crops. Somewhat higher recoveries can be obtained by concentrating these extracts over 1 *N* NaOH instead of distilled water (see section on Isolation, paragraph 1) thereby neutralizing the extract.

The use of the sulfur-sensitive flame photometric detector provides for a highly selective measurement of the desired compound and no interference was encountered in the majority of the untreated controls analyzed. For illustration, Figures 3 and 4 show typical chromatograms. Figure 3 shows a standard chromatogram for the oximino fragment (II). Figure 4 shows chromatograms obtained on extracts of oranges, the upper curve obtained on a sample fortified with 0.04 ppm of oxamyl, the lower curve representing a control orange extract.

Some of the initial chromatography for this method was conducted using a column packed with 30% OV-101 on Gas-Chrom Q. However, the 10% SP 1200/1% $H_3PO_4$ column has proven to be more precise and selective. The column life is equivalent. In addition, the new column requires less conditioning than the earlier OV-101 column.

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# Trifluoroacetylation of Mesurol [4-Methylthio-3,5-xylyl-*N*-methylcarbamate], Its Sulfoxide, Sulfone, and Phenol Analogs for Analysis by Gas Chromatography

Roy Greenhalgh,*[1] William D. Marshall,[1] and Russell R. King[2]

Reaction conditions are established for the trifluoroacetylation of the carbamate insecticide Mesurol and its metabolites, Mesurol sulfoxide and Mesurol sulfone, together with their respective phenol analogs. The reactions with Mesurol sulfoxide and its phenol are anomalous in that they yield di rather than mono TFA derivatives. This is due to initial reaction taking place at the sulfoxide moiety. The carbamate trifluoroacetyl sulfoxide undergoes rearrangement to form an alkyl trifluoroacetoxy derivative, whereas the phenol analog gives an aryl trifluoroacetoxy derivative. The reaction of trifluoroacetic anhydride proceeds more slowly with the carbamate and phenolic moieties. Mass spectra, nuclear magnetic resonance, and infrared spectral data are used to deduce the structures of the compounds. All the trifluoroacetyl derivatives of Mesurol and its metabolites can be chromatographed by gas chromatography and detected by a flame photometric detector in S mode. Thus, trifluoroacetylation can be used for the quantitation of Mesurol and its metabolites or for confirmatory purposes.

Mesurol (I) in common with other thioethers is readily converted to a sulfoxide (II) and sulfone (III) by aerial oxidation, microsomal oxidases, and living organisms. These metabolites have been found in plants (Abdel-Wahab et al., 1966) and are known to be cholinesterase inhibitors (Metcalf et al., 1967). It is desirable that residues of these two metabolites are determined in any analytical method in addition to those of Mesurol. Of the two current methods available for Mesurol (Thornton and Drager, 1973; Bowman and Beroza, 1969), only the latter is capable of determining all three compounds individually, but it is rather involved and a simpler procedure would be an advantage.

Mesurol can be determined directly by gas chromatography (GC) (Lorah and Hemphill, 1974); however, II and III, like most *N*-methylcarbamates, have poor GC characteristics and must be derivatized for analysis. Perfluoroacylation has been employed for this purpose in the case of carbaryl (Khalifa and Mumma, 1972) and carbofuran (Wong and Fisher, 1975). Seiber (1972) has shown that I forms a trifluoroacetyl (TFA) derivative which is suitable for GC analysis. This paper reports on further studies with the reaction of trifluoroacetic anhydride (TFAA) on I, II, and III, together with their phenol analogs, Mesurol phenol IV, Mesurol sulfoxide phenol V, and Mesurol sulfone phenol VI. The TFA derivatives formed are characterized by mass spectrometry (MS), nuclear magnetic resonance (NMR), and infrared (ir) spectroscopy. In addition, the feasibility of the reaction for the GC analysis of Mesurol and its metabolites is demonstrated.

## EXPERIMENTAL SECTION

**Chemicals.** Trifluoroacetic anhydride (TFAA) was obtained from Aldrich Chemical Company and was used as received. Analytical samples of I, II, and III were kindly provided by Chemagro, Kansas City, Kansas.

**Equipment.** Ir spectra were determined as films or Nujol mulls using a Beckman IR-20A spectrophotometer. NMR spectra were obtained in $CDCl_3$ solution with $Me_4Si$ as an internal standard on a Varian T-60 NMR spectrometer. The MS were determined by a Finnigan 3100 GC–MS coupled to a D 6000 data acquisition system.

**Gas Chromatography.** A Pye gas chromatograph, Model 104, fitted with a Bendix Sulphur Phosphorus Emission Detector (flame photometric detector), was operated in the S mode (394 nm). A glass column, 2 ft × 0.25 in. o.d., was packed with acid-washed 80–100 mesh, Chromosorb W coated with 5% DC-200. The column flow was 50 ml/min of nitrogen, and the air and hydrogen flow to the detector selected for optimum response. With a column temperature of 170°C, the retention times of Mesurol TFA (VII), Mesurol sulfoxide di-TFA (VIII), and Mesurol sulfone TFA (IX) were 2.0, 3.2, and 6.3 min, respectively, while those for Mesurol phenol TFA (X), Mesurol sulfoxide phenol di-TFA (XI), and Mesurol

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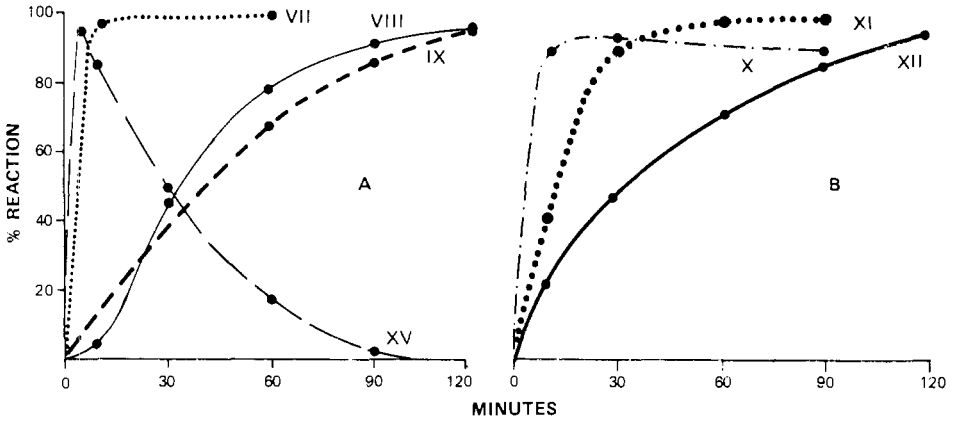



Figure 1. The rate of formation of the TFA derivatives of Mesurol and its metabolites in ethyl acetate at 100°C: (A) Mesurol TFA (VII), Mesurol sulfoxide mono-TFA (XV) and di-TFA (VIII), and Mesurol sulfone TFA (IX); (B) Mesurol phenol TFA (X), Mesurol sulfoxide phenol TFA (XI), and Mesurol sulfone TFA (XII).

sulfone TFA (XII) at 130°C were 2.2, 3.9, and 7.0 min.

**Derivatization.** The carbamate or phenol (10 mg) was dissolved in 4 ml of ethyl acetate and added to a 15-ml screw-capped vial with a Teflon-lined cap containing 0.2 ml of TFAA. The vial was heated at 100°C in a water bath for the required time (0–2 hr). The solvent and excess reagent were removed by a stream of dry nitrogen and made up to 1 ml with ethyl acetate.

**Hydrolysis.** (a) Mesurol sulfoxide di-TFA (VIII) (15 mg) was dissolved in 0.5 ml of 20% aqueous methanol and left to stand at room temperature. After 4 hr, compound XIII was precipitated from solution, and was recrystallized from the same solvent, mp 118–120°C. Anal. Calcd for $C_{10}H_{13}NO_2S$: C, 56.84; H, 6.20. Found: C, 57.11; H, 6.01.

(b) Mesurol sulfoxide phenol di-TFA (XI) (12 mg) was hydrolyzed as above. Compound XIV was obtained after 45 min, and it was recrystallized from chloroform–ether, mp 79–81°C. Anal. Calcd for $C_9H_{12}O_2S$: C, 58.67; H, 6.56. Found: C, 58.22; H, 6.31.

**Thin-Layer Chromatography.** Compounds were spotted on Brinkmann silica gel plates containing a fluorescent indicator and developed in 1:1 ethyl acetate–hexane solvent system. The spots were visualized by ultraviolet (uv) fluorescence and iodine vapor. The $R_f$ values of I, II, III, IV, V, and VI were 0.36, 0.02, 0.11, 0.54, 0.03, and 0.21, respectively, and those of the TFA derivatives VII, VIII, IX, X, XI, and XII were 0.64, 0.61, 0.34, 0.65, 0.62, and 0.35, respectively.

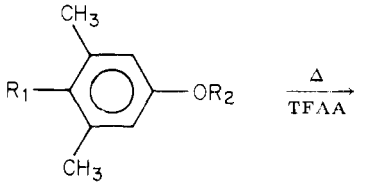
## RESULTS AND DISCUSSION

Seiber (1972) showed that both the solvent polarity and temperature influence the reaction of trifluoroacetic anhydride and carbaryl. Ethyl acetate proved to be a good solvent for this reaction and a similar time study was carried out with Mesurol and its metabolites. The percent reaction for the various carbamate derivatives with time is shown in Figure 1A.

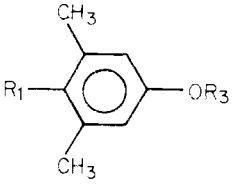
Due to the poor GC characteristics of the sulfoxides and sulfones, the reactions were more conveniently followed by TLC. The amounts of starting material and products present were semiquantitatively determined by measuring the area of the spot. With the exception of the sulfoxides II and V, the reactions were apparently straightforward yielding single products (eq 1).

As in the case of carbaryl, Mesurol (I) was completely trifluoroacylated in 15 min at 100°C in ethyl acetate. The reaction with the sulfone III required 2 hr to go to completion in this solvent.

The NMR spectrum (Table I) confirmed the *N*-trifluoroacetyl structure by the collapse of the N–$CH_3$




| $R_1$ | $R_2$ |
|---|---|
| $CH_3S$ | $C(O)NHCH_3$ (I) |
| $CH_3S(O)_2$ | $C(O)NHCH_3$ (III) |
| $CH_3S$ | H (IV) |
| $CH_3S(O)_2$ | H (VI) |




(1)

| $R_1$ | $R_3$ |
|---|---|
| $CH_3S$ | $C(O)NCH_3C(O)CF_3$ (VII) |
| $CH_3S(O)_2$ | $C(O)NCH_3C(O)CF_3$ (IX) |
| $CH_3S$ | $C(O)CF_3$ (X) |
| $CH_3S(O)_2$ | $C(O)CF_3$ (XII) |

doublet ($\tau$ 7.12, $J_{NHCH_3}$ = 5 Hz) present in I to a singlet ($\tau$ 6.57) in VII. The ir spectrum (Table II) of the TFA derivative VII showed strong absorption at 1780 and 1725 $cm^{-1}$ (Nujol), which was attributed to the C=O band of the $NC(O)CF_3$ and NC(O)OR groups, respectively. In addition, the N–H band at 3310 $cm^{-1}$ and the amide II band at 1535 $cm^{-1}$ of compound I had disappeared in TFA derivative VII. Similar spectral evidence was obtained for the sulfone TFA derivative IX.

The time study for the reaction of the phenol analogs of Mesurol and its oxidation products, i.e. IV, V, and VI, with TFAA is shown in Figure 1B. As in the carbamate series, Mesurol phenol and sulfone phenol gave only one product which the MS showed to be mono-TFA derivatives. The $\tau$ values of the S–$CH_3$, ring $CH_3$, and aryl protons in the NMR were similar to those of the carbamate derivatives (Table I). The ir spectra of the phenol TFA derivatives showed strong absorption at 1810 $cm^{-1}$, which was ascribed to the C=O band of the $CF_3C(O)O$ group.

Reaction of TFAA with Mesurol sulfoxide (II) at 100°C resulted in the formation of a compound VIII, which had parent ion $m/e$ 433, indicative of a di-TFA derivative. Its NMR spectrum showed the N–$CH_3$ protons as a singlet, $\tau$ 4.53, indicating that the nitrogen atom had been trifluoroacetylated whereas the S–$CH_3$, three-proton singlet in II was replaced by a two-proton singlet at $\tau$ 6.54. The

Table I. $^1$H NMR Spectral Data for Mesurol, Mesurol Sulfoxide and Sulfone, the Phenol Analogs, and Their TFA Derivatives

| Compound | No. | $\tau$ values[a] $CH_3S$ | $OCH_2S$ | $CH_3Ar$ | $CH_3N$ | ArH |
|---|---|---|---|---|---|---|
| Mesurol | I | 7.82 | | 7.48 | 7.12 (d) | 3.16 |
| Mesurol TFA | VII | 7.98 | | 7.42 | 6.57 | 3.02 |
| Mesurol sulfoxide | II | 7.04 | | 7.42 | 7.10 (d) | 3.14 |
| Mesurol sulfoxide mono-TFA | XV | | 4.50 | 7.42 | 7.02 (d) | 2.96 |
| Mesurol sulfoxide di-TFA | VII | | 4.52 | 7.42 | 6.54 | 2.94 |
| Mesurol sulfoxide hydrol. prod. | XIII | | | 7.66 | 7.14 (d) | 3.12, 6.90 (SH) |
| Mesurol sulfone | III | 6.96 | | 7.30 | 7.08 (d) | 3.05 |
| Mesurol sulfone TFA | IX | 6.91 | | 7.24 | 6.54 | 2.93 |
| Mesurol phenol | IV | 7.84 | | 7.50 | | 3.40 |
| Mesurol phenol TFA | X | 7.80 | | 7.42 | | 3.02 |
| Mesurol sulfoxide phenol | V | 7.10 | | 7.51 | | 3.46, 1.75 (OH) |
| Mesurol sulfoxide phenol di-TFA | XI | 7.72 | | 7.77, 7.55 | | 2.92 (1 H) |
| Mesurol sulfoxide phenol hydrol. prod. | XIV | 7.83 | | 7.78, 7.56 | | 3.30 (1 H) |
| Mesurol sulfone phenol | VI | 6.95 | | 7.38 | | 3.38 |
| Mesurol sulfone phenol TFA | XII | 6.92 | | 7.25 | | 2.92 |

[a] d = doublet.

Table II. Ir Data for Mesurol, Mesurol Sulfoxide and Sulfone, the Phenol Analogs, and Their TFA Derivatives

| Compound | No. | Absorption, $cm^{-1}$ NH | OH | NC(O)O | NC(O)-$CF_3$ | OC(O)-$CF_3$ | Phase |
|---|---|---|---|---|---|---|---|
| Mesurol | I | 3310, 1535 | | 1720 | | | Nujol |
| Mesurol TFA | VII | | | 1725 | 1780 | | Film |
| Mesurol sulfoxide | II | 3340, 1595 | | 1715 | | | Nujol |
| Mesurol sulfoxide mono-TFA | XV | 3315, 1540 | | 1725 | | 1790 | Film |
| Mesurol sulfoxide di-TFA | VIII | | | 1735 | 1785 | 1795 | Nujol |
| Mesurol sulfoxide hydrol. prod. | XIII | 3310, 1560 | | 1720 | | | Nujol |
| Mesurol sulfone | III | 3370, 1530 | | 1720 | | | Nujol |
| Mesurol sulfone TFA | IX | | | 1730 | 1780 | | Film |
| Mesurol phenol | IV | | 3150-3300 | | | | Nujol |
| Mesurol phenol TFA | X | | | | | 1810 | Film |
| Mesurol sulfoxide phenol | V | | 3000-3200 | | | | Nujol |
| Mesurol sulfoxide phenol di-TFA | XI | | | | | 1810 | Film |
| Mesurol sulfoxide phenol hydrol. prod. | XIV | | 3305, 3400 | | | | Nujol |
| Mesurol sulfone phenol | VI | | 3230, 3410 | | | | Nujol |
| Mesurol sulfone phenol TFA | XII | | | | | 1810 | Film |

ir spectrum of VIII revealed the presence of three carbonyl bands, 1795, 1785, and 1735 $cm^{-1}$, the latter two being attributed to the $NC(O)CF_3$ and NC(O)OR groups. The complexity of the 1200–900 $cm^{-1}$ region of the spectrum prevented the positive identification of the S=O bond.

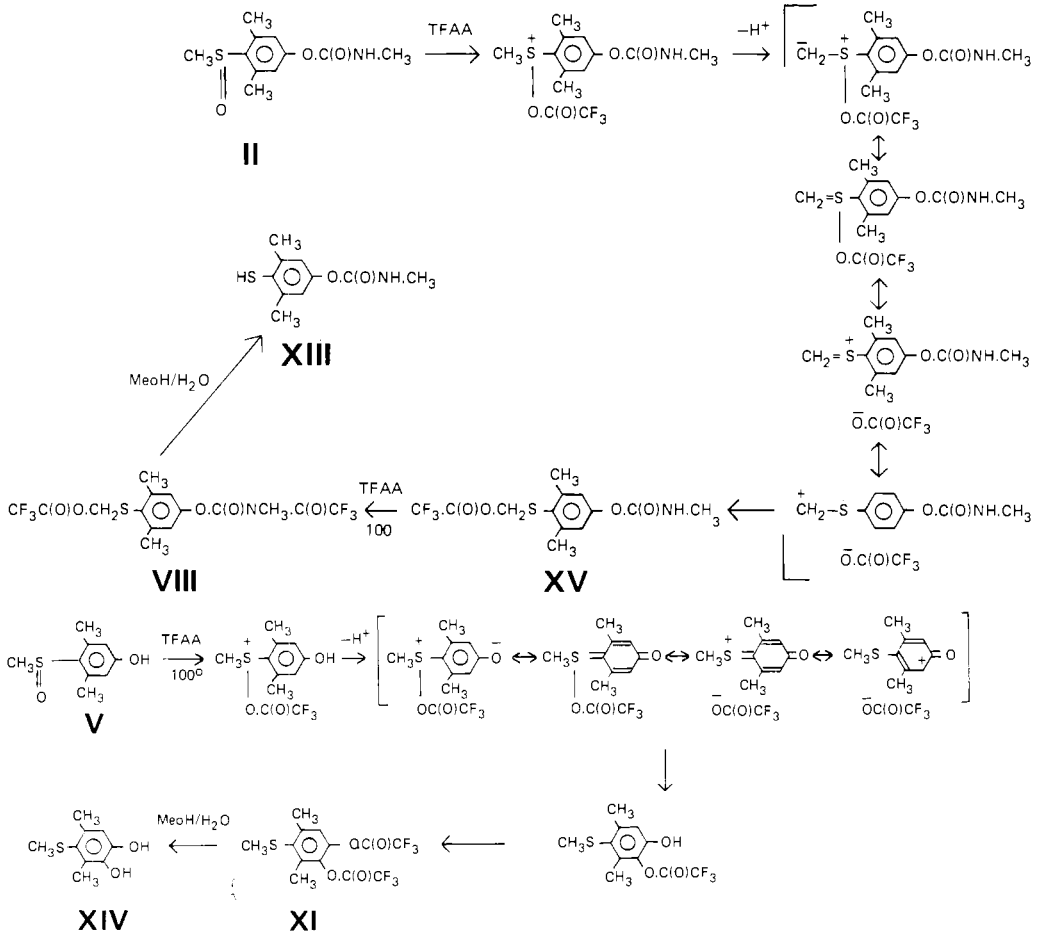
Mesurol sulfoxide (II) and TFAA also react at room temperature, yielding after 15 min a different derivative (XV). This compound was a mono-TFA derivative as indicated by its MS, with a parent ion $m/e$ 337. The $N-CH_3$ protons in the NMR spectrum consisted of a doublet ($\tau$ 7.02, $J_{N-CH_3}$ = 5 Hz) and the *S*-alkyl protons were a singlet ($\tau$ 4.5) but equivalent to only two protons, as with the di-TFA derivative VIII. The presence of an NH group was confirmed by absorption at 3315 and 1540 $cm^{-1}$ (N–H and amide II bands, respectively) in the ir; the spectrum also showed two strong bands at 1790 and 1725 $cm^{-1}$, the latter being assigned to the NC(O)OR group.

These data are consistent with the first site of trifluoroacylation being the oxygen atom of the sulfoxide group, followed by rearrangement involving a ylide intermediate to give the mono-TFA derivative as illustrated in eq 2.

The rearrangement of acylated sulfoxides was first demonstrated by Pummerer (1910) and later elaborated upon by Horner and Kaiser (1959). Kise and Oae (1970) studied the reaction of acetic anhydride and phenyl methyl sulfoxide and found the rate-determining step to be proton removal by the acetate anion to give the ylide.

Further treatment of the mono-TFA derivative XV with TFAA at 100°C converted it quantitatively to the di-TFA derivative VIII. Confirmation of the structure of VIII was obtained by hydrolysis; acetoxy methyl aryl sulfides with mild alkali yield aryl mercaptans (Horner and Kaiser, 1959). The hydrolysis of VIII was very facile and yielded a crystalline product XIII. Its MS revealed a parent ion $m/e$ 211, and its NMR showed the loss of *S*-alkyl protons with the formation of an SH group, $\tau$ 6.90. Both the $NC(O)CF_3$ and $OC(O)CF_3$ groups were also hydrolyzed under these conditions; the ir spectrum of XIII showed only one carbonyl band (1720 $cm^{-1}$) due to the carbamoyl group.

The MS of the TFA derivatives, VII and IX of Mesurol and its sulfone, are typical of *N*-methylcarbamates (Benson and Damico, 1968). Fragmentation takes place initially by loss of *N*-methyl isocyanate via the Damico rearrangement (Damico and Benson, 1965), followed by the loss of $CF_3C(O)^+$ and $CH_3SO_2^+$ to give the precursor ions for the formation of a tropylium ion, $m/e$ 91. Both VII and IX have a base ion, $m/e$ 91, together with an intense ion, $m/e$ 69, which was attributed to the formation of the $CF_3$ ion. The MS of the sulfoxide mono- and di-TFA derivatives, XV and VIII, are further complicated by fragmentation of the *S*-trifluoroacetoxymethyl group, which shows the loss of $CF_3^+$, $CF_3C(O)^+$, and $CF_3C(O)OCH_2^+$ ions. The base ion $m/e$ 153 of the mono-TFA derivative XV results from the loss of $CH_3NCO$ and $CF_3C(O)OCH_2^+$. In contrast, the di-TFA derivative VIII has a base peak, $m/e$ 69, together with an intense ion, $m/e$



(2)



(3)

91. Other strong ions present in the MS of VIII are $m/e$ 249 and 282, which suggests the loss of $CH_3NCO$ and $CF_3NCO$ and $CF_3C(O)OCH_2^+$ or $CF_2C(O)$, respectively. Blessington (1963) reported the loss of ketene, $m/e$ 42, by *N*-acetyl *O*-arylcarbamates on electron impact; none of the TFA derivatives studied here showed an ion, $m/e$ 77, corresponding to the loss of the fluoro analog, $CF_2CO$.

On trifluoroacylation at 100°C, mesurol sulfoxide phenol (V) also gave a di-TFA derivative XI, which had a parent ion, $m/e$ 376. The ir spectrum (Table II), however, showed only one carbonyl band at 1810 $cm^{-1}$, which by analogy with compounds X and XII can be assigned to a $CF_3C(O)O$ aryl group. The NMR spectrum revealed that the methyl groups on the aromatic ring were nonequivalent singlets at $\tau$ 7.77 and 7.55, upfield from those of compound X. The *S*-alkyl protons appeared as a three-proton singlet, $\tau$ 7.72, indicating that substitution had not taken place at this group as was the case of the carbamate analog II. Only one aromatic proton was observed as a singlet, $\tau$ 2.92. The structure suggested for this compound is shown in eq 3, together with a possible mechanism for its formation.

After initial trifluoroacetylation of the sulfoxide oxygen, the trifluoroacetate anion removes a proton from the phenolic OH rather than from the S–$CH_3$ group as was the case for the carbamate sulfoxide II. Kise and Oae (1970) reported that the hydrogen on the least substituted carbon atom is preferentially removed by the acetate ion, but in the above reaction, it appears to be the acidity of the proton rather than the degree of substitution which is most important. A mono-TFA derivative was not isolated in this series due to its high reactivity. Again, confirmation of the structure of the phenol sulfoxide TFA derivative XI was obtained by hydrolysis which gave a crystalline product XIV with a parent ion, $m/e$ 184. Both the $OC(O)CF_3$ groups had been cleaved, since its ir spectrum showed no absorption in the carbonyl region. The NMR spectra showed a singlet ($\tau$ 7.83) equivalent to three protons, indicating that the S–$CH_3$ group was intact, and only one aromatic proton ($\tau$ 3.30). These facts together with the elemental analysis are consistent with the structure of the di-TFA derivative XI shown in eq 3.

Unlike the carbamates, all the phenol metabolite TFA derivatives X, XI, and XII possessed strong parent ions; for X this was also the base ion ($m/e$ 264). The tropylium ion, $m/e$ 91, was present in all three derivatives, being the base ion for the sulfone phenol TFA XII, very intense in X but only weak for XI. This is in agreement with the postulated structure of XI, where the different aromatic ring substitution discourages the formation of the tropylium ion. The fragment (M – 97) was also common to all three compounds, together with ions corresponding with the loss of $CH_3S$ and $CH_3SO_2$ from X and XII, respectively. The $CF_3$ ion, $m/e$ 69, was the base ion for XI, and also present in the spectra of the other two compounds.

All six TFA derivatives of Mesurol and its metabolites VII, VIII, IX, X, XI, and XII gave good GC peaks, which were readily resolved on a 5% DC-200 column as illustrated in Figure 2A, or on a 5% Dexsil 300 column. It was necessary to use temperature programming for the mixture, since the phenol TFA derivatives are normally eluted isothermally at 130°C, whereas the carbamate TFA derivatives require a temperature of 170°C. Derivatization of Mesurol increases the sensitivity by a factor of 2 when using an FPD in the S mode; the sensitivity was even further increased for the sulfoxide II and sulfone III.

The applicability of the derivatization technique for the analysis of residues of Mesurol and its metabolites was tested on a field-treated sample of blueberries. The fruit was extracted with acetone in the presence of a buffer; the extract was partitioned with methylene chloride and after

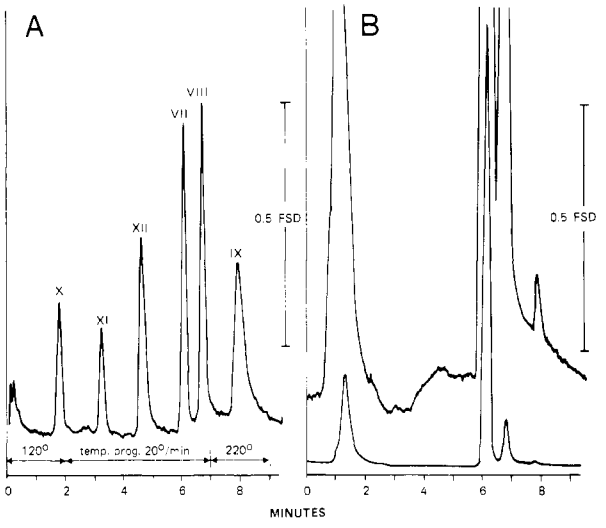



**Figure 2.** Gas chromatograms of the TFA derivatives of Mesurol and its metabolites and a derivatized extract of field-treated blueberries: (A) Mesurol phenol TFA (X) 3 ng, Mesurol sulfoxide phenol TFA (XI) 8 ng, Mesurol sulfone phenol TFA (XII) 6 ng, Mesurol TFA (VII) 5 ng, Mesurol sulfoxide di-TFA (VIII) 10 ng, and Mesurol sulfone TFA (IX) 12 ng; (B) acetone extract of field-treated blueberries after partition and derivatization.

removal of the solvent was derivatized with trifluoroacetic anhydride. A GC chromatogram of the derivatized crude extract is shown in Figure 2B. It indicates the presence of Mesurol, Mesurol sulfoxide, and a small amount of sulfone at an estimated level of 5, 0.9, and 0.03 ppm, respectively. It is interesting to note the absence of phenol metabolites in the sample.

Trifluoroacetylation, together with the use of a selective sulfur GC detector, thus enables the determination of Mesurol and its metabolites to be carried out with virtually crude extracts of blueberries. This eliminates the oxidation, hydrolysis, and column cleanup steps present in the reported methods for the analysis of Mesurol. The trifluoroacetyl derivatives can also be detected by GC–electron capture detector, although cleanup may be required for the extracts in this case.

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# Radiosynthesis and Metabolism in Rats of the 1*R* Isomers of the Insecticide Permethrin

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Permethrin [3-phenoxybenzyl (±)-*cis,trans*-3-(2,2-dichlorovinyl)-2,2-dimethylcyclopropanecarboxylate] is more stable in air and light than previous pyrethroids, and therefore has a greater potential for controlling a wide range of insect pests. Metabolism of the [1*R*,*trans*]- and [1*R*,*cis*]-esters, the active isomers of permethrin, following oral administration to rats at about 1 mg/kg, was examined using compounds labeled with $^{14}C$ in the acid or alcohol moieties. These were synthesized either from [1*R*,*trans*]- or [1*R*,*cis*]-acid labeled in the side chain [$Cl_2{}^{14}C{=}CH-$] or from alcohol labeled at $\alpha$-$CH_2$ or in the phenoxy substituent. The [1*R*,*trans*]- and [1*R*,*cis*]-esters are readily metabolized by ester cleavage, by hydroxylation of the geminal dimethyl group in the acid, or the phenoxy group of the alcohol, and by conjugation of the resulting carboxylic acids and phenols. The metabolites are quickly excreted and do not persist significantly in tissues.

Although natural and synthetic pyrethroids are excellent insecticides with low mammalian toxicity (Elliott, 1976), most are too unstable in air and light to protect agricultural crops effectively. Thus, in chrysanthemates such as pyrethrin I (Ia, Figure 1) and *S*-bioallethrin (Ib) the isobutenyl side chain is a site for photosensitized oxidative attack (Chen and Casida, 1969) and in bioresmethrin (IIa) a second sensitive center is the furan ring (Ueda et al., 1974). However, recent work (Elliott et al., 1973a) has shown that the photolabile groups in pyrethroids can be replaced by others giving much greater stability, and equal or increased insecticidal activity. Table I indicates the insecticidal potency of some important pyrethroids, their

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