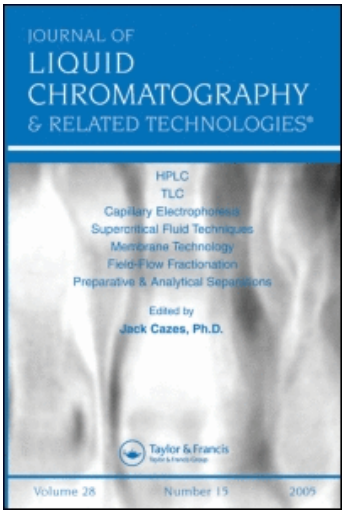

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Liquid Chromatographic and Mass Spectral Analysis of 1-Phenyl-3-Butanamines: Homologues of the Amphetamines

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LIQUID CHROMATOGRAPHIC AND MASS SPECTRAL ANALYSIS OF 1-PHENYL-3-BUTANAMINES: HOMOLOGUES OF THE AMPHETAMINES

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ABSTRACT

The N-substituted 1-phenyl-3-butanamines were prepared from 1-phenyl-3-butanone (benzylacetone) via reductive amination. The 3-butanamines are homologues of the amphetamines, a series of popular drugs of abuse. The N-substituted 3-butanamines were separated via reversed-phase liquid chromatography using an acidic mobile phase (pH 3) and a phenyl silica stationary phase. Similar reversed-phase conditions were used to separate the primary amine homologues amphetamine and 1-phenyl-3-butanamine, and the secondary amine homologues methamphetamine and N-methyl-1-phenyl-3-butanamine. The mass spectra (EI) for the 3-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. The major difference between compounds from the two series possessing identical N-substitutents is the mass of the molecular ion.

INTRODUCTION

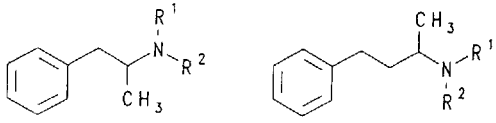
Central nervous system stimulants related to methamphetamine remain popular drugs of abuse in North America. The continued

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.

Recently N-methyl-1-phenyl-3-butanamine, a homologue of methamphetamine, has been encountered in street samples [11]. This amine appeared to be prepared 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 mistakingly assumed that the starting ketone benzylacetone, was the same chemical as P-2-P. The latter hypothesis is reasonable since a similar error has been reported in cases [12]

involving the attempted synthesis of MDA. In these cases the clandestine chemist mistakingly assumed 3,4-methylenedioxybenzyl acetone to be synonymous with methylenedioxyphenyl-2-propanone. Therefore, in these syntheses the homologue 1-(3,4-methylenedioxyphenyl)-3-butanamine was prepared instead of the desired 1-(3,4-methylenedioxy)-2-propanamine (MDA). Whatever the rationale for the production of N-methyl-1-phenyl-3-butanamine, it is essential that analytical methods are available to efficiently differentiate these homologues from the traditional N-substituted 1-phenyl-2-propanamines or amphetamine-type compounds.



$R^1 = R^2 = H$

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

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

$R^1 = R^2 = CH_3$

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 column was 25 cm X 4.6 mm i.d. packed with 5 u Spherisorb-phenyl (Chromanetics, Inc). The amine hydrochlorides (1 mg/mL) were dissolved in HPLC grade methanol and chrom-

atographed 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-160 spectrophotometer.

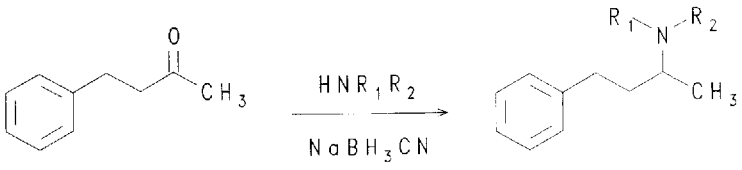
The N-substituted 1-phenyl-3-butanamines were synthesized by reductive amination. The appropriate amine hydrochloride (63 mmoles) was added to a solution of 1-phenyl-3-butanone (benzylacetone, 6.7 mmoles) in methanol (100 mL). Sodium cyanoborohydride (1.0 g, 15.9 mmoles) was added portionwise followed 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-3-butanamine hydrochlorides.

RESULTS AND DISCUSSION

The 1-phenyl-3-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 3-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. Indeed N-methyl-1-phenyl-3-butanamine has appeared in recent street drug samples [11] pointing out the need for specific methods to differentiate these compounds from the homologous amphetamines.

The 1-phenyl-3-butanamines can be prepared from 1-phenyl-3-butanone (benzylacetone) via a reductive amination procedure as shown in Scheme 1. Treatment of 1-phenyl-3-butanone with ammonium acetate or amine hydrochlorides in the presence of



Scheme 1. Synthesis of the 1-phenyl-3-butanamines.

sodium cyanoborohydride at neutral pH afforded the series of N-substituted-1-phenyl-3-butanamines.

The liquid chromatographic separation of the primary 3-butanamine and its N-methyl, N,N-dimethyl and N-ethyl analogues are shown in Figure 1. This separation was achieved in the reversed-phase mode using a mobile phase of pH 3 phosphate buffer, acetontrile and triethylamine (500:100:2) with a phenyl silica stationary phase. The triethylamine serves to improve peak shape and resolution through its role as a competing base for various stationary phase active sites. Amines are widely recognized as strong silanophiles, often yielding broad bands and severe peak tailing. The use of a substance of similar basicity such as triethylamine which is transparent to the mode of detection serves to prevent the analyte silanophilic interactions. The triethylamine is added to the mobile phase in order to continuosly saturate these active sites with a competing base.

The elution order for the 3-butanamines essentially parallels the carbon content of the N-substituent with the primary amine displaying the lowest capacity factor. The N-methyl derivative elutes second, followed by the N-ethyl and

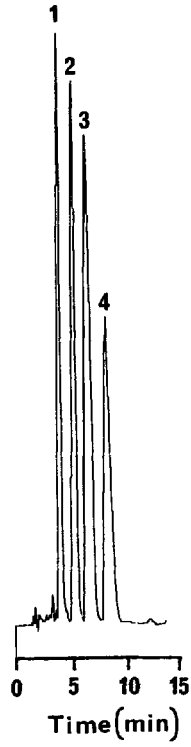


Figure 1. Reversed-phase liquid chromatographic separation of the 1-phenyl-3-butanamines. Peaks: 1 = primary amine, 2 = N-methyl, 3 = N-ethyl and 4 = N,N-dimethyl.

N,N-dimethyl analogues. The tertiary N,N-dimethyl derivative displays a higher capacity factor in this system than the isomeric N-ethyl analog. The results shown for the phenyl stationary phase are significantly better than those obtained on a C_{18} material for these four amines. The N-ethyl and N-N-dimethylamines were incompletely resolved on the C_{18} stationary phase even at 30 minute retention times in a similar solvent system.

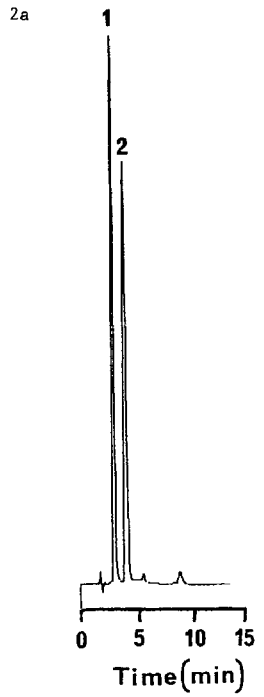


Figure 2. Reversed-phase liquid chromatographic separation of 1-phenyl-2-propanamine (peak 1) from the homologous 1-phenyl-3-butanamine (peak 2). 2a = primary amines and 2b = N-methyl derivatives.

Figure 2a shows the separation of the primary amine amphetamine and its 3-butanamine homologue. Figure 2b shows the separation of the N-methyl derivatives of each series. In each case the additional methylene group of the butanamine results in increased retention when compared to its propanamine homologue. These separations were achieved on the phenyl-silica stationary phase using the aqueous acidic mobile phase already described.

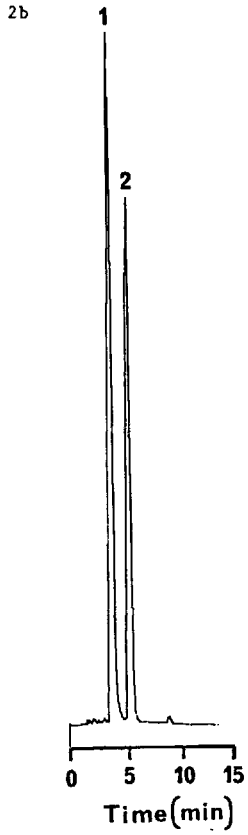


Figure 2 (continued)

The electron impact (EI) mass spectra for the 3-butanamines are shown in Figure 3a-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 = 44 and the other derivatives show this ion at m/z = 58 or 72 depending on the nature of the N-substitutents. The presence of a M-15 peak in

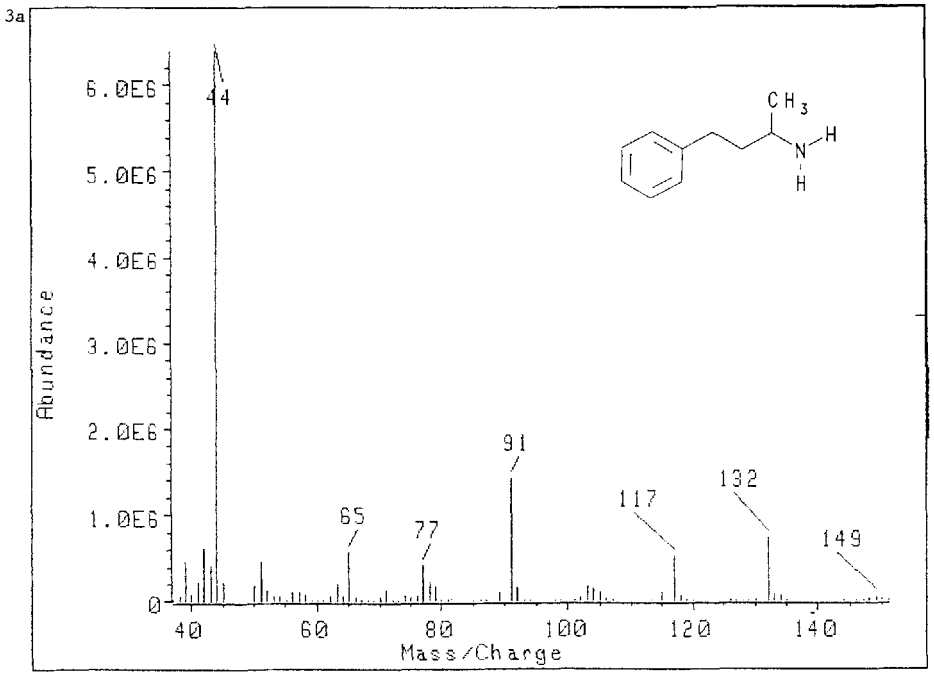
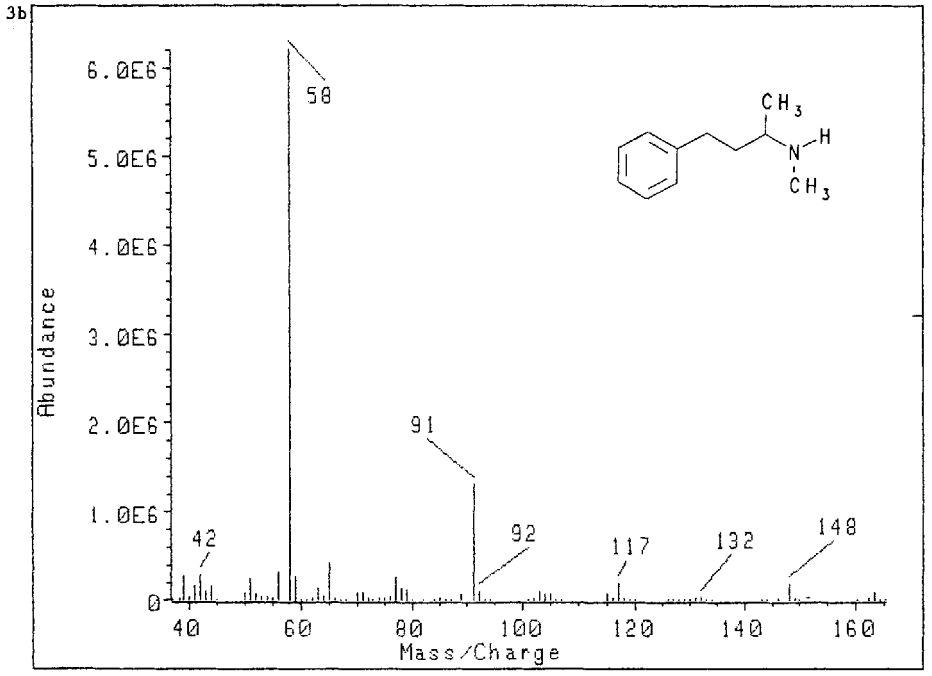


Figure 3. Mass spectra for the 1-phenyl)-3-butanamines: 3a = 1-phenyl-3-butanamine, 3b = N-methyl-1-phenyl-3-butanamine, 3c = N-ethyl-1-phenyl-3-butanamine and 3d = N,N-dimethyl-1-phenyl-3-butanamine.

these spectra results from the loss of the alpha-methyl group to form the less likely imine species. Furthermore, the m/z 132 peak in these spectra is the odd electron ion resulting from loss of the protonated amine fragment (Scheme 2). In comparing the mass spectra of the isomeric N-ethyl and N,N-dimethyl derivatives, the more abundant m/z 44 ion in the spectrum of the N-ethyl compound results from a four-centered rearrangement of the imine base peak (m/z 72) to yield the primary imine [5].



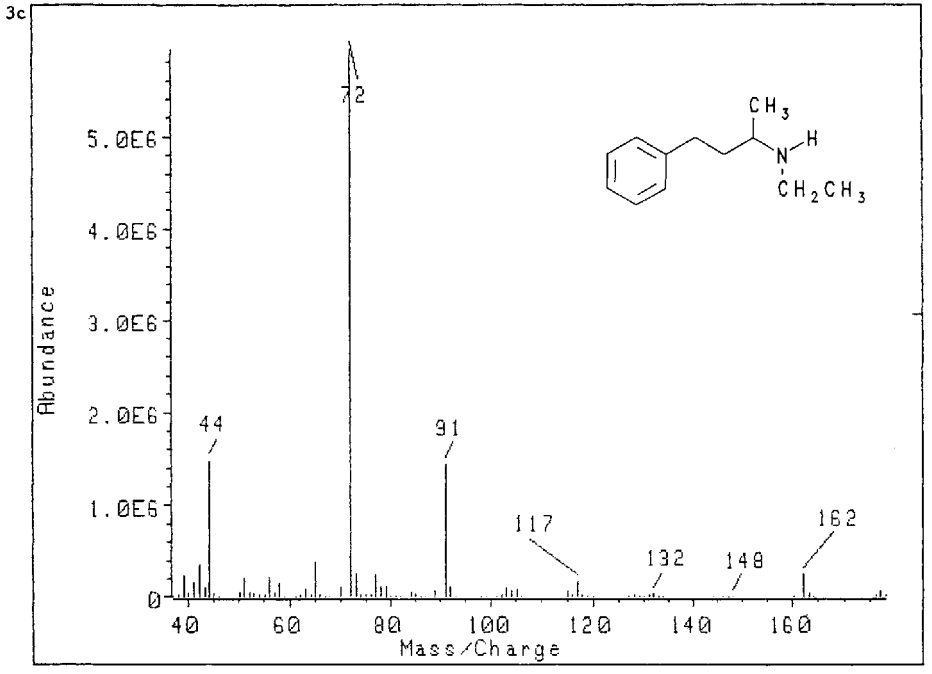


Figure 3 (continued)

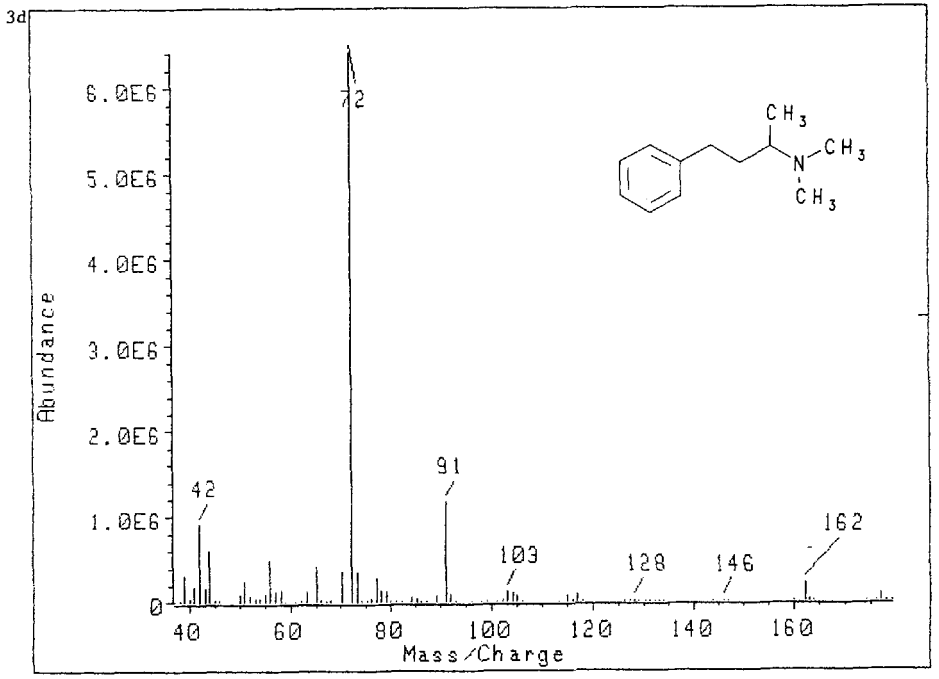
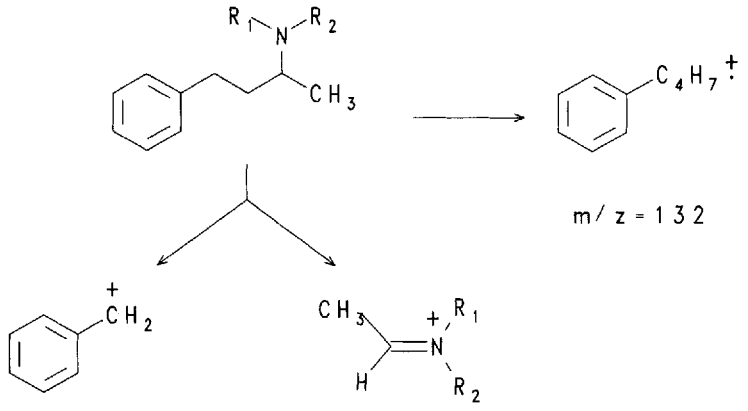


Figure 3 (continued)

The mass spectra for these compounds point out some of the potential problems in using EI MS to differentiate the 1-phenyl-3-butanamines from the corresponding amphetamines. For each series, the low mass imine fragment is the predominant peak in the mass spectra with the molecular ion having a relatively low abundance. For example, methamphetamine and it's homologue N-methyl-1-phenyl-3-butanamine have the identical base peak, m/z = 58 and differ primarily in the mass of their molecular ions. Therefore, this method alone may not be a very effective to differentiate between compounds of these two homologous series.



m/z = 91 $R_1 = R_2 = H$ m/z = 44

$R_1 = CH_3$, $R_2 = H$ m/z = 58

$R_1 = C_2H_5$, $R_2 = H$ m/z = 72

$R_1 = R_2 = CH_3$ m/z = 72

Scheme 2. Mass spectral fragmentation pathway for the 1-phenyl)-3-butanamines.

In summary, the 1-phenyl-3-butanamines are homologues of the common street drugs of the 2-propanamine series, amphetamine, methamphetamine, etc. The 3-butanamines are potential "designer drug" analogues of the amphetamine series since the appropriate starting materials (benzylacetone and amines) are uncontrolled and available from commercial sources. The various N-substituted 3-butanamines were prepared via reductive amination and the resulting amines were separated by reversed-phase liquid chromatography on a phenyl-silica stationary phase. Additionally, the N-

methyl derivatives of the 3-butanamine and 2-propanamine (methamphetamine) series were separated under similar reversed-phase conditions. Mass spectra of the 3-butanamines show characteristic fragmentation which are very similar to the homologous 2-propanamines.

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