are thus expected to be strong nucleophiles; such ions[13–16] in protic solvents have been used for the demethylation of anisoles.

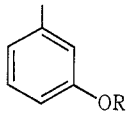
Consequently, thioethoxide ion was chosen as the nucleophile because of its ready preparation from ethanethiol and sodium hydride, and the ease with which the phenol could be separated from excess reagent and the volatile methyl ethyl sulphide (eqn (*1*); Y = EtS). The advantages of using dipolar aprotic solvents in bimolecular reactions involving anions and uncharged species have been detailed by Parker.[17,25,28] *N*,*N*-Dimethylformamide (DMF) was chosen as solvent in the present case because it is an efficient solvent for thioethoxide ion, it is stable to strong bases at reflux temperatures (cf. DMSO[29]), and it is water-soluble, allowing for easy recovery of phenolic products.

Results

When *m*-cresol methyl ether (6a) was heated under reflux (*c.* 150°) with 2·5 equiv. of thioethoxide ion in DMF for 3 hr, *m*-cresol (6b) and ethyl methyl sulphide were formed in high yield. In view of this result, it was decided to investigate the demethylation of a number of other substituted anisoles under these "standard" conditions. It soon became clear, however, that these conditions were more than

[24] Huisgen, R., and Sauer, J., *Angew. Chem.*, 1960, **72**, 91.
[25] Parker, A. J., *Q. Rev. chem. Soc.*, 1962, **16**, 163.
[26] Edwards, J. O., and Pearson, R. G., *J. Am. chem. Soc.*, 1962, **84**, 16.
[27] Bunnett, J. F., *A. Rev. phys. Chem.*, 1963, **14**, 271.
[28] Parker, A. J., *Adv. phys. org. Chem.*, 1967, **5**, 173; Parker, A. J., *Chem. Rev.*, 1969, **69**, 1.
[29] Allan, G. G., Moks, E., and Nelson, E. N., *Chemy Ind.*, 1967, 1706.

necessary for complete reaction in many cases, and that lower temperatures and shorter times of reaction were not only sufficient, but also desirable with certain substrates, as indicated below. When the demethylation of (6a) was monitored by thin-layer chromatography, the reaction was complete at reflux after approximately 45 min. The reaction even proceeded slowly at 25°, and at 100° was also complete after 3 hr. However, the fact that the standard conditions had no detrimental effect, on either the yield or the purity of the product with simple anisoles, was noteworthy.



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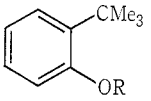

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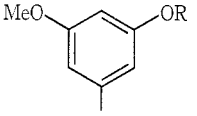

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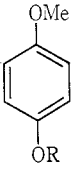

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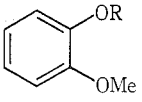

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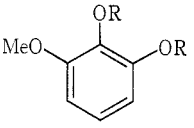

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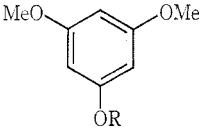

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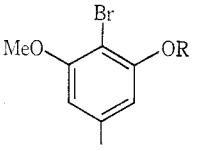


(13)

(a) R = Me (b) R = H

It was found that *o*-t-butylanisole (7a), which, like the bromoanisole (2), contains a bulky substituent *ortho* to the methoxyl group, was converted into *o*-t-butylphenol (7b) in high yield.

It was expected that the methyl ethers of polyhydric phenols would, subsequent to the cleavage of one ether linkage, resist further demethylation, as it seemed unlikely that a negatively charged species would be susceptible to further nucleophilic attack. When orcinol dimethyl ether (8a) was subjected to the standard reaction conditions, orcinol monomethyl ether (8b) was isolated in good yield. Previous preparations of (8b) by monodemethylation of (8a) using potassium hydroxide in refluxing ethylene glycol, or by monomethylation of orcinol at carefully controlled pH, have resulted in lower yields.[11] In the latter case, the formation of *C*-methylated by-products was a further complication.[30] Our procedure has since been used successfully in the preparation of (8b) on a large scale.[31]

p-Dimethoxybenzene (9a) also underwent smooth monodemethylation under the standard conditions and *p*-methoxyphenol (9b) was formed. Surprisingly, veratrole (10a) underwent some bisdemethylation to catechol when the reaction was allowed to proceed for 3 hr, but shortening of the reaction time to 2 hr led to guaiacol (10b) as the sole product.

[30] Ridley, D. D., Ritchie, E., and Taylor, W. C., *Aust. J. Chem.*, 1968, **21**, 2979.

[31] Cannon, J. R., Cresp, T. M., Metcalf, B. W., Sargent, M. V., Vinciguerra, G., and Elix, J. A., *J. chem. Soc.* (*C*), 1971, 3495.

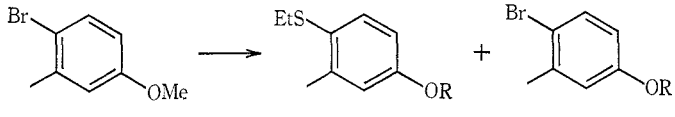
When pyrogallol trimethyl ether (11a) was subjected to the standard conditions, 2,3-dihydroxyanisole (11b) was formed. In the light of the formation of catechol from veratrole, and the fact that the 2-methyl ether linkage of (11a) is cleaved under comparatively mild basic conditions,[32] the isolation of (11b) was not unexpected. This method appears to be the most efficient and convenient for preparing (11b) in high yield.[33]

Bisdemethylation appeared to be intrinsically more facile in *ortho*-dimethoxybenzenes, since phloroglucinol trimethyl ether (12a), under the same conditions, afforded only 3,5-dimethoxyphenol (12b), free from any phloroglucinol monomethyl ether. This result may be contrasted with the usual procedures for preparing (12b) by partial methylation which invariably give mixtures of mono- and di-methyl ethers.[34]

The presence of the bromo substituent in (2) presented a possible complication in the use of the thioethoxide reagent to convert (2) into (1). The same properties that make this reagent a powerful demethylating species also facilitate its participation in S_NAr reactions[35] (eqn (*3*)):

$$Ar\text{–}X + {}^{-}S\text{–}Et \rightarrow Ar\text{–}S\text{–}Et + X^{-} \qquad (3)$$

In order to test the reaction of the thioethoxide reagent with a halo anisole, 4-bromo-3-methylanisole (14)[36] was chosen as a model with a similar substitution pattern to (2). When (14) was subjected to the standard demethylating conditions, the substituted phenol (15b) was the major product. However, when the reaction was conducted at 100° for 3 hr, the bromo phenol (16b) was isolated in 97% yield. Since the phenol (16b) was unaffected when heated with sodium thioethoxide under the standard conditions, it was concluded that the S_NAr reaction on (14) was preceding demethylation at the higher temperature.



(14) (15) (16)

(a) R = Ac
(b) R = H

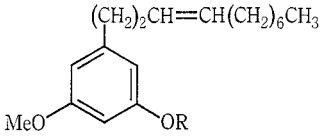
Other workers in this laboratory required a sample of 4-bromo-3-hydroxy-5-methoxytoluene (13b) for part of their study of some acid-catalysed rearrangements of aromatic bromo compounds.[31] A previous preparation of this compound by Inubushi and Nomura,[37] which involved a tedious route from 4-bromo-3,5-dinitrotoluene, resulted in material of dubious purity (m.p. 64–69°). Cannon *et al.*[31] had shown that 4-bromoorcinol dimethyl ether (13a) could be prepared by treatment of

[32] Hurd, C. D., and Winberg, H. E., *J. Am. chem. Soc.*, 1942, **64**, 2085.
[33] Surrey, A. R., *Org. Synth.*, 1953, Coll. Vol. III, 759.
[34] Pratt, D. D., and Robinson, R., *J. chem. Soc.*, 1924, 188.
[35] Miller, J., "Reaction Mechanisms in Organic Chemistry. Aromatic Nucleophilic Substitution." p. 1. (Elsevier: London 1968.)
[36] Zeide, O. A., and Dubinin, B. M., *J. gen. Chem. USSR*, 1932, **2**, 472 (*Chem. Abstr.*, 1933, **27**, 963).
[37] Inubushi, Y., and Nomura, K., *J. pharm. Soc. Japan*, 1961, **81**, 7 (*Chem. Abstr.*, 1961, **55**, 15493).

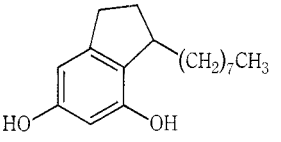
4-lithioorcinol dimethyl ether with 1,2-dibromoethane. It seemed that monodemethylation of (13a) could provide a convenient synthesis of (13b). Nucleophilic displacement of the bromo substituent appeared less likely than in (14), due to more severe hindrance by the two *ortho* methoxy groups.

In fact, demethylation of (13a) proceeded smoothly at 100° to afford the desired product (13b), m.p. 70–72°, in high yield. The n.m.r. spectrum of (13b) showed two multiplets centred at δ 6·79 and 6·26, each integrating for one proton, which together appeared to be a distorted AB quartet. These were attributed to the non-equivalent *meta* aromatic protons, and a three-proton singlet at δ 3·78 was assigned to the methoxy group. These data confirmed that monodemethylation had been effected, and it was evident that no rearrangement of the bromo substituent had occurred, for remethylation of the product afforded (13a).

Cannon and Metcalf attempted to demethylate persoonol dimethyl ether (17)[3b] with boron tribromide, but obtained[11] a bicyclic product, presumably (20) or (21), from this reaction. While it was not expected that the thioethoxide reagent would effect bisdemethylation to the 5-alkenylresorcinol (persoonol), we decided to investigate the effect of this reagent on (17) because the behaviour of the (*Z*)-double bond under the reaction conditions was of interest, especially in view of the fact that some other similar nucleophilic reagents are known[16] to cause isomerization of isolated double bonds.



	Config.	R
(17)	(Z)	Me
(18)	(Z)	H
(19)	(E)	Me



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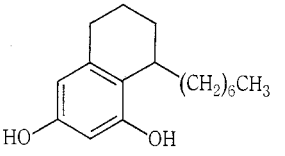

(21)

When (17) was subjected to the standard demethylation procedure, the corresponding monomethyl ether (18) was obtained in good yield. This product had a molecular weight of 276 by mass spectrometry, indicating that monodemethylation had occurred. The n.m.r. spectrum of (18) confirmed this conclusion and the region between δ 5·48 and 5·18 closely resembled that of the starting material, and differed significantly from the same area of the n.m.r. spectrum of the (*E*)-olefin (19).[38] From this evidence, and the lack of infrared absorption near 960 cm^{-1}, characteristic of the (*E*)-olefin (19), it was concluded that no isomerization of the unsaturated side chain had taken place. This was confirmed by remethylation of (18) to the dimethyl ether (17).

The outcome of the treatment of (2) with the thioethoxide reagent will be discussed in a future article on the synthesis of laurinterol. The usefulness of this reagent for the cleavage of methylene ethers and aryloxyacetic acid esters, and for the *O*-alkyl cleavage of methyl esters is discussed in the accompanying article.[39]

[38] Cannon, J. R., and Metcalf, B. W., *Aust. J. Chem.*, 1971, **24**, 1925.
[39] Feutrill, G. I., and Mirrington, R. N., *Aust. J. Chem.*, 1972, **25**, 1731.

Experimental

Analyses were carried out by the Australian Microanalytical Service, Melbourne. Melting points were determined on a Kofler block. All boiling points quoted for less than 2 g of material refer to the bath temperature.

I.r. spectra were measured with a Perkin–Elmer Infracord 137G spectrometer and n.m.r. spectra were measured with a Varian A60A spectrometer using carbon tetrachloride solutions unless stated otherwise. N.m.r. signals are described in terms of multiplicity, intensity, chemical shift in p.p.m., assignment, and coupling constant in Hz (from first-order considerations) with use of the following abbreviations: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; (br), broad. The presence of hydroxyl protons was confirmed by exchange with D_2O. Mass spectra were determined with a Varian MAT-CH7 spectrometer at 70 eV; all ions having an abundance greater than 5% of the base peak and of *m/e* greater than 77 are recorded.

Silica gel for column chromatography was BDH 60–120 mesh; for analytical and preparative thin-layer chromatography (t.l.c.), Ajax S silica gel and Merck Kieselgel GF_{254} (nach Stahl), were used. *N*,*N*-Dimethylformamide was distilled from calcium hydride under a reduced pressure of nitrogen, immediately before use. Ethanethiol (b.p. 36–37°) was purified by distillation from calcium hydride. Light petroleum (b.p. 45–70°) was distilled from phosphorus pentoxide. Organic extracts were dried over magnesium sulphate before evaporation.

G.l.c. analysis was carried out with a Perkin–Elmer 880 gas chromatograph, using oxygen-free nitrogen as carrier gas (flow rate 30 ml/min) and a copper column, 10 ft by 0·125 in., packed with 5% Apiezon L on non-acid-washed Chromosorb W (80/100 mesh). Preparative g.l.c. was carried out with a Wilkens Aerograph A-700 Autoprep, using helium as carrier gas and an aluminium column, 10 ft by 0·375 in., packed with 15% Apiezon L on non-acid-washed Chromosorb W (60/80 mesh).

(i) m-*Cresol* (*6b*)

Ethanethiol (1·25 g), dissolved in dry DMF (20 ml), was added to a suspension of sodium hydride (1·0 g of a 50% oil dispersion) in dry DMF (10 ml) under an atmosphere of nitrogen. The mixture was stirred for 5 min before a solution of *m*-methoxytoluene (6a) (1·0 g) in dry DMF (10 ml) was added; the solution was then refluxed for 3 hr. The cooled mixture was acidified with 10% aqueous HCl and extracted with ether. The ether layer was washed with water and extracted with 5% aq. NaOH; then the alkaline extracts were acidified, and re-extracted with ether. The ethereal solution was washed with water, dried, and evaporated to give *m*-cresol (6b) as a light brown oil (0·85 g). This was converted into *m*-methylphenoxyacetic acid which crystallized from light petroleum as needles, m.p. 102° (lit.[40] 102°). N.m.r. spectrum: s, 1, 9·0 (OH); m, 4, 7·37–6·47 (ArH); s, 2, 4·61 (CH_2); s, 3, 2·30 ($ArCH_3$).

The vapours emitted from this reaction were passed through a cold trap. The n.m.r. spectrum of the condensate was identical with a published spectrum of ethyl methyl sulphide.[41]

(ii) o-*t-Butylphenol* (*7b*)

o-t-Butylanisole (7a) (1·0 g) was treated with 2·5 equiv. of the sodium thioethoxide reagent in refluxing DMF (40 ml) for 3 hr as described in (i). The cooled mixture was acidified with 10% aq. HCl and extracted with ether. The ethereal solution was washed with saturated brine, and dried. Evaporation gave a brown oil (1·25 g) which was chromatographed on silica gel to yield *o*-t-butylphenol (7b) as a pale yellow oil (0·88 g). N.m.r. spectrum: m, 4, 7·31–6·31 (ArH); s(br), 1, 4·73 (OH); s, 9, 1·38 (CMe_3).

The above product was converted into *o*-t-butylphenoxyacetic acid which crystallized from light petroleum as needles, m.p. 144·5–145·5° (lit.[42] 145·5–146·5°). N.m.r. spectrum: s, 1, 9·05 (OH); m, 4, 7·55–6·62 (ArH); s, 2, 4·71 (CH_2); s, 9, 1·42 (CMe_3).

[40] Higginbotham, L., and Stephen, H., *J. chem. Soc.*, 1920, **117**, 1534.

[41] Bhacca, N. S., Johnson, L. F., and Shoolery, J. N., "High Resolution NMR Spectra Catalogue." Spectrum No. 46. (Varian Associates: Palo Alto, Cal., 1962.)

[42] Hart, H., *J. Am. chem. Soc.*, 1949, **71**, 1966.

(iii) *3-Hydroxy-5-methoxytoluene* (*8b*)

Orcinol dimethyl ether (8a) (1·0 g) was treated with 5 equiv. of the sodium thioethoxide reagent in DMF (40 ml) as in (i). The product was obtained as a pale brown oil (0·85 g) which crystallized slowly. Distillation (b.p. 150°/7 mm) followed by crystallization from benzene–light petroleum afforded (8b) as off-white prisms, m.p. 61° (lit.[43] 63°). N.m.r. spectrum: s(br), 1, 6·50 (OH); m, 3, 6·29–6·06 (ArH); s, 3, 3·55 (OCH_3); s, 3, 2·11 ($ArCH_3$).

(iv) p-*Methoxyphenol* (*9b*)

p-Dimethoxybenzene (1·0 g) was treated with 5 equiv. of the thioethoxide reagent in DMF (40 ml) as in (i). *p*-Methoxyphenol was isolated as a pale yellow oil (0·88 g) which crystallized from benzene–light petroleum as needles, m.p. 54° (lit.[44] 56°, 55°, or 53°). N.m.r. spectrum: s, 4, 6·73 (ArH); s(br), 1, 6·17 (OH); s, 3, 3·70 (OCH_3).

(v) o-*Methoxyphenol* (*10b*)

(A) Veratrole (10a) (1·0 g) was heated with 5 equiv. of the thioethoxide reagent in DMF (40 ml) as in (i). When the reaction was worked up as before, a brown oil (0·8 g) was obtained. Analytical g.l.c. of this product at 150° showed the presence of two compounds of relative peak areas 3 : 1. The retention times of these compounds were identical with those of guaiacol and catechol respectively.

(B) Veratrole (1·0 g) was treated as in (A) above except that only 2·5 equiv. of thioethoxide reagent were used, and the reaction time was shortened to 2 hr. After workup, guaiacol (10b) was obtained as a pale yellow oil (0·87 g) which was converted into *o*-methoxyphenoxyacetic acid; this crystallized from ether–n-pentane as needles, m.p. 119° (lit.[45] 121·0–121·4°). N.m.r. spectrum (acetone): s(br), 1, 9·00 (OH); s(br), 4, 6·90 (ArH); s, 2, 4·67 (CH_2); s, 3, 3·86 (OCH_3).

(vi) *2,3-Dihydroxyanisole* (*11b*)

Pyrogallol trimethyl ether (11a) (1·0 g) was treated with 7·5 equiv. of the thioethoxide reagent in DMF (40 ml) as in (i). When the reaction was worked up in the usual way, (11b) was obtained as a dark brown oil (0·80 g). N.m.r. spectrum: s(br), 2, 7·05 (OH); m, 3, 6·75–6·16 (ArH); s, 3, 3·73 (OCH_3).

This product was treated with pyridine (10 ml) and acetyl chloride (5 ml) to give 2,3-diacetoxyanisole (1·2 g) which crystallized from benzene–light petroleum as off-white plates, m.p. 89–90° (lit.[46] 91–92°). N.m.r. spectrum: m, 3, 7·32–6·58 (ArH); s, 3, 3·71 (OCH_3); s, 3, 2·21 ($COCH_3$); s, 3, 2·18 ($COCH_3$).

(vii) *3,5-Dimethoxyphenol* (*12b*)

Phloroglucinol trimethyl ether (12a) (1·0 g) was treated with 7·5 equiv. of the thioethoxide reagent in DMF (40 ml) as in (i). The reaction product was isolated as a pale brown oil (0·9 g). N.m.r. spectrum: s(br), 1, 6·30 (OH); m, 3, 6·08–6·00 (ArH); s, 6, 3·70 (OCH_3).

The foregoing oil was treated with *p*-nitrobenzoyl chloride in pyridine to give 3,5-dimethoxyphenyl *p*-nitrobenzoate which crystallized from benzene–n-pentane as pale yellow plates (1·5 g), m.p. 149·5–150·5° (lit.[47] 150·5°). N.m.r. spectrum ($CDCl_3$): s, 4, 8·52 (ArH); s, 3, 6·40 (ArH); s, 6, 3·81 (OCH_3).

(viii) *4-Bromo-3-methylphenol* (*16b*)

(A) 2-Bromo-5-methoxytoluene (14) (1·0 g) was treated with 2·5 equiv. of the thioethoxide reagent in DMF (40 ml) as in (i). Although the dark oily product (0·85 g) showed only one spot

[43] Henrich, F., and Roters, P., *Ber. dt. chem. Ges.*, 1908, **41**, 4210.
[44] Robinson, R., and Smith, J. C., *J. chem. Soc.*, 1926, 392.
[45] Hayes, N. V., and Branch, G. E. K., *J. Am. chem. Soc.*, 1943, **65**, 1555.
[46] Loudon, J. D., and Scott, J. A., *J. chem. Soc.*, 1953, 269.
[47] Merz, K. W., and Preuss, F. R., *Arch. Pharm.*, 1941, **279**, 134.

on t.l.c., its n.m.r. spectrum indicated that it was a mixture. The oil was dissolved in acetic anhydride (10 ml), pyridine (1 ml) was added, and the solution was allowed to stand at room temperature for 5 hr. The mixture was then poured into water, extracted with ether, and the extract washed with saturated aq. $NaHCO_3$, dried, and evaporated to give a brown oil (0·80 g). Analytical g.l.c. at 150° indicated the presence of two components of relative peak areas 2 : 5, at retention times of 2·0 and 5·0 min respectively. Separation of these components by preparative g.l.c. at 170° gave the compound with the shorter retention time, 4-bromo-3-methylphenyl acetate (16a) as a colourless oil (0·2 g). N.m.r. spectrum: apparent d (A part of AMX), 1, 7·47 (ArH), separation 8 Hz; m, 2, 7·05–6·60 (ArH); s, 3, 2·39 ($ArCH_3$); s, 3, 2·19 ($COCH_3$). Hydrolysis of this oil with 5% aq. NaOH gave, after acidification, 4-bromo-3-methylphenol (16b) as a solid which crystallized from light petroleum as needles (0·13 g), m.p. 61–62° (lit.[36] 61–62°). See (B) below for the n.m.r. spectrum.

Collection of the component with the longer retention time afforded *4-acetoxy-2-methylphenyl ethyl sulphide* (15a) as a colourless oil (0·53 g), b.p. 84°/0·75 mm (Found: C, 63·0; H, 7·0; S, 15·1. $C_{11}H_{14}O_2S$ requires C, 62·8; H, 6·7; S, 15·2%). ν_{max} 1760 (C=O) cm^{-1}; n.m.r. spectrum: m, 3, 7·37–6·67 (ArH); q, 2, 2·82 (SCH_2), *J* 7·5 Hz; s, 3, 2·37 ($ArCH_3$); s, 3, 2·20 ($COCH_3$); t, 3, 1·29 (CH_2CH_3), *J* 7·5 Hz. Mass spectrum: 210 (25%), 169 (10), 108 (100), 153 (7), 139 (15), 138 (25), 107 (7), 77 (11).

(B) 2-Bromo-5-methoxytoluene (14) (1·0 g) was stirred with 2·5 equiv. of the thioethoxide reagent in DMF (40 ml) at 100° for 3 hr. The reaction was worked up as in (i) to give 4-bromo-3-methylphenol (16b) as a pale brown oil which crystallized from light petroleum as needles, m.p. 62·5–63°; n.m.r. spectrum: apparent d (A part of AMX), 1, 7·26 (ArH); m, 2, 6·72–6·33 (ArH); s(br), 1, 5·80 (OH); s, 3, 2·25 ($ArCH_3$).

(ix) *2-Bromo-3-methoxy-5-methylphenol* (*13b*)

4-Bromoorcinol dimethyl ether (13a)[31] (1·0 g) was treated with 2·5 equiv. of the thioethoxide reagent as in (viii) (B) except that heating was continued for 20 hr. When the reaction was worked up as in (i), (13b) was obtained as a pale yellow oil (0·87 g), which crystallized from ether–n-pentane as prisms, m.p. 70–72° (lit.[37] 64–69°) (Found: C, 44·3; H, 4·3; Br, 36·4. Calc. for $C_8H_9BrO_2$: C, 44·2; H, 4·2; Br, 36·8%). ν_{max} 3510 (OH) cm^{-1}; n.m.r. spectrum ($CDCl_3$): m, 1, 6·57–6·41 (ArH); m, 1, 6·31–6·21 (ArH); s(br), 1, 5·65 (OH); s, 3, 3·78 (OCH_3); s, 3, 2·22 ($ArCH_3$). Mass spectrum: 208 (100%), 206 (100), 203 (8), 201 (8), 175 (20), 173 (20), 147 (10), 122 (10), 121 (10), 109 (12), 108 (36), 107 (65), 94 (45), 93 (13), 79 (10), 78 (15), 77 (40).

A mixture of 4-bromoorcinol monomethyl ether (13b) (0·16 g), dimethyl sulphate (0·20 g), and potassium carbonate (0·20 g) in acetone (10 ml) was refluxed under nitrogen for 12 hr. The mixture was then poured into water and extracted with ether; the ether extracts were washed with 30% aq. ammonia, then with water, dried, and evaporated. The resulting solid (0·17 g) crystallized from light petroleum as needles, m.p. 75·0–75·5° alone, or on admixture with an authentic sample of 4-bromoorcinol dimethyl ether (13a) (lit.[31] 75·5–76·0°).

(x) (*Z*)-*1-(3-Hydroxy-5-methoxyphenyl)undec-3-ene* (*Persoonol Monomethyl Ether*) (*18*)

A solution of ethanethiol (0·05 g) in DMF (1 ml) was added to a suspension of sodium hydride (0·037 g of a 50% oil dispersion) in DMF (1 ml) under an atmosphere of nitrogen. The mixture was stirred for 5 min before (*Z*)-1-(3,5-dimethoxyphenyl)undec-3-ene (17) (0·05 g) in DMF (1 ml) was added; the solution was then refluxed for 3 hr. The mixture was acidified with 10% aq. HCl and extracted with ether. The ethereal solution was washed with saturated brine, dried, and evaporated to give a yellow oil (0·067 g) which was insoluble in 5% aq. NaOH. The oil was dissolved in light petroleum and the solution extracted with Claisen's alkali;[48] the extract was acidified with 10% aq. HCl and shaken with ether. The ether extract was washed with water, dried, and evaporated to give a yellow oil (0·05 g). Preparative t.l.c. on silica gel, using ether–n-pentane (5 : 95) as the mobile phase, gave *persoonol monomethyl ether* (18) as an oil (0·04 g) (Found: C, 78·1; H, 10·3. $C_{18}H_{28}O_2$ requires C, 78·2; H, 10·2%). ν_{max} (film) 3400 (OH) cm^{-1}; no significant absorption near 960 cm^{-1}; n.m.r. spectrum: m, 4, 6·33–6·02 (ArH and OH) (inten-

[48] Claisen, L., *Liebigs Ann.*, 1918, **418**, 69.

sity 3 after exchange with D_2O); m, 2, 5·43–5·17 (CH=CH); s, 3, 3·66 (OCH_3); m, 6, 2·66–1·69 ($ArCH_2$ and $C=CCH_2$); s(br), 10, 1·28 (methylenes); m, 3, 1·03–0·85 (CCH_3). Mass spectrum: 276 (10%), 177 (6), 163 (6), 139 (9), 138 (100), 137 (30), 107 (5), 77 (6).

Methylation of this substance with dimethyl sulphate and potassium carbonate in acetone as for (13b) afforded persoonol dimethyl ether (17) as an oil, whose i.r. spectrum (film) was identical with that of an authentic sample.[38]

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