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NEW ELECTRON-CAPTURING PENTAFLUOROPHENYLDIALKYLCHLOROSILANES AS VERSATILE DERIVATIZING REAGENTS FOR GAS CHROMATOGRAPHY

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SUMMARY

Flophemesyl, ISP-flophemesyl, *tert.*-buflophemesyl and CM-flophemesyl derivatives of a wide range of organic functional groups can be prepared and have good gas chromatographic and electron-capture detector properties. The derivatives are compared in terms of volatility, hydrolytic stability, detector response and mass spectral properties. Bis(pentafluorophenyl)chloromethylmethylsilane is evaluated as a reagent for preparing derivatives of strong nucleophiles. CM-flophemesyl chloride is evaluated as a cyclizing reagent for preparing derivatives of β- and γ-hydroxyamines. The flophemesyl derivative of N-nitrosodiethanolamine is shown to be suitable for detecting this compound at trace levels.

INTRODUCTION

In gas chromatography (GC) frequent use is made of the technique of derivatization to improve the thermal stability and the chromatographic performance of polar molecules. Derivatization techniques are also ideally suited for the introduction of specific tags into polar molecules so that they match the requirements of the available selective and sensitive detectors used in GC. In terms of their range of application, the trimethylsilyl reagents are the most versatile and widely employed derivatizing reagents used in GC[1]. Nearly all functional groups which can present a problem in GC can be converted to trimethylsilyl derivatives (Fig. 1). However, no derivative is ideally suited to all problems, and among the less desirable features of the trimethylsilyl derivatives are their limited hydrolytic stability and poor intrinsic detection characteristics for trace analysis. The hydrolytic stability of the silyl derivatives is very much a function of the steric bulk of the alkyl groups attached to silicon and the *tert.*-butyldimethylsilyl and the isopropyldimethylsilyl derivatives are several orders of magnitude more resistant to hydrolysis than the trimethylsilyl

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derivatives[2]. This increase in hydrolytic stability is bought at the expense of a reduced rate of reaction and an increasing probability that hindered functional groups will no longer react to completion. For those compounds that do not possess by virtue of their structure or composition the required features to generate a high response to one of the selective GC detectors [*e.g.* electron-capture (ECD), flame photometric (FPD) and nitrogen–phosphorus (NPD) detectors], the trimethylsilyl derivatives provide few possibilities for trace analysis. Suitable selective and sensitive silicon detectors have not been forthcoming. The microwave emission, hydrogen atmosphere flame ionization, glow discharge and atomic absorption spectrophotometer silicon detectors have inadequate sensitivity to promote their general use for the analysis of the trimethylsilyl derivatives[2].

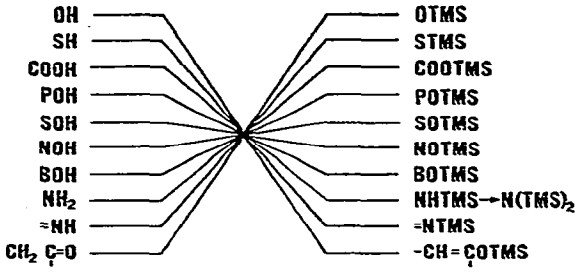
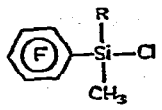


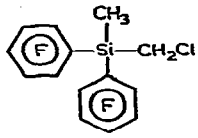
Fig. 1. Organic functional groups forming trimethylsilyl derivatives.

The electron-capture detector (ECD) is a selective detector with unrivaled sensitivity for an ill-defined range of electronegative compounds[3]. The trimethylsilyl group shows no particular electron-capturing properties "*per se*" but the necessary detector oriented response can be conferred on the trimethylsilyl group by introducing a halogen atom (Cl, Br, I) into one of the methyl groups or by replacing a methyl group by a pentafluorophenyl ring. The latter reagents, pentafluorophenyldimethylsilyl (contracted to flophemesyl for convenience) are of particular interest to this paper. The flophemesyl derivatives are surprisingly volatile in spite of their high molecular weight and have good chromatographic properties and detector sensitivity. The flophemesyl derivatives have been used for the analysis of steroids[4–7], alcohols[8–10], phenols, amines and carboxylic acids[9,10], salmefamol and labetalol[11], fatty acid methyl ester chlorohydrins[12,13] and fluoride ions[14] by GC–ECD. The flophemesyl derivatives have similar hydrolytic stability to the trimethylsilyl derivatives. To improve the hydrolytic stability of the flophemesyl derivatives, *tert.*-butylpentafluorophenylmethylchlorosilane (*tert.*-buflophemesyl) derivatives have been prepared[15]. In keeping with the findings for the *tert.*-butyldimethylsilyl derivatives, the *tert.*-buflophemesyl derivatives were much more hydrolytically stable than the flophemesyl derivatives, but reacted less readily with hindered functional groups and were less volatile than the flophemesyl derivatives.

In order to expand the areas of usefulness of the flophemesyl reagents, three new reagents structurally related to the flophemesyl compounds have been prepared. The structures and appropriate abbreviations for the reagents are shown below:



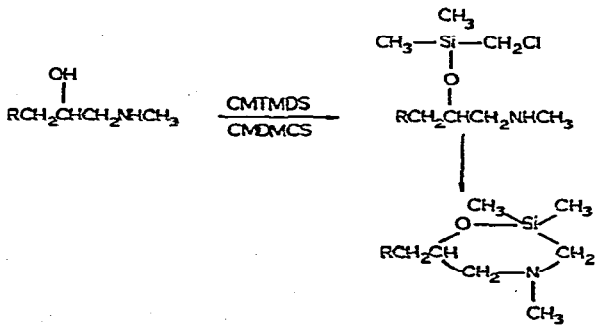
R = CH_3, pentafluorophenyldimethylchlorosilane; flophemesyl chloride
R = $CH(CH_3)_2$, pentafluorophenylisopropylmethylchlorosilane; ISP-flophemesyl chloride
R = $C(CH_3)_3$, *tert.*-butylpentafluorophenylmethylchlorosilane; *tert.*-buflophemesyl chloride
R = CH_2Cl, chloromethylpentafluorophenylmethylchlorosilane; CM-flophemesyl chloride



bis(pentafluorophenyl)chloromethylmethylsilane

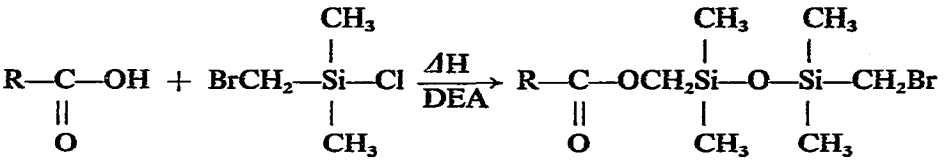
Pentafluorophenylisopropylmethylchlorosilane was prepared in the hope that the less bulky isopropyl group would provide a convenient compromise between the properties of the flophemesyl and *tert.*-buflophemesyl reagents. The isopropyl group should influence the rate and extent of reaction of hindered functional groups less than the bulky *tert.*-butyl group while at the same time providing sufficient hydrolytic stability to prevent the hydrolysis of derivatives subjected to a variety of sample clean-up conditions.

Chloromethylpentafluorophenylmethylchlorosilane was prepared as a selective reagent for the determination of bifunctional compounds by GC–ECD. It was noted by Hammar[16] that β- and γ-hydroxy primary, secondary, tertiary and quaternary amines react with a mixture of 1,3-bis(chloromethyl)-1,1,3,3-tetramethyldisilazane (CMTMDS) and chloromethyldimethylchlorosilane (CMDMCS) in a selective manner to form stable heterocyclic derivatives. This selective derivatization reaction was used to elucidate the metabolism of the β-adrenoceptor antagonist drug, alprenolol in man and dog by GC–mass spectrometry (MS)[17]. To exploit the chemical specificity of the reaction for trace analysis the reagent described by Hammar was modified to contain a pentafluorophenyl group in place of one of the methyl groups bonded to silicon for use with the ECD. This same reagent should also form derivatives of polar functional groups in the usual way by virtue of the much greater reactivity of the chlorosilane group compared to the chloromethylsilyl group. The



reagent should also be suitable for the formation of derivatives of alcohols, phenols and carboxylic acids in which it might be anticipated that the close proximity of the two electron-capturing groups (pentafluorophenyl and chloromethyl groups) would interact synergistically to provide a high detector response. Such synergistic interactions of two electron-capturing groups when brought into close proximity in organic compounds have been found to increase the detector response significantly from the response of either center in isolation provided that some electronic pathway exists for the two centers to interact.

Related to the cyclization reagent of Hammar, it is known that the chlorine atom of the chloromethyl group can be displaced by amines[18] and that the chloromethyl group itself can be displaced by strong nucleophiles under vigorous reaction conditions[5,18]. It has also been observed that short chain aliphatic acids when derivatized with bromomethyldimethylchlorosilane and diethylamine formed bromomethyltetramethylmethyldisiloxane esters rather than the expected bromomethyldimethylsilyl esters[19].



The chloromethyl group is thus a selective leaving group as it only interacts with strong nucleophiles and could be used to derivatize such compounds in the presence of less reactive polar compounds. By incorporating two pentafluorophenyl groups into the reagent exceptional electron-capturing sensitivity with reasonable volatility on GC might be expected. To investigate this possibility, the reagent bis(pentafluorophenyl)chloromethylmethylsilane was prepared.

EXPERIMENTAL

Flophemesyl chloride, flophemesylamine and *tert.*-buflophemesyl chloride were obtained from Lancaster Synthesis (St. Leonardgate, Great Britain) or from the Alfa Products Division (Ventron Corp., Danvers, MA, U.S.A.). All other flophemesyl reagents were prepared for the first time in our laboratories as described below.

All reactions are carried out under argon or nitrogen in oven-dried glassware and using anhydrous solvents. Methyldichlorosilane was obtained from Sigma (St. Louis, MO, U.S.A.), chloromethylmethyldichlorosilane from Fluorochem (Dinting Vale, Great Britain), pentafluorobenzene from PCR Research Chemicals (Gainesville, FA, U.S.A.) and lithium wire, *n*-butyllithium and 2-chloropropane from Aldrich (Milwaukee, WI, U.S.A.).

Synthesis of pentafluorophenylisopropylmethylchlorosilane

Isopropyllithium. To 1.5 moles of 2-chloropropane (117.8 g) in anhydrous pentane (200 ml) under an argon atmosphere were added 3.0 moles (20.8 g of wire flattened and cut into small pieces, washed with ether) of lithium. The stirred solution

was maintained at −10°C for at least 10 h. The violet colored solution was filtered under argon to give a pale yellow solution of isopropyllithium in approximately 40% yield by titration.

Methylisopropylchlorosilane. To a solution of methyldichlorosilane (0.6 moles) in pentane (80.0 ml) was added slowly over about 1.0 h a pentane solution of isopropyllithium (300 ml, 2 *M*) under an argon atmosphere. The reaction flask was surrounded by a coolant bath (−30 to −40°C) under which conditions a gentle reflux was maintained during the addition and for a further 1.0 h after the addition of reagent was complete. When the spontaneous reflux ceased the reaction was completed by heating to reflux for a further 1.0 h. The solution was cooled, the precipitate of lithium chloride filtered off and the solvent removed *in vacuo*. The residue was fractionally distilled at atmospheric pressure to give methylisopropylchlorosilane, b.p. 88–91°C in 65% yield (lit.[20] b.p. 90.6°C), infrared (IR): ν (Si–H) 2175 cm^{-1} (s).

Pentafluorophenylisopropylmethylsilane. To a solution of pentafluorobenzene (0.3 moles) in diethyl ether (100 ml) at −70°C under a nitrogen atmosphere was added dropwise a solution of *n*-butyllithium (0.3 moles, 1.6 *M* solution) in hexane. The mixture was allowed to warm up to −20°C, stirred for a further 0.5 h and cooled again to −70°C. To this solution was added dropwise methylisopropylchlorosilane (0.3 moles) in diethyl ether (50.0 ml) over about 1.0 h, the temperature raised to −20°C and stirred for a further 1.0 h prior to completing the reaction by allowing the reactants to attain room temperature. The precipitate of lithium chloride was filtered off and the solvent removed *in vacuo*. The residue was fractionally distilled to give pentafluorophenylisopropylmethylsilane b.p. 140–144°C at 144 mmHg in 53% yield. IR: ν (Si–H) 2160 cm^{-1} (s); nuclear magnetic resonance (NMR): Si–CH_3 0.53 ppm, Si–CH–$(CH_3)_2$ 1.15 ppm, Si–CH–$(CH_3)_2$ 5.35 ppm; Si–H 4.35 ppm; MS: *m/e* 254 (50) M^+, 211 (38) $[M-CH_3]^+$, 145 (100), 125 (44), 101 (30), 81 (95), 63 (81).

Pentafluorophenylisopropylmethylchlorosilane. Through a solution of pentafluorophenylisopropylmethylsilane (0.15 moles) in anhydrous carbon tetrachloride (250 ml) was bubbled chlorine into a reaction vessel covered with aluminum foil to exclude light and arranged so that it could be intermittently immersed in an ice–salt bath to maintain the reaction temperature below 20°C during the chlorination. A buffer volume in the gas line prior to the reaction vessel and an auxillary supply of nitrogen connected to the chlorine line were used to prevent loss of material due to suck-back. The reaction was complete within 0.5 h (monitored by GC) and excess of chlorine was purged from the solution with nitrogen. The solvent was removed *in vacuo* and the remaining liquid fractionally distilled to give pentafluorophenylisopropylmethylchlorosilane b.p. 94–95°C at 13 mmHg in 56% yield. NMR: Si–CH_3 0.95 ppm, Si–CH–$(CH_3)_2$ 1.18 ppm, Si–CH–$(CH_3)_2$ 5.3 ppm; MS: *m/e* 288/290 (39/13) M^+, 245/247 (100/34) $[M-C_3H_7]^+$, 219 (18), 179/181 (51/19), 141 (42), 129 (30), 125 (69), 97 (83), 81 (49), 75 (31).

Synthesis of chloromethylpentafluorophenylmethylchlorosilane

Chloromethylmethylsilane (H151/28). A 250-ml three-necked flask was fitted with a 30-cm vacuum-jacketed Vigreux column connected to a distillation head, condenser with receiving flask and cold finger protected by a drying tube. In the flask under an argon atmosphere was stirred a solution of chloromethylmethyldichloro-

silane (0.3 moles) in *n*-butyl ether (250 ml) and lithium aluminum hydride (0.45 moles). The reaction mixture was refluxed and the product distilled off through the Vigreux column at a distillation temperature of 40–90°C. The reaction and distillation were complete within a 45-min period. The product collected in the receiving flask and cold finger, 21.0 g in all, contained 16.5 g of chloromethylmethylsilane, 1.1 g of dimethylsilane and 3.4 g of *n*-butyl ether and was used without further purification. NMR: Si–CH_3 0.33 ppm, Si—CH_2Cl 2.93 ppm, Si–H 4.0 ppm.

Chloromethylmethylchlorosilane (H151/27). To 21.0 g of the chloromethylmethylsilane product (containing 0.19 moles of silane) in ether (150 ml) under argon was added dropwise with stirring tin(IV) tetrachloride (0.19 moles, 22.6 ml) over a 0.5-h period. The heavy white precipitate formed was stirred for a further 4.0 h and the solution decanted off and distilled through a 15-cm Vigreux column to give 16.5 g (0.128 moles) of chloromethylmethylchlorosilane b.p. 94–100°C (lit.[21] 95–97°C). NMR: Si–CH_3 0.65 ppm, Si–CH_2Cl 3.06 ppm, Si–H 4.95 ppm.

Chloromethylpentafluorophenylmethylsilane (H151/31). Pentafluorophenyllithium was prepared as described above and transferred to a nitrogen equalized dropping funnel maintained at —70°C. The pentafluorophenyllithium (0.128 moles) solution was added dropwise with stirring under argon to chloromethylmethylchlorosilane (0.128 moles) in ether at —70°C. The solution was allowed to attain room temperature by stirring overnight (without removing the coolant bath), the precipitate of lithium chloride filtered off and the solvent removed *in vacuo*. The residue was fractionally distilled to give chloromethylpentafluorophenylmethylsilane b.p. 88–92°C at 17 mmHg in 67% yield (0.086 moles). NMR: Si–CH_3 0.60 ppm, Si–CH_2Cl 3.17 ppm, Si–H 4.80 ppm; MS: *m/e* 260/262 (21/7) M^+, 211 (72) $[M—CH_2Cl]^+$, 145 (69), 129 (28), 125 (31), 111 (51), 81 (96), 63 (100).

Chloromethylpentafluorophenylmethylchlorosilane (H151/25). Chloromethylpentafluorophenylmethylsilane (0.086 moles) in carbon tetrachloride (100 ml) was chlorinated as described under *Pentafluorophenylisopropylmethylchlorosilane*. After removal of solvent *in vacuo*, the residue was fractionally distilled to give chloromethylpentafluorophenylmethylchlorosilane b.p. 102–107°C at 17 mmHg in 74% yield (0.064 moles). NMR: Si–CH_3 0.98 ppm, Si–CH_2Cl 3.30 ppm; MS: *m/e* 294/296/298 (18/13/2) M^+, 245/247 (100/37), 209 (17), 179/181 (37/16), 125 (71), 97 (96), 81 (84), 63 (36).

Synthesis of bis(pentafluorophenyl)chloromethylmethylsilane (H151/26).* Pentafluorophenyllithium (from 0.14 moles of pentafluorobenzene) was prepared as described under *Pentafluorophenylisopropylmethylsilane* and transferred to a nitrogen equalized dropping funnel maintained at —70°C. The pentafluorophenyllithium was added dropwise with stirring under nitrogen to chloromethyldichlorosilane (0.14 moles) in ether (50 ml) at —70°C. The reaction mixture was allowed to attain room temperature by stirring overnight (without removal of the coolant bath), the precipitate of lithium chloride was filtered off, the solvent removed *in vacuo* and the residue fractionally distilled to give bis(pentafluorophenyl)chloromethylmethylsilane b.p. 164–166°C at 20 mmHg in 50% yield (0.07 moles). IR: 1642, 1520, 1470, 1380, 1295, 1090, 975, 795 cm^{-1}; NMR: Si–CH_3 0.98 ppm, Si–CH_2Cl 3.48 ppm; MS: *m/e* 426/428 (15/5) M^+, 377 (41) $[M—CH_2Cl]^+$, 277 (74), 227 (19), 129 (24), 81 (100).

* Molar ratios not optimized to maximize product yield.

Formation of derivatives

For the preparation of derivatives, 20 μl of reagent (flophemesyl chloride, *tert.*-buflophemesyl chloride or ISP-flophemesyl chloride) and 20 μl of triethylamine were added to 10 μl of alcohol or other substrate in 100 μl of acetonitrile in a 1.0-ml Reacti-vial. The mixture was heated at 60°C until the reaction was complete. The CM-flophemesyl derivatives were prepared by adding 20 μl of CM-flophemesyl chloride and 50 μl of pyridine to 20 μl of substrate in 100 μl of acetonitrile. The mixture was heated at 60°C to completion. For studies on reaction rate and stability towards hydrolysis using *n*-octanol as a representative alcohol, *n*-tridecane or *n*-tetradecane were used as internal standards.

Gas chromatography and mass spectrometry

For GC, a Varian 3700 gas chromatograph with a flame-ionization detector and a ^{63}Ni constant-current ECD was used. Retention times for the low-molecular-weight derivatives were determined on a 3 ft. × 1/8 in. I.D. nickel column packed with 5% SE-30 on Gas-Chrom Q (100–120 mesh) with a nitrogen flow-rate of 40 ml min^{-1}. For GC–MS, a Hewlett-Packard 5992A mass spectrometer equipped with a single-stage glass-jet separator and a 6 ft. × 0.4 cm I.D. glass column packed with 3% OV-1 on Gas-Chrom Q (100–120 mesh) and operated with a helium flow-rate of 30 ml min^{-1} was used. Electron-impact mass spectra were recorded at an ionization potential of 70 eV.

RESULTS AND DISCUSSION

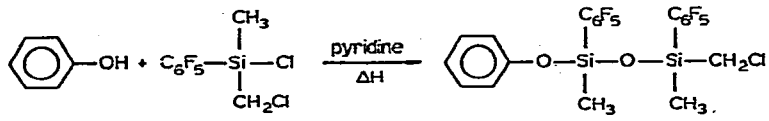
Synthesis of reagents

General methods for the synthesis of pentafluorophenyldialkylchlorosilanes have been developed in our laboratories[5,15]. ISP-Flophemesyl chloride was prepared by this route in the usual way. However, CM-flophemesyl chloride was more problematical and a new scheme was developed for this reagent. To begin with, the addition of pentafluorophenyllithium to chloromethylmethyldichlorosilane resulted in the formation of bis(pentafluorophenyl)chloromethylmethylsilane and not the expected CM-flophemesyl chloride. The key intermediate for the synthesis of CM-flophemesyl chloride was considered to be chloromethylmethylchlorosilane which containing only one chlorosilane group could not give rise to the bis(pentafluorophenyl) compound. This material was prepared in two steps from the commercially available chloromethylmethyldichlorosilane by reduction to the disilane followed by selective chlorination with tin(IV) tetrachloride. Attempts at the selective reduction of the dichlorosilane to the monochlorosilane were unsuccessful. The chloromethylmethylchlorosilane was then converted to the desired product, CM-flophemesyl chloride in the usual way.

Reactivity and volatility of pentafluorophenyldialkylsilyl reagents and derivatives

Flophemesyl, ISP-flophemesyl and *tert.*-buflophemesyl chlorides in the presence of an acid acceptor catalyst such as triethylamine show a similar range of application as far as reacting with alcohols, amines, thiols, phenols and carboxylic acids was concerned. CM-flophemesyl chloride is unstable in the presence of strong organic bases such as triethylamine, undergoing a self-condensation reaction (see

later under cyclic derivatization reactions). It is stable in pyridine which can be used as both solvent and catalyst for its reactions. Under vigorous reaction conditions with phenol a modest amount of a by-product shown below was also formed as well as the expected CM-flophemesyl derivative. To avoid the possibility of such side reactions, derivatization should be performed under mild conditions with this reagent. All the pentafluorophenyldialkylsilyl derivatives studied had good chromatographic properties.



The trimethylsilyl group is more bulky than the *tert.*-butyl group and as such both the rate and extent of reaction are influenced by steric factors. The flophemesyl reagents being studied here are all larger than the trimethylsilyl group and this would be expected to influence their reaction rates with hindered functional groups. For our initial screening, all reagents were prepared in the chloride form and this will also effect reaction rates. From our knowledge of the trimethylsilyl reagents, one would expect the chlorosilane to be a poor silyl donor by comparison with reagents containing such leaving groups as imidazole. The flophemesyl reagents show a different order of silyl donor efficiency than the trimethylsilyl reagents due to the electronic effects of the pentafluorophenyl group but the general analogy regarding the silyl donor power of the chloride ion remains true[5]. Some preliminary data obtained with sterically hindered steroid hydroxyl groups supports the argument that the bulkiness of the new flophemesyl reagents inhibits their reaction rates with hindered functional groups. The 17β-OH group of 17α-methyl-17β-hydroxyandrostan-3-one requires heating at 60°C for 3 h for complete reaction using ISP-flophemesyl chloride or *tert.*-buflophemesyl chloride compared to 15 min at room temperature with flophemesyl chloride. Similarly the 11β-OH group of 11β-hydroxyandrost-4-en-3,17-dione was derivatized in 3 h at 60°C with flophemesyl chloride, *tert.*-buflophemesyl chloride or ISP-flophemsyl chloride. CM-flophemesyl chloride using pyridine as catalyst did not react with either of the steroid hydroxyl groups. None of the flophemesyl reagents reacts quantitatively with the 17α-OH group in 17α,21-dihydroxypregn-4-en-3,11,20-trione. For all the reactions using the flophemesyl reagents, the ketones were converted to their methoxime derivatives prior to derivatization and in some cases this led to the production of two peaks due to the separation of the syn and anti-methoxime isomers.

A wide range of substituted trialkylsilyl or aryldialkylsilyl reagents have been prepared for use with the ECD. In terms of relative volatility, these are compared in Table I for the separation of cholesterol. Compared with the trimethylsilyl ether derivative of cholesterol, all the pentafluorophenyl containing derivatives are less volatile. However, these derivatives are surprisingly volatile when account is taken of the molecular weight of the pentafluorophenyl group (the increase in molecular weight being offset by a decrease in intermolecular bonding forces in the fluorocarbon). Based on Table I, the volatility of the pentafluorophenyl group lies somewhere between that of the chloromethyl and bromomethyl substituents. Of particular interest to this study is the relatively small decrease in volatility observed when one

of the methyl groups in the flophemesyl derivative is changed for an isopropyl group compared to the much greater change in volatility when a *tert.*-butyl or chloromethyl group is introduced. For a series of alcohol derivatives separated on a non-selective SE-30 column (Table II), the order of elution was observed to be

flophemesyl < ISP-flophemesyl < *tert.*-buflophemesyl < CM-flophemesyl

For the low-molecular-weight alcohols, the difference in volatility between the ISP-flophemesyl and *tert.*-buflophemesyl derivatives is less dramatic but still significant.

TABLE I

RELATIVE VOLATILITY OF A SERIES OF $RR_1(CH_3)Si$-CHOLESTEROL ETHERS

Determined on a 1.0 m × 2.0 mm I.D. nickel column of 1% OV-101 on Gas-Chrom Q (100–120 mesh), temperature 250°C, nitrogen flow-rate 75 ml min^{-1}.

R	R_1	*Relative retention time*
CH_3	CH_3	1.00
$CF_3(CH_2)_2$	CH_3	1.26
$CF_3(CF_2)_2(CH_2)_2$	CH_3	1.37
$ClCH_2$	CH_3	2.10
C_6F_5	CH_3	3.14
C_6F_5	$CH(CH_3)_2$	4.57
CH_2Br	CH_3	5.13
C_6F_5	CH_2Cl	6.26
C_6F_5	$C(CH_3)_3$	6.30
CH_2I	CH_3	12.82

Hydrolytic stability of the pentafluorophenyldialkylsilyl derivatives

The limited stability towards hydrolysis of the trimethylsilyl and flophemesyl derivatives is a disadvantage for some applications in which more than the minimum of sample manipulation or preliminary chromatography of the derivatives by thin-layer or column chromatography, etc. is required. The stability towards hydrolysis of the flophemesyl, ISP-flophemesyl, *tert.*-buflophemsyl and CM-flophemesyl derivatives of *n*-octanol under a variety of hydrolytic conditions are compared in Table III. Although there are some inconsistencies in the magnitude of the resistance towards hydrolysis between the ISP-flophemesyl and *tert.*-buflophemesyl derivatives, it can be clearly seen that both of these derivatives are many times more hydrolytically stable to both acid and base hydrolysis than the flophemesyl and CM-flophemesyl derivatives. The hydrolysis conditions employed in this study are severe and it can confidently be predicted that both ISP-flophemesyl and *tert.*-buflophemesyl derivatives can withstand the general clean-up procedures employed in analytical chemistry as far as the analysis of alcohols is concerned. We have previously shown that the *tert.*-buflophemesyl derivatives can be submitted to column and thin-layer chromatography without noticeable hydrolysis[15].

ECD sensitivity

The response of the ECD to the compounds eluting from the column is

TABLE II

RELATIVE VOLATILITY OF PENTAFLUOROPHENYLDIALKYLSILYL ALCOHOL DERIVATIVES

Alcohol	*Flophemesyl ether (R_1, min)*	*ISP-flophemesyl ether (R_2, min)*	*tert.-Buflophemesyl ether (R_3, min)*	*CM-Flophemesyl ether (R_4, min)*	R_2/R_1	R_3/R_1	R_4/R_1	*Column temp. (°C)*
Methanol	1.2	3.2	3.2	3.7	2.6	2.7	3.1	120
Ethanol	1.6	4.0	3.2	5.3	2.5	2.0	3.3	120
1-Propanol	2.0	5.0	5.8	6.6	2.5	2.9	3.3	120
2-Propanol	1.8	4.6	4.8	5.9	2.6	2.7	3.3	120
1-Butanol	3.8	9.1	10.1	12.6	2.4	2.7	3.3	120
2-Butanol	3.3	8.2	8.5	11.0	2.5	2.6	3.3	120
2-Pentanol	1.5	3.1	3.7	4.0	2.1	2.4	2.7	150
1-Hexanol	2.9	5.9	6.5	7.8	2.0	2.2	2.7	150
1-Heptanol	5.1	9.9	10.3	11.4	2.0	2.0	2.1	150
1-Octanol	7.4	14.2	16.4	19.3	1.9	2.2	2.6	150
Benzyl alcohol	6.3	12.9	13.6	16.6	2.1	2.2	2.6	150
Cyclohexyl alcohol	3.4	7.0	8.4	8.6	2.1	2.4	2.5	150
Phenol	3.8	7.6	9.0	10.1	2.0	2.4	2.7	150
1-Decanol	2.6	4.6	5.9	5.9	1.8	1.9	2.3	180
1-Dodecanol	4.9	8.8	9.7	11.3	1.8	2.0	2.3	180

TABLE III

CONDITIONS FOR THE HYDROLYSIS OF *n*-OCTANOL DERIVATIVES

Derivative	*Hydrolysis medium*											
	Acetonitrile–water (4:1)		*Acetonitrile–glacial acetic acid (4:1)*		*Toluene–glacial acetic acid (4:1)*		*Toluene–6 N HCl (4:1)*		*Acetonitrile–6 N HCl (2:1)*		*Acetonitrile–6 N NaOH (2:1)*	
	Time	*Hydrolysis (%)*	*Time*	*Hydrolysis (%)*	*Time*	*Hydrolysis (%)*	*Time*	*Hydrolysis (%)*	*Time*	*Hydrolysis (%)*	*Time*	*Hydrolysis (%)*
Flophemesyl	5 min	100	5 min	68	5 min	21	5 min	31	5 min	99	5 min	98
			7 h	100	15 h	95	15 h	60				
ISP-Flophemesyl	5 min	2	5 min	13	5 min	0	5 min	0	5 min	94	5 min	0
	7 h	13	7 h	26	22 h	17	26 h	33	2 h	100	7 h	33
			30 h	84								
tert.-Bu-flophemesyl	5 min	38	5 min	20	5 min	8	5 min	0	5 min	49	5 min	58
	7 h	93	7 h	31	22 h	23	26 h	0	7 h	90	7 h	67
			30 h	47								
CM-Flophemesyl	5 min	100	5 min	21	5 min	0	5 min	5	5 min	99	5 min	99
			7 h	43	38 h	96	38 h	92				
			30 h	100								

temperature dependent. For this reason it is essential that the detector temperature is optimized for maximum response of each derivative being compared[23]. The data for the peak area (response) of the derivative with respect to detector temperature (T, °K) can be plotted in the form of ln $AT^{3/2}$ *vs.* $1/T$ from which some insight into the detection mechanism can be obtained[24]. In Fig. 2 the flophemesyl, ISP-flophemesyl and CM-flophemesyl derivatives show a dissociative mechanism of electron capture with the bond breaking process being favored by the use of high detector temperatures. The *tert.*-buflophemesyl derivative shows regions of both dissociative and non-dissociative electron capture. To minimize detector contamination with biological extracts, the use of high detector temperatures are preferred and the relative response of all derivatives were determined under these conditions. The minimum detectable quantity of octanol for the four derivatizing reagents is compared in Table IV. All reagents show excellent sensitivity with detection limits at the low picogram level. The nature of the alkyl group (methyl, isopropyl, *tert.*-butyl) has little effect on the detector response. The CM-flophemesyl derivative in which one of the alkyl substituents is the weakly electron-capturing chloromethyl group is approximately five times more responsive to the ECD than the other reagents. Thus the synergistic response of the two electrophores, the pentafluorophenyl and chloromethyl groups, connected through the silicon center is quite small and insufficient to promote the

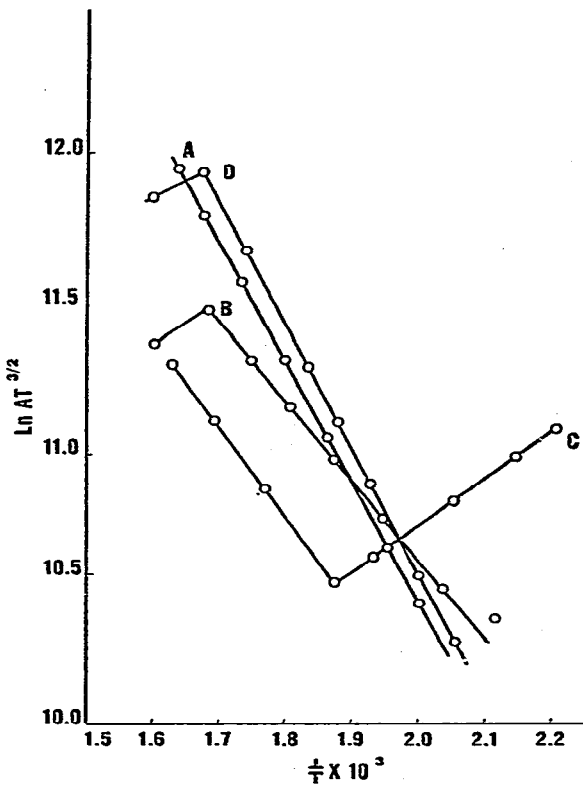


Fig. 2. Temperature dependence of the response of the ECD towards the flophemesyl (A); ISP-flophemesyl (B); *tert.*-buflophemesyl (C); and CM-flophemesyl (D) derivatives of *n*-octanol.

TABLE IV

ECD RESPONSE OF THE PENTAFLUOROPHENYLDIALKYLSILYL DERIVATIVES OF *n*-OCTANOL

Derivative	*Minimum detectable quantity ($\times 10^{-12}$ g)*	*Detector temperature (°C)*
Flophemesyl	4.0	350
ISP-Flophemesyl	5.0	320
tert.-Buflophemesyl	6.0	350
CM-Flophemesyl	0.9	320

use of the CM-flophemesyl reagent over the other reagents studied when account is taken of its unfavorable reaction and hydrolytic stability features.

Mass spectra of ISP-flophemesyl and CM-flophemesyl derivatives

The mass spectra of the ISP-flophemesyl and CM-flophemesyl derivatives are charaterized by weak or absent molecular ions, very few dominant silicon-containing ions and a relatively abundant series of fluorohydrocarbon ions. Also, loss of a methyl or pentafluorophenyl group from the molecular ion or the principal daughter ions does not occur commonly. In the mass spectra of the alcohol derivatives (Fig. 3), elimination of a chloromethyl group in the CM-flophemesyl derivatives and an isopropyl group in the ISP-flophemesyl derivatives occurs readily to give an abundant $[M-CH_2Cl]^+$ or $[M-C_3H_7]^+$ ion, respectively. This ion provides the base peak in most spectra. This cleavage is not so dominant in the non-alcohol derivatives. It is absent in the mass spectra of the CM-flophemesyl derivatives of *n*-butanethiol (Fig. 4), 3-butenoic acid, aniline (Fig. 5) and of only moderate abundance in the benzoic acid (Fig. 6) and phenol (Fig. 7) spectra. For the ISP-flophemesyl derivatives, the relative abundance of the $[M-C_3H_7]^+$ ion is more variable, being weak in the *n*-butanethiol (Fig. 4) and phenol (Fig. 7) derivative mass spectra but is one of the dominant peaks in the mass spectra of the benzoic acid (Fig. 6) derivative. The mass spectra of the ISP-flophemesyl derivatives resemble those of the *tert.*-buflophemesyl derivatives with the exception that the [M—*tert.*-butyl]$^+$ ion is much

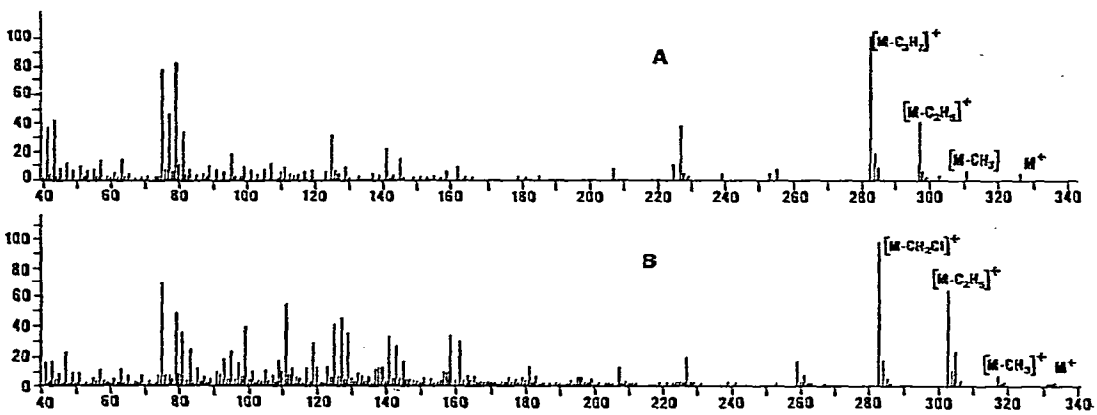


Fig. 3. Electron-impact mass spectra of the ISP-flophemesyl (A) and CM-flophemesyl (B) derivative of 2-butanol.

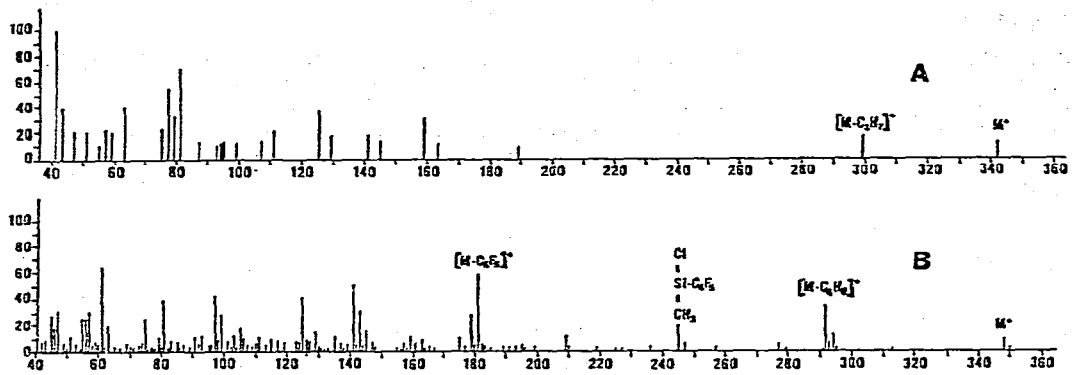
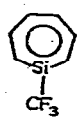


Fig. 4. Electron-impact mass spectra of the ISP-flophemesyl (A) and CM-flophemesyl (B) derivatives of *n*-butanethiol.

more abundant[15]. The base peak in the mass spectra of the phenol derivatives is a silatropylium ion of *m/e* 175 which we have observed previously in the spectra of the flophemesyl[9] and *tert.*-buflophemesyl[15] derivative.



Silatropylium ion
m/e 175

The principal ions of lower *m/e* in all the mass spectra are dominated by the presence of fluorosilane ions (*m/e* 47 $[SiF]^+$, *m/e* 17 $[Si(CH_3)_2F]^+$, *m/e* 81 $[Si(CH_3)F_2]^+$) and fluorohydrocarbon ions originating from the fluorohydrocarbon tropylium ions

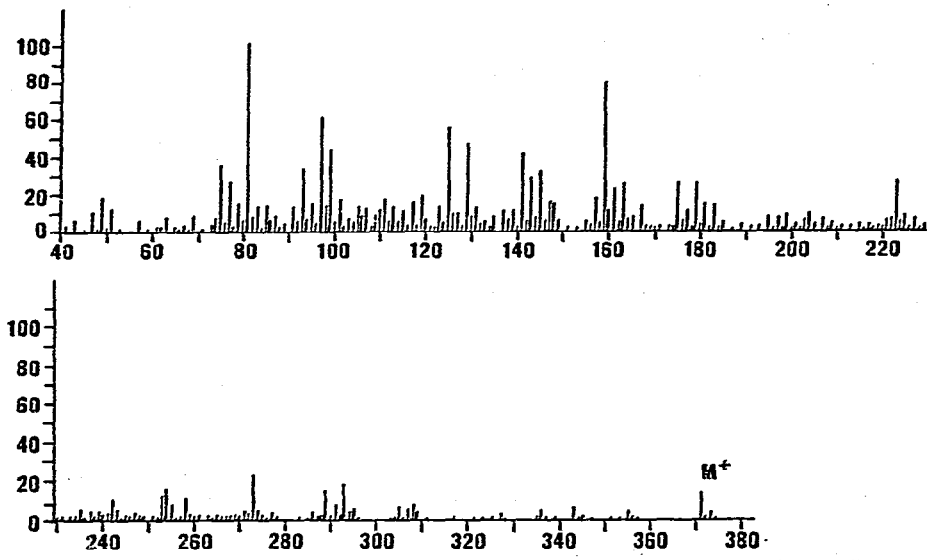


Fig. 5. Electron-impact mass spectra of the CM-flophemesyl derivative of analine.

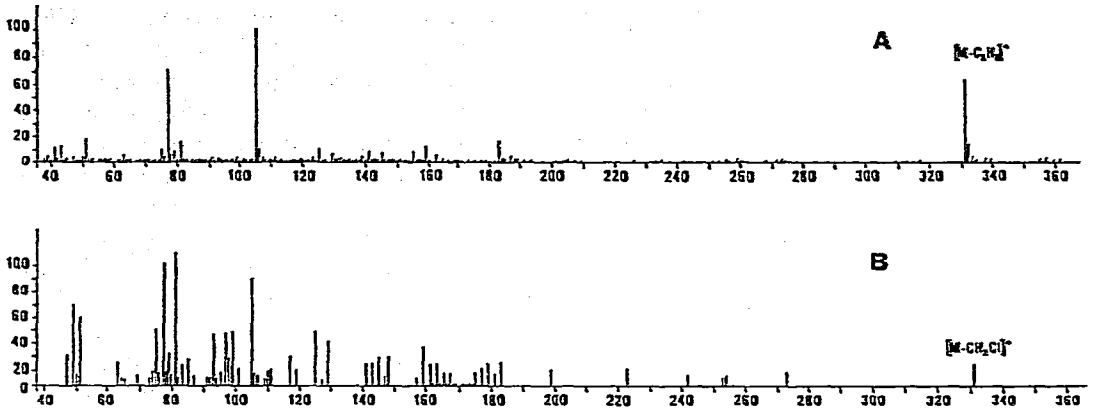


Fig. 6. Electron-impact mass spectra of the ISP-flophemesyl (A) and CM-flophemesyl (B) derivatives of benzoic acid.

(*m/e* 181 $C_7H_2F_5$, *m/e* 163 $C_7H_3F_4$, *m/e* 159 $C_8H_6F_3$ and *m/e* 145 $C_7H_4F_3$). The fluorohydrocarbon tropylium ions arise by exchange between the alkyl groups on silicon and fluorine on the pentafluorobenzene ring, a rearrangement which has been thoroughly investigated for the flophemesyl[6,9,22] and *tert.*-buflophemesyl[15] derivatives. Further fragmentation and elimination of hydrocarbon and fluorocarbon groups from the tropylium ions gives rise to the ions of *m/e* 143, 125, 119, 117, 111, 105, 101, 99, 97, 95 and 93 which are of moderate abundance in all spectra. The characteristic ion *m/e* 129 occurs in all pentafluorophenylsilicon mass spectra and its origin has been discussed previously[22].

Cyclization reactions with CM-flophemesyl chloride and hydroxyamines

As described in the introduction, chloromethyldimethylsilyl reagents undergo a very selective cyclizing reaction with β- and γ-hydroxyamines[16]. Such a grouping is present in the side chain of the β-androceptor antagonist drugs, the so-called β-blockers, used for the long term control of hypertension. To fulfill the need for a

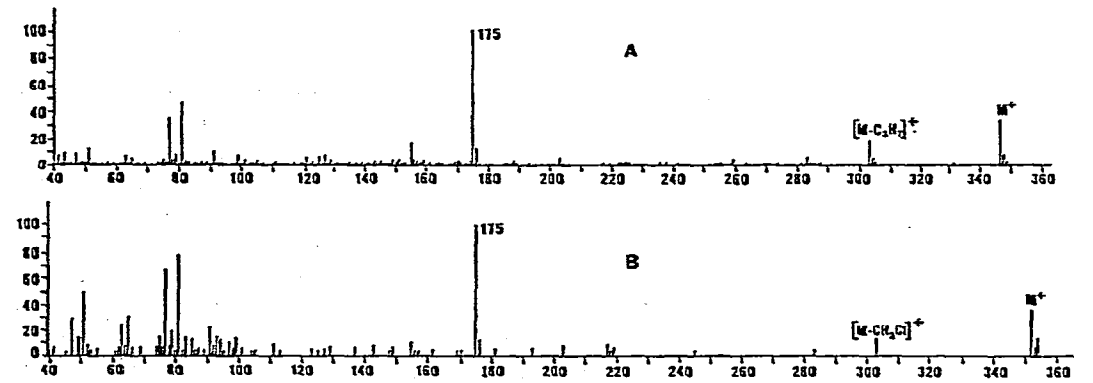


Fig. 7. Electron-impact mass spectra of the ISP-flophemesyl (A) and CM-flophemesyl (B) derivatives of phenol.

very specific reagent for their detection at trace levels in biological fluids, CM-flophemesyl chloride was synthesized and its ability to form cyclic derivatives for use with the ECD investigated. From the outset of this investigation a problem was discovered which presumably does not exist with the chloromethyldimethylsilyl reagents. In the presence of a strong organic base such as diethylamine or triethylamine (added as a catalyst), the CM-flophemesyl chloride reagent undergoes a self-condensation reaction to produce a non-volatile poorly soluble polymeric-like substance. CM-flophemesyl chloride is stable in pyridine but under these reaction conditions no volatile derivatives were formed on GC when alprenolol, metoprolol or propanolol were added to the reaction mixture. Evaporation of most of the pyridine from the reaction mixture gave a heavy oily precipitate. A similar finding was obtained when attempts were made to derivatize 1-methyl-3-isopropylaminopropan-2-ol or 3-amino-1-propanol. We attribute this to the base induced condensation reaction of the reagent. The isopropylamino group of the side chain of the β-blocking drugs is sufficiently basic to catalyze the condensation reaction of the reagent which occurs in preference to the cyclization reaction. In a separate set of experiments, using acetonitrile as solvent and N,N-dimethylaniline, imidazole, acetamide or ammonium carbonate as catalyst, no volatile derivatives for the β-blocking drugs were obtained. It would seem that the pentafluorophenyl group exerts an influence on the reactivity of the chloromethyl group in CM-flophemesyl chloride which is sufficient to inhibit the cyclization reaction with β- and γ-hydroxyamines in favor of a self-condensation reaction to produce a polymeric-like product.

Reactions of bis(pentafluorophenyl)chloromethylmethylsilane

The chloromethyl group when attached to silicon is a labile group undergoing displacement reactions with strong nucleophiles. It also retains some "benzyl-like" character which unables the chloride ion to be displaced by strong nucleophiles resulting in the formation of a new carbon bond. Examples of reactions of the above type are shown below

$$R_3SiCH_2Cl + RXH \rightarrow R_3SiXR + CH_3Cl$$
$$R_3SiCH_2Cl + RNH_2 \rightarrow R_3SiCH_2NHR + HCl$$
$$X = O, N, S \text{ etc.}$$

The chloromethyl group in bis(pentafluorophenyl)chloromethylmethylsilane is more unreactive than would be predicted from a knowledge of the properties of its hydrocarbon analogues. Direct reaction of the reagent with benzoic acid, butanoic acid, phenol and octanol either at room temperature or 60°C for up to 24 h did not show any appreciable consumption of reagent and no new products were found on GC. With *n*-butylamine, β-phenylethylamine, 3-aminopentane and triethylamine some consumption of reagent occurred and four new principal products appeared on GC accompanied by several minor peaks. However, the retention times of the main products remained the same independent of the amine reacted and were increased markedly as the molar excess of bis(pentafluorophenyl)chloromethylmethylsilane was increased to that of the amine. From this information we inferred that the new products formed were generated from the reagent itself in the presence of an organic base catalyst and were not derivatives of the amines. Mass spectra of the four principal products contained few ions of diagnostic value. All spectra contained weak

ions in the high *m/e* region extending beyond *m/e* 1000. On standing, the solutions gave some precipitate, presumably the amine salt (this material was a water soluble fine white powder) indicating that reaction to at least some extent occurred with chloride elimination.

The chloride ion of the chloromethylsilyl group can be replaced by iodine in a halide ion-exchange reaction employing potassium iodide as the nucleophilic source of iodide[24]. Potassium iodide was added as catalyst to the reactions between bis-(pentafluorophenyl)chloromethylmethylsilane and benzoic acid, phenol, octanol and β-phenylethylamine. The hoped for increase in reactivity by *in situ* formation of the iodomethyl group was not found in practice.

The nucleophilicity of phenols and carboxylic acids can be increased by salt formation. For phenol and the carboxylic acids studied here, formation of their sodium or tetrabutylammonium salts did not effect the extent of the reaction and no derivative peaks were obtained on GC.

Thus the chloromethyl group of bis(pentafluorophenyl)chloromethylmethylsilane was found to be relatively inert to nucleophilic attack with the possible exception of some instability towards amines. Under the reaction conditions investigated, this reagent was not found to be useful as a selective derivatization reagent.

Application of a flophemesyl reagent to the detection of N-nitrosodiethanolamine

Triethanolamine is a popular surfactant incorporated into a wide range of cosmetic products. When brought into contact with nitrite ions or nitrogen oxides (*e.g.* NO, NO_2), nitrosation and bond cleavage occurs to produce N-nitrosodi-

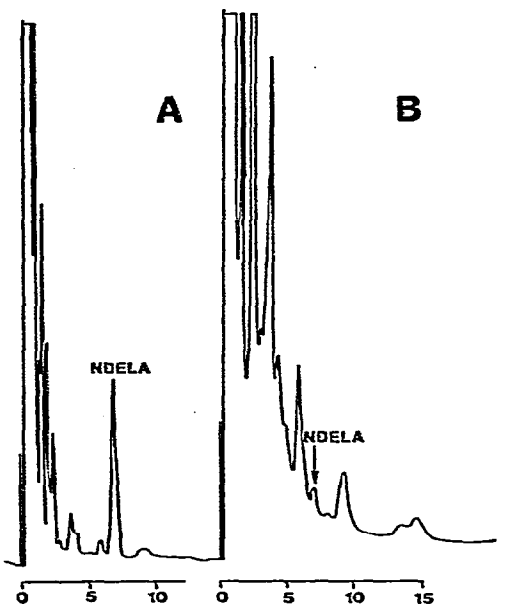
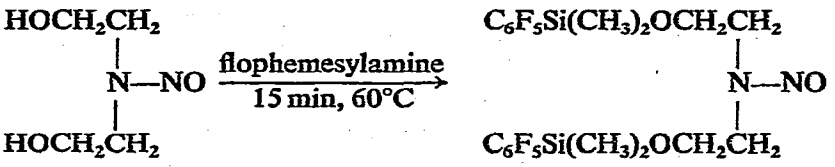


Fig. 8. Gas chromatogram with ECD of the flophemesyl derivative of N-nitrosodiethanolamine before (A) and after (B) UV irradiation. For the separation, a 6 ft. × 0.125 in. I.D. nickel column of 3% OV-17 on Gas-Chrom Q (100–120 mesh) at 220°C isothermally and carrier gas 10% methane in argon at 30 ml min^{-1} was used.

ethanolamine (NDELA). The latter is of interest as it is a mild carcinogen which may accumulate unintentionally in commercial cosmetic products.

Preliminary results in our laboratories have shown that N-nitrosodiethanolamine (20 μl) in toluene (90 μl) reacts quantitatively with flophemesylamine (10 μl) upon heating at 60°C for 15 min to produce a thermally stable flophemesyl derivative with good peak shape on GC. The structure of the derivative was confirmed by mass spectrometry (Fig. 8, *m/e* 582, M^+; 567 $[M-CH_3]^+$; 552, $[M-2(CH_3)]^+$; 536, $[M-C_2H_6O]^+$; 522 $[M-C_2H_6NO]^+$; 517, $[M-C_2H_3F_2]^+$; 503, $[M-C_2H_6FNO]^+$; 415, $[M-C_6F_5]^+$; 384, $[M-C_7F_6]^+$; 296, $[C_6F_5Si(CH_3)_2OC_2H_2N_2]^+$; 282, $[296-N]^+$; 269 $[296-HCN]^+$; 253, $[C_6F_5Si(CH_3)OC_2H_3]^+$.



The principal ions occurring at low *m/e* values are characteristic of the flophemesyl group[5,9,22]. With the ECD the NDELA flophemesyl derivative was easily detected in

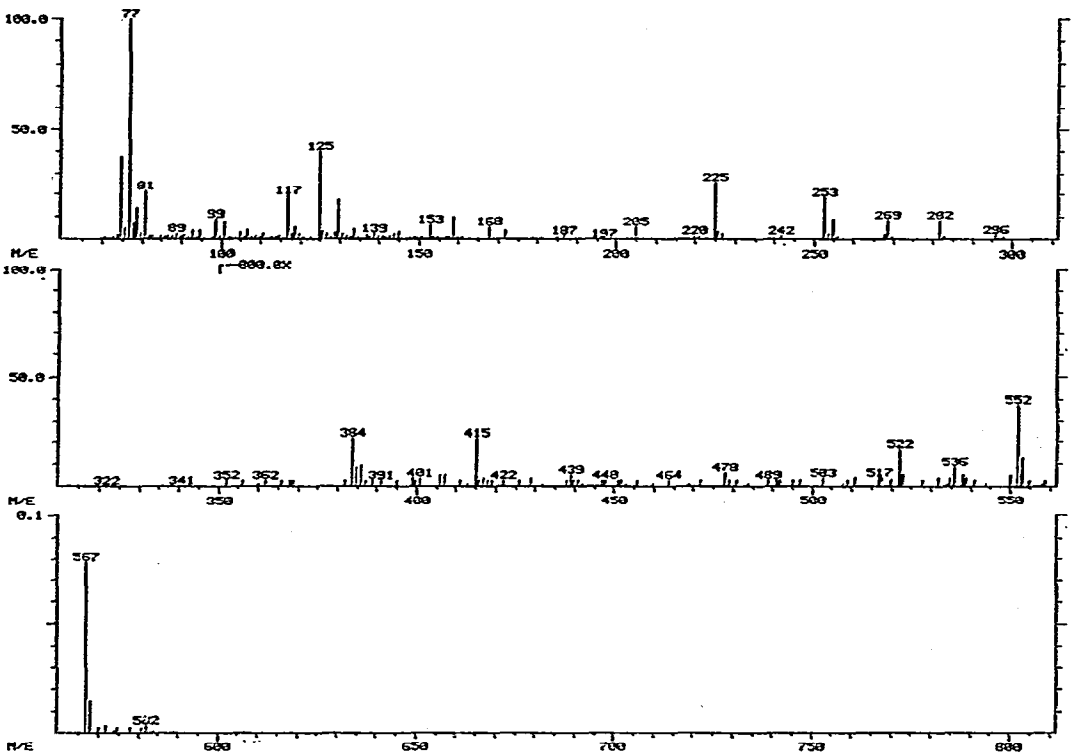


Fig. 9. Electron-impact mass spectra of the flophemesyl derivative of N-nitrosodiethanolamine.

low picogram amounts. As well as MS the instability of the nitroso group to UV irradiation can be used to qualitatively identify N-nitroso compounds in extracts. Fig. 9 shows an ECD chromatogram of 1.0 ng of NDELA as its flophemesyl derivative before (A) and after 4 h UV irradiation (B). After irradiation the peak area for the NDELA derivative is very much reduced. The flophemesyl reagents have useful properties for the determination of NDELA and should prove valuable for the analysis of NDELA at trace levels in cosmetic products.

CONCLUSIONS

The pentafluorophenyldialkylchlorosilanes are useful derivatizing reagents for a wide range of functional groups and can be used with the ECD for the determination of trace quantities of these substances. The volatility order of their derivatives was found to follow the sequence flophemesyl > ISP-flophemesyl > *tert.*-buflophemesyl > CM-flophemesyl and the ISP-flophemesyl and *tert.*-buflophemesyl derivatives were many times more hydrolytically stable than the flophemesyl and CM-flophemesyl derivatives. Bis(pentafluorophenyl)chloromethylmethylsilane was found to be too unreactive for use as a derivatizing reagent. CM-flophemesyl chloride preferred to polymerize rather than act as a cyclizing reagent for γ-hydroxyamines.

ACKNOWLEDGEMENTS

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