Long-chain Phenols. Part 16. A Novel Synthesis of Homologous Orsellinic Acids and their Methyl Ethers

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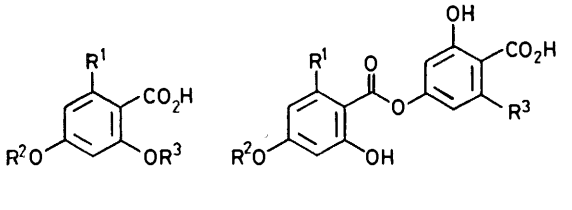
By the novel reaction of 3,5-dimethoxyfluorobenzene with n-alkyl-lithium compounds, followed by carbonation, homologous orsellinic acid dimethyl ethers (6-alkyl-2,4-dimethoxybenzoic acids) have been obtained. The reactions proceeded best with the homologues of methyl-lithium. These reactions are considered to occur by way of 3,5-dimethoxybenzyne. 2,4-Dimethoxyfluorobenzene did not form an aryne but gave 3-fluoro-2,6-dimethoxybenzoic acid instead. Decomposition with water of alkyl-lithium reaction mixtures from 3,5-dimethoxyfluorobenzene yielded 5-n-alkylresorcinol dimethyl ethers. Demethylation of 6-alkyl-2,4-dimethoxybenzoic acids with boron trichloride proceeded partially and selectively to give the 6-alkyl-2-hydroxy-4-methoxybenzoic acids, and completely with aluminium chloride to give the homologous orsellinic acids. Boron tribromide was less effective, but readily gave the 5-alkyl resorcinols from the corresponding dimethyl ethers.

ORSELLINIC acid and its homologues in the form of their monomethyl (or other protected) ethers (1; $R^1 = C_nH_{2n+1}$, $R^2 = Me$, $R^3 = H$; and $R^2 = H$, $R^3 = Me$) are important components of the simple depsides [2] (2a; $R^2 = Me, H$; $R^1, R^3 =$ alkyl) and depsidones (2b).† Zearalenone (3), its dimethyl ether,[3] and curvularin (4) are also based on homologous orsellinic acids as indeed are many other secondary metabolites of plant and fungal origin. *Ceratocystis ulmi*, the agent responsible for Dutch Elm disease, contains the orsellinic acid derivative, 2,4-dihydroxy-6-(1-hydroxyacetonyl)benzoic acid.[4]

Although widely distributed, invariably as derivatives, orsellinic acids remain comparatively little known. Their ready decomposition, and that of the esters,[5] complicates syntheses.

Methods have been based on the formylation [6,7] of 5-alkylresorcinols, for which a variety of procedures are available,[8] on Michael addition reactions,[9] and on biogenetic-type models.[10] In the present work the carboxy- and the alkyl-group were introduced simultaneously, based on an earlier approach.[1] A preliminary account has been given.[11]



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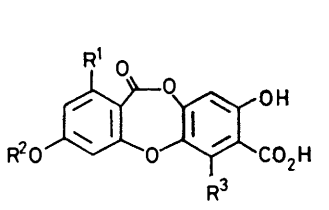
(2a)



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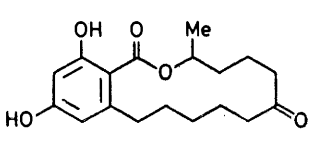

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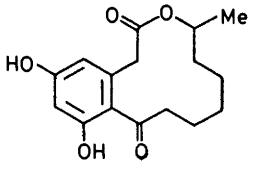

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RESULTS AND DISCUSSION

3,5-Dimethoxyfluorobenzene (5) was obtained from 3,5-dimethoxyaniline by the Schiemann reaction,[12] *via* the diazonium fluoroborate and distillation of the completely dried salt. 2,4-Dimethoxyfluorobenzene (6) was obtained similarly as shown in Scheme 1(*a*).

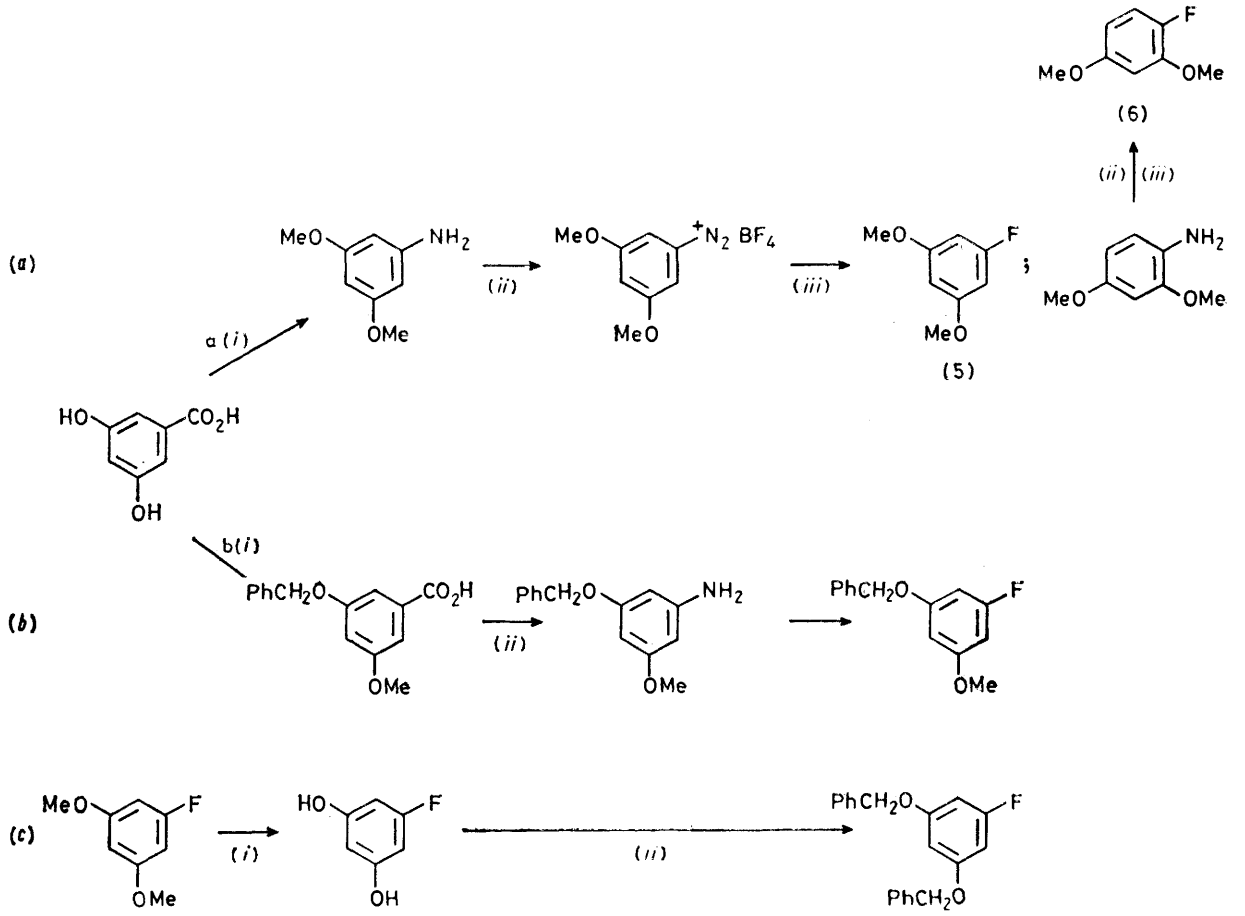
For good yields, and avoidance of formation of phenolic and other materials, it was essential to use the anhydrous diazonium salt. With the 2,4-dimethoxy-compound, resorcinol dimethyl ether tended to be a persistent impurity. The yields depended on the quality of the 3,5-dimethoxy- and 2,4-dimethoxy-aniline used.

Before finding the Hofmann degradation of 3,5-dimethoxybenzamide to be the best approach to 3,5-dimethoxyaniline, we had examined the Curtius reaction [13] on 3,5-dimethoxybenzoyl azide, obtained from the corresponding hydrazide, and produced 3,5-dimethoxyphenyl isocyanate. Attempts to hydrolyse this under a variety of acidic and basic conditions were not success-

† The types shown (2a) and (2b) belong to series B, Group IV, subgroup 1(a), and Group V, subgroup 2, respectively, according to Y. Asahina's classification, *Acta Phytochimica*, 1934, **8**, 30.

ful, and the major product was the very stable *NN'*-di-(3,5-dimethoxyphenyl)urea. In the strongly alkaline hydrolysis of the isocyanate, formation of 3,5-dimethoxybenzoic acid as well as the urea occurred. A simple route to 3,5-dimethoxyaniline by the Schmidt reaction [14] with 3,5-dimethoxybenzoic acid and hydrazoic acid completely failed, although monomethoxy-compounds have been reported to react favourably.[15] Since it was impossible to hydrolyse 3,5-dimethoxyphenyl isocyanate to 3,5-dimethoxyaniline, it seems improbable that the carbon dioxide rather than *vice versa* to avoid ketone formation.[1,16] 6-Alkyl-2,4-dimethoxybenzoic acids (7) resulted; virtually none of the isomeric 2-alkyl-3,5-dimethoxybenzoic acids (9) appeared to be formed, from chromatographic and spectroscopic analysis. The low yield of (7; R^1 = Me), compared with homologous materials, probably indicates [1] the low lithiating power of methyl-lithium. Ethyl-lithium, however, gave a good yield, following carbonation, of (7; R^1 = Et).

By contrast, 2,4-dimethoxyfluorobenzene reacted with



SCHEME 1 (*a*) (*i*) OH^-, Me_2SO_4; PCl_5; concentrated NH_4OH; Br_2, OH^-; (*ii*) HBF_4, $NaNO_2$; (*iii*) heat. (*b*) (*i*) OH^-, Me_2SO_4; $PhCH_2Cl$, K_2CO_3, Me_2CO; (*ii*) $SOCl_2$; concentrated NH_4OH; Br_2, OH^-. (*c*) (*i*) BBr_3, CH_2Cl_2; (*ii*) $PhCH_2Br$, K_2CO_3, Me_2CO; (*iii*) $MeCON[Si(Me)_3]_2$

former is an intermediate in the Hofmann degradation of the amide, a reaction which proceeded very smoothly without the formation of the urea by-product. Both 3,5-dimethoxy- and 2,4-dimethoxy-fluorobenzene were remarkable in being nearly as volatile (g.l.c.) as 1,3-dimethoxybenzene.

The interaction of 3,5-dimethoxyfluorobenzene and of 2,4-dimethoxyfluorobenzene with alkyl-lithium compounds and the subsequent steps are shown in Scheme 2.

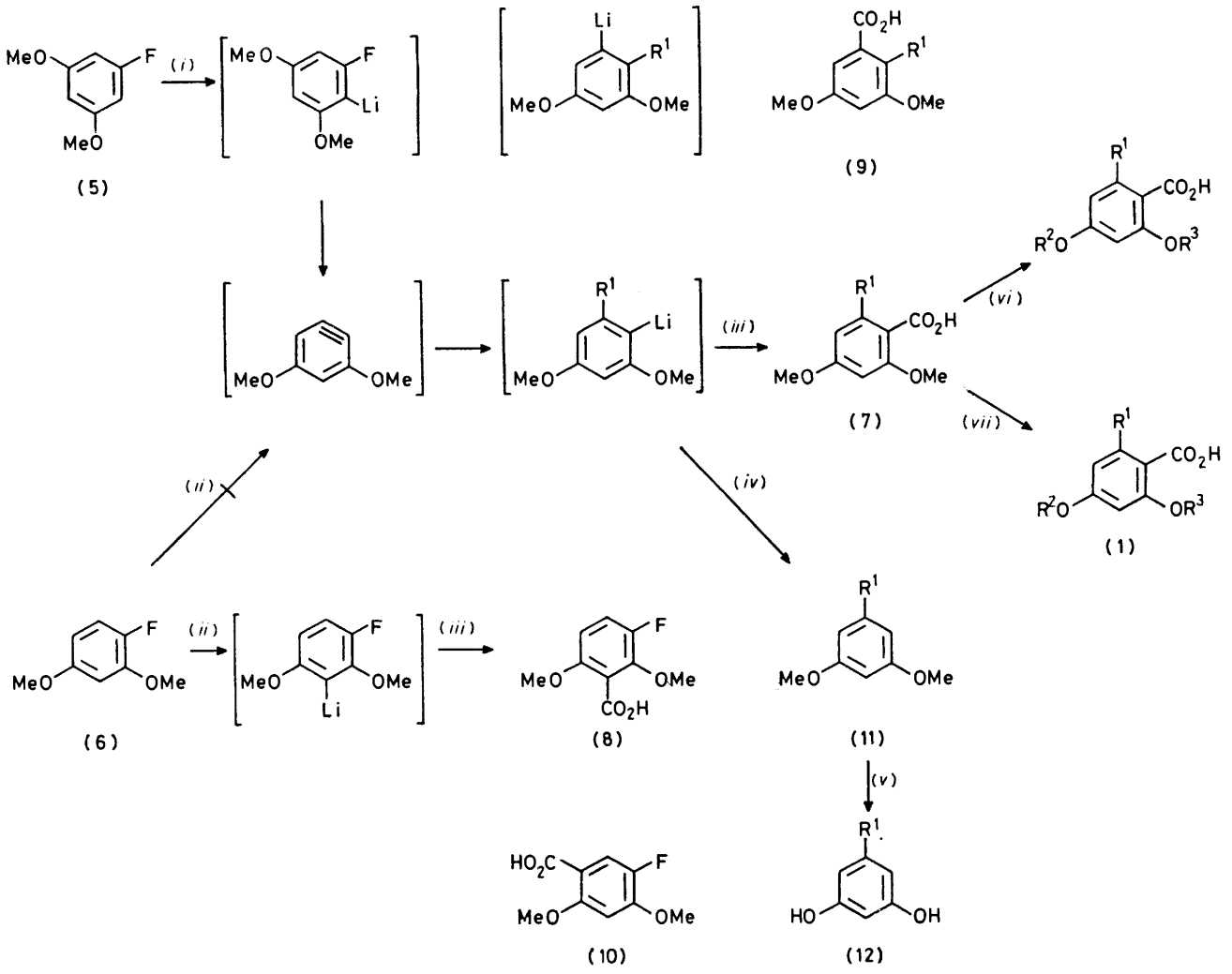
3,5-Dimethoxyfluorobenzene reacted mildly and exothermically with the alkyl-lithium compounds and the mixture, after completion of reaction (marked by a fall in the temperature), was then discharged onto solid ethyl-lithium to give an acidic product considered, from ^1H n.m.r. evidence, to be 3-fluoro-2,6-dimethoxybenzoic acid (8) rather than 5-fluoro-2,4-dimethoxybenzoic acid (10). Little evidence for the formation of (7; R^1 = Et), except in traces, was obtained. From chromatographic and spectroscopic examination, lithiation of 3,5-dimethoxyfluorobenzene at the 4-position to produce 4-fluoro-2,6-dimethoxybenzoic acid was a negligible process.

Dilution of the reaction mixtures of alkyl-lithium and 3,5-dimethoxyfluorobenzene with water led to the 5-n-alkylresorcinol dimethyl ethers (11) in good yield, and the 5-n-propyl, 5-n-pentyl, 5-n-heptyl, and 5-n-pentadecylresorcinol dimethyl ethers were obtained.

The reactions in the series involving 3,5-dimethoxyfluorobenzene appear to be best explained as involving formation of 3,5-dimethoxybenzyne, the more stable *ortho*-aryne [17] (a 1,2-didehydrobenzene), as a reactive intermediate. Due to the substitution of lithium at predominately the *o*- and *p*-positions, vicinal elimination of lithium fluoride with 3,5-dimethoxybenzyne formation can only occur with 3,5-dimethoxyfluorobenzene. Lithiation of 2,4-dimethoxyfluorobenzene at the 6-position is apparently a negligible reaction, due evidently to the influence of the 4-methoxy-group in causing much greater reactivity at the 3-position.[16]

2-Fluoroanisole, by contrast, lithiates predominately, if not exclusively, at the position *meta* to the methoxy-group. The nature of other possible components in the reaction mixture from 2,4-dimethoxyfluorobenzene has not yet been established, and it is a matter of conjecture whether a 1,3-didehydrobenzene could form. The aryllithium precursor of (8) may well compete with alkyllithium for the small proportion of 3,5-dimethoxybenzyne produced.

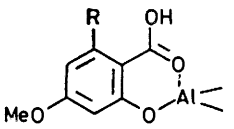
The synthesis of homologous orsellinic acids required an efficient demethylation procedure. Selective partial demethylation of the methoxy-group *ortho* to the carboxy-group occurred smoothly with boron trichloride. Complete demethylation was achieved by boron tribromide at low temperature. Although the preliminary results with the orsellinic acid methyl ethers by this method were promising, later attempts did not reproduce the early behaviour and decarboxylation and other reactions occurred. However, 5-alkylresorcinol dimethyl ethers (11) reacted smoothly to give the corresponding phenols (12). Since all the standard demethylation techniques such as pyridine hydrochloride, ethylene glycol–potassium hydroxide, and methylmagnesium iodide were in applicable, attention was turned to the use of aluminium chloride in various solvents. Dichloromethane did not give sufficient reaction; this was, however, achieved with chlorobenzene. It is possible that decarboxylation was avoided by the chelation possible with aluminium and the presence of the orsellinic acid as a salt. The initial



SCHEME 2 (*i*) R^1Li, Et_2O, (*ii*) EtLi, Et_2O; (*iii*) CO_2, H^+; (*iv*) H_2O, H^+; (*v*) BBr_3, CH_2Cl_2; (*vi*) BCl_3, CH_2Cl_2; (*vii*) $AlCl_3$, PhCl

reaction could involve formation of (13) and finally (14), though precedence of carboxy-acidity over intramolecular chelation (by rotation of the carboxy-group).

The use of aluminium chloride is fairly well established.[18] Like boron trichloride,[19] with *o*-alkoxycarbonyl systems removal of an *o*-methoxy-group can occur preferentially since it has been used in catalytic quantity together with a major proportion of hydrogen bromide



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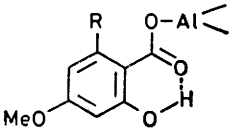

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for the selective demethylation of *o*-methoxybenzophenones.[20] The deleterious effect of the acidity often produced with aluminium chloride may be mitigated by the use of pyridine, and, in dichloromethane containing pyridine, *o*-hydroxyphenyl methyl ethers [21] have been prepared. This system may well be valuable for the dimethyl ethers of orsellinic acids, but the present work had to be concluded before this interesting possibility could be investigated.

In view of the problems with demethylation, alternative protective groups which might be more easily removed were examined. The tetrahydropyranyl group was unsatisfactory at the initial stage, but 3,5-dibenzyloxyfluorobenzene was readily prepared from 5-fluororesorcinol. Interaction of the dibenzyl ether with n-butyl- or n-propyl-lithium failed to produce the 6-alkyl-2,4-dibenzylbenzoic acid in more than trivial yields, due, it would seem, to deactivation of the ring to lithiation rather than to steric hindrance, since 3-benzyloxyfluorobenzene [1] reacted smoothly with ethyl-lithium. The reactivity of 3-benzyloxy-5-methoxyfluorobenzene (accessible from 3-hydroxy-5-methoxybenzoic acid) towards alkyl-lithium compounds, with the possibility of formation of the half methyl ethers, 4-hydroxy-2-methoxy-6-alkylbenzoic acids (1; R^1 = n-alkyl, R^2 = H, R^3 = Me) after the final stages of carbonation and hydrogenolysis, seemed therefore worth investigation, although these experiments are as yet incomplete.

The synthetic method led to the dimethyl ethers of divaric acid (1; $R^1 = C_3H_7$), olivetol carboxylic acid (1; $R^1 = C_5H_{11}$), spherophorol carboxylic acid (1; $R^1 = C_7H_{15}$), orsellinic acid (1; R^1 = Me), and the ethyl compound (1; R^1 = Et). The method works best for the homologous compounds. The pentadecyl member of the orsellinic acids is of interest as a possible precursor of the ' analcardic acids ' [22] by removal of the 4-hydroxyl group, and of the ' cardols ' (5-alkyl and alkenyl resorcinols) by decarboxylation.*

EXPERIMENTAL

I.r. spectra were recorded on a Unicam SP200 instrument (liquids as films and solids as KBr discs). ^{1}H N.m.r. spectra, with tetramethylsilane as internal standard, were determined on Varian T60 and HA100 (PCMU, Harwell) instruments. Microanalyses were by Drs. Weiler and Strauss and Mr. G. Crouch, School of Pharmacy, Brunswick Sq., London WC1. G.l.c. was carried out on a Pye 104 instrument equipped with a flame-ionisation detector. The glass columns were 5 ft × 3/16 in (i.d.). Column A (3% SE30), column B (20% SE52), and column C (10% carbowax) were used, all on diatomite C. Column chromatography was carried out on Spence Grade H alumina. T.l.c. was carried out with Kieselgel G (Merck) on analytical plates (8 × 10 cm × 0.25 mm) and preparative plates (20 × 20 cm × 1 mm) with 0.1% ethanolic rhodamine 6G as visualising agent. Solvent A, chloroform–ethyl acetate (94 : 6); solvent B, chloroform–ethyl acetate (95 : 5); solvent C, chloroform–ethyl acetate (96 : 4); solvent D, chloroform–ethyl acetate–formic acid (95 : 5 : 2); solvent E, chloroform–light petroleum (b.p. 40—60 °C) (1 : 1); solvent F, chloroform–ethyl acetate (85 : 15); and solvent G, chloroform–ethyl acetate–formic acid (96 : 4 : 3).

Alkyl-lithium reagents were prepared as previously described [1] in a magnetically stirred evacuable three-necked flask equipped with pressure-equalised addition funnel, low-temperature thermometer, and condenser, to the top of which was attached a three-way tap having vacuum, nitrogen, and manometer connections.

Materials.—These were prepared as previously described.[1] 3,5-Dimethoxyaniline was at first synthesised but subsequently became commercially available (R. N. Emmanuel) as did 2,4-dimethoxyaniline (Eastman Kodak).

The separation of homologous dimethyl orsellinic acids from fatty acids (produced from excess Li in the carbonation) was easier than that of ' anacardic acids ' due to the greater polarity of the former.

3,5-*Dimethoxyfluorobenzene.*—3,5-Dimethoxybenzoic acid was converted by way of the acid chloride (m.p. 23—24 °C) and the amide (m.p. 143 °C) into 3,5-dimethoxyaniline on a large scale in 65% yield (overall), m.p. 49—51 °C (lit.,[23] b.p. 120 °C at 0.2 mmHg) and mixed m.p. 50—51 °C with commercially available material. 3,5-Dimethoxyaniline (17.0 g, 0.11 mol) was diazotised with 8% fluoroboric acid (155 cm^3) and sodium nitrite (7.9 g) in water (17 cm^3) and the recovered diazonium fluoroborate dried at ambient temperature (28.8 g). The diazonium fluoroborate decomposed easily to give some resorcinol dimethyl ether as an impurity. Subsequently freeze-drying was found to be effective. Upon decomposition by warming and distillation, 3,5-*dimethoxyfluorobenzene* (7.6 g, 44%) was obtained, purified by washing with 5% sodium hydroxide and 5% hydrochloric acid, and the recovered material distilled *in vacuo*, b.p. 88 °C at 6 mmHg (Found: C, 61.2; H, 5.85. $C_8H_9FO_2$ requires C, 61.53; H, 5.76%); R_F 0.83 (solvent B); τ(CCl_4) 3.64—3.85 (3 H, m, Ar-H, J_o 9, J_m 2 Hz) and 6.20 (6 H, s, 2 OMe) [τ (H^2, H^6) (calc.) 3.90; τ (H^4) 3.88].

3,5-*Dimethoxybenzoyl Azide.*—3,5-Dimethoxybenzoic acid was first prepared in much improved yield. 3,5-Dihydroxybenzoic acid (50 g, 0.324 mol) in 20% sodium hydroxide (300 cm^3) was heated with dimethyl sulphate (50 cm^3) to give, after work-up and crystallisation from ethanol, 3,5-dimethoxybenzoic acid (50 g, 84%), m.p. 180—182 °C (lit.,[24] m.p. 185—186 °C). 3,5-Dimethoxybenzoic acid, esterified (16 h) by refluxing with ethanol (100 cm^3) and concentrated sulphuric acid (0.5 cm^3) followed by work-up,

* Natural cashew-nut shell liquid (*Anacardium occidentale*) is perhaps the only example where different component phenols arise by various reactions of an orsellinic acid or a polyketide precursor, followed by cyclisation.

gave ethyl 3,5-dimethoxybenzoate, b.p. 190 °C at 15 mmHg (20.6 g, 88%), as a thick oil (lit.,[24] b.p. 120—125 °C at 3 mmHg). Ethyl 3,5-dimethoxybenzoate (35 g, 0.175 mol) was warmed and then refluxed (2 h) with hydrazine hydrate (11.0 g, 0.22 mol) and the solid product isolated, washed, and crystallised twice from acetone–methanol to give granular 3,5-dimethoxybenzoic hydrazide (30 g, 78%), m.p. 169—170 °C (lit.,[25] 168—169 °C) (Found: C, 54.8; H, 6.25. Calc. for $C_9H_{12}N_2O_3$; C, 55.10; H, 6.12%). 3,5-Dimethoxybenzoic hydrazide (16.8 g, 0.085 mol) in 2M hydrochloric acid (500 cm³) and glacial acetic acid (700 cm³) was treated at 0 °C with sodium nitrite (6.2 g, 0.009 mol) in water (15 cm³), the mixture cooled (1 h) at −10 °C or simply diluted with water, and the white silky needles of 3,5-*dimethoxybenzoic azide* were collected, washed, and dried, m.p. 42.5—43 °C (11.2 g, 63%). Alternatively, the diazotised mixture was diluted with distilled water to yield the azide (Found: C, 51.85; H, 4.4; N, 20.15. $C_9H_9N_3O$ requires C, 52.17; H, 4.34; N, 20.28%).

The preceding compounds have the following ^1H n.m.r. and i.r. spectra: 3,5-dimethoxybenzoic acid τ ($CDCl_3$, +[$^2H_6$]DMSO) 0.12—0.6 (1 H, s, CO_2H, D_2O exchangeable), 2.72—2.85 (H^2, H^6, d, J_m 2.5 Hz), 3.27—3.46 (H^4, t, J_m 2.5 Hz), and 6.17 (6 H, s, 2 OMe); $\nu_{max.}$ (KBr) 1 700s cm^1 (C=O acid).

3,5-Dimethoxybenzoyl chloride τ ($CDCl_3$), 2.70 (H^2, H^6, d, J_m 2.5 Hz), 3.22 (H^4, t, J_m 2.5 Hz), and 6.16 (6 H, s, OMe) (Calc. for H^2, H^6, τ 2.80; H^4, 3.30).

3,5-Dimethoxybenzamide τ ($CDCl_3$ +[$^2H_6$]DMSO) 2.58 (2 H, s, NH_2, D_2O exchangeable), 2.85 (H^2, H^6, J_m 2.5 Hz), 3.40 (H^4, t, J_m 2.5 Hz), and 6.20 (6 H, s, 2 OMe) (Calc. for H^2, H^6, τ 2.95; H^4 3.43); $\nu_{max.}$ (KBr) 3 400 and 1 650 cm^{-1} (amide).

3,5-Dimethoxyaniline τ ($CDCl_3$) 3.0—3.78 (3 H, m, Ar-H), 6.20 (6 H, s, 2 OMe), 6.22 (2 H, s, NH_2, D_2O exchangeable); τ (C_6D_6), 3.82 (H^4, t, J_m 2.5 Hz), 4.20 (H^2, H^6, t, J_m 2.5 Hz), 6.60 (6 H, s, 2 OMe), and 6.84 (2 H, s, NH_2, D_2O exchangeable) (Calc. for H^2, H^6, τ 4.36; H^4, 4.29); $\nu_{max.}$ (KBr) 3 400 (s, NH_2) and 1 625 cm^{-1} (s, N–H bend). For the hydrochloride, τ (C_6D_6 +[$^2H_6$]DMSO) 3.20 (H^2, H^6) and 3.45 (H^4).

Ethyl 3,5-dimethoxybenzoate τ (CCl_4) 2.81 (H^2, H^6, d, J_m 2.5 Hz), 3.47 (H^4, t, J_m 2.5 Hz), 5.5—6.19 (2 H, q, OCH_2), 6.19 (6 H, s, 2 OMe), and 8.60 (3 H, t, CH_2Me) (Calc. for H^2, H^6, τ 2.89; H^4, 3.45); $\nu_{max.}$ (film) 1 720s cm^{-1} (C=O ester). In the appropriate parts the spectrum was identical with that of methyl 3,5-dimethoxybenzoate (Sadtler 3840).

3,5-Dimethoxybenzoic hydrazide τ ($CDCl_3$), 2.50 (1 H, s, NH, D_2O exchangeable), 3.11 (H^2, H^6, d, J_m 2.5 Hz), 3.33 (H^4, t, J_m 2.5 Hz), 5.90 (2 H, s, NH_2, D_2O exchangeable), and 6.14 (6 H, s, OMe); $\nu_{max.}$ (KBr) 3 360m (NH_2), 3 200w (NH), and 1 595m cm^{-1} (NH_2).

3,5-Dimethoxybenzoyl azide τ (CCl_4), 2.80 (H^2, H^6, d, J_m 2.5 Hz), 3.08 (H^4, t, J_m 2.5 Hz), and 6.20 (6 H, s, OMe); $\nu_{max.}$ (KBr) 2 150s cm^{-1} (CON_3).

3,5-*Dimethoxyphenyl Isocyanate*.—3,5-Dimethoxybenzoyl azide (8.0 g, 0.038 mol) was heated in dry toluene (50 cm³) and a vigorous reaction commenced near the boiling point. After nitrogen evolution ceased (15 min) the mixture was refluxed (2.5 h); removal of solvent left an oil, which solidified, m.p. 35—36 °C (6.8 g, 93%), consisting of 3,5-dimethoxyphenyl isocyanate. Excessive heating of the toluene solution gave the urea. The isocyanate was very sensitive to moisture and merely standing it in ether resulted in formation of the urea, and no residual isocyanate. By g.l.c. the sample was pure and gave a single peak, although a satisfactory elemental analysis could not be obtained due to its instability; τ (CCl_4), 3.80 (3 H, s, Ar-H) and 6.09 (6 H, s, OMe); τ (C_6D_6), 3.80 (H^4, t, J_m 2.5 Hz), 3.30 (H^2, H^6, d, J_m 2.5 Hz), and 6.80 (6 H, s, OMe); $\nu_{max.}$ (KBr) 2 300s cm^{-1} (NCO); *m/e*, 179 (M^+) ($C_9H_7NO_3$ requires *M*, 179).

NN′-*Di*-(3,5-*dimethoxyphenyl*)*urea*.— 3,5-Dimethoxyphenyl isocyanate (1.7 g, 0.01 mole) was warmed with concentrated hydrochloric acid (15 cm³) on a steam-bath (10 min), cooled, and the recovered washed solid crystallised from acetone to give NN-*di*-(3,5-*dimethoxyphenyl*)*urea*, m.p. 209—210 °C (1.5 g, 90%) (Found: C, 61.3; H, 6.15. $C_{17}H_{20}N_2O_5$ requires C, 61.45; H, 6.0%); τ ([$^2H_6$]DMSO) 3.30 (4 H, d, Ar-H, J_m 2.5 Hz), 3.80 (2 H, t, Ar-H, J_m 2.5 Hz), 6.23 (12 H, s, OMe), and 6.67 (2 H, s, NH, D_2O exchangeable); $\nu_{max.}$ (KBr), 1 660m cm^{-1} (NCON).

The urea resisted hydrolysis by 50% aqueous sulphuric acid, or by 20% aqueous sodium hydroxide, and was recovered unchanged in both cases. 3,5-Dimethoxyphenyl isocyanate (15.0 g) was treated with warm (60 °C), 20% sodium hydroxide (200 cm³) and a vigorous reaction occurred; the cooled mixture was then ethereally extracted and the recovered material crystallised from n-pentane–chloroform to give substance A (3.1 g), m.p. 199—200 °C, identical with *NN′*-di-(3,5-dimethoxyphenyl)urea. The basic layer was acidified, and the solid collected and crystallised from chloroform–methanol to obtain substance B (8.7 g), a purplish crystalline material, m.p. 168—169 °C, which appeared to be 3,5-dimethoxybenzoic acid from its ^1H n.m.r. spectrum and mixed m.p. An attempt to prepare 3,5-dimethoxyaniline by the Schmidt reaction on 3,5-dimethoxybenzoic acid (18.2 g, 0.1 mol) with hydrazoic acid [in chloroform from sodium azide (6.5 g) in water (6.5 cm³), and chloroform (40 cm³), cooled to 0 °C, followed by addition of concentrated sulphuric acid (0.05 mol), refluxing (30 min), and basification] yielded none of the required product.

2,4-*Dimethoxyfluorobenzene*.—Interaction of 2,4-dimethoxyaniline (17.0 g, 0.11 mol), 22% fluoroboric acid (55 cm³), and sodium nitrite (7.9 g) in water (17 cm³) gave the mauve-purple diazonium fluoroborate which was dried (22 g, 79%), m.p. 100—110 °C [like the 3,5-dimethoxy-compound, formation of resorcinol dimethyl ether readily occurred (revealed by g.l.c.) and could not be removed, owing to its similar b.p., except by preparative g.l.c.]. On decomposition of the salt, by heating and distillation, 2,4-dimethoxyfluorobenzene (10.3 g, 59%) was obtained and was purified by washing with dilute sodium hydroxide and dilute hydrochloric acid as before, b.p. 210 °C. Resorcinol dimethyl ether as an impurity was identified as a slight shoulder on the g.l.c. trace and by ^1H n.m.r. (ratio of Ar-H : OMe); a single spot was shown by t.l.c. (Found: C, 64.1; H, 6.65. $C_8H_9FO_2$ requires C, 61.53, H, 5.76%: the analysis corresponds to the presence of 78% of the product); R_F 0.90 (solvent B); τ ($CDCl_3$) 2.70—3.10 (H^6, m), 3.37—3.67 (H^3, H^5, m), and 6.17—6.23 (6 H, s, 2 OMe). 2,4-Dimethoxyaniline, τ ($CDCl_3$) 3.27—3.73 (3 H, m, Ar-H, J_o 8 and J_m 2 Hz), 6.15 (3 H, s, OMe), 6.73 (3 H, s, OMe), and 6.47 (2 H, br s, NH_2, D_2O exchangeable) (Calc. for H^3, τ 3.90; H^5, 3.85; and H^6 3.69).

Preparation of 6-*n-Alkyl*-2,4-*dimethoxybenzoic Acids*.—The compounds described in Table 1 were prepared by the following general procedure. To the n-alkyl-lithium prepared [1] from the alkyl bromide (*ca.* 0.043 mol) in ether

(25 cm³) and lithium (0.1 mol) in ether (50 cm³), 3,5-dimethoxyfluorobenzene (0.012 8 mol) in ether (10 cm³) was added (2 h). The reaction mixture was then poured onto solid carbon dioxide (100 g) and thoroughly mixed. After work-up by careful acidification and ethereal extraction, the acidic portion was separated by aqueous sodium hydrogencarbonate extraction, recovered, and twice purified by preparative t.l.c. to give the dimethoxy(alkyl)benzoic acid. In all cases some 3.5-dimethoxyfluorobenzene was found in the neutral material.

The products had the following ^{1}H n.m.r. signals: (7; R^1 = n-C_3H_7) τ ($CDCl_3$) 0.1—0.9 (1 H, br s, CO_2H, D_2O exchangeable), 3.47—3.67 (2 H, m, Ar-H), 6.00 (3 H, s, OMe), 6.11 (3H, s, OMe), 6.54—6.94 (2 H, t, CH_2Ar), 8.0—8.8 2 H, sextet, CH_2), and 8.8—9.37 (3 H, t. Me): (7; R^1 = n-C_5H_{11}), τ ($CDCl_3$) −1.2 to −1.0 (1 H, br s, CO_2H, D_2O exchangeable), 3.48—3.74 (2 H, m, Ar-H), 6.10 (3 H, s, OMe), 6.20 (3 H, s, OMe), 7.0—7.55 (2 H, t, CH_2Ar), 8.0—8.94 (6 H, m, $[CH_2]_3$), and 8.94—9.4 (3 H, t, Me): (7; R^1 = n-C_7H_{15}) τ (CCl_4) −0.32 to −0.06 (1 H, br s, CO_2H, D_2O exchangeable), 3.5—3.67 (2 H, m, Ar-H), 6.08 (3 H, s, OMe), 6.13 (3 H, s, OMe), 7.0—7.48 (2 H, t, CH_2Ar), 8.0—8.92 (10 H, m, $[CH_2]_5$), and 8.92—9.34 (3 H, t, Me); τ (C_6D_6) −0.6—+0.11 (1 H, br s, CO_2H), 3.55—3.75 (H^3, d, J_m 2.5 Hz), 3.75—3.90 (H^5, d, J_m 2.5 Hz), 6.67 (3 H, s, OMe), 6.75 (3 H, s, OMe), 6.94—7.33 (2 H, t, CH_2Ar), 8.06—8.96 (10 H, m, $[CH_2]_5$), and 8.96—9.33 (3 H, t, Me): (7; R^1 = n-$C_{15}H_{31}$) τ ($CDCl_3$) −0.3—+1.30 (1 H, br s, CO_2H, D_2O exchangeable), 3.54—3.71 (2 H, m, Ar-H), 6.06 (3 H, s, OMe), 6.15 (3 H, s, OMe), 7.09 (2 H, t, CH_2Ar), 8.74 (26 H, m, $[CH_2]_{13}$), and 9.10 (3 H, t, Me); τ (C_6D_6) −1.3 (1 H, br s, CO_2H), 3.60 (3 H, d, Ar-H, J_m 2.5 Hz), 3.85 (5 H, d, Ar-H, J_m 2.5 Hz), 6.66 (3 H, s, OMe), 6.80 (3 H, s, OMe), 7.10 (2 H, CH_2Ar), 8.69 (26 H, m, $[CH_2]_{13}$), and 9.07 (3 H, t, Me): (7; R^1 = Et) τ ($[^2H_6]$DMSO) 3.37—3.57 (2 H, m, Ar-H), 5.03 (1 H, br s, CO_2H, D_2O exchangeable), 6.14 (3 H, s, OMe), 6.17 (3 H, s, OMe), 7.28—7.57 (2 H, q, CH_2Ar, J 7 Hz), and 8.7—8.94 (3 H, t, Me, J 7 Hz): (7; R^1 = Me) τ ($CDCl_3$) 1.6—3.0 (1 H, br s, CO_2H, D_2O exchangeable), 3.5—3.78 (2 H, m, Ar-H), 6.10 (3 H, s, OMe), 6.20 (3 H, s, OMe), and 7.42 (3 H, s, Ar-*Me*).

TABLE 1

Preparation of 6-n-alkyl-2,4-dimethoxybenzoic acids (7)

R^1 (Compound)	R^{1}Br	3,5-Dimethoxyfluorobenzene	Li	Yield (%)	M.p. (°C)	R_F [a]	Analysis (%) Found C	Found H	Required C	Required H
	mol									
n-C_3H_7 (divaric acid dimethyl ether)	0.043	0.0128	0.1		50—51	0.43	64.5	7.3	64.28	7.14
n-C_5H_{11} (Olivetol carboxylic acid dimethyl ether)	0.049	0.012	0.1	37	34—35	0.45	66.95	8.25	66.66	7.93
n-C_7H_{15} (spheropherol carboxylic acid dimethyl ether)	0.049	0.012	0.1	39	51—52	0.46	67.9	8.25	68.52	8.57
n-$C_{15}H_{31}$	0.038	0.0064	0.092	34	80—81	0.48	73.7	10.4	73.46	10.20
Et	0.045	0.0064	0.17	45	84—85	0.45	62.3	6.75	62.85	6.66
Me (Orsellinic acid dimethyl ether)	0.042	0.0051	0.085	15	140 [b]	0.43 [c]	61.55	6.3	61.22	6.12

[a] Solvent F. [b] Lit., 142—143 °C (R. Adams, S. Mackenzie, jun., and S. Loewe, *J. Amer. Chem. Soc.*, 1948, **70**, 662). [c] Solvent C, R_F 0.28.

Attempted Preparation of 6-Ethyl-2,4-dimethoxybenzoic Acid from 2,4-Dimethoxyfluorobenzene.—To ethyl-lithium [prepared from ethyl bromide (11.0 g, 0.1 mol) in ether (20 cm³) and lithium (1.4 g, 0.20 mol) in ether (50 cm³)], 2,4-dimethoxyfluorobenzene (3.9 g, 0.025 mol) in ether (10 cm³) was added during 2 h at ambient temperature. The reaction mixture was carbonated (100 g solid carbon dioxide), and the acidic part from the usual work-up purified by preparative t.l.c. (solvent C) to give *3-fluoro-2,6-dimethoxybenzoic acid*, m.p. 104—105 °C (2.0 g, 40%); R_F 0.27 (solvent C) (Found: C, 54.1; H, 4.75. $C_9H_9FO_4$ requires C, 54.00; H, 4.5%); τ ($CDCl_3$) −1.50 to −1.10 (1 H, s, CO_2H, D_2O exchangeable), 2.60—3.0 [1 H, dd, Ar-H, J_o (HH) 9 and J_o (H/F) 11 Hz], 3.2—3.48 [1 H, dd, Ar-H, J_o (HH) 9 and J_m (H/F) 6 Hz], 5.90 (3 H, s, OMe), and 6.11 (3 H, s, OMe). Calc. for 3-fluoro-2,6-dimethoxybenzoic acid, H^4 τ 2.98 and H^5 3.46; calc. for 5-fluoro-2,5-dimethoxybenzoic acid, H^3 τ 3.51 and H^6 2.43.

TABLE 2

Preparation of 6-n-alkyl-2,4-dihydroxybenzoic acids (1; R^2 = R^3 = H)

R^1	Dimethoxy-compound (7) (g)	Aluminium chloride (g)	Chlorobenzene (cm³)	Yield (g)	Yield (%)	M.p. (°C)	Analysis (%) Found C	Found H	Required C	Required H
H	0.500	1.0	5	0.300	71	215—220 [a]				
Et	0.500	2.0	5	0.270	63	168—169	59.35	5.6	59.34	5.49
n-C_7H_{15}	0.500	2.0	10	0.200	45	139—140 [b]	66.6	8.0	66.66	7.93

[a] Lit., m.p. 218—219 °C ('Dictionary of Organic Compounds,' Eyre, Spottiswoode, London, 1965, vol. II, p. 1055). [b] Lit., m.p. 142—144 °C (M. T. Harris and R. N. Carney, *J. Amer. Chem. Soc.*, 1966, **88**, 2053; A. Hasimoto, *J. Pharm. Soc. Japan*, 1938, **68**, 776) product in table obtained from chloroform–ether.

Preparation of 6-n-Alkyl-2,4-dihydroxybenzoic Acids (Homologous Orsellinic Acids).—The compounds listed in Table 2 were prepared in the following general way. After

some unsuccessful experiments from demethylations with aluminium chloride in dichloromethane, chlorobenzene was used. The dimethoxyalkylbenzoic acid in dry chlorobenzene was mixed with anhydrous aluminium chloride, refluxed (45 min), cooled, and ice (25 g) added. After acidification with concentrated hydrochloric acid, the mixture was ethereally extracted, the ether removed, and light petroleum added to the residue, which was then just re-dissolved by the addition of a few drops of ether. Creamy white or white crystalline products were obtained.

The products had the following ^{1}H n.m.r. spectra: (1; $R^2 = R^3 = H$, $R^1 = Et$) τ ([$^2H_6$]DMSO) 3.54—3.70 (2 H, m, Ar-H), 4.40—5.80 (3 H, br s, 2 OH + CO_2H, D_2O exchangeable), 6.94—7.30 (2 H, q, CH_2Ar), and 8.68—8.90 (3 H, t, Me): (1; $R^2 = R^3 = H$, $R^1 = n\text{-}C_7H_{15}$) τ ($CDCl_3$ + [$^2H_6$]DMSO) 2.70—3.67 (3 H, br s, 2 OH + CO_2H, D_2O exchangeable), 3.63 (2 H, s, Ar-H), 6.94—7.19 (2 H, t, CH_2Ar), 8.23—8.9 (10 H, m, $[CH_2]_5$), and 9.03—9.34 (3 H, t, Me).

Preparation of 6-n-Alkyl-2-hydroxy-4-methoxybenzoic Acids.—The dimethoxyalkylbenzoic acid in dichloromethane was cooled to −80 °C (acetone–solid carbon dioxide) and a pre-cooled solution of boron trichloride (0.3 g) in dichloromethane added. The reaction mixture was allowed to warm slowly to −10 °C overnight and was then decomposed by the careful addition of water. The organic layer was extracted with ether, washed with dilute hydrochloric acid, the solvent removed, and the residue crystallised to yield the products, which had the following ^{1}H n.m.r. spectra: (1; R^1 = Me, $R^2 = H$, $R^1 = Et$) τ ($CDCl_3$+ [$^2H_6$]DMSO) 2.70—3.26 (2 H, br s, OH and CO_2H, D_2O exchangeable), 3.52 (2 H, m, Ar-H), 6.06 (3 H, s, OMe), 6.73—7.14 (2 H, q, CH_2), and 8.68—8.90 (3 H, t, Me): (1; R^2 = Me, $R^3 = H$, $R^1 = n\text{-}C_7H_{15}$) τ ($CDCl_3$) −2.15 (2 H, br s, OH+ CO_2H, D_2O exchangeable), 2.7—3.6 (2 H, m, Ar-H), 6.38 (3 H, s, OMe), 7.08 (2 H, t, CH_2Ar), 8.15 (10 H, m, $[CH_2]_5$), and 8.65—8.85 (3 H, t, Me).

In an attempted demethylation of (7; $R^1 = n\text{-}C_7H_{15}$) with hydriodic acid–red phosphorus, 5-n-heptyl-3-methoxyphenol was isolated by preparative t.l.c.; τ (CCl_4) 3.87 (3 H, m, Ar-H), 5.20 (1 H, br s, OH, D_2O exchangeable), 6.30 (3 H, s, OMe), 7.53 (2 H, t, CH_2Ar), 8.70 (10 H, m, $[CH_2]_5$), and 9.3 (3 H, t, Me).

5-n-Propyl-, 5-n-Pentyl-, and 5-n-Heptyl-resorcinol Dimethyl Ethers.—In a preliminary preparation of 5-n-propylresorcinol dimethyl ether (divarol dimethyl ether), to a solution of n-propyl-lithium [from n-propyl bromide (6.1 g, 0.045 mol) in ether (25 cm^3) and lithium (0.7 g, 0.1 mol) with ether (10 cm^3)] 3,5-dimethoxyfluorobenzene (2.0 g, 0.012 8 mol) was added. After 2 h the mixture was decomposed with water, and the organic portion washed with 5% sodium hydroxide solution (50 cm^3) and water. After recovery the organic material was chromatographed on alumina (150 g) with chloroform–light petroleum (1 : 1) (750 cm^3) to give 30 fractions (25 cm^3 each). Fractions 17—25 contained 5-n-propylresorcinol dimethyl ether (1.05 g, 44.3%), identical with the product of decarboxylation of divaric acid dimethyl ether using Cu–quinoline; R_F 0.72 (solvent E).

TABLE 3

Preparation of 6-alkyl-2-hydroxy-4-methoxybenzoic acids (1; R^2 = Me, R^3 = H)

R^1	Dimethoxy-compound (7)/g (cm^3 dichloro-methane)$^{-1}$	Boron trichloride (g)	Dichloromethane (cm^3)	Yield (g)	Yield (%)	M.p. (°C)	R_F (solvent)	Analysis (%) Found C	Found H	Required C	Required H
C_2H_5	0.5 (25)	0.3	5	0.250	90	155—156 [a]	0.63 (G)	61.05	6.16	61.22	6.12
n-C_7H_{15}	0.4 (15)	0.36	15	0.30	79	121—122 [b]	0.18 (F)	67.25	8.22	67.66	8.26

[a] Product crystallised from chloroform. [b] Product crystallised from diethyl ether–pentane (1 : 3).

Subsequently standard conditions were used for a further preparation as well as for the 5-n-pentyl and 5-n-heptyl compounds. The n-alkyl-lithium reagents were prepared in ether (100 cm^3) in the usual way by reacting lithium chips (0.70 g) and the required n-alkyl bromide in the quantities given in Table 4. Then 3,5-dimethoxyfluorobenzene (0.56 g) was added to the alkyl-lithium and after a reaction time of 1 h, followed by removal of unreacted lithium, the mixtures were decomposed by the addition of cold dilute hydrochloric acid. The recovered material from ethereal extraction was purified by preparative t.l.c. (solvent C); R_F 0.7 (solvent C).

TABLE 4

Alkyl bromide	Amount/g	Time/h	Amount product (5-n-alkyl-resorcinol dimethyl ether)/g	Yield (%)
n-C_7H_{15}Br [a]	7.2	0.75	1.23 (R_F 0.71 [b])	52
n-C_5H_{11}Br	6.04	0.5	1.25 (R_F 0.73)	60
n-C_3H_7Br	4.92	0.5	1.14 (R_F 0.76)	63.5

[a] Found: C, 76.2; H, 10.4. $C_{15}H_{24}O_2$ requires C, 76.27; H, 10.16%. [b] Solvent E.

Dilution of the reaction mixture from n-pentadecyl bromide with water gave 5-n-pentadecylresorcinol dimethyl ether, identical with cardol dimethyl ether and the decarboxylation product of 2,4-dimethoxy-6-pentadecylbenzoic acid, m.p. 49—50 °C (lit.,[26] 50—51 °C). Demethylation gave 5-n-pentadecylresorcinol, identical with (15 : 0)-cardol, m.p. and mixed m.p. 84—85 °C.

5-n-Propyl-, 5-n-Pentyl-, and 5-n-Heptyl-resorcinols.—Demethylations were carried out with boron tribromide in dichloromethane at −80 °C. Pyridine hydrochloride could also be used. The 5-n-alkylresorcinol dimethyl ether in dichloromethane (15 cm^3) was treated with boron tribromide (2.08 g) in dichloromethane (5 cm^3) at −78 °C. After 24 h (t.l.c. monitoring) the reaction mixture was decomposed by the addition of water and the recovered material from the evaporation of the combined ethereal extracts was purified by preparative t.l.c. (solvent G). In the demethylations the n-heptyl (1.18 g), the n-pentyl (1.04 g), and the n-propyl compounds (0.9 g) were used, and gave

the known 5-n-alkylresorcinols; R_F (solvent G), 0.20 (n-propyl), 0.26 (n-pentyl), 0.3 (n-heptyl).

The dimethyl ethers and the corresponding phenols had the following ^{1}H n.m.r. spectra: 5-n-propylresorcinol dimethyl ether τ (CCl_4) 3.67 (3 H, m, Ar-H), 6.23 (6 H, s, 2 OMe), 7.43 (2 H, t, C*H*$_2$Ar), 8.70 (6 H, m, [CH_2]$_3$), and 8.97—9.28 (3 H, t, Me): 5-n-propylresorcinol τ ($CDCl_3$) 3.43—3.70 (3 H, m, Ar-H), 3.60—4.33 (2 H, br s, *H*O-Ar, D_2O exchangeable), 7.33—7.63 (2 H, t, C*H*$_2$Ar), 8.17—8.68 (2 H, m, CH_2), and 8.93—9.27 (3 H, t, Me): 5-n-pentylresorcinol τ ($CDCl_3$) 3.54—3.73 (3 H, m, Ar-H), 4.48 (2 H, br s, Ar-O*H*, D_2O exchangeable), 7.37—7.68 (2 H, t, C*H*$_2$Ar), 8.37—8.83 (6 H, m, [CH_2]$_3$), and 8.97—9.30 (3 H, t, Me).

3,5-*Dibenxyloxyfluorobenzene*.— 3,5-Dimethoxyfluorobenzene was not demethylated with hydriodic acid–red phoshorus but reacted smoothly with boron tribromide. To 3,5-dimethoxyfluorobenzene (1.66 g) in dichloromethane (10 cm^3) at −80 °C, boron tribromide solution (5.8 cm^3) [from boron tribromide (23 g) and dichloromethane (25 cm^3)] at −80 °C was added, and the stirred mixture kept at −50 °C and then at 0 °C (16 h) (resorcinol dimethyl ether was used as a control, with t.l.c. monitoring of both reactions). When resorcinol dimethyl ether had completely demethylated (16 h) under identical conditions, the fluoro-compound had reacted to *ca.* 70%. Upon standing for a further 36 h, demethylation was complete. The reaction mixture was decomposed with water (50 cm^3) and the organic layer separated and combined with the ethereal extracts (3 × 50 cm^3) of the aqueous layer. The residue, upon removal of the solvent, was dissolved in hot water (50 cm^3) and upon cooling gave boric acid, m.p. 140—150 °C. The ^{1}H n.m.r. spectrum of the filtrate indicated the presence of 5-fluororesorcinol, as well as boric acid possibly combined with the former (δ 3.8, free boric acid OH at δ 5.95). After acidification (20% hydrochloric acid) followed by ethereal extraction and evaporation, the dried residue was crystallised (benzene) to give *5-fluororesorcinol*, m.p. 130—131 °C (1.456 g), which was quite hygroscopic (Found: C, 55.4; H, 3.85. $C_6H_5FO_2$ requires C, 56.05; H, 3.90%); τ ([$^2H_6$]DMSO) 1.8 (2 H, br s, Ar-O*H*, D_2O exchangeable), 3.75. (2 H, s, Ar-H), and 3.92 (1 H, s, Ar-H).

3,5-*Dibenzyloxyfluorobenzene*.—5-Fluororesorcinol (1.30 g) in dry acetone (18 cm^3) containing anhydrous potassium carbonate (4.2 g) was reacted with benzyl bromide (3.2 cm^3) at 25 °C (16 h). The ^{1}H n.m.r. spectrum of a sample showed the reaction to be complete, and 3,5-*dibenzyloxyfluorobenzene* was isolated as prisms, m.p. 86—88 °C; R_F 0.91 (solvent E) (Found: C, 77.7; H, 5.72. $C_{20}H_{17}FO_2$ requires C, 77.92; H, 5.51%); τ ($CDCl_3$) 2.47 (10 H, m, Ar-H), 3.35—3.50 (3 H, m, Ar-H), and 4.77 (4 H, s, 2 × ArOC*H*$_2$Ar).

Attempted reaction with n-alkyl-lithium. Interactions of 3,5-dibenzyloxyfluorobenzene with n-butyl-, n-heptyl-, and n-propyl-lithium under a variety of conditions and with considerable excess (in the latter case) did not give rise to more than trivial amounts of the required n-alkyl-2,4-dibenzyloxybenzoic acids.

3-*Benzyloxy-5-methoxybenzamide*.—3,5-Dihydroxybenzoic acid was methylated by a modification of a described procedure to give 3-hydroxy-5-methoxybenzoic acid as white prisms, m.p. 198—200 °C [lit.,[27] 203—204 °C (with softening at 189 °C)]. Benzylation of the acid in acetone containing potassium carbonate and benzyl chloride gave 3-benzyloxy-5-methoxybenzoic acid, m.p. 140—141 °C (lit.,[28] 143—145 °C) (Found: C, 69.65; H, 5.4. Calc. for $C_{15}H_{14}O_4$: C, 69.26; H, 5.42%). The methyl ester, prepared with ethereal diazomethane, crystallised as white needles (from aqueous ethanol), m.p. 95—96 °C (lit.,[28] 94—95.5 °C).

3-Benzyloxy-5-methoxybenzoic acid (124 g, 0.5 mol) was mixed with thionyl chloride (500 cm^3) and refluxed (3 h). After removal of excess of thionyl chloride, finally under vacuum at 100 °C, the crude acid chloride was purified by distillation, b.p. 130—140 °C at 0.1 mmHg. The oily distillate (118 g, 88.5%) solidified after standing (16 h), m.p. 50—51 °C.

The above acid chloride (53.3 g, 0.2 mol) in ether (75 cm^3) was poured into concentrated aqueous ammonia (500 cm^3, specific gravity 0.88) at 0 °C containing crushed ice (50 g). The mixture was well stirred (1 h) and the snow-white precipitate of 3-*benzyloxy-5-methoxybenzamide* collected by filtration, dried, and crystallised (ethanol) to give white prisms, m.p. 148—149 °C (54 g, 94%) (Found: C, 69.8; H, 5.85; N, 5.4. $C_{15}H_{15}NO_4$ requires C, 69.76; H, 5.81; N, 5.42%).

3-*Benzyloxy-5-methoxyaniline*.—Powdered 3-benzyloxy-5-methoxybenzamide (28.8 g, 0.112 mol) was stirred into a solution of sodium hypobromite [from bromine (7.2 cm^3) and sodium hydroxide (18.8 g) in water (250 cm^3)] and agitation continued (2 h) at 0 °C. The mixture was then heated on a steam-bath (1 h), cooled, ethereally extracted (2 × 50 cm^3), and the combined ethereal extracts washed with 10% hydrochloric acid (2 × 50 cm^3). The total extracts, washed with ether (100 cm^3), were basified with dilute sodium hydroxide solution. Ethereal extraction (2 × 50 cm^3) furnished, after recovery, crude 3-*benzyloxy-5-methoxyaniline* as a brown oil (6.3 g, 25%). Three preparative t.l.c. purifications (solvent B) gave an analytically pure sample as a golden oil (Found: C, 73.05; H, 6.6; N, 6.1. $C_{14}H_{15}NO_2$ requires C, 73.36; H, 6.55; N, 6.11%); τ (CCl_4) 2.52 (5 H, m, Ar-H), 4.00 (1 H, m, Ar-H), 4.12 (2 H, m, Ar-H), 5.03 (2 H, s, ArOC*H*$_2$Ar), 6.33 (3 H, s, OMe), and 6.47 (2 H, s, Ar-N*H*$_2$, D_2O exchangeable).

G.l.c. Retention Data.—The following retention times (min) were observed for fluoro-compounds, 5-n-alkyl resorcinol dimethyl ethers, and homologous methylorsellinate dimethyl ethers.

Column C, 75 °C: 2,4-dimethoxyfluorobenzene (28.5), 3,5-dimethoxyfluorobenzene (25.0), and 1,3-dimethoxybenzene (25.3).

Column B, 75 °C: 2,4-dimethoxyfluorobenzene (30.2), 3,5-dimethoxyfluorobenzene (25.5), 1,3-dimethoxybenzene (26.5), 4-fluoroanisole (5.6), 3-fluoroanisole (5.4), and 2-fluoroanisole (6.0).

Column A, 180 °C: 5-n-propylresorcinol dimethyl ether (4.00), 5-n-pentylresorcinol dimethyl ether (7.00), and 5-n-heptylresorcinol dimethyl ether (13.80).

Column B, 230 °C: for the methyl 6-n-alkyl-2,4-dimethoxybenzoates the following retention times were found (log retention time in parentheses); n-propyl [3.60 (2.335)]; n-butyl [4.00 (2.380)], n-heptyl [6.60 (2.600)], and n-pentadecyl [43.20 (3.414)]. A plot of log (retention time) *vs.* side-chain length gave a straight line.

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