B. A. Dawson,[1] *Ph.D.; D. B. Black;*[1] *A. Lavoie;*[1] *and M. J. LeBelle,*[1] *M.Sc.*

Nuclear Magnetic Resonance Identification of the Phenylalkylamine Alkaloids of Khat Using a Chiral Solvating Agent

REFERENCE: Dawson, B. A., Black, D. B., Lavoie, A., and LeBelle, M. J., "**Nuclear Magnetic Resonance Identification of the Phenylalkylamine Alkaloids of Khat Using a Chiral Solvating Agent.**" *Journal of Forensic Sciences*, JFSCA, Vol. 39, No. 4, July 1994, pp. 1026–1038.

ABSTRACT: Nuclear magnetic resonance was used for the identification of three major alkaloids in dried leaves of the khat plant, *Catha edulis*. Proton nuclear magnetic resonance spectra of plant extracts confirmed the presence of cathinone, norpseudoephedrine and norephedrine. The subsequent addition of a chiral solvating agent, (S)-(−)-1,1′-bi-2-naphthol, to these NMR solutions enabled the identification of the various enantiomers of these alkaloids. Both the (S)- and (R)- enantiomers of cathinone were detected. The results from the determination of the alkaloid ratios in the dried plant material by the NMR method are compared to those obtained by a previously developed gas chromatographic method.

KEYWORDS: criminalistics, Chiral solvating agent, binaphthol, khat, *catha edulis*, cathinone, cathine identification, derivatization

Nuclear magnetic resonance (NMR) has not been reported often as a routine method for the identification of illicit drugs. However, its practicality in the identification of multicomponent samples has been described by a number of authors. Its ability to provide conclusive identification of substances in mixtures with very little sample treatment is the basis of its efficiency. Lackner and Döring [*1*] reported the identification of a series of barbiturates using ^{1}H-NMR. Avdovich and Neville [*2*] later reported a method using ^{13}C-NMR for the simultaneous identification of amobarbital and secobarbital in formulations. ^{1}H-NMR was also applied to the identification of various ingredients in counterfeit formulations of legal controlled stimulants [*3*]. Spectral identification of the components of these mixtures was made without chromatographic separation. The alkyl nitrites, because of their volatility, may also present to the analyst problems of identification. NMR has again proven useful for the identification of mixtures of these substances [*4*]. Indeed, both ^{1}H-NMR [*5*] and a combination of ^{1}H- and ^{13}C-NMR [*6*] have been used for the identification and quantification of pharmaceutical preparations and forensic drug exhibits.

The plant khat, *Catha edulis*, which grows primarily in East Africa has been seized on numerous occasions in Canada. The major active principle of the plant is (−)-cathinone,

[1] Research Scientist, Research Technologist, Undergraduate Student and Research Scientist, respectively, Pharmaceutical Chemistry Division, Bureau of Drug Research, Health Protection Branch, Ottawa, Ontario, Canada

1S, which reportedly undergoes enzymatic reduction in the plant to (+)-norpseudoephedrine (cathine), 3SS, and (−)-norephedrine, 2SR, [7] (Fig. 1). The *trans*-cinnamyl analogues [8] of cathinone, merucathinone, 4S, and of cathine, merucathine, 5SS, were also subsequently identified in khat plants grown in Kenya. The plant can therefore be expected to contain a mixture of at least three optically active alkaloids. The amphetamine-like effects [9], [10] of these alkaloids have resulted in their international control. The Convention on Psychotropic Substances, 1971 lists (−)-cathinone on Schedule I and (+)-cathine on Schedule III. Presently, cathinone and (+)-cathine are listed on Schedule I and IV respectively of the Controlled Substance Act of the United States of America.

Benshafrut and Rothchild [11] have described the determination of the relative amounts of the (S)- and (R)-enantiomers of cathinone in synthetic mixtures after conversion of the alkaloid to the N-acetyl derivative. Subsequent addition of a chiral lanthanide shift reagent permitted ^{1}H-NMR determination of the isomer ratios based on the acetyl methyl signals.

We recently reported [12] the mass spectral identification of the major alkaloids of this plant using gas chromatography-mass spectrometry (GC-MS) after derivatization with the optically active carboxylic acid, (R)-(+)-α-methoxy-α-(trifluoromethyl) phenylacetic acid.

Herein, we report the simultaneous identification of the three major khat alkaloids and the determination of the enantiomeric cathinone content of dried khat samples using the chiral solvating agent, (S)-(−)-1,1′-bi-2-naphthol, and ^{1}H-NMR. A comparison of the results obtained for the enantiomeric composition of the cathinone fraction in samples by both the GC-MS and NMR methods is given.

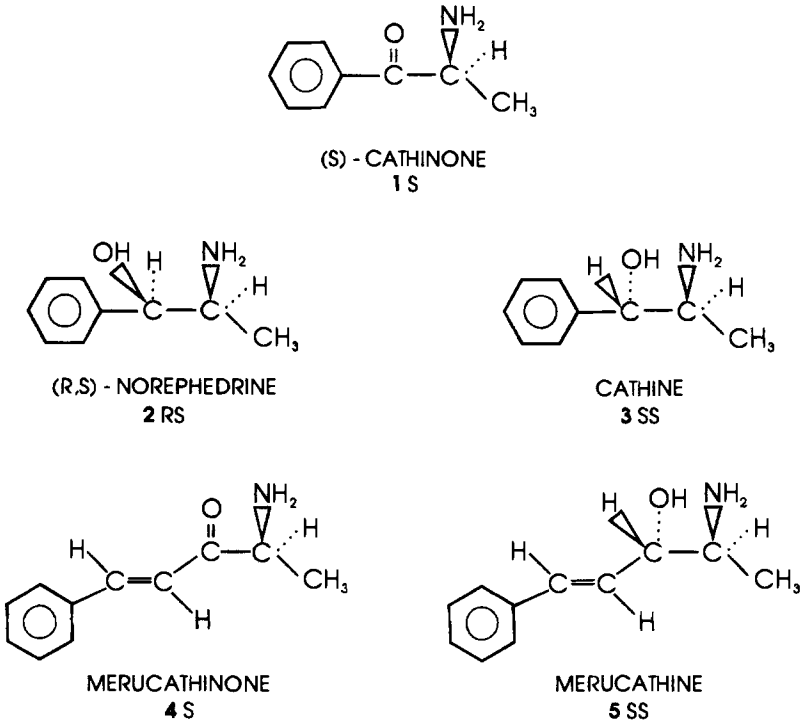

FIG. 1—*Structures of the major phenylalkylamine khat alkaloids; cathinone, 1S; (1R,2S)-(−)-norephedrine, 2RS; cathine, (1S,2S)-(+)-norpseudoephedrine, 3SS; merucathinone, 4S; merucathine, 5SS.*

Experimental Procedure

Reagents and Chemicals

The following reagents were obtained from Aldrich Chemical Co. (Milwaukee, WI,): (R)-(+)-α-methoxy-α-(trifluoromethyl)-phenylacetic acid (MTPA); (+,−)-cathinone hydrochloride, **1**, which is sold as 2-aminopropiophenone hydrochloride; (+,−)-norephedrine hydrochloride, **2**; (1R, 2S)-(−)-norephedrine, **2RS**; (1S, 2R)-(+)-norephedrine hydrochloride, **2SR**; (1S, 2R)-(+)-norephedrine, **2SR**; and (1R, 2R)-(−)-norpseudoephedrine hydrochloride, **3RR**; (S)-(−)-1,1′-bi-2-naphthol; and dicyclohexylcarbodiimide (DCC). Cathine hydrochloride, **3SS**, and cathinone hydrochloride, **1S**, were obtained from the United Nations Drug Control Program Laboratory, Vienna, Austria. Deuterochloroform was from Isotec, Inc. (Miamisburg, OH).

Samples

The samples were seized at Ottawa International Airport over a period of about one year. They were stored in detention under refrigeration (5°C) and sent to the laboratory the day after seizure. Upon receipt in the laboratory they were either freeze dried or air dried in a fume hood. Undried portions of the samples were stored at about 10°C. After drying, they were stored at room temperature in sealed clear jars until analyzed. A summary of the sample information is presented in Table 1.

Nuclear Magnetic Resonance

Spectra were recorded on a Bruker AM-400 spectrometer equipped with an Aspect 3000 computer and process controller. Standard microprograms from the Bruker Software Library were employed. Samples were recorded in a 5 mm NMR tube at 298 K using 32 transients and a standard 5 mm Bruker ^1H probe, a 30° flip angle and acquisition time of 2.92 s. A relaxation delay of 3 s was specified. Data from a sweep width of 5618 Hz was stored in 32K data points. Spectra were processed using Gaussian window function for spectral resolution enhancement with a line broadening of −1 and Gaussian broadening of 0.342.

GC-MS

The GC was a Carlo Erba Vega Series 6000 equipped with a Grob-type split/splitless injector and a 15-m by 0.25-mm i.d. DB-5 column, 0.25-μm film thickness (J & W Scientific Inc., Rancho Cordova, CA, USA). The GC was operated at a head pressure of 40 kPa of

TABLE 1—*Sample history.*

Sample No.	Months stored[a]	Sample history[b]	Drying conditions[c]
1a	17	1	fd
1b	"	4	fd
1c	"	7	fd
1d	"	5	ad
2	13	3	fd
3	11	2	fd
4a	03	1	fd
4b	"	1	ad

[a]Indicates the number of months the sample was stored at room temperature after initial drying.
[b]Refers to the number of days the plant material was stored at approximately 10°C before drying.
[c]Fd, freeze drying; ad, air drying.

helium (linear velocity at 160°C = 55 cm/sec). The injector was maintained at 275°C. One μL injections were made at a split ratio of approximately 25:1. The oven program was: start at 190°C, maintain for 1 min, increase at 2°C/min to 220°C, maintain for 1 min, increase at 20°C/min to 275°C. The mass spectrometer was a Finnigan-MAT Model 800 Ion Trap Detector. The GC's column effluent was introduced to the Ion Trap by direct attachment of the column. No splitting occurred at the GC-MS interface. The Ion Trap was operated in electron impact or chemical ionization mode (methane) and was set to acquire data at 1 scan/s over a mass range of 40 to 500 amu.

GC-FID

The GC was a Hewlett-Packard model 5890, Series I, equipped with a flame ionization detector, split/splitless injector and a model 5895A ChemStation data system/system controller. The column and temperature program were the same as that used in the GC-MS. The GC was operated at a head pressure of 85 kPa (12 psi) (linear velocity at 160°C = 40 cm/sec) of helium. The injector was maintained at 275°C. The temperature of the FID detector was maintained at 275°C with a mixture of air at 400 mL/min and hydrogen at 30 mL/min. Nitrogen was used as make-up gas at a flow of 30–40 mL/min. One μL injections were made at a split ratio of approximately 25:1.

Sample Extraction

NMR Spectra-Standards—Approximately 1 mg of the base form of the standard was dissolved in 0.45 mL of $CDCl_3$. The proton spectrum was recorded. The solvating agent, (S)-(−)-1,1′-bi-2-naphthol, 20 mg, was then added directly to the tube and the tube agitated slightly to dissolve the solid before recording the spectrum again. Where the standard was available as the hydrochloride salt, the base was extracted from aqueous solution with $CHCl_3$ after having been rendered basic with potassium carbonate. The resulting $CHCl_3$ solution was dried over sodium sulfate and evaporated with a stream of nitrogen. The residue was redissolved immediately in 0.45 mL of $CDCl_3$. The spectra were recorded as described.

NMR Spectra-Samples

A 200 mg portion of a finely ground sample of leaves was placed in a 15 mL centrifuge tube. To the tube was added 5 mL of 0.1N hydrochloric acid and the tube placed in an ultra-sonic bath for 30 min. As much as possible of the aqueous solution was withdrawn and transferred to another tube. The aqueous extract was washed once with a 2 mL portion of $CDCl_3$ and the organic phase discarded. The pH of the aqueous solution was adjusted to 8 with a saturated solution of sodium bicarbonate and extracted twice with 2 mL aliquots of $CDCl_3$. The combined organic extracts were then evaporated with a stream of nitrogen to about 800 μL. This solution was used for the acquisition of the proton spectrum. The solvating agent, (S)-(−)-1,1′-bi-2-naphthol, 20 mg, was then added directly to the tube, as for the standards, and the spectrum recorded again.

GC-MS and GC-FID Chromatograms

A portion (200 mg) of dried ground leaves was extracted sequentially four times with 5 mL of 0.1N HCl. Each extraction was performed in an ultrasonic bath for 15 min after which as much as possible of the aqueous solution was withdrawn and transferred to another centrifuge tube. The combined aqueous extracts were then extracted once with a 2 mL aliquot of dichloromethane (DCM). The pH of the aqueous solution was then adjusted to 8 with a saturated aqueous solution of sodium bicarbonate and the solution extracted with

four 5 mL aliquots of DCM. The combined organic extracts were evaporated with the aid of nitrogen and the residues were immediately redissolved in 100 μL of DCM.

Derivatization Procedure

To the 100 μL of DCM extract from the plant was added sequentially 100 μL of a 0.05 M solution of MTPA in DCM followed immediately by 100 μL of a 0.05 M solution of DCC. The reaction was allowed to stand at room temperature for 5 min before injection.

Results and Discussion

Figure 2 is a ^{1}H-NMR of a synthetic mixture of the standards of **1**, **2** and **3**RR and **3**SS. The methyl doublets for the three substances are visible in the 0.9 to 1.5 ppm range. These doublets were centered at 0.97, 1.04 and 1.36 ppm for compounds **2**, **3** and **1** respectively. The benzylic protons of **2** and **3** gave doublets at about 4.6 and 4.3 ppm respectively. The C-2 methine proton signals of **2** and **3** are the multiplets centered at about 3.2 and 3.0 ppm. The methine proton of **1** is the multiplet at about 4.5 ppm. Few characteristic signals are located in the aromatic region. Figure 3 is the same solution to which has been added 20 mg of the binaphthol. This mass of the binaphthol results in a nearly saturated solution. It was found to be acceptable for the solvation of the standards at about 1 mg (in the NMR tube) as well as for the samples. Comparison of spectra of the samples and standards indicated the approximate amount of total alkaloids in the sample extracts to be 100 to 200 μg. As might be expected most of the aromatic signals from the alkaloids are masked by the aromatic signals of the solvating agent. This spectrum also reflects the relative amounts of the alkaloids and reagent. One can see that a general upfield shift of all of the

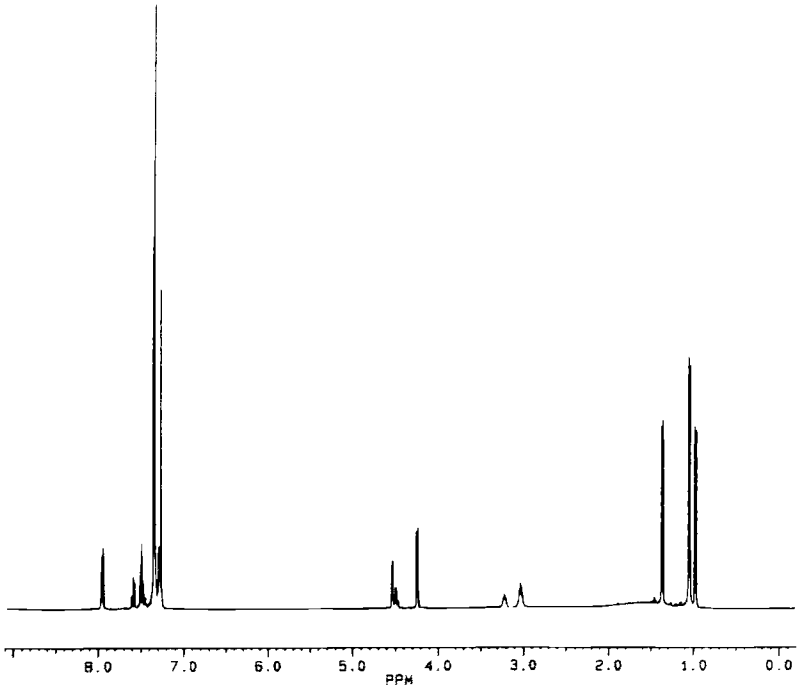

FIG. 2—*^{1}H-NMR spectrum of a mixture of standards of (+,−)-2-aminopropiophenone, (+,−)-norephedrine and (+)- and (−)-norpseudoephedrine. See text for peak assignments.*

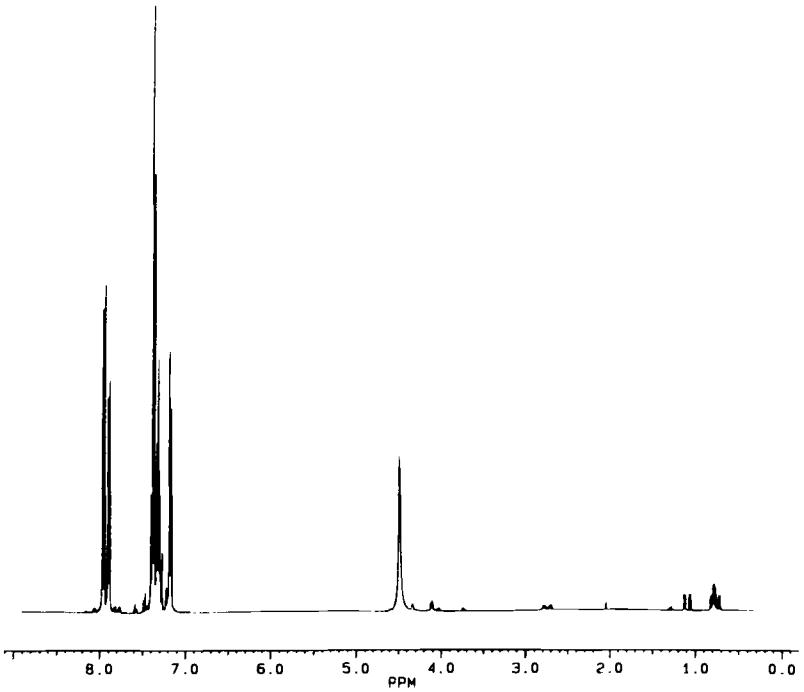

FIG. 3—*^{1}H-NMR spectrum of a mixture of standards of (+,−)-2-aminopropiophenone, (+,−)-norephedrine and (+)- and (−)-norpseudoephedrine after the addition of the chiral solvating agent, (S)-(−)-1,1'-bi-2-naphthol. See text for peak assignments.*

methyl and methine protons has taken place. The resolution of the enantiomeric methyl doublets in the 0.6–1.3 ppm range can also be seen. Figure 4 is an expansion of this latter portion of the spectrum. The two doublets situated at about 1.05 and 1.11 ppm are due to the **1**R and **1**S methyl groups. As expected for a racemic mixture the relative intensities are very similar. The methyl doublets due to the norephedrine/norpseudoephedrine series appear at about 0.71, 0.75, 0.79 and 0.81 ppm. These are, respectively, the signals from **2**SR, **2**RS, **3**SS and **3**RR. The differences in the intensities of these signals is due to the fact that the mixture was prepared from racemic **2** and individual isomers of **3**SS and **3**RR. The assignments were determined by recording the spectrum of each individual isomer.

The isomeric integrity of cathinone during the extraction process and its stability in the $CDCl_3$ was confirmed by comparing the results of the determination of the R and S isomer content of the standard, cathinone hydrochloride, **1**S, by the NMR method and by optical rotation. Two portions of about 1 mg each were used for the NMR determination. One portion was treated as a sample in that it was dissolved in 5 mL of 0.1N HCl, sonicated for 15 min. and extracted and analyzed as described under NMR Spectra-Samples. The second portion was treated by adding 2 mL of 0.1N HCl, immediately adjusting the solution to pH 7–8 and extracting with 2 mL of $CDCl_3$. The organic solvent was concentrated to 0.8 mL for analysis by NMR. The ratios of R and S cathinone in the sample were then determined as described above. No significant peaks other than those ascribed to cathinone were detected in the solutions by NMR either before or after the addition of the solvating agent. The results indicated the presence of 8.7% (as a sample) and 8.8% (fast extraction) of the R-enantiomer of cathinone. Re-analysis of another portion of the $CDCl_3$ solutions after storage at 5°C for 24 hours indicated the presence of 8.8% and 8.9% respectively of

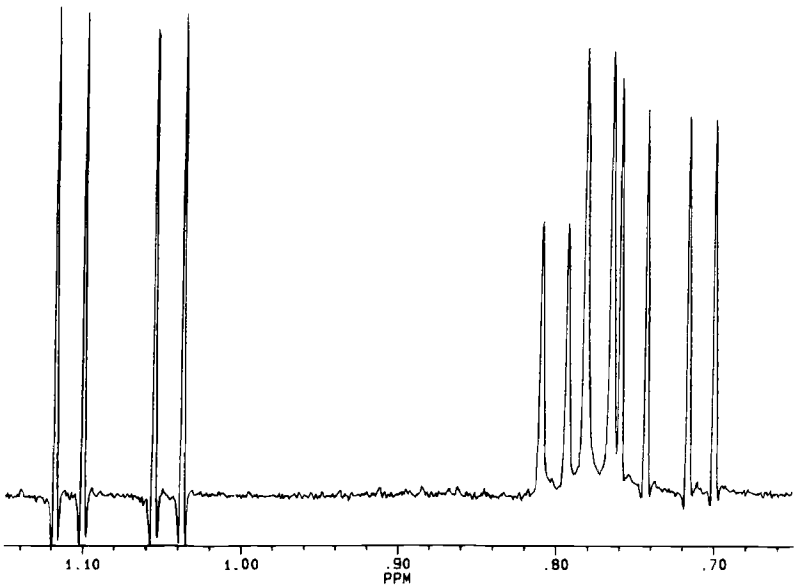

FIG. 4—*Expansion of the upfield (0.6–1.15 ppm) range of the ^{1}H-spectrum of a mixture of standards of (+,−)-2-amino-propiophenone, (+,−)-norephedrine and (+)- and (−)-norpseudoephedrine after the addition of the chiral solvating agent, (S)-(−)-1,1'-bi-2-naphthol. See text for peak assignments.*

the R-enantiomer. These results agree favorably with the results [*12*] from the determination of optical purity by specific rotation which indicated the presence of 11% of the R-enantiomer and indicate that cathinone is stable both under the extraction conditions and in the final $CDCl_3$ solution.

Figure 5 is a full ^{1}H-NMR spectrum of a plant extract. The signals for the most part correspond to those found in the synthetic mixture of the alkaloids (Fig. 2). Two additional sharp singlets at about 2 ppm are seen which are due to unidentified components. However, an additional series of signals suggests the presence of merucathine, **5**SS. The positions of the methyl doublet at about 1.2 ppm and the olefinic multiplet are consistent with the structure of this cathine analogue. The latter gave rise to signals centered at 6.7 ppm (d, $J_{1,2}$ = 15.8) and 6.3 ppm (dd, $J_{2,3}$ = 6.3) which is similar to the description of the multiplet reported by Brenneisen [*8*] for the oxalate salt of the *trans* isomer. The presence of this alkaloid was also indicated by GC-MS (see the following). The extract is sufficiently devoid of interfering substances to confirm that the sample contains 2-amino-propiophenone, norephedrine and norpseudoephedrine. Figure 6 is the expanded upfield region of the spectrum after the addition of the solvating agent. This spectrum confirms the presence in the extract of only the **2**RS and **3**SS enantiomers of the norephedrine/norpseudoephedrine diastereomeric pairs. It is evident from the peak heights that this sample contained approximately equal amounts of **2**RS and **3**SS. The doublet at about 0.86 ppm is most probably due to merucathine. It should be noted that the signals due to both the **1**S and **1**R enantiomers are visible. The presence of the R-enantiomer of cathinone in dried plant material has not previously been reported in the literature. Figure 7 is a spectrum of another sample which contained relatively more of the **1**R isomer.

Table 2 shows the relative amounts of the cathinone enantiomers in the samples as determined by NMR. The relative amounts of the enantiomers were calculated from the averages of the peak heights of the respective methyl doublets.

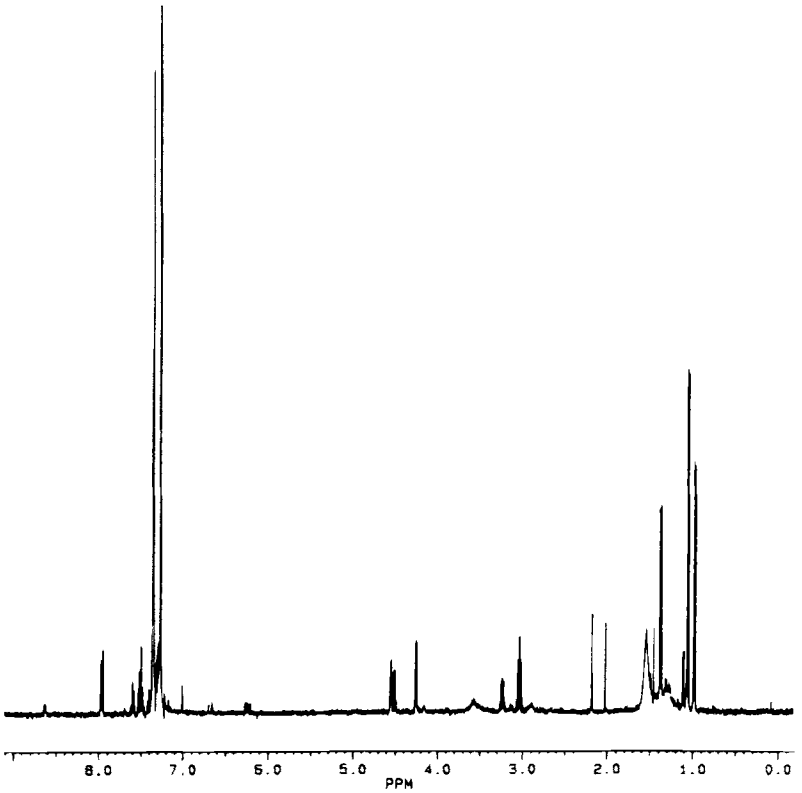

FIG. 5—^{1}*H-spectrum of an extract of the plant, catha edulis indicating the presence of (+,−)-2-aminopropiophenone, (+,−)-norephedrine and (+,−)-norpseudoephedrine.*

The stability of the alkaloids in the NMR medium was confirmed by repeatedly determining the ratios of the enantiomeric contents of the alkaloids in the same NMR tube over a period of 3 hours. No significant changes in the alkaloid ratios were detected indicating chiral integrity of the analytes in the solvating solution.

Figure 8 is the total ion chromatogram of a sample extract after derivatization. The DCC (peak 1), MTPA anhydride (peak 3) and dicyclohexylurea (peak 4) resulting from the reaction elute before the alkaloidal derivatives. The MTPA elutes with the solvent front. Peak 2 is an unidentified component resulting from the reagents only. For this chromatogram the filament of the Trap was activated after 60 seconds to detect these substances but for repeated analysis the filament-off time could be increased to prevent ionization of these reagents. During the course of the work, the repeated injection of the reaction mixtures had no apparent detrimental effects on the column, injector or detection systems of either GC. Peaks 5–8 are, in order of elution, the MTPA amides of **1**S, **1**R, **2**RS and **3**SS. The mass spectra of the derivatives are shown in Figs. 9 and 10. All of the derivatives of MTPA and the alkaloids gave spectra with weak M+1 ions in electron ionization mode. This is a phenomenon of the Ion Trap which is unavoidable with some substances, particularly amines [*13*].

We propose that peak 9 at 910 scans is the derivative of merucathine. Although no standard for this substance was available, its mass spectrum was very similar to those of the derivatives of **3**SS and **2**RS. In addition, the chemical ionization mass spectrum of the

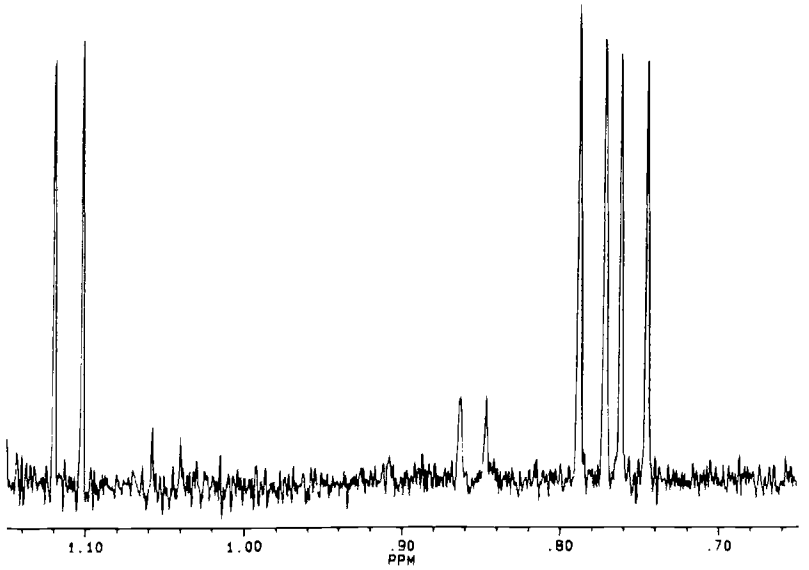

FIG. 6—*Expansion of the upfield (0.6–1.15 ppm) range of the* ^{1}H*-spectrum of a plant extract after the addition of the chiral solvating agent, (S)-(−)-1,1'-bi-2-naphthol, indicating the presence of (S)- and (R)-cathinone, (R,S)-norephedrine and (S,S)-norpseudoephedrine.*

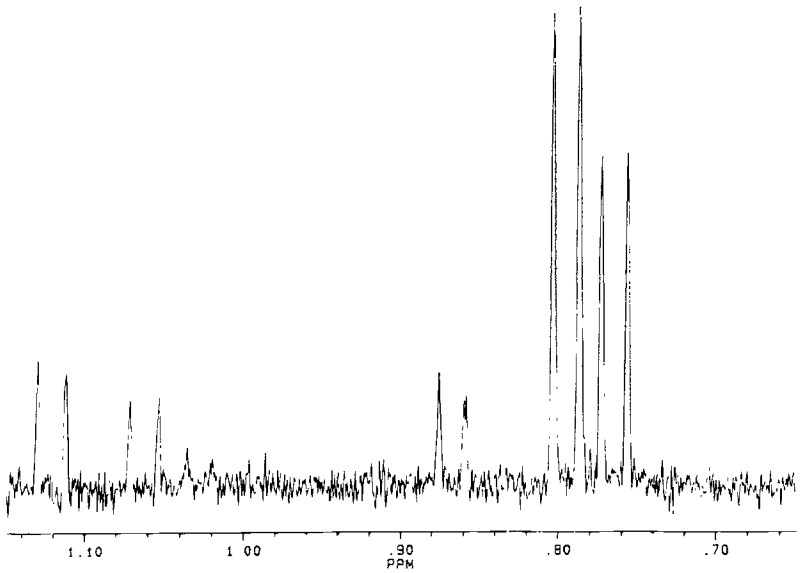

FIG. 7—*Expansion of the upfield (0.6–1.15 ppm) range of the* ^{1}H*-proton spectrum of a different plant extract after the addition of the chiral solvating agent, (S)-(−)-1,1'-bi-2-naphthol, indicating the presence of (S)- and (R)-cathinone, (R,S)-norephedrine and (S,S)-norpseudoephedrine.*

TABLE 2—*Relative amounts of cathinone enantiomers in samples as determined by NMR and GC.*

Sample No.	Relative amounts of **1S** and **1R** as % total **1**			
	NMR		GC	
	1S	**1R**	**1S**	**1R**
1a	88	12	87	13
1b	58	42	58	42
1c	63	37	62	38
1d	55	45	53	47
2	64	36	64	36
3	68	32	64	36
4a	84	16	82	18
4b	81	19	77	23

peak indicated an M+1 of 394, which is consistent with a cinnamyl analogue. However, no peaks in the chromatogram suggestive of the presence of merucathinone could be identified.

The extraction procedure used for the preparation of the samples for GC-MS analysis differs from that used for NMR as the former yielded a more complete extraction. From the results of the analysis of sequential extracts of plant material it could be estimated that more than 95% of the cathinone was extracted into the final DCM solution derived from the GC-MS extraction method. However, results from a similar study of the **2RS** and **3SS** alkaloids indicated only about 75% of the total alkaloid content was extracted into the final DCM solution. The single extraction step for the NMR was adopted to provide a more efficient method of analysis.

The results of the analysis of the samples using the GC derivatization procedure are also presented in Table 2. Comparison of the relative amounts of the (S) - and (R) - enantiomers of cathinone (normalized to total cathinone = 100) indicates an excellent correlation between

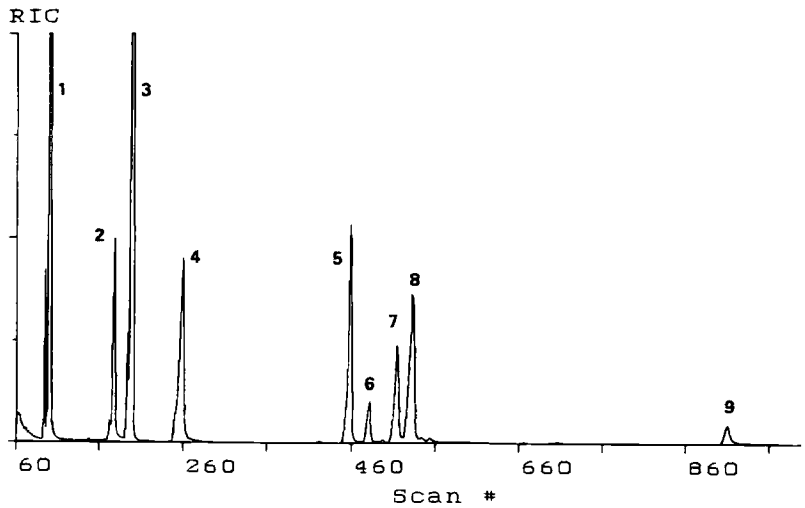

FIG. 8—*Full reconstructed ion chromatogram of a plant extract after derivatization with (R)-(+)-α-methoxy-α-trifluoromethylphenylacetic acid (MTPA). Peak assignments: 1, dicyclohexylcarbodiimide (DCC); 2, unidentified reagent peak; 3, MTPA anhydride; 4, dicyclohexylurea; 5, (S)-cathinone, 1S, derivative; 6, (R)-cathinone, 1R, derivative, ; 7, (R,S)-norephedrine, 2RS, derivative; 8, (S,S)-norpseudoephedrine, 3SS, derivative; 9, proposed merucathine derivative.*

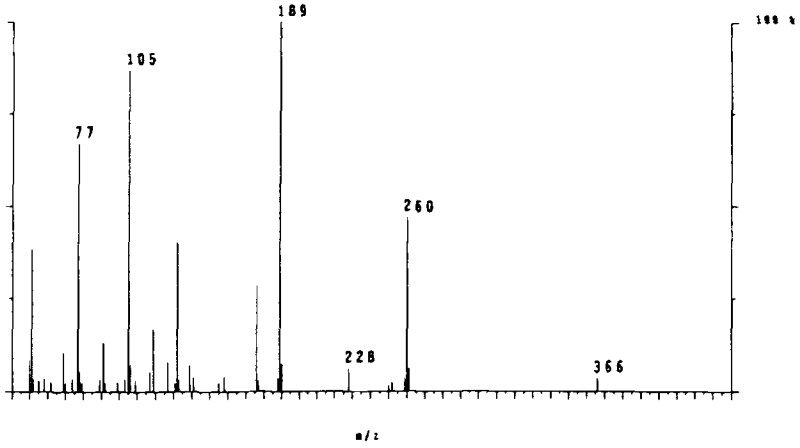

FIG. 9—*Electron impact mass spectrum of the MTPA amide of (S)-cathinone.*

the two methods. It would appear that even though the extraction procedure used for the NMR analysis is less complete than that used for the GC analysis, the relative proportions of the enantiomers determined by NMR still accurately reflect the isomer content in the seized plant material.

Table 3 shows a comparison of the relative amounts of the **2RS** and **3SS** alkaloids (normalized to total **2RS** + **3SS** = 100) in the samples of plant as determined by both NMR and GC. Considering the difference in the extraction techniques for the NMR and GC analyses, good correlation was obtained by the two methods. This would appear to indicate that there is also little difference in the degree of extraction of the diastereomers.

In conclusion, NMR is shown to be an efficient method for the conclusive identification of the alkaloids of khat. It is also able to provide information on the relative amounts of the cathinone enantiomers and the relative amounts of the norephedrine/norpseudoephedrine diastereomers present in the plant at the time of analysis. The presence of the R-enantiomer of cathinone in the samples of the plant imported into Canada is most probably due to the racemization of the naturally produced S-cathinone. This phenomenon may account, to

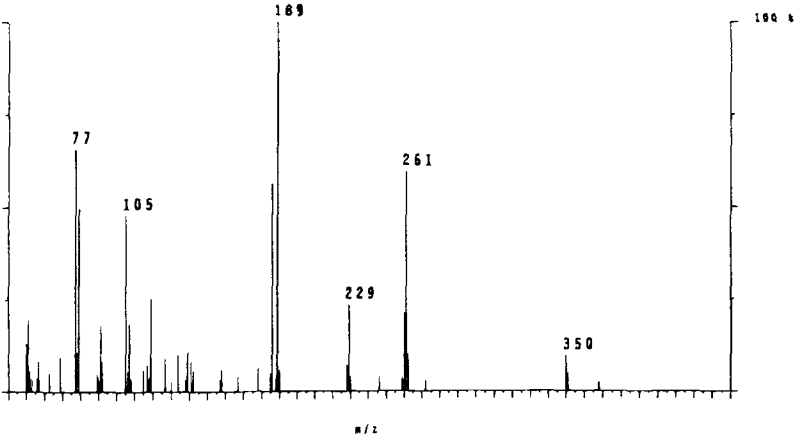

FIG. 10—*Electron impact mass spectrum of the MTPA amide of (S,S)-norpseudoephedrine.*

TABLE 3—*Relative amounts of 2RS and 3SS enantiomers in samples as determined by NMR and GC.*

Sample No.	Relative amounts of 2RS and 3SS			
	NMR		GC	
	2RS	3SS	2RS	3SS
1a	44	56	44	56
1b	41	59	39	61
1c	41	59	39	61
1d	34	66	32	68
2	32	68	31	69
3	41	59	41	59
4a	41	59	41	59
4b	41	59	42	58

some extent, for the recognized loss of activity of the plant after harvest [*10e*] which traditionally has been ascribed to reduction of cathinone [*7,14*] to the corresponding less active alcohols [*15*].

References

[*1*] Lackner, H. and Döring, G., "Die NMR-specktroskopische Identifizierung von Barbituraten," *Archives of Toxicology,* Vol. 26, 1970, pp. 220–236.

[*2*] Avdovich, H. W. and Neville, G. A., "^{13}C Characterization of a Combination Product of Amobarbital Sodium and Secobarbital Sodium," *Canadian Journal of Pharmaceutical Sciences,* Vol. 15, 1980, pp. 75–77.

[*3*] Avdovich, H. W., Jin, S. H., and Wilson, W. L., "NMR Method for Identification of Look-Alike Drugs," *Canadian Society of Forensic Science Journal,* Vol. 18, 1985, pp. 24–31.

[*4*] LeBelle, M., Callahan, S., and Avdovich, H. W., "Identification of Alkyl Nitrites," *Canadian Society of Forensic Science Journal,* Vol. 21, 1988, pp. 66–70.

[*5*] Angelos, S. A., Janovsky, T. J., and Raney, J. K., "The Identification and Quantitation of Pharmaceutical Preparations by Nuclear Magnetic Resonance Spectroscopy," *Journal of Forensic Sciences,* Vol. 36, No. 2, March 1991, pp. 358–365.

[*6*] Alm, S., Bomgren, B., and Borén, H. B., "The Use of ^{13}C NMR Spectroscopy in Forensic Drug Analysis," *Forensic Science International,* Vol. 19, 1982, pp. 271–280.

[*7*] Szendrei, K., "The Chemistry of Khat," *Bulletin on Narcotics,* Vol. 22, 1980, pp. 5–35.

[*8*] Brenneisen, R., Geisshüsler, S., and Schorno, X., "Merucathine, a New Phenylalkylamine from Catha Edulis," *Planta Medica,* Vol. 50, 1984, p. 531.

[*9*] Kalix, P., Geisshüsler, S., Brenneisen, R., Koelbing, U., and Fisch, H.-U., "The Khat Alkaloid Cathinone Has Amphetamine-Like Effects in Humans," *European Journal of Pharmacology,* Vol. 183, 1990, pp. 457–458.

[*10*]a. Zelger, J. L., Schorno, Hj. X., and Carlini, E. A., "Behavioral Effects of Cathinone, an Amine Obtained from Catha Edulis Forsk.: Comparisons with Amphetamine, Norpseudoephedrine, Apomorphine and Nomifensine," *Bulletin on Narcotics,* Vol. 32, 1980, pp. 67–81.

b. Kalix, P. and Glennon, R. A., "Further Evidence for an Amphetamine-Like Mechanism of Action of the Alkaloid Cathinone," *Biochemistry Pharmacology,* Vol. 35, 1986, pp. 3015–3019.

c. Glennon, R. A., Yousif, M., Naiman, N., and Kalix, P., "Merucathinone: A New and Potent Amphetamine-Like Agent," *Pharmacology Biochemistry and Behaviour,* Vol. 26, 1987, pp. 547–551.

d. Brenneisen, R., Fisch, H.-U., Koelbing, U., Geisshüsler, S., and Kalix, P., "Amphetamine-Like Effects in Humans of the Khat Alkaloid," *British Journal of Clinical Pharmacology,* Vol. 30, 1990, pp. 825–828.

e. Kalix, P., "Cathinone, a Natural Amphetamine," *Pharmacology and Toxicology,* Vol. 70, 1992, pp. 77–86.

[*11*] Benshafrut, R. and Rothchild, R., "NMR Studies of Drugs. Enantiomeric Excess Determination of N-acetylcathinone with Eu $(HFC)_3$," *Spectroscopy Letters,* Vol. 25, No. 7, 1992, pp. 1097–1120.

[*12*] LeBelle, M. J., Lauriault, G., and Lavoie, A., "Gas Chromatographic - Mass Spectrometric Identification of Chiral Derivatives of the Alkaloids of Khat," *Forensic Science International,* Vol. 61, 1993, pp. 53–64.

[13] By, A. W., LeBelle, M. J., Lodge, B. A., and Wilson, W. L., "Analysis and Identification of Canadian Designer Drugs," presented at the 103rd Association of Official Analytical Chemists Meeting, September 1989, St. Louis.
[14] Brenneisen, R. and Geisshüsler, S., "Psychotropic Drugs III. Analytical and Chemical Aspects of Catha Edulis Forsk," *Pharmaceutica Acta Helvitetiae*, Vol. 60, 1985, pp. 290–301.
[15] Kalix, P. and Braenden, O., "Pharmacological Aspects of the Chewing of Khat Leaves," *Pharmacological Reviews*, Vol. 37, 1985, pp. 149–164.

Address requests for reprints or additional information to
M. J. LeBelle
Pharmaceutical Chemistry Division
Bureau of Drug Research
Banting Building, Tunney's Pasture
Ottawa, Ontario, Canada
K1A OL2