Long Chain Phenols. Part 15.[1] Synthesis of 6-n-Alkylsalicylic Acids (and Isomeric Acids) from Fluoroanisoles with Alkyl-lithium †

By **Aziz A. Durrani** and **John H. P. Tyman**,* School of Chemistry, Brunel University, Uxbridge, Middlesex UB8 3PH

Various n-alkyl-lithiums have been prepared in ether. They react with both 2- and 3-fluoroanisoles to give, after carbonation, mainly 6-alkyl-2-methoxybenzoic acids. 4-Fluoroanisole gives 2-alkyl-4-methoxybenzoic acids. These reactions probably involve methoxybenzynes and the factors affecting orientation of addition of LiR to these are discussed. Interaction of alkyl-lithium addition products, from 2- and 3-fluoroanisole, with water gave the 3-alkylanisole and, in the case of 4-fluoroanisole, this was accompanied by a small proportion of the 4-alkylanisole. Demethylation of the 6-alkyl-2-methoxybenzoic acids provided syntheses of several naturally occurring anacardic acids.

THE only published synthesis [1,‡] of 6-n-alkylsalicylic acids (1; R = H) (anacardic acids) requires several consecutive operations for the accumulation of sufficient material. To overcome this, 3-methoxyphthalic anhydride was used but the two isomeric acids formed, having similar properties, gave no advantage, while 3-nitrophthalic anhydride, followed by conversion of the nitro- to the hydroxy-group, gave the unwanted isomer.

A method was sought, therefore, which would give the desired product in higher yield.

Despite a report [2] that n-butyl-lithium with 4-fluoroanisole followed by carbonation simply gave 2-methoxy-5-fluorobenzoic acid, we have found that higher alkyl-lithiums form 2-alkyl-4-methoxybenzoic acids (2); 2- and 3-fluoro-anisole with alkyl-lithiums gave 6-alkyl-2-methoxybenzoic acids (1). By reaction
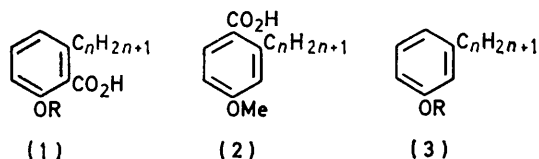
of the intermediate aryl-lithium with water, 3-n-alkylanisoles were produced from 2- and 3-fluoroanisoles, accompanied by a little of the 4-alkyl compound in the case of 4-fluoroanisole (3; R = Me). Both (1) and (3) were demethylated to the corresponding phenolic compounds. The preceding reactions are believed to be best explained by the involvement of ‘ 2-methoxybenzyne ’ and ‘ 3-methoxybenzyne.’

Several naturally occurring anacardic acids have been synthesised § including the unusual (C-14 sidechain ¶) hydroginkgolinic acid [3] and (15 : 0) anacardic acid (6-n-pentadecylsalicyclic acid). Ginkgolic acid, 6-(8′Z)-pentadecenyl)salicylic acid, has been derived [4] using the present method.

RESULTS AND DISCUSSION

The reaction sequences of 2-, 3-, and 4-fluoroanisole with n-alkyl-lithiums are shown in Scheme 1,

The Results and Discussion section relates to the formation of the alkyl-lithium, reaction with the isomeric fluoroanisoles, and carbonation of reaction products.

The n-alkyl-lithiums were formed by interaction of the alkyl bromide and lithium in the presence of ether at below 0 °C since, although the higher bromides were somewhat unreactive, the equilibrium in the exchange reaction of the type shown was infavourable and both the desired alkyl-lithium and n-butyl-lithium were present, together with the Wurtz product, RR (equation 1). Only in one instance, apparently, have higher n-

$$Bu^n Li + RBr \rightleftharpoons RLi + Bu^n Br \qquad (1)$$

alkyl-lithium reagents been prepared.[5] Alkyl-lithium formation in the direct procedures was not complete and preparations were conducted to provide a 1—2 molar proportion of the reagent for interaction with the fluoro-anisole.

At the next stage, to avoid low yields it was found necessary to raise the temperature of the reaction mixture although refluxing was undesirable on account of decomposition (equation 2).[6] Reaction of the alkyl-

$$RLi + Et_2O \longrightarrow LiOEt + REt \qquad (2)$$
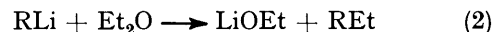
lithium with fluoroanisoles proceeded mildly exo-thermically and invariably with colouration of the reaction mixture. In the examples studied it appears most probable that ‘ methoxybenzynes ’ are involved as reactive intermediates since the same major product resulted independently of whether 2- or 3-fluoroanisole was used. Gas–liquid chromatography in conjunction with mass spectroscopy has indicated reaction mixtures to contain frequently many components and their investigation is still continuing. The acidic products from the reaction of n-butyl-lithium and 2-fluoroanisole were methylated with diazomethane and chromatographed. The reaction pathways likely to be involved are shown in Scheme 2. Mass spectral and analytical evidence indicated the presence of a terphenyl derivative (11) (m/e 434). A diphenyl compound [cf. (12)] was isolated in the synthesis of ginkgolic acid.[4] Methyl 2-

---

† Presented at the 8th and 9th IUPAC Symposia on The Chemistry of Natural Products at Delhi, 1972, and Ottawa, 1974.

‡ Since this work was submitted the authors' attention has been drawn to an unpublished procedure (J. Staunton, personal communication) in which the carbanion of 6-methylsalicylate methyl ether is alkylated.

§ A preliminary communication has appeared, A. A. Durrani and J. H. P. Tyman, *Chem. and Ind.*, 1972, 762.

¶ The described ‘ C14 cardanol ’ by M. T. Harvey and S. Caplan (*Ind. Eng. Chem.*, 1940, **32**, 1306) has never been substantiated and its formulation is now ascribed to experimental error.

anisate and salicylate were identified chromatographically. The former, arising from a proposed elimination, is somewhat analogous to previous experience [7] in which 'benzyne' (from 2-chlorobromobenzene) and butyl-lithium afforded benzoic acid after carbonation. Terphenyls and other polynuclear substances have been observed in different circumstances by others.[8-11]

and fluoro-groups since 2-methoxy-4-fluorobenzoic acid was not found. With 2-fluoroanisole the inductive influence of the methoxy-group might have been expected to encourage o-lithiation but the ready elimination of lithium fluoride from the 3-lithiated product was apparently favoured since 2-methoxy-3-fluorobenzoic acid was not found in the reaction products. The higher
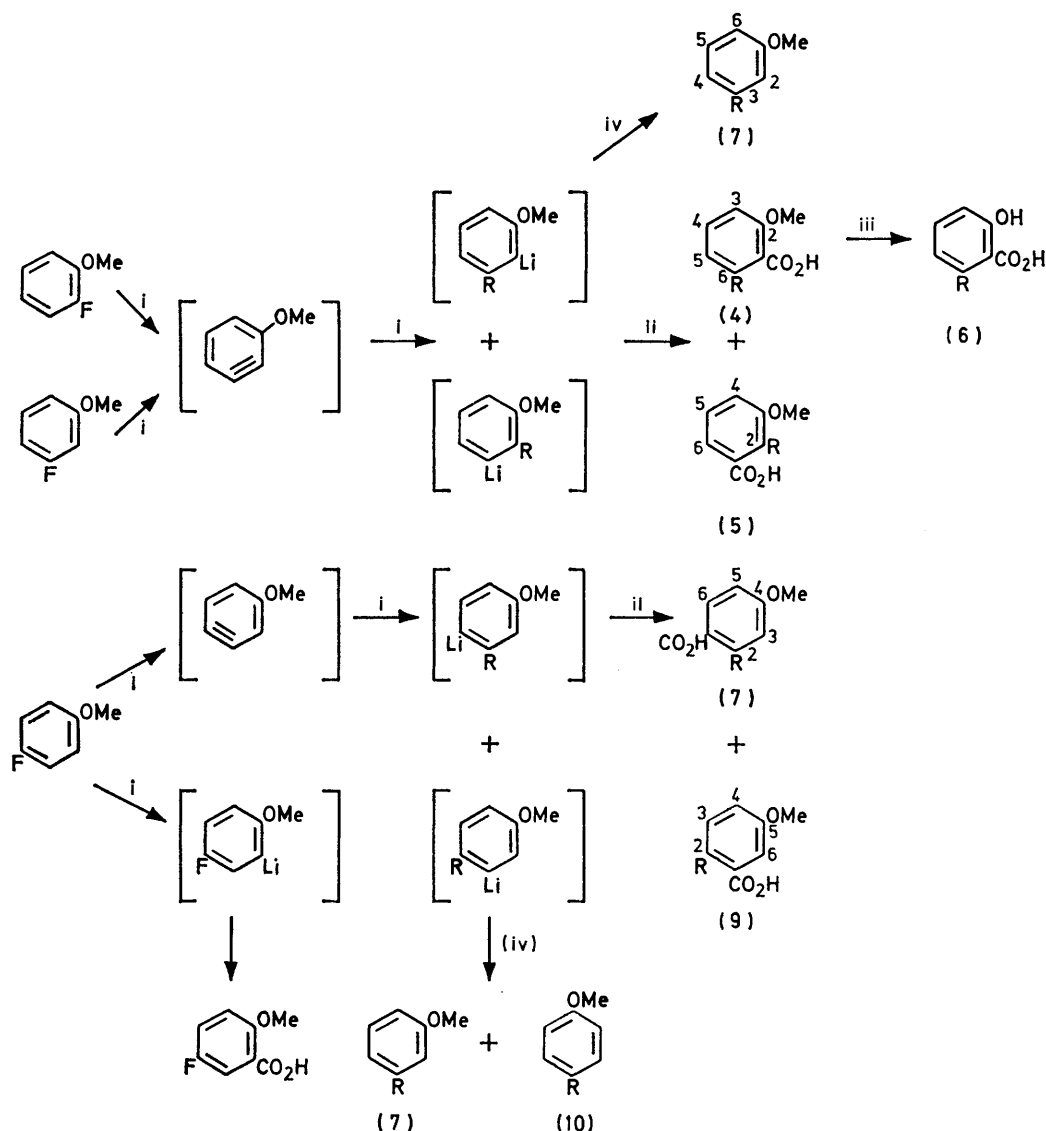
SCHEME 1   Reagents: i, RLi, Et$_2$O; ii, CO$_2$, H$^+$; iii, HI–P; iv, H$_2$O, H$^+$

Despite the presence of acidic impurities the main reaction product of the methylation was methyl 2-butyl-6-methoxybenzoate.

The believed formation of '2-methoxybenzyne' would indicate the displacement of the fluorine atom as lithium fluoride from lithiated 2- and 3-fluoroanisole. There was no evidence in the case of 3-fluoroanisole of '3-methoxybenzyne' formation which would have given 2-butyl-4-methoxybenzoic acid. Lithiation of 3-fluoroanisole took place primarily *ortho* to the methoxy-

yields from the use of 3- compared with 2-fluoroanisole, shown in Tables 1 and 2, indicate that 2-lithiation with '2-methoxybenzyne' formation occurs more readily than 3-lithiation. The *ortho* carbon is better able to accommodate a carbanion. In practically all cases 3-fluoroanisole gave better yields than 2-fluoroanisole in reactions with alkyl-lithiums. Table 1 gives a comparison of the yields of the acids and Table 2 shows a comparison of the yields of 3-n-alkylanisoles from the two sources.

TABLE 1

Yields (%) of 6-n-alkyl-2-methoxybenzoic acids

6-n-Alkyl group	3-Fluoroanisole	2-Fluoroanisole
Me	7	6.0
Et	54	29
Pr	84	40
Pr^i	0	0
Bu	25	16
Dodecyl	29	28
Tetradecyl	37	39
Pentadecyl	41	35

TABLE 2

Yields % of 3-n-alkylanisoles

3-n-Alkyl group	3-Fluoroanisole	2-Fluoroanisole
Et	54	28
Pr^i	0	0
Bu	45	41.5
Dodecyl	50	64
Tetradecyl	49	40.5
Pentadecyl	40	34

The failure of Pr^{i}Li to afford any product (although from the series [12] Bu^{t}Li > Pr^{i}Li > Bu^{n}Li > PhLi > MeLi, it is an effective lithiating reagent) suggests there may be a steric or other influence in the reaction of the alkyl-lithium with the fluoroanisoles, since the results with Bu^{n}Li and MeLi appear to indicate that there is a correlation between lithiating power and the percentage yield of the final product.

By contrast with the 2- and 3-fluoroanisoles, 4-fluoroanisole with n-butyl-lithium gave 2-methoxy-5-fluorobenzoic acid, a result [2] which we have confirmed, although evidence of butylated products was also found. Dodecyl- and pentadecyl-lithium yielded 2-dodecyl-4-methoxy- and 2-pentadecyl-4-methoxy-benzoic acids, presumably by way of ' 3-methoxybenzyne.' Interaction of the intermediate lithiated products with water yielded primarily the 3-n-alkylanisoles accompanied by some of the 4-isomer. Chromatographic and [1]H n.m.r. evidence indicated the presence of a small proportion of the latter.

With 2- and 3-fluoroanisole the ' methoxybenzyne ' intermediate can in theory add the alkyl-lithium in two ways to give finally, after carbonation, the isomeric acids (4) and (5). The major and only identified product was (4), with (7) in the water-treated products. Chromatographic and [1]H n.m.r. examination showed the absence of isomeric materials. In the reactions of phenyl-lithium with 2-fluoroanisole,[8] 61% of (4; R = Ph) and 3.9% of (5; R = Ph) were formed, and with 3-fluoroanisole the proportions were 80 and 2.5%, respectively.
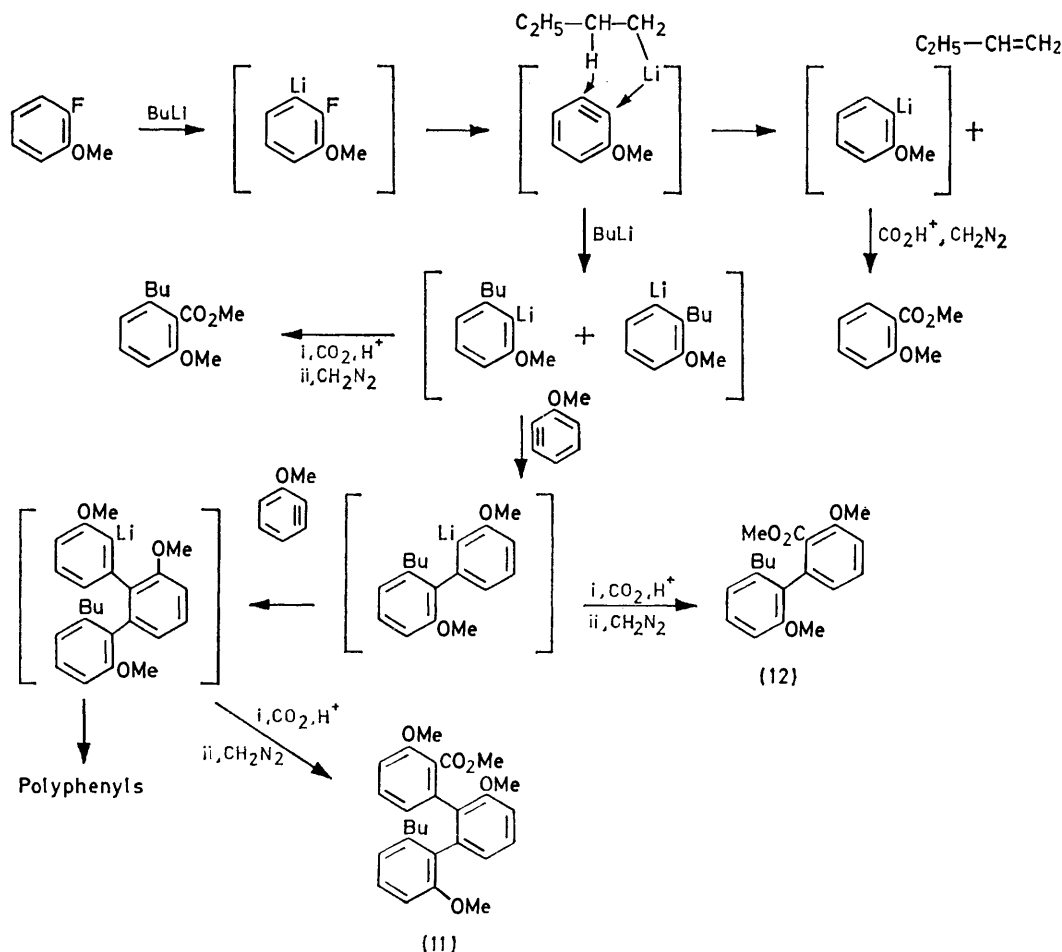

SCHEME 2

It is of interest that Wittig and Fuhrmann [13] only obtained ' an ill-defined yellow resin ' from the latter reaction whereas with 3-bromoanisole, 3-phenylanisole was isolated, its formation being attributed to a simple exchange reaction. The same authors reported that 2-fluoroanisole with phenyl-lithium gave 2-phenylanisole (25%), an ' ill-defined resin,' and recovered 2-fluoroanisole (45%), results which are opposite to those of Huisgen and Rist.[8]

The availability of 2- and 3-bromoanisoles makes them of some interest for aryne-type reactions. In the present work 2-bromoanisole with alkyl- or phenyl-lithiums followed by carbonation gave 2-methoxybenzoic acid, while 3-bromoanisole with tetradecyl-lithium gave a low yield of 2-tetradecyl-6-methoxybenzoic acid and 3-methoxybenzoic acid. These results are partially in agreement with earlier work and indicate both exchange and ' methoxybenzyne ' formation to a low degree. Attempts to improve proton abstraction by the use of $NNN'N'$-tetramethylethylenediamine [14] were not effective.

The reactions, followed by addition of water, of 2- and 3-fluoroanisole with alkyl-lithiums gave virtually one product with *meta* orientation, and with 4-fluoroanisole the same material accompanied by a minor proportion of the *para* product. In the reactions of 4-(dimethyl-amino)bromobenzene and 4-methylbromobenzene with potassium amide in liquid ammonia, 3- and 4-(dimethyl-amino)aniline and toluidine, respectively, in similar ratios were formed.[15] The view that arynes, which are thought to possess two non-interacting π systems in different planes, are influenced by inductive rather than mesomeric effects is not substantiated by these findings since the inductive influences of CH_3^- and $N(CH_3)_2^-$ are opposite and the mesomeric effect of the latter is greater.* If in the present work with 3-methoxy-benzene (from 4-fluoranisole) the inductive effect solely were operative, it would be weak at positions 3 and 4, and m/p isomers in more or less equal proportion would be expected afrer alkyl-lithium addition. Prior to aryne formation the mesomeric effect explains 2- and 4-lithiation (and also the high basicity of the alkyl carb-anion in the transition state may be a factor) but its influence has apparently not vanished after aryne formation. Alkyl-lithium addition probably occurs
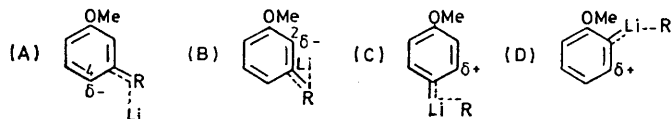

not by a simultaneous process, but so as to locate a developing negative charge at the 2- and 4-positions [as in (B) and (A), the positions best able to accommodate such a charge], rather than a positive charge at the 3-position [as in (C) and (D)]. (B) is explicable but not (A) by the inductive effect of methoxy.

* The interaction of the fluorotoluenes compared with the fluoroanisoles towards alkyl-lithiums would be of interest.

The situation is complex, with the existence of lithiation, aryne formation, and aryne addition as distinct steps, all influenced electronically, and further experimentation is required to clarify the mechanism.

In the reaction of alkyl-lithium with fluoroanisoles, ketone formation was observed at the carbonation stage. While the addition of the reaction mixture to water, or *vice versa*, did not affect the yield of the 3-alkylanisole, the yield in the carbonation was influenced by the procedure. Passage of carbon dioxide into the reaction mixture at the conclusion of the reaction of the fluoro-anisole (indicated by a drop in the temperature following the initial mildly exothermic reaction) resulted in a vigorous reaction and formation of a high proportion of ketone, RCOR. This was very largely derived from the excess of RLi but clearly the aryl-lithium can also react since the formation of ketones was first observed in the reactions of phenyl-lithium,[16] which formed benzo-phenone, and the process has been developed into a useful synthetic procedure. In the present work dissipation of the required product as (13) and (14) could

(13)   (14)
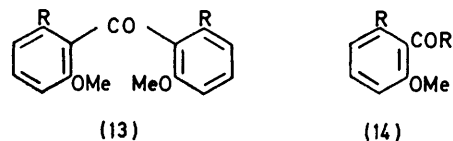
occur. Addition of the reaction mixtures to solid carbon dioxide however, resulted in little ketonic impurity of the type RCOR, and (13) and (14) would be likely to be absent also.

The synthesis of anacardic acids required the demethylation of the methyl ethers, and hydriodic acid containing red phosphorus was the most effective reagent. Alternative reagents such as boron tribromide,[17] boron trichloride,[18] and lithium iodide–collidine [19] were of no assistance.

Since, however, the yields with hydriodic acid were moderate, other protective groups than methyl such as tetrahydropyranyl [20] were considered for the fluoro-phenols. With the benzyl group, lithiation and the ensuing reactions proceeded equally well with 3-benzyl-oxyfluorobenzene and ethyl-lithium to give 2-benzyloxy-6-ethylbenzoic acid. Hydrogenolysis with Pd–C and hydrogen went smoothly with this compound and with 2-benzyloxy-6-pentadecylbenzoic acid. Further work is envisaged with the benzyloxyfluorobenzenes and with trimethylsilyloxyfluorobenzenes.

EXPERIMENTAL

Infrared spectra were recorded on a Unicam SP 200 instrument (liquids as films, solids as KBr discs). ¹H N.m.r. spectra (tetramethylsilane as internal standard) were determined on Varian T60 and HA100 (PCMU, Harwell) instruments. Microanalyses were by Drs. Weiler and Strauss. Gas–liquid chromatography was carried out on a Pye 104 instrument equipped with flame-ionisation detector. The glass columns were 5-ft × 3/16-in (internal diameter); columns employed were A (3% SE30), B (20%

SE52), and C (10% carbowax), all on diatomite C. Nitrogen flow rate was 40 cm³ min⁻¹; pressure 71 lbf in⁻². Column chromatography was carried out on Spence grade H alumina. Thin-layer chromatography was carried out with Kieselgel G (Merck) on analytical (8 × 10 cm × 0.25 mm) and preparative plates (20 × 20 cm × 1 mm) with 0.1% ethanolic rhodamine 6G as visualising agent. Solvent systems employed were A, chloroform–ethyl acetate (94 : 6); B, chloroform–ethyl acetate (95 : 5); C, chloroform–ethyl acetate (96 : 4); D, chloroform–ethyl acetate–formic acid (95 : 5 : 2); E, chloroform–light petroleum (b.p. 40—60°), (1 : 1); F, chloroform–ethyl acetate (17 : 3); G, chloroform–ethyl acetate–formic acid (96 : 4 : 3).

Materials.—Alkyl bromides were prepared according to Vogel [21] and examined (i.r.) for absence of OH absorption. From acids, certain bromides were prepared according to published procedures.[22] Alkyl-lithium reagents were prepared in a magnetically-stirred, evacuable 3-necked flask equipped with pressure-equalised funnel, low-temperature thermometer, and condenser to the top of which was a 3-way tap for vacuum, nitrogen, and manometer connection. Approximately 2 g atoms of lithium were allowed to react with a 1 molar proportion of the alkyl bromide at 0 to −10 °C. In practice 1 g of lithium was cut under dry ether into *ca.* 100 pieces and ⅛—¼ of the alkyl halide in ether added, followed by the rest dropwise. Methoxy-fluorobenzenes were prepared analogously by the method described for 4-fluoroanisole.[21] The diazonium fluoro-borate suspensions were saturated with sodium chloride, cooled to 0 to −20 °C, and filtered. 2-Methoxyfluoroben-zene (36% yield; b.p. 159—161°), 3-methoxyfluorobenzene (60% yield; b.p. 156—158°) and 4-methoxyfluorobenzene (63% yield, b.p. 130—134°) had the following properties. G.l.c. retention [column, retention (s), temperature (°C)]: 2-fluoroanisole, A, 96, 90; B, 360, 75; 3,fluoroanisole, A, 84, 90; B, 324, 75; 4-fluoroanisole, A, 96, 90; B, 336, 75; 2-fluorophenol, B, 768, 70; phenol, B, 600, 70. ¹H N.m.r. spectra: 2-fluoroanisole, δ(CCl₄) 6.92 (4 H, m, ArH) and 3.84 (3 H, s, OMe); 3-fluoroanisole, δ(CCl₄) 7.13 (1 H, ' q ', ArH), 6.5 (3 H, m, ArH), and 3.73 (3 H, s, OMe). The calculated values for H-3, H-4, H-5, and H-6 in 2-fluoroanisole were 6.87, 6.84, 6.94, and 6.79 and the observed spectrum showed no clear resolution. For 3-fluoroanisole the calculated values for H-2, H-4, H-5, and H-6 were 6.51, 6.56, 7.15, and 6.58. Only H-5 was distinct and, due to H–F coupling (J_m 6—8 Hz), appeared as a ' quartet ' rather than a ' triplet.'

Hydriodic acid was decolourised by boiling with red phosphorus followed by redistillation and was stored in the dark. n-Butyl-lithium (25% solution by weight) was purchased from Alfa Inorganics Ltd., Beverly, Mass.

Separation of Anacardic Acid Methyl Ethers from Fatty Acids.—The t.l.c. separation of anacardic acid methyl ethers and fatty acids required several operations on account of the similar R_F values. Esterification after demethyl-ation followed by alkaline extraction gave a precise simple separation.

2-Ethyl-6-methoxybenzoic Acid.—To ethyl-lithium [from ethyl bromide (22.0 g, 0.20 mol) in ether (40 cm³) with lithium (2.8 g, 0.4 mol) and ether (75 cm³) over 50 min] 2-fluoroanisole (16.3 g, 0.129 mol) in ether (40 cm³) was added at 0 °C (5 min) and the temperature allowed to rise to normal. After the exothermic reaction had ceased (1.5 h), the reaction mixture was poured onto solid carbon dioxide (200 g), mixed, and acidified with dilute hydro-

chloric acid. The ethereal layer was washed with 2.5 M-sodium hydroxide solution (3 × 25 cm³), and the oily material recovered from the alkaline layer by acidification and extraction was crystallised from pentane–ether to give *2-ethyl-6-methoxybenzoic acid* as white prisms (6.7 g, 29%), m.p. 145—146°, R_F 0.25 (solvent C) (Found: C, 66.5; H, 6.6. $C_{10}H_{13}O_3$ requires C, 66.65; H, 6.65%), τ(CDCl₃) −2.51 (1 H, S, CO₂H, D₂O exch.), 2.6 (1 H, m, ArH), 2.85—3.29 (2 H, m, ArH), 6.04 (3 H, s, OMe), 7.07 (2 H, q, CH₂Ar), and 8.61 (3 H, t, Me), $\nu_{max.}$ (KBr) 1 700 cm⁻¹ (C=O). Some fluoroanisole was present in the neutral material.

6-Ethylsalicylic Acid.—2-Ethyl-6-methoxybenzoic acid (1.0 g, 0.005 4 mol) heated (30 min) with colourless hydriodic acid (25 cm³) and red phosphorus (0.3 g) on a steam-bath followed by work-up in the usual way (ether solution washed with aqueous sodium thiosulphate) gave, after preparative t.l.c., *6-ethylsalicylic acid* as prisms (200 mg, 22%), m.p. 118—120°, R_F 0.11 (solvent B) (single spot) (Found: C, 65.9; H, 6.2. $C_9H_{10}O_3$ requires C, 65.05; H, 6.0%) (this substance appears to be homogeneous and the analytical discrepancy remains inexplicable), τ(CDCl₃) 1.6—2.3 (2 H, s, CO₂H · · · HO, D₂O exch.), 2.3—3.7 (3 H, m, ArH), 6.66—7.3 (2 H, q, CH₂Ar), and 8.55—9.0 (3 H, t, Me), $\nu_{max.}$ (KBr), 3 200 (S, OH) and 1 710 cm⁻¹ (C=O). Demethylation with boron tribromide was not satisfactory but with boron trichloride 6-ethylsalicylic acid was obtained.

2-Methoxy-6-n-propylbenzoic Acid.—n-Propyl-lithium [from n-propyl bromide (12.3 g, 0.1 mol) in ether (40 cm³) with lithium (1.4 g, 0.2 mol) and ether (75 cm³) at −10 °C (1.5 h)] was treated with 2-fluoroanisole (4.0 g, 0.31 mol) in ether (10 cm³) at 0 °C initially and then at ambient temperature (2 h). The mixture after carbonation with solid carbon dioxide (100 g) was worked up in the usual way to give *2-methoxy-6-n-propylbenzoic acid* (2.47 g, 40.1%), m.p. 34—36°, R_F 0.25 (solvent C) (Found: C, 67.8; H, 7.45. $C_{11}H_{14}O_3$ requires C, 68.05; H, 7.2%), τ(CCl₃) (1 H, s, CO₂H, D₂O exch.), 2.75 (1 H, m, ArH), 3.14 (2 H, m, ArH), 6.12 (3 H, s, MeO), 7.36 (2 H, t, CH₂Ar), 8.35 (2 H, sextet, CH₂), and 9.17 (3 H, t, Me), $\nu_{max.}$ (KBr) 3 275 (s, OH) and 17.05 cm⁻¹ (s, C=O).

Attempts to prepare 6-isopropyl- and 6-t-butyl-2-methoxybenzoic acids were not successful, although the alkyl-lithiums were formed.

Methyl 2-n-Butyl-6-methoxybenzoate.—n-Butyl-lithium (50 cm³) and 2-fluoroanisole (10.1 g, 0.08 mol) in ether (50 cm³) were allowed to react (2 h) in the nitrogen-filled apparatus at ambient temperature and the mixture was then poured onto solid carbon dioxide (200 g). The crude acidic part (7.8 g) from the work-up in ether was methylated with ethereal diazomethane. The product was chromatographed on alumina (750 g) with solvent E (30 fractions), chloroform (10 fractions), and ethyl acetate (10 fractions). Fractions 7—25 were combined and evaporated to give methyl 2-*n-butyl-6-methoxybenzoate* as an oil (2.9 g, 16.3%), R_F 0.83 (solvent C) (Found: C, 70.75; H, 8.2. $C_{13}H_{18}O_3$ requires C, 70.25; H, 8.1%), τ(CCl₄) 2.84 (1 H, m, ArH), 3.26 (2 H, m, ArH), 6.21 (3 H, s, OMe), 6.30 (3 H, s, CO₂Me), 7.52 (2 H, t, CH₂Ar), 8.58 (4 H, m, C₂H₄), and 9.01 (3 H, t, Me), $\nu_{max.}$ (film) 1 700 cm⁻¹ (s, C=O ester).

Alternatively the crude product, after carbonation and recovery of the acidic portion, was extracted with boiling light petroleum (b.p. 60—80°) (3 × 35 cm³) and the residue upon evaporation (5.80 g) was dissolved in ether (30 cm³) and methylated with ethereal diazomethane. Chromato-graphy as before gave the same product (3.01 g, 17.0%).

The chloroform fractions contained some of the required products (t.l.c.). The ethyl acetate was substantially removed from the last ten fractions and large needle crystals, m.p. 162—163.5°, separated (Found: C, 74.2, 74.6; H, 6.35, 6.65%; m/e, 434. $C_{27}H_{30}O_5$ requires C, 74.65; H, 6.9; M, 434), $\tau(CCl_4)$ 2.8—3.8 (6 H, m, ArH), 6.22 (3 H, s, OMe), 6.25 (6.25, s, OMe), 6.41 (3 H, s, CO_2Me), 7.75 (2 H, t, CH_2Ar), 8.80 (4 H, m, C_2H_4), and 9.10 (3 H, t, Me), $\nu_{max.}$ (KBr) 2 950 (s, CH, and aryl CH) and 1 720 cm^{-1} (s, C=O, ester).

2-n-Butyl-6-methoxybenzoic acid.—Methyl 2-n-butyl-6-methoxybenzoate (2.0 g, 0.000 9 mol) was refluxed (1 h) with 20% w/v potassium hydroxide–ethanol (25 cm^3). The acidic material was separated in the usual way and the product purified by preparative t.l.c. (solvent A) to give *2-n-butyl-6-methoxybenzoic acid* as an colourless oil (1.42 g, 76.3%), R_F 0.25 (solvent C) (Found: C, 69.55; H, 7.7. $C_{12}H_{16}O_3$ requires C, 69.25; H, 7.7%), $\tau(CCl_4)$ 1.95 (1 H, s, CO_2H, D_2O exch.), 2.75 (1 H, m, ArH), 3.21 (2 H, m, ArH), 6.19 (3 H, s, OMe), 7.44 (2 H, t, CH_2Ar), 8.60 (4 H, m, C_2H_4), and 9.10 (3 H, t, Me), $\nu_{max.}$ (film) 1 690 cm^{-1} (s, C=O).

6-n-Butylsalicylic Acid.—2-n-Butyl-6-methoxybenzoic acid (1.0 g, 0.004 7 mol) was treated with colourless hydriodic acid (25 cm^3) and red phosphorus (0.5 g) on a steam-bath (30 min) and then worked up in the usual way (sodium thiosulphate solution wash of the ether solution) to give *6-n-butylsalicylic acid* as needles, m.p. 94—95° (from light petroleum), mixed m.p. 93—95°, R_F 0.12 (solvent C) (Found: C, 67.75; H, 7.2. $C_{11}H_{14}O_3$ requires C, 68.0; H, 7.2%), $\tau(CCl_4)$ −2.00 (2 H, br s, HO $\cdots$ CO$_2$H, D_2O exch.), 2.19 (3 H, m, ArH), 6.48—7.00 (2 H, t, CH_2Ar), 8.40 (4 H, m, C_2H_4), and 8.98 (3 H, t, Me), $\nu_{max.}$ (KBr) 1 715 cm^{-1} (s, C=O).

Attempted Preparation of 2-n-Butyl-6-methoxybenzoic Acid from 2-Bromoanisole.—n-Butyl-lithium (20 cm^3) and 2-bromoanisole (4.7 g, 0.025 mol) in ether (25 cm^3) were refluxed (1 h), cooled overnight, carbonated with solid carbon dioxide (100 g), and the acidic part worked up in the usual way. Crystallisation from light petroleum–ether gave 2-methoxybenzoic acid (1.37 g, 35.8%), m.p. 91—94°, identified by its mixed m.p., ^{1}H n.m.r. spectrum, and R_F value (0.13, solvent B).

3-n-Butylanisole.—(*i*) To n-butyl-lithium (60 cm^3) was rapidly added 2-fluoroanisole (7.0 g, 0.055 mol) in ether (30 cm^3) and the mixture stirred (3 h) at ambient temperature. After decomposition with dilute hydrochloric acid, the neutral material was worked up in the usual way. Chromatography on alumina (750 g) and elution with light petroleum (500 cm^3) and solvent E (500 cm^3) gave forty fractions (25 cm^3 each). From fractions 18—30, *3-n-butylanisole* was obtained (3.74 g, 41.5%), R_F 0.8 (solvent C) (Found: C, 80.65; H, 9.6. $C_{11}H_{16}O$ requires C, 80.5; H, 9.75%).

(*ii*) Decarboxylation of 2-n-butyl-6-methoxybenzoic acid (1.0 g, 0.004 7 mol) in refluxing quinoline (15 cm^3) with copper powder (0.1 g) for 6 h followed by the usual work-up gave a brown oil (0.55 g, 70%) which was purified by preparative t.l.c. (solvent C) to give 3-n-butylanisole, identical chromatographically with the product from (*i*) and a sample synthesised by a standard method. 3-n-Butylanisole has been referred to [23] but no preparative details given and accordingly the method used in the present work is described.

To the Grignard reagent prepared over 10 min from n-propyl bromide (6.15 g, 0.05 mol) in ether (25 cm^3) and magnesium (1.3 g, 0.054 mol) in ether (50 cm^3), 3-methoxybenzaldehyde (6.5 g, 0.047 mol) in ether (25 cm^3) was added. After ½ h, the reaction mixture was worked up in the usual way and the ethereal layer, washed with dilute sodium hydroxide and concentrated, gave an oil, 1-(3-methoxyphenyl)butan-1-ol (7.75 g, 90.1%), R_F 0.79 (solvent C), $\nu_{max.}$ (film) 3 350 cm^{-1} (s, OH).

The alcohol (3.6 g) and fused potassium hydrogensulphate (0.5 g) were heated together until formation of water droplets occurred (15 min). Cooling and work-up gave 3-(but-1-enyl)anisole as an oil (3.0 g, 92.5%), R_F 0.8 (solvent C), $\nu_{max.}$ (film) 705 cm^{-1} (m, olefin).

The olefin (2.0 g, 0.012 mol) in ethanol (20 cm^3) was hydrogenated in the presence of 10% Pd–C (0.05 g) and when no further hydrogen was adsorbed, the mixture was filtered and 3-n-butylanisole recovered as an oil (2.0 g, 98.7%), R_F 0.8 (solvent C), $\nu_{max.}$ (film) 3 025 and 2 860 cm^{-1} (s, CH$_2$, Ar C–H). The various materials had the following ^{1}H n.m.r. spectra: 1-(3-methoxyphenyl)butan-1-ol, $\tau(CCl_4)$ 2.8 (1 H, m, ArH), 3.21 (3 H, m, ArH), 5.53 (1 H, t, CH), 6.30, (3 H, s, OMe), 6.79 (1 H, s, OH, D_2O exch.), 8.2—8.92 (4 H, m, C_2H_4), and 9.0 (3 H, t, Me); 3-(but-1-enyl)anisole, $\tau(CCl_4)$ 2.80 (4 H, m, ArH), 3.66—3.84 (2 H, m, CH=CH), 6.20 (3 H, s, OMe), 7.4—8.12 (2 H, q, CH$_2$), and 8.6—9.0 (3 H, t, Me); 3-n-butylanisole, $\tau(CCl_4)$ 3.00 (4 H, m, ArH), 6.22 (3 H, s, OMe), 7.62 (2 H, t, CH$_2$Ar), 8.60 (4 H, m, C_2H_4), and 9.18 (3 H, t, Me).

2-n-Butylanisole.—The preparation of 2-n-butylanisole from 2-(but-1-enyl)anisole has been described.[24] In the present work interaction of 2-methoxybenzaldehyde with n-propylmagnesium bromide gave 1-(2-methoxyphenyl)-butan-1-ol as an oil (89.4%), $\nu_{max.}$ (film) 3 350 cm^{-1} (s, OH), dehydration of which with potassium hydrogensulphate in the usual way gave 2-(but-1-enyl)anisole as an oil which was hydrogenated to 2-n-butylanisole (99% yield), b.p. 217° (lit.,[22] 217°), $\nu_{max.}$ (film) 3 030 and 2 860 cm^{-1} (s, C–H).

The following ^{1}H n.m.r. spectra were recorded: 1-(2-methoxyphenyl)butan-1-ol had $\tau(CCl_4)$ 2.90 (4 H, m, ArH), 5.1—5.4 (1 H, t, CH), 6.22 (3 H, s, OMe), 7.7 (1 H, s, OH, D_2O exch.), 8.1—8.98 (4 H, m, C_2H_4), and 8.98—9.4 (3 H, t, Me); 2-(but-1-enyl)anisole had $\tau(CCl_4)$ 2.96 (4 H, m, ArH), 3.9 (2 H, m, CH=CH), 6.20 (3 H, s, OMe), 7.47—8.08 (2 H, q, CH$_2$), and 8.5—9.19 (3 H, t, Me); 2-n-butylanisole had $\tau(CCl_4)$ 2.79—3.44 (4 H, m, ArH), 6.2 (3 H, s, OMe), 7.30 (2 H, t, CH$_2$Ar), 8.40 (4 H, m, C_2H_4), and 9.05 (3 H, t, Me).

Reaction of n-Butyl-lithium with 4-Fluoroanisole to form 5-Fluoro-2-methoxybenzoic Acid.—To n-butyl-lithium (23.1%; 44 cm^3) was cautiously added 4-fluoroanisole (10 g) in ether (25 cm^3). As the reaction temperature increased, the mixture was cooled in ice–water. After completion of the addition the temperature was 18 °C but upon removal of the coolant it rose to 35 °C (½ h). The colour of the reaction mixture passed from orange to dark red and finally brown. When the temperature finally dropped, the mixture was poured onto solid carbon dioxide (200 g), then acidified with 10% hydrochloric acid (150 cm^3). The acidic products (7.0 g) were separated from neutral material (4.1 g) in the usual way and after extraction with n-pentane, the residual material was crystallised from light petroleum (b.p. 60—80°) to give 5-fluoro-2-methoxybenzoic acid, m.p. 84—85° (lit.,[2] 87°), $\tau(CDCl_3)$ 0 (1 H, br s, CO$_2$H, D_2O exch.), 2.16 (1 H, q, ArH), 7.1 (2 H, m, ArH), and 4.1 (3 H, s, OMe). Evidence (^{1}H n.m.r.) of the presence of a 4-me,

thoxybenzoic acid was obtained in the n-pentane soluble material.

2-n-Dodecyl-6-methoxybenzoic Acid.—To n-dodecyl-lithium [prepared from n-dodecyl bromide (15.0 g, 0.06 mol) in ether (40 cm³) and lithium (1.4 g), 0.2 mol) in ether (50 cm³) at 0 to −10 °C over 2 h, and from which the undissolved lithium had been removed], 2-fluoroanisole (3.0 g, 0.024 mol) in ether (20 cm³) was added at 0 °C. The mixture was stirred (2 h) and then treated with solid carbon dioxide (100 g). The acidic portion (4.2 g) from the usual work-up was crystallised from light petroleum to give aggregates of *2-n-dodecyl-6-methoxybenzoic acid* (1.05 g, 28%), m.p. 62—64°, R_F 0.13 (solvent C) (Found: C, 74.4; H, 10.25. $C_{20}H_{32}O_3$ requires C, 75.0; H, 10.0%), $\tau(CDCl_3)$ −1.67 (1 H, s, CO_2H, D_2O exch.), 2.43 (1 H, m, ArH), 3.03 (3 H, m, ArH), 6.15 (3 H, s, OMe), 7.37 (2 H, t, CH_2Ar), 8.54 (20 H, m, $C_{10}H_{20}$), and 9.00 (3 H, t, Me), $\nu_{max.}$ (KBr) 1 700 cm⁻¹ (s, C=O).

2-n-Dodecyl-4-methoxybenzoic Acid.—To n-dodecyl-lithium [prepared from n-dodecyl bromide (15.0 g, 0.06 mol) in ether (40 cm³) and lithium (1.4 g, 0.2 mol) in ether (50 cm³) at 0 to −10 °C over 2 h, the undissolved lithium having been removed], 4-fluoroanisole (3.0 g, 0.0238 mol) in ether (10 cm³) was added at 0 °C. The mixture was stirred (2 h) and poured onto solid carbon dioxide (100 g), and the acidic portion (2.9 g) obtained from the usual work-up was crystallised from pentane to give prisms of *2-n-dodecyl-4-methoxybenzoic acid* (1.28 g, 17%), m.p. 77—79°, R_F 0.12 (solvent B) (Found: C, 74.85; H, 9.9. $C_{20}H_{32}O_3$ requires C, 75.0; H, 10.0%), $\tau(CCl_4)$ −3.1 (1 H, s, CO_2H, D_2O exch.), 1.8—2.1 (1 H, m, ArH), 3.2—3.51 (2 H, m, ArH), 6.16 (3 H, s, OMe), 6.8—7.2 (2 H, t, CH_2Ar), 8.22—8.98 (20 H, m, $C_{10}H_{20}$), and 8.98—9.4 (3 H, t, Me). Methylation gave the methyl ester which showed a single g.l.c. peak. 5-Fluoro-2-methoxybenzoic acid [2] was not isolated.

3-n-Dodecylanisole.—(*i*) n-Dodecyl-lithium [from n-dodecyl bromide (15.0 g) prepared as before] was treated (2 h) at room temperature with 2-fluoroanisole (3.0 g, 0.023 8 mol) in ether (10 cm³). The neutral material (17.0 g) obtained was purified by preparative t.l.c. (solvent E) to give *3-n-dodecylanisole* as an oil (1.05 g, 64%), identical with that from (*ii*) and (*iii*), R_F 0.83 (solvent C) (single band), $\tau(CCl_4)$, 3.00 (1 H, m, ArH), 3 131 (3 H, m, ArH), 6.25 (3 H, s, OMe), 7.55 (2 H, t, CH_2Ar), 8.60 [20 H, m $(CH_2)_{10}$], and 9.16 (3 H, t, Me).

(*ii*) n-Dodecyl-lithium [prepared from n-dodecyl bromide (15.0 g) as in (*i*), the undissolved lithium having been removed] was treated (2 h) with 4-fluoroanisole (3.0 g, 0.023 8 mol) and the mixture worked up in the usual way to give a neutral portion (17.5 g). Preparative t.l.c. (solvent E) of 4.4 g gave an oil (1.0 g, 62%), identical with that from (*i*), R_F 0.83 (solvent C).

(*iii*) 2-n-Dodecyl-4-methoxybenzoic acid (1.0 g, 0.003 1 mol) and copper powder (0.12 g) in quinoline (10 cm³) was refluxed (3 h) and the mixture worked up to remove the quinoline. The neutral material was purified by preparative t.l.c. (solvent E) to give an oil (0.25 g, 29%), identical with that from (*i*) and (*ii*), R_F 0.83 (solvent C) (Found: C, 82.9; H, 11.85. $C_{19}H_{32}O$ requires C, 82.6; H, 11.6%), $\tau(CCl_4)$, 3.00 (1 H m, ArH), 3.32 (3 H, m, ArH), 6.25 (3 H, s, OMe), 7.5 (2 H, t, CH_2Ar), 8.61 [20 H, m, $(CH_2)_{10}$], and 9.16 (3 H, t, Me).

2-Methoxy-6-n-Tetradecylbenzoic Acid (Hydroginkgolinic Acid Methyl Ether).—(*i*) To n-tetradecyl-lithium [prepared from n-tetradecyl bromide (27.7 g, 0.1 mol) in ether (40

cm³) with lithium (1.4 g, 0.2 mol) in ether (50 cm³) at 0 to −10 °C, the undissolved lithium having been removed], 2-fluoroanisole (6.3 g, 0.05 mol) in ether (15 cm³) was added at 0 °C. After stirring (2 h) the mixture was poured onto solid carbon dioxide (100 g), and the acidic material, obtained from the usual work-up, crystallised from n-pentane to give 2-*methoxy-6-n-tetradecylbenzoic acid* (5.22 g, 30%) as prisms, m.p. 69—71° (lit.,[3] 71—72°), R_F 0.14 (solvent C) (Found: C, 75.9; H, 10.4. $C_{22}H_{36}O_3$ requires C, 75.85; H, 10.35%), $\tau(CCl_4)$ −1.9 (1 H, s, CO_2H, D_2O exch.), 2.6—2.93 (1 H, m, ArH), 3.1—3.4 (2 H, m, ArH), 6.10 (3 H, s, OMe), 7.40 (2 H, t, CH_2Ar), 8.63 [24 H, m, $(CH_2)_{12}$], and 9.10 (3 H, t, Me), $\nu_{max.}$ (KBr) 3 300 (s, OH), and 1 725 cm⁻¹ (s, C=O).

(*ii*) n-Tetradecyl-lithium, prepared as in (*i*), was treated (2 h) with 3-bromoanisole (9.3 g, 0.05 mol) in ether (25 cm³). The carbonated mixture (solid CO_2, 100 g) was worked up in the usual way to isolate the acidic part. Extraction with n-pentane left a dark sticky residue and the concentrate (50 cm³) was allowed to crystallise at 0 °C, m.p. 49—55° (1.2 g). Preparative t.l.c. (solvent A) gave a substance A, m.p. 52—58°, R_F 0.14 (solvent C) which was identified as 2-methoxy-6-n-tetradecylbenzoic acid with pentadecanoic acid as an impurity. The filtrate from the initial crystallisation, on concentration, gave upon standing at 0 °C a substance B, m.p. 93—96°, which upon further purification was identified as 3-methoxybenzoic acid, m.p. 106°, R_F 0.13 (solvent C). Substance A showed $\tau(CCl_4)$ −1.95 (1 H, s, CO_2H, D_2O exch.), 2.6—2.93 (1 H, m, ArH), 3.1—3.4 (2 H, m, ArH), 6.10 (3 H, s, OMe), 7.15 (2 H, t, CH_2Ar), 8.65 [24 H, m, $(CH_2)_{12}$], and 9.15 (3 H, t, CH_3) (Found: C, 72.1; H, 9.05. $C_{22}H_{36}O_3$ requires C, 75.85; H, 10.35%). Substance B showed $\tau(CDCl_3)$ −2.25 (1 H, s, CO_2H, D_2O exch.), 2.24 (4 H, m, ArH), and 6.16 (3 H, s, OMe) (Found: C 63.25; H, 5.7. Calc. for $C_8H_8O_3$: C, 63.15; H, 5.25%.)

3-n-Tetradecylanisole.—To n-tetradecyl-lithium [prepared (2½ h) from n-tetradecyl bromide (14.0 g, 0.05 mol) in ether (30 cm³) with lithium (0.7 g, 0.1 mol) in ether (50 cm³) at 9 to −10 °C], 2-fluoroanisole (2.0 g, 0.016 mol) in ether (25 cm³) was added at 0 °C. The mixture was stirred at ambient temperature (2 h) and the neutral portion (2.5 g) obtained upon work-up was chromatographed on alumina (500 g) with light petroleum as solvent. From the forty 25-cm³ fractions, fractions 17—25 yielded 3-*n-tetradecylanisole* (1.19 g, 40.5%) as an oil which was purified by preparative t.l.c. (solvent E), R_F 0.84 (solvent C) (Found: C, 82.6; H, 11.75. $C_{21}H_{36}O$ requires C, 82.9; H, 11.85%), $\tau(CCl_4)$ 2.82 (1 H, m, ArH), 3.10 (3 H, m, ArH), 6.27 (3 H, s, OMe) 7.40 (2 H, t, CH_2Ar), 8.70 [24 H, m $(CH_2)_{12}$], and 9.11 (3 H, t, Me), $\nu_{max.}$ (KBr) 2 925 (s, CH_2) and 780 cm⁻¹ (Ar C−H).

2-Methoxy-6-n-pentadecylbenzoic Acid [(15 : 0) *Anacardic Acid Methyl Ether*].—To n-Pentadecyl-lithium [prepared from n-pentadecyl bromide [22] (7.5 g, 0.025 mol) in ether (25 cm³) and lithium (0.35 g, 0.05 mol) in the usual way], 2-fluoroanisole (1.5 g, 0.011 mol) was added in ether (20 cm³) at 0 °C and the mixture stirred (2 h) at ambient temperature. After reaction with solid carbon dioxide (100 g). the acidic part (2.4 g) was isolated in the usual way and crystallised from light petroleum to afford prisms, m.p. 61—66° (1.51 g, 35%) of 2-*methoxy-6-n-pentadecylbenzoic acid.* Two purifications by preparative t.l.c. yielded a product of m.p. 71—73° (lit.,[25] 82—82.5°), R_F 0.15 (solvent C) (Found: C, 75.9; H, 11.1. $C_{23}H_{38}O_3$ requires C, 76.25;

H, 10.5%), τ(CCl$_4$) -1.65 (1 H, s, CO$_2$H, D$_2$O exch.), 2.58 (1 H, m, ArH), 3.23 (2 H, m, ArH), 6.17 (3 H, s, OMe), 7.29 (2 H, t, CH$_2$Ar), 8.70 [26 H, m, (CH$_2$)$_{13}$], and 9.10 (3 H, t, Me), $\nu_{max.}$ (KBr) 3 450 (w, OH) and 1 705 cm^{-1} (s, C=O).

6-n-Pentadecylsalicyclic Acid [(15 : 0) *Anacardic Acid*].— 2-Methoxy-6-n-pentadecylbenzoic acid (0.2 g, 0.000 5 mol) was warmed (30 min) on a steam-bath with colourless hydriodic acid (10 cm^3) and red phosphorus (0.3 g). The mixture was diluted and worked up in the usual way (including a wash of the ethereal extract with sodium thiosulphate solution) and the recovered acidic material, crystallised from benzene–light petroleum, gave prisms, m.p. 88—90°, of 6-n-pentadecylsalicylic acid (0.08 g, 42%), mixed m.p. with the (15 : 0) natural product, 88—90°, R_F 0.16 (solvent B) (Found: C, 76.15; H, 10.25. C$_{22}$-H$_{36}$O$_2$ requires C, 75.85; H, 10.35%), τ(CCl$_4$) 0.20 (2 H, br s, CO$_2$H $\cdots$ OH, D$_2$O exch.), 2.70 (1 H, m, ArH), 3.00 (2 H, m, ArH), 7.00 (2 H, t, CH$_2$Ar), 8.68 [26 H, m, (CH$_2$)$_{13}$], and 9.12 (3 H, t, Me). $\nu_{max.}$ (KBr) 3 100 (m, OH) and 1 750 cm^{-1} (s, C=O).

4-Methoxy-2-n-pentadecylbenzoic Acid.—To n-pentadecyl-lithium [prepared from n-pentadecyl bromide [22] (14.5 g, 0.05 mol) in the usual way], 4-fluoroanisole (3.3 g, 0.026 mol) in ether (15 cm^3) was added at 0 °C and the mixture stirred (2 h) at ambient temperature. After addition to solid carbon dioxide (150 g), the mixture was worked up as previously to give an acidic portion (9.0 g) which upon several crystallisations from light petroleum yielded yellowish aggregates, m.p. 78—80°, of 4-methoxy-2-n-pentadecylbenzoic acid (4.01 g, 42.5%), R_F 0.15 (solvent C). (Found: C, 76.0; H, 10.65. C$_{23}$H$_{38}$O$_3$ requires C, 76.25; H, 10.4%), τ(CCl$_4$) -3.11 (1 H, s, CO$_2$H, D$_2$O exch.), 2.01 (3 H, m, ArH), 6.16 (3 H, s, Me), 7.00 (2 H, t, CH$_2$Ar), 8.62 [26 H, m (CH$_2$)$_{13}$], and 9.50 (3 H, t, Me), $\nu_{max.}$ (KBr) 3 300 (m, OH) and 1 680 cm^{-1} (s C=O).

3-n-Pentadecylanisole [(15 : 0) *Cardanol Methyl Ether*].— n-Pentadecyl-lithium [prepared from n-pentadecyl bromide [22] (7.5 g, 0.025 mol) in the usual way (see 2-methoxy-6-pentadecylbenzoic acid)] was treated (2 h) with 2-fluoro-anisole (1.5 g, 0.001 mol) in ether (10 cm^3) at ambient temperature. Worked up as before, the neutral portion (4.5 g) was purified by preparative t.l.c. (solvent E) to give 3-n-pentadecylanisole as an oil (1.26 g, 34%), identical with (15 : 0) cardanol methyl ether, R_F 0.85 (solvent C) (Found: C, 83.2; H, 11.95. Calc. for C$_{22}$H$_{38}$O: C, 83.0; H, 11.95%), τ(CCl$_4$) 2.79 (4 H, m, ArH), 6.26 (3 H, s, OMe), 7.23 (2 H, t, CH$_2$Ar), 8.62 [26 H, m, (CH$_2$)$_{13}$], and 9.02 (3 H, t, Me).

2-Benzyloxy-6-ethylbenzoic Acid.—3-Fluorophenol (2.24 g, 0.02 mol) was refluxed (6 h) in dry benzene (25 cm^3) containing anhydrous potassium carbonate (4.0 g) and benzyl chloride (2.52 g, 0.02 mol). The cooled mixture was worked up to recover the neutral material, after washing with 5% w/v aqueous sodium hydroxide (2 × 24 cm^3). Preparative t.l.c. (solvent A) yielded 1-benzyloxy-3-fluorobenzene as an oil (2.2 g, 54%), R_F 0.88 (solvent B), τ(CCl$_4$) 2.61 (4 H, m, ArH), 3.2—3.66 (4 H, m, ArH), and 5.00 (2 H, s, OCH$_2$Ar).

To ethyl-lithium [prepared (30 min) from ethyl bromide (4.36 g, 0.04 mol) in ether (20 cm^3) with lithium (0.56 g, 0.08 mol), in ether (75 cm^3)], 1-benzyloxy-3-fluorobenzene (2.02 g, 0.01 mol) in ether (20 cm^3) was added and the reaction mixture stirred at ambient temperature (1½ h). After pouring onto solid carbon dioxide (50 g), the mixture was worked up to obtain the acidic part which was purified

by preparative t.l.c. (solvent B) and crystallisation from light petroleum to yield needles, m.p. 71—72°, of 2-*benzyloxy-6-ethylbenzoic acid* * (1.4 g, 31%), R_F 0.25 (solvent C) (Found: C, 75.35; H, 6.25. C$_{16}$H$_{16}$O$_3$ requires C, 75.0; H, 6.25%), τ(CDCl$_3$) 0.41 (1 H, s, CO$_2$H, D$_2$O exch.), 2.42—3.34 (9 H, m, ArH), 4.85 (2 H, s, OCH$_2$Ar), 7.0—7.5 (2 H, q, CH$_2$Ar), and 8.6—9.0 (3 H, t, Me).

Attempted Synthesis of 6-Ethylsalicylic Acid from 3-*Flurophenol.*—To ethyl-lithium [prepared from ethyl bromide (10.9 g, 0.1 mol) in tetrahydrofuran (25 cm^3) and lithium (1.4 g, 0.2 mol) in tetrahydrofuran (35 cm^3), the undissolved lithium (0.3 g) having been removed], 3-fluorophenol (2 g, 0.017 mol) in tetrahydrofuran (10 cm^3) was added and the reaction mixture stirred (3 h) and refluxed (½ h). After carbonation with solid carbon dioxide (25 g) and work-up in the usual way the acidic material (2.0 g) was found to be the starting material. A similar result was obtained with ether as solvent.

^{1}H *N.M.R. Absorption Spectra in the Aromatic Region.*— The ^{1}H n.m.r. spectra of the anacardic acids and other substances have been described in the Experimental section as multiplets. It was of interest to compare the calculated values [26] with those found.

6-n-Alkyl-2-methoxybenzoic acids (4): calc. τ values, H(3) 2.98, H(4) 2.53, H(5) 2.93.† The observed values and couplings were for H(3), H(5), two superimposed sets of four lines centred at τ 3.33 with J_o 8, J_m 3 Hz; H(4) centred at *ca.* 2.8, a 'triplet', J_o 8 Hz.

2-Alkyl-3-methoxybenzoic acids (5): calc. τ values, H(4) 2.89, H(5) 2.83, H(6) 1.98. No peaks were observed in the region τ 2.0 and these isomers were concluded to be absent (also supported by chromatographic evidence).

3-n-Alkylanisoles (7): calc. τ values, H(2) 3.14, H(4) 3.09, H(5) 2.78, H(6) 3.14. The observed values and couplings were for H(5), centred at *ca,* 3.03, a 'triplet', J_o 8, J_p 2 Hz; for H(2), H(4), and H(6), the lines centred at *ca.* 3.47 were unresolved (the spacing of signals allowed the detection of 2-n-alkylanisoles and they were not present in water-treated products from lithiations).

2-n-Alkylanisoles: calc. τ values, H(3) 2.78, H(4) 3.09, H(5) 2.78, H(6) 3.14. The observed values and couplings were for H(3), centred at *ca.* 2.7, J_o 8, J_p 2.5 Hz; H(4) centred at 3.23, J_o 8, J_m 2 Hz; H(5) centred at *ca.* 2.9, J_o 8, J_m 2.5 Hz; H(6) centred at *ca.* 3.33, J_m 2.5 Hz.

4-n-Alkylanisoles (10): calc. τ values, H(2) 3.14, H(3) 3.78, H(5) 3.78, H(6) 3.14. An observed 'quartet', J_o Hz, was a very small set of peaks superimposed on the lines for the 3-alkylanisole.

2-n-Alkyl-4-methoxybenzoic acids (8): calc. τ values, H(3) 2.98, H(5) 2.98, H(6) 1.98. The observed values and couplings were for H(3), H(5) centred at *ca.* 3.3 (unresolved) J_m 3, J_o *ca.* 9 Hz; H(6) *ca.* 1.75, d, J_o 9 Hz. A small peak at *ca.* τ 2.8 was attributed to H(6) in (9), J_m *ca.* 2 Hz. For the isomeric compounds, 2-alkyl-5-methoxybenzoic acids (9): calc. τ values, H(3) 3.62, H(4) 2.79, H(6) 2.32.

5-Fluoro-2-methoxybenzoic acid: calc. τ values, H(6) 2.33, H(4) 2.97, H(3) 3.01. In the observed values, H(6) appeared as a 'quartet' with J_o (H–F) 9 and J_m (H–H) *ca.* 3 Hz. H(3) and H(4) were not sufficiently resolved but J_o (H–H), J_m (H–F), and J_o (H–F) were in evidence.

---

* Hydrogenolysis in ethanol with Pd–C gave 6-ethylsalicylic acid identical with previously obtained material. In a similar way 2-benzyloxy-6-pentadecylbenzoic acid gave 6-pentadecyl-salicyclic acid identical with the natural product.
† Numbering as shown in Scheme 1.

Gas–Liquid Chromatography.—For further characterisation the 6-n-alkyl-2-methoxysalicylic acids were converted into methyl esters and examined chromatographically. On column A the following retention times in seconds $(T/^{\circ}C)$ were found for the homologous compounds: C-15, 2 148 (220); 5 472 (200); C-14, 1 152 (220); C-12, 380 (220); C-4, 122 (180); C-3, 56 (180); C-2, 39 (180). With column B, C-4, 996 (180); for the 3-n-alkylanisoles on column A: C-15, 924 (220); C-14, 1 632 (190); C-14, 1 872 (180); C-14, 575 (220); C-14, 948 (200); C-12, 16 (220); C-4, 540 (140); C-1, 492 (80). For other compounds on column B: methyl 2-n-butyl-4-methoxybenzoate, 876 (180); methyl 2-n-dodecyl-4-methoxybenzoate, 2 928 (160); methyl 2-n-dodecyl-4-methoxybenzoate, 396 (220); methyl 2-n-pentadecyl-4-methoxybenzoate 2 772 (220);

[8/1487 *Received, 14th August,* 1978]

REFERENCES

[1] Part 14, J. H. P. Tyman and A. A. Durrani, preceding paper.
[2] H. Gilman, W. Langham, and F. W. Moore, *J. Amer. Chem. Soc.,* 1940, **62**, 2327.
[3] F-Y. Fu, T-C. Yu, W-L. Sung, Y. F. Jai, and N-C. Sun, *Hua Hsuch Pao,* 1962, **28**, 52.
[4] J. H. P. Tyman, *J. Org. Chem.,* 1976, **41**, 894.
[5] R. N. Meals, *J. Org. Chem.,* 1944, **9**, 211.
[6] H. Gilman and R. G. Jones, *J. Amer. Chem. Soc.,* 1941, **63**, 1441.
[7] V. Franzen and H. I. Joschek, *Angew. Chem.,* 1960, **72**, 564.
[8] R. Huisgen and H. Rist, *Annalen,* 1955, **594**, 137.
[9] K. B. Bartle, H. Heaney, D. W. Jones, and P. Lecs, *Tetrahedron,* 1965, **21**, 3289.
[10] R. S. Berry, J. Clardy, and M. E. Schafer, *J. Amer. Chem. Soc.,* 1964, **86**, 738.
[11] R. F. C. Brown, D. V. Gardner, J. F. W. McOmie, and R. F. Solly, *Chem. Comm.,* 1966, **13**, 407.
[12] H. Gilman and J. W. Morton, ' Organic Reactions,' Wiley, 1954, vol. 8, 258; A. I. Shatenstein, ' Isotopentaustaush and Substitution des Wasserstoffs in Organischer Verbindungen,' VEB Deutschen Verlag des Wissenschapten, Berlin, 1963.
[13] G. Wittig and G. Furhrmann, *Ber.,* 1940, **B73**, 1193.
[14] C. D. Broaddus, *J. Org. Chem.,* 1970, **35**, 10.
[15] G. B. R. de Graeff, H. J. den Hartog, and W. Ch. Melger, *Tetrahedron Letters,* 1965, 963.
[16] H. Gilman and P. R. Van Ess, *J. Amer. Chem. Soc.,* 1933, **55**, 1258; M. Jorgensen, ' Organic Reactions,' 1970, **18** 1, Wiley, New York.
[17] J. F. W. McOmie, M. L. Watts, and D. E. West, *Tetrahedron,* 1968, **24**, 2289.
[18] F. M. Dean, J. Goodchild, L. E. Houghton, and J. A. Martin, *Tetrahedron Letters,* 1966, 4153.
[19] I. T. Harrison, *Chem. Comm.,* 1969, 616.
[20] W. E. Parham and E. L. Anderson, *J. Amer. Chem. Soc.,* 1957, **79**, 5797; J. H. P. Tyman and J. Caplin, *Chem. and Ind.,* 1973, 953.
[21] A. I. Vogel, ' Practical Organic Chemistry,' 3rd edn., Longmans, London, p. 611.
[22] *Org. Synth.,* 1946, **26**, 52.
[23] D. C. Bishop, R. A. Selway, and N. E. Webb, *J. Medicin. Chem.,* 1965, **8**, 316.
[24] M. J. S. Dewar and N. A. Puttnam, *J. Chem. Soc.,* 1959, 4080.
[25] H. J. Backer and N. H. Haack, *Rec. Trav. chim.,* 1941, **60**, 661.
[26] D. H. Williams and I. Fleming, ' Spectroscopic Methods in Organic Chemistry,' McGraw-Hill, Maidenhead, 2nd edn., 1973, p. 135; W. W. Paudler, ' Nuclear Magnetic Resonance,' Allyn and Bacon Inc., Boston, 1971, pp. 39, 53.