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Note

Persilylation of phenolic ketones*

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The utility of silylation for the gas chromatographic analysis of phenolic compounds has been appreciated for some time[1]. The versatility of such analysis has been greatly enhanced by the availability of a variety of silylating reagents. To the extensive literature on the silylation of phenolic compounds we now wish to add a precautionary note pertaining to the use of silylating reagents with certain phenolic ketones.

MATERIALS AND METHODS

The experimental conditions for gas chromatography (GC) and gas chromatography–mass spectrometry (GC–MS) have been described before[2]. Essentially, GC was performed with a Pye Series 105 gas chromatograph fitted with a 7 ft. × $^1/_4$ in. O.D. glass column packed with 3% UCW-98 on 100–200 mesh Chromosorb W-HP. The column was heated from 100° to 250° at 6°/min during analysis. Eicosane used as an internal standard had a retention time of 18.4 min.

The trimethylsilyl (TMS) derivatives were prepared by adding, at room temperature, 100 μl of the silylating reagent (Pierce, Rockford, Ill., U.S.A.) to about 5 nmoles of the recrystallized phenolic compounds. The silylating reagents were: N,O-bis(trimethylsilyl)acetamide (BSA), hexamethyldisilazane and trimethylsilane in pyridine (Tri-Sil), N,O-bis(trimethylsilyl)trifluoroacetamide (BSTFA), and N-trimethylsilylimidazole (TSIM).

Apocynol [α-(4-hydroxy-3-methoxyphenyl)ethanol] was synthesized by reducing acetovanillone (4-hydroxy-3-methoxyacetophenone) with sodium borohydride[3]. The 4-hydroxyacetophenone ester of palmitic acid (m.p. 70°–71°) was prepared by acylating the phenolic ketone with palmitoyl chloride.

The infrared spectra were obtained from chloroform solutions using a Perkin-Elmer Model IR20 spectrophotometer fitted with dual beam condensers.

RESULTS AND DISCUSSION

In our hands, silylation of acetovanillone with BSA afforded, initially, a quantitative amount of a single TMS derivative whose GC retention time was 12.3 min. Silylation for 4 h afforded two derivatives with retention times of 12.3 and 15.1 min.

* Contribution No. 507.

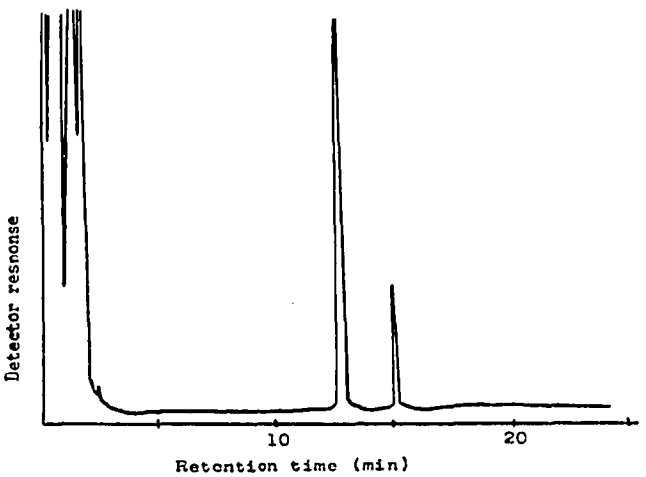

Fig. 1. Gas chromatogram of silylated acetovanillone using 3% UCW-98 on Chromosorb W-HP with column temperature programmed at 6°/min from 100°.

as shown in Fig. 1. After 10 h, equimolar amounts of the two derivatives were formed. After 24 h, the silylated derivative was exclusively the least volatile one. Silylation with Tril-Sil gave results similar to those obtained with BSA.

The rate of formation of the least volatile TMS derivative of acetovanillone was not markedly affected by: (a) variations in the relative proportions of the reagent (from 50 μl to 300 μl), (b) addition of pyridine, dimethylformamide or potassium carbonate, (c) heating at 85° for 5 min.

In contrast to derivatization with BSA, silylation with BSTFA or TSIM formed only the more volatile derivative, even after a reaction time of 24 h.

Evidence pertaining to the identity of the two silylated derivatives was provided by spectroscopic analysis. Application of GC–MS to the more volatile silylated acetovanillone gave a mass spectrum depicted in Fig. 2. The molecular ion at *m/e* 238 indicates that only one TMS group was incorporated into the phenolic ketone. The infrared spectrum of the monosilylated acetovanillone revealed strong absorption bands at 1670 cm^{-1} (carbonyl) and at 1030 cm^{-1} (Si–O–C).

The mass spectrum of the least volatile silylated derivative of acetovanillone showed the following fragmentation pattern: *m/e* (relative intensity) 311 (11.1), 310 (28.6), 296 (7.3), 295 (22.9), 281 (11.4), 280 (31.4), 239 (7.3), 228 (38.6), 224 (9.4), 223 (54.3), 209 (7.3), 208 (32.9), 194 (27.1), 193 (6.1), 75 (41.4), 73 (13.0), 59 (100). Here, the molecular ion at *m/e* 310 demonstrates that two TMS groups were incorporated into the ketone.

The infrared spectrum of the disilylated acetovanillone was devoid of the carbonyl absorption band at 1670 cm^{-1} but there was a strong absorption band at 895 cm^{-1} not shown by the monosilylated analogue. The absence of the carbonyl group eliminates the likelihood of derivatization occurring at the methyl group of the ketonic function as is the case with the sulphonation of acetophenone[4].

It is possible, however, that disilylation of acetovanillone may involve a prior reduction of the carbonyl to an alcoholic function. This possibility was tested by the

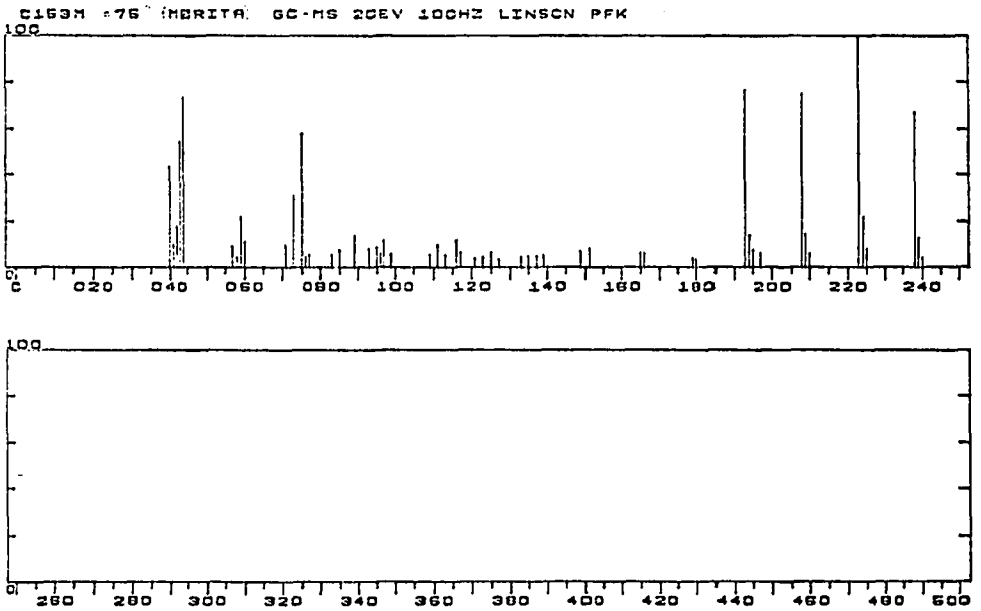

Fig. 2. Mass spectrum of monosilylated acetovanillone. Spectrum obtained with DuPont 490 mass spectrometer (accelerating voltage −1.9 kV; ion source temperature 250°).

GC–MS of silylated apocynol. Silylation of this phenolic alcohol with BSA afforded a single disilylated derivative whose GC retention time was 13.5 min and whose mass spectrum showed the following ion fragments: *m/e* (relative intensity) 313 (5.3), 312 (16.0) (molecular ion), 298 (19.0), 297 (76.7), 282 (2.2), 281 (2.4), 224 (3.3), 223 (16.0), 208 (1.7), 207 (8.0), 194 (14.0), 193 (33.3), 148 (2.6), 147 (147.7), 75 (40.0), 73 (100), 59 (11.7). Clearly, silylated apocynol is quite distinct from disilylated acetovanillone.

The foregoing evidence leads to the conclusion that disilylation of acetovanillone involves derivatization at the carbonyl group and is, in all probability, derived from the enolization of the carbonyl function. In fact, the prominent infrared absorption band observed at 895 cm^{-1} can be assigned to the C=C moiety[5]. The formation of TMS enol ethers from a carbonyl function is well known[6].

The formation of di-TMS derivatives was observed with BSA and a number of other ketones including 4-hydroxy-3-methylacetophenone (GC retention times of 11.7 and 14.1 min), 2-hydroxy-2-methoxyacetophenone (12.7 and 13.9 min), acetosyringone (15.0 and 16.9 min) and 4-hydroxypropiophenone (12.5 and 14.8 min). Monosubstituted TMS enol ethers were obtained with acetophenone and flavonone whereas 3,4-dihydroxyacetophenone formed the trisubstituted TMS derivative (16.3 min) in addition to the expected di-TMS compound (14.3 min).

It is of interest to note that vanillin formed only the mono-TMS derivative (10.6 min) even though the phenolic carbonyl compound is known to form a triacetyl derivative, m.p. 88°.

Thus the formation of more than one silyl derivative makes quantitative analysis of phenolic ketones by GC alone hazardous especially when the derivatization is carried out over extended periods as is the case with certain natural products[7]. This is

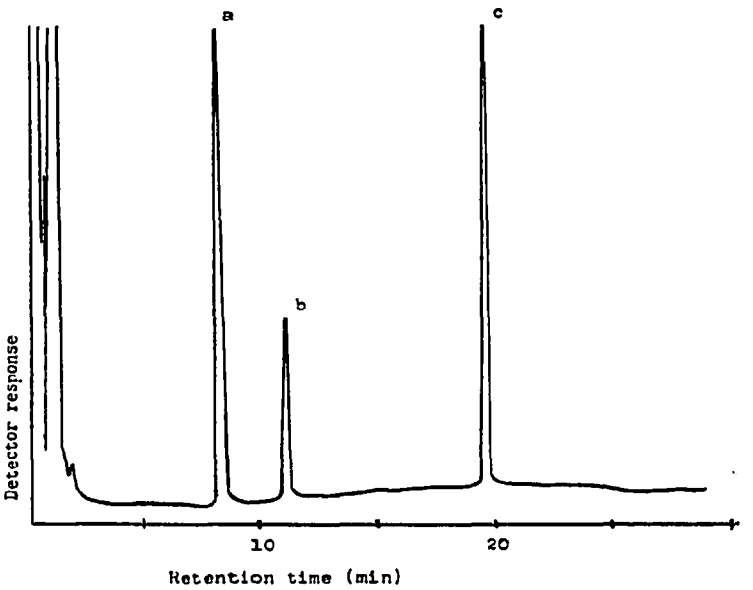

Fig. 3. Gas chromatogram of silylated (BSA) hydrolysis products from the 4-hydroxyacetophenone ester of palmitic acid. (a) Monosilylated ketone, (b) disilylated ketone, (c) silylated palmitic acid. The ester is gas chromatographically non-volatile.

illustrated by the application of GC for the identification of the 4-hydroxyacetophenone ester of palmitic acid, a natural product derived from soil organic matter. Complete hydrolysis of the ester should afford equimolar amounts of the ketone and acid. The gas chromatogram of the silylated hydrolysis products is illustrated in Fig. 3.

ACKNOWLEDGEMENT

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