A Note on the Synthesis and Gas Chromatographic—Mass Spectrometric Properties of N-(Trimethylsilyl)-acetates of Amphetamine and Analogs

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Abstract

Amphetamine, some N-alkyl homologs, and ring-methoxylated analogs were each treated with a slight excess of trimethylsilylketene in dimethoxyethane or carbon tetrachloride. N-(trimethylsilyl)acetate derivatives formed almost quantitatively within a few minutes at room temperature; this was ascertained by nuclear magnetic resonance and infrared studies on the compounds. The N-(trimethylsilyl)acetate derivatives decomposed to varying extents on GC; some were relatively stable with barely detectable decomposition, while others decomposed extensively to the corresponding N-acetates. The N-(trimethylsilyl)acetates were converted quantitatively to the corresponding N-acetates by the action of aqueous hydrochloric acid.

Introduction

Amphetamine and its analogs are metabolized by animals *in vitro* by a variety of pathways (1), but not all metabolites can be separated and identified, underivatized, by gas chromatography-mass spectrometry (GC/MS). To aid in their identification and characterization, it was decided to investigate the possibility of reacting some N-alkylated amphetamines and metabolites with trimethylsilylketene (TMSK), a reagent used by Ruden (2) to derivatize hindered amines and alcohols, and which has been used to characterize cannabinoid constituents of *Cannabis sativa* L (3), and to gain some knowledge of the GC and GC/MS properties of trimethylsilylacetates.

Experimental

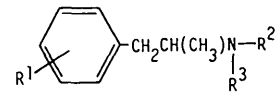
Materials and Methods

Trimethylsilylketene [$(CH_3)_3SiCH=C=O$] was synthesized by the method of Ruden (2); ethoxyacetylene was obtained from ICN-K & K Laboratories, Inc. (Cleveland, Ohio) and the trimethylchlorosilane (TMCS) from Pierce Chemical Company (Rockford, Illinois). The GC analyses were performed on a Hewlett Packard (Palo Alto, California) gas chromatograph, Model HP 5700A, incorporating a flame ionization detector and using helium as the carrier gas (60 ml min^{-1}). System A: 1% Carbowax 20M coated on Chromosorb W, 80/100 mesh, packed in a 1.3 m glass column of 4 mm i.d.; system B: 5% OV-101 coated on Chromosorb 750, 80/100 mesh, packed in a 1.3 m glass column of 4 mm i.d. Samples were injected on-column; the injector and detector temperatures were 250°C, and the oven temperature varied from 130° to 170°C. Combined GC/MS was performed on a Hewlett-Packard HP 5710A GC coupled to a Model HP 5981A mass spectrometer using similar GC conditions as described above. Helium was the carrier gas (60 ml min^{-1}), the ion source temperature 190°C, and the ionizing energy, 70 eV. Direct inlet mass spectra were run on the HP 5981A mass spectrometer. Infrared (IR) spectra were run on a Perkin Elmer (Norwalk, Connecticut) Model 267 spectrophotometer as thin films or KBr discs, and nuclear magnetic resonance (NMR) spectra were recorded on a Varian (Palo Alto, California) EM 360A spectrometer as 10% solutions in $CDCl_3$ or CCl_4 using tetramethylsilane (TMS) as the internal standard, except where the compound was a TMS derivative.

Preparation of N-(trimethylsilyl)acetate Derivatives of Amphetamines

The following procedure is representative. (See Chemical Structures) To amphetamine (Ia, 2-amino-1-phenylpropane, 0.11 g, 0.79 mmoles) in dry dimethoxyethane (DME, 1 ml) was added trimethylsilylketene (TMSK, 0.13 ml, 0.94 mmoles; d = 0.84 g/cm^3), and the solution was stirred for 10 min (slightly exothermic reaction). Removal of the solvent and excess TMSK under vacuum gave the N-(trimethylsilyl)acetate in a virtually quantitative yield (NMR evidence) as a colorless oil;

Chemical Structures



I R^3 = H
II R^3 = $COCH_2Si(CH_3)_3$
III R^3 = $COCH_3$

	R^1	R^2
a.	H	H
b.	H	C_2H_5
c.	H	nC_3H_7
d.	2-OCH_3	H
e.	3-OCH_3	H
f.	4-OCH_3	H

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NMR (CCl_4), δ 0.0 (s, 9, $Si(CH_3)_3$), 1.02 (d, 3, CH_3), 1.63 (s, 2, $COCH_2$), 2.68 (dq, 2, $CHCH_2$), 4.12 (m, 1, $CHCH_3$), 6.45 (bd, 1, NHCO), 7.11 (s, 5, Ar); IR (film) γ_{max} 860 and 1255 (C-Si), 1635 (C=O), 3310 (NH amide) cm^{-1}.

The N-(trimethylsilyl)acetates prepared in this manner (IIa-IIf) all gave an NMR absorption near δ 1.7 ($NHCOCH_2$-TMS) (*cf* $NHCOCH_3$ near δ 1.9) and absorbed in the following regions of the infrared, 850-860 and 1250-1260 (C-Si), 1625-1635 (C=O), and 3310-3330 cm^{-1} (NH, amide, except IIb and IIc).

Hydrolysis of N-(trimethylsilyl)acetates to N-acetates

The following procedure is representative. To the N-(trimethylsilyl)acetate derivative of amphetamine (IIa, 0.1 g, 0.40 mmoles) in DME (1 ml) was added 6 M HCl (1 ml) and the mixture was stirred for 10 min at 20°C. The solution was adjusted to pH 7.0 with $NaHCO_3$ and extracted with ether (2 × 5 ml), which, upon evaporation, gave the corresponding N-acetate, as a white solid, mp 94° in almost quantitative yield; NMR ($CDCl_3$) δ 1.13 (d, 3, $CHCH_3$), 1.92 (s, 3, $COCH_3$), 2.78 (dq, 2, CH_2CH, 4.28 (m, 1, $CHCH_3$), 5.70 (bs, 1, NHCO), 7.25 (s, 5, Ar); IR (KBr disc) 1650 (C=O), 3270 (NH amide) cm^{-1}.

All the amphetamines (Ia-If) reacted rapidly with a slight excess of TMSK at room temperature to give virtually quantitative yields of the N-(trimethylsilyl)acetates. The derivatives were characterized by IR and NMR spectroscopy and all compounds were examined by GC and GC/MS. NMR data indicated less than 5% of the corresponding N-acetates were formed if the solvents (DME or CCl_4) were dried thoroughly before use; the N-(trimethylsilyl)acetates each gave a two proton amide singlet absorption near δ 1.7 and the N-acetates gave a three proton amide singlet absorption near δ 1.9.

When the N-(trimethylsilyl)acetates were examined by GC, however, all underwent decomposition to varying degrees on an OV-101 column (Figure 1). On a Carbowax GC column, the four primary amine derivatives (IIa, IId-IIf) chromatographed with negligible decomposition; the other secondary amine derivatives underwent extensive decomposition. The major decomposition products were readily identified as the corresponding N-acetates by comparison of their GC and MS properties with those of authentic reference samples, prepared by acetylating the amines with acetic anhydride. A possible mechanism for the thermal formation of the N-acetates, which involves the expulsion of dimethylmethylenesilane [$(CH_3)_2Si = CH_2$] from the N-(trimethylsilyl)acetates, is given (Scheme 1).

The N-acetates were readily identified from their mass spectral fragmentations (Scheme 2). The presence of a ring methoxyl group had a profound effect on the fragmentation pathways resulting in charge retention predominently on the aromatic fragment. In the non-ring-substituted N-acetate spectra, the charge is retained mainly on the side chain.

The N-(trimethylsilyl)acetates also fragmented characteristically in the mass spectrometer (Scheme 3) by pathways similar to those displayed by the N-acetates. In addition, an m/e 73 ion was always observed, due to the trimethylsilyl moiety, as well as an abundant ion (ion vi, Scheme 3) due to the N-(trimethylsilyl)acetate side chain. The presence of a methoxyl group on the aromatic ring had the same effect as on the fragmentation of N-acetates making the β-methylstyrene ion-radical the base peak (IId-IIf, Scheme 4).

The conversion of the N-(trimethylsilyl)acetates to N-acetates was readily accomplished by hydrolysis with 6 M

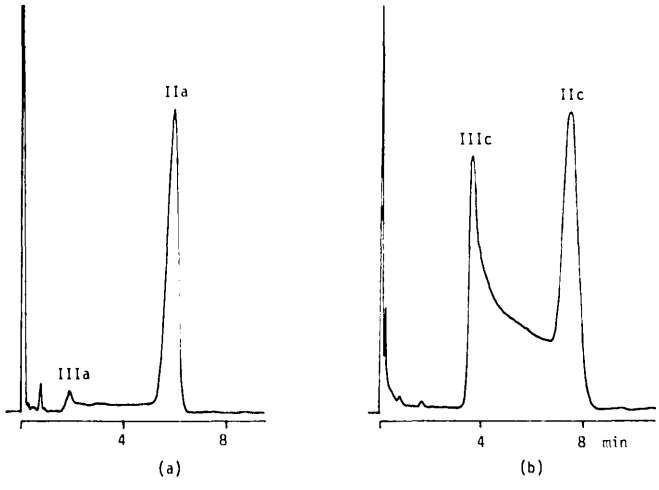
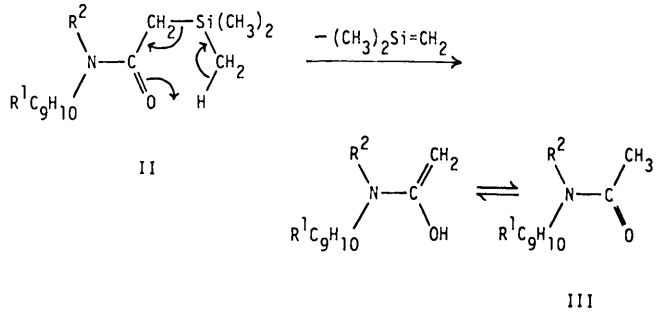
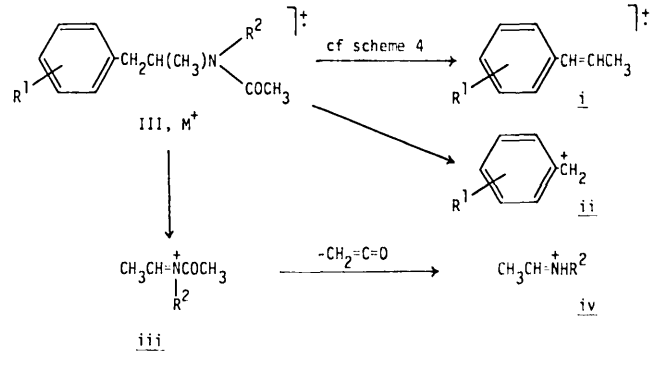


Figure 1. GC traces of the TMS-ketene derivatives of (a) amphetamine and (b) N-*n*-propylamphetamine (IIa and IIc) showing the relative extent of their decomposition on GC system B to the corresponding N-acetates (IIIa and IIIc).

Scheme 1



Scheme 2

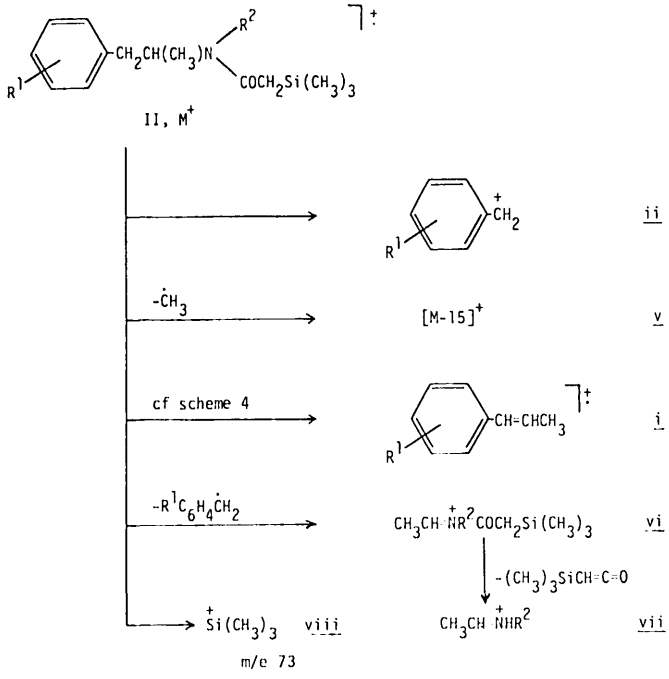


m/e (% Relative Abundance)

Compound	M+	i	ii	iii	iv	other diagnostic ions
IIIa	177(4)	118(24)	91(17)	86(34)	44(100)	
IIIb	205(3)	118(8)	91(16)	114(100)	72(91)	
IIIc	219(2)	118(9)	91(19)	128(100)	86(92)	
IIId	207(7)	148(100)	122(10)	86(22)	44(16)	91(20)*
IIIe	207(11)	148(100)	121(15)	86(18)	44(25)	91(15)*
IIIf	207(3)	148(100)	121(23)	86(7)	44(9)	91(4)*

*m/e 91 is formed by the explusion of CH_2O from m/e 121

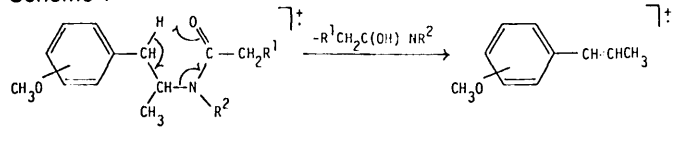
Scheme 3



m/e (% Relative Abundance)

Compound	M+	i	ii	v	vi	vii	viii
IIa	249(3)	118(21)	91(75)	234(38)	158(84)	44(18)	73(100)
IIb	277(3)	118(16)	91(46)	262(22)	186(34)	72(100)	73(43)
IIc	291(-)	118(5)	91(21)	276(10)	200(18)/	86(100)	73(24)
IId	279(6)	148(100)	121(20)	264(14)	158(28)	44(16)	73(29)
IIe	279(6)	148(100)	121(19)	264(14)	158(52)	44(16)	73(19)
IIf	279(4)	148(100)	121(15)	264(17)	158(9)	44(9)	73(18)

Scheme 4



(IId - IIf)

HCl at room temperature. This represents a rapid and efficient way of preparing N-acetates of amines since the products are readily separated from excess acetylating agent. This method is, in the authors' opinion, superior to the conventional use of acetyl chloride or acetic anhydride for this purpose.

This study has shown that amphetamines and some analogous primary and secondary amines react readily with trimethylsilylketene to form N-(trimethylsilyl)acetates, which can be conveniently characterized by NMR, IR, and direct inlet MS, but which undergo thermal decomposition to varying extents on GC to N-acetates by the expulsion of dimethylmethylenesilane.

Acknowledgements

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