

Spectrophotometric and Liquid Chromatographic Identification of 3,4-Methylenedioxyphenylisopropylamine and Its *N*-Methyl and *N*-Ethyl Homologs

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3,4-Methylenedioxyphenylisopropylamine (MDA) is an hallucinogenic drug that somewhat resembles lysergic acid diethylamide (LSD) in its effects. Recently, widespread abuse of the *N*-methyl homolog (MDMA) of MDA has led to federal control. This article reports on the synthesis of the *N*-ethyl homolog (MDEA) of MDA as well as spectrophotometric and chromatographic methods for identification of the 3 homologs.

Over the years, 3,4-methylenedioxyphenylisopropylamine (3,4-methylenedioxyamphetamine; MDA), *N*-methyl-3,4-methylenedioxyphenylisopropylamine (3,4-methylenedioxymethamphetamine; MDMA), and *N*-ethyl-3,4-methylenedioxyphenylisopropylamine (3,4-methylenedioxy-*N*-ethylamphetamine; MDEA) have been abused to varying degrees. MDA has for a number of years been subject to federal control. There were no such controls over the homologs MDMA and MDEA until June 1985 when the Drug Enforcement Administration (DEA) placed MDMA, or Ecstasy as it is known on the street, under a 1-year emergency Schedule I controlled-substance classification. MDEA has not met with such significant abuse as to warrant federal control, but yet it and other *N*-substituted amines of MDA, such as MDMA, fall into the rapidly expanding category of drugs referred to as "designer drugs."

Martin and Sloan (1) categorized the effects of MDA as probably LSD-like but with other properties. At least one case has been reported in the scientific literature which involves a fatality after use of MDA (2). Since control of MDMA, a vociferous group of psychiatrists, psychologists, and scientists contend that MDMA has enormous therapeutic potential (3); however, not all researchers agree with these findings. MDMA has no currently accepted medical use in the United States since the Food and Drug Administration (FDA) has no investigational new drug applications, new drug applications, or approvals on file for MDMA. No manufacturer of MDMA is registered with FDA (U.S. Department of Justice, Drug Enforcement Administration, 1985, personal communication). At least one encounter with MDEA has been reported (I. M. Vallejo, 1982, personal communication). MDA, MDMA, and MDEA can all be produced in clandestine laboratories using methods similar to those used to produce methamphetamine.

The purpose of this paper is to report the results of infrared (IR) spectrophotometric and liquid chromatographic (LC) studies of the 3 amine homologs, MDA, MDMA, and MDEA.

Experimental

Reagents and Chemicals

Samples of 3,4-methylenedioxyamphetamine HCl (MDA) and 3,4-methylenedioxymethamphetamine HCl (MDMA) were

obtained from DEA. Phenylisothiocyanate (PIT) was obtained from Fisher Scientific Co.; LC grade methanol and acetic acid from J. T. Baker Chemical Co.; and 3,4-methylenedioxyphenyl-2-propanone from Fluka Chemical Corp. (255 Oser Ave, Hauppauge, NY 11788). Water was double distilled. Phosphate buffer pH 3.0 was prepared by mixing 9.2 g monobasic sodium phosphate (NaH_2PO_4) in 1 L double-distilled water and adjusting to pH 3.0 with 2N H_3PO_4 .

Apparatus

The liquid chromatograph was a modular system and consisted of a Waters Associates (34 Maple St, Milford, MA 01757) Model 6000A pump, Model U6K injector, Model 440 UV detector with dual wavelength accessory operated at 254 and 280 nm, and a Houston Instrument (8500 Cameron Rd, Austin, TX 78753) Omniscrite dual pen recorder. IR spectra were recorded on a Perkin-Elmer Model 1500 Fourier transform infrared (FTIR) spectrophotometer. Ultraviolet (UV) spectra were recorded on a Hitachi (Tokyo, Japan) 100-80 spectrophotometer. Nuclear magnetic resonance (NMR) spectra (^1H) were determined in DMSO (dimethyl sulfoxide) solution using a Varian T-60A spectrometer (Varian Instrument Group, 611 Hansen Way, Palo Alto, CA 94303). Elemental analyses (C, H, and N) were performed by Atlantic Microlab Inc., Atlanta, GA.

Chromatographic Procedures

Reverse phase separations were carried out on a 30 cm \times 3.9 mm id μ Bondapak C_{18} column (Water Associates) at ambient temperature. The analytical column was preceded by a 7 cm \times 2.1 mm id guard column dry-packed with Co:Pell ODS (Whatman Inc., 9 Bridewell Pl, Clifton, NJ 07014). Mobile phase flow rate was 1.5 mL/min. All separations were carried out with pH 3.0 phosphate buffer-methanol (5 + 1) or methanol-water-acetic acid (50 + 49 + 1). Amine hydrochlorides were detected at 0.2 AUFS, and PIT-derivatized amines at 1.0 AUFS. Absorbance ratios were calculated from the average peak height measurements of a minimum of 3 injections for each compound. Sample solutions of the amine hydrochlorides (1 mg/mL) were prepared in LC grade methanol and 10 μ L aliquots were injected into the liquid chromatograph.

Formation of Phenylisothiocyanate Derivatives

The phenylisothiocyanate (PIT) derivatives were prepared by extraction of ca 2 mg of each amine hydrochloride from dilute NaOH into CHCl_3 (2 \times 20 mL). Phenylisothiocyanate (10 μ L) was added to the organic layer and then the organic layer was evaporated to dryness under a stream of air. For LC studies, the residues were dissolved in 1 mL methanol and 7.5 μ L was injected into the liquid chromatograph. For

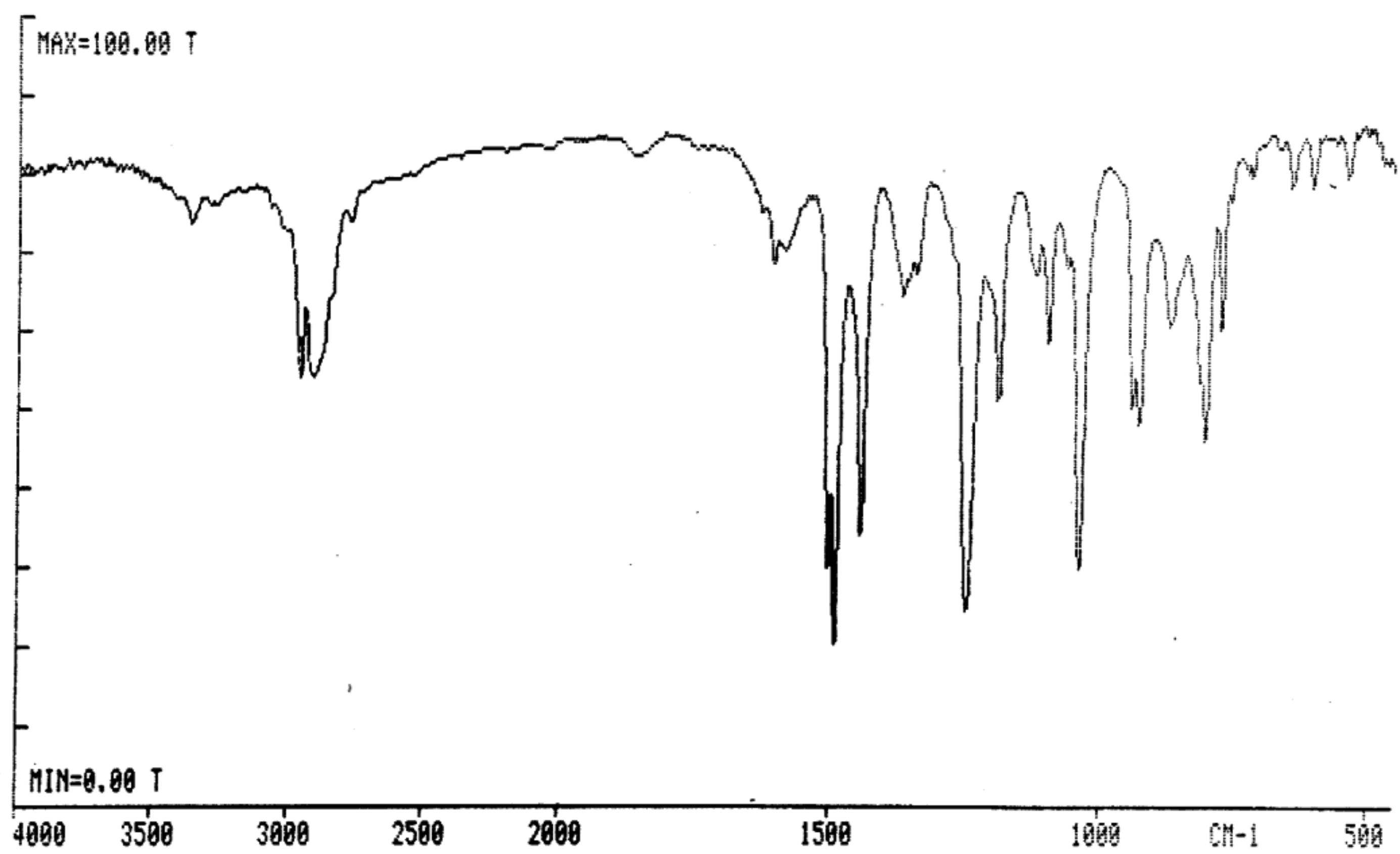


Figure 1. IR spectrum of MDA (base).

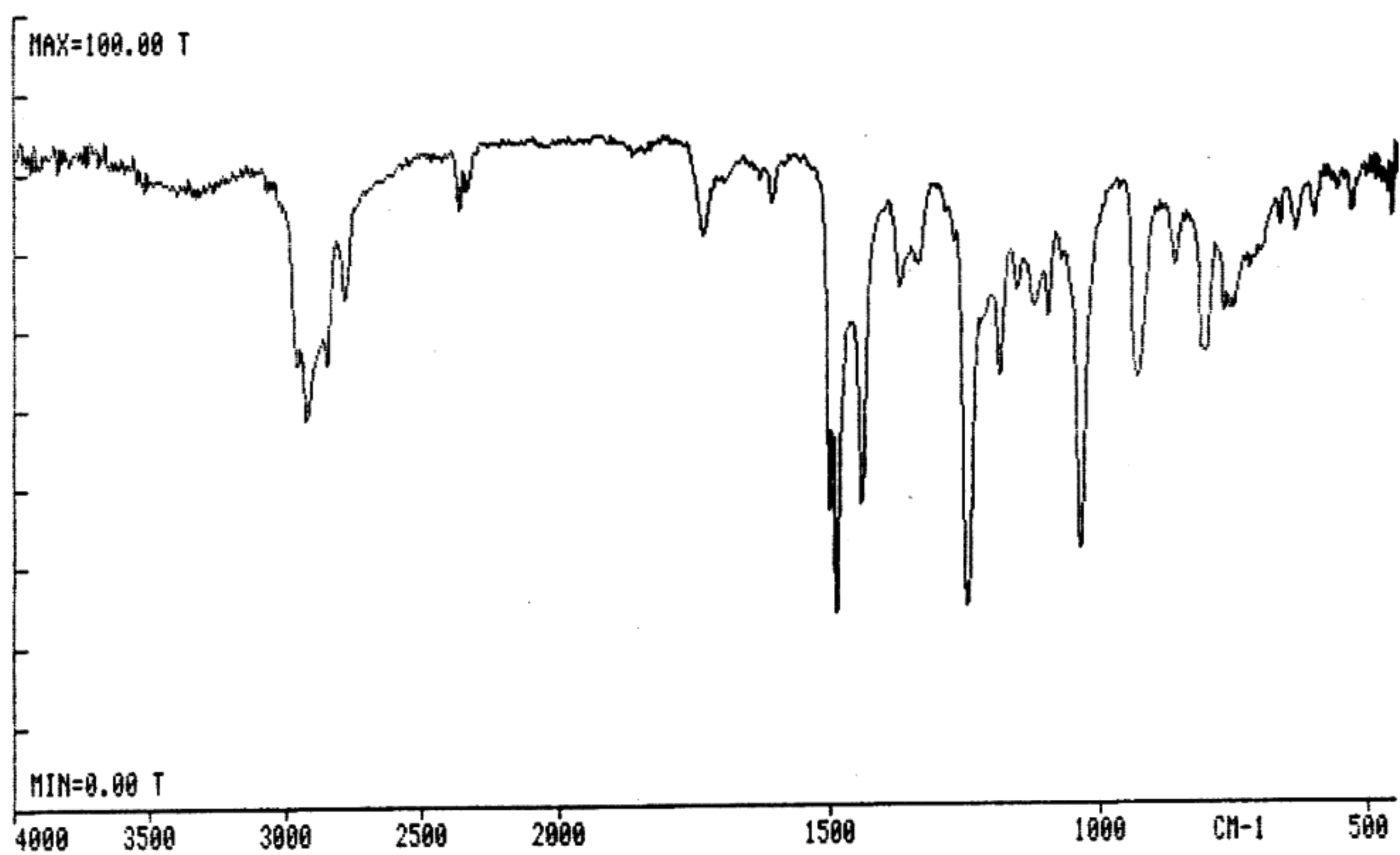


Figure 2. IR spectrum of MDMA (base).

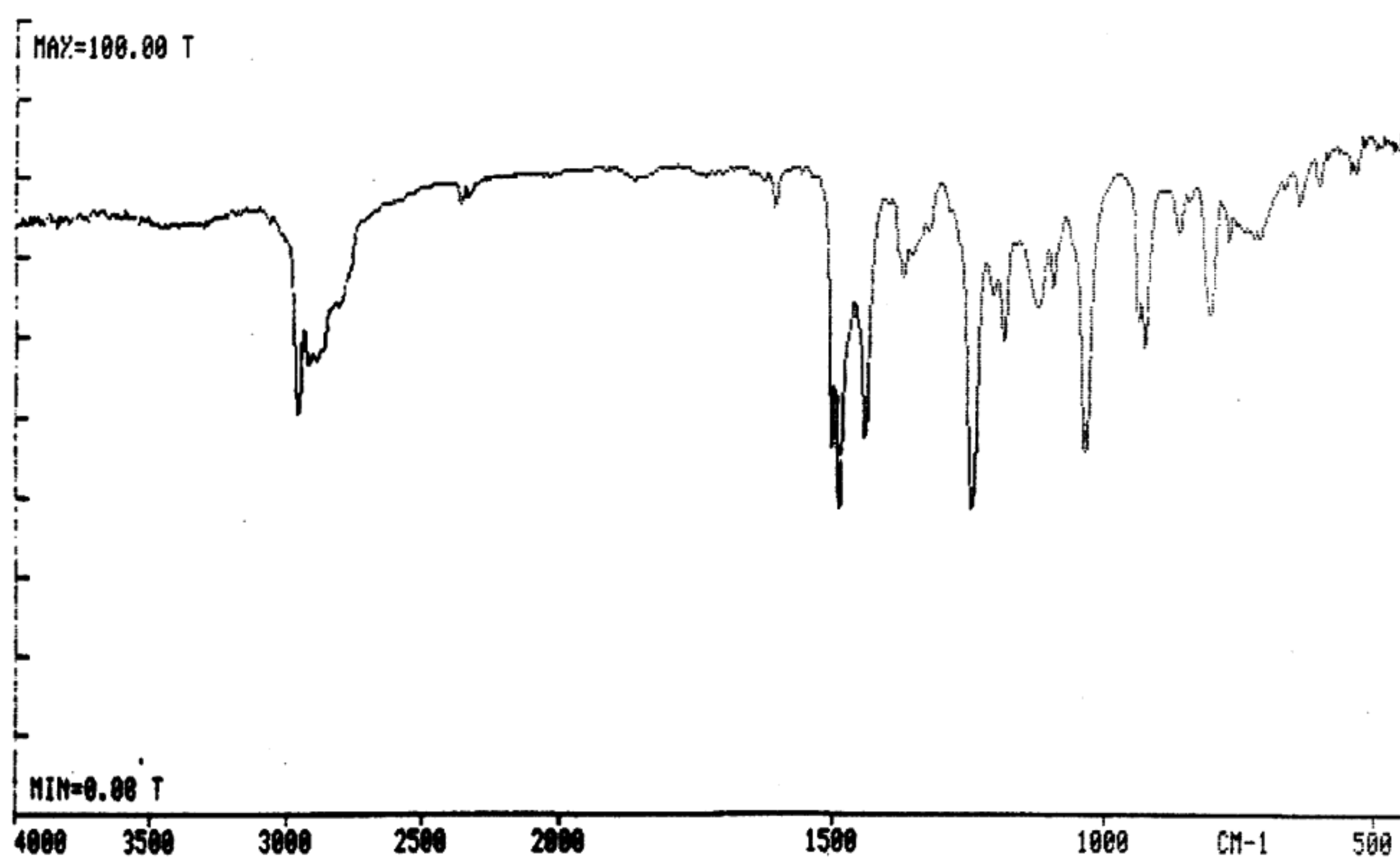


Figure 3. IR spectrum of MDEA (base).

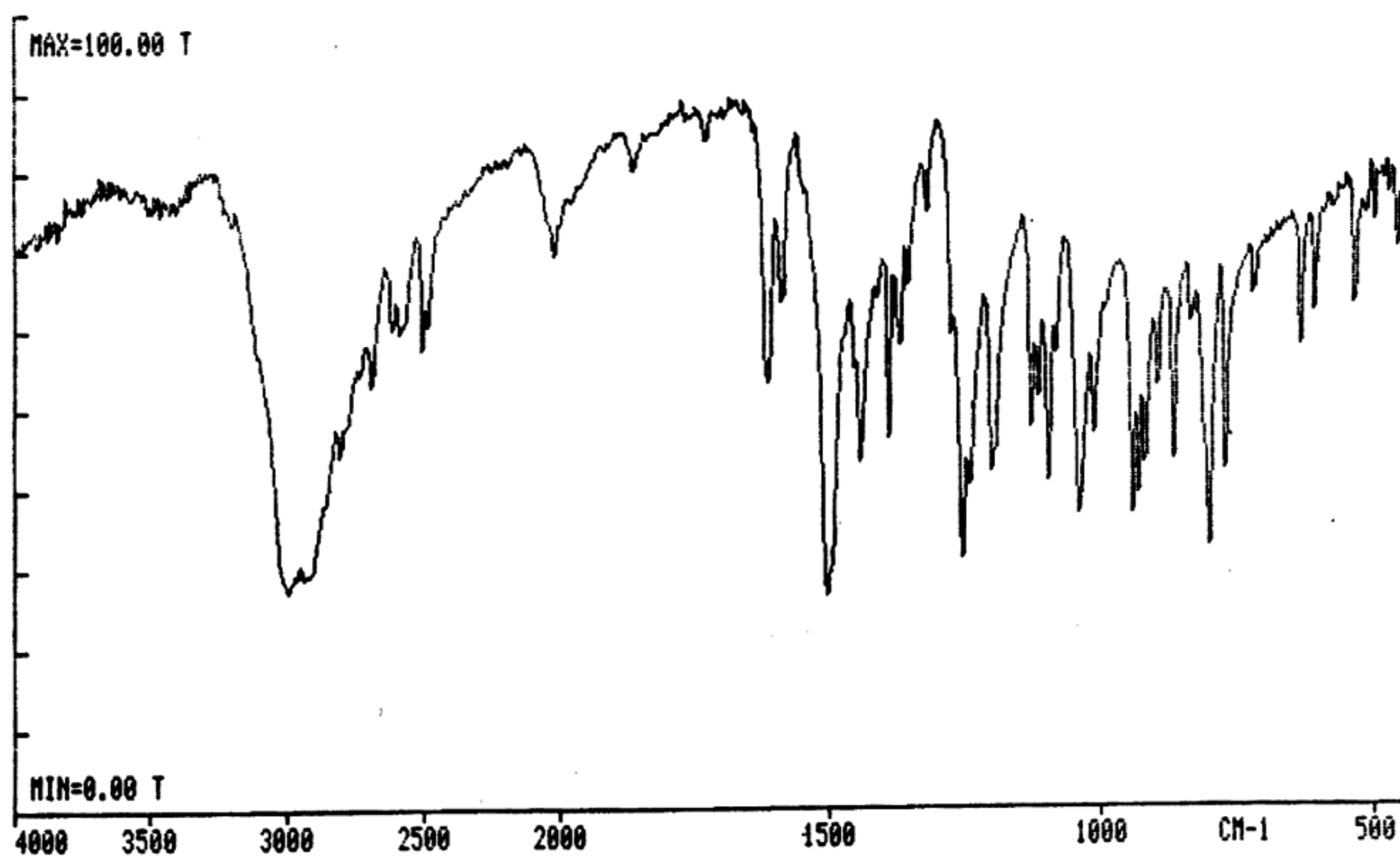


Figure 4. IR spectrum of MDA hydrochloride.

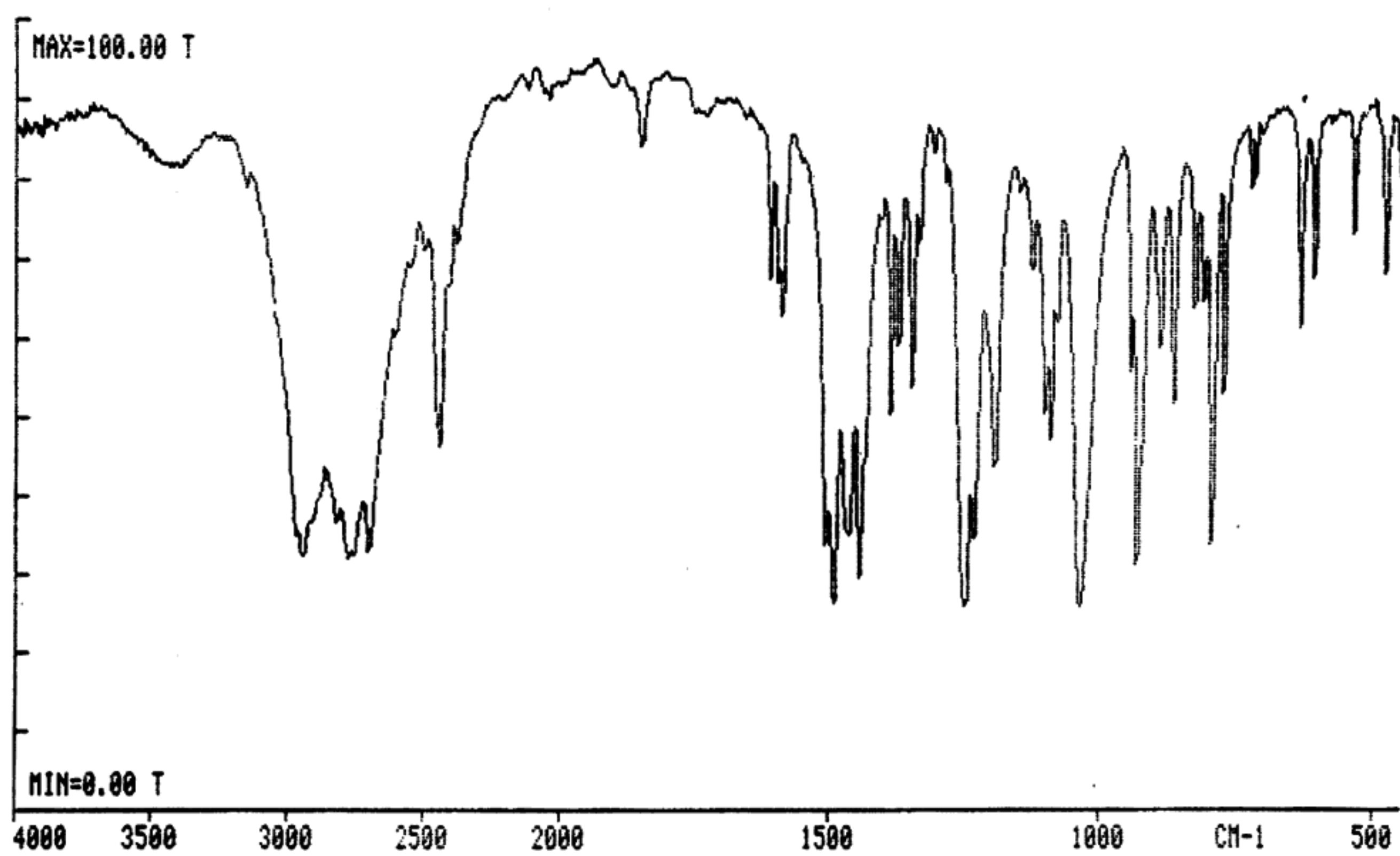


Figure 5. IR spectrum of MDMA hydrochloride.

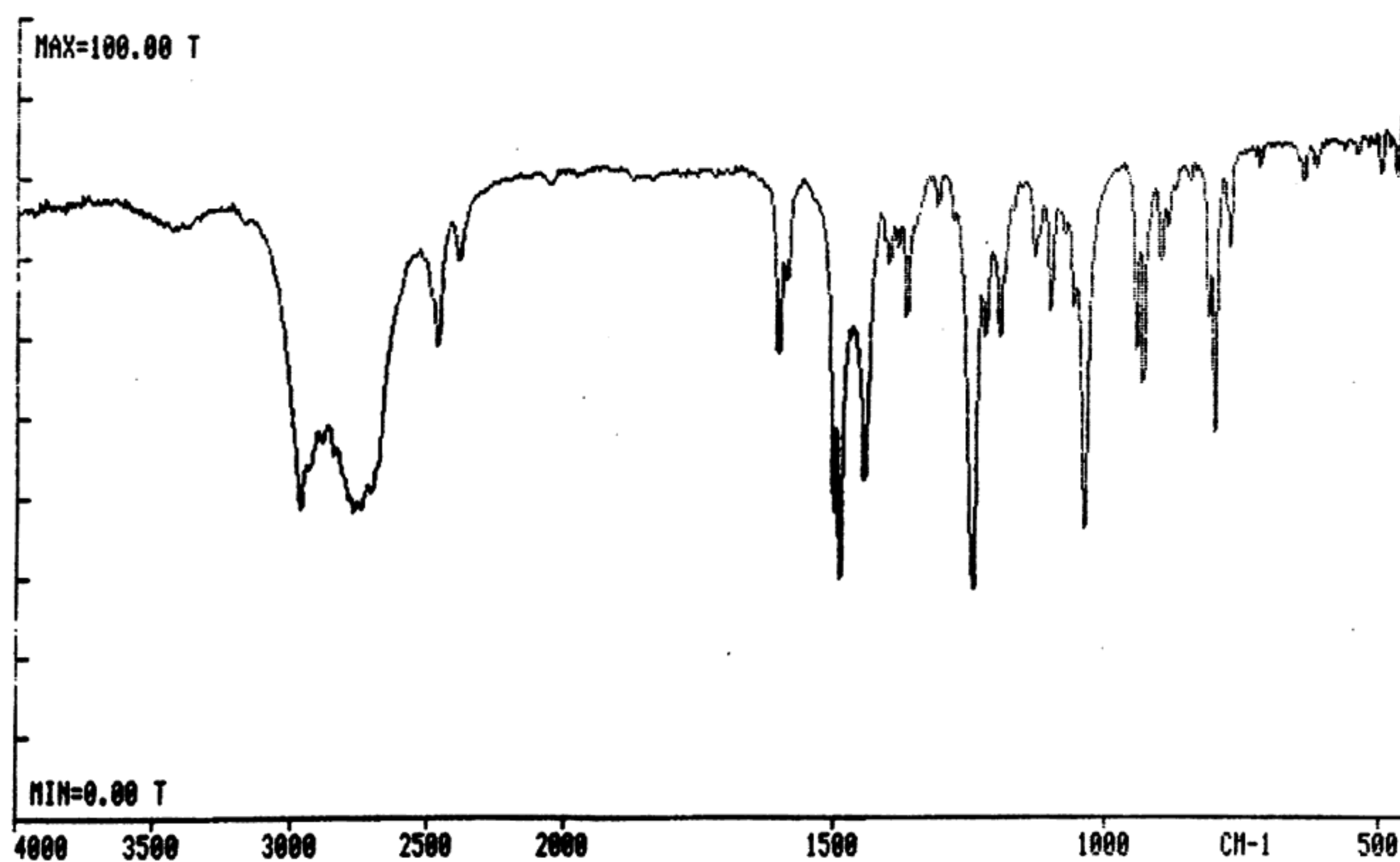


Figure 6. IR spectrum of MDEA hydrochloride.

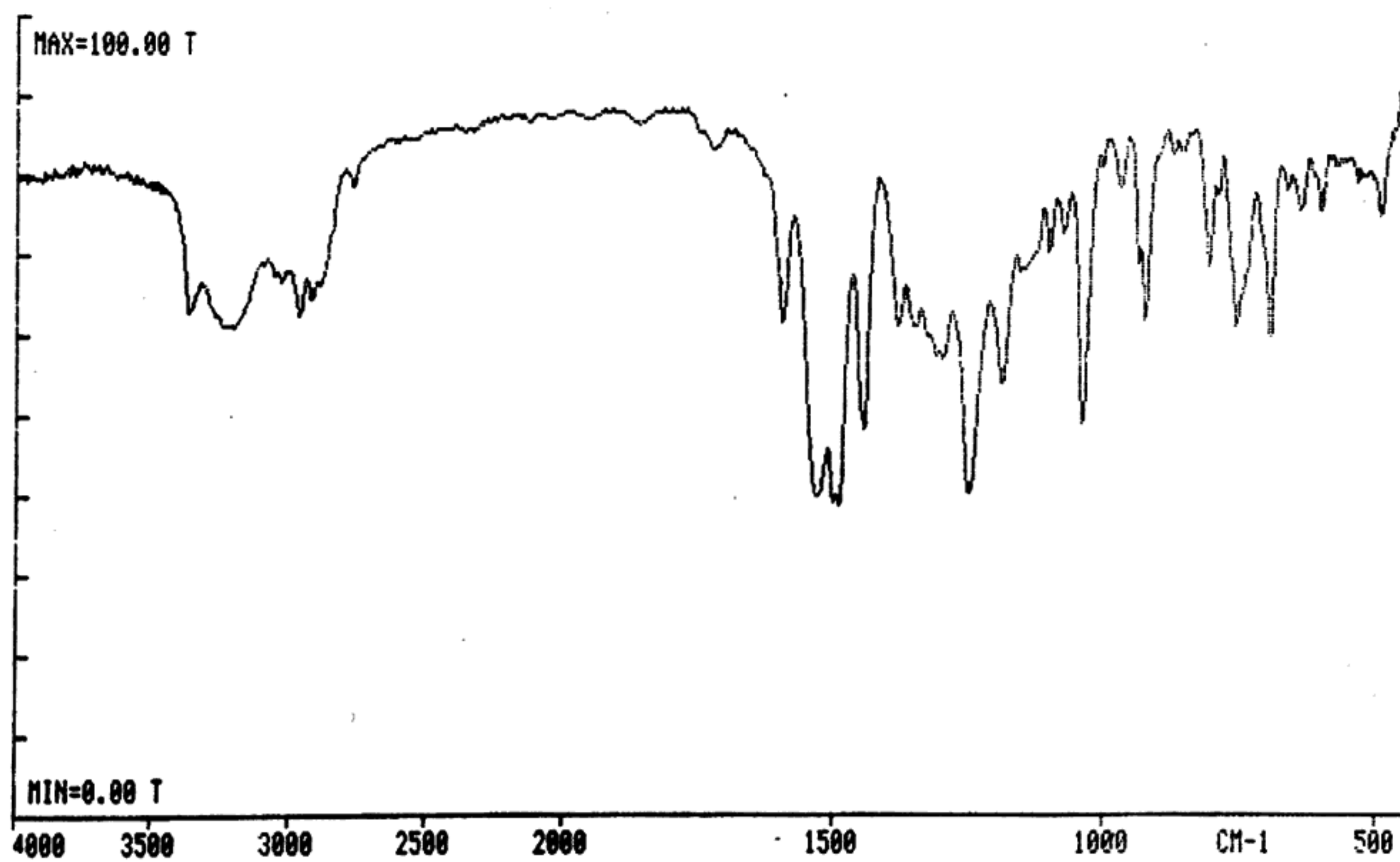


Figure 7. IR spectrum of MDA phenylisothiocyanate.

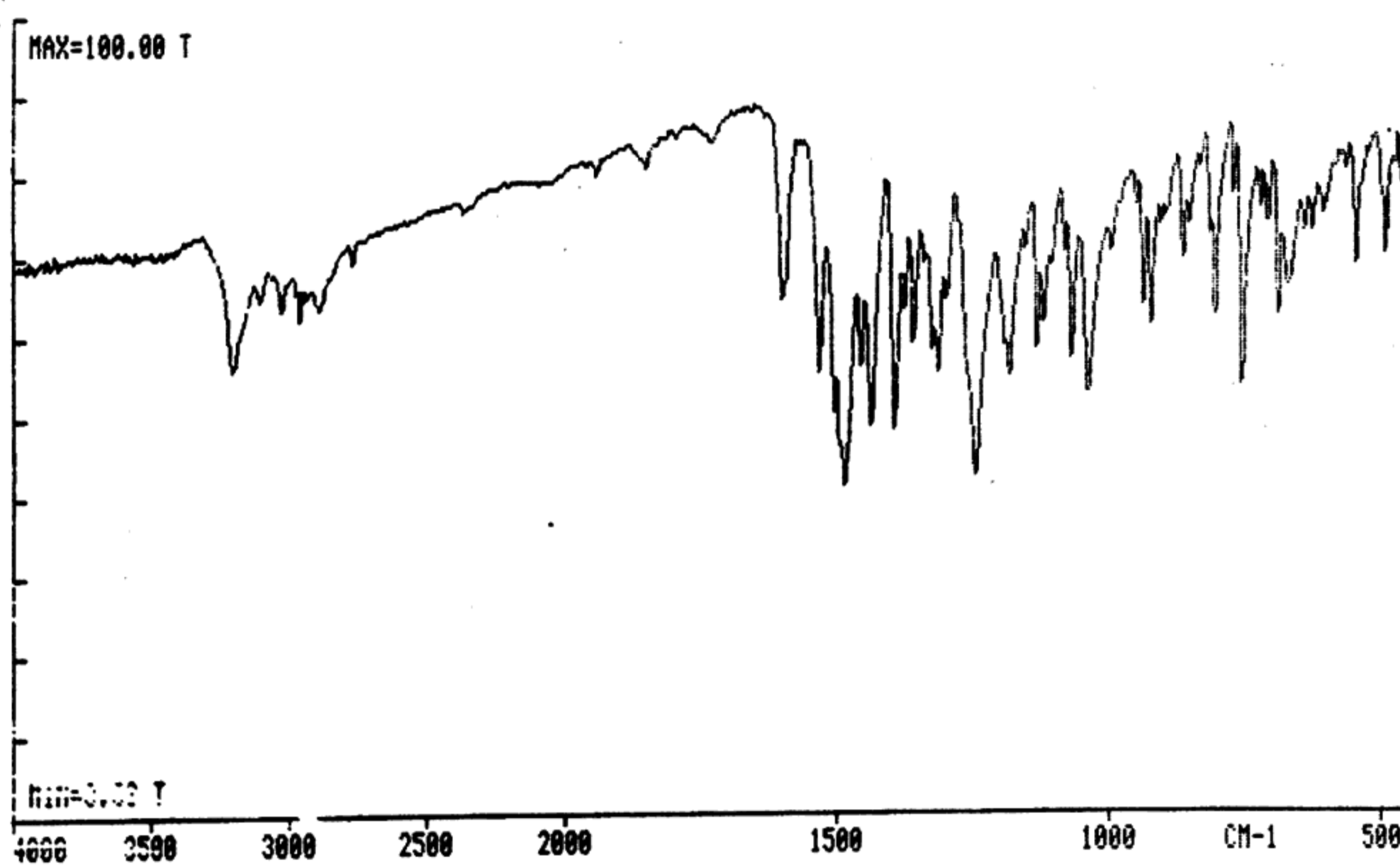


Figure 8. IR spectrum of MDMA phenylisothiocyanate.

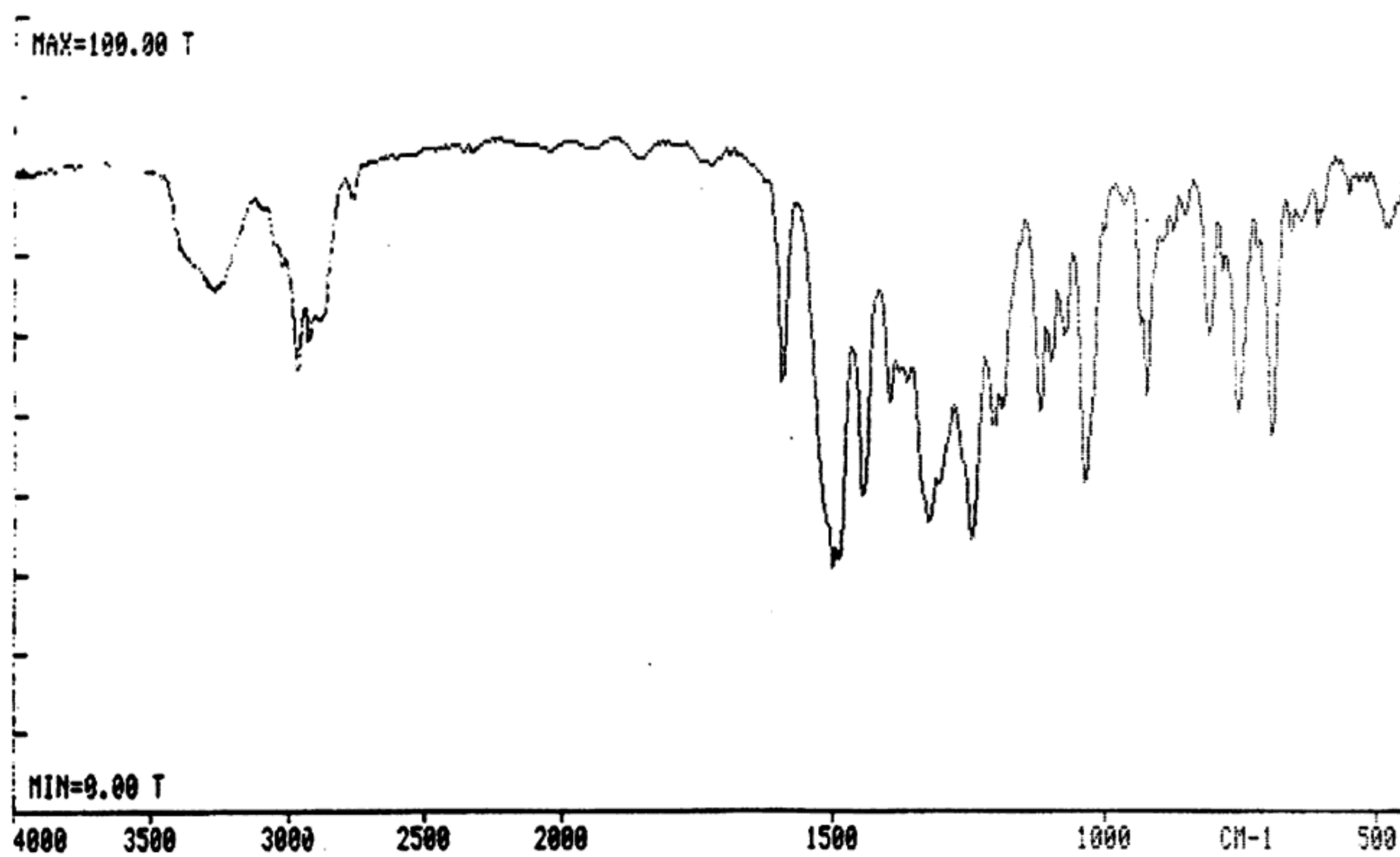
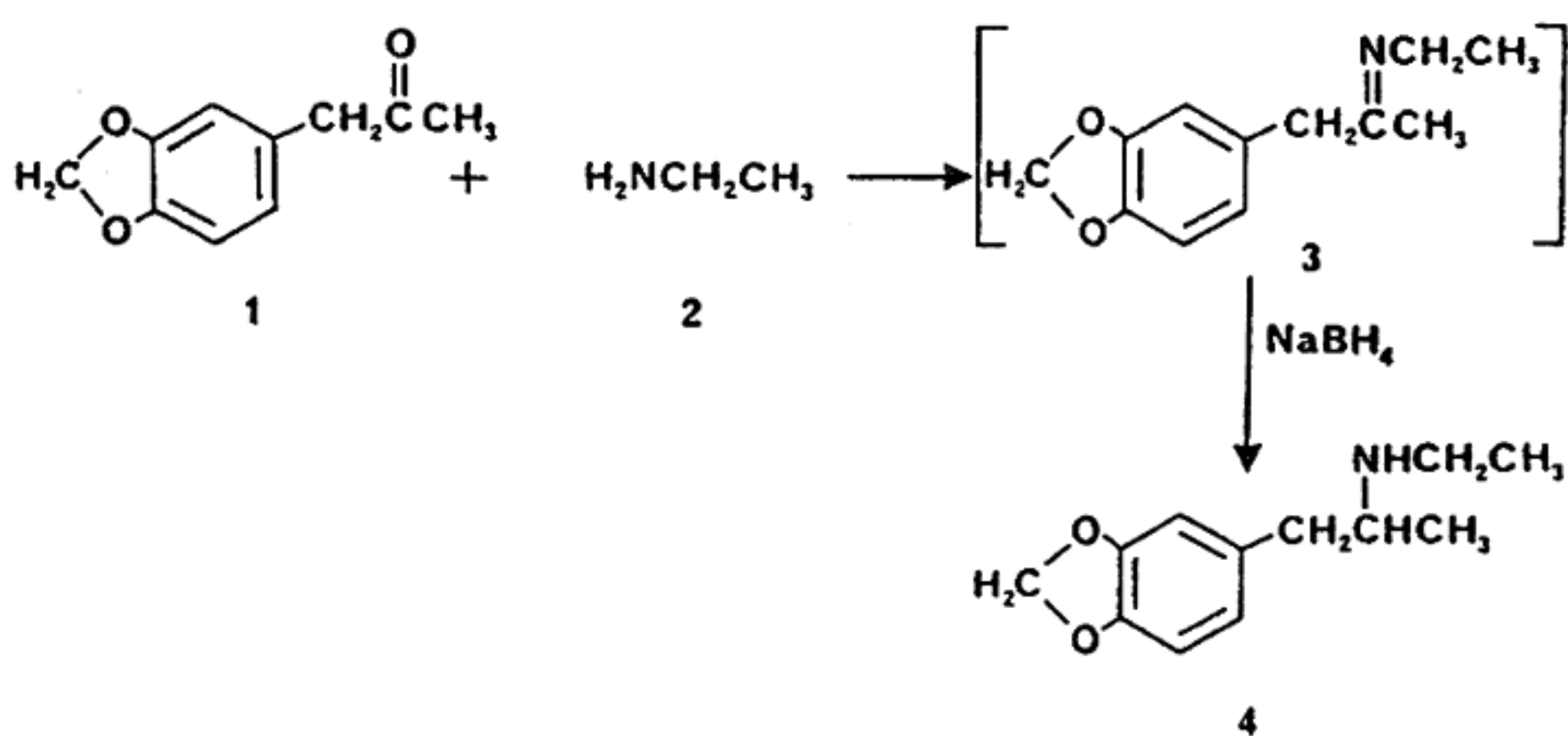


Figure 9. IR spectrum of MDEA phenylisothiocyanate.



Scheme 1. Reductive alkylation reaction for preparation of MDEA.

IR studies, the PIT derivatives were recrystallized from hexane.

Synthesis of *N*-Ethyl-3,4-Methylenedioxyphenylisopropylamine

A solution of 3,4-methylenedioxyphenyl-2-propanone (1.78 g, 10mmol) in 70% aqueous ethylamine (50 mL) was stirred at reflux for 30 min. Sodium borohydride (2.0 g, 53mmol) was then added to the reaction mixture over a period of 10 min, and the mixture was stirred at reflux for an additional hour. The reaction mixture was cooled in an ice bath and acidified carefully with 6N HCl (pH = 1), yielding a thick white precipitate. The aqueous suspension was washed with CHCl_3 (3×75 mL), then made basic with 1N NaOH (pH = 12). The basic aqueous solution was extracted with CHCl_3 (3×100 mL), and the combined CHCl_3 extracts were washed with 150 mL water and dried (MgSO_4). Filtration, followed by evaporation of the filtrate solvent, gave a light brown oil. Addition of an ether solution (100 mL) saturated with HCl gas to the oil afforded a white precipitate, which was isolated by filtration and recrystallized twice from ethanol/ether to give *N*-ethyl-3,4-methylenedioxyphenylisopropylamine HCl (750 mg, 31%) as fine white needles. The melting point was determined to be 197–198°C. IR and NMR spectra (^1H NMR) were consistent with structure.

Elemental Analysis (C, H, N):

Theory, %C = 59.13; %H = 7.44; %N = 5.75

Found, %C = 58.94; %H = 7.46; %N = 5.70.

Results and Discussion

In this study, MDEA was prepared from commercially available, 3,4-methylenedioxyphenyl-2-propanone (1) by using the general reductive alkylation procedure described by Schellenberg (4) shown in Scheme 1. Treatment of ketone (1) with aqueous ethylamine (2) presumably results in the formation of the imine intermediate (3). Addition of sodium borohydride to the reaction mixture containing (3) reduces the imine moiety, providing MDEA (4) as the free base. The free base is converted to the corresponding hydrochloride salt on treatment with an ether solution saturated with hydrochloric acid gas. NMR data are as follows: ^1H NMR ($(\text{CD}_3)_2\text{SO}$) δ 1.03 (t, 3H, $J = 7.0\text{Hz}$, $-\text{NHCH}_2\text{CH}_3$), 1.08 (d, 3H $J = 6.0\text{Hz}$, $-\text{NHCH}_2\text{CH}_3$), 2.32–2.91 (complex m, 5H, $\text{ArCH}_2\text{CHNH}-\text{CH}_2$), 5.85 (s, 2H, $-\text{OCH}_2\text{O}-$), 6.50–6.75 (m, 3H, ArH).

After MDEA was synthesized, the IR spectra of the 3 amine compounds studied were determined by FTIR. The free bases of the 3 amines were oils, so the IR spectra were prepared by placing each oil as a thin film on a blank KBr disk. The IR spectrum of 3,4-methylenedioxyphenylisopropylamine base (MDA) is shown in Figure 1; the spectrum of *N*-methyl-3,4-methylenedioxyphenylisopropylamine base (MDMA) in Fig-

ure 2; and the spectrum of *N*-ethyl-3,4-methylenedioxyphenylisopropylamine base (MDEA) in Figure 3. The IR spectra of the free bases of the amines are very similar as would be expected.

The IR spectra of the hydrochloride salts of MDA, MDMA, and MDEA are shown in Figures 4, 5, and 6, respectively. The spectras of the salts are readily distinguished.

The IR studies of the PIT derivatives of the amines were conducted by preparing KBr disks from the recrystallized compounds. Figures 7, 8, and 9 show the spectra of MDA-PIT, MDMA-PIT, and MDEA-PIT, respectively. MDA-PIT and MDEA-PIT were difficult to crystallize; there was no difficulty in crystallizing MDMA-PIT. The marked differences between Figures 8 and Figures 7 and 9 are obvious. The differences between Figures 7 and 9 are not as apparent but are readily distinguished. Figures 7, 8, and 9 illustrate the usefulness of PIT derivatives for IR differentiation of the primary amine MDA and the secondary amines MDMA and MDEA due to the absence of the N-H absorption in the 3300 to 3400 cm^{-1} region of both Figures 8 and 9.

Reference samples of the amines were prepared by dissolving 10 mg of each amine hydrochloride in 10 mL metha-

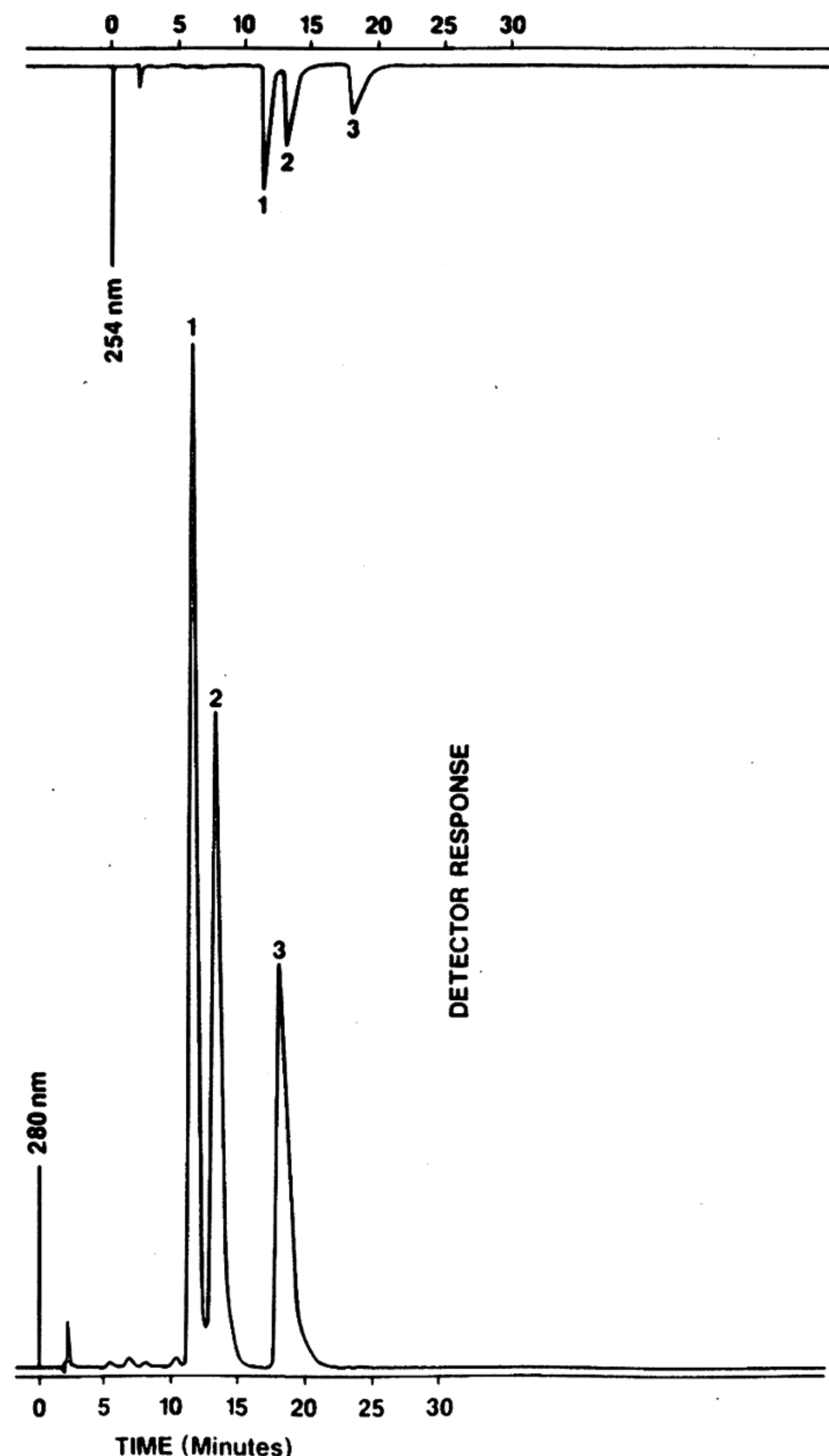


Figure 10. LC separation of 3,4-methylenedioxyphenylisopropylamines using pH 3.0 phosphate buffer-methanol (5 + 1). Peaks: 1, MDA; 2, MDMA; 3, MDEA.

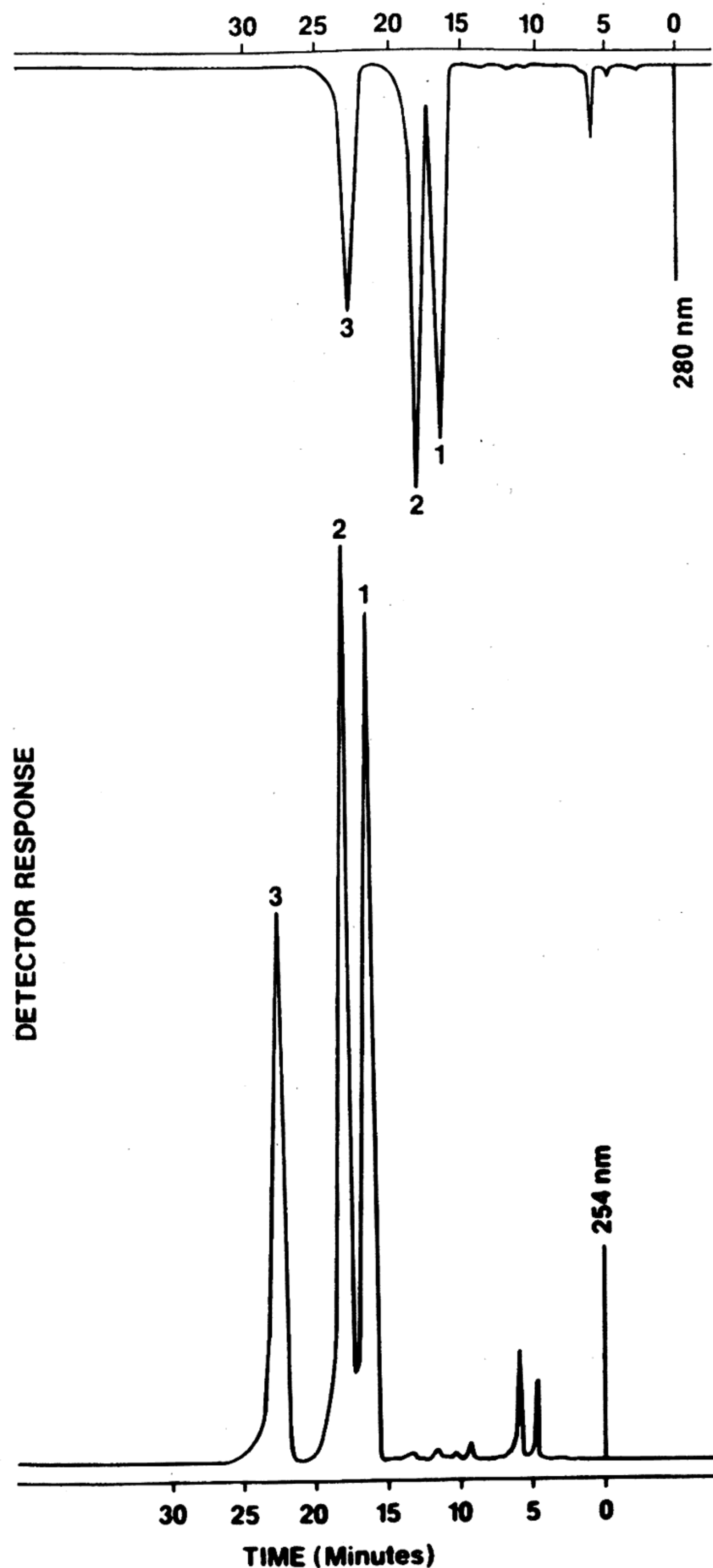


Figure 11. LC separation of PIT-derivatized 3,4-methylenedioxyphenylisopropylamines using methanol-water-acetic acid (50 + 49 + 1). Peaks: 1, MDMA; 2, MDA; 3, MDEA.

nol. The samples were used to develop an LC procedure for screening the 3,4-methylenedioxyphenylisopropylamines. The 3 amines were separated for differentiation by using a reverse phase chromatographic system consisting of a C_{18} stationary

Table 1. Chromatographic data for 3,4-methylenedioxyphenylisopropylamine and *N*-methyl and *N*-ethyl homologs

Solvent system ^a	Drug	Elution time, min	Absorbance ratios, A_{254}/A_{280}
1	MDA	11.4	0.122
1	MDMA	13.2	0.127
1	MDEA	18.0	0.122
2	MDA	17.9	2.173
2	MDMA	16.1	2.303
2	MDEA	22.4	2.227

^aSolvent system 1: pH 3.0 phosphate buffer-methanol (5 + 1); solvent system 2: methanol-water-acetic acid (50 + 49 + 1).

phase and a pH 3.0 phosphate buffer-methanol (5 + 1) solvent system. Figure 10 shows the separation of the 3 amines. The elution order of the amines appears to follow the general trend of increased retention with an increase in the hydrocarbonaceous nature of the solute.

Reference samples of the amines were derivatized with phenylisothiocyanate (PIT) and used to develop a second LC screening procedure. Figure 11 shows the separation of the 3 PIT-derivatized amines. The solvent system was methanol-water-acetic acid (50 + 49 + 1). An interesting point of comparison between the chromatograms in Figures 10 and 11 is the elution order reversal between MDA and MDMA. This same elution order reversal has been noted with amphetamine-PIT and methamphetamine-PIT derivatives (5).

In addition to comparison of elution times, further proof of the identity of the individual amines may be obtained from a comparison of the ratio of absorbances at 254 and 280 nm (A_{254}/A_{280}). Baker et al. (6) used this ratio to identify drugs that have similar elution characteristics in an LC system. The elution times and absorbance ratios for the 3 underivatized amines and PIT-derivatized amines are given in Table 1. The absorbance ratios of the underivatized amines are similar as are the ratios for the PIT-derivatized amines because the UV chromophores are the same in each instance. As can be observed from the absorbance ratios, the absorbance of the underivatized amines (UV maximum \cong 285 nm) is greatest at 280 nm ($A_{254}/A_{280} < 1$) and the absorbance of the PIT-derivatized amines is greatest at 254 nm ($A_{254}/A_{280} > 1$) due to the strong absorbing PIT-chromophore.

In conclusion, liquid chromatography in combination with infrared spectrophotometry is very useful for identification of 3,4-methylenedioxyphenylisopropylamine and its *N*-methyl and *N*-ethyl homologs.

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