Synthesis, Identification, and Acute Toxicity of Some *N*-Alkyl Derivatives of 3,4-Methylenedioxyamphetamine

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A series of *N*-alkyl derivatives of 3,4-methylenedioxyamphetamine (MDA) was prepared in an effort to characterize these potential drugs of abuse. These secondary amines were synthesized via reductive amination of the corresponding ketone with alkylamines. The ultraviolet absorption spectra for these compounds produced almost equally intense absorbance at 234 and 285 nm. The compounds were separated by liquid chromatography using reverse phase (C_{18}) procedures with a ternary mobile phase mixture. Toxicity studies showed all of the compounds to have LD_{50} values similar to *N*-methyl MDA (MDMA).

The pharmacological actions of 3,4-methylenedioxyamphetamine (MDA) allow for its classification as a hallucinogen (1). It has other atypical effects such as a low potential to produce severe sensory disruption; however, MDA became a popular drug of abuse primarily because of its enhancing effect on empathy (2).

Methylation to yield the secondary amine, MDMA, produces significant changes in the pharmacological properties: a shorter duration of effect, a general decrease in potency, and elimination of the hallucinogenic properties. However, the empathy-enhancing properties are retained and appear to be more pronounced in MDMA (3). MDMA is claimed to have unique properties in psychotherapy, reducing the anxiety that normally accompanies the discussion of emotionally unpleasant events (4). The recent appearance of this drug on the street market as "Ecstasy" indicates the popularity and potential for abuse of this drug. Its popularity is probably due to its mild effects and its ability to facilitate interpersonal communication (5).

The work of Hardman et al. (6) compared the toxicity and behavioral aspects of MDA and MDMA to mescaline in 5 animal species. The LD_{50} for MDA was significantly lower than that for mescaline, with the lethality of MDMA intermediate between the two. The toxicity for MDA ranged from 2.68 times that of mescaline in the mouse to 17.65 in the monkey. Similar values for MDMA were 2.04 in the mouse and 5.89 in the monkey.

The recent appearance of the *N*-ethyl derivative of MDA in clandestine drug samples has prompted this investigation. In this study a series of *N*-alkyl derivatives of MDA has been prepared and characterized. The ultraviolet (UV) and nuclear magnetic resonance spectral properties, liquid chromatographic analysis, and acute toxicity data are reported.

Experimental

General

Melting points were determined in open glass capillaries using a Thomas-Hoover melting point apparatus and are uncorrected. All ^{1}H NMR spectra were measured in DMSO on a Varian T-60A spectrometer with an internal standard of tetramethylsilane. Infrared (IR) spectra were recorded on a Perkin-Elmer Model 1500 Fourier transform infrared spectrophotometer. The UV absorption spectra were determined using a Shimadzu 160 spectrophotometer. Solutions for UV studies were prepared in 0.1N H_2SO_4 at a concentration of 1×10^{-4} M.

Synthesis of *N*-alkyl-MDA Analogs

Method A.—A solution of the ketone (1.78 g, 10 mmol) in 50 mL 70% aqueous ethylamine was stirred at reflux for 30 min. The mixture was then cooled to room temperature, and 2.0 g NaBH$_4$ was added portionwise over a period of 10 min. The mixture was then stirred at reflux for 30 min, cooled in an ice bath, and acidified to pH 1 with concentrated HCl. The resultant aqueous suspension was extracted 3 times with 75 mL each of CHCl$_3$, and then was made basic (pH 14) with 1N NaOH. The basic aqueous solution was extracted 3 times with 100 mL each of CHCl$_3$, and the combined CHCl$_3$ extracts were dried over MgSO$_4$. Filtration, followed by evaporation of the filtrate solvent, yielded the product base as a brown oil. Treatment of the base with ethereal HCl gave a white solid which was recrystallized from ethanol–ether to give *N*-ethyl methylenedioxyamphetamine HCl as a fine white granular solid (Table 1).

Method B.—Sodium cyanoborohydride (1.9 g, 30 mmol) was added portionwise to a solution of the ketone (1.78 g, 10 mmol) and 5.0 mL amine in 50 mL acetonitrile. This mixture was stirred at room temperature and 1.0 mL glacial acetic acid added. After stirring for 2 h, more glacial acetic acid was added (1.0 mL) and the mixture was stirred an additional 30 min. The reaction mixture was then extracted twice with 100 mL each of ether, and the combined ether extracts were washed successively with 100 mL 1N NaOH, 100 mL saturated NaHCO$_3$ solution, and 100 mL water. The ether solution was then extracted twice with 100 mL each of 3N HCl, and the combined HCl extracts were washed with 100 mL CHCl$_3$. The aqueous acid solution was then made basic (pH 12) with 2N NaOH, and this suspension was extracted 3 times with 150 mL each of CHCl$_3$. The combined CHCl$_3$ extracts were washed with 200 mL water and dried over Na$_2$SO$_4$. Filtration, followed by evaporation of the filtrate, gave the product base as an oil. The base was converted to the corresponding HCl or HBr salt after treatment with ethereal HCl or HBr, respectively, and recrystallized from mixtures of ethanol and ether (Table 1).
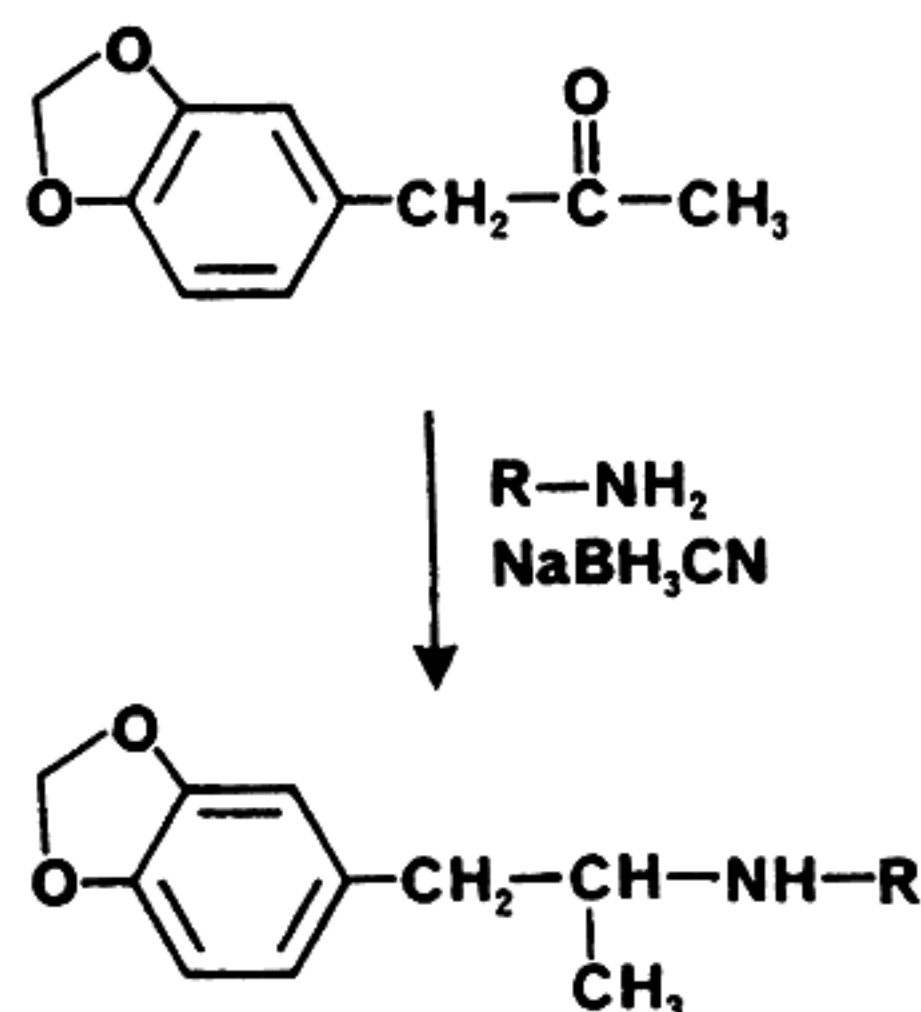

Figure 1. Synthesis procedure for preparation of *N*-alkyl analogs of 3,4-methylenedioxyamphetamine.

Table 1. N-Alkyl methylenedioxyamphetamine derivatives and their acute toxicities in mice

Compound No.	R	Synthetic method	Yield, %	mp, °C	Formula	LD₅₀, mg/kg (95% confidence limits)
1	-CH$_2$CH$_3$	A	31	197–198	C$_{12}$H$_{17}$NO$_2$·HCl	102 (96–108)
2	-CH$_2$CH$_2$CH$_3$	B	42	183–186	C$_{13}$H$_{19}$NO$_2$·HCl	102 (96–108)
3	-CH(CH$_3$)$_2$	B	63	174–179	C$_{13}$H$_{19}$NO$_2$·HCl	116 (109–123)
4	-CH$_2$CH$_2$CH$_2$CH$_3$	B	10	180–183	C$_{14}$H$_{21}$NO$_2$·HBr	85 (77–93)
5	-CH$_2$CH(CH$_3$)$_2$	B	9	175–178	C$_{14}$H$_{21}$NO$_2$·HCl	132 (124–140)
6	-CH(CH$_3$)CH$_2$CH$_3$	B	46	100–110	C$_{14}$H$_{21}$NO$_2$·HCl	104 (98–110)
MDA	-H					68 (50–92)ᵃ
MDMA	-CH$_3$					97 (89–106)ᵃ
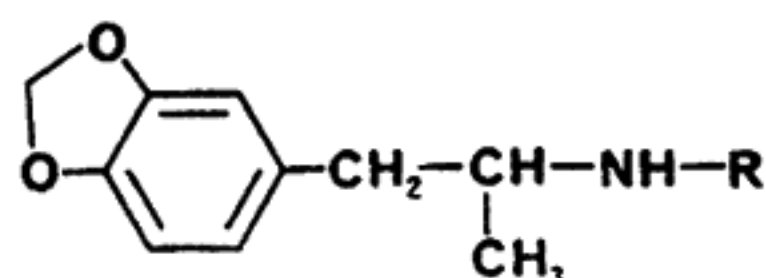
ᵃ Data from Ref. 6.

Chromatographic Procedures

The liquid chromatograph consisted of a Waters Associates (Milford, MA 01757) Model 6000A pump, U6K injector, 440 UV detector with dual-wavelength accessory operated at 254 and 280 nm, and Houston Instrument (Austin, TX 78753) Omniscribe dual-pen recorder. The column was 30 cm × 3.9 mm id packed with μBondapak C$_{18}$ (Waters Associates), and the mobile phase consisted of pH 3.0 phosphate buffer–methanol–acetonitrile–triethylamine (500 + 100 + 25 + 1). The mobile phase flow rate was 1.5 mL/min and the UV absorbance detector was operated at 0.2 AUFS. Sample solutions for analysis were prepared in methanol and all separations were done at ambient temperature.

Acute Toxicological Evaluation

Male ICR Swiss mice were used from Southern Animal Farms, Prattville, AL. Food and water were available to the animals ad libitum, and animals were housed in temperature- and light-controlled quarters. The compounds were administered intraperitoneally as the salts in distilled water. The animals weighed between 30 and 40 g. The concentration of the solution injected was 1–2% so that the total volume never exceeded 0.5 mL. Three dosing levels were used with 6 animals per dose. Mortality was determined after 24 h for the LD$_{50}$. The Lithchfield and Wilcoxon (7) method was used to calculate the LD$_{50}$ values with upper and lower confidence limits at the 0.05 level of significance.

Results and Discussion

The N-alkyl analogs of 3,4-methylenedioxyamphetamine (MDA) were prepared according to the synthesis procedure shown in Figure 1. The synthesis of these amines involves condensation of the carbonyl moiety of 3,4-methylenedioxy-phenyl-2-propanone with the appropriate amine to yield the imine which is reduced in situ to the corresponding secondary amine. The imine is reduced by using sodium cyanoboro-
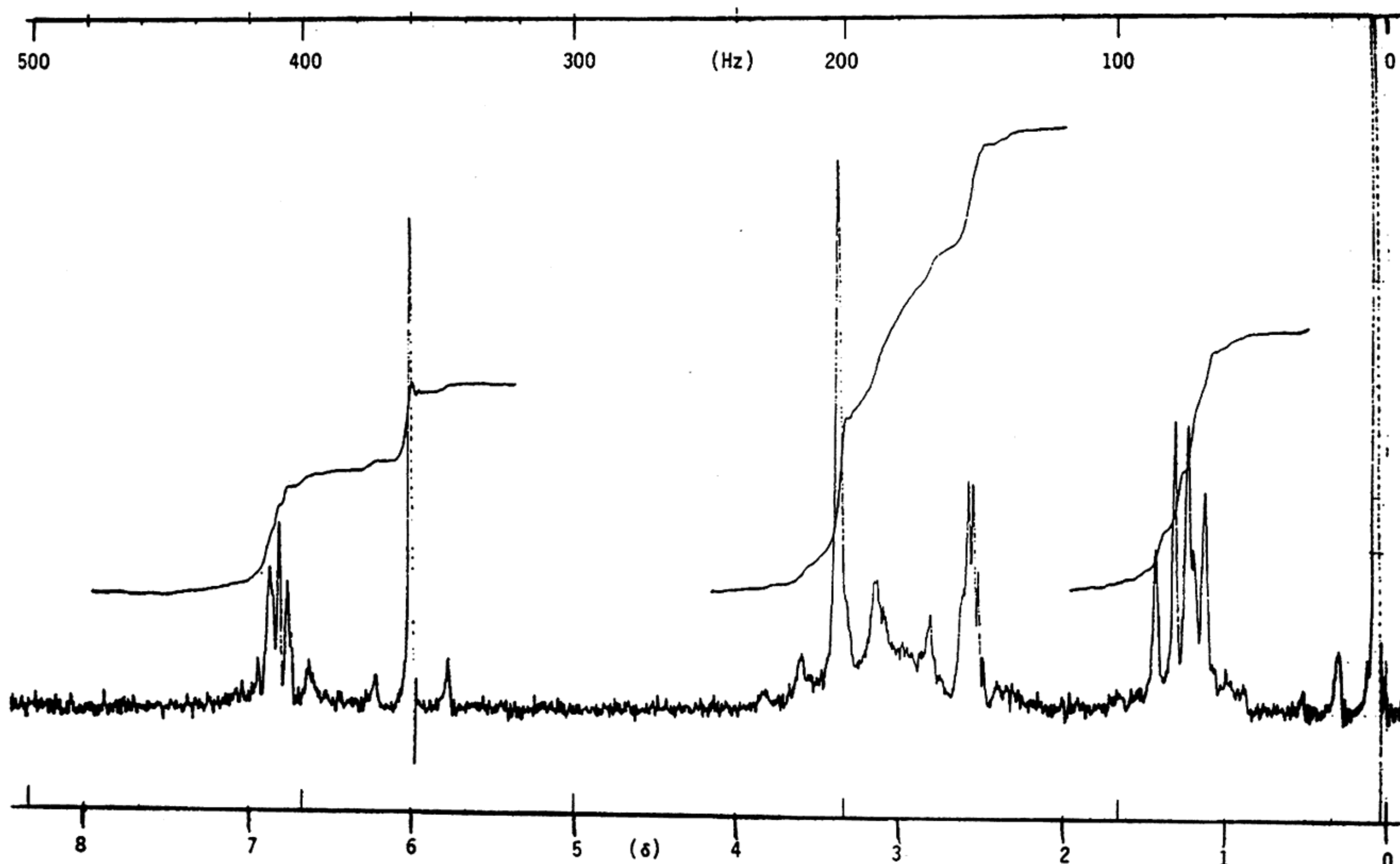

Figure 2A. Proton NMR spectrum for N-alkyl 3,4-methylenedioxyamphetamine compound 1. See Table 1 for structure of compound.
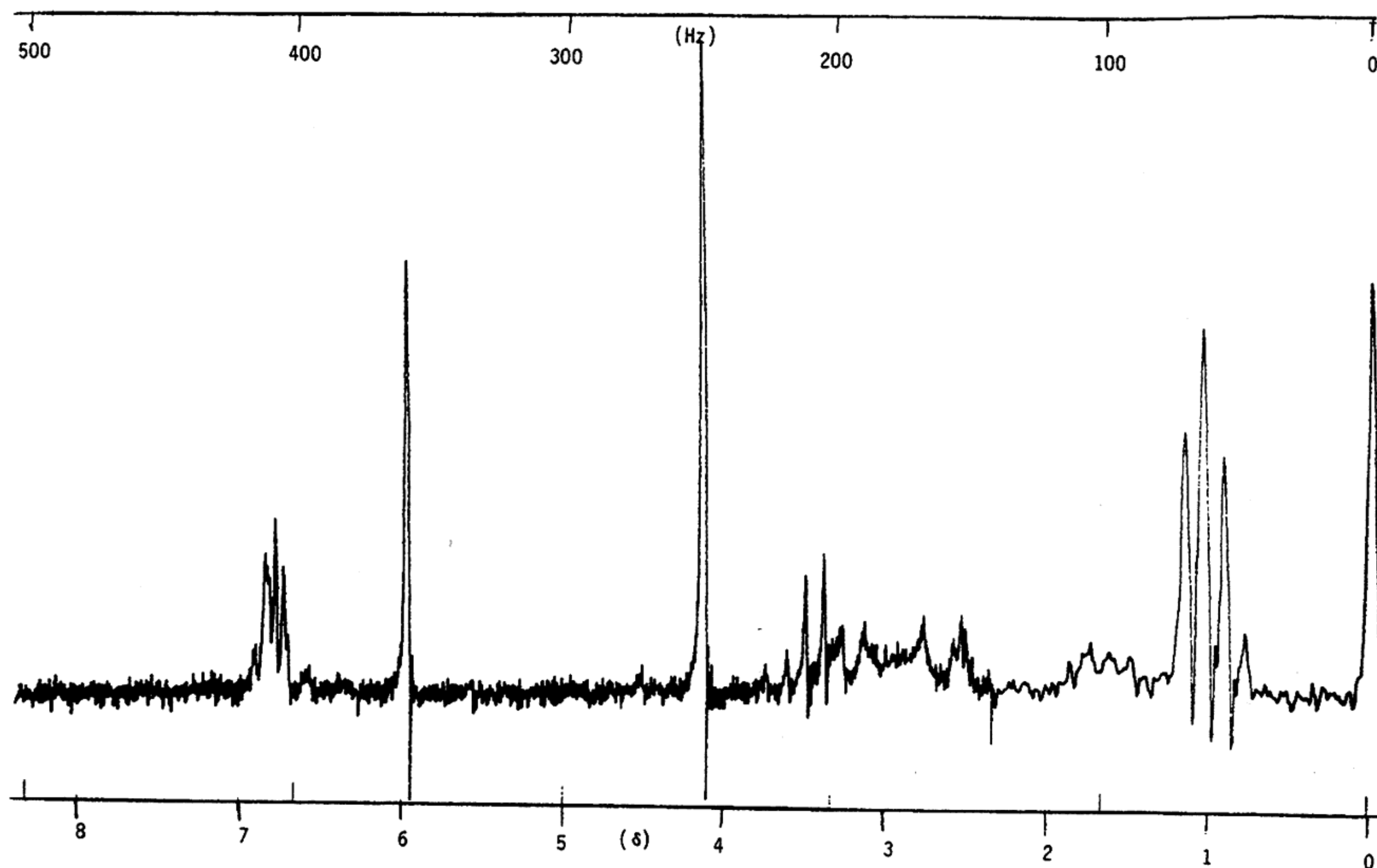
Figure 2B. Proton NMR spectrum for *N*-alkyl 3,4-methylenedioxyamphetamine compound 2. See Table 1 for structure of compound.

hydride, a hydride source selective for imines. Thus, the imines are reduced selectively as formed, and carbonyl reduction is not a competing reaction (8). The amines were converted to the hydrochloride salt using HCl in diethyl ether, except for compound 4 which was prepared as the HBr salt. The compounds prepared in this study included the C_1–C_4 *N*-alkyl derivatives of MDA; Table 1 summarizes the synthetic data obtained for these compounds. The proton NMR spectra are shown in Figures 2A–2F and are consistent with the assigned structures.

The UV absorption characteristics for all these compounds were quite similar, as expected. The 3,4-methylenedioxyphenyl group is the major chromophoric unit common to all these compounds. Figure 3 shows an example UV spectrum
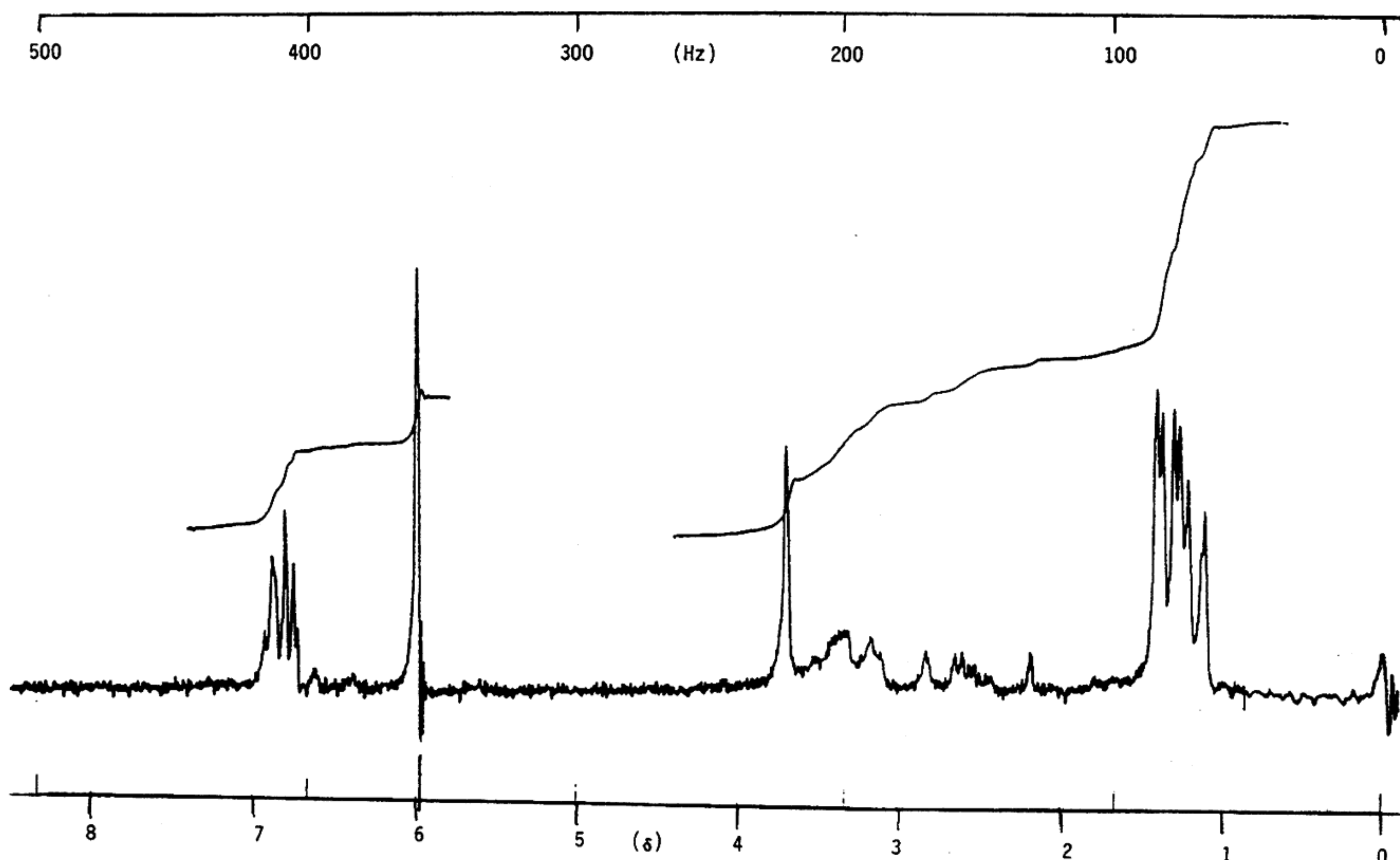

Figure 2C. Proton NMR spectrum for *N*-alkyl 3,4-methylenedioxyamphetamine compound 3. See Table 1 for structure of compound.
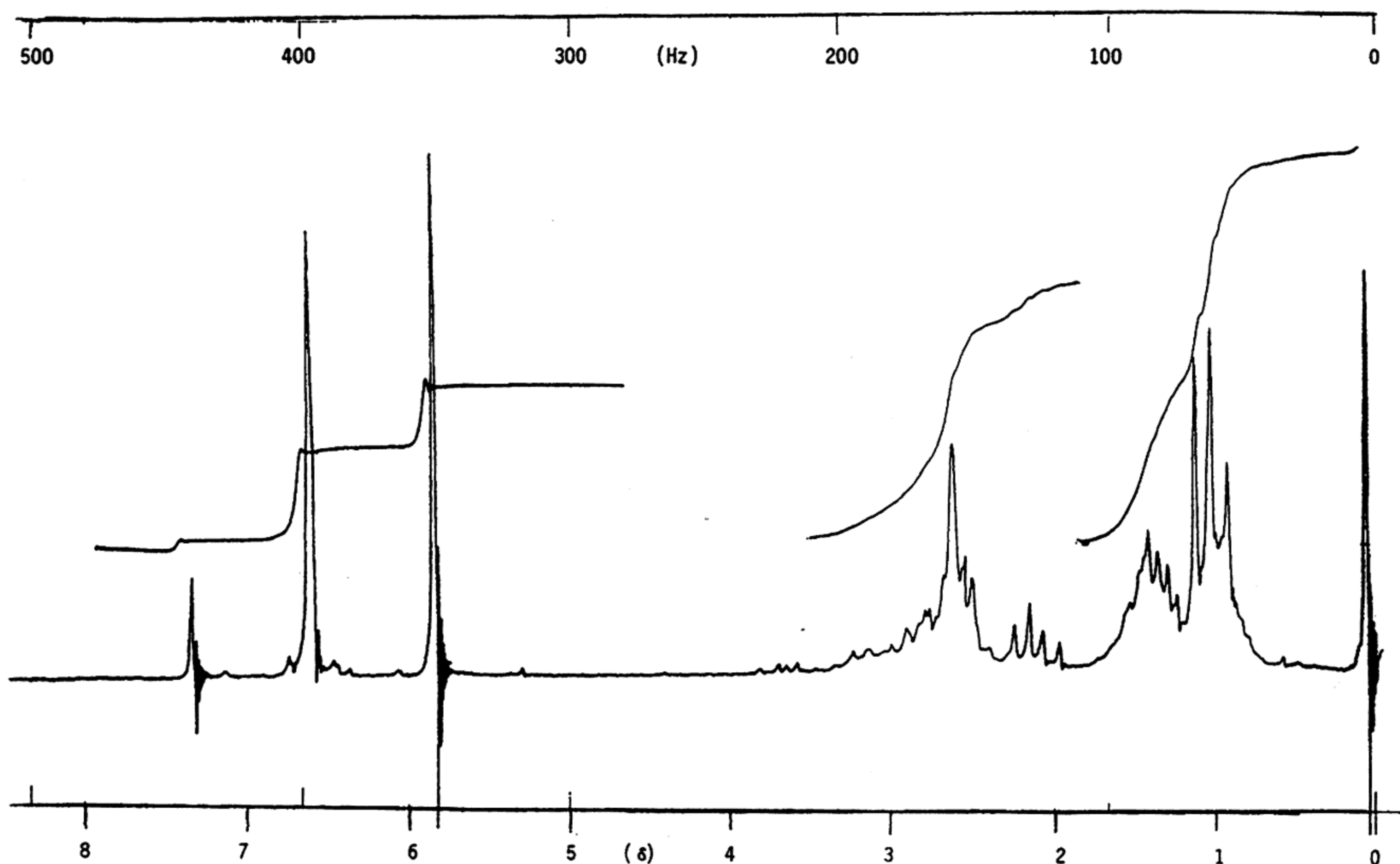
Figure 2D. Proton NMR spectrum for *N*-alkyl 3,4-methylenedioxyamphetamine compound 4. See Table 1 for structure of compound.

for the *N-n*-propyl-MDA analog. All the *N*-alkyl derivatives of MDA showed UV spectral properties similar to those of MDA. The major absorption bands occurred at 285 and 234 nm with the absorptivity slightly higher at the lower wavelength. The observed molar absorptivities were 3.3–3.7×10^3 L/mole-cm at 285 nm and 3.6–3.9×10^3 L/mole-cm at

234 nm. These absorptivities are considerably higher than the values for the amphetamines, which fall in the range of 2.0×10^2 L/mole-cm.

The liquid chromatographic separation of these MDA derivatives was accomplished using reverse phase techniques which consisted of a C_{18} stationary phase and a ternary mo-
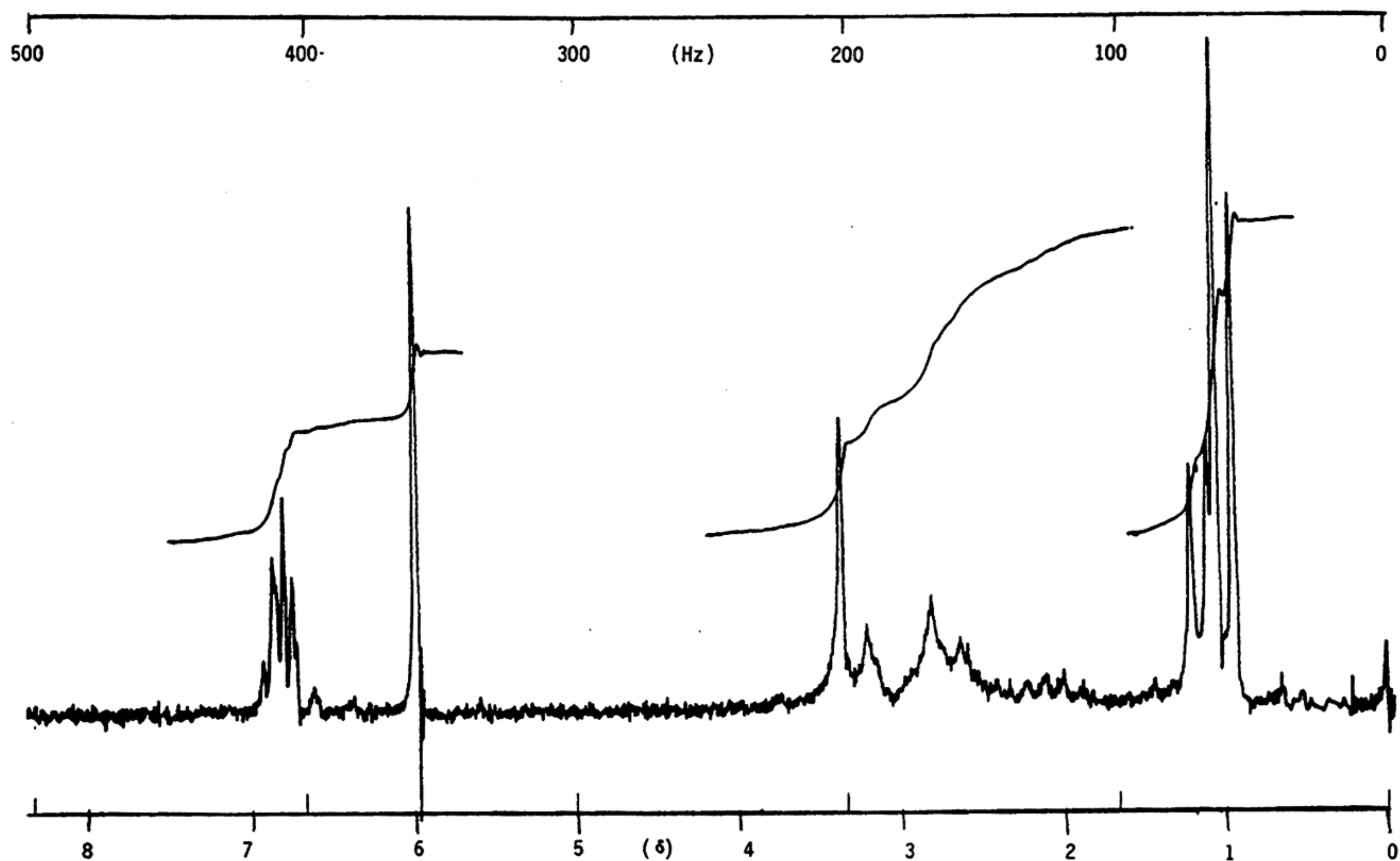
Figure 2E. Proton NMR spectrum for *N*-alkyl 3,4-methylenedioxyamphetamine compound 5. See Table 1 for structure of compound.
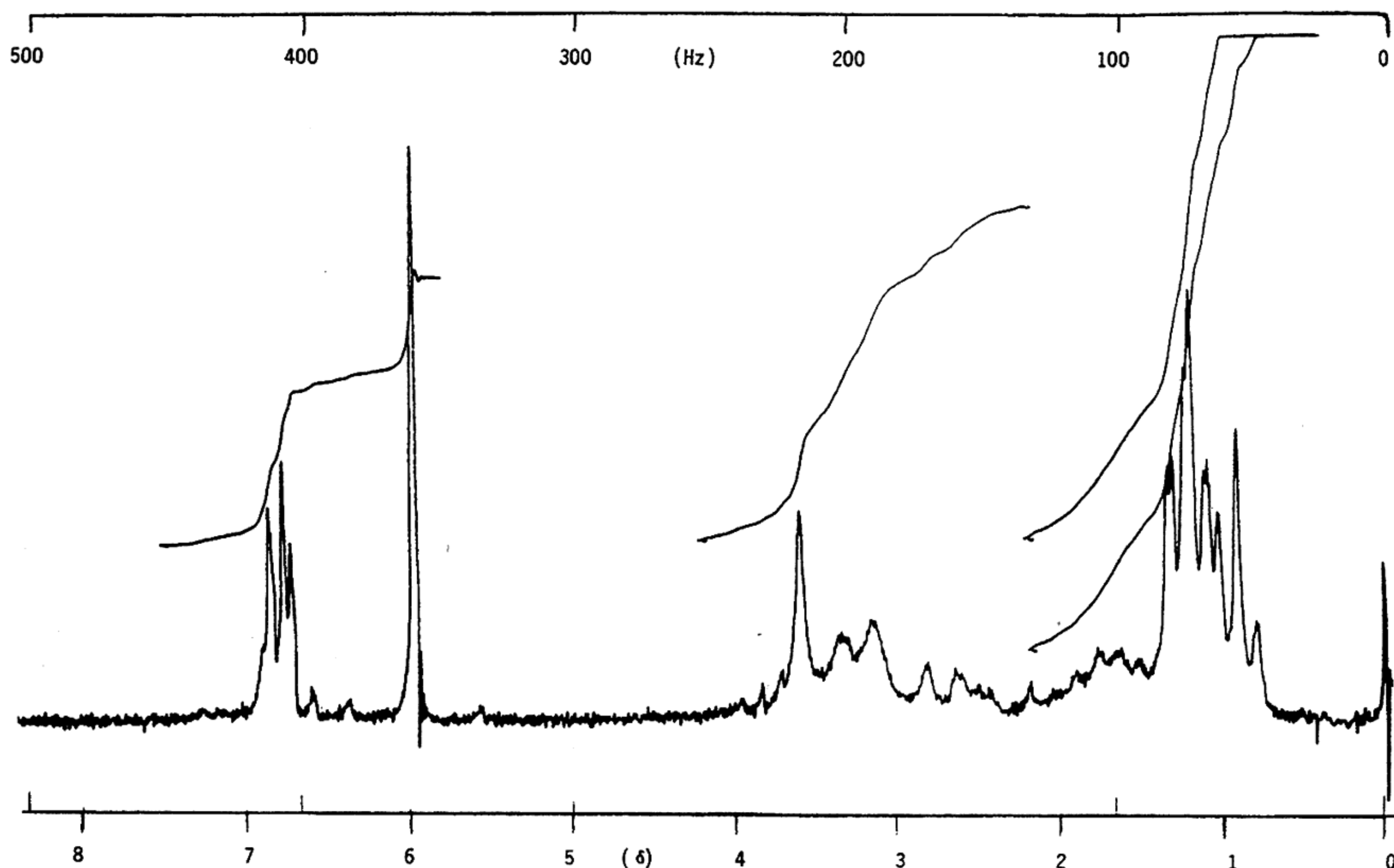
Figure 2F. Proton NMR spectrum for N-alkyl 3,4-methylenedioxyamphetamine compound 6. See Table 1 for structure of compound.

bile phase. The ternary mobile phase, which produced maximum resolution for these amines, consisted of pH 3 phosphate buffer, acetonitrile, and methanol containing triethylamine. The triethylamine was necessary to improve peak shape for the basic MDA compounds.

The chromatogram in Figure 4 shows the separation of all of the compounds described in Table 1 with the exception of the sec-butyl-MDA derivative. The elution order of the compounds is as expected, showing higher k' values for the more lipophilic compounds. The elution order essentially parallels the size of the alkyl group attached to nitrogen. The synthesis of the N-sec-butyl-MDA derivative via reductive amination of the appropriate ketone produces 2 diastereomeric products from racemic sec-butylamine. Figure 5 shows the presence of 2 diastereomeric forms of the sec-butyl-MDA. This separation was obtained using the mobile phase that produced the chromatogram in Figure 4. No attempts were made to maximize the resolution of these 2 diastereomers. These compounds, when added to the mixture separated in Figure 4, produce significant peak overlap with the isobutyl-MDA derivative. The chromatograms in Figures 4 and 5 were obtained using dual-wavelength UV detection at 254 and 280 nm. These amines are much stronger chromophores than the amphetamines and do not require chromophoric derivatization for detectability. The use of 254 and 280 nm for dual-wavelength detection produces large peak area ratios (absorbance ratios) since these wavelengths are very close to the absorbance minimum and maximum, respectively.

The acute toxicity (LD$_{50}$) data for the N-alkyl MDA derivatives were determined in male mice following intraperitoneal administration. The results of these studies are given in Table 1. These data indicate that N-alkylation of MDA produces a general decrease in toxicity. Hardman et al. (6) observed that N-methylation of both MDA and mescaline produced an increase in LD$_{50}$ values when compared to the parent compounds. The LD$_{50}$ for mescaline (6), 3,4,5-tri-

methoxyphenethylamine, is 212 mg/kg in mice for intraperitoneal administration. Thus, MDA and all its N-alkyl derivatives are considerably more toxic than mescaline. The increased toxicity of the MDA derivatives may be a result of their enhanced metabolic stability. Mescaline, a primary amine, is rapidly inactivated in central and peripheral tissues by oxidative deamination. The presence of the α-methyl moiety in MDA or both an α-methyl and N-alkyl moiety in MDMA and analogs 1–6 would retard oxidative destruction of these compounds by a steric mechanism and thereby increase their toxicity. The effect of N-methylation of amphetamine to yield methamphetamine (9), however, produces an increase in toxicity. The LD$_{50}$ for amphetamine is 91 (86–96) mg/kg in mice (intraperitoneal) while the value for methamphetamine is 57 (52–62) mg/kg. The observed differences in the relative toxicities of amphetamine and methamphetamine compared to MDA and MDMA are consistent with earlier results (5) and provide additional support for the hypothesis that the amphetamines and MDA derivatives alter neurotransmission in the central nervous system by somewhat different mechanisms. The MDA derivatives
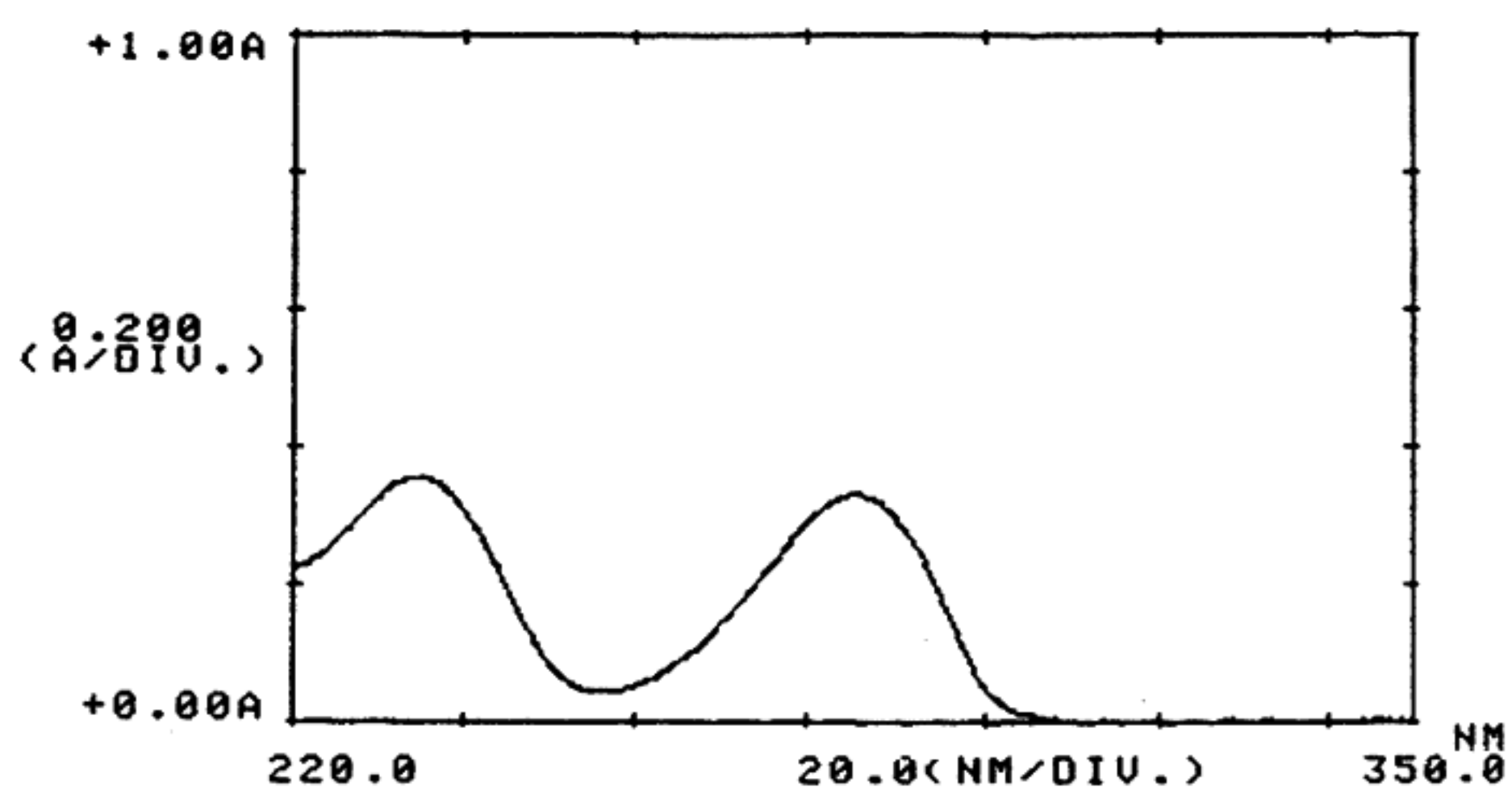

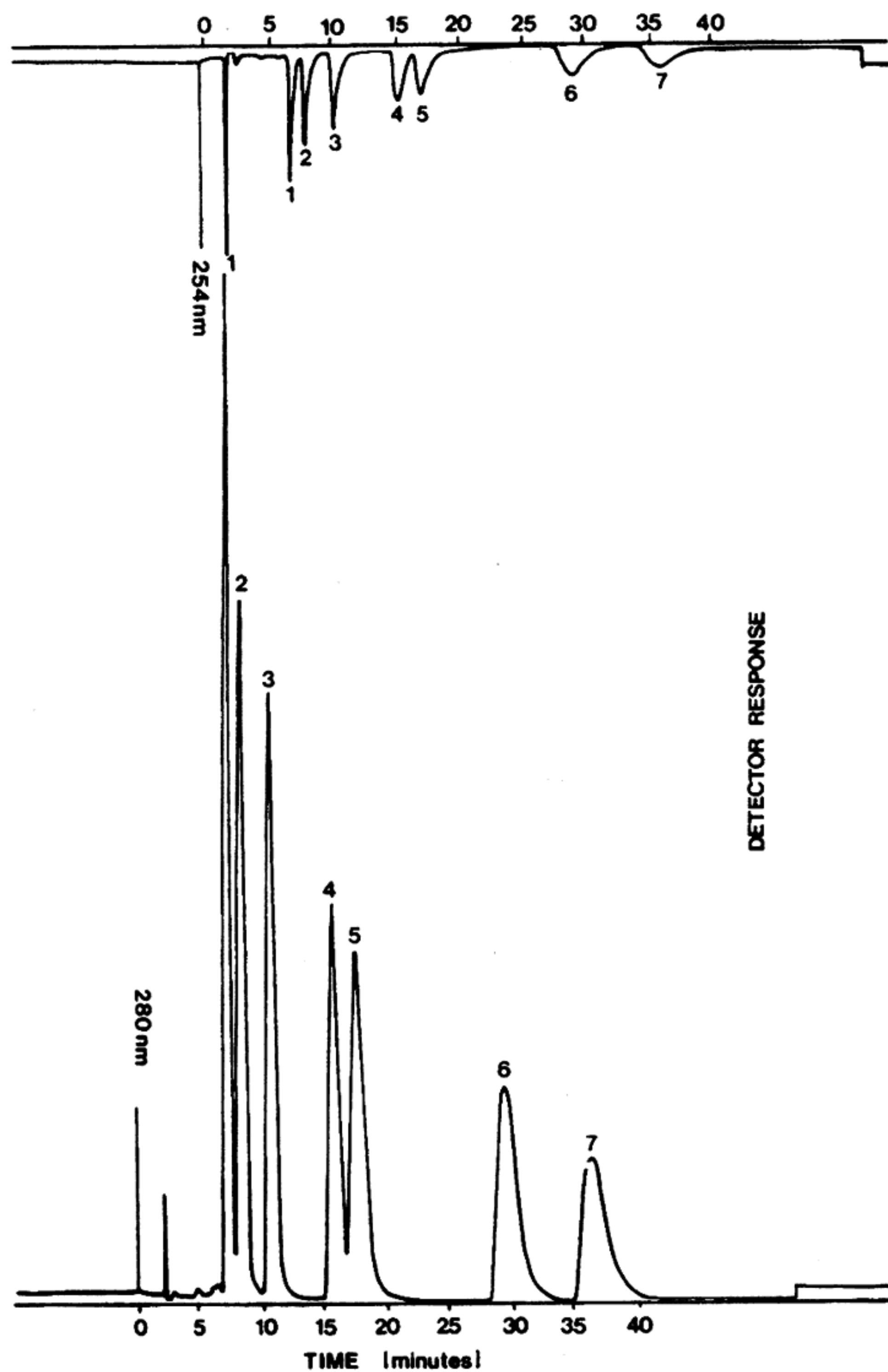**Figure 3. Ultraviolet absorption spectrum for N-n-propyl MDA (1 × 10^{-4}M in 0.1N H$_2$SO$_4$).**

Figure 4.   Reverse-phase liquid chromatographic separation of MDA and N-alkyl MDA derivatives at 254 and 280 nm. Peaks: 1, MDA; 2, N-methyl MDA; 3, N-ethyl MDA; 4, N-isopropyl MDA; 5, N-n-propyl MDA; 6, N-isobutyl MDA; 7, N-n-butyl MDA.

Figure 5.   Reverse-phase liquid chromatographic analysis of N-sec-butyl MDA diastereomers.

evaluated in this study seemed to retain the peripheral sympathomimetic effects of the amphetamines such as salivation and the dopaminergic stereotyped effects. All compounds produced increased central nervous system activity, with death by clonic and tonic convulsions.

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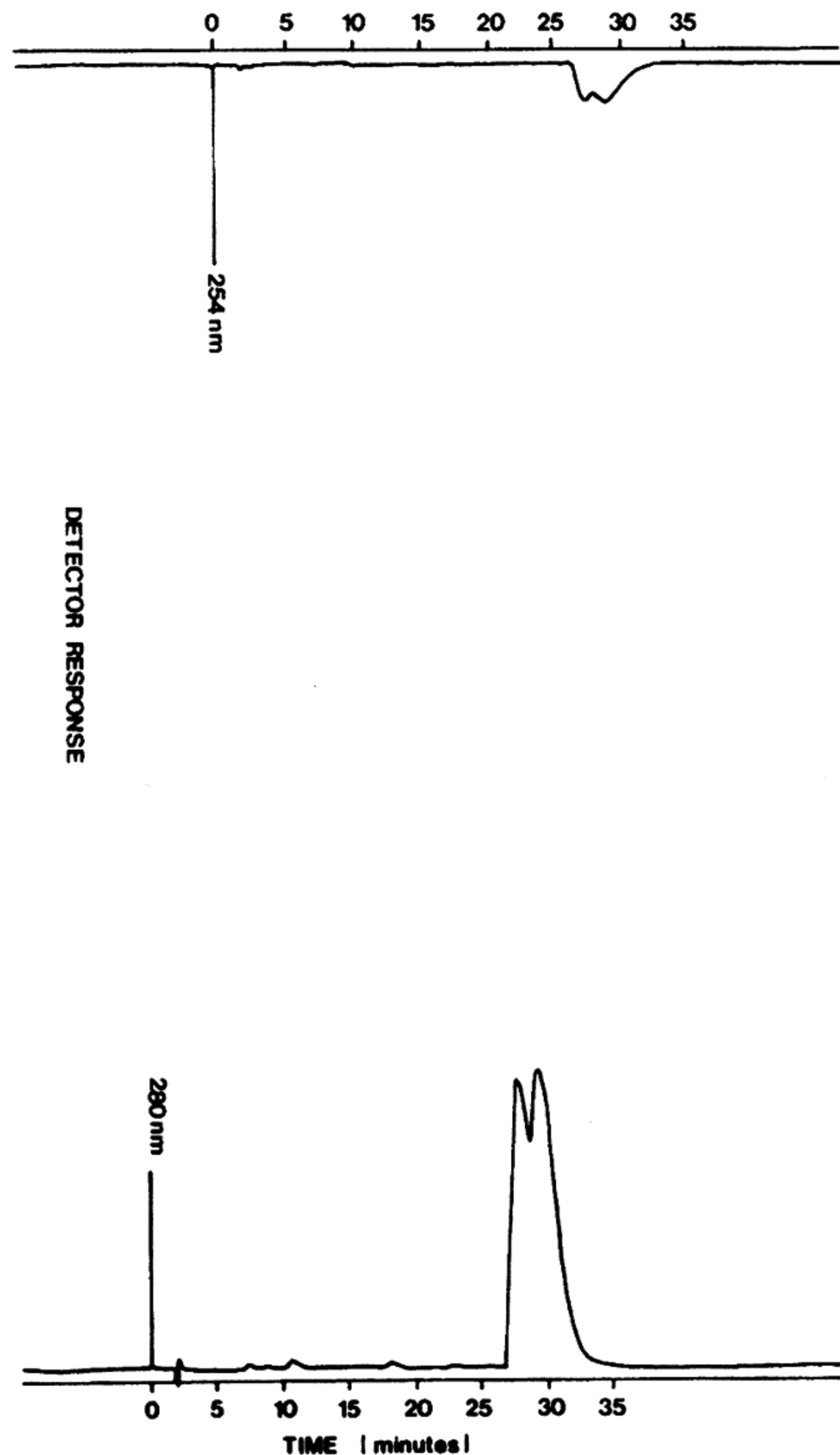(3) Shulgin, A. T., & Nichols, D. E. (1978) in *The Psychopharma-cology of Hallucinogens,* R. C. Stillman & R. E. Willett (Eds), Pergamon Press, Inc., New York, NY, p. 74

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