Technical Note

Analytical Profile of Modafinil

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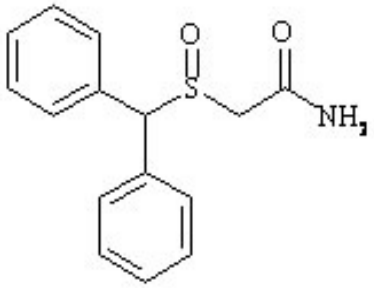
ABSTRACT: Analytical data (color tests, GC/MS, and FTIR) are reported for modafinil.

KEYWORDS: Modafinil, Provigil, Color Testing, GC/MS, FTIR, Forensic Chemistry.

Figure 1

Modafinil: 2-[(Diphenylmethyl)sulfinyl]acetamide;
$C_{15}H_{15}NO_2S$; mw = 273.36



Introduction

Modafinil (Figure 1), the active constituent of Provigil® tablets, became a Schedule IV controlled substance in January 1999. According to the manufacturer, modafinil is a CNS stimulant which possesses, "wake-promoting actions like sympathomimetic agents including amphetamine and methylphenidate, although the pharmacologic profile is not identical to that of sympathomimetic amines" [1].

Presumptive testing and instrumental data were collected to assist in the identification of submissions of modafinil tablets.

Experimental

Standard and Reagents
A reference standard of modafinil (Lot# 084K4633) was obtained from Sigma. Potassium bromide (IR grade, lot# 035261) and methylene chloride (ACS grade, lot# 040933) were obtained from Fisher. The derivatizing agent BSTFA+TMCS (99:1, lot# LA90822) was obtained from Supelco.

Methods and Instrumentation
Presumptive Color Tests: Portions of modafinil were placed in reagent wells followed by the addition of various presumptive color test reagents.

Tablet Extraction: A Provigil tablet extraction procedure was obtained from Cephalon [2]. A single tablet was ground and placed in a separatory funnel followed by the addition of 50-mL de-ionized water and 50-mL methylene chloride. The mixture was shook for approximately one minute with venting. A portion of the lower layer was drained, filtered, and evaporated to dryness, leaving a white powder residue.

Derivatization: A small portion of modafinil reference standard was placed in an autosampler vial followed by ~1 mL de-ionized water and ~0.5 mL BSTFA-TMCS derivatizing agent. The vial was capped tightly, mixed well, and incubated at ~70 ºC for 30 minutes.

GC/MS Analysis: Analysis was performed with a HP 6890 GC equipped with a DB-35MS column (15 m x 0.25 mm ID, and film thickness 0.25 μm) and coupled to a HP 5973 Mass Selective Detector. The temperature during the analysis run increased from 90 ºC to 300 ºC at 20 ºC/minute, held for 5 minutes, increased up to 310 ºC at 30 ºC/minute, and held for 0.5 minute. The temperatures of the injection port and transfer line were 250 ºC and 280 ºC, respectively. Helium was used as the carrier gas at a flow rate of 1 mL/minute. The MSD was operated in the Electron Ionization mode. Mass spectra were recorded at 70 eV, with a scanning range of *m/z* 40 - 400.

FTIR Analysis: FTIR analysis was performed using a Perkin Elmer Spectrum 1000 spectrometer. Samples were analyzed in KBr and scanned 16 times from 4000 - 400 cm^{-1} at a resolution of 4 cm^{-1}.

Results and Discussion

The results of five presumptive color tests are summarized in Table 1. Based on the results, only the Marquis and Liebermann's reagents give a positive test (however, neither is very specific or definitive).

Table 1.

Reagent	**Resulting Color**
Marquis	Yellow/Orange ⇒ Brown
Liebermann's	Darkening Orange
Sodium Nitroprusside	No Color
Cobalt Thiocyanate	No Color
Ehrlich's	No Color

Underivatized modafinil (reference standard) severely degraded during GC/MS analysis, displaying five primary peaks under the specified conditions. The latest eluting compound (Rt = 11.13 minutes) had a base ion at *m/z* = 167 (likely a rearranged ion derived from the diphenylmethinyl fragment). Derivatizing with BSTFA resulted in a substantially more abundant peak at 11.15 minutes. The mass spectrum of this peak is shown in Figure 2. Figure 2 also suggests that the ion at *m/z* = 167 is the expected ion for either derivatized or underivatized modafinil. While the TMS derivative shows some degradation, the derivative is much more stable than modafinil under under GC conditions, and is therefore more suitable for GC/MS analysis.

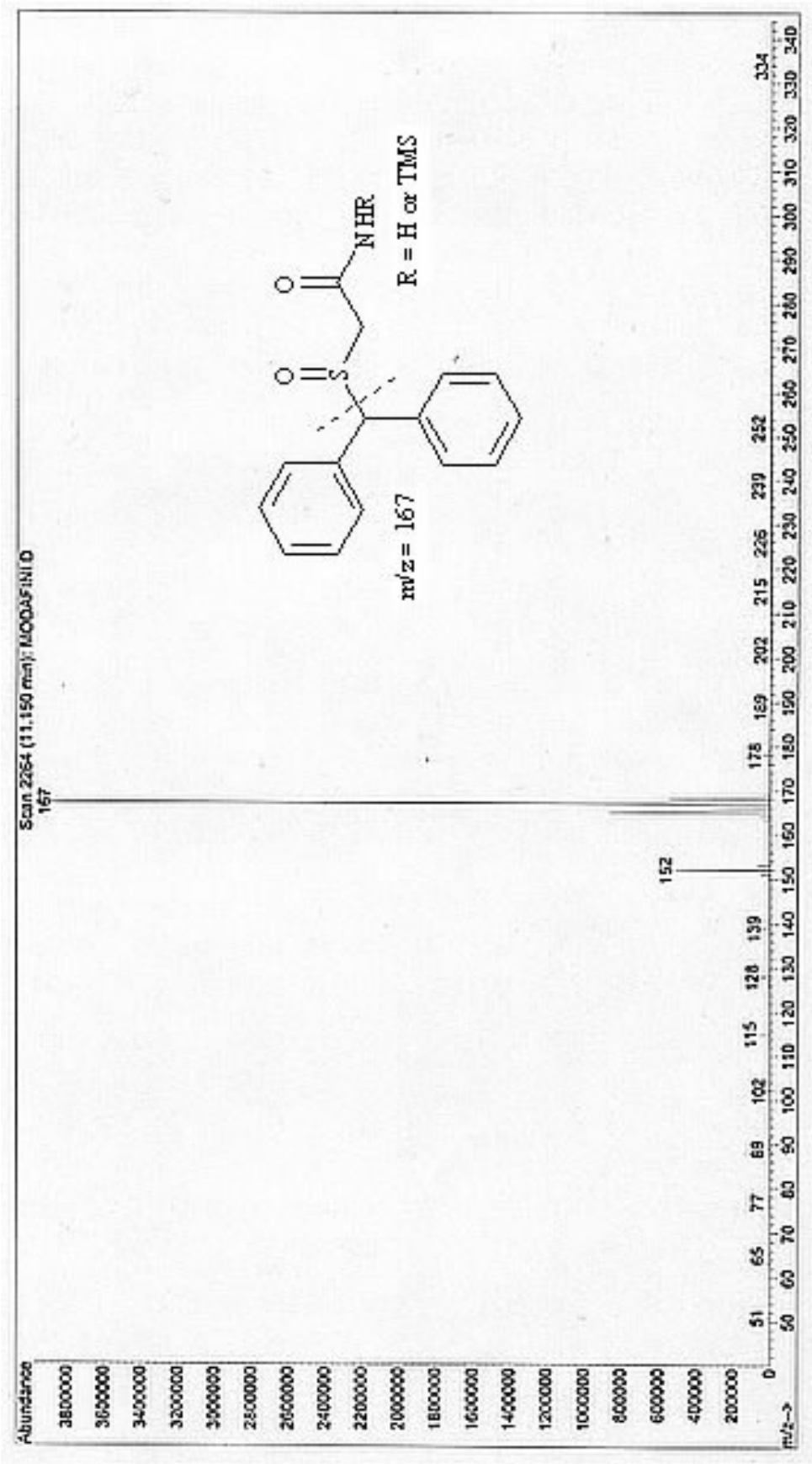
The FTIR spectrum of modafinil is presented in Figure 3. Discussions with technical staff at Cephalon indicate that the spectrum changes when extracted into methylene chloride and evaporated down, suggesting a hydrated form and an anhydrous form, or polymorphism. Figure 4 depicts the latter spectrum; comparison between the two spectra reveal minor differences in the range of 4000-3000 cm^{-1}, indicating that polymorphism is more likely.

References

1. Provigil® Patient Information Leaflet.

2. Cephalon, Inc. Analytical Test Method, MET-0023-1538, Version 1.

Figure 2 – Mass Spectrum of Modafinil-TMS



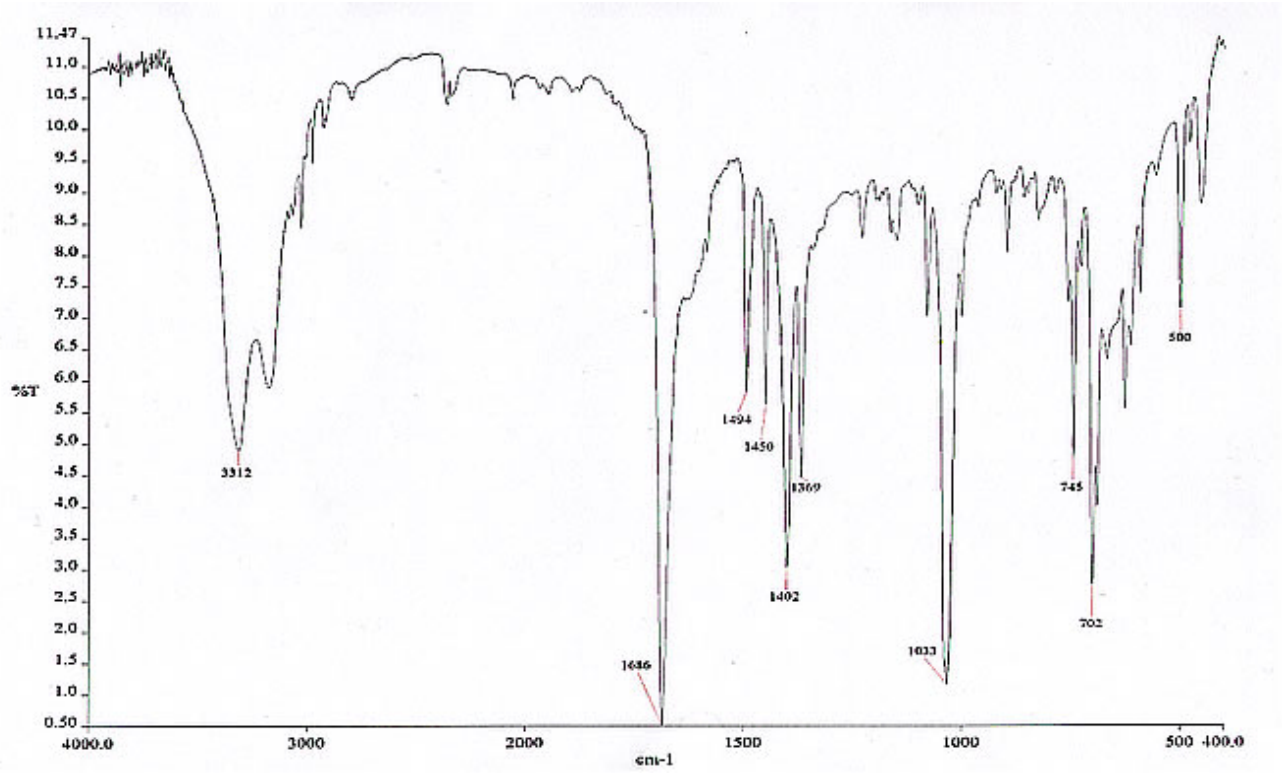


Figure 3 – Infrared Spectrum of Neat Modafinil

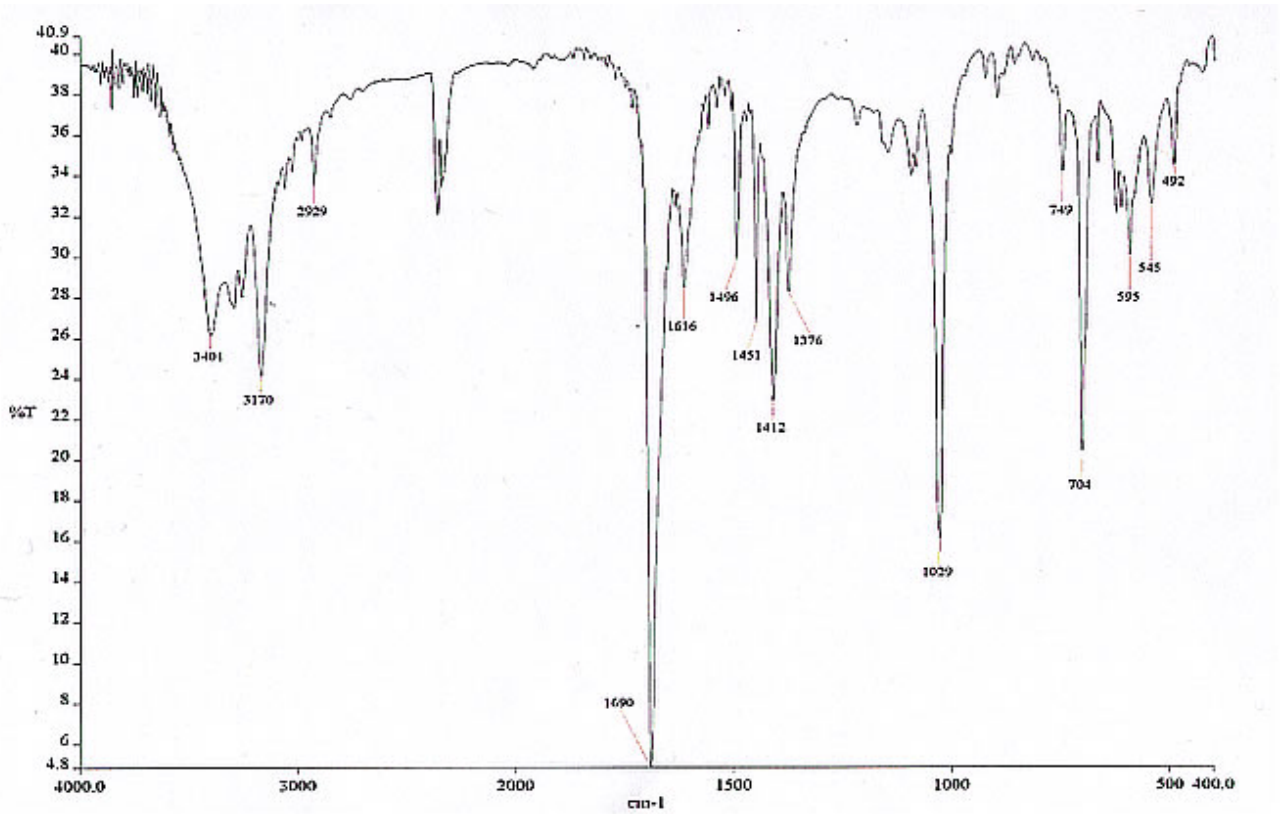


Figure 4 – Infrared Spectrum of Extracted Modafinil