Synthesis of *trans*-4-Methylaminorex from Norephedrine and Potassium Cyanate

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ABSTRACT: An unusual and previously undocumented synthesis for *trans*-4-methylaminorex was determined to be in use at a clandestine laboratory. Conventional references unanimously describe the use of norephedrine (phenylpropanolamine, 2-amino-1-phenylpropan-1-ol) and cyanogen bromide to synthesize *cis*-4-methyl-aminorex. In this case, use of norephedrine and potassium cyanate gave predominantly *trans*-4-methylaminorex. This new synthesis is explored, and its intermediates and byproducts are characterized.

KEYWORDS: 4-Methylaminorex, Oxazoline, Norephedrine, Phenylpropanolamine, Potassium Cyanate, Diastereomers, Clandestine Laboratory, Controlled Substance Analogue, Isomer, Forensic Chemistry

Introduction

In December 2004, a clandestine laboratory raid was conducted at a private residence in Ft. Lauderdale, Florida. The operator was an educated chemist (degree in Chemical Engineering). In his post-Miranda statements, he indicated that he had been synthesizing "Euphoria" (4-Methylaminorex, also known as: U4Euh, Ice*, 4-MAR, Intellex) in his home since June 2004, and stated that he was capable of producing batches as large as 1 kilogram. He also admitted to manufacturing lesser quantities of amphetamine, methamphetamine, and 3,4-methylene-dioxymethamphetamine. The chemicals and materials seized at the site supported his claims.

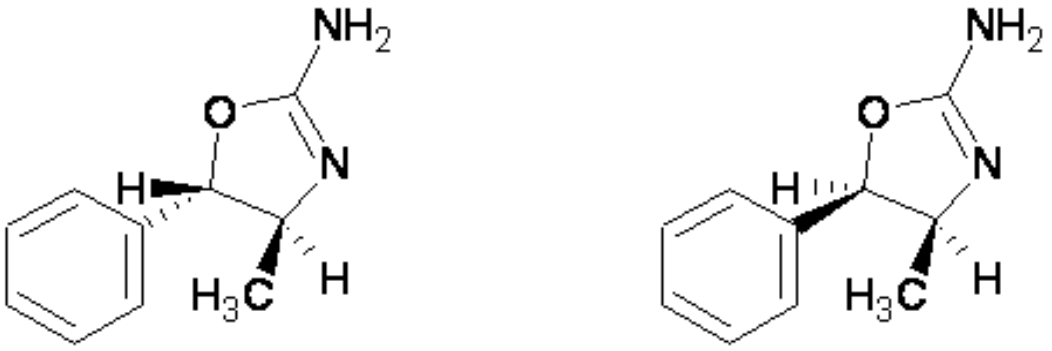
Of particular interest was 20 kilograms of a white powder alleged to be potassium cyanate (later confirmed to be a cyanate salt (cation not identified)). This compound had never been previously reported as a primary reagent at a clandestine laboratory. By the cook's account, he followed an internet recipe for synthesis of *trans*-4-methyl-aminorex from norephedrine and potassium cyanate.

This statement was surprising in that exhaustive literature searches indicated that the only reported syntheses starting with norephedrine used cyanogen bromide (not potassium cyanate) and produced *cis* (not *trans*) 4-methylaminorex [1]. The internet recipe (which had been posted on a website dedicated to drug abuse) was derived from the work of Fodor and Koczka [2], who investigated the stereochemistry of the conversion of 2-ureidoalcohols to oxazolidines. Included were the conversions of ephedrine and pseudoephedrine to the corresponding 2-ureidoalcohols, followed by their cyclization to their corresponding oxazolidines. Extrapolating from these results, the internet author theorized that the same reaction sequence could be applied to norephedrine, resulting in *trans*-4-methylaminorex [3] (Figure 1).

Klein *et al*. reported that the cyanogen bromide method is stereoselective and proceeds with retention of configuration at the benzylic carbon (C-1) of norephedrine [4]. Thus, norephedrine produces *cis*-4-methyl-

[* *In the late 1980's and early 1990's, "Ice" was a street name for 4-methylaminorex. Since then, however, it has shifted to a street name for high purity methamphetamine hydrochloride in large crystal form*.]

aminorex and norpseudoephedrine yields *trans*-4-methylaminorex (Figure 1). Therefore, if the classic synthesis (with cyanogen bromide) had been used, the *trans* isomer could only have been synthesized from norephedrine if stereochemical inversion was first performed on norephedrine to produce norpseudoephedrine [4]. This "stereoinversion" requires a tedious series of steps that is unlikely to ever be attempted in a clandestine setting. In contrast, in the potassium cyanate synthesis, *trans*-4-methylaminorex is allegedly generated directly from norephedrine without preliminary "stereoinversion" at C-1.



trans-4-Methylaminorex *cis*-4-Methylaminorex

Figure 1. The Diastereomers of 4-Methylaminorex (the Corresponding Enantiomers Have Been Omitted for Clarity).

Analysis of the seized exhibits confirmed that *trans*-4-methylaminorex was in fact the major product. Herein, the synthesis of *trans*-4-methylaminorex from norephedrine and potassium cyanate is characterized.

Legal Issues

When 4-methylaminorex was first temporarily controlled [5] in the summer of 1987, very little was known regarding the individual optical isomers of both the *cis* and *trans* forms [6]. Since the clandestine procedure employed at the time resulted in the production of the racemic *cis* isomer, there was no evidence that the *trans* isomer had any abuse potential, much less if it even existed in the clandestine market. As a result, only the *cis* isomer was explicitly controlled [7]. This marked the first and to date the only time a specific diastereomer has been listed as a controlled substance.

The production of *trans*-4-methylaminorex therefore raised an interesting legal issue. Since *cis*-4-methylaminorex is a Schedule I controlled substance, it can be inferred that "...its salts, isomers, and salts of isomers..." would also be Schedule I controlled substances. However, the term isomer, as defined in 21 CFR 1300.01(b)(21) means "...the optical isomer except as used in... [Schedules I(d) and II(b)]." *cis*-4-Methylaminorex is specifically listed as a stimulant in Schedule I(f). Since *trans*-4-methylaminorex is not an optical isomer of *cis*-4-methylaminorex, the "isomer" provision does not apply and it is not formally controlled.

Therefore, the legal issue is whether *trans*-4-methylaminorex is a controlled substance analogue. Under the Controlled Substance Analogue provision of the Controlled Substances Act, it must first be demonstrated that *trans*-4-methylaminorex has a chemical structure that is substantially similar to the chemical structure of controlled substance in Schedule I or II. The controlled substance in this case is *cis*-4-methylaminorex. The diastereomeric relationship between these two compounds clearly satisfies the requirements of the first "prong" of the provision.

Secondly, *trans*-4-methylaminorex must exhibit a stimulant effect that is substantially similar to or greater than the stimulant effect of *cis*-4-methylaminorex -OR- must be represented or intended to have a stimulant effect that is substantially similar to or greater than the stimulant effect of *cis*-4-methylaminorex. The rank order of potencies of the four enantiomers of 4-methylaminorex has been shown to be:

trans-4S,5S > *cis*-4S,5R ~ *cis*-4R,5S > *trans*-4R,5R

in several pharmacological studies [6,8-11]. One group of researchers suggested that the *trans*-4S,5S- isomer may have sufficient abuse potential to warrant its classification as a Schedule I controlled substance [10]. Thus, the second "prong" of the Controlled Substance Analogue provision is also met.

Finally, the *trans*-4-methylaminorex seized in this case was specifically stated by the clandestine chemist to be "Euphoria," which is the generic street nomenclature for 4-methylaminorex without any stereochemical (*cis* or *trans*) designation [12,13]. Therefore, all three "prongs" of the Controlled Substance Analogue provision are satisfied, and it is virtually certain that Federal prosecution of *trans*-4-methylaminorex as a "controlled substance analogue" would be successful. In this case, the clandestine chemist was convicted of manufacture of a controlled substance.

Experimental

Reagents were obtained from Sigma-Aldrich, and were used without further purification.

Gas chromatograph/mass spectrometry (GC/MS) data was obtained from an Agilent 6890 Gas Chromatograph (GC) coupled to an Agilent 5973 Mass Selective Detector (MSD) operating in electron impact (EI) mode. The mass spectral scan range was *m/z* 34 to 520. The ion source and quadrupole temperature zones were set to 230 °C and 150 °C, respectively. The interface was heated to 280 °C. The GC was equipped with a 30 meter ZB-1 column with an internal diameter of 0.25 mm and a 0.25 μm film thickness (Phenomenex). The inlet was set to 250 °C and the carrier gas was Helium with a constant flow rate of 1.3 mL/min. The oven was ramped from 100 °C - 295 °C at 35 °C/min, with a 6.43 minute hold at 295 °C, for a total run time of 12 minutes.

Fourier Transform ^{1}H Nuclear Magnetic Resonance (FT-NMR) analyses were performed on a Varian Mercury-plus spectrometer operating at 400 MHz. Eight scans were collected for each sample. Internal reference standards were not used.

Fourier Transform Infrared (FTIR) spectra were collected on a Thermo-Nicolet Nexus 470 FTIR equipped with a SensIR Technologies Durascope 3-bounce ATR attachment. The scan range was 4000 cm^{-1} to 550 cm^{-1}, with a 4 cm^{-1} resolution. 32 scans were collected for each sample.

Molecular drawings, 3-D optimizations, and IUPAC names were generated with ACD Labs ChemSketch software, version 7.0.

Preparation of *trans*-4-Methylaminorex

Because this synthesis is no longer readily accessible on the internet, experimental details have been omitted, in accordance with *Microgram Journal* policy. Law enforcement personnel with a legitimate need to know should contact the authors for further information.

Results and Discussion

It is uncommon for trained, professional chemists to produce illicit drugs. It is even more unusual that a genuinely new clandestine manufacturing process is encountered. It was helpful in this case that the cook not

only documented his reaction, batch, and scale-up information, but also was willing to discuss his "work" in a proffer hearing. As detailed above, the synthesis of *trans*-4-methylaminorex was performed using a procedure partially described on the internet and further expanded by the clandestine chemist [14]. A scaled-down version of this method was used in this study.

Analysis of the reaction mixture from the illicit method after the first 2.5 hours revealed the presence of N-(2-hydroxy-1-methyl-2-phenethyl)urea, 4-methyl-5-phenyl-1,3-oxazolidin-2-one and unreacted norephedrine (see Figure 2). No *trans*-4-methylaminorex was detected up to this point.

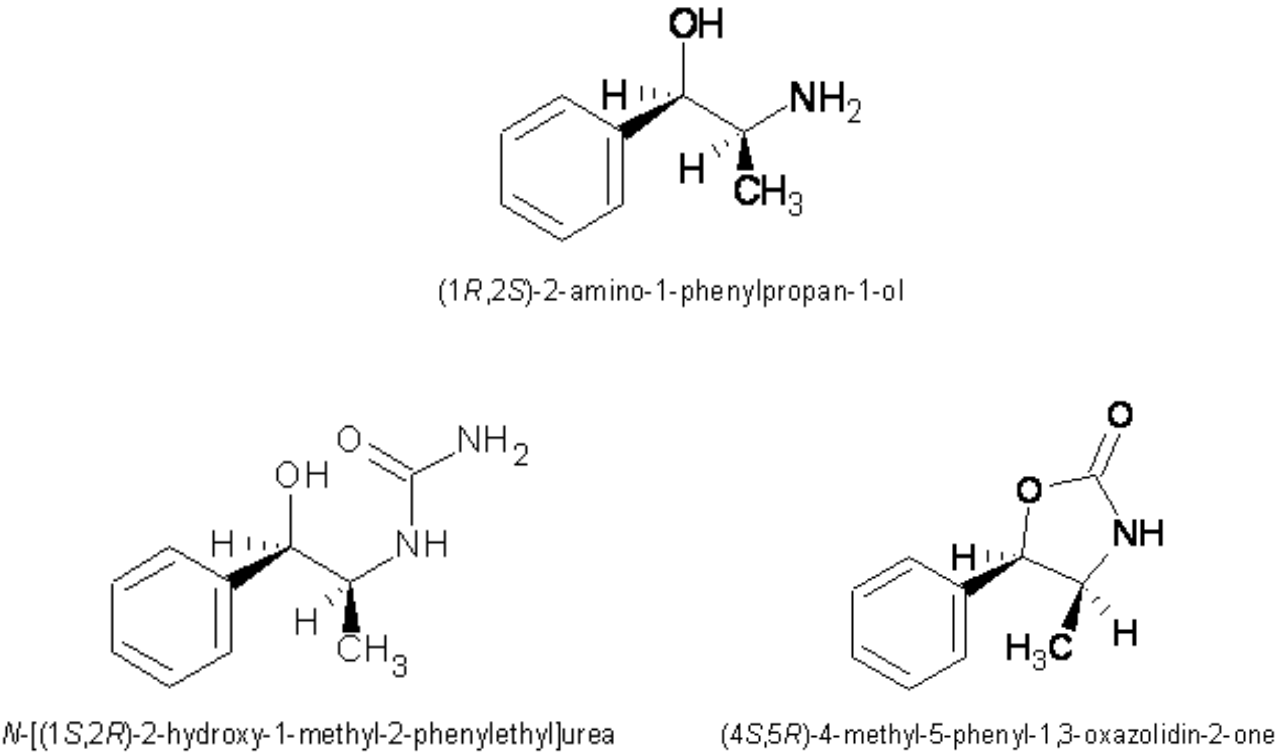


Figure 2. The Components of the Reaction Mixture from the Illicit Method after the First 2.5 Hour Reflux Period. Only One of Each Enantiomeric Pair Is Shown.

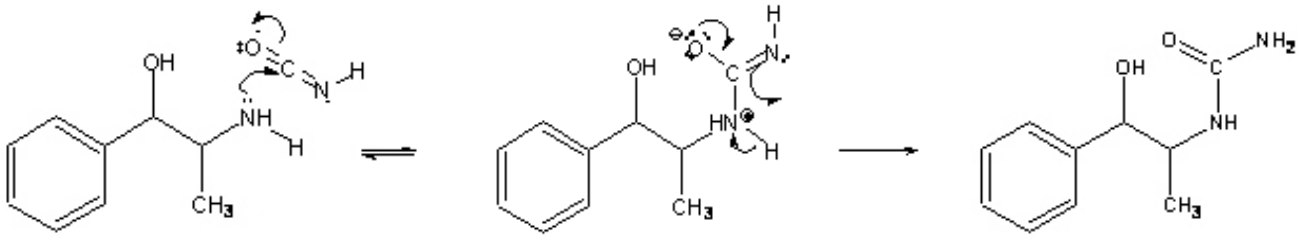
The final reaction mixture was similar in composition to the actual evidence seized from the clandestine laboratory. In addition to *trans*-4-methylaminorex, small amounts of *cis*-4-methylaminorex were also found. The crude mixture also contained 4-methyl-5-phenyl-1,3-oxazolidin-2-one, N-(2-hydroxy-1-methyl-2-phenethyl)urea, and unreacted norephedrine. For this study, this mixture was cleaned up prior to isolation of the final product.

It is likely that the synthesis occurs through the intermediate 2-ureidoalcohol *alpha*-methyl-*beta*-hydroxy-phenethylurea [15] which cyclizes to the oxazoline with inversion of configuration at C-1 [2]. Therefore, the synthesis was also conducted by the initial production and isolation of N-(2-hydroxy-1-methyl-2-phenethyl)urea intermediate. The general stoichiometric reaction is shown below:

$$\text{Norephedrine} + \text{Potassium Cyanate} + H_2O \rightarrow \text{Norephedrine-Urea} + KOH \qquad \text{(Equation 1)}$$

The pH of the solution immediately upon complete dissolution of the reactants was about 5-6. After the reaction had gone to completion, the pH of the remaining liquid was about 10-11, supporting Equation 1.

It is generally accepted that the reaction of cyanates in water does not proceed via the cyanate but via isocyanic acid [16-18]. This scenario (Scheme 1) involves nucleophilic attack by the amino group of norephedrine on the somewhat positively polarized carbon of isocyanic acid, with a subsequent proton shift from the amino group of norephedrine.



Scheme 1

This mechanism shows that the chiral centers remain unchanged during the formation of the urea intermediate. Since norephedrine produces *trans*-4-methylaminorex, inversion of configuration must occur via an intramolecular SN_2-type attack at the benzylic carbon by the carbonyl group of the urea portion of the intermediate. This can occur because N-(2-hydroxy-1-methyl-2-phenethyl)urea can achieve a favorable conformation to allow the reaction to occur [2]. The pseudo-5-membered ring conformation places the carbonyl oxygen in proximity to the benzylic carbon, enabling the SN_2 type attack. This conformation is depicted in the 3-D image shown below (Figure 3).

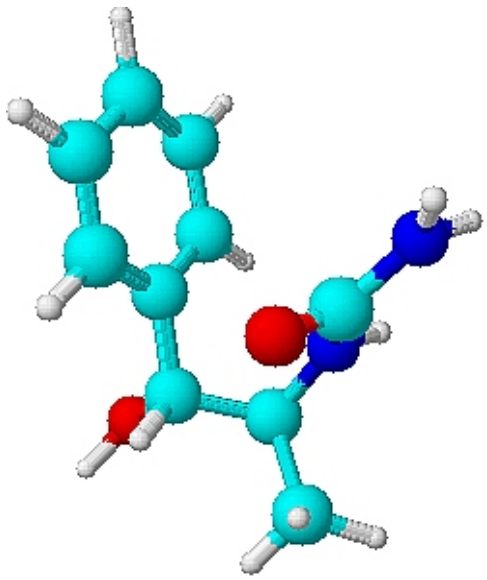


Figure 3. Three Dimensional Image of N-[(1S,2R)-(2-Hydroxy-1-methyl-2-phenethyl)]urea in a Conformation Enabling SN_2 Attack at the Benzylic Carbon (C-2) by the Ureido Carbonyl.

Note the changes in the numbering system of the various compounds. The benzylic carbon in norephedrine is designated as C-1. The same carbon is labeled as C-2 in the urea intermediate, and as C-5 in 4-methylaminorex. Thus, the (1R,2S) isomer of norephedrine becomes the (1S,2R) isomer of the urea intermediate, which is subsequently converted to the *trans*-(4S,5S)- isomer of 4-methylaminorex.

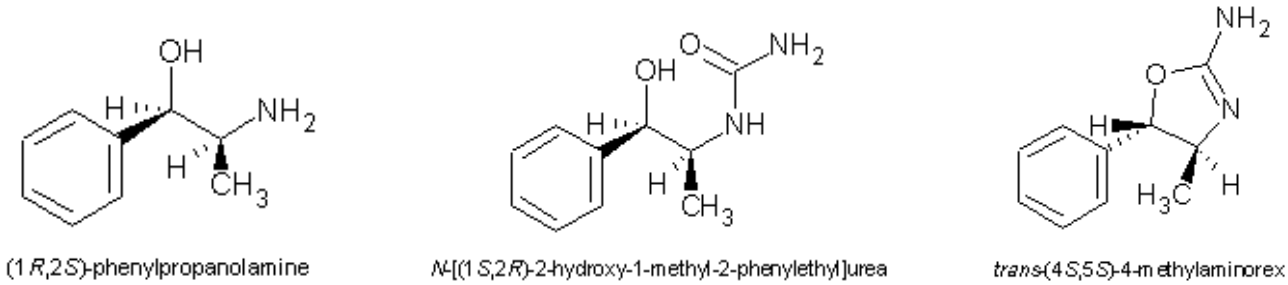


Figure 4. Summary of Absolute Configurations of Chiral Centers of Key Molecules. One of Each Enantiomeric Pair Is Shown.

The small amount of the oxazolidinone detected in the reaction mixture at the half-way point is probably formed by the attack of the benzylic hydroxyl on the carbonyl of the urea (Figure 5), liberating a molecule of ammonia into the solution (presumably as NH_4OH), which may also contribute to the already moderately high pH observed at the end of the reaction (Equation 1).

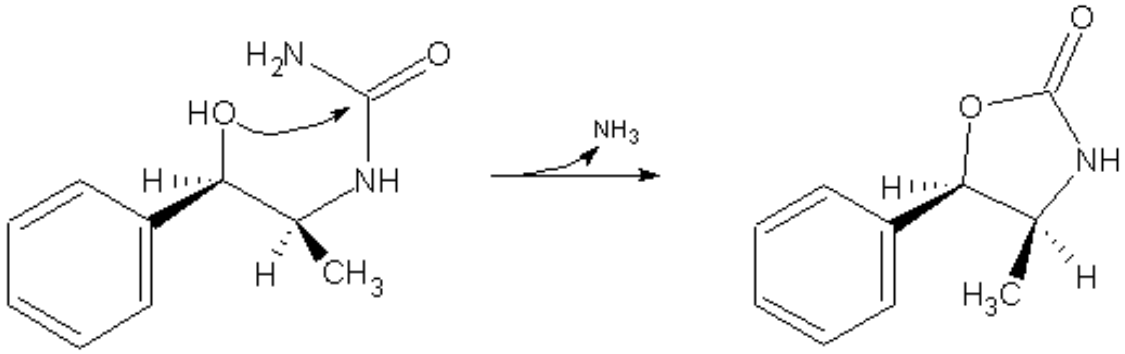


Figure 5. Formation of *cis*-4-Methyl-5-phenyl-1,3-oxazolidin-2-one from the Urea Intermediate.

This results in retention of configuration. The phenyl and methyl groups of the oxazolidinone by-product must be *cis* since no change in the configuration at C-4 or C-5 could occur. This is confirmed by NMR data. The coupling constant for the C-5 proton is consistent with a *cis* configuration ($J_{4\text{-}5}$ = 8.02 Hz). This value is comparable to literature values for the electronically similar 3,4-dimethyl-2-imino-5-phenyloxazolidine [19].

Acknowledgements

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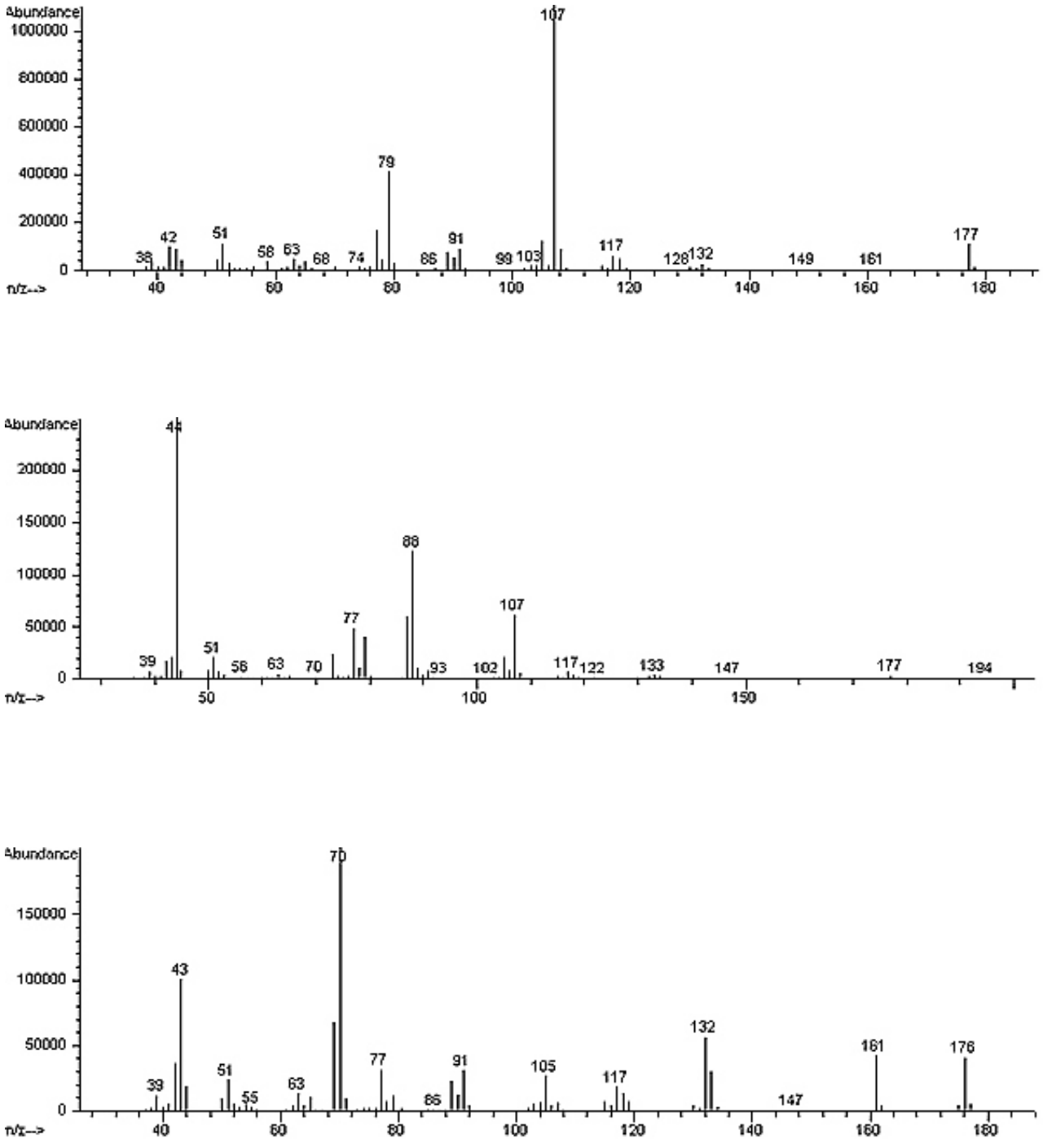

Figure 6. EI Mass Spectra. Top: 4-Methyl-5-phenyl-1,3-oxazolidin-2-one; Middle: N-(2-Hydroxy-1-methyl-2-phenethyl)urea; Bottom: *trans*-4-Methylaminorex.

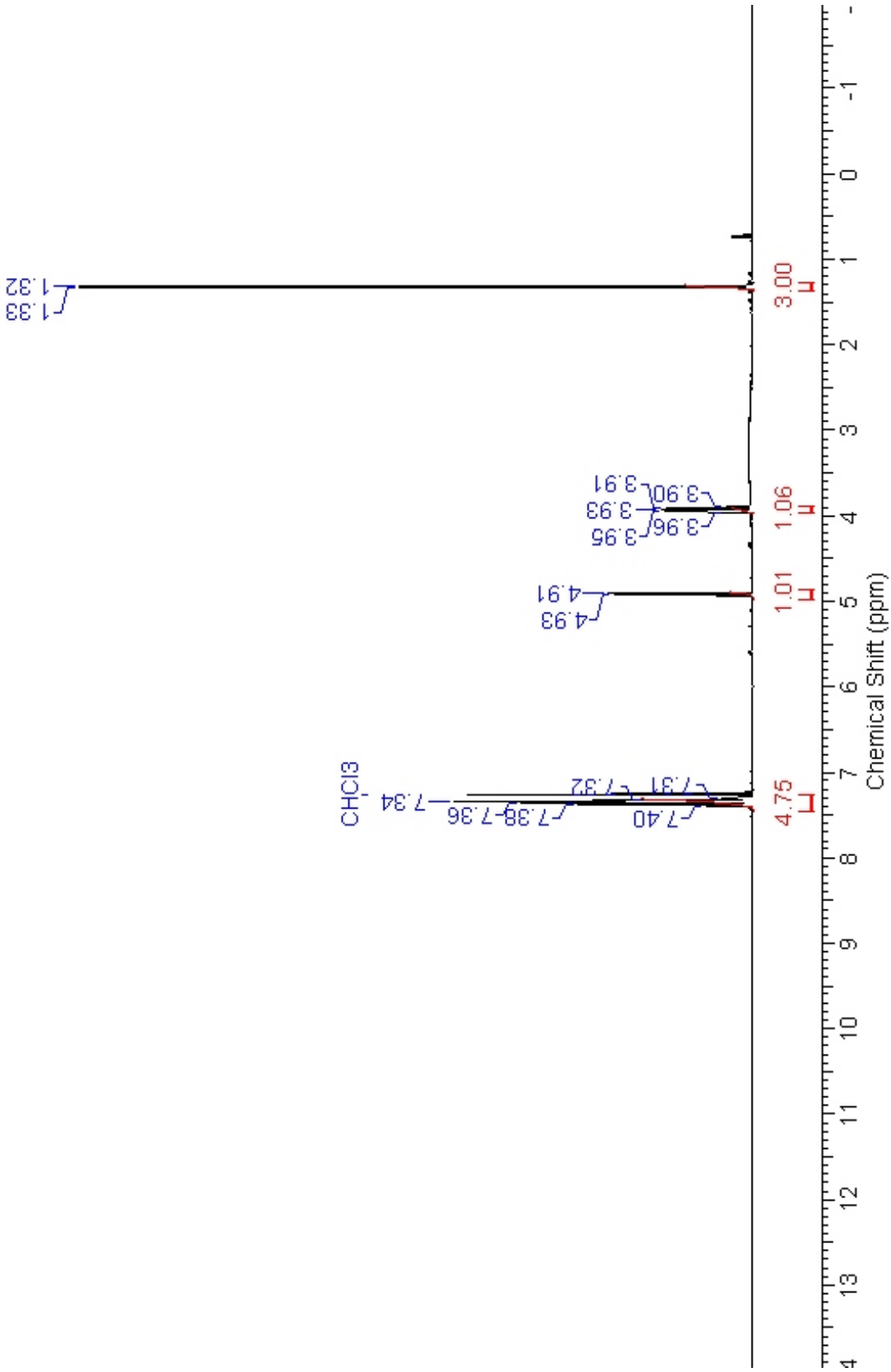

Figure 7. [1]H NMR, 8 scans, *trans*-4-Methylaminorex.

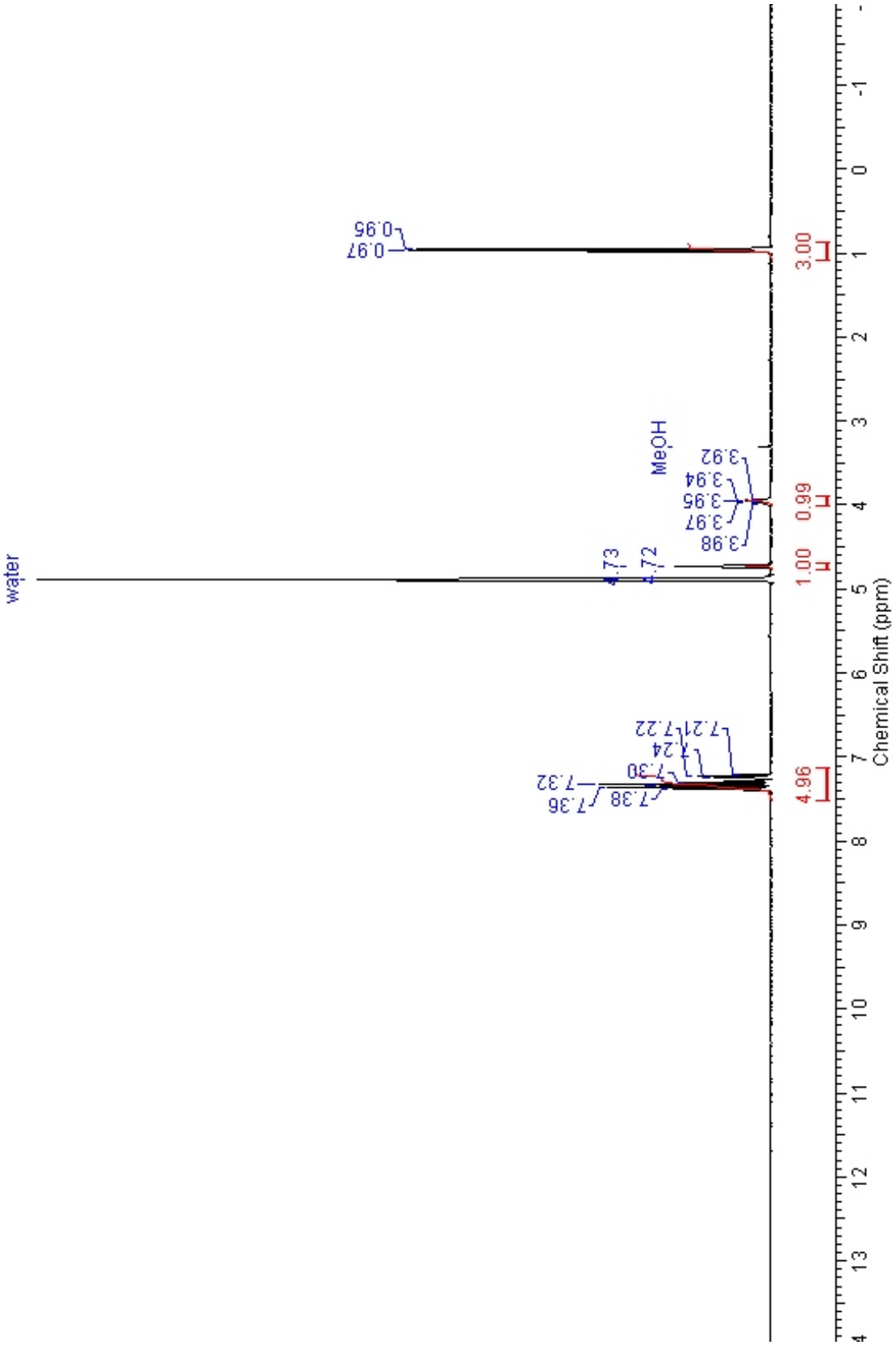

Figure 8. [1]H NMR, 8 scans, N-(2-Hydroxy-1-methyl-2-phenethyl)urea.

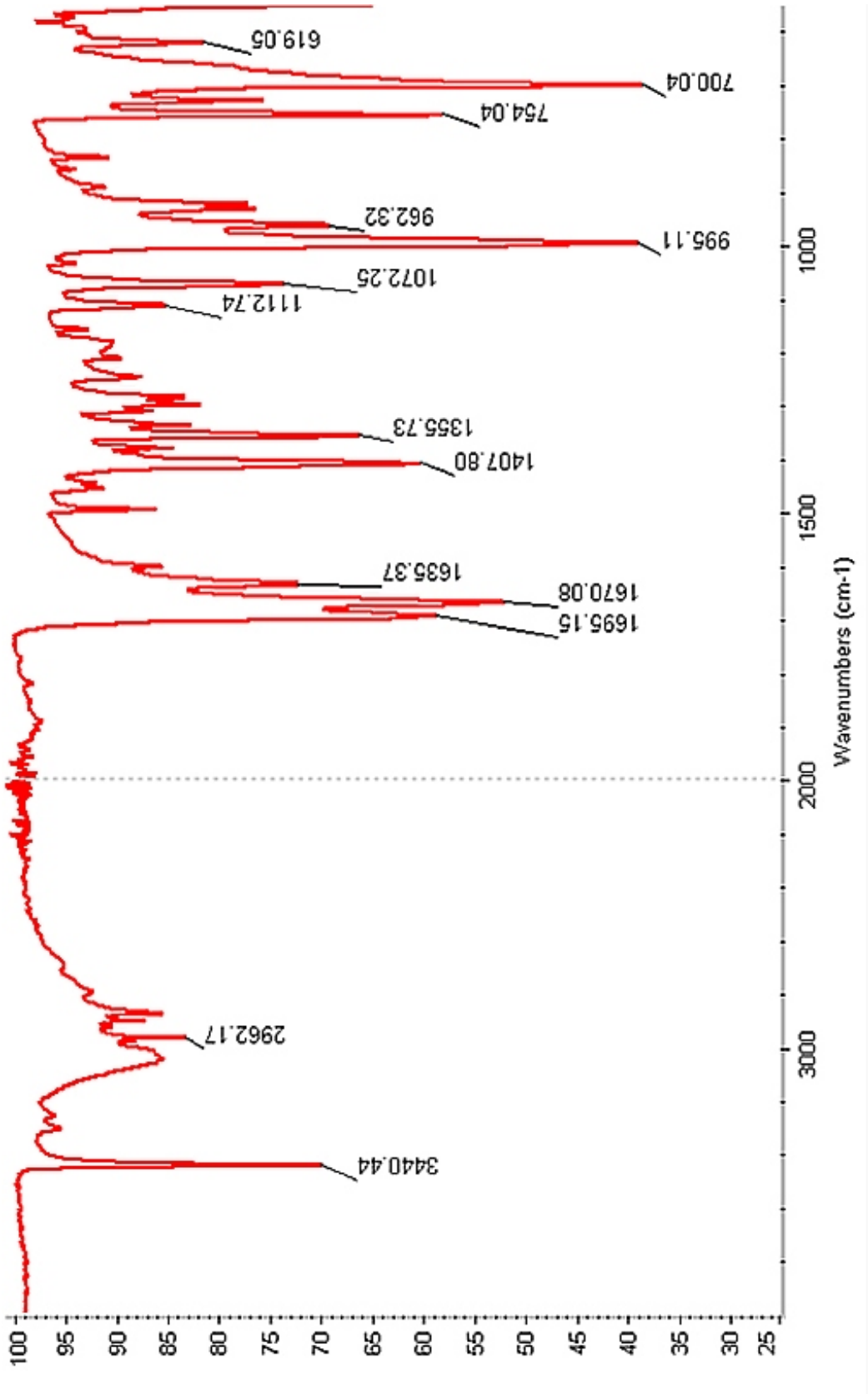

Figure 9. FTIR. 32 scans, *trans*-4-Methylaminorex.

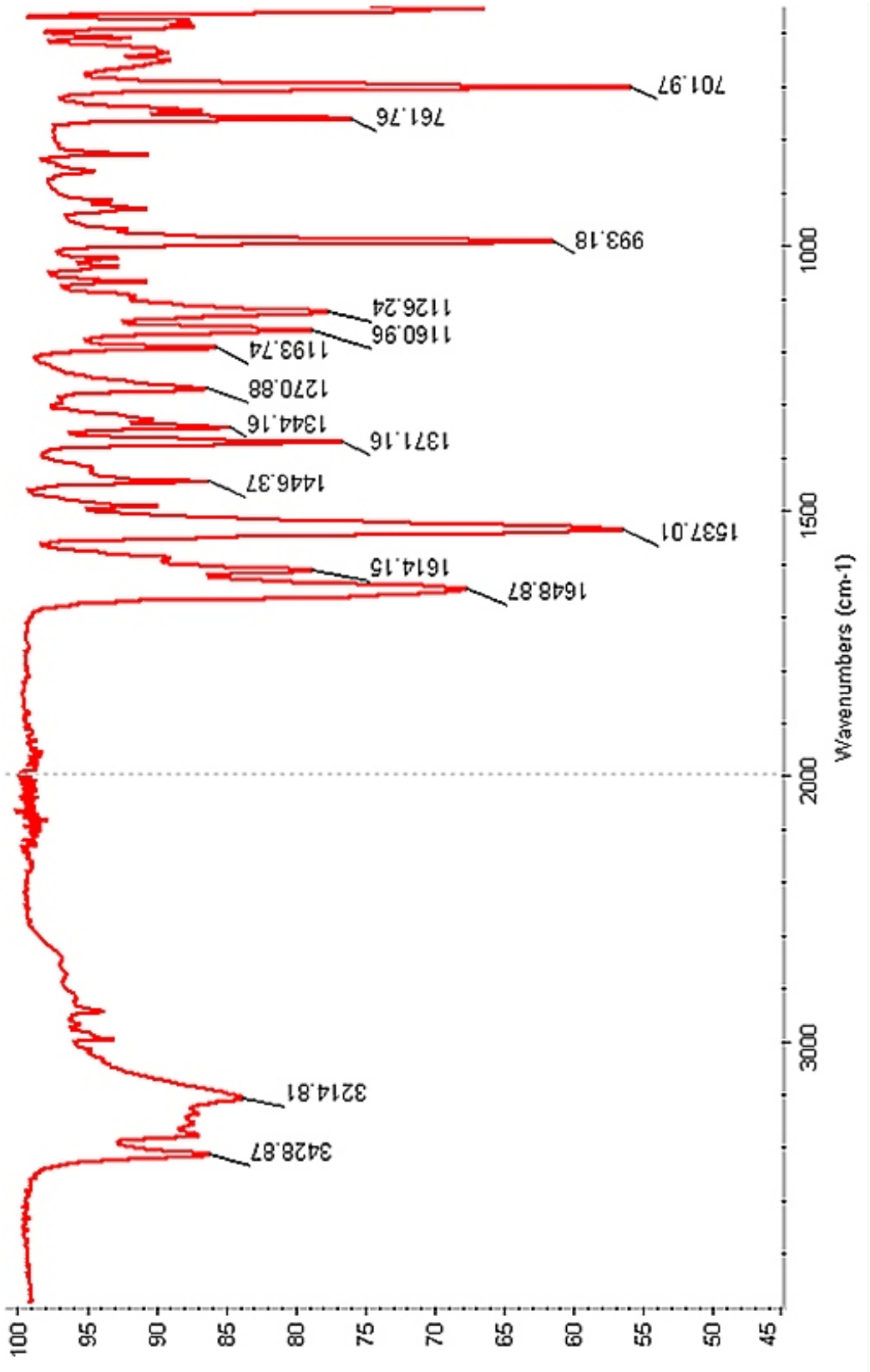

Figure 10. FTIR. 32 scans, N-(2-Hydroxy-1-methyl-2-phenethyl)urea.