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tert.-BUTYLPENTAFLUOROPHENYLMETHYLCHLOROSILANE AS A REAGENT FOR THE FORMATION OF HYDROLYTICALLY STABLE ALKYLSILYL DERIVATIVES WITH ELECTRON-CAPTURING PROPERTIES

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SUMMARY

The synthesis of a new silylating reagent, *tert.*-butylpentafluorophenylmethylchlorosilane (*tert.*-buflophemesyl chloride) is described. The reagent forms volatile derivatives of alcohols, phenols, carboxylic acids, thiols and amines which are suitable for gas chromatography with electron-capture detection. The *tert.*-buflophemesyl derivatives are many-fold more stable towards hydrolysis than the flophemesyl derivatives to conditions such as partitioning between organic solvents and acid or base, thin-layer chromatography and column chromatography. The mass spectra of the derivatives show characteristics of both the flophemesyl and *tert.*-butyldimethylsilyl derivatives and are suitable for compound identification.
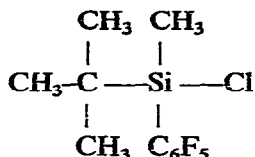

INTRODUCTION

Trimethylsilyl reagents are the most versatile of all derivatization reagents, reacting with a wide range of protonic functional groups and some enolizable ketone groups[1]. Their derivatives are volatile and generally thermally stable, with good separation characteristics, which has led to their widespread use in gas chromatography (GC). However, for use in trace analysis two problems remain. The trimethylsilyl derivatives are not very stable towards hydrolysis, which makes the manipulation of trace amounts in preliminary purification or sample clean-up operations [e.g., thin-layer chromatography (TLC), column chromatography, partition with protonic solvents] likely to result in large and variable losses of derivatives through hydrolysis. Secondly, the search for a silicon-selective and specific detector for trace analysis has not been successful[2].

Owing to their poor stability towards hydrolysis, trimethylsilyl ethers have made little impact as a protecting group in organic synthesis. Recently, higher alkyl homologues than the trimethylsilyl ethers have been used in the synthesis of prostaglandins and nucleosides and shown to be stable to a wide range of chemical reagents (for a review, see ref. 2). Corey and Venkateswarlu[3] found that *tert.*-butyldimethylsilyl ethers were 10^3–10^4 times more stable towards hydrolysis than trimethylsilyl ethers. This

observation has not gone unnoticed by analytical chemists and the last few years have seen an increasing use of reagents of this type in gas chromatography[2].

To improve the detection limit of the silyl ethers, reagents have been devised that contain halomethyl or pentafluorophenyl groups, which can be used with the selective and sensitive electron-capture detector. Halomethylsilanes are vulnerable to nucleophilic attack, resulting in displacement of the halomethyl group and thus limiting their general usefulness[2]. Pentafluorophenyldimethylsilyl reagents (abbreviated to flophemesyl for convenience) have been shown to form derivatives with steroids[4-6], alcohols[7-10] and phenols, amines and carboxylic acids[9,10]. These derivatives can be detected with the electron-capture detector at the picogram to femtogram (10^{-12}–10^{-15} g) level and have similar stabilities towards hydrolysis to trimethylsilyl derivatives.

In an attempt to improve the stability towards hydrolysis of flophemesyl derivatives while maintaining the high response to the electron-capture detector, the new reagent *tert.*-butylpentafluorophenylmethylchlorosilane was synthesized and evaluated. For convenience this reagent has been given the name *tert.*-buflophemesyl chloride:

$$
\begin{array}{ccc}
& CH_3 & CH_3 \\
& | & | \\
CH_3\text{--}C & \text{---}Si\text{---} & Cl \\
& | & | \\
& CH_3 & C_6F_5
\end{array}
$$

EXPERIMENTAL

Flophemesyl chloride and *tert.*-buflophemesyl chloride are available from Lancaster Synthesis (St. Leonard Gate, Lancaster, Great Britain) and Alfa Products Division, Ventron Corp. (Danvers, Mass., U.S.A.).

tert.-Buflophemesyl chloride was prepared for the first time in this laboratory by a three-step reaction sequence as described below.

All reactions were carried out under a nitrogen atmosphere in oven-dried glassware and using anhydrous solvents. Methyldichlorosilane was obtained from Sigma (St. Louis, Mo., U.S.A.), *tert.*-butyllithium from Tridom Chemical (Hauppauge, New York, N.Y., U.S.A.), *n*-butyllithium from Aldrich Chemical (Milwaukee, Wisc., U.S.A.) and pentafluorobenzene from PCR Research Chemicals (Gainesville, Fla., U.S.A.).

tert.-Butylmethylchlorosilane

To a solution of methyldichlorosilane (1.0 *M*) in approximately 250 ml of *n*-pentane was added slowly over about 2 h a solution of *tert.*-butyllithium (500 ml, 2 *M*) in *n*-pentane. The mixture was allowed to reflux spontaneously for about 1 h and was then heated to reflux for a further 1 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 *tert.*-butylmethylchlorosilane, b.p. 89–91 °C, in 56% yield. IR: v (Si–H) 2160 cm^{-1} (s). NMR: CH$_3$–Si 0.38 ppm (d), (CH$_3$)$_3$ C–Si 0.95 ppm (s), Si–H 4.50 ppm (q). MS: *m/e* 136/138 (16.4/5.9) M$^+$, 93/95 (31.8/15.6), 79/81 (46.2/17.1) [M–*tert.*-Bu]$^+$, 57 (100).

tert.-Butylpentafluorophenylmethylsilane

A solution of *n*-butyllithium (0.5 moles of a 1.6 *M* solution in *n*-hexane) was added slowly with stirring to pentafluorobenzene (0.5 *M*) in diethyl ether (160 ml) at −70 °C. The mixture was allowed to warm up to −20 °C, stirred for 0.5 h and cooled again to −70 °C. To this was added slowly *tert.*-butylmethylchlorosilane (0.5 *M*) in diethyl ether (50 ml) over about 1 h and the mixture allowed to warm up to −20 °C for 1 h and finally to reach room temperature. The precipitate of lithium chloride was filtered off and the solvent removed *in vacuo*. The remaining liquid was distilled to give *tert.*-butylpentafluorophenylmethylsilane, b.p. 105–107 °C at 152 mmHg, in 61% yield. IR: v (Si–H) 2160 cm^{-1} (s). NMR: CH_3–Si 0.40 ppm (d), $(CH_3)_3C$–Si 0.93 ppm (s), Si–H 4.35 ppm (q). MS: m/e 268 (15.1) M$^+$, 129 (10), 125 (11.5), 81 (21.8) 77 (15.8), 75 (10.2), 63 (22.2), 57 (100) 47 (11.9), 41 (25.3).

tert.-Butylpentafluorophenylmethylchlorosilane

Chlorine was bubbled through a solution of *tert.*-butylpentafluorophenylsilane (0.5 *M*) in cabon tetrachloride (250 ml) in a reaction vessel covered with aluminium foil to exclude light and arranged so that it could be intermittently immersed in an *ice*–salt bath to maintain the temperature below 25 °C. A buffer volume in the gas line prior to the reaction vessel and an auxilliary supply of nitrogen connected to the chlorine were used in order to prevent loss of material due to suck-back. The reaction was rapid and when complete (approximately 1 h, monitored by GC), excess of chlorine was purged with nitrogen, the solvent removed *in vacuo* and the remaining liquid distilled to give *tert*-butylpentafluorophenylmethylchlorosilane, b.p. 99–100 °C at 12 mmHg, in 77% yield. NMR: Si–CH_3 0.73 ppm, Si–$C(CH_3)_2$ 0.97 ppm (s). MS: m/e 302/304 (24.9/8.7) M$^+$, 245/247 (7.9/4.0) [M−*tert.*-Bu]$^+$, 129 (10.2) 125 (9.5), 99 (11.5), 97 (22.9), 81 (13.6), 57 (100).

Preparation of derivatives

For the preparation of derivatives, 20 µl of reagent (flophemesyl chloride or *tert.*-buflophemesyl chloride) and 20 µl of triethylamine were added to 20 µl of ethanol (or other substrate) in 100 µl of acetronitrile or *n*-hexane in a 1.0 ml Reacti-Vial. The mixture was heated at 60 °C until the reaction was complete. For studies on reaction rate and stability towards hydrolysis using *n*-octanol as a representative alcohol, *n*-tridecane for the flophenesyl derivative and *n*-tetradecane for the *tert.*-buflophemesyl derivative were used as internal standards.

Gas chromatography

For gas chromatography, a Perkin-Elmer Sigma 2 gas chromatograph with a flame-ionization and a nickel-63 constant-current electron-capture detector was used. Retention times 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 gas chromatography–mass spectrometry, 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

Flophemesyl and *tert.*-buflophemesyl chlorides in the presence of an acid accep-
tor catalyst such as triethylamine show a similar range of application as far as the
alcohols, amines, thiols, carboxylic acids and phenols used in this study are concerned.
Although we were primarily interested in the determination of alcohols, for which
retention time data are given in Table I, derivatives of phenol, 1-propionic acid,
1-butenoic acid, benzoic acid, *n*-butylamine, *sec.*-butylamine, *tert.*-butylamine, aniline,
n-butanethiol and *n*-dodecanethiol were also easily formed with *tert.*-buflophemesyl
chloride. For some derivatives *tert.*-buflophemesyl chloride reacted more slowly than
the flophemesyl chloride; whereas the latter gave a complete reaction within 0.25 h at
room temperature, the former occasionally required heating at 60° for 0.5–1.0 h. This
slower rate of reaction is probably a consequence of the greater steric bulk of the
reagent due to the presence of the *tert.*-butyl group. All derivatives showed good
separation properties and peak shapes in gas chromatography. For the alcohols listed
in Table I, the *tert.*-buflophemesyl derivatives were approximately 2–3 times less
volatile than the equivalent flophemesyl derivatives on the non-polar SE-30 column.

TABLE I

RELATIVE VOLATILITIES OF FLOPHEMESYL AND *tert.*-BUTYLPENTAFLUORO-
PHENYLMETHYLSILYL ALCOHOL DERIVATIVES

Alcohol	Flophemesyl derivative (R_1) (min)	tert.-Butylpentafluorophenyl-methylsilyl derivative (R_2) (min)	R_2/R_1	Column temperature (°C)
Methanol	1.2	3.2	2.67	120
Ethanol	1.6	3.2	2.00	120
1-Propanol	2.0	5.8	2.90	120
2-Propanol	1.8	4.8	2.67	120
1-Butanol	3.8	10.1	2.66	120
2-Butanol	3.3	8.5	2.58	120
tert.-Butanol	—	—	—	—
2-Pentanol	1.5	3.7	2.43	150
1-Hexanol	2.9	6.5	2.24	150
1-Heptanol	5.1	10.3	2.00	150
1-Octanol	7.4	16.4	2.22	150
Benzyl alcohol	6.3	13.6	2.16	150
Cyclohexanol	3.4	8.3	2.44	150
Phenol	3.8	9.0	2.37	150
1-Decanol	2.6	5.0	1.92	180
1-Dodecanol	4.9	9.7	1.98	180

Stability towards hydrolysis

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 stabilities of the flophemesyl
and *tert.*-buflophemesyl derivatives of *n*-octanol under a variety of hydrolytic condi-
tions are compare in Table II. The *tert.*-buflophemesyl derivative is many times more

TABLE II

CONDITIONS FOR HYDROLYSIS OF n-OCTANOL DERIVATIVES

Hydrolysis medium	Hydrolysis (%) *	
	Flophemesyl derivative	tert.-Butylpentafluorophenylmethyl-silyl derivative
Acetonitrile–water (4:1)	70% in 5 min	5% in 5 min
	95% in 30 min	5% in 6 h
Acetonitrile–acetic acid (4:1)	78% in 5 min	5% in 5 min
	95% in 2 h	5% in 2 h
	100% in 24 h	12% in 24 h
Toluene–acetic acid (4:1)	50% in 5 min	5% in 5 min
	95% in 2 h	8% in 24 h
Toluene–6 N HCl (4:1)	10% in 5 min	No change over 24 h
	17% in 30 min	
Acetonitrile–6 N HCl (2:1)	90% in 5 min	5% in 5 min
	100% in 30 min	5% in 24 h
Acetonitrile–6 N NaOH (2:1)	95% in 5 min	No change over 24 h
	100% in 30 min	

* ±5% is approximately the reproducibility of the analytical data.

stable towards hydrolysis than the flophemesyl derivative and is not affected by partitioning an organic solution of the derivative against 6 M sodium hydroxide or hydrochloric acid. The tert.-buflophemesyl derivative is also remarkably stable towards dissolution in acidic or basic media under conditions in which the flophemesyl derivative is extensively hydrolysed. The tert.-buflophemesyl alcohol derivatives have also been submitted to column and thin-layer chromatography without noticeable hydrolysis. The tert.-buflophemesyl derivatives can be detected by their absorption of UV light on fluorescent TLC plates.

Sensitivity to the electron-capture detector

A general feature of the operation of the electron-capture detector is the dependence of its sensitivity on temperature[11]. This feature arises as a consequence of the mechanism of the interaction between thermal electrons and the compound being determined[12]. The mechanism can be evaluated by a plot of ln $AT^{3/2}$ versus $1/T$ ($A =$ peak area for a fixed mass of derivative and $T =$ absolute detector temperature). For the flophemesyl derivatives, the mechanism is dissociative and the optimal detector temperature for their determination is the highest that can practically be used[7]. For the tert.-buflophemesyl derivative of n-octanol, a plot of ln $AT^{3/2}$ versus $1/T$ shows regions of both dissociative and non-dissociative electron-capture (Fig. 1).

For convenience a high detector temperature is preferred as this allows the downtime due to contamination to be minimized as well as providing the highest detector response for the derivatives over the temperature range likely to be used for the gas chromatographic separations. With a detector temperature of 350 °C, the detection limit for the n-octanol derivative was $12 \cdot 10^{-12}$ g. This response is of the same order as that obtained with the flophemesyl derivative previously discussed[7,9].
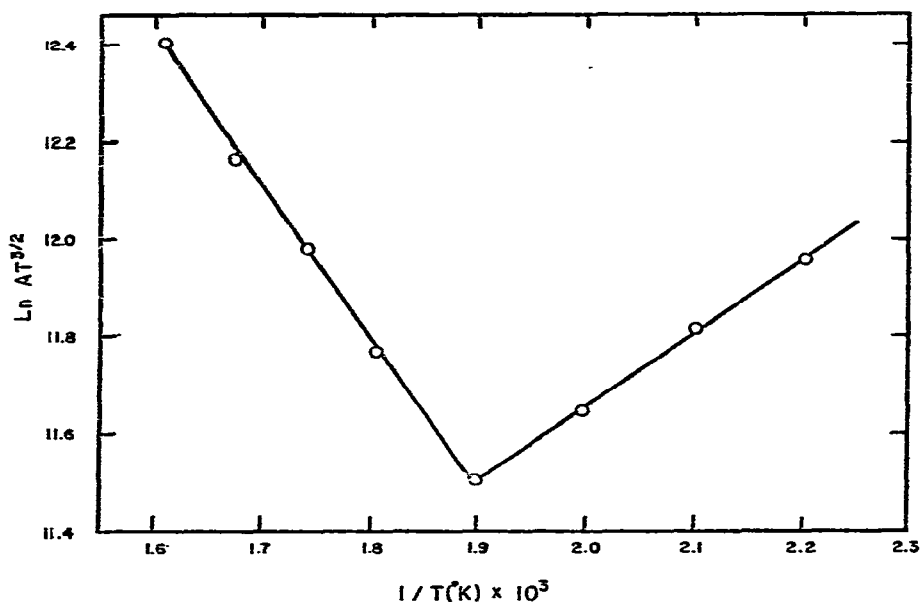
Fig. 1. Temperature dependence of electron-capture detector response to the *tert.*-buflophemesyl derivative of *n*-octanol.

Mass spectra of tert.-buflophemesyl derivatives

The mass spectra of the *tert.*-buflophemesyl derivatives show the combined features of the prominent modes of fragmentation observed with the *tert.*-butyl-dimethylsilyl[2] and the flophemesyl derivatives[6,10]. The molecular ion is generally weak or absent but the molecular weight can be established by the abundant ion [M—57]+ due to facile loss of the *tert.*-butyl radical (phenols show a loss of 56 rather than 57 a.m.u.). An abundant *tert.*-butyl (*m/e* 57) and allylic ion (*m/e* 41) are also characteristic of the mass spectra. The allylic ion is usually very abundant, in some instances the base peak, and is presumably derived directly from the *tert.*-butyl radical or by exchange of a methyl group in *tert.*-butyl with fluorine on the pentafluorobenzene ring with involvement of the silicon centre and elimination as indicated in Fig. 2 (ref. 13). An exchange of this type is the probable origin of the ion at *m/e* 225 $[C_6F_5Si(CH_3)_2]^+$ observed in some mass spectra. Phillipou[14] has discussed the origin of ions characteristic of the trimethylsilyl group in the mass spectra of *tert.*-butyldimethylsilyl derivatives. Unlike the flophemesyl derivatives, silicon-containing fragments are more prominent although relatively few in number. The mass spectra of the derivatives of *n*-propanol (Fig. 3), 3-butenoic acid (Fig. 4), aniline (Fig. 5), *n*-butanethiol (Fig. 6) and phenol (Fig. 7) are typical of those studied. The phenol and aniline *tert.*-buflophemesyl derivatives, analogous to the flophemesyl derivatives[10], have some characteristic differences in the mass spectra from those of the alcohols, carboxylic acids and thiols. The presence of a prominent silatropylium ion (*m/e* 175) is observed and is derived from the aromatic portion of the derivative by an as yet unknown rearrangement process. Cyclic fluorohydrocarbon ions are not important in the mass spectrum of the phenol derivative. Stable ions of this type (Fig. 2) derived from methyl and fluorine
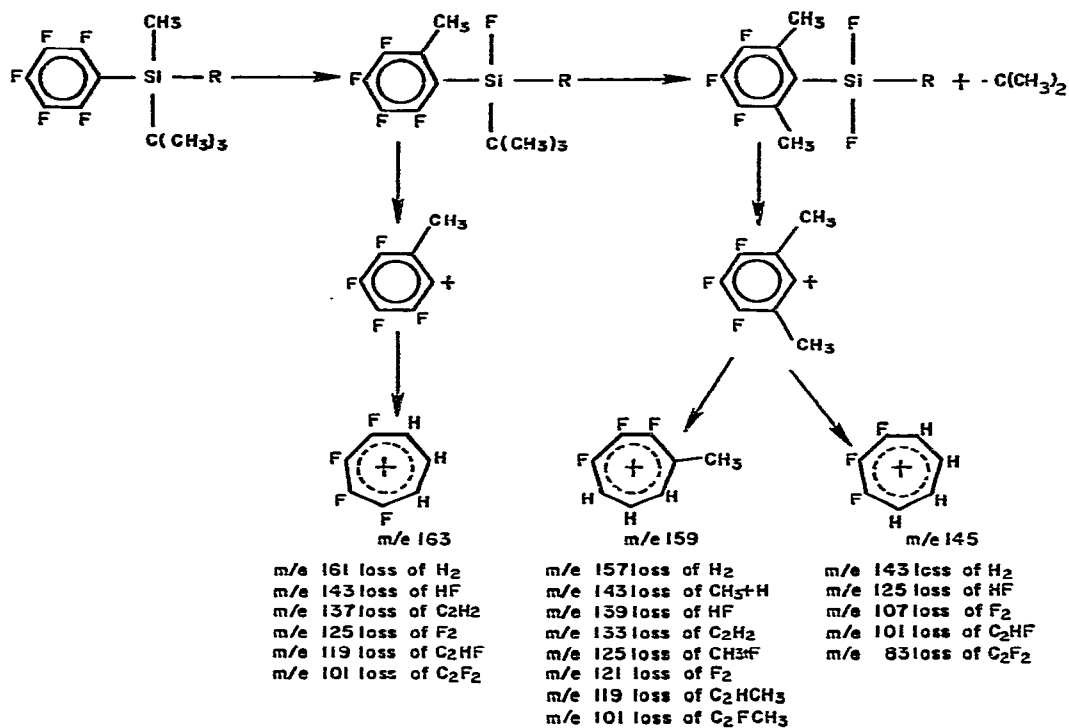
m/e 163

| m/e 161 loss of H₂ |
| m/e 143 loss of HF |
| m/e 137 loss of C₂H₂ |
| m/e 125 loss of F₂ |
| m/e 119 loss of C₂HF |
| m/e 101 loss of C₂F₂ |

m/e 159

| m/e 157 loss of H₂ |
| m/e 143 loss of CH₅+H |
| m/e 139 loss of HF |
| m/e 133 loss of C₂H₂ |
| m/e 125 loss of CH₃+F |
| m/e 121 loss of F₂ |
| m/e 119 loss of C₂HCH₃ |
| m/e 101 loss of C₂FCH₃ |

m/e 145

| m/e 143 loss of H₂ |
| m/e 125 loss of HF |
| m/e 107 loss of F₂ |
| m/e 101 loss of C₂HF |
| m/e 83 loss of C₂F₂ |

Fig. 2. Schematic representation of the origin of fluorohydrocarbon tropylium ions in the mass spectra of *tert.*-buflophemesyl derivatives.
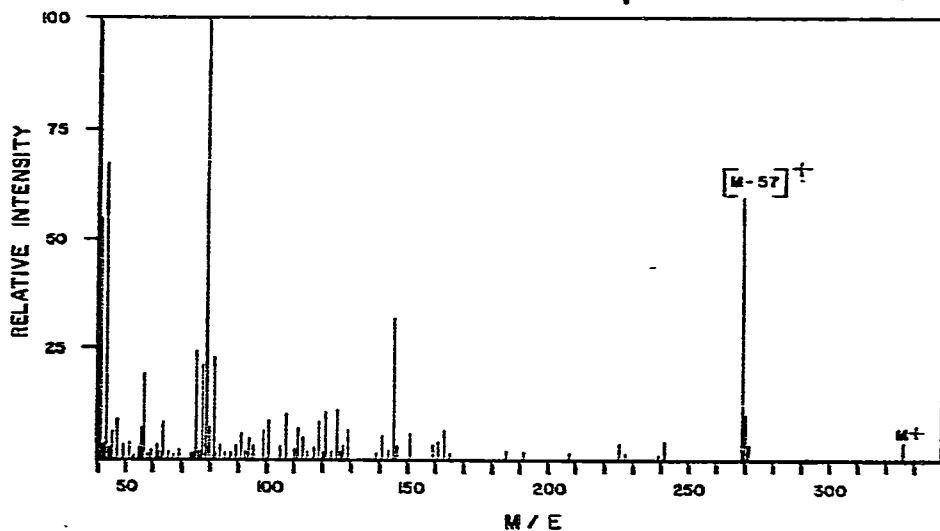
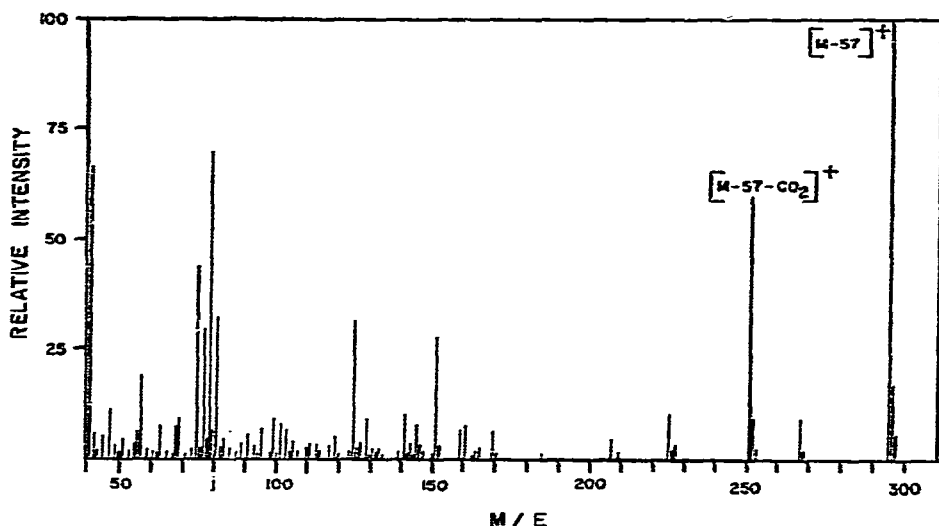Fig. 3. Electron-impact mass spectra of the *tert.*-buflophemesyl derivative of *n*-propanol.

Fig. 4. Electron-impact mass spectra of the *tert.*-buflophemesyl derivative of 3-butenoic acid.
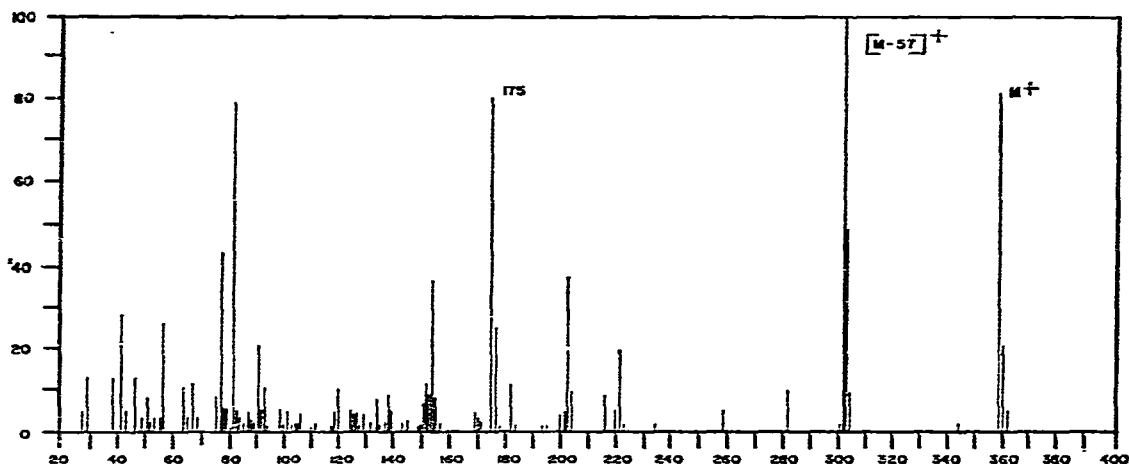

Fig. 5. Electron-impact mass spectra of the *tert.*-buflophemesyl derivative of aniline.

interchange and elimination dominate the remaining features of the alcohol, carboxylic acid, thiol and amine mass spectra. The ions at *m/e* 163, 159 and 145 (formulated as tropylium ions) and their further decomposition by elimination of neutral fragments are of moderate intensity[13].
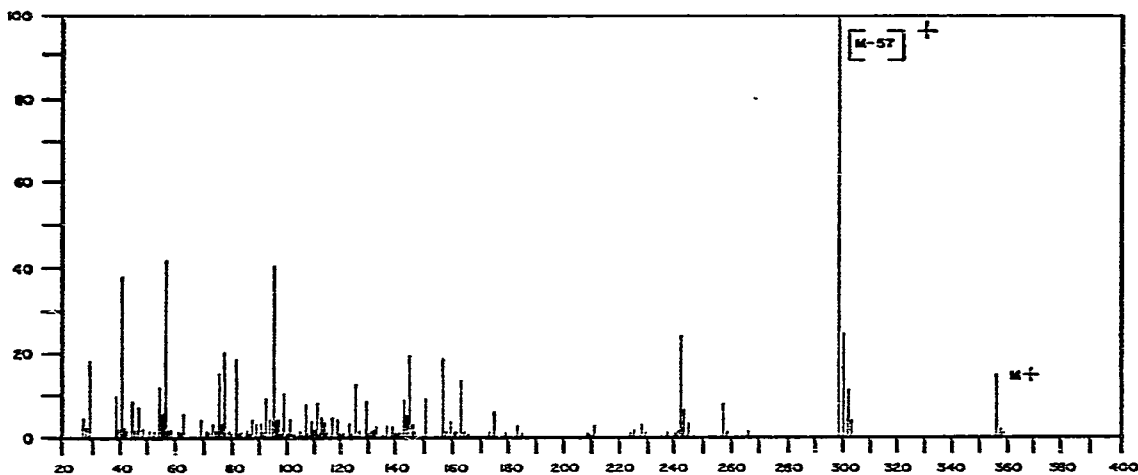

Silatropylium ion (*m/e* 175)

Fig. 6. Electron-impact mass spectra of the *tert.*-buflophemesyl derivative of *n*-butanethiol.
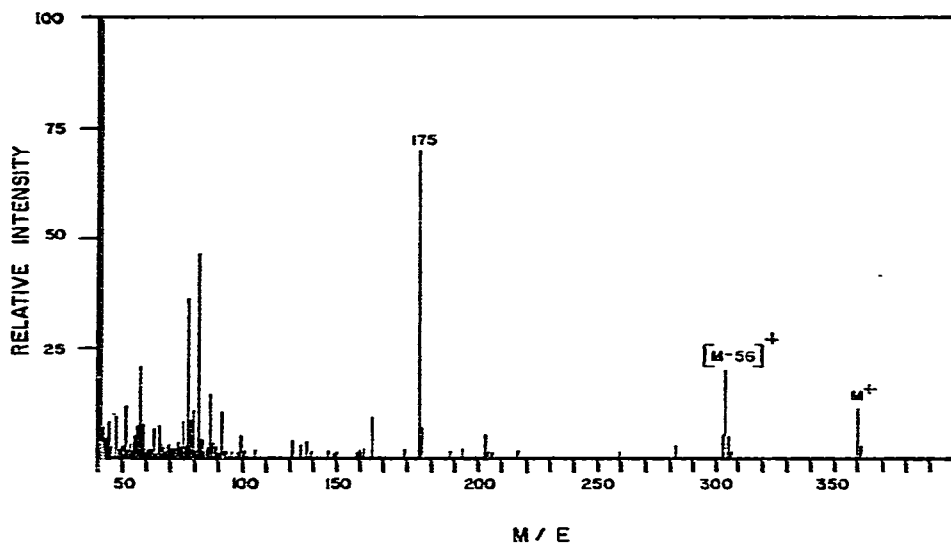
Fig. 7. Electron-impact mass spectra of the *tert.*-buflophemesyl derivative of phenol.

CONCLUSIONS

In comparison with flophemesyl chloride, *tert.*-buflophemesyl chloride reacts less rapidly but to completion under mild conditions, forms derivatives with alcohols that have retention times longer by a factor of 2–3 on GC, has similar sensitivity to the electron-capture detector and forms derivatives that are many times more stable towards hydrolysis. The mass spectra of these derivatives show characteristic features with fragmentation being directed by both the *tert.*-butyl and the pentafluorophenyl group. The greater stability towards hydrolysis of the *tert.*-buflophemesyl derivatives

and their high response to the electron-capture detector should make them very useful for trace level analyses of complex mixtures for which derivative stables to a wide range of chemical conditions are required.

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