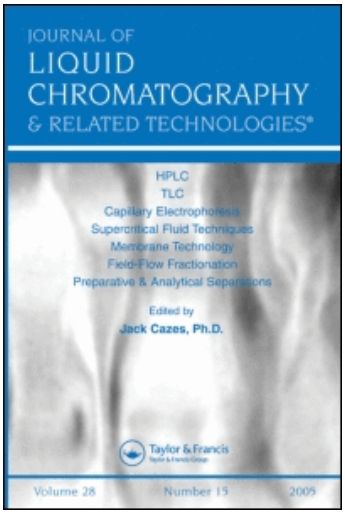


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# Liquid Chromatographic and Mass Spectral Analysis of 1-Phenyl-2-Butanamines: Homologues of the Amphetamines

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# LIQUID CHROMATOGRAPHIC AND MASS SPECTRAL ANALYSIS OF 1-PHENYL-2-BUTANAMINES: HOMOLOGUES OF THE AMPHETAMINES

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## ABSTRACT

The N-substituted 1-phenyl-2-butanamines were prepared from 1-phenyl-2-butanone via reductive amination. The 2-butanamines are homologues of the amphetamine-type drugs of abuse. The N-substituted 2-butanamines were separated via reversed-phase liquid chromatography using an acidic mobile phase (pH 3) and $C_{18}$ and phenyl silica stationary phases. Similar reversed-phase conditions allowed for excellent resolution of methamphetamine from its regiosiomer 1-phenyl-2-butanamine. The mass spectra (EI) for the 2-butanamines show the characteristic imine base peaks which are identical to those for the N-substituted amphetamines making these two series of compounds very similar by EI fragmentation.

## INTRODUCTION

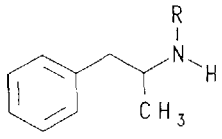
Central nervous system stimulants related to methamphetamine remain popular drugs of abuse in North America. The continued interest in drugs of this type is highlighted by the emergence of

crystalline methamphetamine or "ice" in recent years, as well as the appearance of analogues including N,N-dimethylamphetamine and N-ethylamphetamine in street samples [1]. Also, over the past decade the scope of the substance abuse problem in the US has broadened with the appearance of the methylenedioxyamphetamine-type drugs, MDA and MDMA [2-4], and a number of "designer drug" analogues of this type [5-7] as well as the narcotic analgesics [8], PCP [9], and the hallucinogens [10].

Methamphetamine is produced in clandestine laboratories in the US by a variety of methods. The most common method appears to involve reductive amination of phenyl-2-propanone (P-2-P). In recent years the availabililty of P-2-P has been restricted (controlled), therefore it has become necessary for the clandestine chemist to devise methods for the synthesis of P-2-P, and the most common of these methods is via the phenylacetic acid route. Phenylacetic acid has recently been added to the list of controlled precursor chemicals. Thus clandestine laboratories are likely to employ other starting materials to synthesize "designer drug" analogues of the amphetamines. Such appears to be the case with the recent appearance of N-methyl-1-phenyl-3-butanamine, a homologue of methamphetamine, in street samples [11]. This amine was apparently synthesized by reductive amination using benzylacetone, a commercially available chemical not under legal control. It is not clear if this substance was produced as a "designer" derivative of methamphetamine or if the laboratory operator mistakenly assumed that the starting ketone benzylacetone, was the same chemical as phenylacetone (P-2-P). The latter hypothesis is reasonable since a similar error has been reported in cases [12] involving the attempted synthesis of MDA.

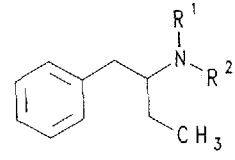
Another series of potential designer analogues are the alpha-ethyl derivatives of amphetamine or 1-phenyl-2-butanamines. These derivatives could be prepared by reductive amination using 1-phenyl-2-butanone, a commercially available chemical not under legal control. This designer series may be particularly attractive since the parent compound, 1-phenyl-2-butanamine has been synthesized and reported to possess CNS stimulant activity [13]. Therefore a number of N-substituted 1-phenyl-2-butanamines were prepared and chromatographic and spectral methods explored to distinguish these compounds from the homologous amphetamines.






R = H: Amphetamine

R = $CH_3$: Methamphetamine




1-Phenyl-2-butanamines

$R^1 = R^2 = H$

$R^1 = H$, $R^2 = CH_3$

$R^1 = H$, $R^2 = CH_2CH_3$

$R^1 = R^2 = CH_3$

## MATERIALS AND METHODS

The liquid chromatograph consisted of a Laboratory Data Control Constametric 3000 pump, 3100 Spectromonitor UV detector operated at 220 nm, CI 4100 Integrator and a Rheodyne 7125 Injector. The analytical columns used included a 25 cm X 4.6 mm i.d. 5 u Spherisorb-phenyl column (Chromanetics, Inc) and a 30 cm X 3.9 mm i.d. uBondapak $C_{18}$ column (Waters Associates). The amine hydrochlorides (1 mg/mL) were dissolved in HPLC grade

methanol and chromatographed using a mobile phase of pH 3.0 phosphate buffer, acetonitrile and triethylamine (600:100:1). The pH 3.0 phosphate buffer was prepared by mixing 9.2 g monobasic sodium phosphate ($NaH_2PO_4$) in 1 L of double-distilled water and adjusting the pH to 3.0 with $H_3PO_4$. The mobile phase flow rate was 1.5 mL/min and the detector was operated at 0.2 AUFS. A 5 uL aliquot of each amine solution was injected into the liquid chromatograph.

The electron impact (EI) mass spectra were obtained using a Hewlett-Packard 5970B mass selective detector. The ionization voltage was 70 eV and the source temperature was 220° C. The individual amine hydrochlorides were dissolved in methanol (1 mg/mL) and 0.5 uL introduced into the mass spectrometer via a gas chromatograph equipped with a 12 m X 0.20 mm i.d. fused silica column with a 0.33 um thickness of OV-1 methyl silicone (HP-1). The column temperature was programmed at 70°C for 2.5 min and from 70° C to 150° C at a rate of 25° C/min and from 150° C to 250° C at a rate of 15° C/min. The split ratio for the GC was 10:1 and all sample components eluted within approximately 7 minutes.

Infrared spectra were recorded on a Perkin-Elmer Model 1710 Fourier transform infrared (FTIR) spectrophotometer. Ultraviolet spectra were recorded on a Shimadzu Instruments Model UV-265 spectrophotometer.

The N-substituted 1-phenyl-2-butanamines were synthesized by reductive amination. The appropriate amine hydrochloride (63 mmoles) was added to a solution of 1-phenyl-2-butanone (6.7 mmoles) in methanol (100 mL). Sodium cyanoborohydride (1.0 g,

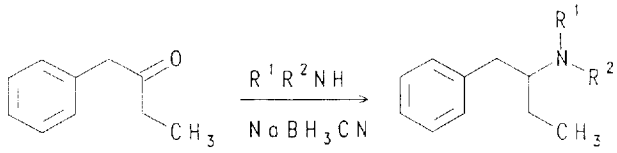
15.9 mmoles) was added portionwise followed by the addition of methanol to yield a solution. Several drops of conc. HCl were added to maintain the pH of the reaction solution at neutrality. The mixture was stirred at room temperature for 48 hours and evaporated under reduced pressure. The resulting oil was suspended in 3N HCl (25 mL) and washed with ether (2 x 25 mL). The acid solution was then made basic (pH 12) by the addition of NaOH pellets. The resulting aqueous base suspension was extracted with ether (2 x 30 mL) and the ether extracts combined, dried over anhydrous $MgSO_4$ and filtered. Treatment of the ether filtrate with HCl gas afforded the N-substituted 1-phenyl-2-butanamine hydrochlorides.



## RESULTS AND DISCUSSION

The 1-phenyl-2-butanamines are homologues of the 2-propanamine stimulants amphetamine and methamphetamine. The availability of appropriate precursor chemicals and the increasing interest in designer drug modifications makes the 2-butanamine homolgues potential targets for clandestine synthesis. Additionally, these compounds could display similar analytical profiles to comparably substituted amphetamine derivatives by some techniques. Thus, it is critical to establish forensic methods to differentiate between these various compounds.

The 1-phenyl-2-butanamines can be prepared from 1-phenyl-2-butanone via a reductive amination procedure as shown in Scheme 1. Treatment of 1-phenyl-2-butanone with ammonium acetate or amine hydrochlorides in the presence of sodium cyanoborohydride at neutral pH afforded the series of N-substituted-1-phenyl-2-butanamines. In these reactions the intermediate imine is formed




Scheme 1. Synthesis of the 1-phenyl-2-butanamines.

and reduced *in situ* by sodium cyanoborohydride. Sodium cyanoborohydride is used for these reactions instead of other reducing agents because of its selectivity for imine versus carbonyl reduction.

The ultraviolet absorption spectrum for N-methyl-1-phenyl-2-butanamine is shown in Figure 1. This spectrum was recorded in both acidic and basic solution and is characteristic of all of the various 1-phenyl-2-butanamines prepared for this study. This spectrum also is essentially equivalent to that of methamphetamine recorded under similar conditions. This general UV absorption pattern is characteristic of phenethylamine-type compounds and the variation from the methyl branch of the 1-phenyl-2-propanamines (amphetamines) to the ethyl side chain of the 1-phenyl-2-butanamines at the alpha-carbon of the phenethylamine skeleton does not significantly affect the electronic spectra for these compounds.

The four 1-phenyl-2-butanamines were separated by reversed-phase liquid chromatographic procedures and the chromatogram in Figure 2 is representative of the results obtained on a $C_{18}$ stationary phase. The mobile phase for this separation consisted of a pH 3 phosphate buffer, acetonitrile and triethylamine

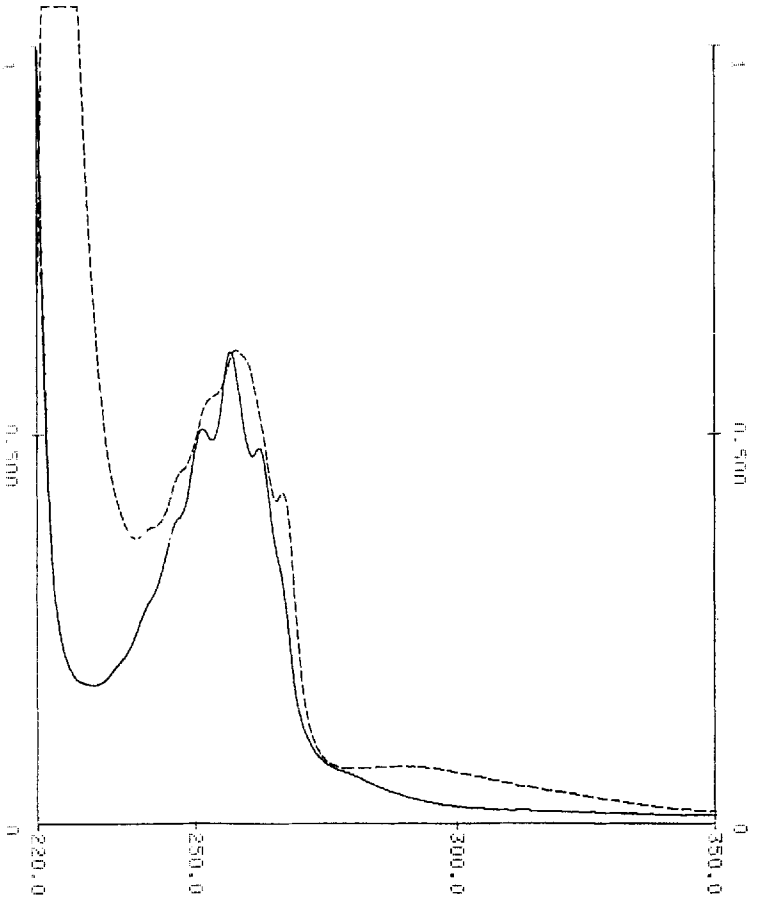



Figure 1. Ultraviolet spectrum of N-methyl-1-phenyl-2-butanamine: $H_2SO_4$ (———) and NaOH (-----).

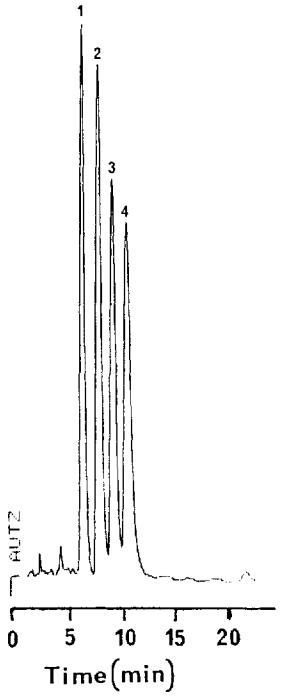



Figure 2. Reversed-phase liquid chromatographic separation of the 1-phenyl-2-butanamines using a $C_{18}$ uBondapak stationary phase. Peaks: 1 = primary amine, 2 = N-methyl, 3 = N,N-dimethyl and 4 = N-ethyl.

(600:100:1) and the total analysis time was about 12 minutes at a flow rate of 1.5 mL per minute. The buffer system is sufficiently acidic to maintain the 1-phenyl-2-butanamines as the protonated conjugate acid species during the separation. Under these conditions the triethylamine is also present in the conjugate acid form and this mobile phase additive improves peak shape and resolution via dynamic saturation of stationary phase active

sites. Amines are widely recognized as strong silanophiles, often yielding broad bands and severe peak tailing due to multiple interaction modes with the stationary phase. The use of a substance of similar basicity such as triethylamine which is transparent to the method of detection serves to prevent the analyte-silanophilic interactions.

The elution order for the 1-phenyl-2-butanamines in Figure 2 corresponds to the carbon content of the N-substituent with the primary amine eluting first, followed by the N-methyl derivative. The isomeric two-carbon derivatives display higher capacity factors with the N,N-dimethyl eluting prior to the N-ethyl derivative.



The chromatogram in Figure 3 was obtained using a phenyl silica stationary phase and the same pH 3 phosphate buffer, acetonitrile and triethylamine mobile phase as that described for the separation in Figure 2. The phenyl silica stationary phase yields excellent peak shape and resolution for these amines in an analysis time of about 9 minutes. This chromatogram shows improved resolution for the isomeric two-carbon N-substituted derivatives on the phenyl silica staionary phase with a reversal of the elution order when compared to the results obtained from the $C_{18}$ stationary phase in Figure 2. The tertiary amine, N,N-dimethyl-1-phenyl-2-butanamine has the highest elution volume in this chromatographic system.

The chromatogram in Figure 4 shows the separation of methamphetamine (N-methyl-1-phenyl-2-propanamine) and 1-phenyl-2-butanamine using the $C_{18}$ stationary phase and the mobile phase described earlier. These two compounds are uniquely similar,

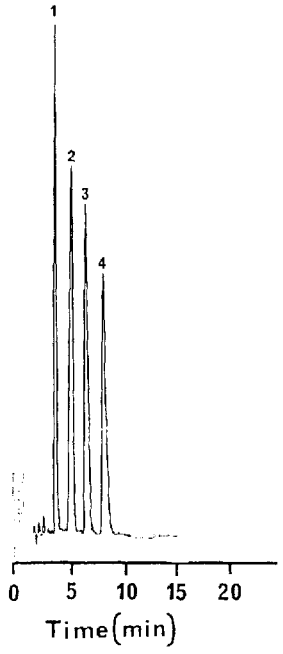



Figure 3. Reversed-phase liquid chromatographic separation of 1-phenyl-2-butanamines using a phenyl-silica stationary phase. Peaks: 1 = primary amine, 2 = N-methyl, 3 = N-ethyl and 4 = N,N-dimethyl.

having the same empirical formula ($C_{10}H_{15}N$) and molecular weight. These two compounds are regioisomeric in the position of a methyl group; it is on the nitrogen atom of methamphetamine and part of the alpha-ethyl side chain in 1-phenyl-2-butanamine. These two compounds are well resolved in this chromatographic system with the side chain methylated compound (1-phenyl-2-butanamine) having the higher capacity factor. These two compounds coeluted on the phenyl silica stationary phase using the conditions described previously.

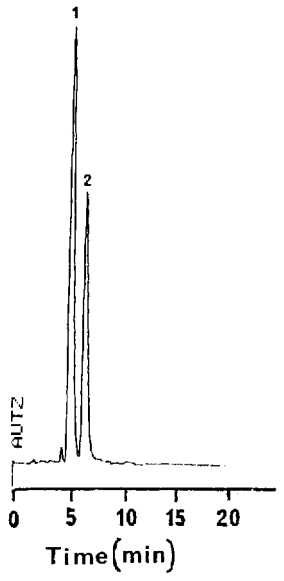



Figure 4. Reversed separation of methamphetamine and 1-phenyl-2-butanamine using a $C_{18}$ stationary phase. Peaks: 1 = methamphetamine and 2 = 1-phenyl-2-butanamine.



The electron impact (EI) mass spectra for the 1-phenyl-2-butanamines are shown in Figure 5A-D. These compounds show the low mass base peak resulting from imine formation as illustrated in Scheme 2. The imine from the primary amine has m/z = 58 and the other derivatives show this ion at m/z = 72 or 86 depending on the nature of the N-substitutents. In comparing the mass spectra of the isomeric N-ethyl and N,N-dimethyl derivatives, the more abundant m/z 58 ion in the spectrum of the N-ethyl compound results from a four-centered rearrangement of the imine base peak (m/z 86) to yield the primary imine.

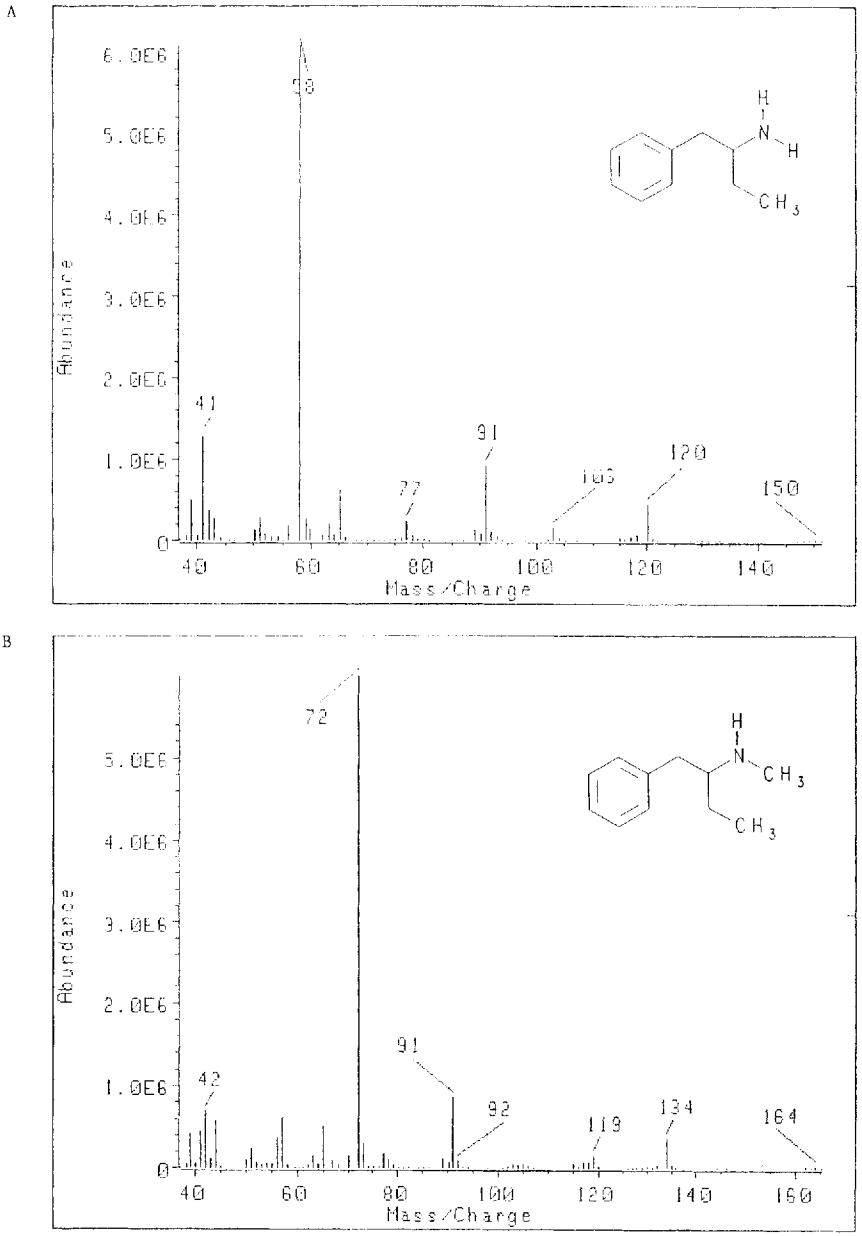
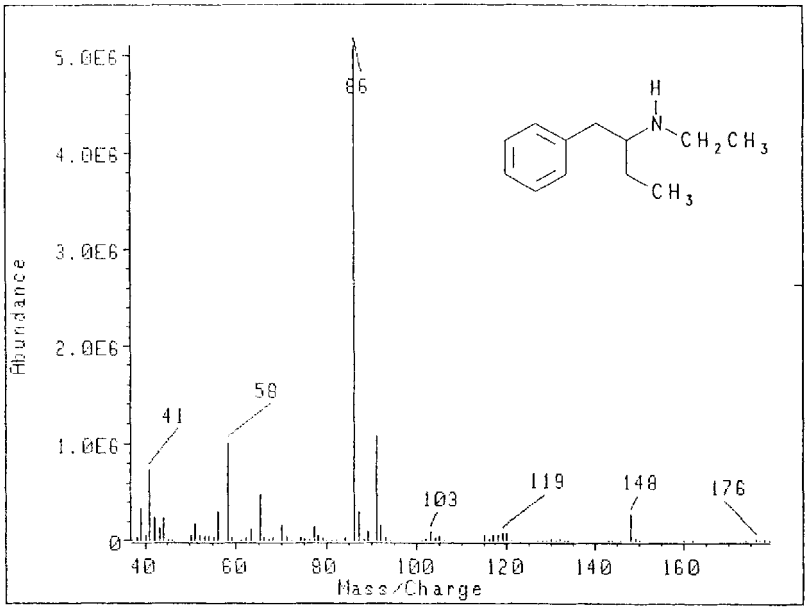



Figure 5. Mass spectra for the 1-phenyl-2-butanamines: 5A = 1-phenyl-2-butanamine, 5B = N-methyl-1-phenyl-2-butanamine, 5C = N-ethyl-1-phenyl-2-butanamine and 5D = N,N-dimethyl-1-phenyl-2-butanamine.

C




D

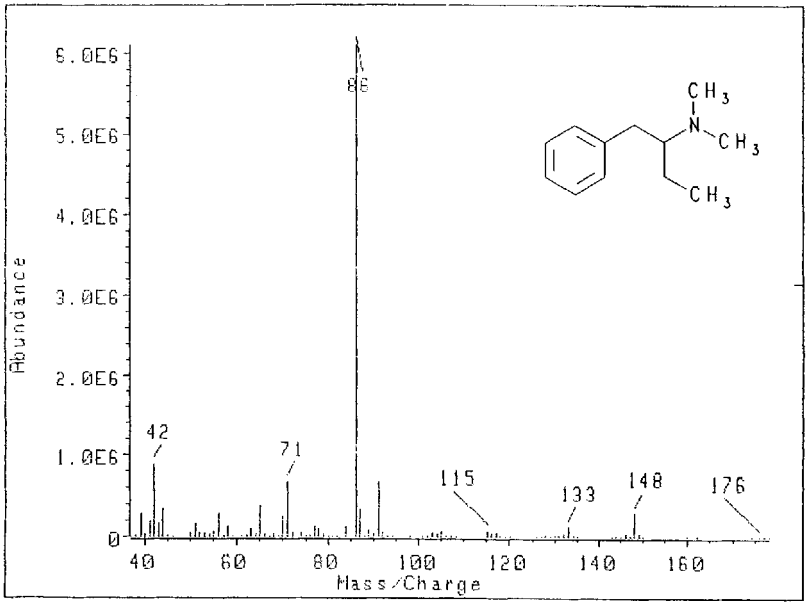
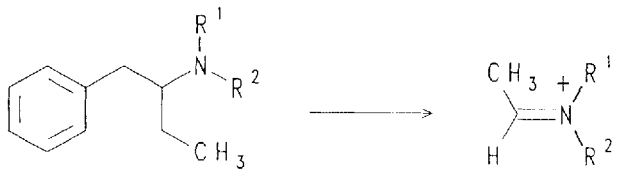



Figure 5 (continued)



| $R^1$ | $R^2$ | m/z |
|---|---|---|
| H | H | 58 |
| H | $CH_3$ | 72 |
| H | $CH_2CH_3$ | 86 |
| $CH_3$ | $CH_3$ | 86 |

Scheme 2. Mass spectral fragmentation pathway for the 1-phenyl-2-butanamines.



The mass spectra for these compounds point out some of the potential problems in using EI MS to differentiate the 1-phenyl-2-butanamines from the corresponding amphetamines (1-phenyl-2-propanamines). For each series, the low mass imine fragment is the predominant peak in the mass spectra with the molecular ion having a low abundance. For example, methamphetamine and it's regioisomer 1-phenyl-2-butanamine have the identical base peak, m/z = 58 and the same molecular weight. Therefore, this method alone may not be a very effective to differentiate between compounds of these very similar groups of amines.

In summary, the 1-phenyl-2-butanamines are homologues of the common street drugs of the 2-propanamine series, amphetamine, methamphetamine, etc. The 2-butanamines are potential "designer drug" analogues of the amphetamine series since the appropriate starting materials (1-phenyl-2-butanone and amines) are uncon-

trolled and available from commercial sources. The various N-substituted 2-butanamines were prepared via reductive amination and the resulting amines were separated by reversed-phase liquid chromatography on $C_{18}$ and phenyl-silica stationary phases. The regiosiomeric substances methamphetamine and 1-phenyl-2-butanamine were well resolved on a $C_{18}$ stationary phase. The EI mass spectra for these compounds show the characteristic low mass imine base peak with no other major fragmentation products.

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