1997

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Palladium(II)-catalyzed organic transformations employing oxygen gas as the stoichiometric reoxidant

by

Karl Patrick Peterson

A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Major Professor: Richard C. Larock

Iowa State University

Ames, Iowa

1997

Graduate College
Iowa State University

This is to certify that the Doctoral dissertation of

Karl Patrick Peterson

has met the dissertation requirements of Iowa State University

Signature was redacted for privacy.

Major Professor

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For the Major Program

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For the Graduate College

To my parents, Charles and Lora Peterson, for their ever-present love, support and encouragement. Even though you may have never understood very much about the work I was doing, you never doubted for a minute that I could do it.

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LIST OF ABBREVIATIONS

Ac	acetyl
aq	aqueous
Ar	aryl
br	broad
Bu	butyl
calcd	calculated
dba	dibenzylideneacetone
dd	doublet of doublets
DMA	*N*, *N*-dimethylacetamide
DMF	*N*, *N*-dimethylformamide
DMSO	dimethylsulfoxide
dt	doublet of triplets
eq	equation
equiv	equivalent(s)
Et	ethyl
EtOAc	ethyl acetate
h	hour(s)
HRMS	high resolution mass spectroscopy
Hz	hertz
IR	infrared
m	meta
Me	methyl
mL	milliliter(s)
mmol	millimole(s)
mol	mole(s)

mp	melting point
Ms	methanesulfonyl
n	normal
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
q	quartet
s	singlet
t	tertiary
t	triplet
TLC	thin-layer chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

GENERAL INTRODUCTION

The organic transformations promoted by palladium(II) species have historically required either stoichiometric amounts of metal or the stoichiometric use of a chemical reoxidant, such as benzoquinone or Cu(II) salts. In recent years, several reports have described the use of oxygen gas as the stoichiometric reoxidant in Pd(II) chemistry. This advance has made the chemistry of Pd(II) more attractive because of reductions in cost and waste generation. This development has also encouraged researchers to probe the scope and limitation of Pd(II) chemistry using oxygen gas as the sole reoxidant of the metal. This manuscript describes the development of three organic transformations using a Pd(II)-O_2 catalyst system. The author of this manuscript was the primary investigator and author for each of the papers reported in this dissertation.

Dissertation Organization

Chapter 1 is a modified version of a manuscript submitted to the *Journal of Organic Chemistry* and describes the development of an efficient system for the palladium-catalyzed oxidation of primary and secondary allylic and benzylic alcohols using O_2 as the sole reoxidant of the palladium. The conditions have been applied to a wide variety of substrates, producing the desired carbonyl compounds in moderate to excellent yields. The reaction has been shown to be effective on a 100 mmol scale with no change in reactivity or yield.

Chapter 2 describes efforts toward the development of reaction conditions for the Pd(II)-catalyzed dehydrogenation of β-dicarbonyl compounds. The optimized conditions showed good results with benzyl substituted β-dicarbonyl compounds, but simple aliphatic substituents proved relatively unreactive. By varying the reaction conditions, low yields of unsaturated products could be obtained from the aliphatic substituted substrates.

Chapter 3 describes the Pd(II)-catalyzed cyclization of several derivatives of 2-(2-cyclopentenyl)ethanamine to form 5,5-bicyclic amine derivatives. The reactivity order for the derivatives was found to be tosylamide, formamide > urea, benzylcarbamate > acetamide > benzamide > trifluoroacetamide. The same derivatives of 2-(2-cyclohexenyl)ethanamine, 2,2-dimethyl-4-hexen-1-amine and 3-(2-cyclopentenyl)propan-1-amine were also examined to determine their efficiency in forming 6,5- and 5,6-bicyclic and 5-cyclic ring systems, respectively. The reactivity order was not observed to change with system, but only the tosylamide and formamide were found to be synthetically useful for every system examined. Substrates that were intended to contain the carbonyl function of the derivative within the newly forming ring were found to be unreactive except in one case involving a biscyclization of a benzylurea derivative to form a tricyclic product.

The general conclusion discusses the current scope and limitations of the described methodology as it applies to synthetic organic chemistry.

Finally, the appendix will provide ^{1}H and ^{13}C spectra for all substrates and products of the palladium reactions from chapter 3. These same supplementary materials will be available through the American Chemical Society after publication in the *Journal of Organic Chemistry*.

CHAPTER 1: PALLADIUM-CATALYZED OXIDATION OF ALLYLIC AND BENZYLIC ALCOHOLS

A paper submitted to the *Journal of Organic Chemistry*

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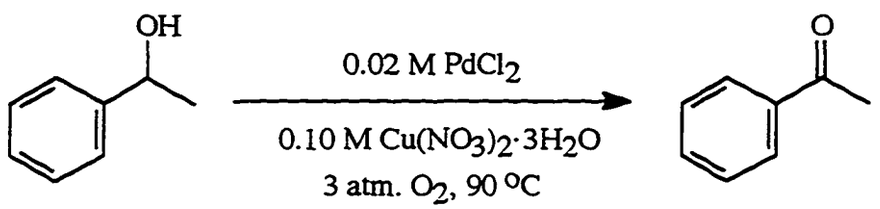
Introduction

The palladium-catalyzed oxidation of alcohols was perhaps first described by Berzelius in 1828, when he reported the reduction of most of the palladium from a wet ethanolic solution of K_2PdCl_4.[1] Recent efforts to make this oxidation synthetically useful have focused on the need to make the process catalytic in palladium, thereby requiring a means of oxidizing the reduced palladium back to the active state. Efforts toward the development of catalytic procedures have concentrated on the use of reoxidants, such as metal salts,[2] peroxides[3] and organic halides[4] or have used an allylic carbonate derivative of the alcohol to be oxidized.[5]

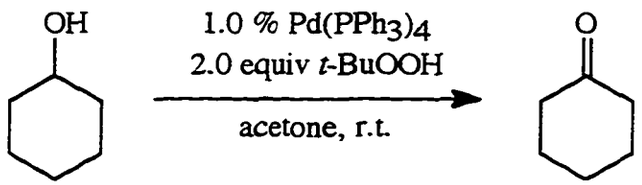
In 1967, Lloyd reported reaction conditions using catalytic $PdCl_2$ and copper(II) salts as the reoxidant of the palladium (eq 1).[2] The reactions were performed with neat alcohol at 70-100 °C. High yields of oxidation products were obtained with a variety of primary and secondary aliphatic and benzylic alcohols, although oftentimes products from over oxidation, such as acetals and esters, were formed in significant quantities. Lloyd also observed that



(1)

excess water and excess chloride ion both inhibited the reaction.

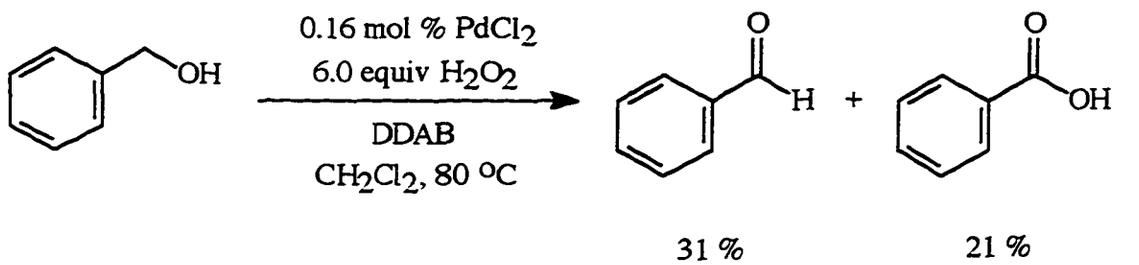
Peroxides have also seen limited use as the reoxidant in the palladium-catalyzed oxidation of alcohols.[3] Tsuji and co-workers employed 1 mol % $Pd(PPh_3)_4$ as the catalyst and *t*-butyl hydroperoxide as the reoxidant.[3a] A single example was given, producing cyclohexanone from cyclohexanol in 13 % yield as determined by gas chromatographic analysis (eq 2). This palladium-based catalyst system compared quite unfavorably with a



(2)

similar ruthenium-based system, which seemed to be the metal of choice when using peroxides as reoxidants.

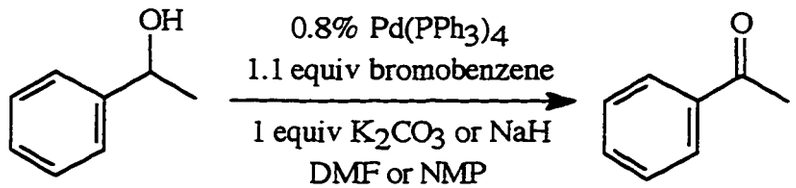
A second report employing a peroxide reoxidant, by Sasson and co-workers, involved the use of phase-transfer conditions to achieve the desired oxidations (eq 3).[3b] This report



(3)

contained one example using 0.16 mol % $PdCl_2$ as the catalyst in CH_2Cl_2 at 80 °C. Didecyldimethylammonium bromide (DDAB) was used as a phase transfer catalyst and 30 % H_2O_2 solution (6 equiv) was slowly added as the reoxidant. These conditions gave amodest yield of the desired benzaldehyde with a significant amount of benzoic acid as a by-product.

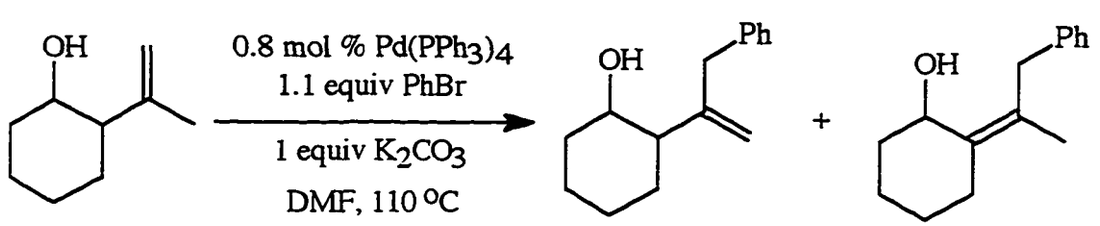
A third strategy for achieving the reoxidation of the palladium catalyst uses organic halides.[4] The first such system was reported in 1979 by Yoshida and co-workers.[4a] Equimolar amounts of secondary alcohols and either K_2CO_3 or NaH, with a slight excess of bromobenzene, were used with 0.8 mol % $Pd(PPh_3)_4$ as the catalyst in *N*,*N*-dimethylformamide (DMF) or *N*-methylpyrrolidone (NMP) to obtain high yields of the desired ketone products (eq 4). This procedure was highly successful on secondary substrates, but no



(4)

examples of primary substrates were reported. This is probably due to the propensity of the desired aldehyde products from the oxidation reaction to undergo condensation reactions under the basic reaction conditions.

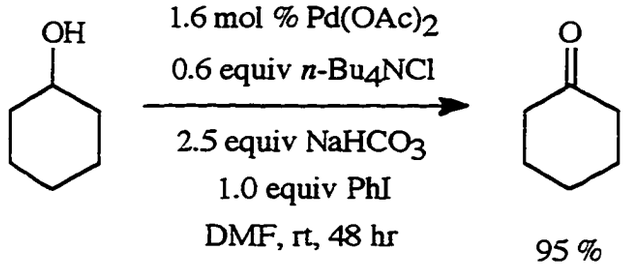
In 1981, Yoshida and co-workers published an improved procedure for the palladium-catalyzed oxidation of alcohols.[4b] This new method used bromomesitylene as the aryl halide reoxidant of the palladium and allowed for the oxidation of a variety of unsaturated primary and secondary alcohol substrates. The problem with the previous procedure for unsaturated alcohols was addition of the aryl group to the olefin (eq 5). The more hindered bromomesitylene proved to be unreactive towards olefins, thereby allowing the desired oxidation chemistry to occur. Yoshida published a full account of his work using aryl halides



(5)

as the reoxidant in the palladium(II)-catalyzed oxidation of alcohols in 1983.[4c]

Iodobenzene was employed by Choudary and co-workers as the palladium reoxidant under solid-liquid phase transfer conditions (eq 6).[4e] A variety of saturated primary and secondary alcohols were treated with 1.6 mol % $Pd(OAc)_2$, 2.5 equiv of $NaHCO_3$, 0.6 equiv

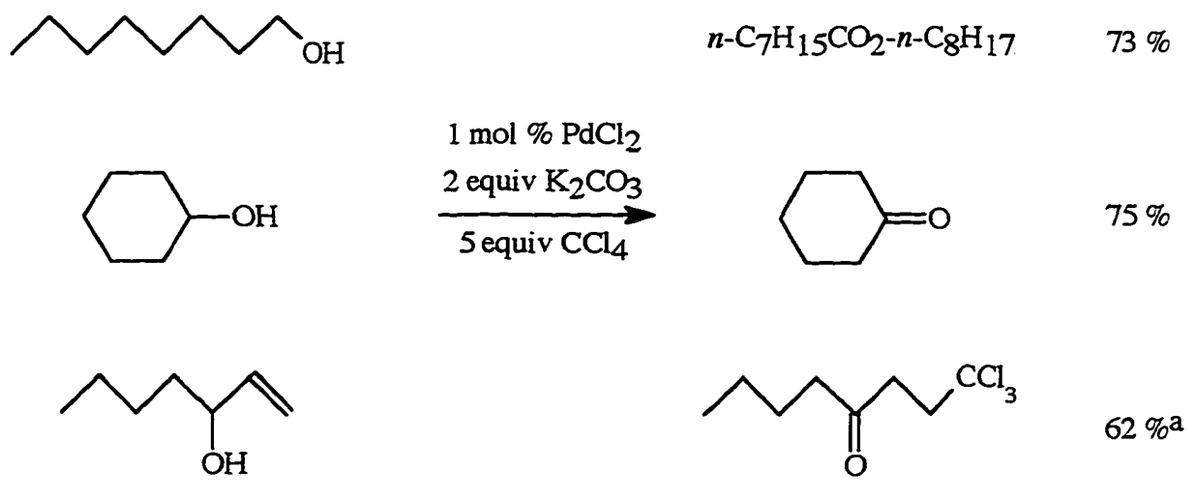


(6)

of *n*-Bu_4NCl and 1.0 equiv of iodobenzene at room temperature in DMF leading to good to excellent yields of the desired carbonyl products. The conspicuous absence of unsaturated substrates leads one to believe that this procedure was also limited by aryl addition to the olefin moiety of such substrates.

Tsuji and co-workers reported that palladium salts catalyze the oxidation of alcohols using CCl_4 in the presence of K_2CO_3 (Scheme 1).[4d] Primary alcohols were oxidized to esters

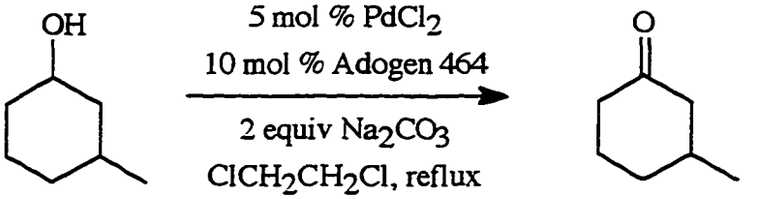
Scheme 1



[a]Benzene was used as the solvent along with 5 equiv of CCl_4 and 2 mol % P(*o*-Tol)$_3$.

and secondary alcohols to ketones, while CCl_4 is converted to $CHCl_3$. The reaction of allylic alcohols bearing a terminal olefinic bond afforded an addition product. Although the yields under these reaction conditions are generally fairly high, the scope is narrow.

The oxidation of primary and secondary, saturated, allylic or benzylic alcohols has been achieved under phase-transfer conditions in 1,2-dichloroethane at reflux using catalytic amounts of both $PdCl_2$ and Adogen 464 (methyltrialkyl(C_8-C_{10})ammonium chloride) in the presence of excess Na_2CO_3 (eq 7).[4f] Primary alcohols afford mixtures of aldehydes and esters.



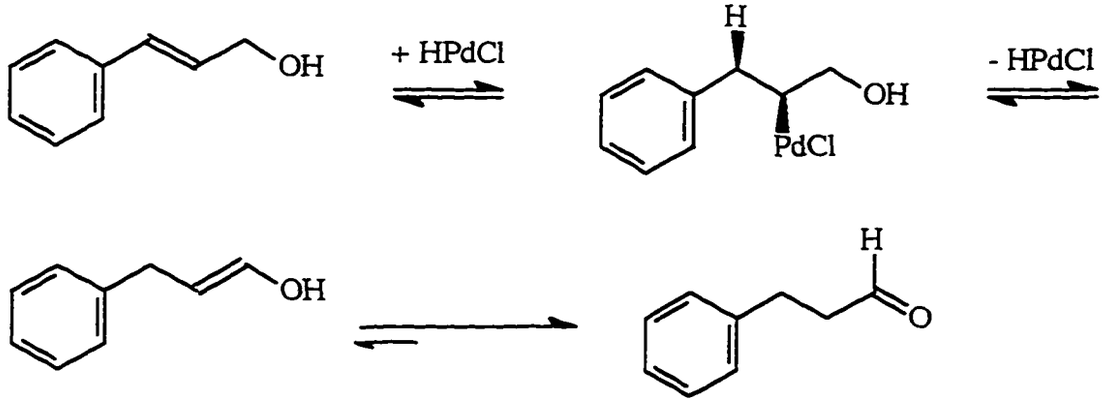
73 %

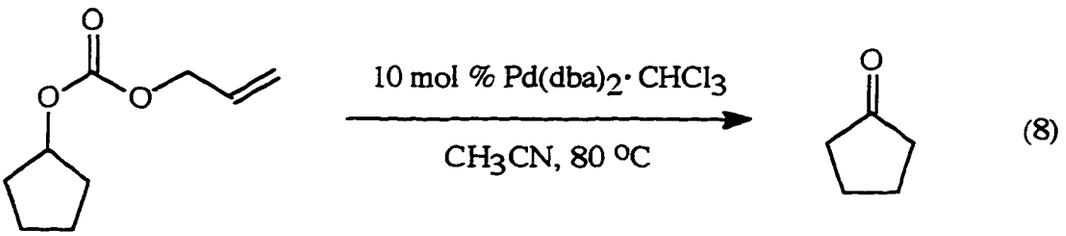
(7)

Allylic alcohols produce small amounts of saturated carbonyl products by a double bond migration mechanism (Scheme 2).

A final strategy for achieving the palladium-catalyzed oxidation of alcohols employs an allylic carbonate derivative of the alcohol substrate (eq 8).[5] This approach differs from the

Scheme 2

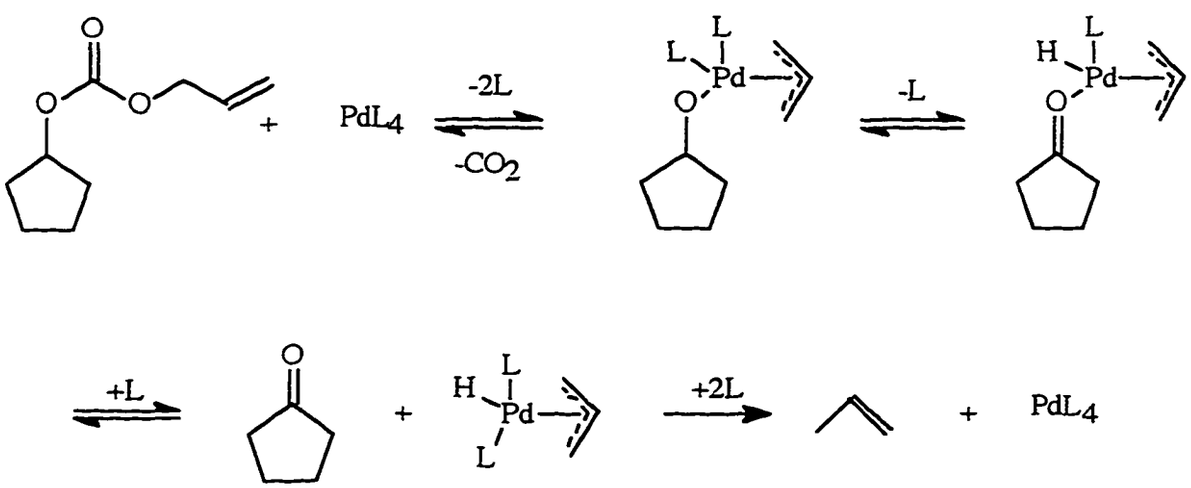




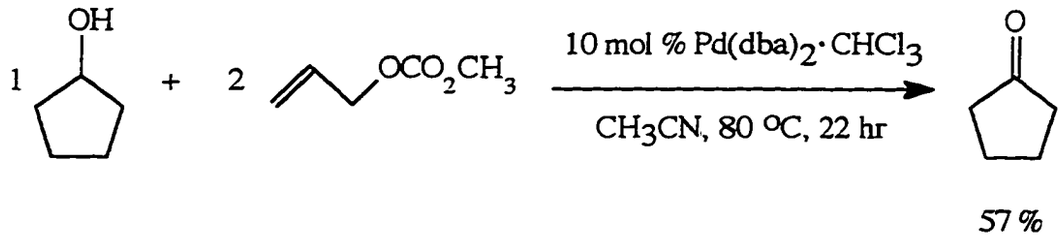
(8)

others in that the transformation involves a Pd(0) catalytic cycle, rather than a Pd(II) catalytic cycle, which means there is no need for a reoxidant. This reaction proceeds by an oxidative addition of the allylic carbonate to a Pd(0) species, followed by decarboxylation to form a π-allylpalladium alkoxide (Scheme 3). This species then undergoes β-hydride elimination to give

Scheme 3

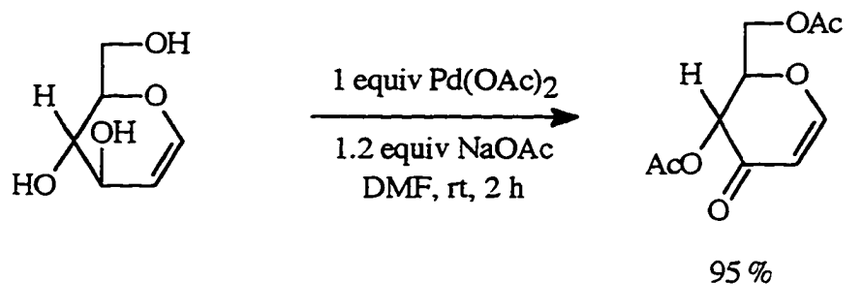


the desired carbonyl product. This reaction also produces significant quantities of the protonated alcohol or the allylic ether as by-products. The best results were obtained using a 10 mol % $Pd(dba)_3 \cdot CHCl_3$ catalyst at 80 °C in acetonitrile. A variation on this procedure allowed for the use of allyl methyl carbonate to generate the π-allylpalladium intermediate,which then undergoes ligand exchange of the methoxy ligand for the substrate alcohol to achieve the desired oxidation (eq 9).



(9)

A stoichiometric procedure for the selective oxidation of allylic alcohols in the presence of other hydroxyl groups was reported by Czernecki and co-workers in 1993.[6] Readily available D-glucal was treated with 1 equiv of $Pd(OAc)_2$ and 1.2 equiv of NaOAc at room temperature in dimethylformamide (DMF) containing 1 volume % water (eq 10). The



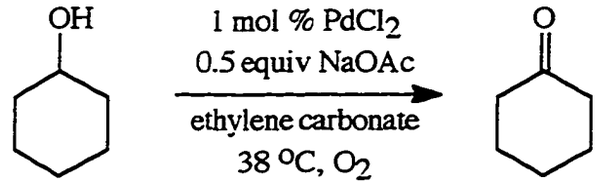
(10)

corresponding acetylated enone was isolated in 95 % yield. This procedure was very selective for the oxidation of the allylic hydroxyl, but lead to epimerization α to the product carbonyl insome instances.

The ability of palladium(II) salts to effect the oxidation of alcohols to carbonyl compounds has clearly been established. However, the procedures are limited as to the type of substrate that can be used, the requirement for a co-oxidant to make the transformation catalytic or the need to synthesize the allylic carbonate derivative of the alcohol substrate. The ideal reagent for the purpose of reoxidizing the palladium is molecular oxygen, which is readily available, inexpensive, non-toxic and should produce water as the sole by-product.

Procedures for the palladium-catalyzed oxidation of alcohols using O_2 as the reoxidant have been developed, but have been limited as to the type of substrate which can be oxidized or

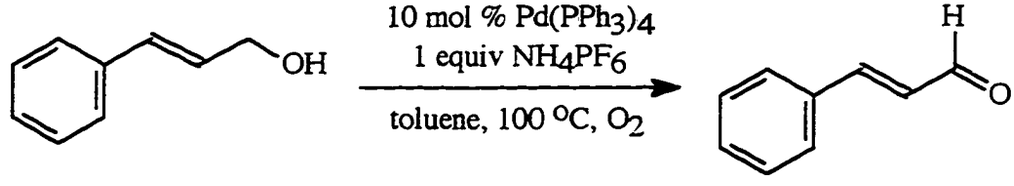
the need for co-reagents in order to obtain reasonable yields of the desired carbonyl products.[7] The use of oxygen as the sole reoxidant of palladium was first reported by Schwartz and co-workers in 1977.[7a] A catalytic system consisting of 1 mol % $PdCl_2$ and 0.5 equiv of NaOAc in ethylene carbonate at 38 °C with an O_2 atmosphere led to efficient oxidation of saturated primary and secondary alcohols (eq 11). An attempt to oxidize an olefinic alcohol failed. This



88 % (11)

was reported to be due to poisoning of the catalyst by strong complexation of palladium by the olefin.

In 1994, Echavarren and co-workers reported the oxidation of allylic alcohols using a catalyst system consisting of 10 mol % $Pd(PPh_3)_4$ in toluene in the presence or absence of both NH_4PF_6 and K_2CO_3 (eq 12).[7b] This system was only applied to allylic substrates. Variations



90 % (12)

of this procedure were shown to produce diallyl ethers as major by-products.

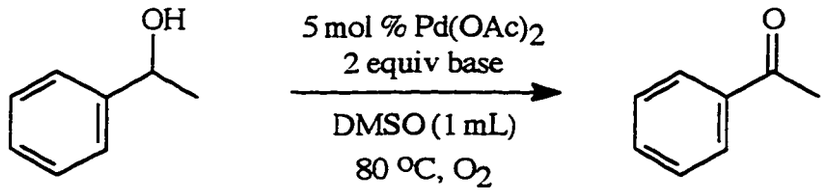
Catalytic oxidations of alcohols using O_2 as the ultimate stoichiometric oxidant have not been limited to palladium chemistry. Many procedures using a variety of metals and co-oxidants have been reported. Oxygen gas has been used as the sole reoxidant in combination

with Ru,[8] Co,[9] Cu,[10] Pt[11] and Rh[12] catalysts and procedures using Cu,[13] Ru,[14] Zr[15] and Co[16] catalysts plus additional co-oxidants in combination with oxygen gas have been reported.

The goal of our work was to develop a simple general procedure for the palladium-catalyzed oxidation of allylic and benzylic alcohols, since a satisfactory procedure for the palladium-catalyzed oxidation of saturated primary and secondary alcohols, using oxygen gas as the sole reoxidant of the palladium, had been put forth by Schwartz.[7a] Previous work in this research group[17] and others[18] has suggested that a catalyst consisting of 5 mol % $Pd(OAc)_2$ in DMSO with an O_2 atmosphere leads to high turnovers of the palladium(II) catalyst. This same catalyst system has indeed proven to be effective for the oxidation of allylic and benzylic alcohols as herein described.

Results and Discussion

Our investigation began with an effort to optimize reaction conditions for the oxidation of alcohols using catalytic palladium and O_2 gas as the stoichiometric reoxidant. *sec*-Phenethyl alcohol (1 mmol) was chosen as a model substrate for the optimization process (eq 13). The



(13)

reaction yields were determined by gas chromatographic analysis using an internal standard unless otherwise stated. Randomly selected reactions were isolated to compare the isolated yields to those determined by gas chromatography. In each case, the isolated yield was within 4 % of the value determined by gas chromatography.

A set of initial conditions was selected consisting of 1 mmol of substrate alcohol, 5 mol % $Pd(OAc)_2$, 2 equiv of Na_2CO_3 in 1 mL of solvent under an atmosphere of oxygen with

stirring at 80 °C for 72 h. The first variable examined was the solvent (Table 1). Previous work in this group[17] and others[18] suggested that DMSO is likely to be the solvent of choice for such palladium(II)-catalyzed transformations using O_2 as the reoxidant. Nevertheless, other solvents that displayed moderate results in other Pd(II)-catalyzed transformations were

Table 1. Optimization of Solvent for the Palladium-Catalyzed Oxidation of *sec*-Phenethyl Alcohol.

entry	catalyst	equiv base	temp. (°C)	solvent	yield (%)
1	5% $Pd(OAc)_2$	2 Na_2CO_3	80	DMSO	70
2	5% $Pd(OAc)_2$	2 Na_2CO_3	80	DMSO/H_2O (9:1)	23
3	5% $Pd(OAc)_2$	2 Na_2CO_3	80	CH_3CN	7

examined. The use of DMSO as the solvent led to complete conversion of the starting alcohol and afforded the desired ketone in 70 % yield. Acetonitrile or a 9:1 mixture of DMSO/H_2O showed greatly diminished reactivity and yields under the selected reaction conditions. As expected, DMSO appears to be the most effective solvent for oxidation of the chosen substrate under the selected reaction conditions.

The next task was to find the best catalyst for the transformation. A series of four catalysts was examined with three commonly employed inorganic bases (Table 2). Three bases were examined to prevent a catalyst from being excluded because it did not perform well with a particular base. A survey of the results show $Pd(OAc)_2$ to be the most effective catalyst for the reaction under the various conditions examined. The other palladium(II) salts examined, $PdCl_2$ and $Pd(O_2CCF_3)_2$, gave moderate results, while the palladium(0) salt, $Pd(dba)_2$, gave poor

The reaction temperature was the next variable examined (Table 3). The best reactions from those presented above were complete within the allowed three days reaction time. The temperature of a series of reactions was reduced from 80 °C to 60 °C to see if the higher

Table 2. Optimization of the Catalyst for the Palladium-Catalyzed Oxidation of *sec*-Phenethyl Alcohol.

entry	catalyst	equiv base	temp. (°C)	time (h)	solvent	yield (%)
1	5% $Pd(OAc)_2$	2 $NaHCO_3$	80	72	DMSO	80
2	5% $Pd(OAc)_2$	2 NaOAc	80	72	DMSO	24
3	5% $Pd(OAc)_2$	2 Na_2CO_3	80	72	DMSO	68
4	5% $PdCl_2$	2 $NaHCO_3$	80	72	DMSO	19
5	5% $PdCl_2$	2 NaOAc	80	72	DMSO	40
6	5% $PdCl_2$	2 Na_2CO_3	80	72	DMSO	29
7	5% $Pd(O_2CCF_3)_2$	2 $NaHCO_3$	80	72	DMSO	59
8	5% $Pd(O_2CCF_3)_2$	2 NaOAc	80	72	DMSO	54
9	5% $Pd(O_2CCF_3)_2$	2 Na_2CO_3	80	72	DMSO	33
10	5% $Pd(dba)_2$	2 $NaHCO_3$	80	72	DMSO	17
11	5% $Pd(dba)_2$	2 NaOAc	80	72	DMSO	15
12	5% $Pd(dba)_2$	2 Na_2CO_3	80	72	DMSO	21

Table 3. Optimization of Reaction Temperature for the Palladium-Catalyzed Oxidation of *sec*-Phenethyl Alcohol.

entry	catalyst	equiv base	temp. (°C)	time (h)	solvent	yield (%)
1	5 % $Pd(OAc)_2$	2 $NaHCO_3$	80	72	DMSO	68
2	5 % $Pd(OAc)_2$	2 $KHCO_3$	80	72	DMSO	64
3	5 % $Pd(OAc)_2$	2 Na_2CO_3	80	72	DMSO	68
4	5 % $Pd(OAc)_2$	2 K_2CO_3	80	72	DMSO	66
5	5 % $Pd(OAc)_2$	2 $NaHCO_3$	60	72	DMSO	56
6	5 % $Pd(OAc)_2$	2 $KHCO_3$	60	72	DMSO	37
7	5 % $Pd(OAc)_2$	2 Na_2CO_3	60	72	DMSO	43
8	5 % $Pd(OAc)_2$	2 K_2CO_3	60	72	DMSO	37

temperature is indeed necessary to achieve complete reaction in the allotted time. Again, a series of commonly used inorganic bases was employed, including a couple not examined earlier. The results indicate that the higher temperature is necessary to achieve complete conversion of starting material and the highest yields of product. None of the reactions at 60 °C had reached completion in the 72 h reaction period.

Having established what appeared to be the optimal solvent, catalyst and temperature, attention was turned toward the base. A series of inorganic bases and one organic base, triethylamine, were examined (Table 4). From this data, $NaHCO_3$, $KHCO_3$, Na_2CO_3 andK_2CO_3 were observed to afford the highest yields. The results from these four bases were similar enough that one could not select a single best base under the reaction conditions examined.

Table 4. Optimization of Base for the Palladium-Catalyzed Oxidation of *sec*-Phenethyl Alcohol.

entry	catalyst	equiv base	temp. (°C)	time (h)	solvent	yield (%)
1	5 % $Pd(OAc)_2$	2 $LiOAc{\cdot}2H_2O$	80	72	DMSO	48
2	5 % $Pd(OAc)_2$	2 NaOAc	80	72	DMSO	24
3	5 % $Pd(OAc)_2$	2 KOAc	80	72	DMSO	24
4	5 % $Pd(OAc)_2$	2 CsOAc	80	72	DMSO	24
5	5 % $Pd(OAc)_2$	2 $NaHCO_3$	80	72	DMSO	68
6	5 % $Pd(OAc)_2$	2 $KHCO_3$	80	72	DMSO	64
7	5 % $Pd(OAc)_2$	2 Li_2CO_3	80	72	DMSO	57
8	5 % $Pd(OAc)_2$	2 Na_2CO_3	80	72	DMSO	68
9	5 % $Pd(OAc)_2$	2 K_2CO_3	80	72	DMSO	66
10	5 % $Pd(OAc)_2$	1 Et_3N	80	72	DMSO	14

The four bases observed above were each used in a series of experiments designed to examine the reaction time (Table 5). Up to this point, the reactions were allowed to stir at 80 °C for 72 h regardless of how long the reaction may have taken to reach completion. All of the reaction time had not been determined. Preliminary data indicated that the product is not

Table 5. Optimization of Reaction Time for the Palladium-Catalyzed Oxidation of *sec*-Phenethyl Alcohol.

entry	catalyst	equiv base	temp. (°C)	time (h)	solvent	yield (%)
1	5 % $Pd(OAc)_2$	2 $NaHCO_3$	80	72	DMSO	68
2	5 % $Pd(OAc)_2$	2 $KHCO_3$	80	72	DMSO	64
3	5 % $Pd(OAc)_2$	2 Na_2CO_3	80	72	DMSO	68
4	5 % $Pd(OAc)_2$	2 K_2CO_3	80	72	DMSO	66
5	5 % $Pd(OAc)_2$	2 $NaHCO_3$	80	48	DMSO	65
6	5 % $Pd(OAc)_2$	2 $KHCO_3$	80	48	DMSO	69
7	5 % $Pd(OAc)_2$	2 Na_2CO_3	80	48	DMSO	74
8	5 % $Pd(OAc)_2$	2 K_2CO_3	80	48	DMSO	67
9	5 % $Pd(OAc)_2$	2 $NaHCO_3$	80	24	DMSO	91
10	5 % $Pd(OAc)_2$	2 $KHCO_3$	80	24	DMSO	74
11	5 % $Pd(OAc)_2$	2 Na_2CO_3	80	24	DMSO	50
12	5 % $Pd(OAc)_2$	2 K_2CO_3	80	24	DMSO	66
13	5 % $Pd(OAc)_2$	2 $NaHCO_3$	80	12	DMSO	77

completely stable under the reaction conditions. In several instances, the product yields were observed to decrease over time. This is most likely due to base-induced condensation reactions of the product, although no products of this type have actually been isolated. With shorter reaction times, differences in the reactivity and yields of the different bases might also be

established. The highest yield (91 %) in fact was obtained using $NaHCO_3$ and only a 24 h reaction time (Table 5, entry 9).

The stoichiometry of the base was examined using a variety of concentrations of $NaHCO_3$, from none to 2 molar equivalents (Table 6). The yields of the desired product

Table 6. The Optimization of Base Stoichiometry for the Palladium(II)-Catalyzed Oxidation of *sec*-Phenethyl Alcohol.

entry	catalyst	equiv base	temp. °C	time (h)	solvent	yield (%)
1	5 % $Pd(OAc)_2$	no base	80	24	DMSO	30
2	5 % $Pd(OAc)_2$	0.1 $NaHCO_3$	80	24	DMSO	44
3	5 % $Pd(OAc)_2$	0.5 $NaHCO_3$	80	24	DMSO	65
4	5 % $Pd(OAc)_2$	1 $NaHCO_3$	80	24	DMSO	83
5	5 % $Pd(OAc)_2$	2 $NaHCO_3$	80	24	DMSO	91

increased as the amount of $NaHCO_3$ increased. Above 2 equivalents, the reaction mixture became clearly heterogeneous and magnetic stirring was impeded.

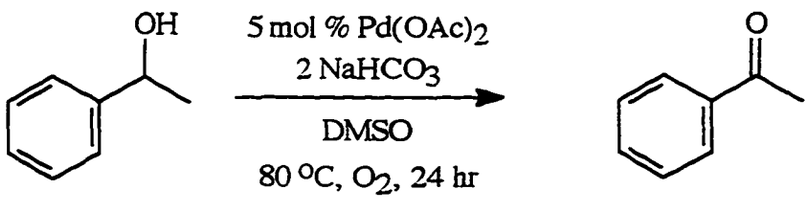
Finally, the concentration of the reaction was examined (Table 7). All previous reactions had employed 1 mL of solvent for 1 mmol of substrate. Reducing the amount of solvent would be desirable to limit the amount of waste generation from this procedure, especially if the oxidation were performed on a larger scale. Reducing the amount of solvent

Table 7. The Optimization of Reaction Concentration for the Palladium(II)-Catalyzed Oxidation of *sec*-Phenethyl Alcohol.

entry	catalyst	equiv. base	temp. (°C)	time (h)	solvent	yield (%)
1	5 % $Pd(OAc)_2$	2 $NaHCO_3$	80	24	1 ml DMSO	92
2	5 % $Pd(OAc)_2$	2 $NaHCO_3$	80	24	0.5 mL DMSO	61
3	5 % $Pd(OAc)_2$	2 $NaHCO_3$	80	24	0.25 mL DMSO	62

made the reactions clearly heterogeneous and magnetic stirring was impeded. The yields for the reactions run at higher concentrations were diminished compared to the standard concentration.

The final optimized reaction conditions for the palladium(II)-catalyzed oxidation of 1 mmol of *sec*-phenethyl alcohol were determined to be 5 mol % $Pd(OAc)_2$ and 2 equiv of $NaHCO_3$ in 1 mL of DMSO for 24 h at 80 °C under an atmosphere of O_2 (Procedure A, eq 14).



91 %

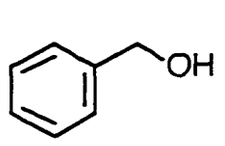
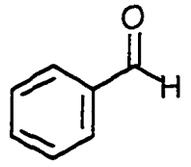
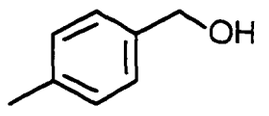
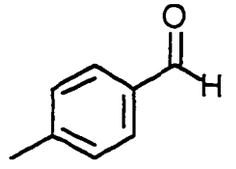
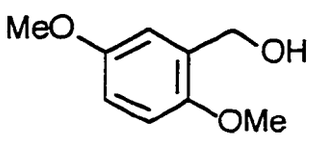
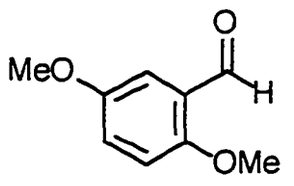
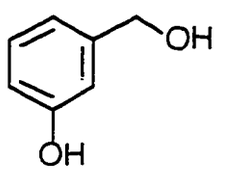
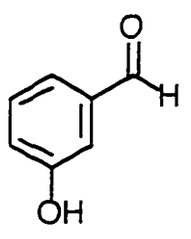
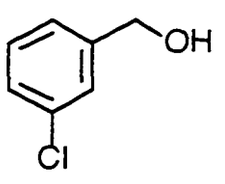
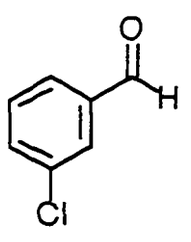
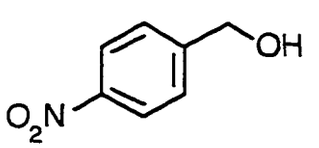
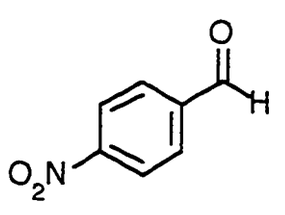
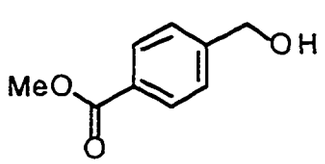
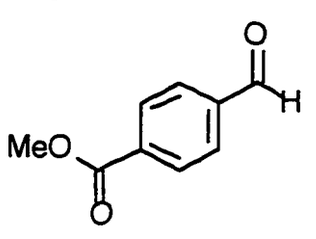
(14)

The goal was now to apply the optimized conditions to a variety of primary and secondary allylic and benzylic alcohols (Table 8).

Application of the optimized reaction conditions to benzyl alcohol lead to a complex mixture of products, although the desired benzaldehyde was the major component of the mixture. By removing the base from the reaction, benzaldehyde was obtained cleanly in a 90 % yield as determined by gas chromatography. This problem of the optimized conditions leading to significant by-product formation was prevalent with most primary alcohol substrates, so this base-free procedure was adopted as an alternative procedure (Procedure B).

In summary, two general procedures for the oxidation of allylic and benzylic alcohols by $Pd(OAc)_2$ have been developed, the use of which depends on the nature of the alcohol undergoing oxidation: procedure A, 1 mmol of substrate, 5 mol % $Pd(OAc)_2$, 2 equiv of $NaHCO_3$, an O_2 atmosphere, 1 mL of DMSO at 80 °C; procedure B, 1 mmol of substrate, 5 mol % $Pd(OAc)_2$, an O_2 atmosphere, 1 mL of DMSO at 80 °C. Results using these procedures are summarized in Table 8.

Table 8. Palladium(II)-Catalyzed Oxidation of Primary and Secondary Allylic and Benzylic Alcohols.

entry	substrate	product	procedure	time (d)	% isolated yield
1			B	2	90[a]
2			B	1	92
3			B	0.5	95
4			B	3	66
5			B	3	48[a]
6			B	3	57
7			B	3	59

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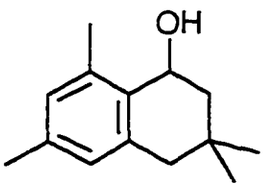
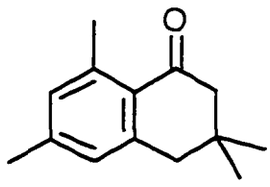
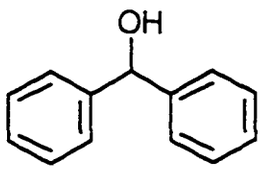
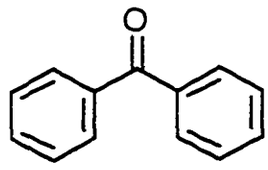
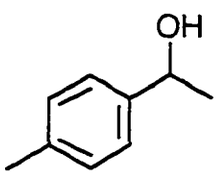
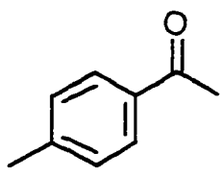
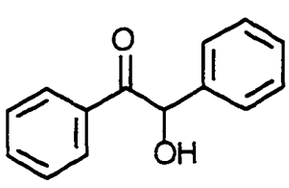
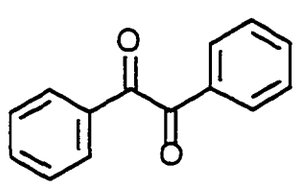
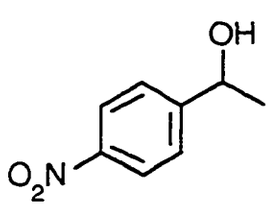
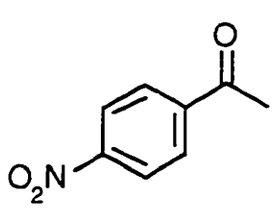
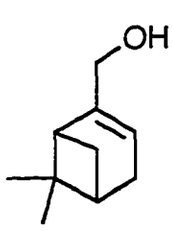
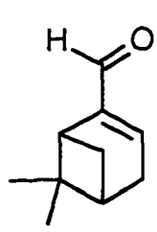
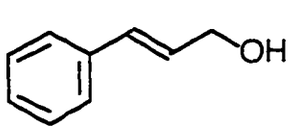
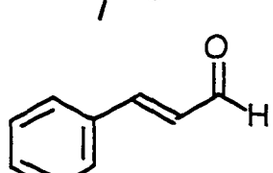
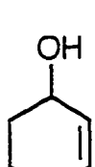
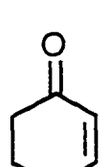
8			A	7	96
9			A	1	95
10			A	1	81
11			A	1	83
12			A	3	57
13			B	2	50[a]
14			B	1.5	69[b]
15			B	1	42[a, c]

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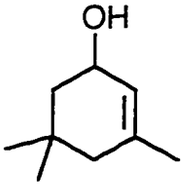
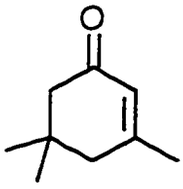
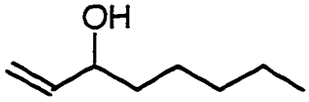
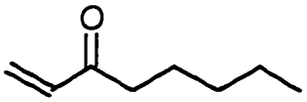
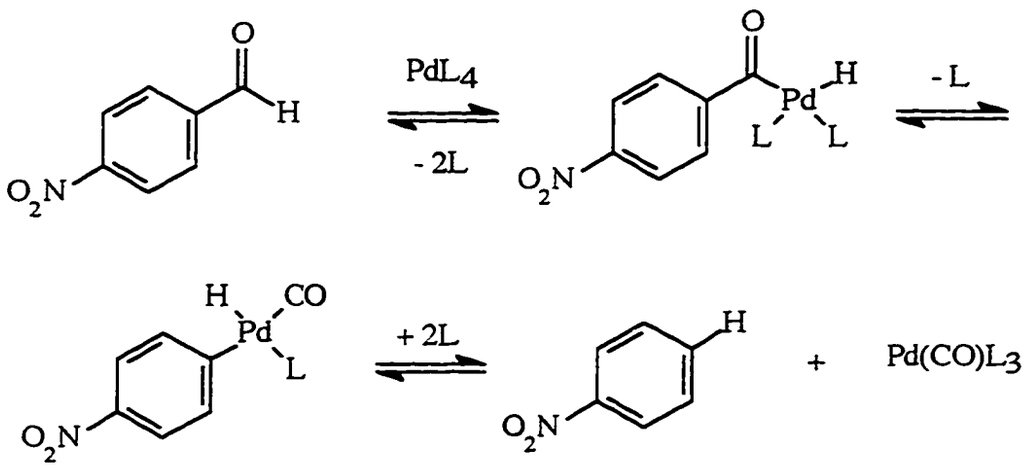
16	 	A	2	67
17	 	B	1	53[a]

[a]Yield determined by gas chromatography. [b]Reaction used 1 mmol of substrate in 5 mL of DMSO. [c]Phenol observed in 37 % yield by gas chromatography.

Procedure A works well for secondary allylic and benzylic substrates. The base present in procedure A tends to promote the generation of side-products when primary allylicand benzylic substrates are used; therefore, procedure B was developed. Procedure B also works on most secondary allylic and benzylic alcohols, but the rates of reaction are generally significantly slower in the absence of the base.

In general, the reactions of primary benzylic alcohols were very clean using procedure B (Table 8, entries 1-7). An interesting electronic effect seems to exist for these benzylic systems. Comparing benzyl alcohol (entry 1) to the benzylic alcohols with electron-releasing substituents (entries 2 and 3), the reaction times for the electron-rich arenes were significantly shorter. The oxidation of *m*-hydroxybenzyl alcohol required a longer reaction time (entry 4), which might be attributed to coordination of the phenoxide to the palladium catalyst, thereby decreasing the rate of reaction. Primary benzylic systems with electron-withdrawing groups (entries 5-7) also required longer reaction times and gave lower yields. Most of the reactions of these substrates did not go to completion. In the case of *p*-nitrobenzyl alcohol (entry 6), a significant amount of the product *p*-nitrobenzaldehyde (>20%) was converted to nitrobenzene, presumably by palladium-catalyzed decarbonylation (Scheme 4).[19] Increasing the temperature and/or adding base to these reactions did not improve the yields.

Scheme 4



Secondary benzylic substrates generally gave very clean, high yielding reactions (Table 8, entries 8-12). The addition of base served to increase the rate of reaction without leading to significant amounts of side-products. In some cases, the rate enhancement was substantial. For example, the oxidation of benzoin (entry 11) with base is complete in 1 day, but without base the reaction requires more than 5 days to reach completion. The electronic effect observed for the primary benzylic systems also seems to be prevalent in the case of secondary benzylic systems. *p*-Nitroacetophenone (entry 12) required a longer reaction time and gave a decreased yield when compared to more electron-rich secondary benzylic substrates.

In general, reactions of primary and secondary allylic substrates were not as clean as the benzylic systems and lead to lower yields (Table 8, entries 13-17). Allylic alcohols have been shown to form diallyl ethers under conditions similar to those used for this oxidation, although none have been observed using our procedures.[6b] Some modifications to the general procedure were made to optimize the yields for some allylic substrates. For example, cinnamyl alcohol (entry 14) gave best results when the reaction was diluted to 1 mmol of substrate in 5 mL of DMSO. The increased yield can possibly be attributed to the fact that we are disfavoring intermolecular processes by dilution of the reaction mixture. Using procedure A on 2-cyclohexen-1-ol led to phenol as the major product. By using procedure B with no base, the

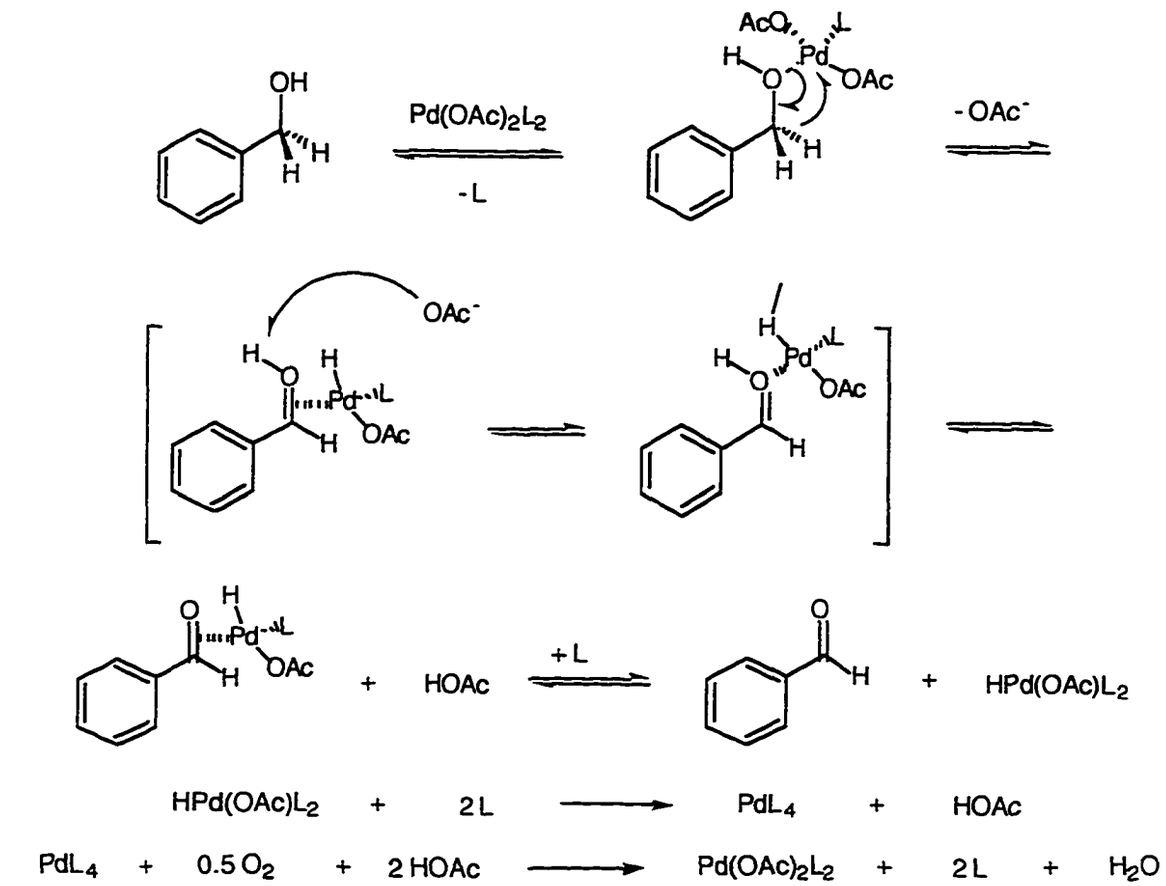
yield of 2-cyclohexen-1-one was increased to 42%, but phenol was still observed in 37% yield (entry 15).

While most reactions were run on just a 1 mmol scale, the oxidation conditions also proved successful on a larger scale. A 10 mmol reaction of 2,5-dimethoxybenzyl alcohol using procedure B provided the aldehyde in an 81% isolated yield and a 100 mmol reaction of benzhydrol using procedure A provided the corresponding diketone in an 83% isolated yield.

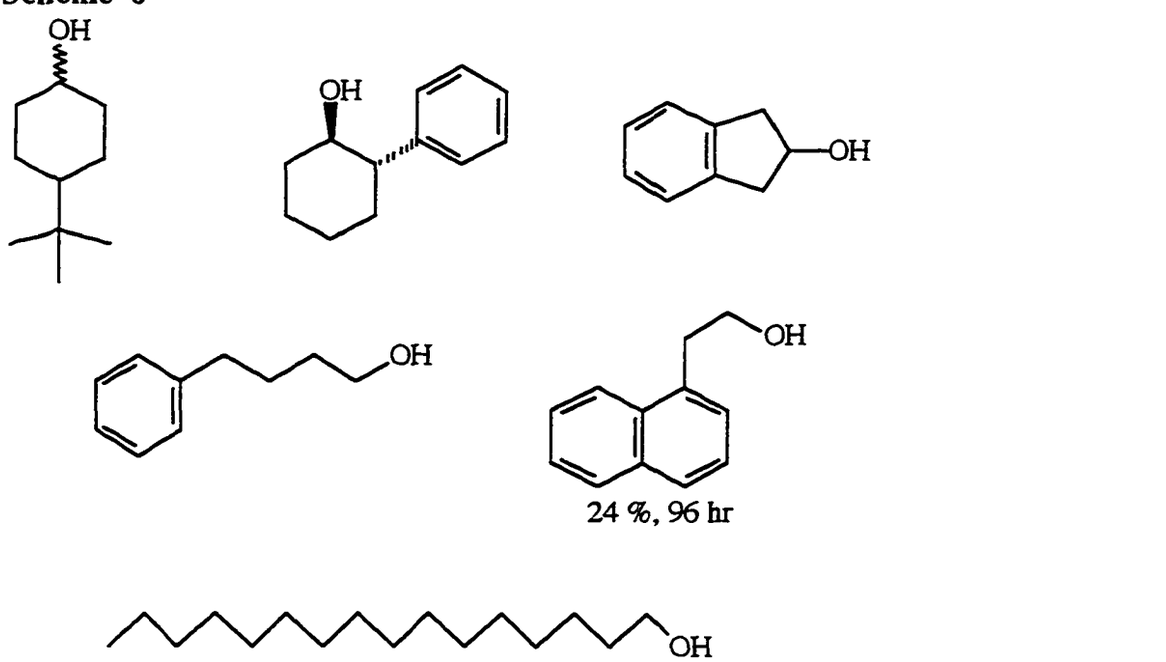
This catalytic process is believed to proceed via coordination of the alcohol substrate to the palladium(II) catalyst, followed by β-hydride elimination to form the carbonyl product and a palladium hydride species. The palladium hydride species then undergoes reductive elimination to form palladium(0). Molecular oxygen oxidizes the palladium(0) species back to the active state, thereby allowing the cycle to continue (Scheme 5).

The optimized reaction conditions were applied to a variety of saturated primary and secondary substrates with no success (Scheme 6). The reactions were conducted using both procedures A and B with a minimum reaction time of 72 hours. In most cases, the starting material remained unchanged. An explanation for the unreactivity of these substrates under the optimized conditions, while the same substrates showed good reactivity under Schwartz's conditions using ethylene carbonate as the solvent, can be found in the nature of the solvents as ligands for the palladium and the reactivity of the alcohol substrates. Ethylene carbonate is a polar, aprotic solvent that is weakly coordinating with palladium. In a reaction mixture with an alcohol substrate, the alcohol will tend to dominate the neutral coordination sites on the metal, which allows significantly long coordination lifetime for the oxidation to occur. Olefinic alcohols do not work well under these conditions, because the olefin competes favorably for the coordination sites, thereby reducing the catalyst activity. DMSO is also a polar, aprotic solvent, but is a good ligand for palladium, coordinating through either the sulfur or the oxygen atom, usually the sulfur atom.[20] In a reaction mixture with an alcohol substrate,

Scheme 5

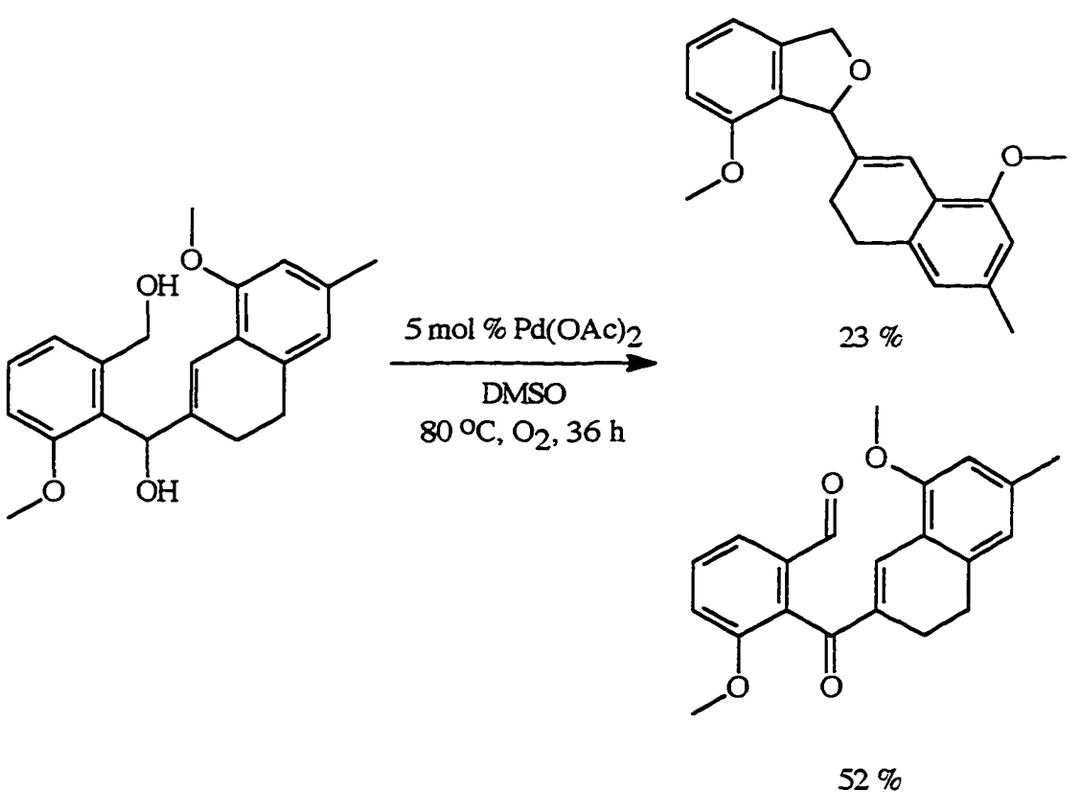


Scheme 6



DMSO molecules compete with alcohols and olefins, in the case of allylic alcohols, for the coordination sites. This competition shortens the coordination lifetime of the alcohol, thereby allowing only the oxidation of the more reactive allylic and benzylic substrates on a synthetically useful time scale.

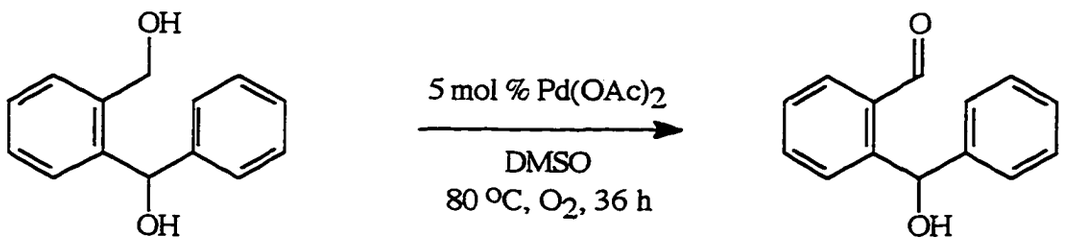
The inability of this catalyst system to oxidize saturated primary and secondary alcohols suggests that there may be a possibility to achieve selective oxidation of one hydroxyl over another if one were allylic or benzylic and the other were saturated. A limited number of experiments have been conducted. The first substrate was obtained from another research group and consisted of a primary benzylic hydroxyl and a secondary allylic and benzylic hydroxyl (eq 14).[21] The expectation was that the primary benzylic hydroxyl would oxidize quickly, thereby becoming a deactivating substituent for the secondary hydroxyl and allowing



(14)

for selective oxidation. Two products were obtained from the reaction. A cyclic ether was obtained in 23 % isolated yield. This product may have been generated by two conceivable mechanisms. One possibilty involves the reaction of a Pd(0) species with the allylic hydroxyl to form a π-allylic palladium species, followed by nucleophilic attack by the 1° benzylic hydroxyl to form the observed product. A second possibility would be an acid catalyzed ring closure employing the acetic acid that is generated during the Pd(II) catalytic cycle (Scheme 5). A dicarbonyl product was also obtained in 52 % isolated yield. The lack of selectivity in this system may be attributed to the presence of the activating methoxy substituent on the aromatic ring counteracting the proposed selectivity-generating deactivation by the newly formed aldehyde function.

A second attempt at selective oxidation involved a simpler model of the complex substrate previously described (eq 15). This reaction gave a fairly complex product mixture



(15)

20 %

4 other products

from which the desired product from selective oxidation could be obtained in 20 % isolated yield. GCMS analysis of the product mixture indicated the presence of four other products. Two of the compounds, which accounted for 18 and 12 % or the product mixture by gas chromatography, were found to exhibit a mass of 210, which could be the dicarbonylproduct and a product from the palladium-catalyzed lactonization of the the desired product. There was also a compound of mass 196 that accounted for 60 % of the mixture which is suspected to be

a cyclic ether corresponding to the product observed from the previous substrate, but the structure could not be confirmed. Only the structure of the desired product could be identified by ^{1}H NMR.

The potential for selective oxidation with this palladium(II)-DMSO-O_2 catalyst system has been demonstrated. A substrate containing both a 1° and a 2° hydroxyl attached to the same aromatic ring was observed to generate low to moderate yields of products resulting from the selective oxidation of the 1° hydroxyl. The selection of proper substrates and optimization of the reaction conditions could see this selective oxidation develop into a useful procedure.

Conclusion

An efficient system for the palladium-catalyzed oxidation of primary and secondary allylic and benzylic alcohols has been developed using O_2 as the sole reoxidant of the palladium. The conditions have been applied to a wide variety of substrates producing the desired carbonyl compounds in moderate to excellent yields. The reaction has been shown to be effective on a 100 mmol scale with no change in reactivity or yield.

Experimental

General. All ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.5 MHz, respectively. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) or basic $KMnO_4$ solution [3 g $KMnO_4$ + 20 g K_2CO_3 + 5 mL NaOH (5%) + 300 mL H_2O]. All melting points are uncorrected.

Reagents. All reagents were used directly as obtained commercially unless otherwise stated. $KMnO_4$, K_2CO_3, NaOH, $NaHCO_3$, benzophenone and dimethylsulfoxide were obtained from Fisher Scientific. $CeCl_3$, benzyl alcohol, benzaldehyde, *p*-methylbenzyl alcohol, *p*-tolualdehyde, 2,5-dimethoxybenzyl alcohol, 2,5-dimethoxybenzaldehyde, 3-

hydroxybenzyl alcohol, 3-hydroxybenzaldehyde, 3-chlorobenzyl alcohol, 3-chlorobenzaldehyde, 4-nitrobenzyl alcohol, 4-nitrobenzaldehyde, methyl 4-(hydroxymethyl)benzoate, methyl 4-formylbenzoate, 3,3,6,8-tetramethyltetralone, benzhydrol, methyl *p*-tolylcarbinol, 4-methylacetophenone, benzoin, benzil, 4-nitroacetophenone, myrtenol, myrtenal, cinnamyl alcohol, cinnamaldehyde, 2-cyclohexen-1-ol, 2-cyclohexen-1-one, isophorone and 1-octen-3-ol were obtained from Aldrich Chemical Co. Palladium acetate was obtained from Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd.

General procedure for alcohol oxidation. To a mixture of substrate (1 mmol) in DMSO (1 mL) was added 5 mol % $Pd(OAc)_2$ and $NaHCO_3$ (2 equiv where indicated). The flask was equipped with a magnetic stir bar and purged with oxygen gas. A septum was placed over the opening of the flask and a balloon of oxygen gas attached to the flask through the septum by a needle. The reaction was stirred at 80 °C until the reaction had reached completion as indicated by thin-layer chromatographic analysis. The reaction mixture was cooled to room temperature and then placed directly onto a column of silica gel and eluted with an appropriate combination of hexane/ethyl acetate. The fractions containing the product were combined and concentrated in vacuo.

The products of Table 8, entries 2-4, 6-12, 14 and 16 were identified by comparing their ^1H and ^{13}C NMR spectra and melting points (where possible) with authentic samples. The yields for the products of entries 1, 5, 13, 15 and 17 were determined by gas chromatography using authentic samples and appropriate correction factors.

***p*-Methylbenzaldehyde** (entry 2). ^1H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 7.30 (d, J = 7.9 Hz, 2 H), 7.75 (d, J = 7.9 Hz, 2 H), 9.94 (s, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 21.86, 129.73, 129.84, 134.22, 145.55, 191.97.

2,5-Dimethoxybenzaldehyde (entry 3). mp 50-52 °C; ^1H NMR (400 MHz, CDCl3) δ 3.80 (s, 3 H), 3.90 (s, 3 H), 6.96 (d, J = 9.0 Hz, 1 H), 7.14 (dd, J = 8.0, 4.0 Hz,

1 H), 7.33 (d, J = 4.0 Hz, 1 H), 10.45 (s, 1H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 55.85, 56.19, 110.41, 113.37, 123.54, 124.94, 153.63, 156.75, 189.64.

3-Hydroxybenzaldehyde (entry 4). mp 103-105 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.92 (br s, 1 H), 7.16 (dt, J = 8.0, 4.0 Hz, 1 H), 7.39-7.47 (m, 3 H), 9.96 (s, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 114.81, 122.18, 123.62, 130.47, 137.83, 156.45, 192.61.

4-Nitrobenzaldehyde (entry 6). mp 106-107 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.0 Hz, 2 H), 8.41 (d, J = 8.0 Hz, 2 H), 10.17 (s, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 124.71, 130.88, 140.43, 151.52, 190.71.

Methyl 4-formylbenzoate (entry 7). mp 61-62 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.97 (s, 3 H), 7.96 (d, J = 8.0 Hz, 2 H), 8.21 (d, J = 8.0 Hz, 2 H), 10.11 (s, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 52.63, 129.56, 130.23, 135.13, 139.18, 166.10, 191.68.

3,3,6,8-Tetramethyltetralone (entry 8). mp 58-59 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.04 (s, 6 H), 2.31 (s, 3 H), 2.46 (s, 2 H), 2.61 (s, 3 H), 2.79 (s, 2 H), 6.87 (s, 1 H), 6.89 (s, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 21.80, 23.58, 28.46, 33.51, 45.17, 54.83, 128.26, 128.34, 131.69, 141.65, 143.39, 144.45, 200.34.

Benzophenone (entry 9). mp 49-51 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (tt, J = 8.0, 4.0 Hz, 4 H), 7.59 (tt, J = 8.0, 4.0 Hz, 2 H), 7.79-7.83 (m, 4 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 128.15, 129.92, 132.29, 137.45, 196.79.

4-Methylacetophenone (entry 10). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3 H), 2.57 (s, 3 H), 7.25 (d, J = 8.0 Hz, 2 H), 7.85 (d, J = 8.0, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 21.65, 26.56, 128.47, 129.27, 134.72, 143.91, 198.88.

Benzil (entry 11). mp 94-95 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (t, J = 8.0 Hz, 4 H), 7.66 (t, J = 8.0 Hz, 2 H), 7.98 (d, J = 8.0 Hz, 4 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 129.08, 129.96, 133.03, 134.95, 194.63.

4-Nitroacetophenone (entry 12). mp 79-80 °C; ^{1}H NMR (400 MHz, CDCl3) δ 2.69 (s, 3 H), 8.12 (d, J = 8.0 Hz, 2 H), 8.325 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100.5 MHz, CDCl3) δ 27.04, 123.91, 129.36, 141.41, 150.40, 196.35.

***trans*-Cinnamaldehyde** (entry 14). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.70 (dd, J = 16.0, 7.7 Hz, 1 H), 7.42 (m, 3H), 7.45 (d, J = 16.0 Hz, 1 H), 7.54 (m, 2 H), 9.69 (d, J = 7.7 Hz, 1 H); ^{13}C NMR (100.5 MHz, CDCl3) δ 128.57, 128.59, 129.16, 131.34, 134.04, 152.86, 193.77.

Isophorone (entry 16). ^{1}H NMR (400 MHz, CDCl3) δ 1.04 (s, 6 H), 1.95 (d, J = 0.44 Hz, 3 H), 2.19 (s, 4 H), 5.86 (t, J = 1.28 Hz, 1 H); ^{13}C NMR (100.5 MHz, CDCl3) δ 24.44, 28.22, 33.42, 45.12, 50.70, 125.35, 160.22, 199.61.

Cyclic ether product (eq 14). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (m, 1 H), 2.21 (m, 1 H), 2.30 (s, 3 H), 2.72 (m, 2 H), 3.72 (s, 3 H), 3.82 (s, 3 H), 5.10 (d, J = 12.4 Hz, 1 H), 5.23 (dd, J = 12.4, 2.8 Hz, 1 H), 5.87 (s, 1 H), 6.54 (s, 2 H), 6.72 (d, J = 8.4 Hz, 1 H), 6.83 (d, J = 8.4 Hz, 1 H), 6.90 (s, 1 H), 7.27 (t, J = 8.4 Hz, 1 H); GCMS found 322.

Dicarbonyl product (eq 14). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3 H), 2.81 (m, 4 H), 3.69 (s, 3 H), 3.82 (s, 3 H), 6.48 (s, 1 H), 6.63 (s, 1 H), 7.23 (m, 2 H), 7.56 (m, 2 H), 9.91 (s, 1 H); GCMS found 336.

2-Formylbenzhydrol (eq 15). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65 (br s, 1 H), 6.41 (s, 1 H), 7.50 (m, 9 H), 10.04 (s, 1 H); GCMS found 212.

Acknowledgement

The Larock group gratefully acknowledges partial financial support of this research by the donors of the Petroleum Research Fund administered by the American Chemical Society and a Graduate Assistantship in Areas of National Need (GAANN) Fellowship from the U. S. Department of Education. We would like to acknowledge Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for contributing the palladium acetate. We would also like

to acknowledge Guohua Zhao of Professor G. A. Kraus' research group for the gift of the compounds used in the selective oxidation work (eqs 14 and 15).

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(21) Sample supplied by Guohua Zhao of Professor G. A. Kraus' research group at Iowa State University.

CHAPTER 2: EFFORTS TOWARD THE PALLADIUM(II)-CATALYZED DEHYDROGENATION OF β-DICARBONYL COMPOUNDS

A paper to be submitted to the *Journal of Organic Chemistry*

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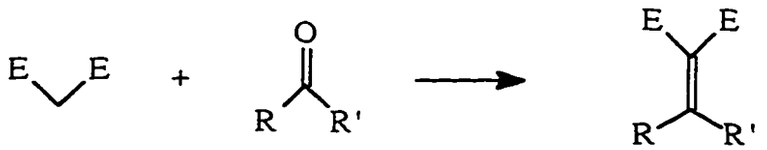
Introduction

Perhaps the most common synthesis of alkylidene β-dicarbonyl compounds involves the Knoevenagel condensation of an activated methylene compound with an aldehyde or ketone (eq 1). Occasionally in a synthesis, one may desire to achieve the same type of product from a



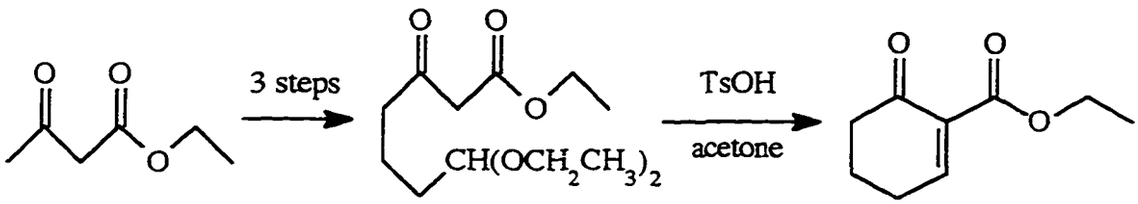
(1)

E = CO_2R, COR, CN, SO_2R, NO_2 R, R' = H, alkyl, aryl

saturated precursor. This has proven to be a fairly challenging problem in organic synthesis relying on the labor-intensive construction of complex substrate molecules for intramolecular condensations or the stoichiometric use of toxic reagents.

An early approach to this type of substrate focused on the synthesis of 2-carboethoxy-2-cyclohexenone via an intramolecular Knoevenagel condensation.[1] The substrate for the condensation was synthesized from acetylacetone in three steps and was self-condensed with catalytic TsOH in acetone to give the desired compound in 35-50 % yield (Scheme 1). Although this approach is suitable for the synthesis of simple cyclic unsaturated

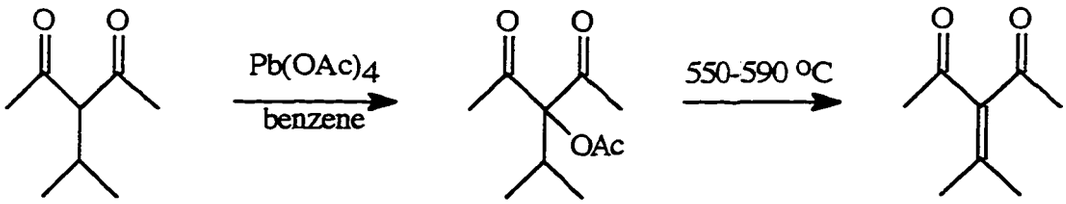
Scheme 1



β-dicarbonyl compounds, more complex compounds would require the synthesis of more complex condensation precursors, which takes away from the generality of this synthetic method.

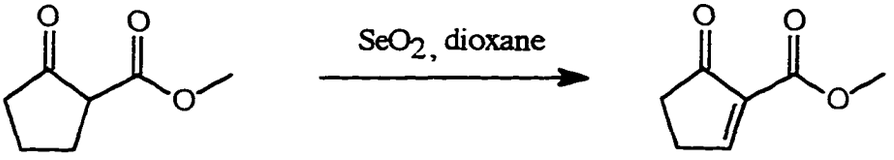
In 1970, Gorenstein and co-workers used a procedure suggested by Corey for the synthesis of alkylidene acetylacetone.[2] This strategy involved the acetoxylation of alkyl acetylacetone derivatives with $Pb(OAc)_4$, followed by pyrolysis (Scheme 2). The overall yield

Scheme 2



of this process for isopropyl acetylacetone was 14 %. This process offers the flexibility for incorporation of a wide variety of primary or secondary alkyl substituents on the acetylacetone, but suffers from a low yield and the need for pyrolysis equipment.

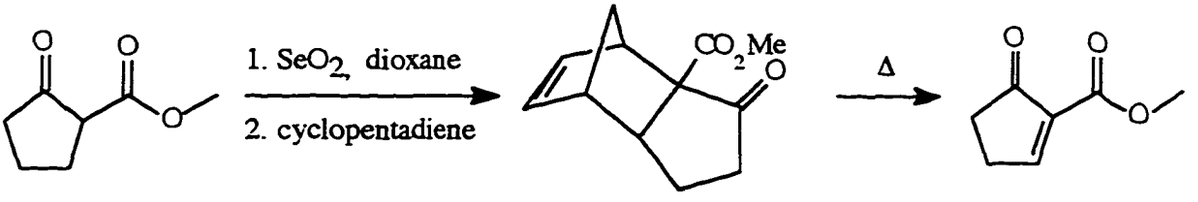
Procedures for the dehydrogenation of β-dicarbonyl compounds have also borrowed from the synthetic approaches for converting ketones into enones. One such report, by Marx,[3] involved oxidation of 2-carbomethoxycyclopentanone with selenium dioxide in refluxing dioxane (eq 2). The product enone was unstable under the reaction conditions and polymerized rapidly on attempted purification. The unstable product could, however, be trapped as a Diels-Alder adduct with cyclopentadiene and subsequently purified (Scheme 3). The desired enone could then be released via a retro Diels-Alder process at 438 °C and collected at -10 °C where it



45 %

(2)

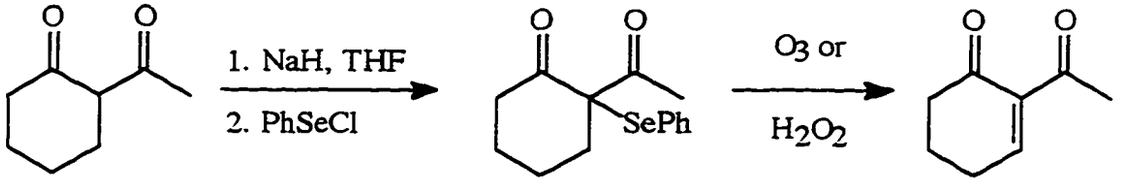
Scheme 3



could be kept for several hours before the onset of polymerization. Marx later used this methodology in the synthesis of natural products, including (-)-acorone,[4] sarkomycin[5] and sarkomycin analogues.[6]

In 1974, Reich and co-workers reported the extension of the selenoxide syn elimination methods for the synthesis of enones to the preparation of unsaturated β-dicarbonyl compounds (Scheme 4).[7] In this method, a THF solution of the β-dicarbonyl compound is treated with

Scheme 4



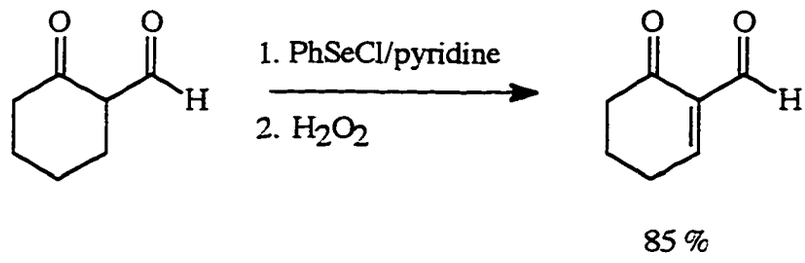
86 %

90 %

excess NaH, followed by the addition of 1.05 equiv of PhSeCl. The α-phenylseleno-β-dicarbonyl compound can then be oxidized and eliminated by ozonolysis or H_2O_2. A full account of this work was published in 1975.[8]

Another variation of the α-selenation procedure was reported by Liotta and co-workers in 1981.[9] This procedure was restricted to β-dicarbonyl compounds that substantially

enolized. The procedure involves selenation using a 1:1 complex of PhSeCl/pyridine and in situ oxidation with 30 % H_2O_2, after removal of the pyridine (eq 3). The advantages of this methodology are: (a) strong base and anhydrous solvents are unnecessary; (b) isolation of intermediate selenides is unnecessary; (c) the reaction conditions are compatible with a variety

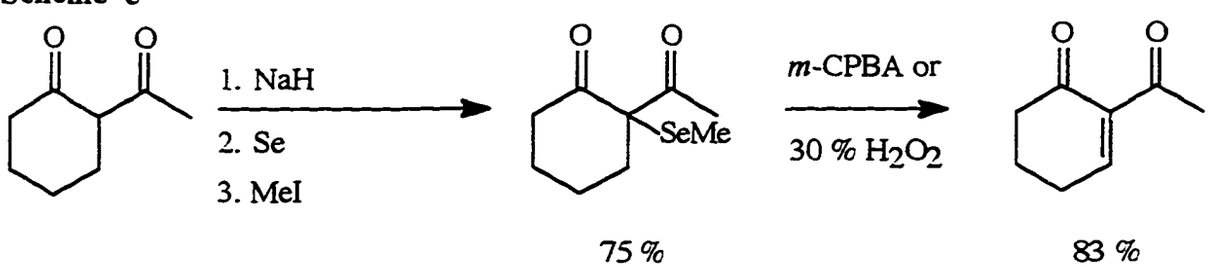


85 % (3)

of other functional groups, such as ketones, esters, alcohols, ethers.

Another approach to unsaturated β-dicarbonyl compounds, reported by Liotta, Ensley and co-workers, uses the direct reaction of the β-dicarbonyl anion with selenium metal, followed by alkylation with methyl iodide to form the methylseleno derivative. This compound can then be subjected to oxidative elimination using either *m*-chloroperbenzoic acid or 30 % H_2O_2 as oxidants (Scheme 5).[10] This procedure has the disadvantages of requiring the

Scheme 5



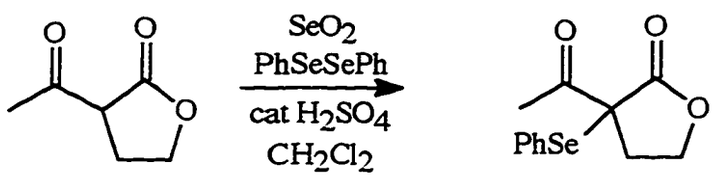
75 % 83 %

isolation of the intermediate methylselenide and not being effective on β-ketoaldehydes, but is more cost effective than procedures employing the more expensive PhSeX reagents (X = Cl, Br, SePh).

Still another approach to α-phenylseleno β-dicarbonyl compounds, which could be

subjected to oxidative elimination, employs selenium dioxide and diphenyl diselenide and catalytic H_2SO_4 (eq 4).[11] This procedure affords moderate to good yields and offers a suitable alternative to the strongly basic conditions previously employed.

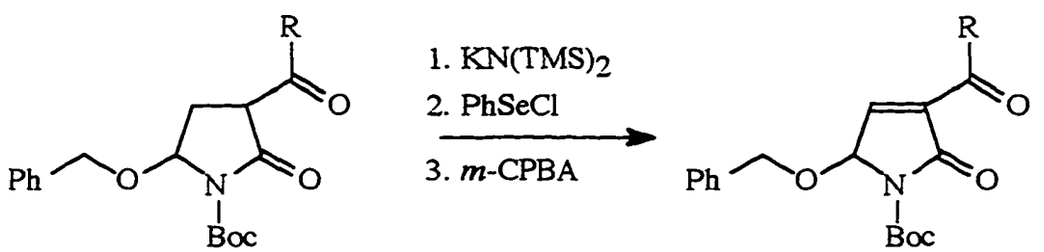
The selenium-based methodology for introducing unsaturation in β-dicarbonyl



66 %

(4)

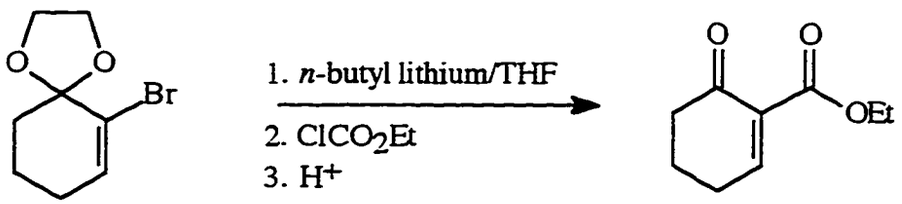
compounds was extended by Krafft and co-workers to include β-ketolactams in their synthetic approach to cytochalasins.[12] This procedure used the strong base/anhydrous solvent approach to anion generation and employed *m*-CBPA to induce the oxidative elimination (eq 5). The desired unsaturated β-ketolactams were obtained in good yields.



(5)

R = CH_3, Ph

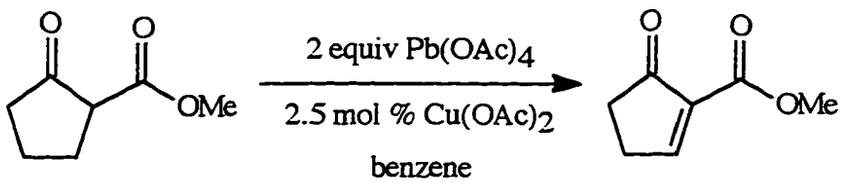
A completely different approach to the synthesis of β-dicarbonyl compounds was reported by Smith and co-workers in 1978.[13] This strategy used α-ketovinyl anion equivalents In 1993, Schultz reported that cyclic β-ketoesters and β-ketoamides could be converted generated from the reaction of *n*-butyllithium and ketals of α-bromoenones (eq 6). The α-ketovinyl anion equivalent could be quenched with a variety of electrophiles. This strategy was only applied to cyclic enones.



(6)

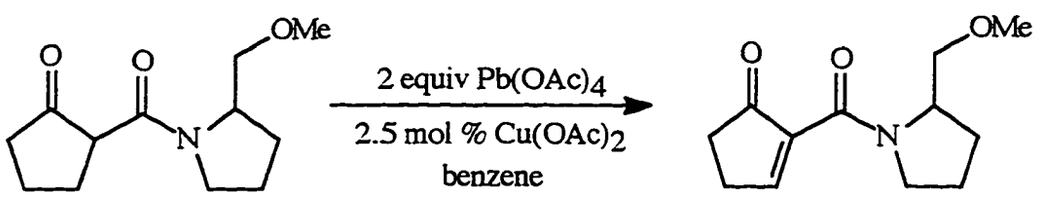
81 %

In 1993, Schultz reported that cyclic β-ketoesters and β-ketoamides could be converted into 2-(carbalkoxy)- and 2-(aminocarbonyl)-2-cycloalken-1-ones by $Pb(OAc)_4$ and $Cu(OAc)_2$ in benzene (eqs 7 and 8).[14] The yields for this reaction are moderate to good for 5-, 6- and 7-membered ring β-ketoesters and β-ketoamides. The reaction conditions were only applied to



(7)

20 %



(8)

55 %

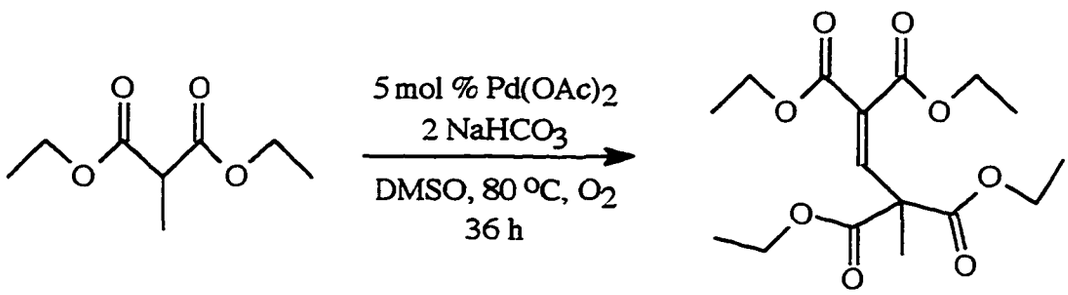
cyclic systems.

The current synthetic methodology for the synthesis of α,β-unsaturated-β-dicarbonyl compounds from saturated precursors rely on labor-intensive construction of complex substrate molecules for intamolecular condensations or the stoichiometric use of toxic reagents. A

catalytic procedure employing palladium(II) methodology would offer an attractive alternative to these other approaches.

Results and Discussion

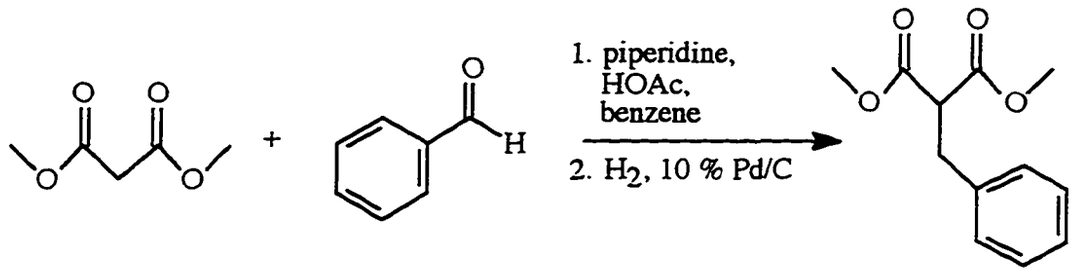
The development of a procedure for the palladium(II)-catalyzed dehydrogenation of β-dicarbonyl compounds began with an effort to find and optimize reaction conditions for a model substrate. The first choice of substrate was diethyl methylmalonate (eq 9). The reaction



77 % (9)

proceeded very well, but the observed product was actually the result of three sequential reactions: (1) palladium(II)-catalyzed dehydrogenation, (2) Michael addition and (3) palladium(II)-catalyzed dehydrogenation. The propensity of the expected product, diethyl methylenemalonate, to undergo Michael addition made this a poor choice for a model system, although the success of this transformation was encouraging.

Dimethyl benzylmalonate, which is easily prepared by a Knoevenagel condensation of dimethyl malonate and benzaldehyde, followed by hydrogenation with 10 % Pd/C, was selected as an alternative model system (eq 10). The new model substrate was subjected to a variety of reaction conditions (Table 1). A set of standard conditions for the cyclization of olefinic tosylamides was used as the starting point for the optimization process.[15] One difficulty became apparent from these experiments, that being the fact that the starting material and product have the same R_f by TLC. The product is very UV active and quickly dominates



(10)

the chromatogram, thereby giving a false indication that the reaction is complete.

The standard conditions with and without base (Table 1, entries 1 and 2, respectively) gave what appeared to be complete reactions within 13 h. The reaction without base gave excellent recovery of material, but the ^{1}H NMR spectrum of the product mixture indicated that the reaction had not proceeded very far. The reaction with base provided a moderate recovery of material, but also had not proceeded very far. These results suggest that base in general, or the acetate anion specifically, is bad for the reaction. Intuitively, one would suspect that base would be beneficial by promoting the enolization of the substrate for bonding to palladium.

The standard conditions without base were tried again with a 24 h reaction time (Table 1, entry 3). The recovery of material was down to 71 %, but the ratio of product to starting material had improved. The concentration of the reaction was increased to facilitate a faster reaction (Table 1, entry 4). After 36 h, the recovery of material was excellent, but the conversion was reduced, yielding a mixture that was 36:64 product to starting material.

At this point, the conditions without base appeared to give a very slow reaction that would not be complete on a synthetically useful time scale, so a series of reactions with a variety of bases was examined using a 24 h reaction time (Table 1, entries 5-11). A reaction with 2 equiv of NaOAc gave an extremely messy reaction (Table 1, entry 5). The desired product could be identified in about 5 % yield. A reaction with 1 equiv of triethylamine gave no reaction (Table 1, entry 6). The reaction with 1 equiv of KOAc led to a moderate recovery of a 64:36 mixture of product and starting material (Table 1, entry 7). A reaction employing 1

Table 1. Base Optimization for the Dehydrogenation of Dimethyl Benzylmalonate.

entry	base	conc (mL : mmol)	time (h)	% recovery	ratio (prod : SM)
1	----	4 : 1	13	99	30:70
2	2 NaOAc	4 : 1	13	65	25:75
3	----	4 : 1	24	71	50:50
4	----	1 : 1	36	90	36:64
5	2 NaOAc	1 : 1	36	?	~5 % product
6	1 Et_3N	1 : 1	24	no reaction	----
7	1 KOAc	1 : 1	24	54	64:36
8	1 LiOAc	1 : 1	24	messy	----
9	1 $Mg(OAc)_2$	1 : 1	24	47	product only
10	1 $MgCO_3$	1 : 1	24	89	96:4
11	1 $MgSO_4$	1 : 1	24	91	83:17
12	1 $MgCO_3$	1 : 1	32	82	product only
13	1 $MgCO_3$	2 : 1	32	84	product only
14	1 $MgSO_4$	2 : 1	48	83	product only
15	1 $CaCO_3$	2 : 1	32	90	33:67
16	1 $ZnCO_3$·2 $Zn(OH)_2$·H_2O	2 : 1	32	85	67:33
17	1 $BaCO_3$	2 : 1	32	90	33:67
18	1 MgO	2 : 1	32	85	product only

equiv of LiOAc gave a very messy reaction from which the desired product could not be identified.

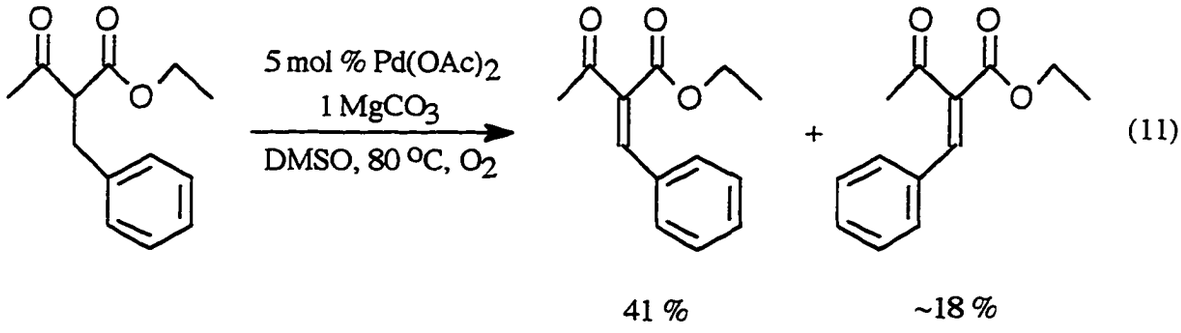
The standard acetate salts had proven unsatisfactory, so the scope of bases was expanded to include divalent cations with gratifying results (Table 1, entries 10-18). A reaction employing 1 equiv of $Mg(OAc)_2$ afforded a complete reaction from which the desired product could be isolated in 47 % yield (Table 1, entry 9). Earlier results had suggested that the acetate anion might have a detrimental effect on the reaction, so reactions were run using $MgCO_3$ and $MgSO_4$ (Table 1, entries 10 and 11, respectively). Both reactions afforded excellent recoveries of material; however, the conversions were quite different. The reaction with the more basic $MgCO_3$ led to a 96:4 mixture of the desired product to starting material, while the non-basic $MgSO_4$ led to a 83:17 mixture. The results from these experiments seem to indicate that the cation may be more important than the anion for aiding in the palladium-catalyzed dehydrogenation and that a basic anion may not be necessary. The same bases were run using longer reaction times. A complete reaction could be achieved with $MgCO_3$ within 32 h, affording an 82 % isolated yield of the desired product, but there was also present a small amount of unidentifiable by-product (Table 1, entry 12). By running this same reaction at higher dilution, using 2 mL of DMSO for 1 mmol of substrate, the by-product could be eliminated with a slight increase in yield (Table 1, entry 13). A reaction using this new concentration and $MgSO_4$ as the base was complete within 48 h and afforded the desired product in 83 % isolated yield (Table 1, entry 14).

Given the success with the divalent magnesium salts, other salts containing divalent cations were examined (Table 1, entries 15-18). The reactions were allowed to stir at 80 °C for 32 h so the reactivity of these salts could be directly compared with $MgCO_3$ and $MgSO_4$. Reactions using 1 equiv of $CaCO_3$ or $BaCO_3$ offered high recoveries of material, but low conversions, both yielding 33:67 mixtures of product to starting material (Table 1, entries 15 and 17). A reaction using 1 equiv of $ZnCO_3 \cdot Zn(OH)_2 \cdot H_2O$ gave an incomplete reaction after 32

h, but had a high recovery of material (Table 1, entry 16). A reaction using 1 equiv of MgO gave results very similar to $MgCO_3$, affording a complete reaction and an 85 % isolated yield of the desired product.

The results of this optimization work showed $MgCO_3$, $MgSO_4$ and MgO to be the most effective co-reagents for the palladium(II)-catalyzed dehydrogenation of dimethyl benzylmalonate. The less basic salt, $MgSO_4$, required a slightly longer reaction time. The final optimized conditions consist of 1 mmol of substrate in 1 mL of DMSO at 80 °C with 5 mol % of $Pd(OAc)_2$ as the catalyst and 1 equiv of either $MgCO_3$, $MgSO_4$ or MgO. These optimized conditions were then applied to other β-dicarbonyl compounds.

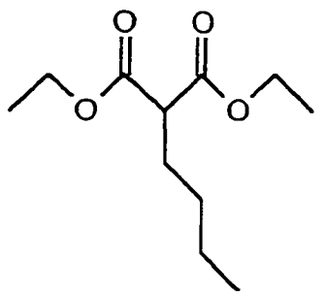
Ethyl benzylacetylacetone was synthesized and subjected to the optimized dehydrogenation conditions using $MgCO_3$ as the co-reagent (eq 11). The chemistry of this



(11)

substrate was also plagued by the problem of the starting material and product having nearly identical R_f values by TLC. The reaction was stirred at 80 °C for 32 h and afforded the desired product as a mixture of (E) and (Z) isomers in good yield. The (E) and (Z) assignments were made from the chemical shift of the vinylic proton. The (Z) isomer was obtained as a pure substance, but the (E) isomer was obtained as a 1:1 mixture with unreacted starting material. Integration of the ^1H NMR spectrum was used to determine the yield of this isomer as being about 18 %.

Diethyl *n*-butylmalonate was synthesized and subjected to the optimized dehydrogenation conditions (eq 12). This substrate showed no signs of reaction by TLC after 24 h. Chromatography of the same reaction mixture after 48 h yielded only starting material. This substrate was rerun using several of the co-reagents tested in the earlier optimization work



5 mol % $Pd(OAc)_2$
1 $MgCO_3$
DMSO, 80 °C, O_2

no reaction (12)

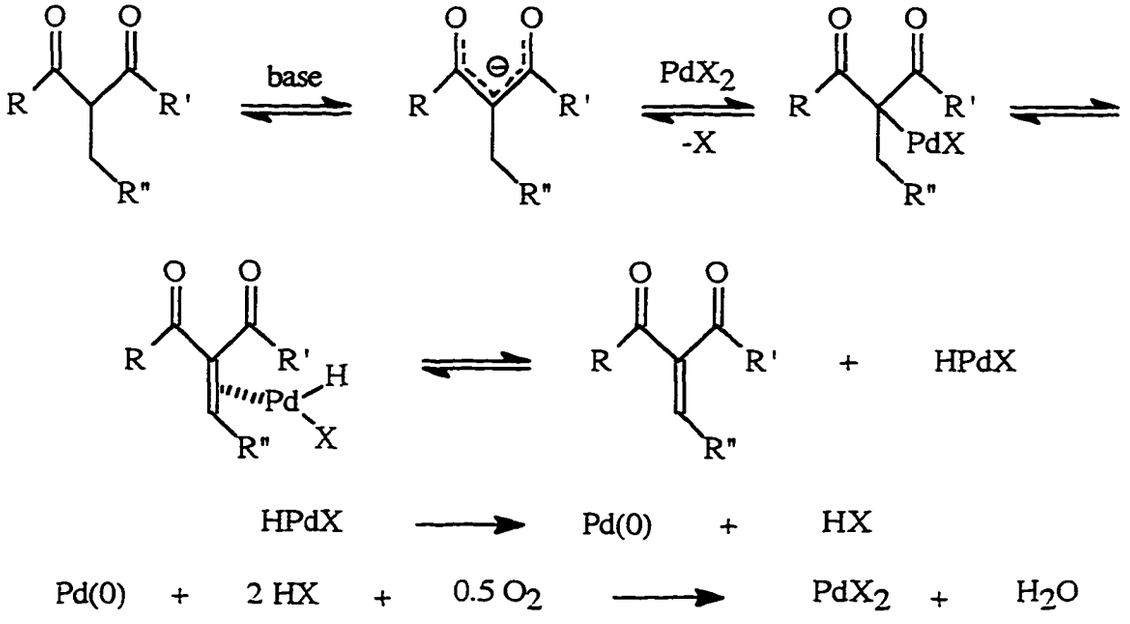
with similar results. The lack of reactivity with this substrate compels one to compare this structure with dimethyl benzylmalonate to find the root of this reactivity difference. Diethyl *n*-butylmalonate should be of similar acidity to dimethyl benzyl malonate, so this was not suspected to be the cause of the difficulty with this substrate.

The mechanism of this reaction is believed to proceed through the formation of a σ-bonded species between the palladium(II) and the enolized β-dicarbonyl compound, followed by β-hydride elimination to form the desired unsaturated β-dicarbonyl compound and a palladium hydride species. The palladium hydride species can then undergo reductive elimination to form a palladium(0) species, which gets oxidized back to the active palladium(II) state by oxygen gas (Scheme 6).

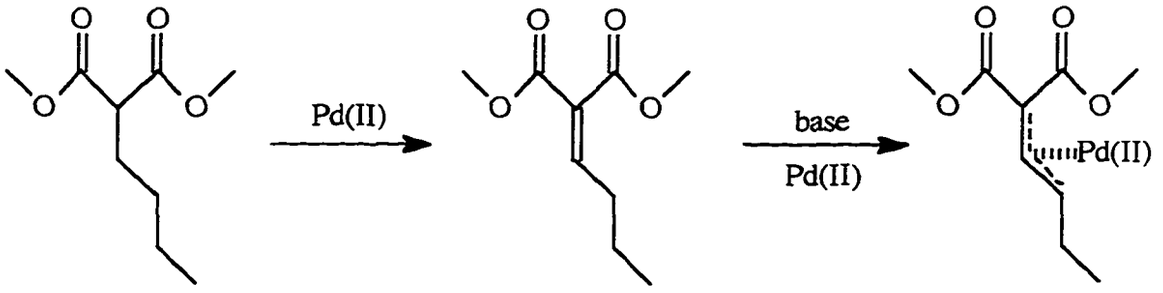
The difficulty in this transformation could stem from the β-elimination step. One could suggest that the elimination of a benzylic hydrogen in the model system proceeds more readily than the elimination of the secondary aliphatic hydrogen in this system, but β-eliminations of both types are generally quite facile and are frequently observed in organopalladium chemistry.

Another possible reason for the failure of this system to react could be the formation of a stable π-allyl palladium complex (Scheme 7). This type of complex is quite common with

Scheme 6

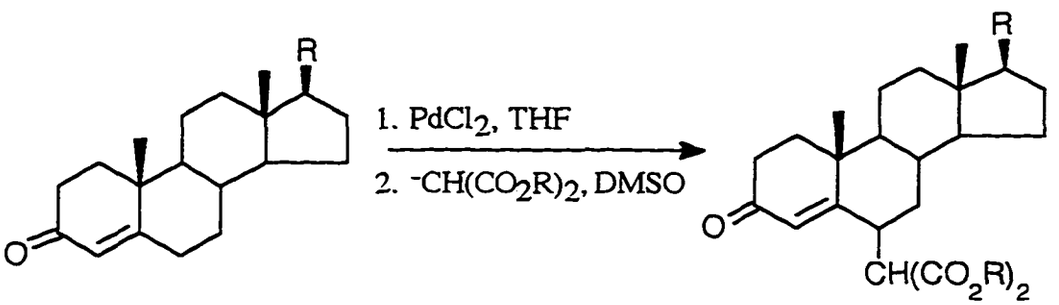


Scheme 7

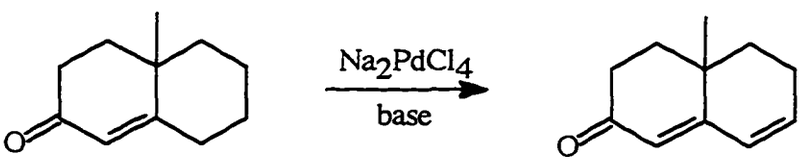


enone systems and can be treated with soft nucleophiles to form substitution products[16] (eq 13) or treated with base to form elimination products (eq 14).[17] The benzylmalonate does not possess any γ-hydrogens and is unable to form such a π-allyl complex.

A strong argument against the formation of a π-allyl complex foiling the reactivity of dimethyl *n*-butyl malonate is the presence of excess malonate anion (deprotonated, uncomplexed substrate) in the reaction mixture. There was no evidence for a product from nucleophilic substitution on the suspected π-allyl palladium complex. Clearly, a good test of this hypothesis would be to design a different substrate that does not have γ-hydrogen atoms,



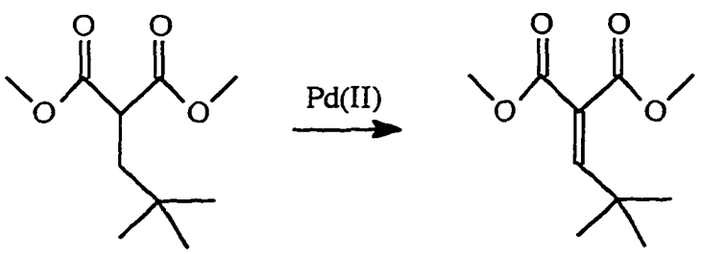
(13)



(14)

but is also not benzylic. One such substrate would be dimethyl (2,2-dimethylpropyl)malonate eq 15). Unfortunately, several attempts to synthesize this material yielded a product that was contaminated by an inseparable by-product.

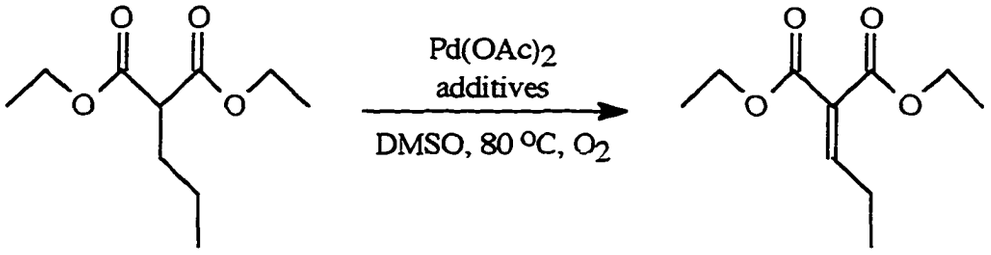
Some variations in conditions were examined to try to improve this transformation



(15)

(Table 2). Some additives were added to bind to the neutral ligand sites of the catalyst. The addition of 10 mol % of PPh_3 led to the generation of a trace amount of the desired product (Table 2, entry 1). The product is inseparable from the starting material, so the reaction was allowed to stir for a certain amount of time and then the yield was obtained from integration of the ^1H NMR spectrum of the mixture. Decreasing the amount of PPh_3 to 5 mol % showed no sign of reaction by TLC analysis (Table 2, entry 2). Addition of 5 mol % of 1,2-bis(diphenylphosphino)ethane (dppe) led to a rather complex mixture that contained starting

Table 2. Optimization of the Palladium(II)-Catalyzed Dehydrogenation of Dimethyl *n*-Butylmalonate.



entry	catalyst	additives	time (h)	yield (%)
1	5 % $Pd(OAc)_2$	10 % PPh_3, 1 equiv $MgCO_3$	48	trace
2	5 % $Pd(OAc)_2$	5 % PPh_3, 1 equiv $MgCO_3$	48	----
3	5 % $Pd(OAc)_2$	5 % dppe, 1 equiv $MgCO_3$	48	mixture
4	10 % $Pd(OAc)_2$	20 % $Cu(OAc)_2$	24	19
5	10 % $Pd(OAc)_2$	1 equiv $Cu(OAc)_2$	24	31
6	10 % $Pd(OAc)_2$	2 equiv $Cu(OAc)_2$	48	----

material, product and at least two by-products (Table 2, entry 3).

A reaction using 20 mol % $Cu(OAc)_2$ and 10 mol % $Pd(OAc)_2$ gave a slow reaction that generated a 19 % yield of the desired product (Table 2, entry 4). This reaction was very clean. Only signals for the starting material and desired product were present in the ^1H NMR spectrum of the product mixture. Increasing the amount of $Cu(OAc)_2$ to 1 equiv led to an increase in yield to 31 % (Table 2, entry 5). This reaction was also very clean. Increasing the amount of $Cu(OAc)_2$ again to 2 equiv looked to give a similar reaction to the 1 equiv reaction by TLC after 24 h, but all evidence of product had disappeared by 48 h (Table 2, entry 6).

There are two major concerns when dealing with products of the type generated by this procedure. First, the substrates are very susceptible to Michael addition reactions. There has been no evidence for this type of product in the reaction mixtures, except for the original reaction where the unhindered diethyl methylenemalonate was the desired product (eq 9).

Second, the substrates have a strong propensity to undergo polymerization. For the most part, the reactions give excellent recoveries of material even when there is significant amounts of product present. This suggests that the product is at least moderately stable under the reaction conditions. There has also been no evidence of any polymeric substance in the ^{1}H NMR spectra. The only support for such a process is from the reaction with 2 equiv of $Cu(OAc)_2$ (Table 2, entry 6), where there was evidence for product by TLC analysis after 24 h, but not after 48 h. Again, there was no evidence of any polymer in the ^{1}H NMR spectra.

Conclusion

Reaction conditions for the palladium(II)-catalyzed dehydrogenation of β-dicarbonyl compounds have been pursued. The optimized conditions showed good results with benzyl substituted β-dicarbonyl compounds, but simple aliphatic substituents proved relatively unreactive. By varying the reaction conditions, low yields of unsaturated products from the aliphatic substituted substrates could be achieved. More work is necessary to make this process a synthetically useful one.

Experimental

General. All ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.5 MHz, respectively. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) or basic $KMnO_4$ solution [3 g $KMnO_4$ + 20 g K_2CO_3 + 5 mL NaOH (5%) + 300 mL H_2O].

Reagents. All reagents were used directly as obtained from commercial sources unless otherwise stated. $KMnO_4$, HOAc, NaOAc, KOAc, LiOAc, $Mg(OAc)_2$, $MgCO_3$, $MgSO_4$, $CaCO_3$, Na, benzene and DMSO were obtained from Fisher Scientific. $BaCO_3$, $ZnCO_3 \cdot 2\,Zn(OH)_2 \cdot H_2O$, diethyl methylmalonate, dimethyl malonate, benzaldehyde, piperidine,

benzyl chloride, ethyl acetoacetate, diethyl malonate, 1-bromobutane, 1,2-bis(diphenylphosphino)ethane and $Cu(OAc)_2$ were obtained from Aldrich Chemical Co. Palladium acetate and PPh_3 were obtained from Kawaken Fine Chemicals Co., Ltd.

Dimethyl benzylidenemalonate:[18] To a solution of dimethyl malonate (6.60 g, 50 mmol) and benzaldehyde (5.80 g, 55 mmol) in benzene (20 mL) was added piperidine (0.17 g, 2 mmol) and acetic acid (0.60 g, 10 mmol). The flask was equipped with a magnetic stir bar and a Dean-Stark water separator and refluxed for 18 h. The mixture was cooled, diluted with ether and extracted with saturated NaCl solution. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel using 10:1 hexane/EtOAc as the eluent. The product was obtained as a clear oil in 95 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.84 (s, 3 H), 3.85 (s, 3 H), 7.39 (m, 5 H), 7.78 (s, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 52.73, 52.74, 125.52, 128.94, 129.44, 130.76, 132.79, 142.99, 164.53, 167.19.

Dimethyl benzylmalonate:[19] To a solution of dimethyl benzylidene malonate (2.20 g, 10 mmol) in ethanol (60 mL) was added 10 % Pd/C (200 mg). The flask was stirred at room temperature under an atmosphere of hydrogen gas until the consumption of gas had ceased. The mixture was filtered through celite and concentrated. The crude product was purified by column chromatography on silica gel using 10:1 hexane/EtOAc as the eluent. The product was obtained as a clear oil in 90 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.22 (d, J = 7.8 Hz, 2 H), 3.68 (t, J = 7.8 Hz, 1 H), 3.68 (s, 6 H), 7.18-7.30 (m, 5 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 34.80, 52.60, 53.65, 126.86, 128.61, 128.80, 137.79, 169.26.

Ethyl benzylacetoacetate:[20] Sodium metal (0.23 g, 10 mmol) was added to ethanol (40 mL) and stirred until the evolution of hydrogen had ceased. Ethyl acetoacetate (1.30 g, 10 mmol) was added and allowed to stir for 15 min before benzyl chloride (1.27 g, 10 mmol) was slowly added. The reaction mixture was stirred for 4 h and then diluted with ether and washed with saturated NaCl solution. The organic layer was dried over $MgSO_4$ and concentrated. The

crude product was purified by column chromatography on silica gel using 10:1 hexane/EtOAc as the eluent. The product was obtained as a clear oil in 80 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.19 (t, J = 7.2 Hz, 3 H), 2.18 (s, 3 H), 3.15 (d, J = 4.0 Hz, 2 H), 3.78 (t, J = 7.6 Hz, 1 H), 4.13 (q, J = 7.2 Hz, 2 H), 7.18-7.30 (m, 5 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 14.05, 29.66, 34.00, 61.33, 61.51, 126.71, 128.60, 128.83, 138.18, 169.15, 202.54.

Diethyl *n*-butylmalonate:[16] This compound was made using the same procedure as ethyl benzylacetoacetate above, except for the use of 1-bromobutane as the alkylating agent. The product was obtained as a clear oil in 79 % isolated yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, J = 6.8 Hz, 3 H), 1.27 (t, J = 7.2 Hz, 6 H), 1.35 (m, 4 H), 1.89 (q, J = 7.6 Hz, 2 H), 3.31 (t, J = 7.6 Hz, 1 H), 4.19 (q, J = 7.2 Hz, 4 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 13.75, 14.03, 22.30, 28.42, 29.44, 52.00, 61.17, 169.54.

General procedure for dehydrogenation. To a mixture of substrate (1 mmol) in DMSO (1 mL) was added 5 mol % $Pd(OAc)_2$ and 1 equiv of $MgCO_3$. The flask was equipped with a magnetic stir bar and purged with oxygen gas. A septum was placed over the opening of the flask and a balloon of oxygen gas attached to the flask through the septum by a needle. The reaction was stirred at 80 °C until the reaction had reached completion as indicated by thin-layer chromatographic analysis. The reaction mixture was cooled to room temperature and then placed directly onto a column of silica gel and eluted with an appropriate combination of hexane/ethyl acetate. The fractions containing the product were combined and concentrated in vacuo.

Diethyl 2,2-di(ethoxycarbonyl)propylidenemalonate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (t, J = 7.2 Hz, 6 H), 1.31 (t, J = 7.2 Hz, 3 H), 1.32 (t, J = 7.2 Hz, 3 H), 1.66 (s, 3 H), 4.10-4.29 (m, 8 H), 7.56 (s, 1 H); GCMS calcd 344, found 344.

(Z)-Ethyl benzylideneacetoacetate: ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20 (t, J = 7.2 Hz, 3 H), 2.35 (s, 3 H), 4.26 (q, J = 7.2 Hz, 2 H), 7.29-7.40 (m, 5 H), 7.50 (s, 1 H);

^{13}C NMR (100.5 MHz, $CDCl_3$) δ 13.92, 26.60, 61.77, 128.89, 129.57, 130.77, 132.97, 134.67, 141.33, 167.85, 194.72.

(E)-Ethyl benzylideneacetoacetate: ^1H NMR (400 MHz, $CDCl_3$) δ 1.27 (t, J = 7.2 Hz, 3 H), 2.28 (s, 3 H), 4.23 (q, J = 7.2 Hz, 2 H), 7.31 (m, 5 H), 7.61 (s, 1 H).

Acknowledgement

The Larock group gratefully acknowledges partial financial support of this research by the donors of the Petroleum Research Fund administered by the American Chemical Society and a Graduate Assistantship in Areas of National Need (GAANN) Fellowship from the U. S. Department of Education. We would also like to acknowledge Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for contributing the palladium acetate.

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*CHAPTER 3: PALLADIUM-CATALYZED CYCLIZATION OF OLEFINIC AMINE DERIVATIVES

A paper to be submitted to the *Journal of Organic Chemistry*

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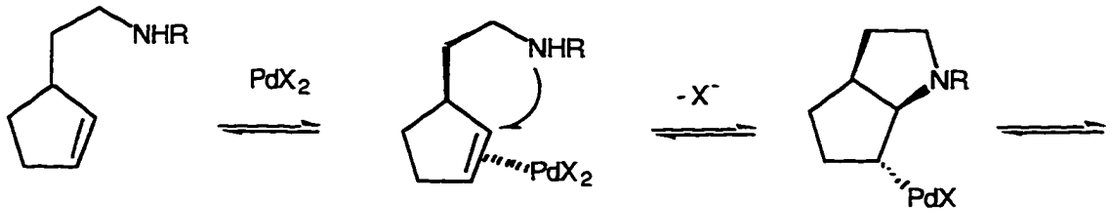
Introduction

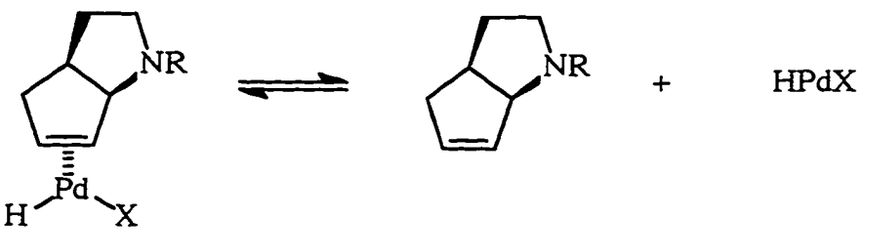
In recent years, palladium-catalyzed amination of olefins has become a useful and versatile method for the synthesis of nitrogen-containing heterocycles. These palladium-catalyzed methods have invoked both Pd(II) and Pd(0) catalytic cycles. This introduction will review the literature of catalytic transformations involving Pd(II) and the formation of nitrogen-containing heterocycles from olefinic amine derivatives as it relates to the current work being reported.

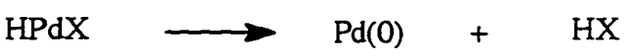
The cyclization of olefinic amine derivatives by Pd(II) is believed to proceed through coodination of the olefin to the metal. This π-complex undergoes intramolecular nucleophilic attack by the amine derivative in a ring forming step that also generates a σ-palladium species which often undergoes β-hydride elimination to form the desired cyclized product and a palladium hydride species. The palladium hydride species then undergoes reductive elimination to form a Pd(0) species. This process can be made catalytic in palladium by adding a reoxidant, such as benzoquinone, a Cu(II) salt or O_2 gas, to oxidize the Pd(0) back to the active state (Scheme 1).

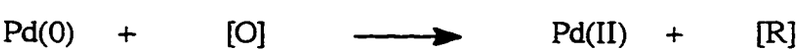
Hegedus and co-workers reported both stoichiometric[1] and catalytic[2] procedure for the oxidative cyclization of 2-allylic anilines. Benzoquinone was used as the reoxidant for the palladium in most cases. The catalytic cyclization of 2-(2-propenyl)aniline in THF gave 2-

Scheme 1



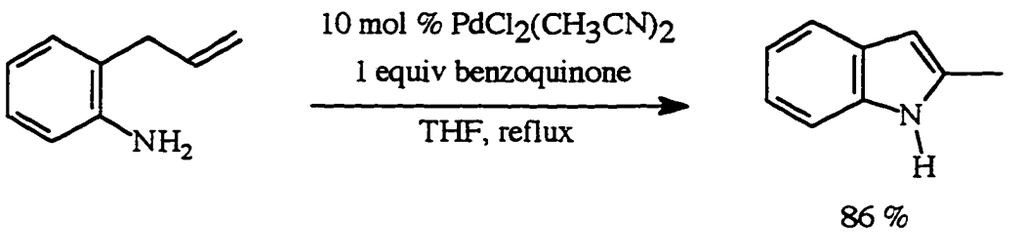




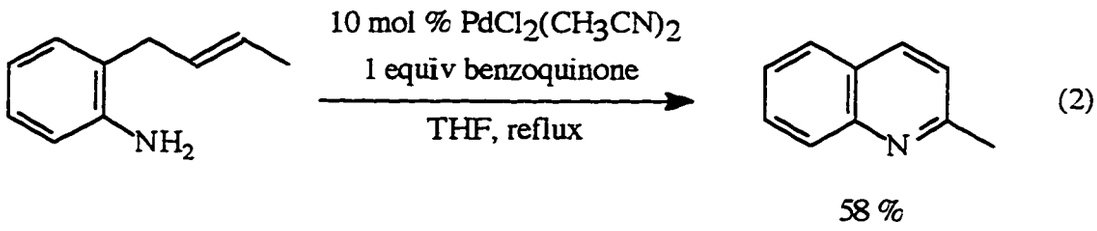


[O] = benzoquinone, Cu(II) salt or O_2 gas

methylindole in 86 % isolated yield (eq 1). This cyclization also worked with the *N*-acetyl derivative. Alkyl substituents on the allyl group led to the generation of quinolines (eq 2). The cyclization of 2-crotylaniline led to 2-methylquinoline in a 58 % isolated yield. Hegedus noted that cyclizations to form five-membered ring products tended to proceed more readily than



(1)

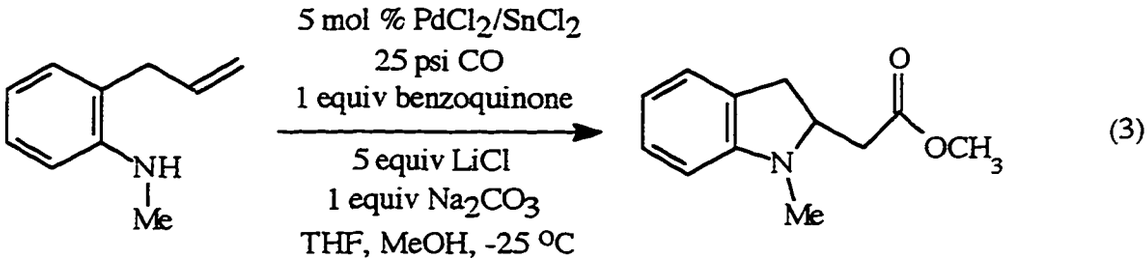


58 %

(2)

those forming six-membered rings.

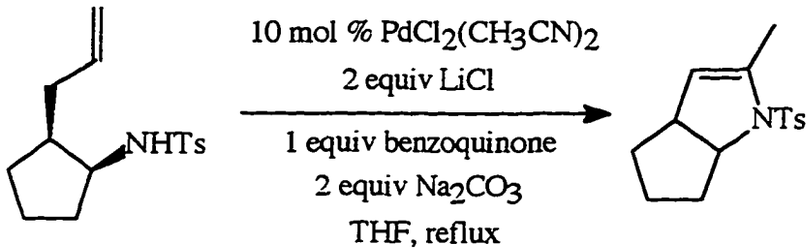
In 1980, Hegedus and co-workers extended their cyclization procedures to involve carbon monoxide insertions.[3, 4] *N*-Monosubstituted anilines could be cyclized under suitable conditions so as to allow CO insertion to prevail over β-hydride elimination of the intermediate σ-palladium(II) species. The cyclization of 2-allyl-*N*-methylaniline led to methyl 2,3-dihydro-1-methyl-1*H*-indole-2-acetate in good yield (eq 3). At temperatures higher than -25 °C, 2-



(3)

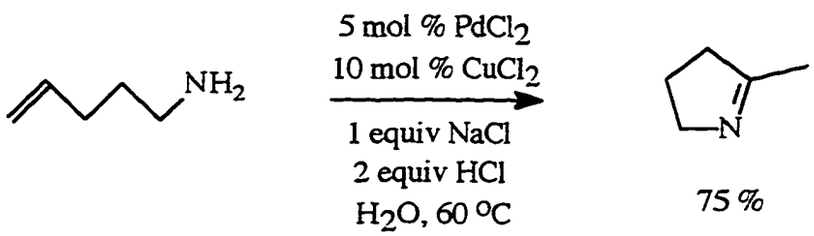
methyl indole was the major product, which suggested that β-hydride elimination was occurring faster than CO insertion. This methodology is much more effective with substrates that cannot undergo β-hydride elimination after cyclization.

Hegedus and co-workers reported the efficient cyclization of ω-olefinic tosylamides in 1982 using 1-10 mol % $PdCl_2$ as the catalyst and benzoquinone as the reoxidant.[2, 5] A wide variety of olefinic tosylamides were subjected to the cyclization conditions to obtained 5- and 6-membered ring enamine products in good to excellent yields (eq 4). In some cases, the cyclic enamine was hydrolyzed on work-up and/or purification and the corresponding tosylamido ketone was isolated.



(4)

Venanzi and co-workers reported the palladium-catalyzed oxidation of amino alkenes to cyclic imines or enamines and amino ketones.[6] The reaction of 4-penten-1-amine under unoptimized standard conditions resulted in the formation of 2-methyl-1-pyrroline in 75 % yield as determined by gas chromatographic analysis (eq 5). This process was proposed to

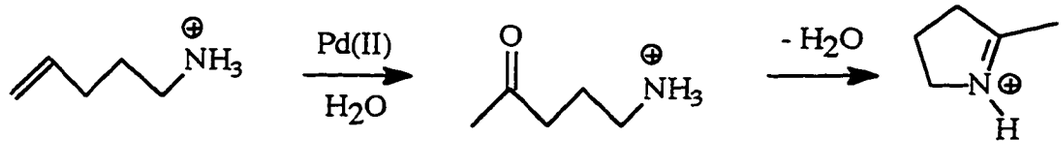


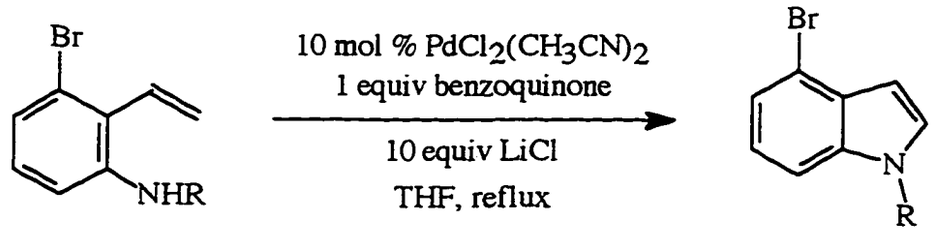
(5)

proceed through a Wacker type oxidation of the olefin to the ketone, followed by imine formation via intramolecular condensation with the amino group (Scheme 2).

Hegedus and co-workers reported the palladium(II)-catalyzed cyclization of *o*-ethenylanilines for the synthesis of 3- and 4-substituted indoles (eq 6).[7] *N*-Acetyl and *N*-tosyl derivatives of 3-bromo-2-ethenylaniline were cyclized. The acetyl derivative was sluggish using either $CuCl_2$ or benzoquinone as the reoxidant of the palladium. The *N*-tosyl derivative

Scheme 2

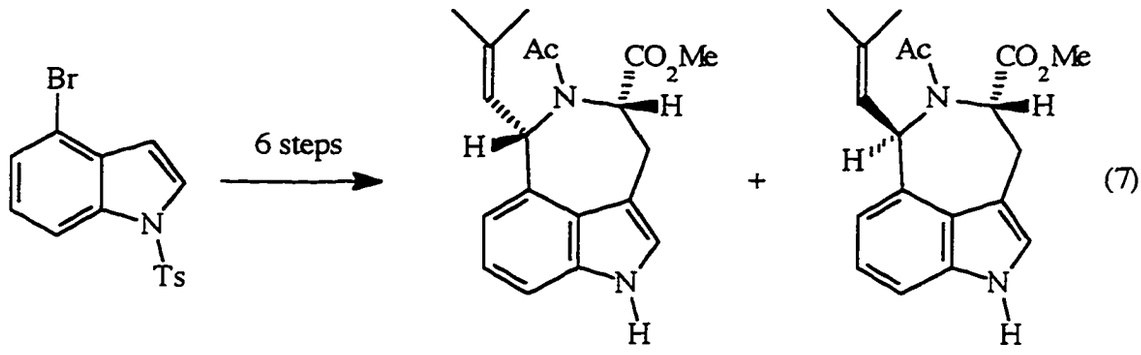




(6)

cyclized efficiently using benzoquinone as the reoxidant. Further transformations led to the generation of a variety of 3- and 4-substituted indoles. This same methodology was applied to the synthesis of the *N*-acetyl methyl ester of racemic claviciptic acids (eq 7).[8]

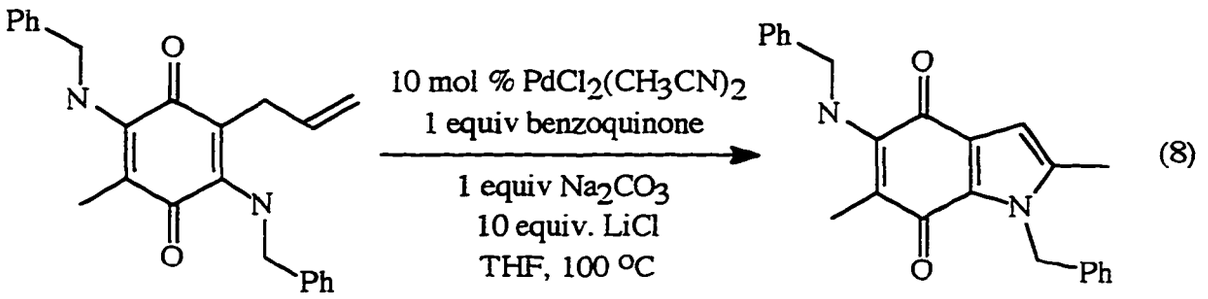
Hegedus and co-workers reported the oxidative cyclization of unsaturated



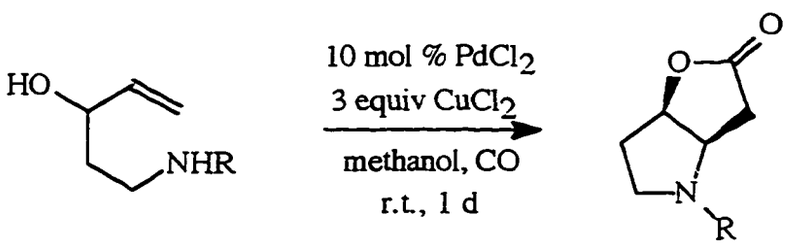
(7)

aminoquinones for the synthesis of pyrroloindoloquinones.[2, 9] The cyclization of *N*-substituted allyl(bisamino)quinones was accomplished using standard catalytic palladium(II) conditions (eq 8). Analogous unsubstituted allyl(amino) quinones gave quiniloquinones by a process that did not require the presence of the palladium catalyst.

Yoshida, Tamaru and co-workers have published a series of reports showing their success in developing palladium(II) methodology for the aminocarbonylation of a variety of olefinic amine derivatives.[10-14] The first such system involved the cyclization of the methylurethane and tosylamide derivatives of 3-hydroxypent-4-enylamine to selectively generate *cis*-3-hydroxypyrrolidine 2-acetic acid lactone (eq 9).[10,12] The reaction system worked



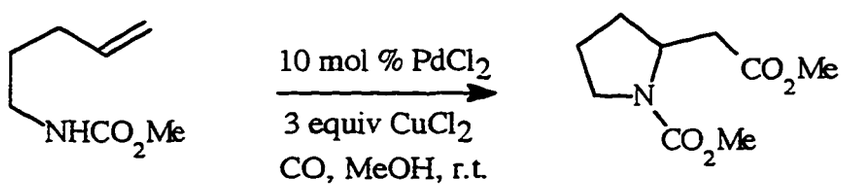
(8)



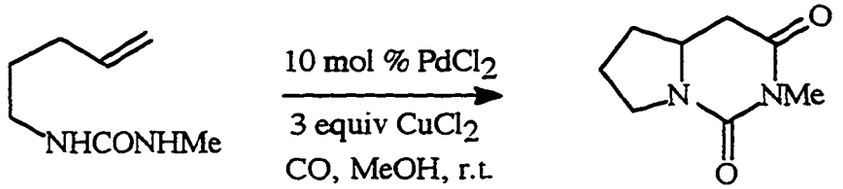
(9)

well for the formation of 5-membered rings, but low yields and significant by-product formation plagued attempts to form 6-membered rings.

Yoshida and Tamura later reported related work employing urethane and urea derivatives of olefinic amines.[11,12] They were able to achieve the exo and endo cyclization of both derivatives with the exocyclic ureas using the second nitrogen of the urea as a nucleophile in the formation of bicyclic products (eqs 10-13). The endocyclic urethane did not work under



(10)



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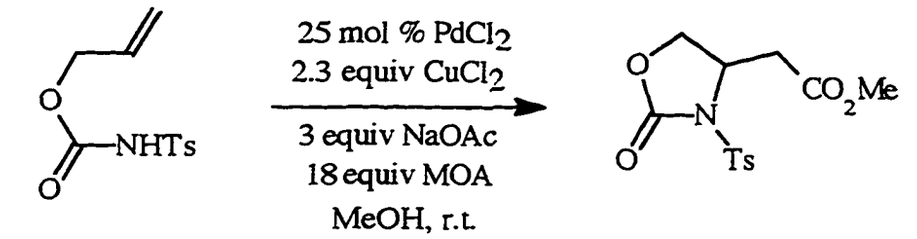

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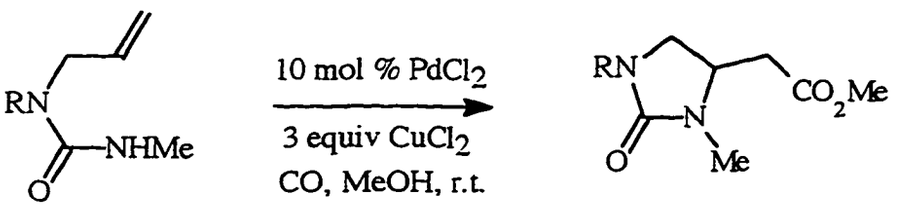
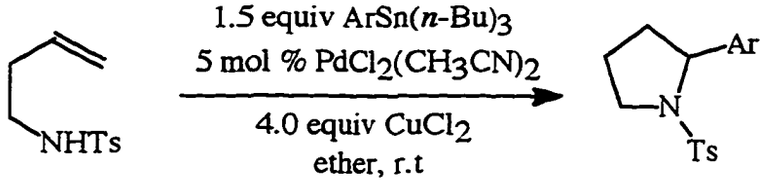


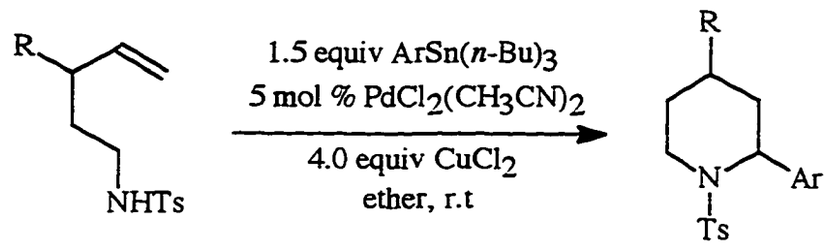
(13)

the standard conditions for cyclization. However, the *N*-tosyl urethane was cyclized under more basic reaction conditions, where the nitrogen nucleophile was suggested to be in the deprotonated form (eq 12). These conditions also employed an excess of methyl orthoacetate (MOA), which was suggested to suppress undesired $PdCl_2$ reactions, such as oxidations of methanol to formaldehyde and carbon monoxide to dimethyl carbonate. These systems demonstrated reduced yields for substrates designed to form 6-membered rings.

Tamaru, Yoshida and co-workers have also developed reaction conditions for the 1,1-arylation-amination of unsaturated amides, which provides 2-arylated 5- and 6-membered ring nitrogen heterocycles (eqs 14 and 15).[15] Terminal olefins were used to favor regioselective



(14)

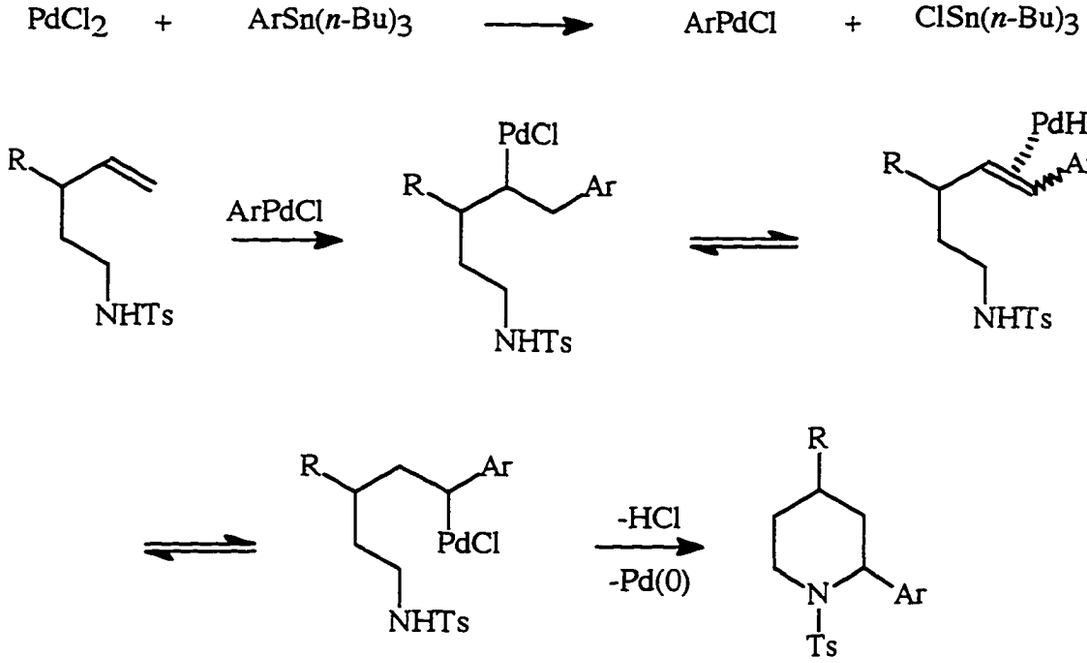


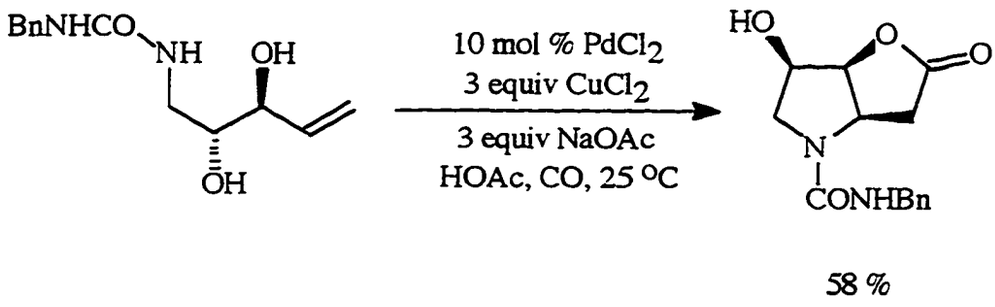
(15)

addition of the aryl group to the less hindered end of the double bond. The reaction was believed to proceed via transmetallation of an aryl group from either an aryltin or arylmercury compound, followed by addition to the olefin and isomerization to a σ-benzylic palladium species, which then chelates to the nucleophile and reductively eliminates the desiredproduct (Scheme 3).

In 1990, Jäger and Hümmer described an intramolecular amidocarbonylation using both *N*-benzylaminocarbonyl and benzyloxycarbonyl derivatives of 2,3-dihydroxypent-4-en-1-amine (eq 16).[16] The reactions gave the desired bicyclic pyrrolidinolactones in 58 and 83 %

Scheme 3



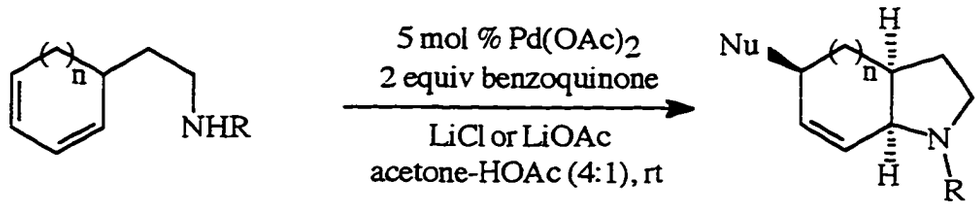


(16)

58 %

yields, respectively. The unprotected amine did not react, reportedly due to competing strong N-Pd complexation.

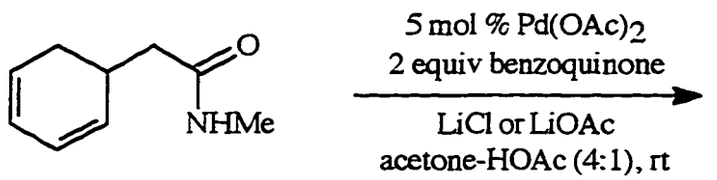
Bäckvall and co-workers reported stereocontrolled, intramolecular 1,4-additions to cyclic 1,3-dienes employing amides as nucleophiles (eq 17).[17-20] This transformation involves



(17)

R = Ts, CO_2Me, CO_2Bn, CONHBn Nu = Cl, OAc

the palladium-catalyzed addition of the amide nucleophile to the proximal alkene moiety resulting in the formation of a π-allylpalladium species that is attacked by either Cl^- or OAc^- as a second nucleophile, depending on the specific reaction conditions. The stereochemistry of the acetate addition could be controlled through the use of LiCl to favor the formation of either the *cis* or the *trans* isomer. This reaction worked well for several amido derivatives, but failed for the *N*-methyl amide derivative (eq 18). The failure of this system was proposed to be due to the ring strain involved in attempting to place the carbonyl within the newly forming five-membered ring. Bäckvall applied this methodology to the synthesis of racemic α- and γ-

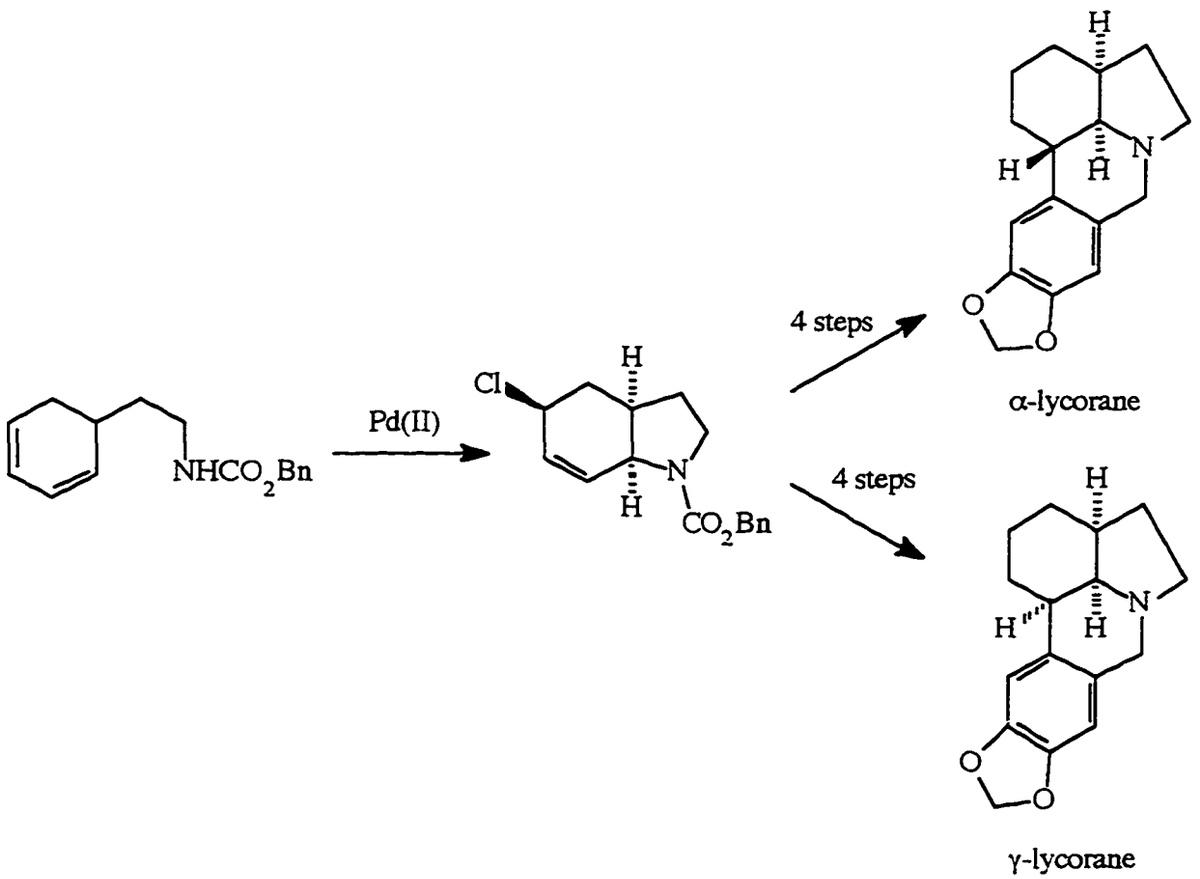


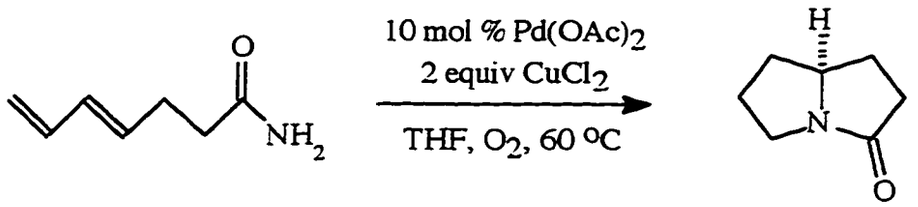
(18)

lycorane (Scheme 4)[18] and later published a full account of his work on palladium-catalyzed intramolecular 1,4-additions to conjugated dienes.[19]

In 1992, Bäckvall reported an extension of this work demonstrating the palladium-catalyzed tandem cyclization of 4,6- and 5,7-diene amides (eq 19).[20] The primary amide acts as the nucleophile for both the initial cyclization reaction and the attack on the intermediate π-allylpalladium species. The reaction conditions for this reaction apparently accommodate the formation of a 5-membered ring containing a carbonyl, where the previous system had failed

Scheme 4.

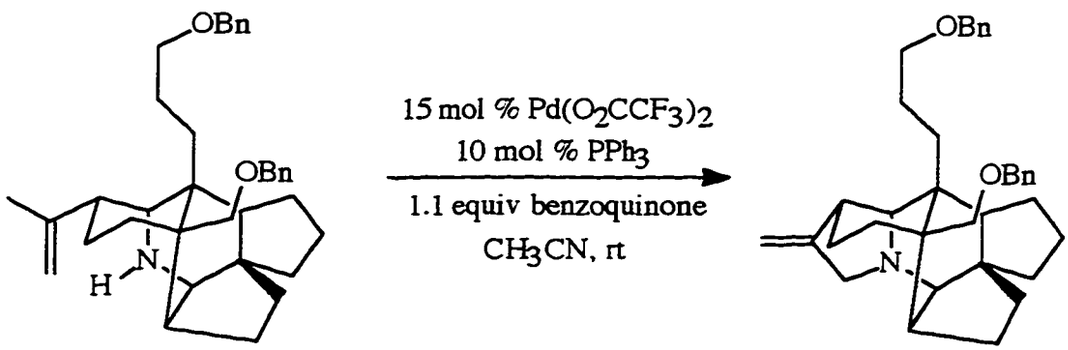




(19)

(compare eqs 18 and 19).

Heathcock and co-workers used a palladium-catalyzed cyclization of a hindered secondary amine as a key step in the total synthesis of racemic bukittinggine (eq 20).[21] This transformation involved the use of highly electrophilic $Pd(O_2CCF_3)_2$ in the non-nucleophilic

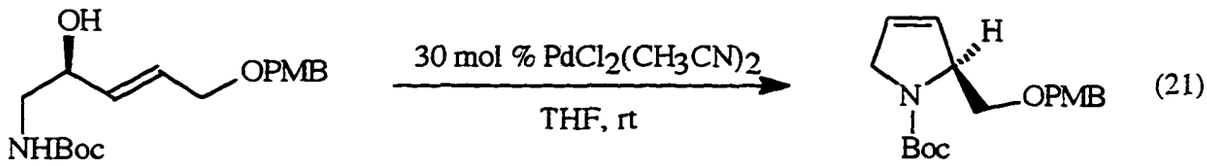


(20)

70 %

solvent acetonitrile. Amines are generally not successful in this type of palladium-catalyzed reaction due to strong complexation to the palladium. Heathcock postulated that the hindered nature of his substrate allowed the reaction to take place.

Saito and Moriwake and co-workers reported the synthesis of optically active substituted dihydropyrroles via a palladium(II)-promoted diastereoselective dehydroxylative heterocyclization (eq 21).[22] This process is significantly different from the others discussed so far in that the reaction does not proceed through a Pd(II)-Pd(0) oxidative cycle. It was suggested that $PdCl_2$ adds across the olefin, followed by intramolecular nucleophilic

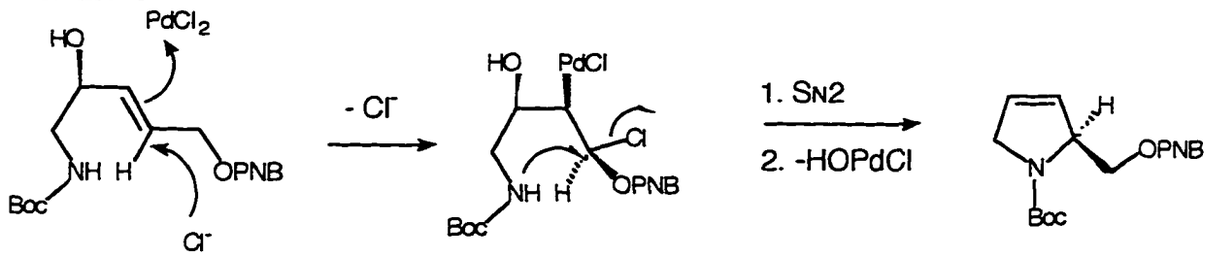


(21)

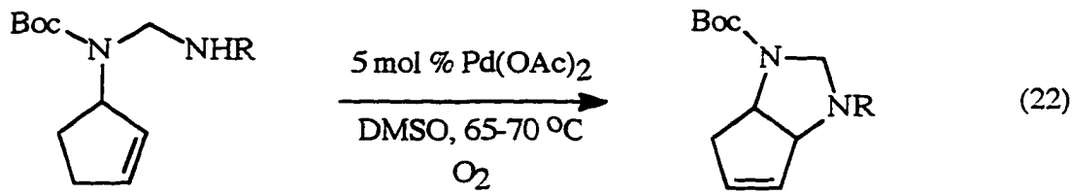
67 % yield, 97 % ee

displacement of the chloride to form the ring and β-hydroxide elimination to generate the dihydropyrrole product and a palladium(II) species that can carry on the reaction (Scheme 5). The reaction also succeeded with a hydroxy nucleophile for the synthesis of optically active dihydropyrans.

Scheme 5

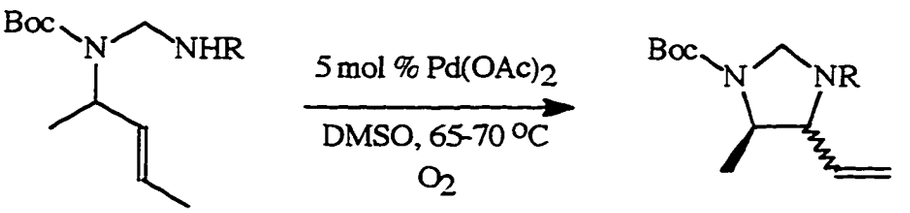


Hiemstra and co-workers reported the cyclization of a variety of nitrogen nuleophiles in a palladium(II)-mediated synthesis of imidazolidines.[23] Two systems were studied, one cyclic (eq 22) and one acyclic (eq 23). This study was significant in that it was the first attempt at a comprehensive examination of a series of amine derivatives aimed at comparing reactivity and utility. Tosyl, formyl, acetyl, aminocarbonyl, methoxycarbonyl and benzyloxycarbonyl



(22)

R = Ts, CHO, $COCH_3$, $CONH_2$, CO_2Me, CO_2Bn

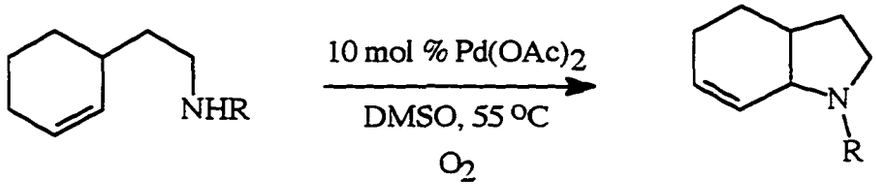


(23)

R = Ts, CHO, CO_2Me

derivatives all worked well, giving the desired products in 50-90 % isolated yields. The formamide was determined to be the most useful derivative because of its high reactivity and ease of removal from the cyclic product. This study provided useful information about the reactivity of various amine derivatives in palladium(II)-catalyzed cyclizations, but used a rather specialized substrate and only looked at the formation of 5-membered rings.

In 1995, Andersson and co-workers reported the cyclization of two simple olefinic amine derivatives under conditions similar to those used above by Hiemstra (eq 24).[24] These

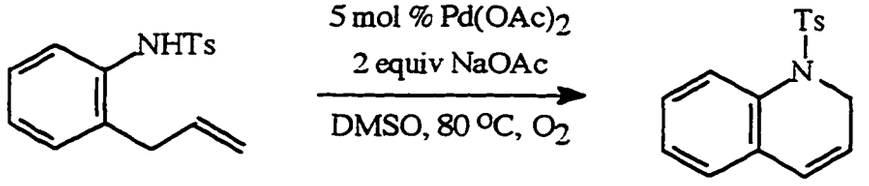


(24)

R = Ts, CO_2Bn

simple systems appear to be less reactive than the aminals used by Hiemstra, requiring 10 mol % $Pd(OAc)_2$ and a 24 h reaction time compared with the 5 mol % $Pd(OAc)_2$ and 4 h reaction time employed above. Again, only two derivatives were examined and only 5-membered rings were constructed.

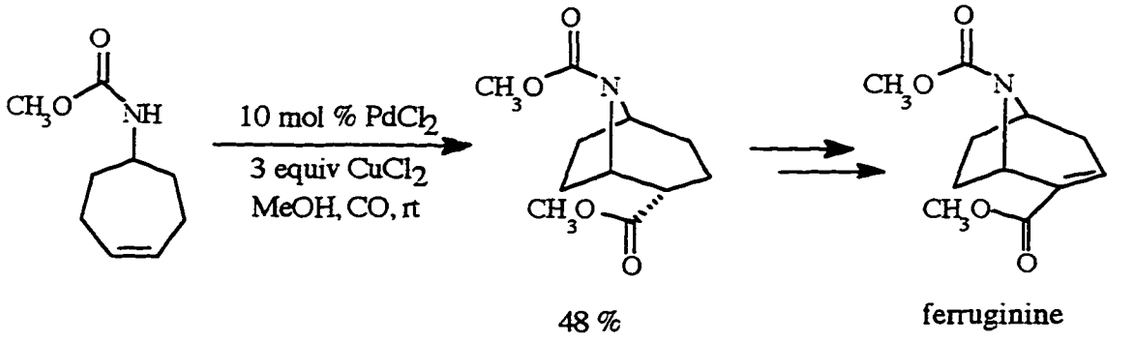
Larock and co-workers have studied the tosylamide functional group under the same type of catalytic conditions (eq 25).[25] A variety of 5- and 6-membered rings were formed using both tosylamides and tosylanilides. In general, tosylanilides were found to be less reactive than tosylamides, requiring higher temperatures and longer reaction times. The



(25)

construction of 6-membered rings using *o*-allylic tosylanilides is significant because *o*-allylaniline, using either stoichiometric or catalytic amounts (plus benzoquinone) of $PdCl_2$, has been reported to form 2-methylindole (compare eqs 1 and 25). Other significant findings from this study include obtaining the same product from the cis and trans isomers of *o*-crotyl tosylanilide and the use of trisubstituted olefins.

Ham and co-workers employed a palladium-catalyzed intramolecular amino-carbonylation as a key step in their synthesis of racemic ferruginine (eq 26).[26] This is the first



48 % ferruginine

(26)

example of intramolecular amidocarbonylation being applied to the synthesis of tropane alkaloids.

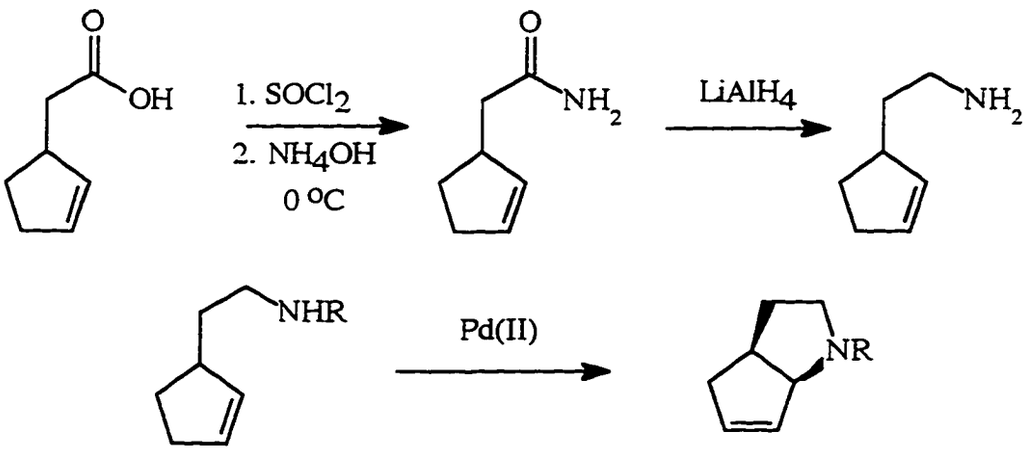
There has also been a significant body of literature concerning palladium(II)-catalyzed cyclizations of amine derivatives with allenes[27-29] and alkynes.[30-34] Although the initial interaction in these cases is electrophilic coordination of Pd(II) to the carbon-carbon multiple bond, very similar to the interaction with simple olefins, the rest of the transformation is mechanistically quite different from simple olefins and will not be discussed in detail here.

The goal of the present work was to examine the reactivity of several common amine derivatives in rather simple systems and to examine the efficiency of the same derivatives in the formation of various 5- and 6-membered ring systems. The results of these efforts are reported herein.

Results and Discussion

This study of the palladium(II)-catalyzed cyclization of olefinic amine derivatives started with the selection of a model system. A system based on 2-(2-cyclopentenyl)-ethanamine was selected. The tosyl derivative had shown good reactivity and yields (72 h at 25 °C, 86 %) in earlier work performed in this research group.[25] The amine was synthesized in three steps from commercially available (2-cyclopentenyl)acetic acid and the derivatives were prepared as described in the experimental section of this chapter (Scheme 6).

Scheme 6



The cyclization of the derivatives commenced with the goal of determining a reactivity order for the various functional derivatives (Table 1). The strategy was to run each derivative under three sets of reaction conditions: Procedure A involved 0.25 mmol of substrate and 1 equiv of $Pd(OAc)_2$ in 1 mL of DMSO under an atmosphere of O_2. Procedure B involved 0.25 mmol of substrate and 5 mol % $Pd(OAc)_2$ in 1 mL of DMSO under an atmosphere of O_2.

Table 1. Palladium(II)-catalyzed Cyclization of Derivatives of 2-(2-Cyclopentenyl)-ethanamine.

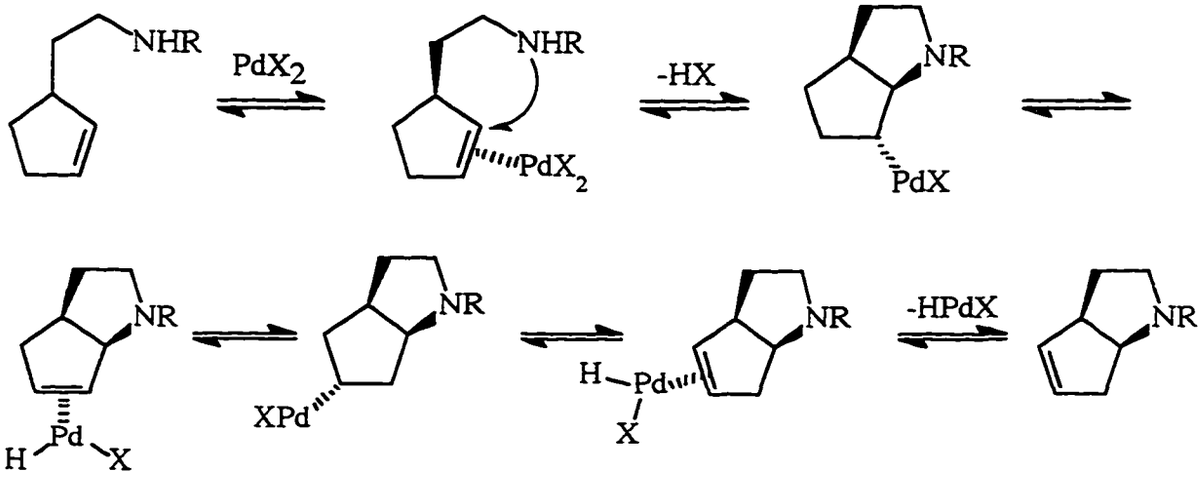
entry	R	procedure	temp (°C)	time (h)	yield (%)[a]
1	Ts	A	80	2	85
2	Ts	B	80	8	91
3	Ts	C	80	8	86
4	CHO	A	80	2	62
5	CHO	B	80	6	65
6	CHO	C	80	12	63
7	CO_2CH_2Ph	A	80	2	79
8	CO_2CH_2Ph	B	80	36	76
9	CO_2CH_2Ph	C	80	36	86
10	$CONMe_2$	A	80	2.5	69
11	$CONMe_2$	B	80	48	42
12	$CONMe_2$	C	80	72	36
13	COMe	A	80	2	66
14	COMe	B	80	24	28
15	COMe	C	80	24	42
16	COPh	A	80	8	68
17	COPh	B	80	72	43 (66)
18	COPh	C	80	72	60 (67)
19	$COCF_3$	A	80	24	52 (55)
20	$CONHCH_2Ph$	A	22	8	68
21	$CONHCH_2Ph$	A	80	2 (24)[b]	42

[a] Values in parentheses indicate yields based on unrecovered starting material for incomplete reactions. [b] First cyclization was complete within 2 h but the reaction was stirred for 24 h in an effort to achieve the second cyclization.

Procedure C involved 0.25 mmol of substrate, 2 equiv of NaOAc and 5 mol % $Pd(OAc)_2$ in 1 mL of DMSO under an atmosphere of O_2. The first experiment in each case used procedure A to identify the product of the reaction by TLC so the catalytic reaction could be more accurately monitored.

The first derivative investigated was the tosyl derivative (Table 1, entries 1-3). The stoichiometric procedure was complete within 2 h. The desired bicyclic product was obtained in 85 % isolated yield as a single isomer. There is concern about double bond migration in the product to the homoallylic position with substrates containing cyclic olefins (Scheme 7). This

Scheme 7



problem was overcome in the cyclization of olefinic carboxylic acids by using DMSO as the solvent.[35] The reactions using procedures B and C were complete within 8 h and afforded the same product as procedure A in 91 and 86 % yields, respectively.

The formamide derivative was submitted to the cyclization conditions to give good yields of the cyclic product (Table 1, entries 4-6). The stoichiometric procedure was complete within 2 h and provided the desired product in 62 % isolated yield. The reactions using procedures B and C were complete within 6 h and 12 h, respectively, and afforded the desired cyclized product in 65 and 62 % isolated yields, respectively. The ^1H and ^{13}C NMR spectra of

the product were much more complex than expected (Appendix A, p128-29). It appeared as though there were two compounds present in the product sample. Compounds of this type have been observed to exist as mixtures of amide rotomers,[24] but, with the possibility of double bond isomerization also present, steps had to be taken to determine the nature of the product mixture. The typical solution to this problem is to obtain ^{1}H and ^{13}C NMR spectra at elevated temperatures; unfortunately, attempts at 50 °C in $CDCl_3$ and DMSO and 90 °C in DMSO were not effective for achieving a clean spectrum of a single rotomer. The rotomer populations were observed to change considerably when the solvent was switched from $CDCl_3$ to DMSO, which supports the existence of rotomers rather than double bond isomers. As a final means of determining the composition of the product sample, a solution of the product was analyzed by gas chromatography. The chromatograph showed a single high-boiling peak for the product under a variety of conditions, again supporting the existence of rotomers, rather than double bond isomers.

The benzyloxycarbonyl derivative was submitted to the cyclization conditions and afforded the desired cyclized product in good yields (Table 1, entries 7-9). The stoichiometric procedure was complete within 2 h and afforded the desired product in 79 % isolated yield. This product was observed to exist as a 1:1 mixture of amide rotomers by ^{1}H and ^{13}C NMR at 22 °C in $CDCl_3$ and produced only one high-boiling peak by gas chromatography under a variety of conditions. The reactions employing procedures B and C were complete within 36 h and afforded the desired product in 76 and 86 % isolated yields, respectively.

The *N*,*N*-dimethylaminocarbonyl derivative was submitted to the cyclization conditions and afforded the desired cyclization product in moderate to good yields (Table 1, entries 10-12). The stoichiometric procedure was complete within 2.5 h and afforded the desired product in 69 % isolated yield. This compound appeared to exist as a single amide rotomer. The reaction employing procedure B was complete within 48 h and afforded the desired product in 42 % isolated yield, while the reaction employing procedure C was complete in 72 h and

afforded the desired product in only a 36 % isolated yields. The lower yields of this substrate may be due to having to submit the very polar product to 2 or 3 silica gel columns to remove the majority of a yellow impurity in order to obtain clean spectral data. There were no other products observed by TLC to explain the observed loss of material.

The acetyl derivative was submitted to the cyclization conditions and afforded the desired cyclization product in good yields (Table 1, entries 13-15). The stoichiometric procedure was complete within 2 h and provided the desired product in 66 % isolated yield. This product was observed to exist as a 42:58 mixture of amide rotomers by ^{1}H and ^{13}C NMR at 22 °C in $CDCl_3$ and produced only one high-boiling peak by gas chromatography under a variety of conditions. The catalytic reactions employing procedure B and C gave complete reactions within 24 h and afforded the desired cyclization product in 28 and 42 % isolated yields respectively. The lower yields of this substrate may be due to having to submit the very polar product to 2 or 3 silica gel columns to remove the majority of a yellow impurity in order to obtain clean spectral data. There were no other products observed by TLC to explain the observed loss of material.

The benzamide derivative was submitted to the cyclization conditions and afforded the desired cyclization product in low to good yields (Table 1, entries 16-18). The stoichiometric procedure was complete within 8 h and afforded the desired product in 68 % isolated yield. This product was observed to exist as a 33:67 mixture of amide rotomers by ^{1}H and ^{13}C NMR at 22 °C in $CDCl_3$ and produced only a single high-boiling peak by gas chromatography under a variety of conditions. The catalytic reactions employing procedures B and C were not complete within 72 h. Procedure B afforded a 43 % isolated yield of the desired cyclization product at 65 % conversion. Procedure C afforded the desired cyclization product in 60 % isolated yield at 90 % conversion.

The trifluoroacetyl derivative was submitted to the stoichiometric procedure resulting in an incomplete reaction after 24 h. The desired cyclization product was obtained as a mixture

with unreacted starting material. The desired product was present as a 50:50 mixture of amide rotomers in 52 % yield at 95 % conversion. The trifluoroacetyl derivative was deemed relatively unreactive and was not examined under the catalytic conditions.

A second urea derivative was prepared such that both nitrogen atoms of the urea would be capable of acting as a nucleophile in a cyclization reaction. *N*-Benzyl-*N*'-(2-(2-cyclopentenyl)ethyl)urea was submitted to procedure A at room temperature, resulting in monocyclization to form a 5-membered ring (Table 1, entry 20). The same conditions were tried again at 80 °C, hoping to induce a second cyclization to form a tricyclic urea (Table 1, entry 21). The first cyclization was complete by TLC within 2 h, but the reaction was stirred for 24 h to allow time for the second cyclization to occur. The second cyclization did not occur and the bicyclic urea was obtained in 42 % isolated yield. The difficulty in achieving the second cyclization may be due to the strain of placing a trigonal carbonyl functionality into a 5-membered ring.[17-20]

The experiments from the three procedures run on the derivatives of 2-(2-cyclopentenyl)ethanamine allow one to start to piece together a reactivity series for the various derivatives. Clearly, the tosylamide and the formamide were the most reactive substrates, having the shortest reaction times using the catalytic procedures. The tosylamide tended to give cleaner reactions than the formamide. The benzyloxycarbonyl, urea and acetyl derivatives showed intermediate reactivity. The benzyloxycarbonyl derivative gave clean reactions, but the starting material and product had very similar R_f's by TLC. The *N*,*N*-dimethylurea and the acetyl derivatives formed very polar products that required at least two passes through a silica gel chromatography column in order to obtain a product of reasonable purity. The benzylurea showed similar reactivity to *N*,*N*-dimethylurea under the stoichiometric conditions, but the reaction was much cleaner and required only one pass through a silica gel column to obtained the pure product. The benzamide and trifluoroacetamide derivatives were by far the least reactive substrates and did not give complete reactions under the catalytic conditions. The

trifluoroacetamide did not give a complete reaction within 24 h even under stoichiometric conditions.

The next system examined involved the derivatives of 2-(2-cyclohexenyl)ethanamine (Table 2). The tosylamide was cyclized using procedures B and C giving complete reactions within 12 h at 80 °C and isolated yields of 87 and 91 %, respectively (Table 2, entries 1 and 2). The reactions were very clean and gave the desired product as a single double bond isomer.

The formamide derivative was submitted to procedure A and gave a complete reaction within 3 h (Table 2, entry 3). The reaction was clean and gave the desired product in high yield and good purity after a single pass through a silica gel column. The product existed as a 50:50 mixture of amide rotomers that gave a single high-boiling peak by gas chromatographic analysis. The catalytic reactions gave somewhat diminished yields and the products required at least two passes through silica gel to achieve acceptable purities (Table 2, entries 4 and 5). The diminished yields might be attributable to the extended purification processes. Formamides have also been hydrolyzed under basic conditions[36] (NaOH, H_2O, reflux) and therefore it is not inconceivable that some product was lost to hydrolysis over the 12 and 24 h reaction times.

The benzyloxycarbonyl derivative gave a complete reaction within 5 h using procedure A (Table 2, entry 6). The starting material and product had similar R_f's by TLC so it was difficult to judge when a reaction was complete. The product existed as a 50:50 mixture of amide rotomers that gave a single high-boiling peak by gas chromatographic analysis. The catalytic reactions employing procedures B and C were complete within 36 and 44 h, respectively, and afforded the expected cyclization product in excellent yield (Table 2, entries 7 and 8).

The benzylurea derivative was used in place of the dimethylurea derivative with this system because the reactions were much cleaner and easier to purify in the previous system. The reaction using procedure A at 22 °C was complete within 8 h and afforded the monocyclization product in excellent yield (Table 2, entry 9). The catalytic reactions

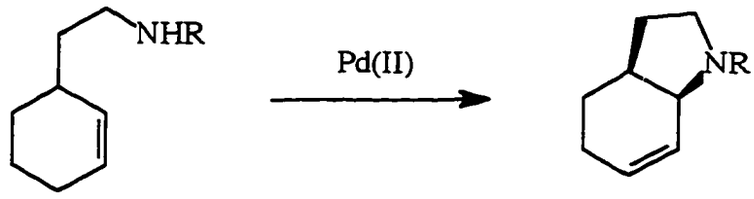


Table 2. Palladium(II)-catalyzed Cyclization of Derivatives of 2-(2-Cyclohexenyl)-ethanamine.

entry	R	procedure	temp (°C)	time (h)	yield (%)[a]
1	Ts	B	80	12	87
2	Ts	C	80	12	91
3	CHO	A	80	3	95
4	CHO	B	80	12	78
5	CHO	C	80	24	61
6	CO_2CH_2Ph	A	80	5	79
7	CO_2CH_2Ph	B	80	36	94
8	CO_2CH_2Ph	C	80	44	92
9	$CONHCH_2Ph$	A	22	8	95
10	$CONHCH_2Ph$	B	80	8	94
11	$CONHCH_2Ph$	C	80	12	91
12	COMe	A	80	2	73
13	COMe	B	80	48	54 (65)
14	COMe	C	80	48	63
15	COPh	A	80	12	69
16	$COCF_3$	A	80	24	18 (66)

[a] Values in parentheses indicate yields based on unrecovered starting material for incomplete reactions.

employing procedure B and C were complete within 8 and 12 h, respectively, and gave excellent yields of the desired monocyclization product (Table 2, entries 10 and 11). This substrate has the potential to undergo a second cyclization to produce a tricyclic structure, but does not do so under the reaction conditions examined. The difficulty in achieving the second cyclization may be due to the strain of placing a trigonal carbonyl functionality into a 5-membered ring.[10]

The acetamide derivative gave a complete reaction by procedure A within 2 h and the desired product was obtained in good yield (Table 2, entry 12). The desired product exists as a 33:67 mixture of amide rotomers. The sample gave a single high-boiling peak by gas chromatographic analysis. The catalytic reactions employing procedures B and C were stopped after 48 h. Procedure B afforded the desired product in 54 % yield at 83 % conversion (Table 2, entry 13). Procedure C gave a complete reaction from which the desired product was obtained in 63 % isolated yield (Table 2, entry 14). The lower yields with this substrate may be due to the need to pass the product through at least two silica gel columns in order to obtain a substance of acceptable purity.

The benzamide derivative was only submitted to procedure A because of the failure of this same derivative to react completely using the catalytic procedures in the previous system. Procedure A gave a complete reaction within 12 h and the desired cyclization product was obtained in 69 % isolated yield (Table 2, entry 15). The product exists as a 33:67 mixture of amide rotomers. The sample produced a single high-boiling peak by gas chromatographic analysis.

The trifluoroacetamide was submitted to procedure A and gave an incomplete reaction after 24 h (Table 2, entry 16). Gas chromatography of the reaction mixture indicate a mixture containing two major high-boiling substances in a 29:71 ratio. The ^{1}H NMR spectrum of the product mixture indicated that the major component was the desired cyclization product and the minor component was unreacted starting material. The desired product was determined to be

present in ~18 % yield. The low recovery of material in this case may be due to the ease of hydrolysis of the trifluoroacteyl group under basic conditions.[37]

The derivatives of 2-(2-cyclohexenyl)ethanamine supported the reactivity series determined in the previous system. Overall, this system was less reactive than the previous system, but the tosyl, formyl, benzyloxycarbonyl, benzylaminocarbonyl and acetyl derivatives all proved to be useful for the formation of 6,5-bicyclic amino derivatives by a palladium(II)-catalyzed process under our standard conditions.

To complete the study of the formation of 5-membered rings by the palladium(II)-catalyzed cyclization of olefinic amine derivatives, an acyclic substrate was prepared and cyclized (Table 3). The derivatives of 2,2-dimethyl-4-hexenamine were obtained as a 94:6 mixture of trans/cis double bond isomers. Double bond isomers of this type have been observed to demonstrate similar reactivity and generate identical product mixtures in previous palladium(II)-catalyzed cyclizations.[38]

The tosylamide derivative gave a complete reaction within 2 h using procedure A (Table 3, entry 1). The desired cyclization product was isolated in 86 % yield. The reaction using procedure B was complete within 21 h and afforded the desired product in 87 % isolated yield (Table 3, entry 2). Likewise, the reaction using procedure C was complete within 12 h and afforded the desired product in 82 % isolated yield (Table 3, entry 3). The longer reaction times from this tosylamide derivative indicate that this system is significantly less reactive than those containing a cyclic olefin moiety.

The formamide derivative gave a complete reaction within 12 h using procedure A (Table 3, entry 4). The desired product existed as a 25:75 mixture of amide rotomers. The sample produced a single high-boiling peak by gas chromatographic analysis. The reactions using procedures B and C were both complete within 24 h (Table 3, entries 5 and 6). Procedure B afforded the desired product in 53 % isolated yield, while procedure C managed only a 46 % isolated yield.

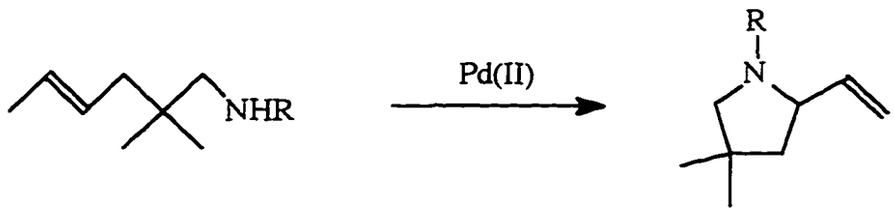


Table 3. Palladium-catalyzed Cyclization of Derivatives of 2,2-Dimethyl-4-hexenamine.

entry	R	procedure	temp (°C)	time (h)	yield (%)[a]
1	Ts	A	80	2	86
2	Ts	B	80	21	87
3	Ts	C	80	12	82
4	CHO	A	80	12	50
5	CHO	B	80	24	53
6	CHO	C	80	24	46
7	CO_2CH_2Ph	A	80	24	54 (57)
8	CO_2CH_2Ph	B	80	72	32 (50)
9	CO_2CH_2Ph	C	80	72	48 (56)
10	COMe	A	80	24	40 (53)
11	COPh	A	80	24	----

[a] Values in parentheses indicate yields based on unrecovered starting material for incomplete reactions.

The benzyloxycarbonyl derivative did not give a complete reaction within 24 h using procedure A (Table 3, entry 7). The desired product was obtained in 54 % yield as a mixture with unreacted starting material. The catalytic reactions using procedures B and C did not reach completion within 72 h (Table 3, entries 8 and 9). The starting material and product were not separable by column chromatography so the yields were determined by integration of the ^{1}H NMR spectra. Procedure B afforded the desired product in 32 % yield at 64 % conversion, while procedure C afforded the desired product in 48 % yield at 75 % conversion.

The acetyl derivative did not give a complete reaction within 24 h (Table 3, entry 10). The desired product existed as a 33:67 mixture of amide rotomers and was determined to be present in 43 % yield at 80 % conversion.

The benzamide derivative showed only a trace of product formation by TLC analysis after 24 h (Table 3, entry 11). The amount of product was judged to be too small to attempt to isolate the product or determine a yield.

The acyclic olefinic amine derivatives proved to be much less reactive than their cyclic counterparts. The reactivity order remained pretty well intact with the tosyl, formyl and benzyloxycarbonyl derivatives demonstrating suitable reactivity to be synthetically useful. The acetamide and benzamide derivatives were unreactive under our standard conditions.

The cyclization of amine derivatives was extended to examine the formation of 6-membered rings. The most reactive olefin for the formation of 5-membered rings was the cyclopentenyl, so 3-(2-cyclopentenyl)propan-1-amine was synthesized and derivatized to examine the efficiency of the various derivatives in forming 6-membered rings (Table 4).

The tosyl derivative was subjected to the stoichiometric procedure and afforded the desired 5,6-bicyclic product as a single double bond isomers in 85 % isolated yield after 4 h at 80 °C (Table 4, entry 1). Neither of the catalytic reactions were complete after 72 h, so the reactions were stopped and the products isolated. Procedure B afforded the desired product in 63 % isolated yield at 95 % conversion (Table 4, entry 2), while procedure C afforded the desired product in only 54 % yield at 60 % conversion (Table 4, entry 3). This reaction clearly illustrates the difficulty in forming 6-membered rings in comparison with their 5-membered ring counterparts.

The formamide and benzyloxycarbonyl derivatives were also subjected to the cyclization conditions. The formamide derivative afforded a 49 % isolated yield of the desired product after 6 h (Table 4, entry 4), but neither catalytic procedure showed evidence of reaction by TLC analysis after 72 h (Table 4, entries 5 and 6). The benzyloxycarbonyl derivative using

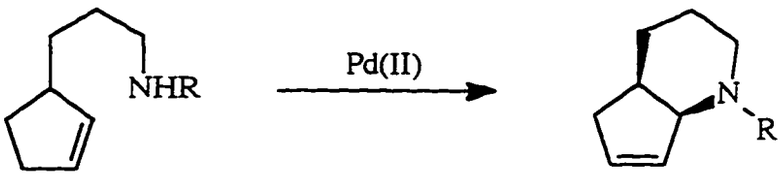


Table 4. Palladium-catalyzed Cyclization of Derivatives of 3-(2-Cyclopentenyl)propan-1-amine.

entry	R	procedure	temp (°C)	time (h)	yield (%)[a]
1	Ts	A	80	4	85
2	Ts	B	80	72	60 (63)
3	Ts	C	80	72	32 (54)
4	CHO	A	80	6	49
5	CHO	B	80	72	----
6	CHO	C	80	72	----
7	CO_2CH_2Ph	A	80	24	68
8	CO_2CH_2Ph	B	80	72	----
9	CO_2CH_2Ph	C	80	72	----
10	$CONHCH_2Ph$	A	80	24	30
11	$CONHCH_2Ph$	B	80	72	----
12	$CONHCH_2Ph$	C	80	72	----

[a] Values in parentheses indicate yields based on unrecovered starting material for incomplete reactions.

procedure A gave a complete reaction within 24 h and provided the desired product in only a 30 % isolated yield (Table 4, entry 7), but neither catalytic procedure showed evidence of reaction by TLC analysis after 72 h (Table 4, entries 8 and 9).

The benzylurea derivative gave a complete reaction within 24 h using procedure A (Table 4, entry 10). Surprisingly, the product was identified as the tricyclic urea (**1**) generated by a double cyclization employing both nitrogen atoms of the urea as nucleophiles (eq 27).

(27)

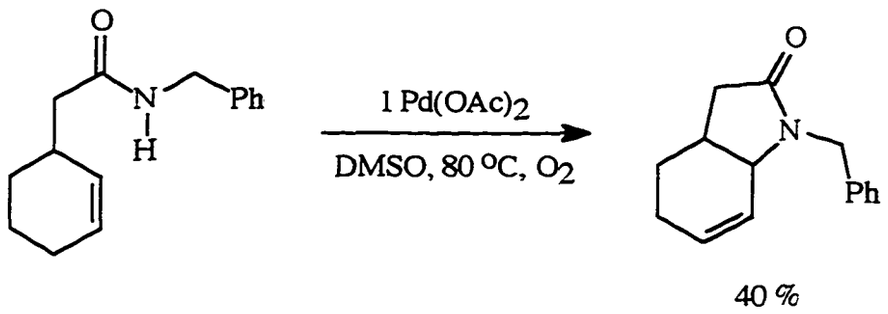
(1)

This was the first case observed where the benzylurea derivative proceeded to undergo the second cyclization reaction. The 5,5- and 6,5-bicyclic benzyl ureas (Table 1, entry 21 and Table 2, entry 9, respectively) were not observed to undergo the second cyclization. The combination of having the second nucleophile attached to a more flexible 6-membered ring coupled with the more reactive cyclopentenyl olefin moiety must make the reaction possible where it had failed with the other substrates.

The derivatives that were determined to be less reactive than the benzyloxycarbonyl derivative in the model system were not pursued with this substrate. The assumption was made that the lower reactivity of the other derivatives would prevent them from providing complete reactions, even under the stoichiometric reaction conditions.

The experimentation with the four model systems described above allow some generalizations to be drawn concerning the Pd(II)-catalyzed cyclization of olefinic amine derivatives. (1) Olefin reactivity: cyclopentenyl > cyclohexenyl > acyclic. (2) Ring size formed: five > six. (3) Derivative reactivity: tosylamide, formamide > urea, benzylcarbamate > acetamide > benzamide > trifluoroacetamide.

All of the substrates discussed thus far contained functionality that ended up outside of the newly formed ring system except for the biscyclization of the benzylurea. A few substrates were examined to determine the feasibility of having the functionality ending up inside the newly formed ring. *N*-Benzyl-(2-(2-cyclohexenyl)ethanecarboxamide was prepared and submitted to procedure A (eq 28). The reaction was not complete within 24 h, but the desired

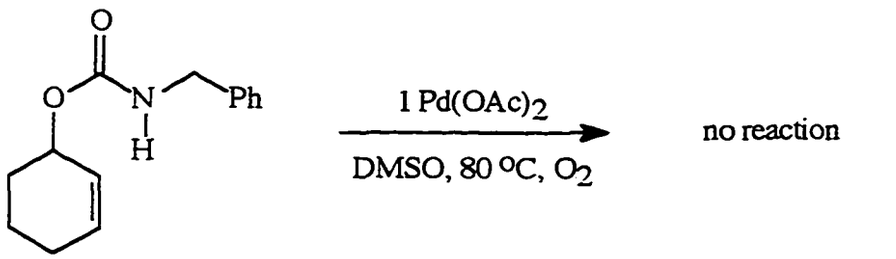


40 %

(28)

cyclization product was obtained in 40 % isolated yield. The nucleophilic portion of this molecule should be similar electronically to the acetamide derivative, where the amide moiety is connected to saturated aliphatic carbon atoms on both sides. The low reactivity of this substrate must be due to the strain that develops in trying to place the trigonal carbonyl carbon into the 5-membered ring of a bicyclic product.

An endocyclic carbamate was synthesized from 2-cyclohexen-1-ol and was submitted to procedure A (eq 29). This substrate should be electronically very similar to the

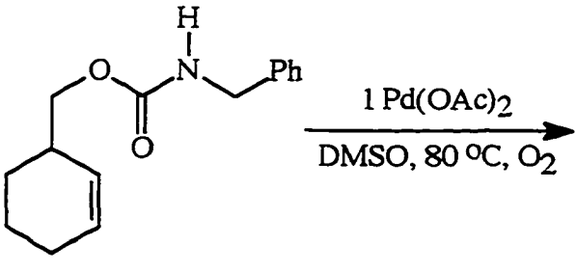


no reaction

(29)

benzyloxycarbonyl derivative examined above. The substrate showed no sign of reacting within 24 h as determined by TLC analysis. Gas chromatography of the reaction mixture showed only one high-boiling component with the same retention time as the starting material.

A similar substrate was synthesized from (2-cyclohexenyl)methanol and submitted to procedure A (eq 30). This substrate has the advantage of having the nucleophile attached to a longer, more flexible tether, but the disadvantage of having to form a 6-membered ring. The substrate showed no sign of reaction within 24 h as determined by TLC analysis. Gas



no reaction (30)

chromatography of the reaction mixture showed only one high-boiling component with the same retention time as the starting material.

Clearly, an endocyclic carbonyl presents a sizable barrier to cyclization under our standard conditions. Nucleophiles that are otherwise very similar electronically to corresponding exocyclic derivatives fail to react to form either 5- or 6-membered rings. The only exception being the unexpected biscyclization of the benzylurea to form a tricyclic product described above.

Conclusion

Several derivatives of 2-(2-cyclopentenyl)ethanamine have been subjected to palladium(II)-catalyzed cyclization conditions to form 5,5-bicyclic amine derivatives. The reactivity order for the derivatives was found to be tosylamide, formamide > urea, benzylcarbamate > acetamide > benzamide > trifluoroacetamide. The same derivatives were also examined for their efficiency in forming 6,5- and 5,6-bicyclic and 5-monocyclic ring systems. The reactivity order was not observed to change with the system examined, but only the cyclization of tosylamide, formamide, benzylcarbamate and benzylurea derivatives were found to be synthetically useful for each system examined. Substrates that were intended to contain the carbonyl functional group of the derivative within the newly forming ring were found to be unreactive, except in one case involving a biscyclization of a benzylurea derivative to form a tricyclic product.

Experimental

General. All ^{1}H and ^{13}C NMR spectra were recorded at 400 and 100.5 MHz, respectively. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) or basic $KMnO_4$ solution [3 g $KMnO_4$ + 20 g K_2CO_3 + 5 mL NaOH (5%) + 300 mL H_2O]. All melting points are uncorrected.

Reagents. All reagents were used directly as obtained from commercial sources unless otherwise stated. $KMnO_4$, NaOAc, $LiAlH_4$, NaCl, potassium *t*-butoxide, acetic anhydride, hydrochloric acid, methanol, ethyl ether, methylene chloride, pentane, dimethylsulfoxide, $MgSO_4$, ammonium hydroxide, hexane and ethyl acetate were obtained from Fischer Scientific. 2-(2-Cyclopentenyl)acetic acid, thionyl chloride, triethylamine, *p*-toluenesulfonyl chloride, ethyl formate, benzyl chloroformate, benzoyl chloride, *N*,*N*-dimethylcarbamoyl chloride, trifluoroacetic anhydride, benzyl isocyanate, methyl cyanoacetate, NaCN, crotyl alcohol, methanesulfonyl chloride, diisopropylamine, *n*-butyllithium, isobutyronitrile and carbon tetrabromide were obtained from Aldrich Chemical Co. Palladium acetate and PPh_3 were obtained from Kawaken Fine Chemicals Co., Ltd.

General procedure for cyclization. Procedure A: To a mixture of substrate (1 mmol) in DMSO (1 mL) was added 1 equiv of $Pd(OAc)_2$. The flask was equipped with a magnetic stir bar and purged with oxygen gas. A septum was placed over the opening of the flask and a balloon of oxygen gas attached to the flask through the septum by a needle. The reaction was stirred at 80 °C until the reaction had reached completion as indicated by thin-layer chromatographic analysis. The reaction mixture was cooled to room temperature and then placed directly onto a column of silica gel and eluted with an appropriate combination of hexane/ethyl acetate. The fractions containing the product were combined and concentrated in vacuo. **Procedures B and C.** Procedures B and C follow procedure A except for the use

of only 5 mol % $Pd(OAc)_2$ (procedure B), and 5 mol % $Pd(OAc)_2$ plus 2 equiv of NaOAc (procedure C).

2-(2-Cyclopentenyl)ethanamine. To a stirred solution of 2-(2-cyclopentenyl)acetic acid (6.30 g, 50 mmol) in ether (25 mL) at 0 °C was added thionyl chloride (7.4 mL, 100 mmol). The solution was allowed to warm to room temperature and stirred overnight. Excess thionyl chloride and solvent were evaporated and the resulting yellowish residue was slowly added to concentrated NH_4OH (40 mL) at 0 °C. The reaction was stirred for 30 min, followed by isolation of the resulting solid by filtration. The crude product was dissolved in EtOAc, subjected to decolorizing charcoal, filtered and concentrated to yield 2-(2-cyclopentenyl)acetamide as a white solid (79 %): mp = 128-129 °C; IR ($CHCl_3$) 3351, 3177, 3053, 2958, 2851, 1669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (m, 1 H), 2.27 (m, 5 H), 3.09 (m, 1 H), 5.69 (m, 1 H), 5.78 (m, 1 H), 5.87 (br s, 1 H), 6.35 (br s, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 29.61, 31.88, 42.10, 42.41, 131.58, 133.82, 175.42.

To a slurry of $LiAlH_4$ (1.70 g, 45 mmol) in dry ether (30 mL) at 0 °C was slowly added 2-(2-cyclopentenyl)acetamide (3.45 g, 30 mmol). The solution was refluxed for 4 h, followed by cooling to 0 °C and quenching with water. The organic layer was separated and dried over $MgSO_4$. The solution was concentrated and the product purified by vacuum distillation to afford 2-(2-cyclopentenyl)ethanamine as a clear liquid (82 %): IR (neat) 3368, 3299, 3049, 2969, 2848, 1669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.20 (br s, 2 H), 1.44 (m, 2 H), 1.59 (m, 1 H), 2.04 (m, 1 H), 2.31 (m, 2 H), 2.73 (m, 3 H), 5.67 (m, 1 H), 5.72 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 29.73, 31.84, 40.09, 40.72, 43.03, 130.29, 137.70; HRMS calcd for $C_7H_{13}N$ 111.1048, found 111.1049.

(2-Cyclopentenyl)-*N*-tosylethanamine. To a vigorously stirred solution of 2-(2-cyclopentenyl)ethanamine (0.55 g, 5 mmol) and triethylamine (0.70 mL, 5.1 mmol) in ether (20 mL) at 0 °C was slowly added tosyl chloride (0.95 g, 5 mmol). The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was washed with dilute

HCl and the organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel using 4:1 hexane/EtOAc as the eluent to afford a clear oil (87 %): IR ($CDCl_3$) 3278, 3048, 2932, 2849, 1324; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30 (m, 1 H), 1.45 (m, 1 H), 1.54 (m, 1 H), 1.97 (m, 1 H), 2.25 (m, 2 H), 2.43 (s, 3 H), 2.64 (m, 1 H), 2.95 (m, 1 H), 4.75 (t, J = 6.0 Hz, 1 H), 5.55 (m, 1 H), 5.70 (m, 1 H), 7.31 (d, J = 8.0 Hz, 2 H), 7.76 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 21.57, 29.49, 31.92, 35.64, 41.93, 42.75, 127.15, 129.75, 131.20, 133.85, 136.93, 143.39; HRMS calcd for fragments $C_{10}H_{14}NO_2S$ 212.0745, found 212.0750 and $C_8H_{10}NO_2S$ 184.0432, found 184.0436. The molecular ion was confirmed at 265.1 by CI.

***N*-(2-(2-Cyclopentenyl)ethyl)formamide.** In a flask at 0 °C was combined 2-(2-cyclopentenyl)ethanamine (0.55 g, 5 mmol) and ethyl formate (5 mL). The reaction was then stirred at reflux for 24 h. The reaction mixture was cooled to room temperature and concentrated to yield a yellow oil. The crude product was purified by column chromatography on silica gel using 1:1 hexanes/EtOAc as the eluent. A clear oil was obtained (82 %): IR (neat) 3269, 3050, 2931, 2849, 1680 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (two rotomers, 90:10) δ major rotomer 1.42 (m, 1 H), 1.52 (m, 1 H), 1.64 (m, 1 H), 2.06 (m, 1 H), 2.31 (m, 2 H), 2.69 (br s, 1 H), 3.28 (m, 2 H), 5.65 (m, 1 H), 5.74 (m, 1 H), 6.77 (br s, 1 H), 8.13 (s, 1 H); δ minor rotomer 3.23 (m), 6.57 (br s), 8.03 (d, J = 12.0 Hz), the remaining peaks coincided with the major rotomer. ^{13}C NMR (100.5 MHz, $CDCl_3$) (two rotomers, 90:10) δ major rotomer 29.59, 31.92, 35.51, 36.85, 43.04, 131.02, 134.00, 161.59; δ minor rotomer 29.51, 37.32, 40.56, 42.52, 131.34, 133.59, 164.86, the remaining peaks coincided with the major rotomer; HRMS calcd for $C_8H_{13}NO$ 139.0997, found 139.0998.

Benzyl *N*-(2-(2-cyclopentenyl)ethyl)carbamate. To a stirred solution of 2-(2-cyclopentenyl)ethanamine (0.55 g, 5 mmol) and triethylamine (0.70 mL, 5 mmol) in ether (20 mL) at 0 °C was slowly added benzyl chloroformate (0.85 g, 5 mmol). The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was washed

with dilute HCl solution and the organic layer was dried over $MgSO_4$ and concentrated to afford a clear oil. The crude product was purified by column chromatography on silica gel using 10:1 hexane/EtOAc as the eluent. The product was obtained as a white solid (82 %): mp = 45-47 °C; IR ($CHCl_3$) 3344, 3048, 2934, 2850, 1700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.45 (m, 2 H), 1.61 (m, 1 H), 2.06 (m, 1 H), 2.30 (m, 2 H), 2.68 (br s, 1 H), 3.23 (q, J = 6.4 Hz, 2 H), 4.77 (br s, 1 H), 5.09 (s, 2 H), 5.65 (m, 1 H), 5.74 (m, 1 H), 7.33 (m, 5 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 29.69, 31.99, 36.14, 39.86, 43.01, 66.65, 128.14, 128.18, 128.56, 131.02, 134.21, 136.68, 156.39; HRMS calcd for fragment $C_8H_{12}NO_2$ 154.0868, found 154.0869. The molecular ion was confirmed at 245.1 by CI.

***N*-(2-(2-Cyclopentenyl)ethyl)-*N'*, *N'*-dimethylurea.** To a stirred mixture of 2-(2-cyclopentenyl)ethanamine (0.55 g, 5 mmol) and Et_3N (0.70 mL, 5 mmol) in Et_2O (20 mL) at 0 °C was added *N*,*N*-dimethylcarbamoyl chloride (0.54 g, 5 mmol). The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was washed with dilute HCl solution. The organic layer was dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel using 1:1 hexane/EtOAc as the eluent. The product was obtained as a clear oil (72 %): IR (neat) 3327, 3046, 2925, 2848, 1640 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.46 (m, 2 H), 1.62 (m, 1 H), 2.06 (m, 1 H), 2.31 (m, 2 H), 2.69 (m, 1 H), 2.90 (s, 6 H), 3.25 (q, J = 6.4 Hz, 2 H), 4.59 (br s, 1 H), 5.67 (m, 1 H), 5.72 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 29.70, 31.96, 36.15, 36.57, 39.67, 43.20, 130.64, 134.56, 158.57; HRMS calcd for $C_{10}H_{18}N_2O$ 182.1419, found 182.1418.

***N*-(2-(2-Cyclopentenyl)ethyl)acetamide.** To a stirred solution of 2-(2-cyclopentenyl)ethanamine (0.55 g, 5 mmol) and Et_3N (0.70 mL, 5 mmol) in Et_2O (20 mL) at 0 °C was added Ac_2O (0.51 g, 5 mmol). The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was washed with dilute HCl, dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel using 3:1 EtOAc/hexane as the eluent. The product was obtained as a clear oil (86 %): IR (neat)

3280, 3083, 2926, 2848, 1656 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.37 (m, 2 H), 1.55 (m, 1 H), 1.90 (s, 3 H), 1.98 (m, 1 H), 2.25 (m, 2 H), 2.61 (m, 1 H), 3.19 (q, J = 6.8 Hz, 2 H), 5.58 (m, 1 H), 5.66 (m, 1 H), 6.19 (br s, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 23.23, 29.67, 31.94, 35.66, 38.35, 43.14, 130.92, 134.19, 170.29; HRMS calcd for $C_9H_{15}NO$ 153.1154, found 153.1154.

***N*-(2-(2-Cyclopentenyl)ethyl)benzamide.** To a stirred solution of 2-(2-cyclopentenyl)ethanamine (0.55 g, 5 mmol) and Et_3N (0.70 mL, 5 mmol) in Et_2O (20 mL) at 0 °C was added benzoyl chloride (0.70 g, 5 mmol). The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was washed with dilute HCl, dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel using 4:1 hexane/EtOAc as the eluent. The product was obtained as a clear oil (95 %): IR (neat) 3308, 3056, 2931, 2847, 1639 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.41 (m, 1 H), 1.57 (m, 1 H), 1.69 (m, 1 H), 2.05 (m, 1 H), 2.29 (m, 1 H), 2.69 (m, 2 H), 3.43 (q, J = 6.0 Hz, 2 H), 5.64 (m, 1 H), 5.71 (m, 1 H), 7.00 (br s, 1 H), 7.35 (t, J = 7.6 Hz, 2 H), 7.44 (t, J = 7.2 Hz, 1 H), 7.79 (d, J = 7.2 Hz, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 29.71, 32.02, 35.72, 38.87, 43.28, 127.05, 128.44, 130.91, 131.25, 134.34, 134.80, 167.76; HRMS calcd for $C_{14}H_{17}NO$ 215.1310, found 215.1313.

***N*-(2-(2-Cyclopentenyl)ethyl)trifluoroacetamide.** To a stirred solution of 2-(2-cyclopentenyl)ethanamine (0.55 g, 5 mmol) and Et_3N (0.70 mL, 5 mmol) in Et_2O (20 mL) at 0 °C was added trifluoroacetic anhydride (1.05 g, 5 mmol). The mixture was allowed to warm to room temperature and stirred for 2 h. The reaction mixture was washed with dilute HCl, dried over $MgSO_4$ and concentrated. The crude product was purified by column chromatography on silica gel using 10:1 hexane/EtOAc as the eluent. The product was obtained as a clear oil (85 %): IR (neat) 3316, 3104, 3053, 2938, 2853, 1712 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (m, 1 H), 1.59 (m, 1 H), 1.70 (m, 1 H), 2.07 (m, 1 H), 2.36 (m, 2 H), 2.73 (m, 1 H), 3.41 (q, J = 6.0 Hz, 2 H), 5.65 (m, 1 H), 5.78 (m, 1 H), 6.35 (br s, 1 H);

^{13}C NMR (100.5 MHz, $CDCl_3$) δ 29.48, 31.95, 34.84, 38.69, 42.93, (111.63, 114.49, 117.35, 120.21), 131.51, 133.57, (156.81, 157.17, 157.54, 157.92); HRMS calcd for $C_8H_{12}NO$ 138.0919, found 138.0916 and $C_3H_4F_3NO$ 127.0245, found 127.0246. The molecular ion was confirmed at 207.1 by CI.

***N*-Benzyl-*N*'-(2-(2-cyclopentenyl)ethyl)urea.** To a stirred solution of 2-(2-cyclopentenyl)ethanamine (0.55 g, 5 mmol) in ether (20 mL) was slowly added benzyl isocyanate (0.67 g, 5 mmol). The reaction was stirred for 1 h with the formation of a white precipitate. The reaction mixture was filtered and the crystals were washed with hexane. The product was isolated as a white solid (88 %): mp = 100-102 °C; IR ($CDCl_3$) 3359, 3322, 3043, 2927, 2851, 1627 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.36 (m, 2 H), 1.51 (m, 1 H), 1.97 (m, 1 H), 2.25 (m, 2 H), 2.60 (br s, 1 H), 3.10 (q, J = 6.4 Hz, 2 H), 4.24 (d, J = 5.6 Hz, 2 H), 5.13 (br s, 1 H), 5.45 (br s, 1 H), 5.58 (m, 1 H), 5.69 (m, 1 H), 7.24 (m, 5 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 29.74, 31.97, 36.42, 39.15, 43.11, 44.26, 127.14, 127.29, 128.56, 130.78, 134.43, 139.55, 158.77; HRMS calcd for $C_{15}H_{20}N_2O$ 244.1576, found 244.1576.

***N*-Tosyl-2-azabicyclo[3.3.0]oct-7-ene.** The product was obtained as a clear oil: IR (neat) 3053, 2946, 2853, 1341 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.45 (m, 1 H), 1.80 (m, 1 H), 2.05 (dt, J = 17.2, 2.0 Hz, 1 H), 2.38 (s, 3 H), 2.44 (m, 1 H), 2.56 (m, 1 H), 3.01 (m, 1 H), 3.31 (m, 1 H), 4.49 (d, J = 8.4 Hz, 1 H), 5.68 (m, 1 H), 5.76 (m, 1 H), 7.26 (d, J = 8.4 Hz, 2 H), 7.67 (d, J = 8.4 Hz, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 21.56, 32.39, 37.99, 39.87, 48.31, 70.09, 127.61, 129.68, 131.25, 131.98, 134.66, 143.37; HRMS calcd for $C_{14}H_{17}NO_2S$ 263.0980, found 263.0978.

***N*-Formyl-2-azabicyclo[3.3.0]oct-7-ene.** The product was obtained as a clear oil: IR (neat) 3049, 2932, 2852, 1719 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (two rotomers 55:45) δ 1.63 (m, 1 H), 2.06 (m, 1 H), 2.18 (m, 1 H), 2.65 and 2.67 (m, 1 H), 2.97 (m, 1 H), 3.33 and 3.41 (m, 1 H), 3.51 and 3.58 (m, 1 H), 4.81 and 4.96 (d, J = 7.6 Hz, 1 H),

5.65 and 5.86 (m, 1 H), 5.82 and 5.86 (m, 1 H), 8.20 and 8.28 (s, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) (two rotomers 55:45) δ 31.38, 31.92, 38.38, 38.51, 38.86, 39.31, 42.41, 45.29, 65.61, 67.85, 129.08, 130.20, 132.98, 133.85, 160.16, 160.78; HRMS calcd for $C_8H_{11}NO$ 137.0841, found 137.0844.

***N*-Benzyloxycarbonyl-2-azabicyclo[3.3.0]oct-7-ene.** The product was obtained as a clear oil: IR (neat) 3060, 3033, 2945, 2868, 1705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (two rotomers 55:45) δ 1.56 (m, 1 H), 2.03 (m, 1 H), 2.09 and 2.14 (d, J = 2.0 Hz, 1 H), 2.56 (m, 1 H), 2.86 (m, 1 H), 3.41 (m, 2 H), 4.71 and 4.77 (d, J = 7.6 Hz, 1 H), 5.13 (m, 2 H), 5.73 and 5.76 (m, 1 H), 5.73 and 5.92 (m, 1 H), 7.27 (m, 5 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) (two rotomers 55:45) δ 31.38, 32.18, 38.06, 39.22, 40.26, 45.56, 45.86, 66.58, 66.68, 67.68, 68.35, 127.82, 127.88, 128.49, 128.50, 130.64, 130.91, 131.73, 131.94, 137.15, 154.58, 154.76; HRMS calcd for $C_{15}H_{17}NO_2$ 243.1259, found 243.1259.

***N*,*N*-Dimethylaminocarbonyl-2-azabicyclo[3.3.0]oct-7-ene.** The product was obtained as a yellow oil: IR (neat) 3049, 2940, 2851, 1633 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.59 (m, 1 H), 1.95 (m, 1 H), 2.13 (m, 1 H), 2.62 (m, 1 H), 2.85 (s, 6 H), 2.90 (m, 1 H), 3.21 (dt, J = 6.4, 10.0 Hz, 1 H), 3.44 (m, 1 H), 5.02 (d, J = 7.6 Hz, 1 H), 5.71 (m, 1 H), 5.80 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 32.55, 38.43, 39.02, 39.05, 47.12, 68.74, 130.62, 133.05, 163.07; HRMS calcd for $C_{10}H_{16}N_2O$ 180.1263, found 180.1260.

***N*-Acetyl-2-azabicyclo[3.3.0]oct-7-ene.** The product was obtained as a yellow oil: IR (neat) 3050, 2928, 2853, 1645 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) (two rotomers 55:45) δ 1.63 and 1.68 (m, 1 H), 1.98-2.24 (m, 2 H), 2.06 and 2.14 (s, 3 H), 2.62 (m, 1 H), 2.86 and 3.00 (m, 1 H), 3.43 and 3.45 (d, J = 6.0 Hz, 1 H), 3.42 and 3.60 (m, 1 H), 4.76 and 4.93 (d, J = 7.6 Hz, 1 H), 5.74 and 5.87 (m, 1 H), 5.74 and 5.94 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) (two rotomers 55:45) δ 21.02, 22.07, 22.63, 30.81, 32.27, 37.86,

38.12, 38.79, 40.69, 44.94, 47.13, 67.90, 68.83, 129.37, 130.40, 131.47, 133.75, 169.16, 174.04; HRMS calcd for $C_9H_{13}NO$ 151.0997, found 151.0997.

***N*-Benzoyl-2-azabicyclo[3.3.0]oct-7-ene.** The product was obtained as a clear oil: IR (neat) 3055, 2946, 2851, 1629 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (two rotomers 67:33) δ 1.63 (m, 1 H), 1.99 and 2.17 (d, J = 15.2 Hz, 1 H), 2.01 and 2.10 (m, 1 H), 2.55 and 2.66 (dd, J = 17.2, 8.8 Hz, 1 H), 2.96 (m, 1 H), 3.41 (m, 1 H), 3.48 and 3.89 (m, 1 H), 4.76 and 5.24 (d, J = 7.2 Hz, 1 H), 5.29 and 5.85 (m, 1 H), 5.74 and 6.05 (m, 1 H), 7.38 (m, 3 H), 7.48 (m, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) (two rotomers 67:33) δ 31.04, 32.70, 38.48, 38.54, 38.64, 40.56, 44.93, 48.26, 67.87, 69.72, 126.77, 127.09, 128.21, 128.44, 129.49, 129.69, 130.03, 130.25, 132.77, 133.66, 137.26, 168.78; HRMS calcd for $C_{14}H_{15}NO$ 213.1154, found 213.1157.

***N*-Benzylaminocarbonyl-2-azabicyclo[3.3.0]oct-7-ene.** The product was obtained as a white solid: mp = 103-103 °C; IR (neat) 3332, 3060, 3029, 2916, 2850, 1635 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.64 (m, 1 H), 2.11 (m, 1 H), 2.15 (dt, J = 17.2, 2.4 Hz, 1 H), 2.56 (ddd, J = 16.8, 7.6, 2.0 Hz, 1 H), 2.88 (m, 1 H), 3.33 (m, 2 H), 4.45 (m, 2 H), 4.55 (br s, 1 H), 4.76 (d, J = 7.6 Hz, 1 H), 5.75 (m, 1 H), 5.88 (m, 1 H), 7.23-7.35 (m, 5 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 32.04, 37.80, 39.83, 44.74, 45.39, 67.84, 127.26, 127.78, 128.63, 130.84, 131.64, 139.83, 156.55; HRMS calcd for $C_{15}H_{18}N_2O$ 242.1419, found 242.1420.

2-(2-Cyclohexenyl)ethanamine. To a stirred solution of methyl cyanoacetate (0.99 g, 10 mmol) in methanol (20 mL) was added KO-*t*-Bu (1.12 g, 10 mmol). After 15 min, 3-bromocyclohexene (1.60 g, 10 mmol) was slowly added. The mixture was allowed to stir for 2 h and then was diluted with saturated NaCl solution and extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated to give a yellow oil. The crude product was purified by column chromatography on silica gel using 10:1 hexane/EtOAc as the eluent. Methyl (2-cyclohexenyl)cyanoacetate was obtained as a clear oil (83 %): IR

(neat) 3023, 2935, 2249, 1750 cm^{-1}; ^1H NMR (two diastereomers) (400 MHz, $CDCl_3$) δ 1.55 (m, 2 H), 1.85 (m, 2 H), 3.44 (d, J = 6.3 Hz, 0.5 H), 3.52 (d, J = 6.2 Hz, 0.5 H), 3.83 (s, 3 H), 5.47 (dd, J = 10.0, 0.9 Hz, 0.5 H), 5.60 (dd, J = 10.2, 1.0 Hz, 0.5 H), 5.94 (m, 2 x 0.5 H); ^{13}C NMR (two diastereomers) (100.5 MHz, $CDCl_3$) δ 14.16, 20.81, 20.98, 24.58, 24.59, 25.81, 27.29, 36.62, 43.15, 43.31, 53.34, 53.36, 60.33, 115.52, 115.64, 124.89, 125.70, 131.78, 131.85, 166.06, 166.13.

To a stirred solution of methyl (2-cyclohexenyl)cyanoacetate (0.90 g, 5 mmol) in DMSO (30 mL) was added NaCN (0.49 g, 10 mmol) and water (0.5 mL). The mixture was heated at 110 °C for 4 h and then cooled to room temperature. The reaction was dilute with saturated NaCl solution and extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated to give a yellow oil. The crude product was purified by column chromatography on silica gel using 10:1 hexane/EtOAc as the eluent. 2-(2-Cyclohexenyl)-acetonitrile was obtained as a clear oil (68 %): IR (neat) 3020, 2930, 2245, 1652 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.40 (m, 1 H), 1.58 (m, 1 H), 1.76 (m, 1 H), 1.93 (m, 1 H), 2.02 (m, 2 H), 2.32 (d, J = 2.6 Hz, 1 H), 2.34 (d, J = 1.5 Hz, 1 H), 2.50 (m, 1 H), 5.57 (dd, J = 10.0, 1.6 Hz, 1 H), 5.83 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 20.72, 23.73, 24.77, 28.46, 32.35, 118.81, 127.84, 130.09.

To a slurry of $LiAlH_4$ (0.28 g, 7.5 mmol) under an atmosphere of nitrogen in ether (20 mL) at 0 °C was slowly added a solution of 2-(2-cyclohexenyl)acetonitrile (0.61 g, 5 mmol) in ether (10 mL). The mixture was stirred for 30 min and then was quenched by the slow addition of water until a white solid coated the bottom of the flask under a clear organic layer. The organic layer was decanted. The white residue was washed twice with ether and each time decanted. The combined organic layer was dried over $MgSO_4$ and concentrated to give pure 2-(2-cyclohexenyl)ethanamine as a clear oil (92 %): IR (neat) 3365, 3284, 3014, 2914, 2836 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (m, 3 H), 1.52 (m, 3 H), 1.75 (m, 2 H), 1.97 (br s, 2 H), 2.15 (br s, 1 H), 2.75 (t, J = 8.0 Hz, 2 H), 5.55 (d, J = 12.0 Hz, 1 H), 5.67 (m, 1

H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 21.39, 25.27, 29.01, 32.81, 39.86, 40.49, 127.00, 131.70; HRMS calcd for $C_8H_{15}N$ 125.1205, found 125.1208.

2-(2-Cyclohexenyl)-*N*-tosylethanamine. This compound was prepared by the same procedure as 2-(2-cyclopentenyl)-*N*-tosylethanamine above. The product was obtained as a white solid (86 %): mp = 58-59 °C; IR ($CDCl_3$) 3280, 3015, 2921, 2836, 1324 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.12 (m, 1 H), 1.46 (m, 3 H), 1.67 (m, 2 H), 1.93 (m, 2 H), 2.08 (m, 1 H), 2.43 (s, 3 H), 2.99 (q, J = 6.8 Hz, 2 H), 4.43 (br s, 1 H), 5.42 (dd, J = 10.0, 1.65 Hz, 1 H), 5.65 (m, 1 H), 7.31 (d, J = 8.0 Hz, 2 H), 7.75 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 21.18, 21.57, 25.17, 28.55, 32.44, 35.89, 41.06, 127.16, 127.94, 129.76, 130.54, 136.94, 143.43; HRMS calcd for $C_{15}H_{21}NO_2S$ 279.1293, found 279.1299.

***N*-(2-(2-Cyclohexenyl)ethyl)formamide.** This compound was prepared by the same procedure as *N*-(2-(2-cyclopentenyl)ethyl)formamide above. The product was obtained as a clear oil (79 %): IR (neat) 3279, 3056, 3016, 2925, 2856, 1675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (two rotomers 90:10) δ major rotomer 1.16 (m, 1 H), 1.47 (m, 3 H), 1.63 (m, 1 H), 1.71 (m, 1 H), 1.89 (m, 2 H), 2.06 (br s, 1 H), 3.26 (q, J = 6.8 Hz, 2 H), 5.46 (d, J = 10.4 Hz, 1 H), 5.61 (m, 1 H), 6.77 (br s, 1 H), 8.05 (s, 1 H); δ minor rotomer 3.20 (q, J = 6.8 Hz, 1 H), 7.95 (d, J = 12.0 Hz, 1 H), the remaining peaks coincided with the major rotomer; ^{13}C NMR (100.5 MHz, $CDCl_3$) (two rotomers 90:10) δ major rotomer 21.23, 25.17, 28.70, 32.71, 35.68, 36.00, 127.68, 130.75, 161.77; δ minor rotomer 21.15, 25.12, 28.64, 32.18, 37.48, 39.75, 128.04, 130.26, 165.14; HRMS calcd for fragment C_8H_{12} 108.0939, found 108.0938. The molecular ion was confirmed at 153.1 by CI.

Benzyl *N*-(2-(2-cyclohexenyl)ethyl)carbamate. This compound was prepared by the same procedure as benzyl *N*-(2-(2-cyclopentenyl)ethylcarbamate above. The product was obtained as a clear oil (73 %): IR (neat) 3333, 3017, 2927, 2851, 1695 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.24 (q, J = 8.0 Hz, 1 H), 1.50 (m, 3 H), 1.70 (m, 1 H), 1.78 (m, 1

H), 1.97 (br s, 2 H), 2.13 (br s, 1 H), 3.26 (q, J = 6.0 Hz, 2 H), 4.70 (br s, 1 H), 5.10 (s, 2 H), 5.54 (d, J = 12.0 Hz, 1 H), 5.69 (m, 1 H), 7.35 (m, 5 H); ^{13}C NMR (10.5 MHz, $CDCl_3$) δ 21.34, 25.26, 28.82, 32.70, 36.37, 38.92, 66.64, 127.67, 128.14, 128.18, 128.56, 131.01, 136.69, 156.40; HRMS calcd for $C_{16}H_{21}NO_2$ 259.1572, found 259.1573.

***N*-(2-(2-Cyclohexenyl)ethyl)acetamide.** This compound was prepared by the same procedure as *N*-(2-(2-cyclopentenyl)ethyl)acetamide above. The product was isolated as a clear oil (83 %): IR (neat) 3288, 3088, 3014, 2920, 2856, 1661 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.23 (m, 1 H), 1.51 (m, 3 H), 1.70 (m, 1 H), 1.78 (m, 1 H), 1.95 (m, 2 H), 1.96 (s, 3 H), 2.12 (br s, 1 H), 3.29 (q, J = 6.0 Hz, 2 H), 5.54 (dd, J = 10.0, 1.2 Hz, 1 H), 5.68 (m, 1 H), 6.20 (br s, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 21.30, 23.24, 25.22, 28.79, 32.85, 35.90, 37.45, 127.59, 130.99, 170.30; HRMS calcd for $C_{10}H_{17}NO$ 167.1310, found 167.1309.

***N*-(2-(2-Cyclohexenyl)ethyl)benzamide.** This compound was prepared by the same procedure as *N*-(2-(2-cyclopentenyl)ethyl)benzamide above. The compound was isolated as a clear oil (95 %): IR (neat) 3312, 3059, 2923, 2860, 1636 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.30 (m, 1 H), 1.64 (m, 4 H), 1.84 (m, 1 H), 1.98 (br s, 2 H), 2.21 (m, 1 H), 3.53 (q, J = 6.0 Hz, 2 H), 5.61 (m, 1 H), 5.73 (m, 1 H), 6.14 (br s, 1 H), 7.42 (t, J = 7.2 Hz, 2 H), 7.49 (t, J = 7.2 Hz, 1 H), 7.75 (d, J = 6.8 Hz, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 21.36, 25.27, 28.83, 33.02, 36.05, 37.92, 126.86, 127.83, 128.60, 131.03, 131.37, 134.85, 167.49; HRMS calcd for $C_{15}H_{19}NO$ 229.1467, found 229.1464.

***N*-(2-(2-Cyclohexenyl)ethyl)trifluoroacetamide.** This compound was prepared by the same procedure as *N*-(2-(2-cyclopentenyl)ethyl)trifluoroacetamide above. The product was isolated as a clear oil (63 %): IR (neat) 3316, 3103, 3052, 2942, 2853, 1700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (m, 1 H), 1.47-1.86 (m, 5 H), 1.98 (m, 2 H), 2.15 (m, 1 H), 3.41 (q, J = 6.4 Hz, 2 H), 5.53 (dd, J = 10.0, 2.0 Hz, 1 H), 5.71 (m, 1 H), 7.08 (br s, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 21.19, 25.13, 38.60, 32.72, 35.06, 37.87,

(111.64, 114.50, 117.36, 120.22), 128.11, 130.32, (156.89, 157.25, 157.62, 157.98); HRMS calcd for $C_{10}H_{14}F_3NO$ 221.1028, found 221.1028.

***N*-Benzyl-*N*'-(2-(2-cyclohexenyl)ethyl)urea.** This compound was prepared by the same procedure as *N*-benzyl-*N*'-(2-(2-cyclopentenyl)ethyl)urea above. The product was isolated as a white solid (84 %): mp = 85-87 °C; IR ($CDCl_3$) 3337, 3018, 2926, 2861, 1627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.13 (m, 1 H), 1.32 (m, 1 H), 1.44 (m, 2 H), 1.65 (m, 2 H), 1.93 (m, 2 H), 2.02 (br s, 1 H), 3.09 (s, 2 H), 4.20 (s, 2 H), 5.38 (br s, 1 H), 5.46 (dd, J = 10.0, 1.6 Hz, 1 H), 5.64 (m, 1 H), 5.75 (br s, 1 H), 7.19 (m, 5 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 21.36, 25.29, 28.88, 32.79, 36.65, 38.12, 44.09, 127.03, 127.18, 127.35, 128.51, 131.28, 139.69, 159.07; HRMS calcd for $C_{16}H_{22}N_2O$ 258.1732, found 258.1738.

***N*-Tosyl-7-azabicyclo[4.3.0]non-4-ene.** The product was obtained as a clear oil: IR (neat) 3056, 2938, 2853, 1330 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.21 (m, 1 H), 1.34 (m, 1 H), 1.50 (m, 2 H), 1.90 (d, J = 16.0 Hz, 1 H), 2.27 (m, 1 H), 2.36 (m, 1 H), 2.43 (s, 3 H), 2.77 (dt, J = 12.8, 2.8 Hz, 1 H), 3.78 (m, 1 H), 4.86 (s, 1 H), 5.31 (m, 1 H), 5.77 (m, 1 H), 7.29 (d, J = 8.0 Hz, 2 H), 7.71 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 21.55, 22.93, 26.33, 35.38, 37.73, 41.91, 61.74, 127.08, 129.60, 129.71, 132.95, 137.81, 143.06; HRMS calcd for $C_{15}H_{18}NO_2S$ ($[M-H]^+$) 276.1058, found 276.1056.

***N*-Formyl-7-azabicyclo[4.3.0]non-4-ene.** The product was obtained as a yellow oil: IR (neat) 3059, 2930, 2853, 1673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (two rotomers 50:50) δ 1.40 (m, 2 H), 1.62 (m, 1 H), 1.71 (m, 1 H), 2.05 (m, 1 H), 2.32 and 2.37 (m, 1 H), 2.49 and 2.53 (m, 1 H), 2.66 and 3.06 (m, 1 H), 3.47 and 4.21 (m, 1 H), 4.56 and 5.35 (br s, 1 H), 5.53 and 5.56 (m, 1 H), 5.89 and 5.92 (m, 1 H), 8.11 and 8.14 (s, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) (two rotomers 50:50) δ 21.14, 21.64, 22.39, 22.90, 26.26, 27.22, 35.63, 35.94, 42.22, 44.67, 53.38, 54.97, 125.01, 125.62, 128.53, 130.40, 161.06, 161.24; HRMS calcd for $C_9H_{13}NO$ 151.0997, found 151.0999.

***N*-Benzyloxycarbonyl-7-azabicyclo[4.3.0]non-4-ene.** This product was obtained as a clear oil: IR (neat) 3060, 3033, 2934, 2855, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (two rotomers 45:55) δ 1.27 (m, 1 H), 1.36 (m, 1 H), 1.53 (br s, 1 H), 1.61 (m, 1 H), 1.98 (dd, J = 16.0, 1.2 Hz, 1 H), 2.33 (br s, 1 H), 2.44 (br s, 1 H), 2.75 (m, 1 H), 4.04 (m, 1 H), 5.11 (m, 1 H), 5.15 (s, 2 H), 5.57 (br d, 1 H), 5.82 (br s, 1 H), 7.30 (m, 5 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) (two rotomers 45:55) δ 20.63, 20.91, 22.55, 22.65, 26.24, 27.25, 35.73, 36.51, 45.07, 45.46, 55.04, 55.45, 66.50, 66.71, 126.11, 126.58, 127.71, 127.86, 128.48, 128.50, 137.09, 137.19, 155.03, 155.07; HRMS calcd for $C_{16}H_{19}NO_2$ 257.1416, found 257.1422.

***N*-Benzylaminocarbonyl-7-azabicyclo[4.3.0]non-4-ene.** The product was obtained as a clear oil: IR ($CDCl_3$) 3333, 3027, 2921, 2858, 1633 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.67 (m, 1 H), 1.74-2.07 (m, 5 H), 2.36 (m, 1 H), 3.29 (q, J = 8.0 Hz, 1 H), 3.36 (dt, J = 8.8, 2.8 Hz, 1 H), 4.31 (d, J = 6.0 Hz, 1 H), 4.40 (m, 2 H), 4.73 (br s, 1 H), 5.68 (d, J = 10.4 Hz, 1 H), 5.83 (d, J = 10.0 Hz, 1 H), 7.20-7.32 (m, 5 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 20.56, 22.52, 26.92, 35.86, 44.60, 44.71, 55.04, 126.73, 127.13, 127.27, 127.69, 128.55, 139.94, 156.81; HRMS calcd for $C_{16}H_{20}N_2O$ 256.15756, found 256.15806.

***N*-Acetyl-7-azabicyclo[4.3.0]non-4-ene.** This product was obtained as a yellow oil: IR (neat) 3025, 2923, 2882, 1643 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (two rotomers 67:33) δ major rotomer 1.73 (m, 1 H), 1.82-1.97 (m, 3 H), 1.98-2.10 (m, 2 H), 2.08 (s, 3 H), 2.42 (m, 1 H), 3.44-3.62 (m, 2 H), 5.57 (m, 1 H), 5.76 (m, 1 H), 5.94 (dd, J = 8.0, 4.0 Hz, 1 H); δ minor rotomer 2.18 (s, 3 H), 2.53 (m, 1 H), 4.28 (m, 1 H), 5.62 (m, 1 H), 5.83 (m, 1 H), the remaining peaks coincided with the major rotomer; ^{13}C NMR (100.5 MHz, $CDCl_3$) (two rotomers 67:33) δ 20.06, 20.50, 22.02, 22.26, 22.40, 22.68, 25.02, 27.17, 35.30, 36.71, 44.87, 46.63, 55.03, 56.50, 125.62, 125.90, 127.32, 129.07, 169.14, 169.34; HRMS calcd for $C_{10}H_{15}NO$ 165.1154, found 165.1154.

***N*-Benzoyl-7-azabicyclo[4.3.0]non-4-ene.** This product was obtained as a clear oil: IR (neat) 3029, 2923, 2884, 1626 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (two rotomers 67:33) δ major rotomer 1.60 (m, 1 H), 1.70 (m, 1 H), 1.85 (m, 2 H), 2.03 (m, 2 H), 2.43 (m, 1 H), 3.38 (m, 1 H), 3.57 (m, 1 H), 4.65 (d, J = 4.8 Hz, 1 H), 5.85 (m, 1 H), 6.14 (d, J = 10.0 Hz, 1 H), 7.39-7.51 (m, 5 H); δ minor rotomer 3.73 (m, 2 H), 4.25 (d, J = 4.8 Hz, 1 H), 5.23 (d, J = 10.0 Hz, 1 H), 5.66 (m, 1 H), the remaining peaks coincided with the major rotomer; ^{13}C NMR (100.5 MHz, $CDCl_3$) (two rotomers 67:33) δ 20.27, 21.88, 22.05, 23.22, 25.10, 29.01, 35.44, 36.69, 36.70, 45.01, 48.27, 55.43, 57.14, 125.57, 125.55, 127.17, 128.24, 128.48, 128.70, 129.32, 129.79, 137.29, 137.71, 170.16; HRMS calcd for $C_{15}H_{17}NO$ 227.1310, found 227.1315.

2,2-Dimethyl-4-hexen-1-amine. To a stirred solution of 2-buten-1-ol (0.79 g, 11 mmol) and Et_3N (1.53 mL, 11 mmol) in THF (20 mL) at 0 °C was added mesyl chloride (1.26 g, 11 mmol). The reaction was stirred for 30 min, followed by filtration. The filtrate was concentrated for use later in the procedure.

To a stirred solution of diisopropylamine (1.01 g, 10 mmol) in THF (20 mL) under a nitrogen atmosphere at 0 °C was slowly added *n*-BuLi (4.95 mL of a 2.05 M solution in hexane, 10 mmol). The mixture was stirred for 30 min, followed by the slow addition of isobutyronitrile (0.69 g, 10 mmol) in THF (10 mL). The resulting mixture was stirred at 0 °C for 1 h, followed by the slow addition of the newly prepared mesylate described above. The reaction was stirred for 1 h, followed by quenching with saturated NaCl solution. The organic layer was separated, dried over $MgSO_4$ and concentrated to give a yellow oil. The crude product was purified by column chromatography on silica gel using 10:1 hexane/EtOAc as the eluent. The product, 2,2-dimethyl-4-hexenenitrile, was obtained as a clear oil (56 %): IR (neat) 3025, 2976, 2920, 2233 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.31 (s, 6 H), 1.71 (d, J = 5.6 Hz, 3 H), 2.19 (d, J = 7.2 Hz, 2 H), 5.49 (m, 1 H), 5.59 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 17.97, 26.19, 32.51, 43.96, 127.76, 125.00, 130.65.

To a slurry of $LiAlH_4$ (0.28 g, 7.5 mmol) in ether (20 mL) at 0 °C under a nitrogen atmosphere was slowly added a solution of 2,2-dimethyl-4-hexenenitrile (0.56 g, 5 mmol) in ether (10 mL). The mixture was stirred for 30 min and then was quenched by the slow addition of water until a white solid coated the bottom of the flask under a clear organic layer. The organic layer was decanted. The white residue was washed twice with ether and each time decanted. The combined organic layer was dried over $MgSO_4$ and concentrated to give pure 2,2-dimethyl-4-hexenamine as a clear oil (90 %): IR (neat) 3390, 3318, 3019, 2954, 2865 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.75 (s, 6 H), 1.15 (br s, 2 H), 1.61 (d, J = 6.8 Hz, 3 H), 1.88 (d, J = 2.8 Hz, 2 H), 2.43 (s, 2 H), 5.42 (m, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 18.00, 24.60, 34.92, 42.63, 52.48, 127.29, 127.51; HRMS calcd for $C_8H_{17}N$ 127.1361, found 127.1363. Note: the 2-buten-1-ol used in this procedure was a 96:4 *trans/cis* mixture. The products derived from the use of this compound reflect this ratio. Only the spectral data for the major isomer is reported.

2,2-Dimethyl-*N*-tosyl-4-hexen-1-amine. This compound was prepared by the same procedure as 2-(2-cyclopentenyl)-*N*-tosylethanamine above. The product was isolated as a white solid (85 %): mp = 62-64 °C; IR ($CDCl_3$) 3282, 3025, 2958, 2928, 2870, 1320 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (s, 6 H), 1.61 (d, J = 6.8 Hz, 3 H), 1.86 (d, J = 7.2 Hz, 2 H), 2.42 (s, 3 H), 2.65 (d, J = 6.8 Hz, 2 H), 4.80 (br s, 1 H), 5.33 (m, 2 H), 7.30 (d, J = 8.0 Hz, 2 H), 7.75 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 17.96, 21.51, 24.93, 34.23, 42.73, 52.80, 126.60, 127.13, 128.32, 129.67, 137.13, 143.24; HRMS calcd for $C_{15}H_{23}NO_2S$ 281.1450, found 281.1447.

***N*-(2,2-Dimethyl-4-hexenyl)formamide.** This compound was prepared by the same procedure as *N*-(2-(2-cyclopentenyl)ethyl)formamide above. The product was obtained as a clear oil (77 %): IR (neat) 3317, 3060, 3025, 2957, 2857, 1689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (two rotomers 61:39) δ major rotomer 0.87 (s, 6 H), 1.68 (d, J = 4.4 Hz, 3 H), 1.91 (d, J = 4.0 Hz, 2 H), 3.13 (d, J = 6.4 Hz, 2 H), 5.46 (m, 2 H), 5.60 (br s, 1 H), 8.24

(s, 1 H); δ minor rotomer 0.91 (s, 6 H), 1.90 (d, J = 4.0 Hz, 2 H), 2.95 (d, J = 6.4 Hz, 2 H), 5.76 (br s, 1 H), 7.96 (d, J = 11.6 Hz, 1 H), the remaining peaks coincided with the major rotomer; ^{13}C NMR (100.5 MHz, $CDCl_3$) (two rotomers 61:39) δ 15.24, 18.00, 24.75, 24.85, 34.61, 42.61, 43.13, 47.42, 51.82, 65.81, 126.35, 126.84, 128.12, 128.57, 161.60, 165.37; HRMS calcd for $C_9H_{17}NO$ 155.1310, found 155.1313.

Benzyl *N*-(2,2-dimethyl-4-hexenyl)carbamate. This compound was prepared by the same procedure as benzyl *N*-(2-(2-cyclopentenyl)ethyl)carbamate above. The product was obtained as a clear oil (83 %): IR (neat) 3340, 3030, 2957, 2917, 1701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (s, 6 H), 1.66 (d, J = 2.8 Hz, 3 H), 1.88 (d, J = 2.8 Hz, 2 H), 3.00 (d, J = 6.4 Hz, 2 H), 4.80 (br s, 1 H), 5.09 (s, 2 H), 5.42 (br s, 2 H), 7.30 (m, 5 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 18.02, 24.81, 34.86, 43.06, 50.85, 66.68, 127.04, 128.01, 128.12, 128.17, 128.55, 136.78, 156.75; HRMS calcd for $C_{16}H_{23}NO_2$ 261.1729, found 261.1727.

***N*-(2,2-Dimethyl-4-hexenyl)acetamide.** This compound was prepared by the same procedure as *N*-(2-(2-cyclopentenyl)ethyl)acetamide above. The product was obtained as a clear oil (81 %): IR (neat) 3311, 3090, 2958, 2919, 2869, 1666 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (s, 6 H), 1.67 (d, J = 3.2 Hz, 3 H), 1.89 (d, J = 2.4 Hz, 2 H), 2.00 (s, 3 H), 3.06 (d, J = 6.4 Hz, 2 H), 5.43 (m, 2 H), 6.07 (br s, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 18.02, 23.31, 24.88, 34.67, 43.23, 49.08, 127.11, 127.88, 170.36; HRMS calcd for $C_{10}H_{19}NO$ 169.14667, found 169.1463.

***N*-(2,2-Dimethyl-4-hexenyl)benzamide.** This compound was prepared by the same procedure as *N*-(2-(2-cyclopentenyl)ethyl)benzamide above. The product was obtained as a clear oil (86 %): mp = 60-62 °C; IR (neat) 3328, 3061, 3024, 2959, 2919, 1651 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.94 (s, 6 H), 1.69 (d, J = 4.0 Hz, 3 H), 1.99 (d, J = 4.8 Hz, 2 H), 3.29 (d, J = 6.0 Hz, 2 H), 5.51 (m, 2 H), 6.29 (br s, 1 H), 7.42 (m, 2 H), 7.48 (m, 1 H), 7.75 (d, J = 6.9 Hz, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 18.13, 25.21, 35.14, 43.71,

49.49, 126.84, 127.46, 128.10, 128.62, 131.37, 135.07, 167.61; HRMS calcd for $C_{15}H_{21}NO$ 231.1623, found 231.1623.

4,4-Dimethyl-*N*-tosyl-2-vinylpyrrolidine. The product was obtained as a white solid: mp = 58-60 °C; IR ($CDCl_3$) 3084, 2959, 2871, 1347 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.68 (s, 3 H), 1.05 (s, 3 H), 1.57 (dd, *J* = 12.8, 8.4 Hz, 1 H), 1.73 (dd, *J* = 13.2, 8.0 Hz, 1 H), 2.42 (s, 3 H), 3.16 (q, *J* = 10.0 Hz, 2 H), 4.01 (q, *J* = 8.0 Hz, 1 H), 5.07 (d, *J* = 10.0 Hz, 1 H), 5.18 (d, *J* = 17.2 Hz, 1 H), 5.87 (m, 1 H), 7.30 (d, *J* = 8.0 Hz, 2 H), 7.70 (d, *J* = 8.0 Hz, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 21.56, 26.05, 26.53, 37.48, 47.51, 61.49, 62.48, 115.15, 127.58, 129.51, 135.28, 139.83, 143.25; HRMS calcd for $C_{15}H_{21}NO_2S$ 279.1293, found 279.1294.

***N*-Formyl-4,4-dimethyl-2-vinylpyrrolidine.** The product was obtained as a yellow oil: IR (neat) 3081, 2958, 2870, 1673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (two rotomers 75:25) δ major rotomer 1.07 (s, 3 H), 1.15 (s, 3 H), 1.57 (dd, *J* = 12.4, 9.6 Hz, 1 H), 1.91 (ddd, *J* = 12.8, 6.8, 1.2 Hz, 1 H), 3.05 (d, *J* = 11.6 Hz, 1 H), 3.47 (d, *J* = 12.0 Hz, 1 H), 4.28 (q, *J* = 9.2 Hz, 1 H), 5.20 (d, *J* = 10.0 Hz, 1 H), 5.27 (d, *J* = 17.2 Hz, 1 H), 5.74 (m, 1 H), 8.15 (s, 1 H); δ minor rotomer 1.02 (s, 3 H), 1.14 (s, 3 H), 1.97 (m, 1 H), 3.19 (d, *J* = 11.6 Hz, 1 H), 3.28 (d, *J* = 12.0 Hz, 1 H), 4.48 (q, *J* = 9.2 Hz, 1 H), 5.10 (d, *J* = 10.0 Hz, 1 H), 5.18 (d, *J* = 17.2 Hz, 1 H), 5.78 (m, 1 H), 8.28 (s, 1 H), the remaining peaks coincided with the major rotomer; ^{13}C NMR (100.5 MHz, $CDCl_3$) (two rotomers 75:25) δ major rotomer 26.46, 26.55, 36.75, 46.72, 56.41, 60.44, 117.69, 138.51, 162.01; minor rotomer 25.65, 25.70, 37.71, 45.99, 57.07, 59.20, 114.53, 137.55, 161.36; HRMS calcd for $C_9H_{15}NO$ 153.1154, found 153.1156.

3-(2-Cyclopentenyl)propan-1-amine. To a slurry of $LiAlH_4$ (0.57 g, 15 mmol) at 0 °C under a nitrogen atmosphere was slowly added 2-cyclopentenylacetic acid (1.26 g, 10 mmol). The mixture was stirred for 1 h and then was quenched by the slow addition of water until a white solid coated the bottom of the flask under a clear organic layer. The organic layer

was decanted. The white residue was washed twice with ether and each time decanted. The combined organic layer was dried over $MgSO_4$ and concentrated to give pure 2-(2-cyclohexenyl)ethanol as a clear oil (95 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (m, 1 H), 1.57 (m, 1 H), 1.68 (m, 1 H), 2.06 (m, 1 H), 2.29 (m, 2 H), 2.49 (br s, 1 H), 2.75 (m, 1 H), 3.67 (m, 2 H), 5.68 (m, 1 H), 5.74 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 29.82, 31.94, 38.87, 42.13, 61.60, 130.61, 134.72.

To a stirred solution of 2-(2-cyclopentenyl)ethanol (1.01 g, 9.0 mmol) and CBr_4 (4.50 g, 13.5 mmol) in dry CH_2Cl_2 (2.0 mL) at 0 °C was slowly added a solution of triphenylphosphine (2.36 g, 9.0 mmol) in CH_2Cl_2 (2.7 mL). After stirring for 1 h, the reaction mixture was diluted with pentane (75 mL) and the resulting precipitate was removed by filtration and washed several times with pentane. The combined organic phase was washed with saturated NaCl solution, dried over $MgSO_4$ and concentrated to give a clear oil. The crude product was purified by column chromatography on silica gel using pentane as the eluent. The product 1-bromo-2-(2-cyclopentenyl)ethane was obtained as a clear oil (78 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (m, 1 H), 1.85 (m, 1 H), 1.95 (m, 1 H), 2.08 (m, 1 H), 2.33 (m, 2 H), 2.84 (m, 1 H), 3.43 (m, 2 H), 5.66 (m, 1 H), 5.77 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 29.31, 31.94, 32.23, 39.10, 44.28, 131.64, 133.49.

To a stirred solution of NaCN (0.59 g, 12 mmol) in DMSO (12 mL) at 80 °C was slowly added 1-bromo-2-(2-cyclopentenyl)ethane (1.05 g, 6.0 mmol). After 1 h, the reaction mixture was diluted with saturated NaCl solution and extracted with ether. The combined organic layers were dried over $MgSO_4$ and concentrated to give a yellowish oil. The crude product was purified by column chromatography on silica gel using 10:1 hexane/EtOAc as the eluent. The product 3-(2-cyclopentenyl)propanenitrile was obtained as a clear oil (54 %): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.42 (m, 1 H), 1.65 (m, 1 H), 1.77 (m, 1 H), 2.08 (m, 1 H), 2.35 (m, 4 H), 2.81 (br s, 1 H), 5.63 (m, 1 H), 5.80 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 15.40, 29.08, 31.24, 31.96, 44.52, 119.99, 132.13, 132.82.

To a slurry of $LiAlH_4$ (0.22 g, 6.0 mmol) in ether (12 mmol) at 0 °C under a nitrogen atmosphere was slowly added 3-(2-cyclopentenyl)propanenitrile (0.375 g, 3.0 mmol). The mixture was stirred for 30 min and then was quenched by the slow addition of water until a white solid coated the bottom of the flask under a clear organic layer. The organic layer was decanted. The white residue was washed twice with ether and each time decanted. The combined organic layer was dried over $MgSO_4$ and concentrated to give pure 3-(2-cyclopentenyl)propan-1-amine as a clear oil (95 %): IR (neat) 3365, 3299, 3048, 2921, 2847, 1608 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.30-1.55 (m, 5 H), 1.79 (br s, 2 H), 2.02 (m, 1 H), 2.31 (m, 2 H), 2.64 (br s, 1 H), 2.70 (t, J = 6.8 Hz, 2 H), 5.68 (m, 1 H), 5.72 (m, 1 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 29.79, 31.82, 31.95, 33.26, 42.26, 45.35, 130.35, 134.97; HRMS calcd for $C_8H_{15}N$ 125.1205, found 125.1202.

3-(2-Cyclopentenyl)-*N*-tosylpropan-1-amine. This compound was prepared by the same procedure as 2-(2-cyclopentenyl)-*N*-tosylethanamine above. The product was isolated as a white solid (83 %): mp = 39-40.5 °C; IR ($CDCl_3$) 3297, 3050, 2935, 2849, 1324 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.28 (m, 3 H), 1.46 (m, 2 H), 1.95 (m, 1 H), 2.25 (m, 2 H), 2.43 (s, 3 H), 2.53 (m, 1 H), 2.94 (q, J = 6.4 Hz, 2 H), 4.38 (br s, 1 H), 5.55 (m, 1 H), 5.69 (m, 1 H), 7.31 (d, J = 8.0 Hz, 2 H), 7.74 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 21.55, 27.85, 29.62, 31.95, 32.84, 43.45, 44.98, 127.15, 129.72, 130.59, 134.58, 137.02, 143.31; HRMS calcd for $C_{15}H_{21}NO_2S$ 279.1293, found 279.1290.

***N*-(3-(2-Cyclopentenyl)propyl)formamide.** This compound was prepared by the same procedure as *N*-(2-(2-cyclopentenyl)ethyl)formamide above. The product was obtained as a clear oil (two rotomers 77:23, 82 %): IR (neat) 3303, 3049, 2928, 2849, 1663 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (two rotomers 77:23) δ major rotomer 1.19-1.46 (m, 3 H), 1.58 (m, 2 H), 2.04 (m, 1 H), 2.30 (m, 2 H), 2.64 (m, 1 H), 3.27 (q, J = 6.8 Hz, 2 H), 5.65 (m, 1 H), 5.72 (m, 1 H), 6.26 (br s, 1 H), 8.15 (s, 1 H); δ minor rotomer 3.22 (q, J = 6.8 Hz, 2 H), 8.04 (d, J = 11.6 Hz, 1 H), the remaining peaks coincided with the major rotomer;

^{13}C NMR (100.5 MHz, $CDCl_3$) (two rotomers 77:23) δ major rotomer 27.83, 29.72, 31.97, 33.17, 38.39, 45.13, 130.66, 134.62, 161.44; δ minor rotomer 29.52, 29.69, 32.72, 42.14, 45.02, 130.89, 134.36, 164.88, the remaining peaks coincided with the major rotomer; HRMS calcd for fragment C_8H_{12} 108.0939, found 108.0941. The molecular ion was confirmed at 153.1 by CI.

Benzyl *N*-(3-(2-cyclopentenyl)propyl)carbamate. This compound was prepared by the same procedure as benzyl *N*-(2-(2-cyclopentenyl)ethyl)carbamate above. The product was obtained as a clear oil (80 %): IR (neat) 3332, 3047, 2932, 2849, 1700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.37 (m, 3 H), 1.51 (m, 2 H), 2.03 (m, 1 H), 2.30 (m, 2 H), 2.63 (br s, 1 H), 3.19 (q, J = 6.8 Hz, 2 H), 4.79 (br s, 1 H), 5.09 (s, 2 H), 5.64 (m, 1 H), 5.72 (m, 1 H), 7.33 (m, 5 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 28.36, 29.77, 32.02, 33.10, 41.34, 45.21, 66.62, 128.13, 128.17, 128.56, 130.63, 134.77, 136.70, 156.42; HRMS calcd for $C_{16}H_{21}NO_2$ 259.1572, found 259.1573.

***N*-Benzyl-*N*'-(3-(2-cyclopentenyl)propyl)urea.** This compound was prepared by the same procedure as *N*-benzyl-*N*'-(3-(2-cyclopentenyl)propyl)urea above. The product was obtained as a white solid (91 %): mp = 88.5-89.5 °C; IR ($CDCl_3$) 3357, 3050, 2928, 2951, 1633 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.20-1.52 (m, 5 H), 2.01 (m, 1 H), 2.29 (m, 2 H), 2.61 (br s, 1 H), 3.13 (d, J = 5.6 Hz, 2 H), 4.33 (d, J = 4.8 Hz, 2 H), 4.57 (br s, 1 H), 4.87 (br s, 1 H), 5.63 (m, 1 H), 5.70 (m, 1 H), 7.28 (m, 5 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 28.58, 29.78, 32.01, 33.21, 40.82, 44.57, 45.25, 127.35, 127.48, 128.67, 130.57, 134.82, 139.33, 158.30; HRMS calcd for $C_{16}H_{22}N_2O$ 258.1732, found 258.1732.

***N*-Tosyl-2-azabicyclo[4.3.0]non-8-ene.** The product was obtained as a clear oil.: IR (neat) 3056, 2938, 2853, 1330 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (m, 1 H), 1.34 (m, 1 H), 1.50 (m, 2 H), 1.90 (d, J = 16.0 Hz, 1 H), 2.27 (m, 1 H), 2.36 (m, 1 H), 2.43 (s, 3 H), 2.77 (dt, J = 12.8, 2.8 Hz, 1 H), 3.78 (m, 1 H), 4.86 (s, 1 H), 5.31 (m, 1 H), 5.77 (m, 1 H), 7.29 (d, J = 8.0 Hz, 2 H), 7.71 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100.5 MHz,

$CDCl_3$) δ 21.55, 22.93, 26.33, 35.38, 37.73, 41.91, 61.74, 127.08, 129.60, 129.71, 132.95, 137.81, 143.06; HRMS calcd for fragment $C_{15}H_{18}NO_2S$ 276.1058, found 276.1056.

***N*-Formyl-2-azabicyclo[4.3.0]non-8-ene.** The product was obtained as a clear oil: IR (neat) 3059, 2930, 2853, 1673 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) (two rotomers 50:50) δ 1.40 (m, 2 H), 1.60 (m, 1 H), 1.72 (m, 1 H), 2.05 (m, 1 H), 2.34 (m, 1 H), 2.48 (m, 0.5 H), 2.52 (m, 0.5 H), 2.66 (m, 0.5 H), 3.05 (m, 0.5 H), 3.45 (m, 0.5 H), 4.21 (m, 0.5 H), 4.56 (br s, 0.5 H), 5.34 (br s, 0.5 H), 5.53 (m, 0.5 H), 5.56 (m, 0.5 H), 5.89 (m, 1 H), 8.11 (s, 0.5 H), 8.14 (s, 0.5 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) (two rotomers 50:50) δ 22.66, 24.34, 27.64, 27.79, 34.97, 35.88, 37.26, 38.42, 43.61, 56.95, 63.35, 130.31, 130.81, 132.80, 133.75, 161.57, 162.04; HRMS calcd for $C_9H_{13}NO$ 151.0997, found 151.0999.

***N*-Benzyloxycarbonyl-2-azabicyclo[4.3.0]non-8-ene.** The product was obtained as a clear oil: IR (neat) 3060, 3033, 2934, 2855, 1697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.22-1.39 (m, 2 H), 1.53 (br s, 1 H), 1.62 (m, 1 H), 1.98 (dd, J = 16.0, 1.2 Hz, 1 H), 2.33 (br s, 1 H), 2.44 (br s, 1 H), 2.75 (m, 1 H), 4.06 (m, 1 H), 5.14 (m, 1 H), 5.15 (s, 2 H), 5.55 (m, 1 H), 5.82 (br s, 1 H), 7.29 (m, 5 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 23.28, 27.02, 35.38, 38.49, 40.79, 60.30, 67.01, 127.84, 127.93, 128.51, 131.52, 132.05, 137.06, 155.87; HRMS calcd for $C_{16}H_{19}NO_2$ 257.1416, found 257.1422.

Tricyclic benzylurea (1). The product was obtained as a clear oil: IR (neat) 3062, 3029, 2926, 2857, 1675 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.43 (m, 1 H), 1.49 (m, 1 H), 1.79 (m, 2 H), 2.72 (m, 1 H), 2.91 (br s, 1 H), 3.90 (dt, J = 13.2, 4.0 Hz, 1 H), 4.04 (t, J = 6.4 Hz, 1 H), 4.09 (d, J = 15.2 Hz, 1 H), 4.33 (dd, J = 7.2, 1.2 Hz, 1 H), 4.76 (d, J = 15.2 Hz, 1 H), 5.60 (m, 1 H), 5.68 (d, J = 5.6 Hz, 1 H), 7.31 (m, 5 H); ^{13}C NMR (100.5 MHz, $CDCl_3$) δ 21.56, 25.23, 39.25, 43.71, 46.37, 54.46, 64.37, 127.31, 127.70, 128.15, 128.57, 136.47, 138.30, 158.29; HRMS calcd for $C_{16}H_{18}N_2O$ 254.1419, found 254.1420.

Acknowledgement

The Larock group gratefully acknowledges partial financial support of this research by the donors of the Petroleum Research Fund administered by the American Chemical Society and a Graduate Assistantship in Areas of National Need (GAANN) Fellowship from the U. S. Department of Education. We would also like to acknowledge Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for contributing the palladium acetate.

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GENERAL CONCLUSION

In this dissertation, the scope and limitations of a Pd(II)-DMSO-O_2 catalyst system were examined in three unrelated organic transformations: oxidation of alcohols, dehydrogenation of β-dicarbonyl compounds and cyclization of olefinic amines derivatives.

Chapter 1 described the oxidation of allylic and benzylic alcohols. Although there are many examples of procedures for the oxidation of alcohols to aldehydes and ketones, they often require the stoichiometric use of toxic metal reagents. The current procedure offers the advantage of being catalytic in Pd, while using the inexpensive, non-toxic oxygen gas as the stoichiometric reoxidant. The procedure worked well for a variety of 1° and 2° allylic and benzylic substrates, but was quite unreactive toward saturated substrates. This suggests the potential for this procedure to be capable of selective oxidation with the proper choice of substrate and reaction conditions.

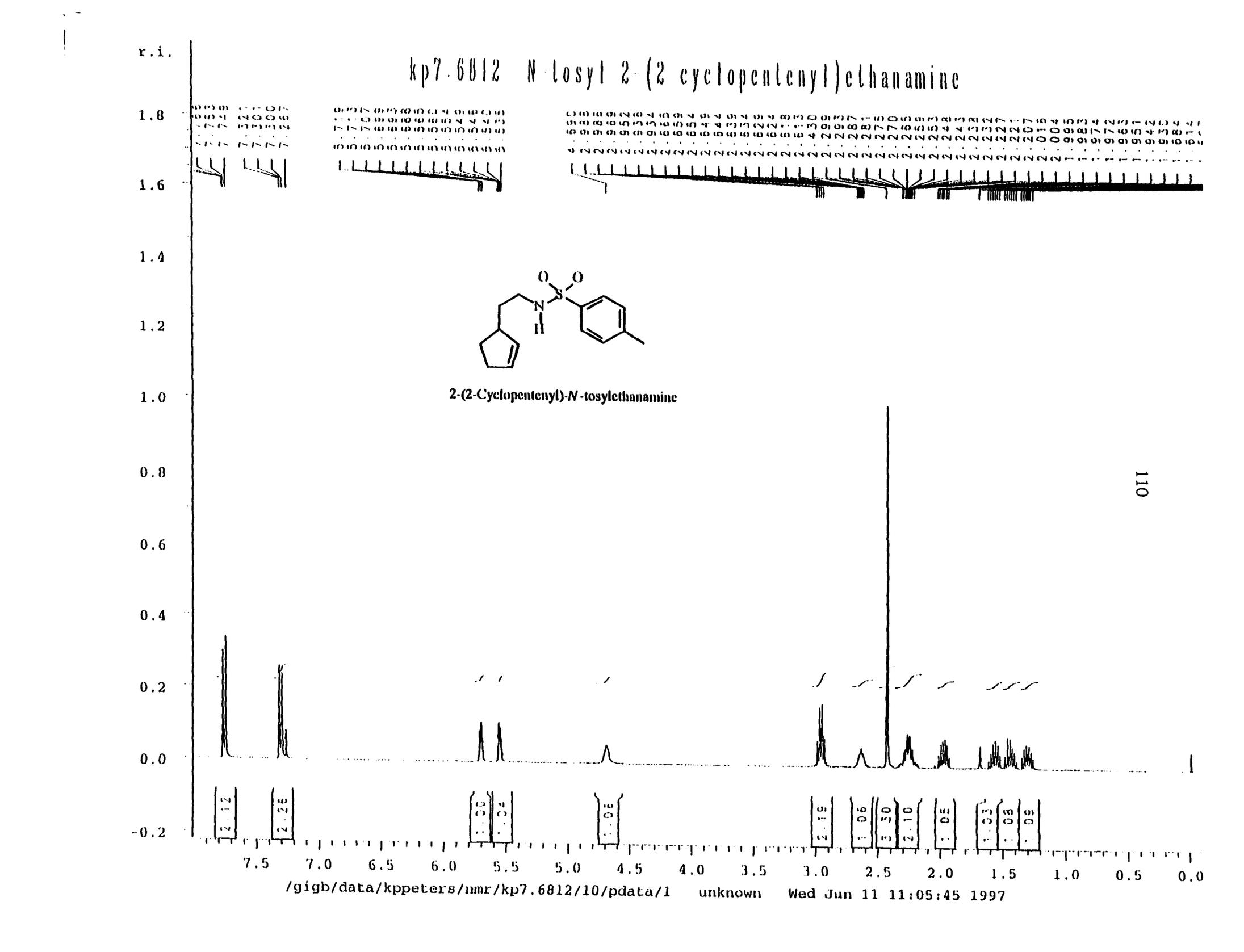
Chapter 2 described the dehydrogenation of β-dicarbonyl compounds. There are several procedures for obtaining this type of product, but they are limited by either the need to synthesize very elaborate substrate molecules for an intramolecular condensation reaction or the stoichiometric use of toxic reagents. The current procedure offers the advantage of being catalytic in Pd, while using the inexpensive, non-toxic oxygen gas as the stoichiometric reoxidant. This reaction proved to be successful with benzyl-substituted β-dicarbonyl compounds, but suffered from low yields with alkyl-substituted β-dicarbonyl compounds. More work needs to be done before this becomes a useful synthetic procedure.

Chapter 3 described the cyclization of olefinic amine derivatives. There are a number of stoichiometric and catalytic procedures using Pd for the cyclization of olefinic amines and their derivatives. The current study is significant by being the first to compare a wide variety of common, synthetically useful amine derivatives of several different substrate structures with the goal of determining the relative reactivity of the various derivatives, as well as their

efficiency in forming a variety of bicyclic and monocyclic products. This study has advanced the understanding of the reactivity of various nitrogen-containing nucleophiles in Pd(II) chemistry, as well as the efficiency of these nucleophiles in forming various ring systems.

In summary, the scope and limitations of three organic transformations, induced by a Pd(II)-DMSO-O_2 catalyst system, have been examined and reported. The procedures offer advantages over current methodology by being catalytic in Pd and by using O_2 gas as the stoichiometric reoxidant. This work has also served to expand the understanding of this useful catalyst system.

APPENDIX A: CHAPTER 3 ^{1}H AND ^{13}C NMR SPECTRA


kp7.6812 N-tosyl 2-(2 cyclopentenyl)ethanamine
r.i.
2-(2-Cyclopentenyl)-N-tosylethanamine
110
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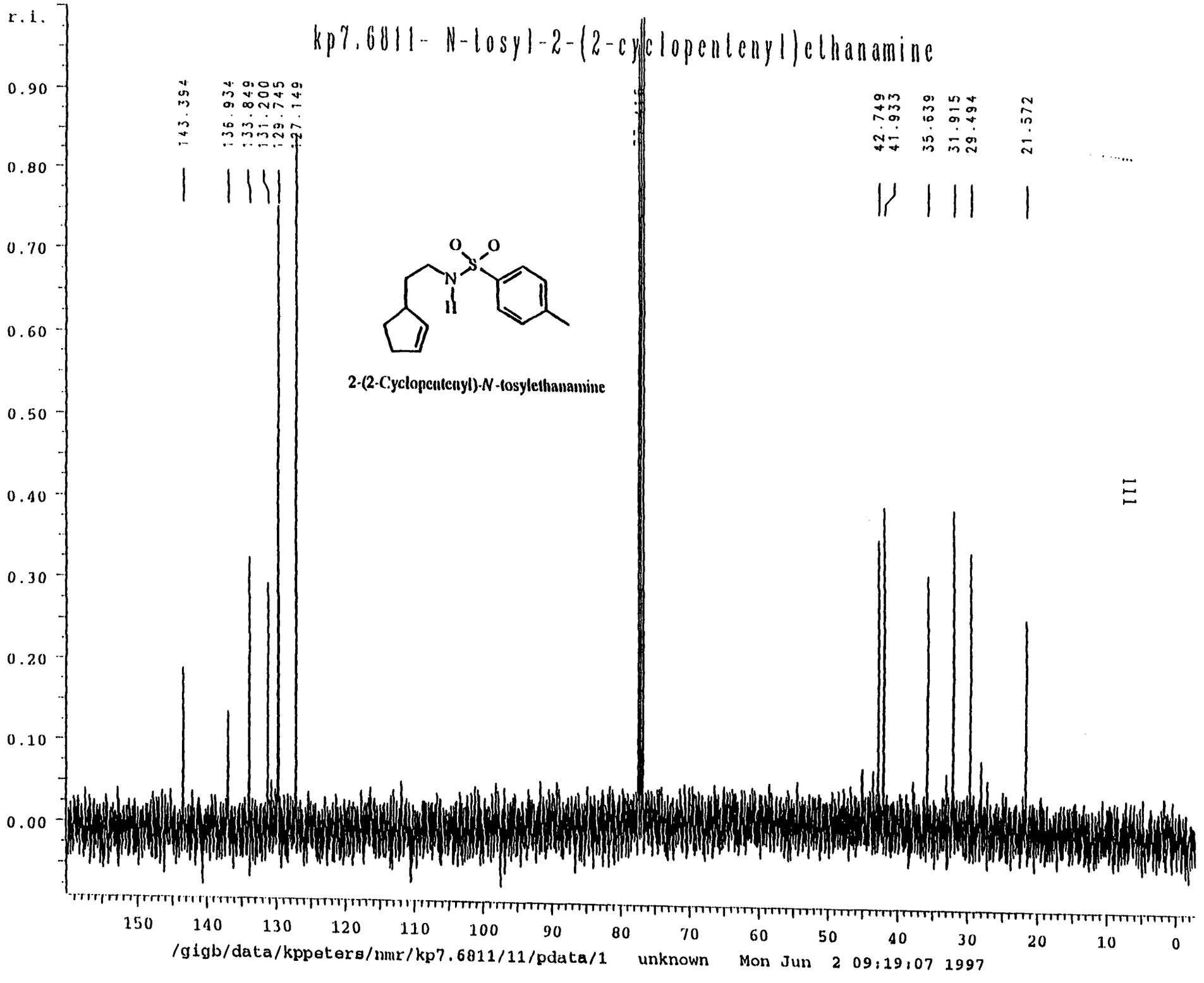
kp7.6811- N-tosyl-2-(2-cyclopentenyl)ethanamine
r.i.
143.394
136.934
133.849
131.200
129.745
127.149
42.749
41.933
35.639
31.915
29.494
21.572
2-(2-Cyclopentenyl)-N-tosylethanamine
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
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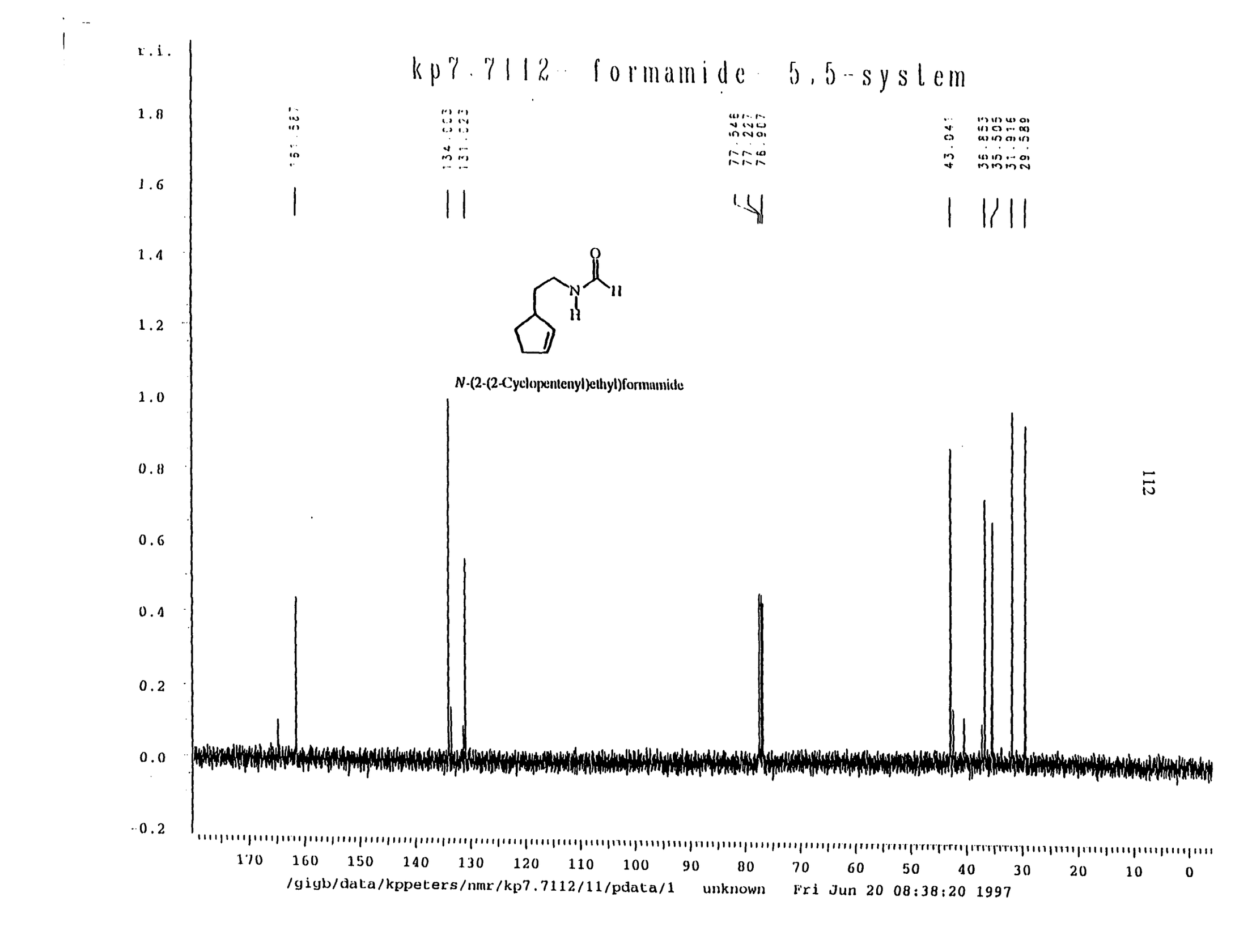
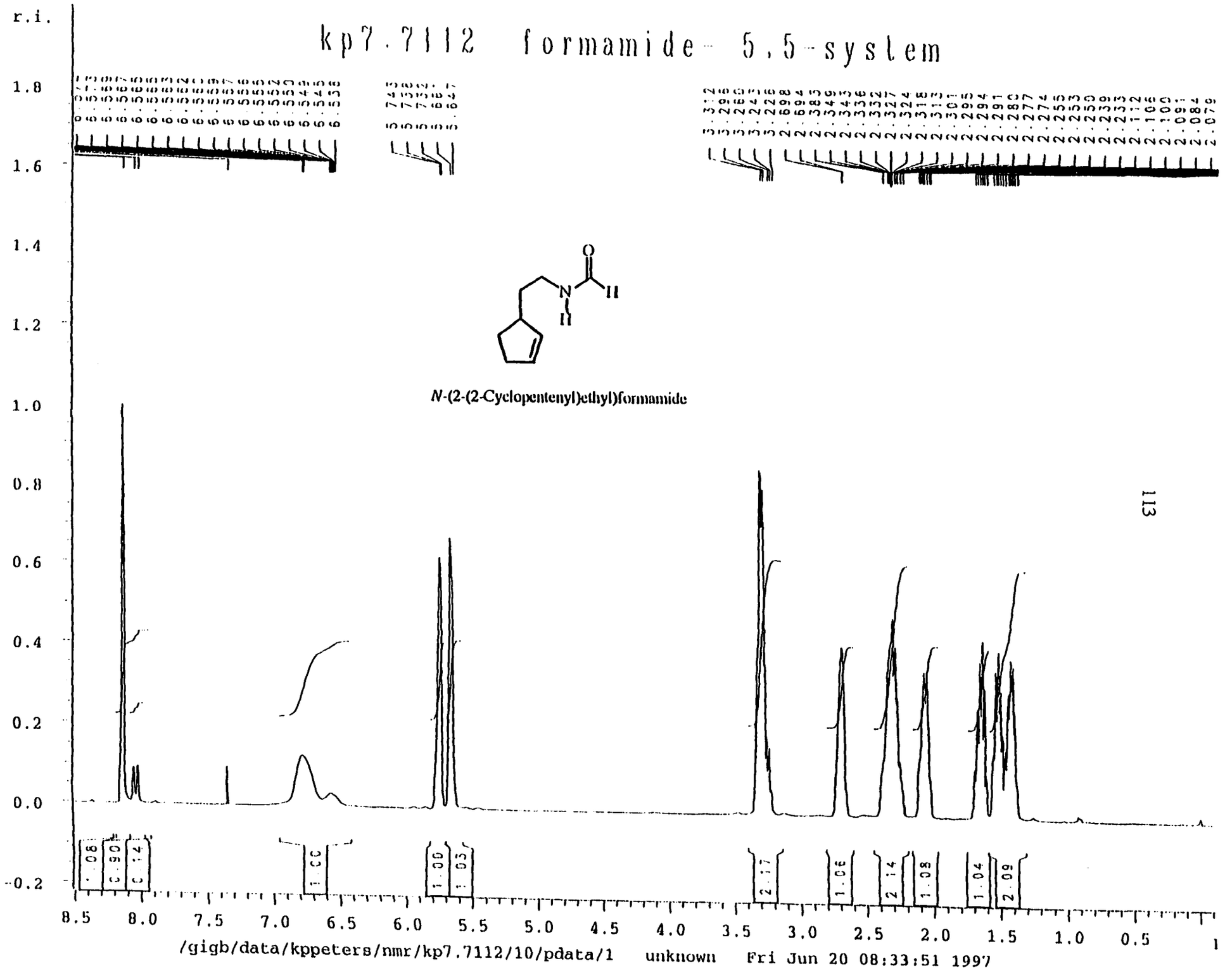

kp7.7112 formamide 5,5-system
r.i.
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
161.887
134.033
131.023
77.546
77.227
76.907
43.041
36.853
35.505
31.916
29.589
N-(2-(2-Cyclopentenyl)ethyl)formamide
112
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
/gigb/data/kppeters/nmr/kp7.7112/11/pdata/1 unknown Fri Jun 20 08:38:20 1997


kp7.7112 formamide- 5,5-system
r.i.
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
N-(2-(2-Cyclopentenyl)ethyl)formamide
113
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
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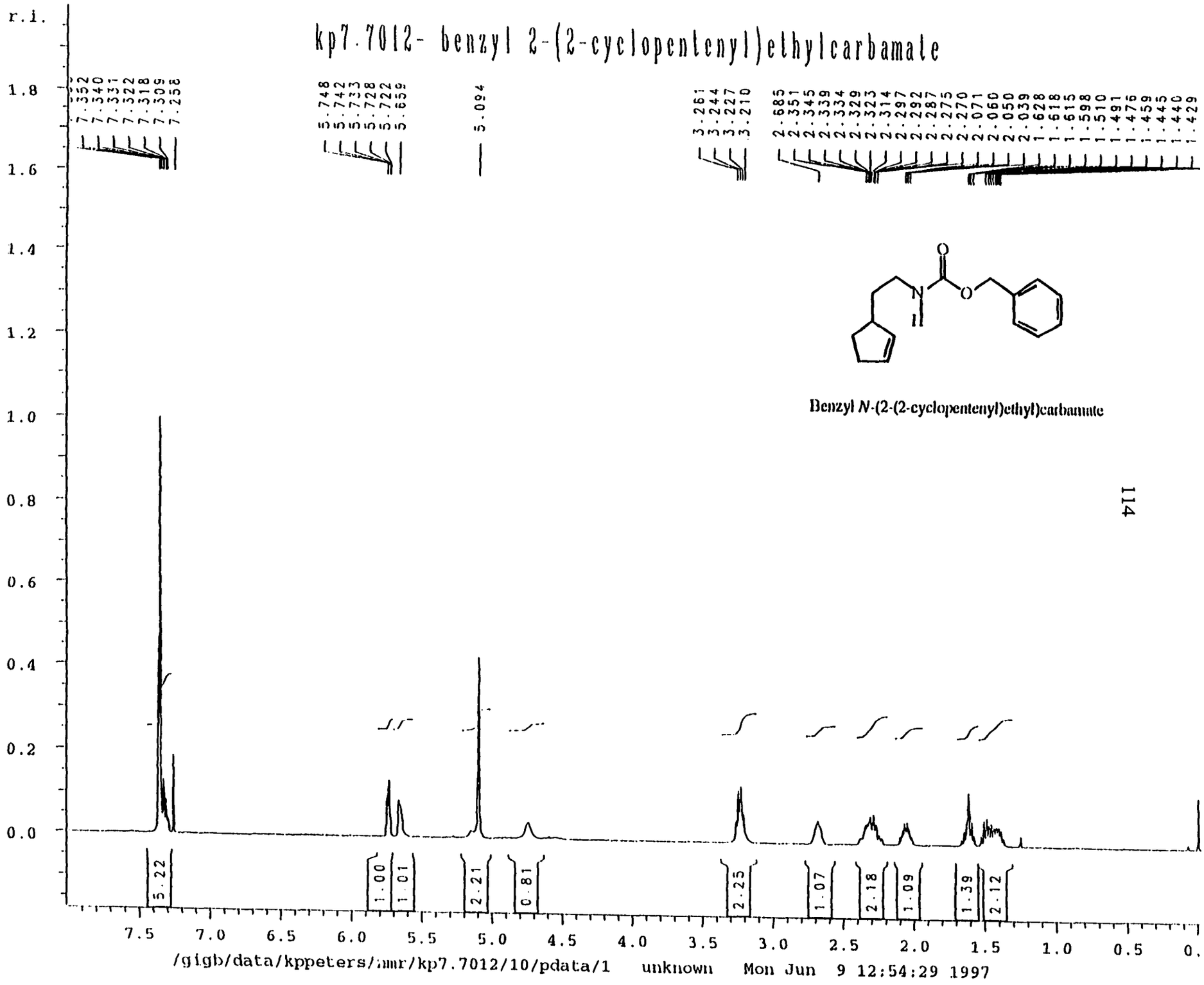
kp7.7012- benzyl 2-(2-cyclopentenyl)ethylcarbamate
r.i.
7.352
7.340
7.331
7.322
7.318
7.309
7.258
5.748
5.742
5.733
5.728
5.722
5.659
5.094
3.261
3.244
3.227
3.210
2.685
2.351
2.345
2.339
2.334
2.329
2.323
2.314
2.297
2.292
2.287
2.275
2.270
2.071
2.060
2.050
2.039
1.628
1.618
1.615
1.598
1.510
1.491
1.476
1.459
1.445
1.440
1.429
Benzyl N-(2-(2-cyclopentenyl)ethyl)carbamate
5.22
1.00
1.01
2.21
0.81
2.25
1.07
2.18
1.09
1.39
2.12
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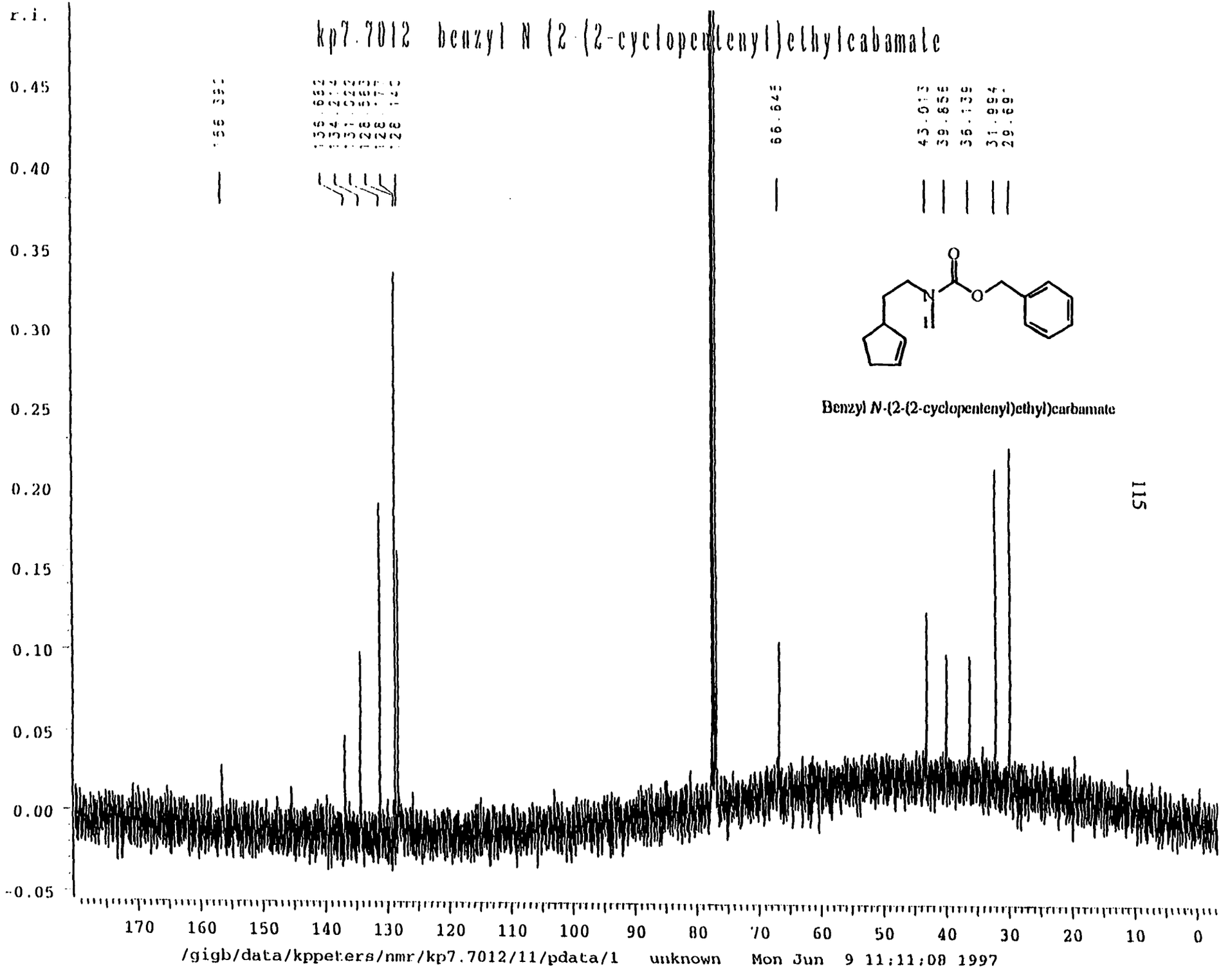
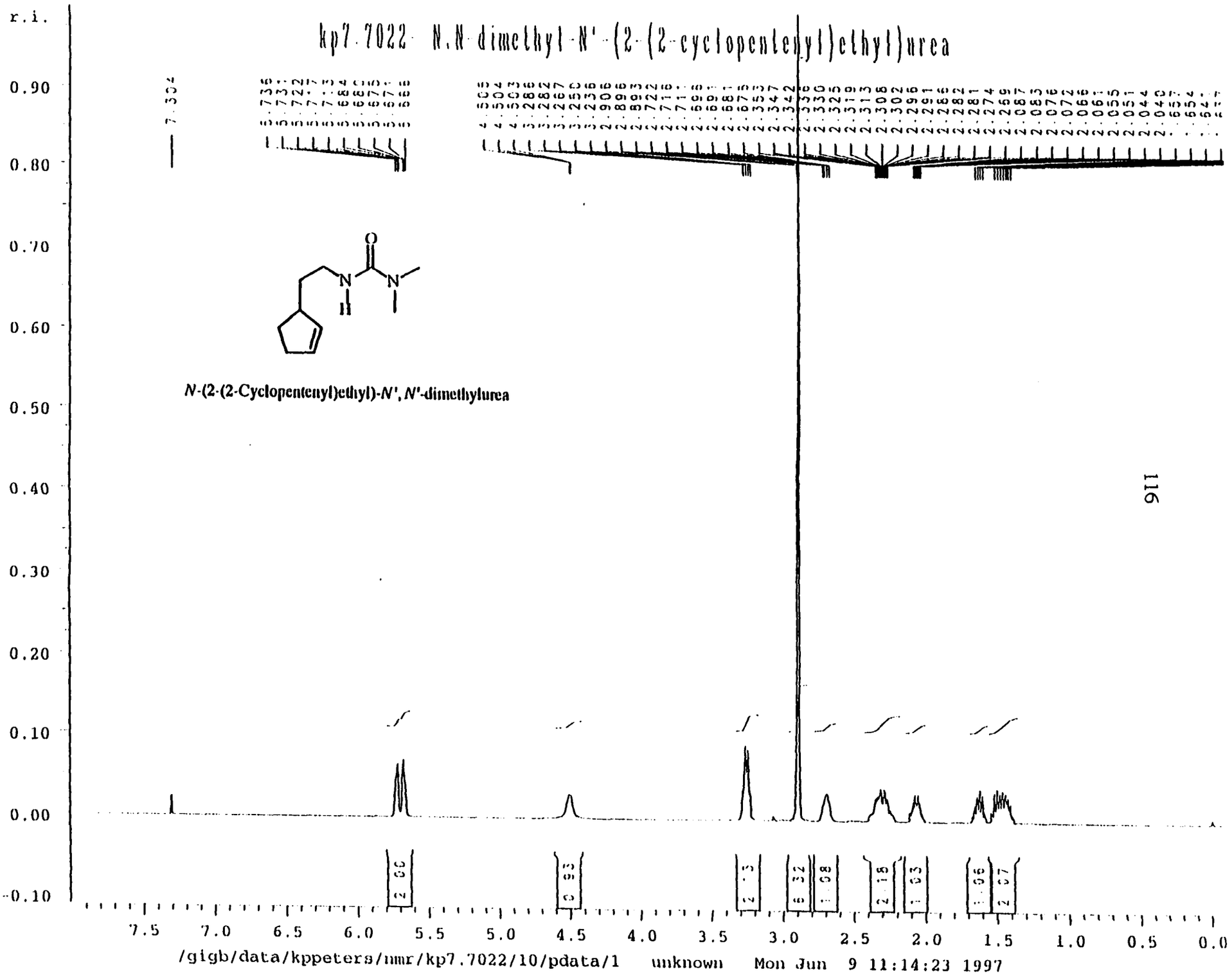


Benzyl *N*-(2-(2-cyclopentenyl)ethyl)carbamate


kp7.7022 N,N-dimethyl-N'-(2-(2-cyclopentenyl)ethyl)urea
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
N-(2-(2-Cyclopentenyl)ethyl)-N',N'-dimethylurea
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
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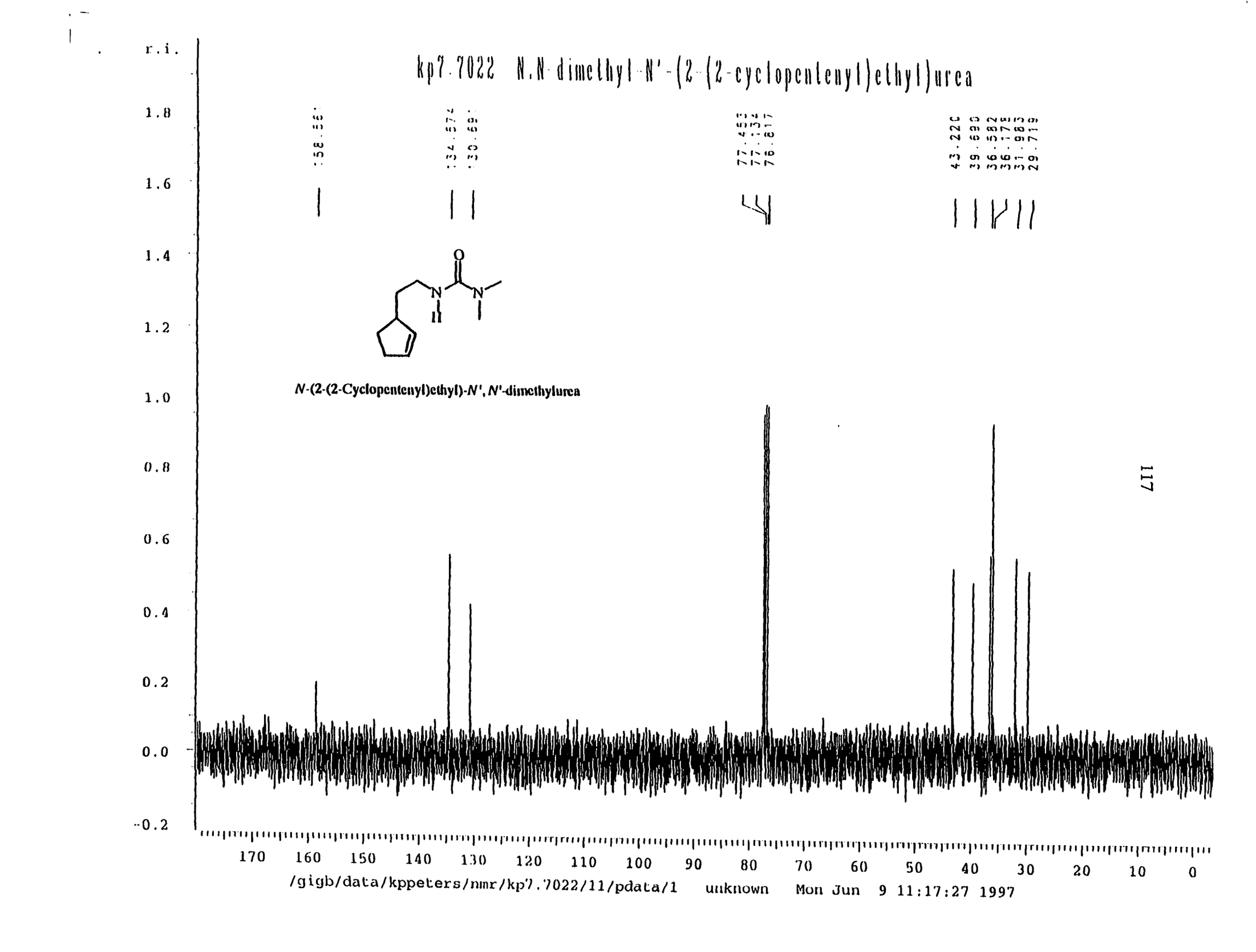
kp7.7022 N,N-dimethyl-N'-(2-(2-cyclopentenyl)ethyl)urea
r.i.
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
158.881
134.574
130.691
77.455
77.134
76.817
43.220
39.695
36.582
36.178
31.983
29.719
N-(2-(2-Cyclopentenyl)ethyl)-N',N'-dimethylurea
117
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
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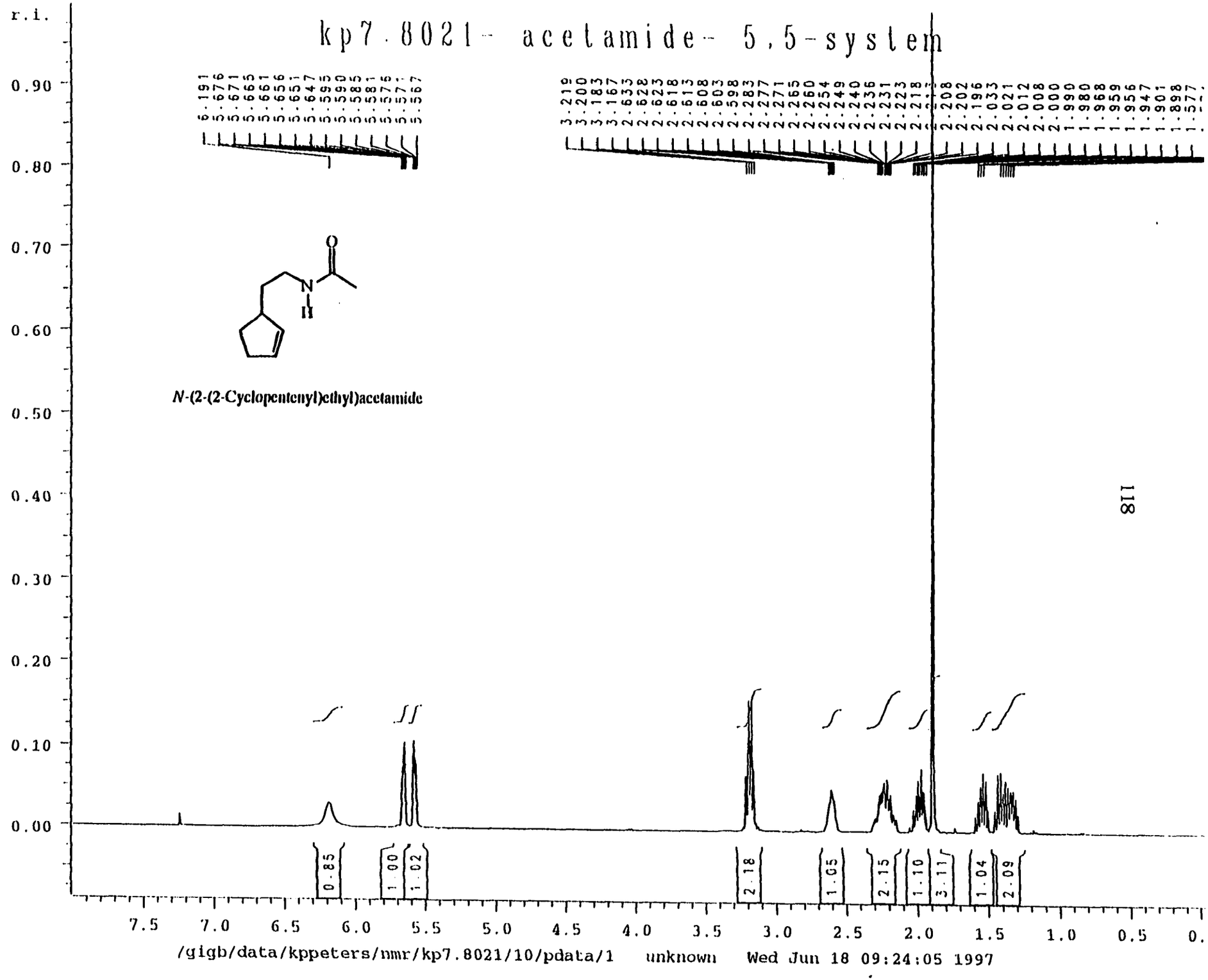
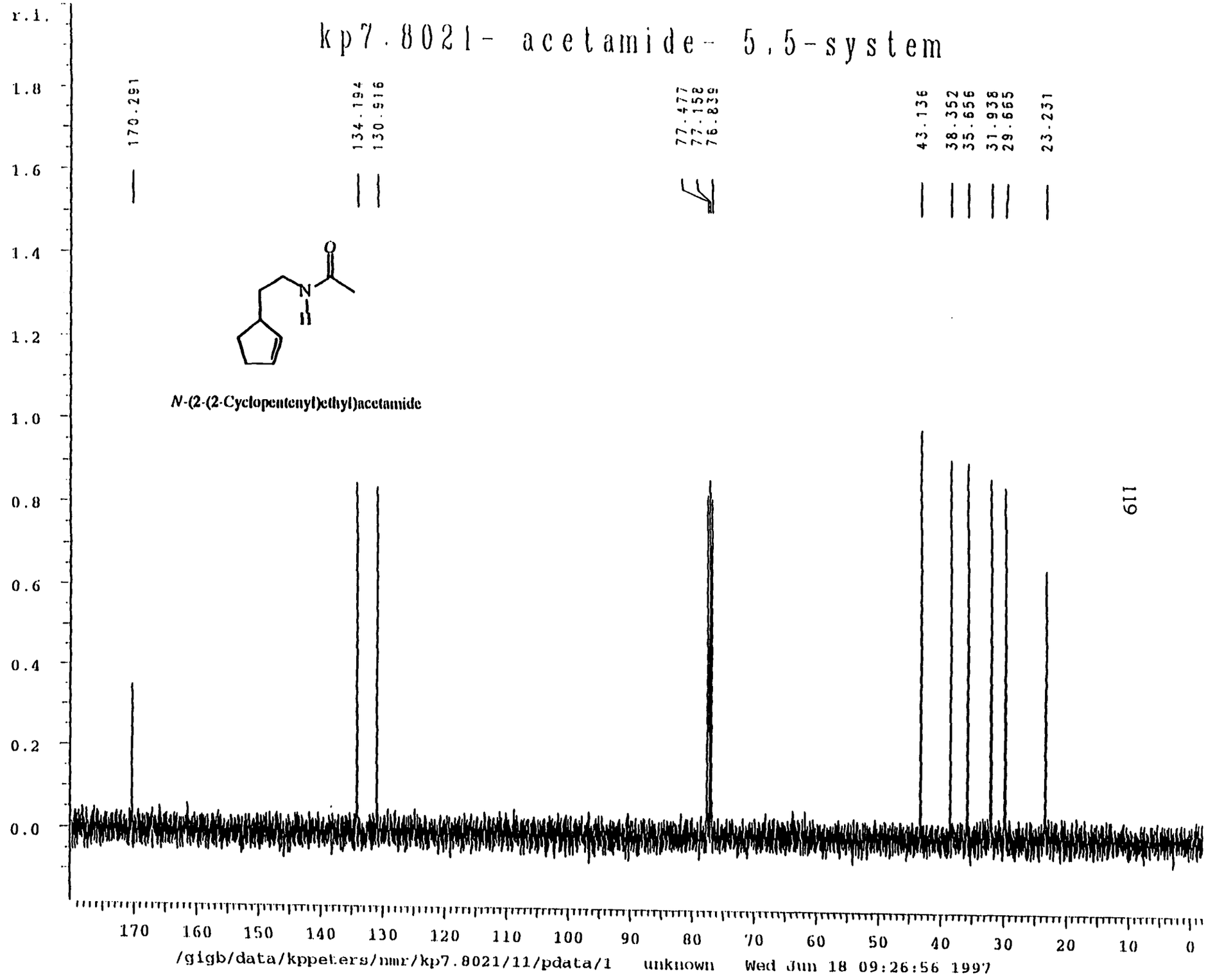
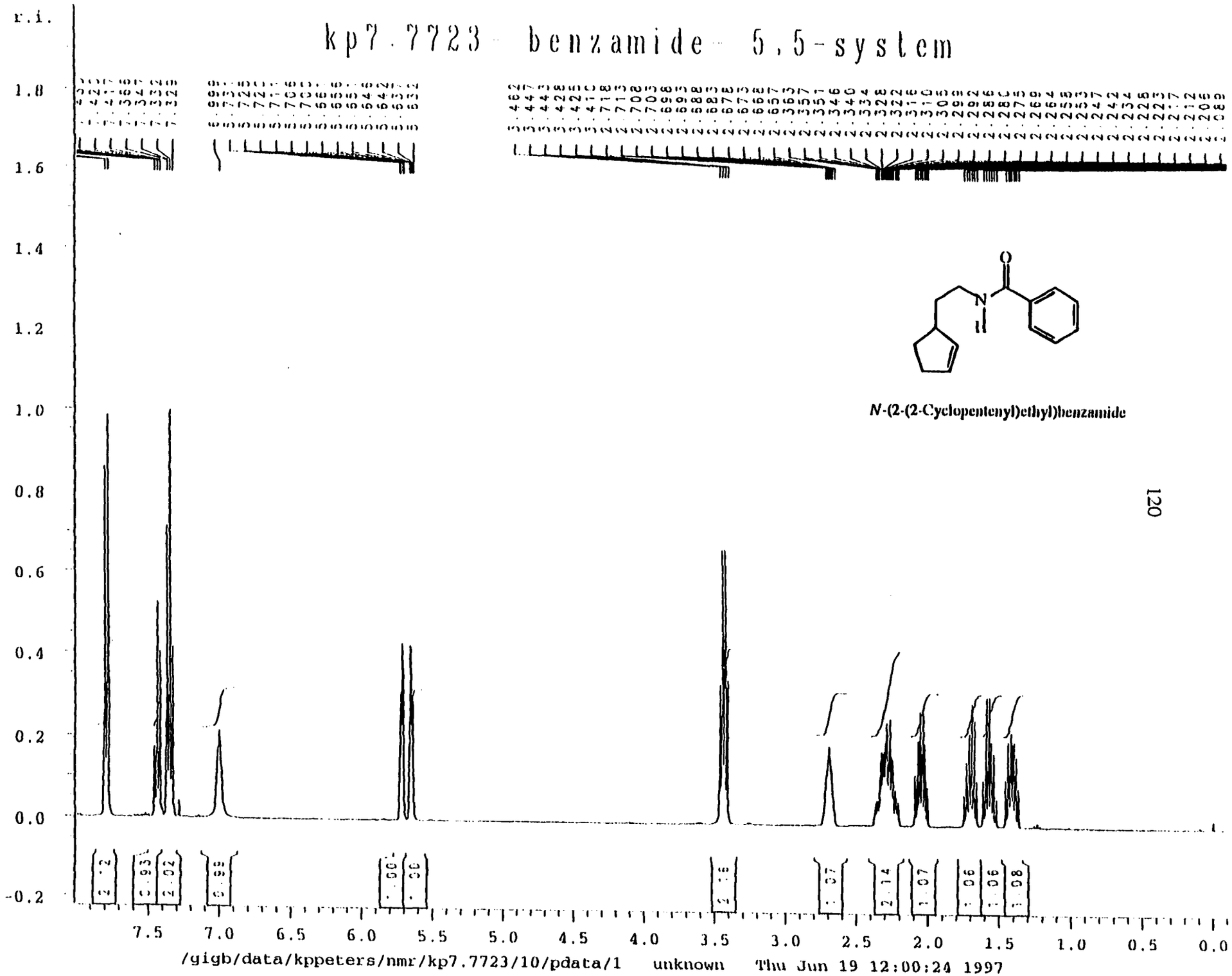
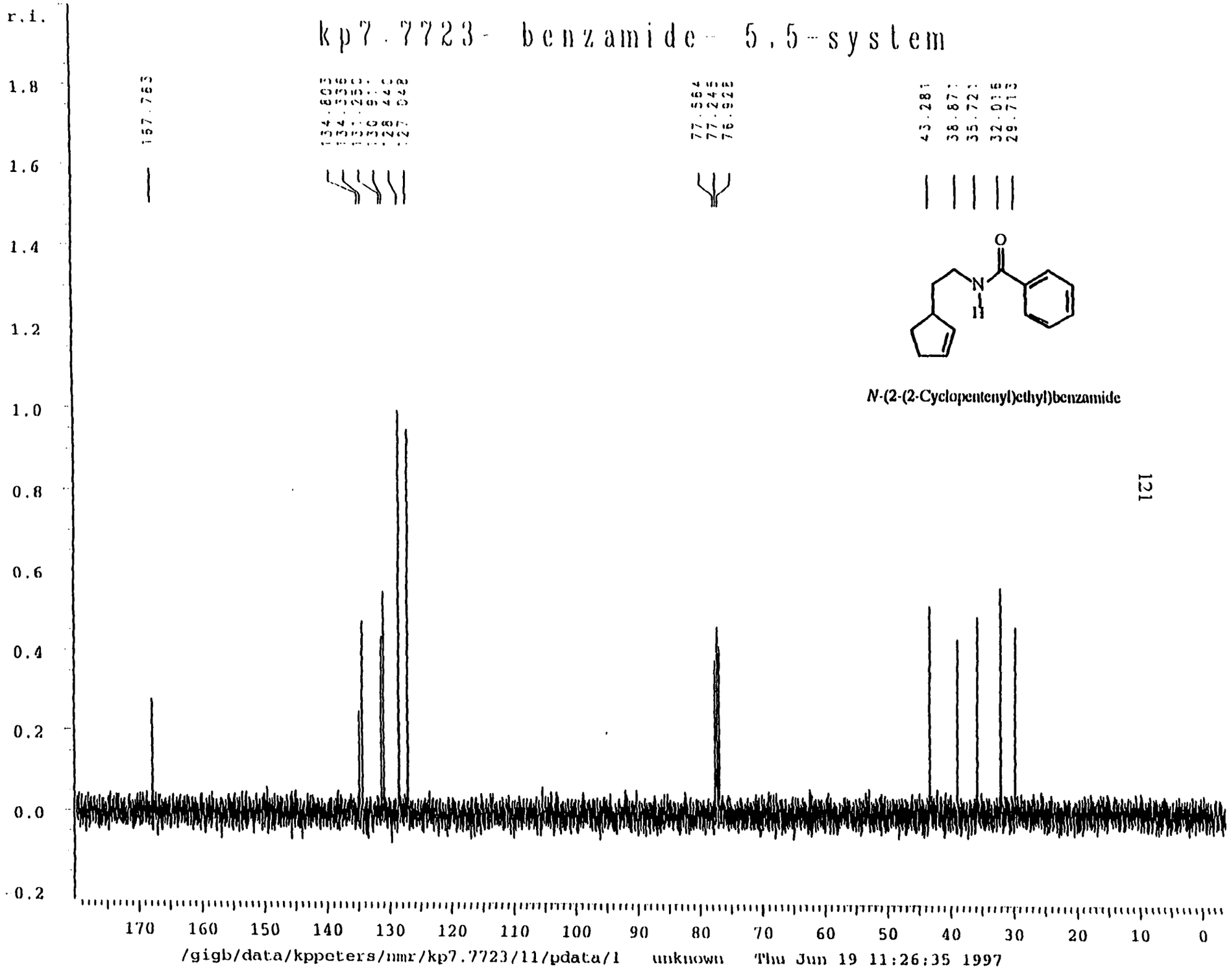


N-(2-(2-Cyclopentenyl)ethyl)acetamide


kp7.8021- acetamide- 5,5-system
r.i.
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
170.291
134.194
130.916
77.477
77.158
76.839
43.136
38.352
35.656
31.938
29.665
23.231
O
N
N-(2-(2-Cyclopentenyl)ethyl)acetamide
119
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
/gigb/data/kppeters/nmr/kp7.8021/11/pdata/1 unknown Wed Jun 18 09:26:56 1997

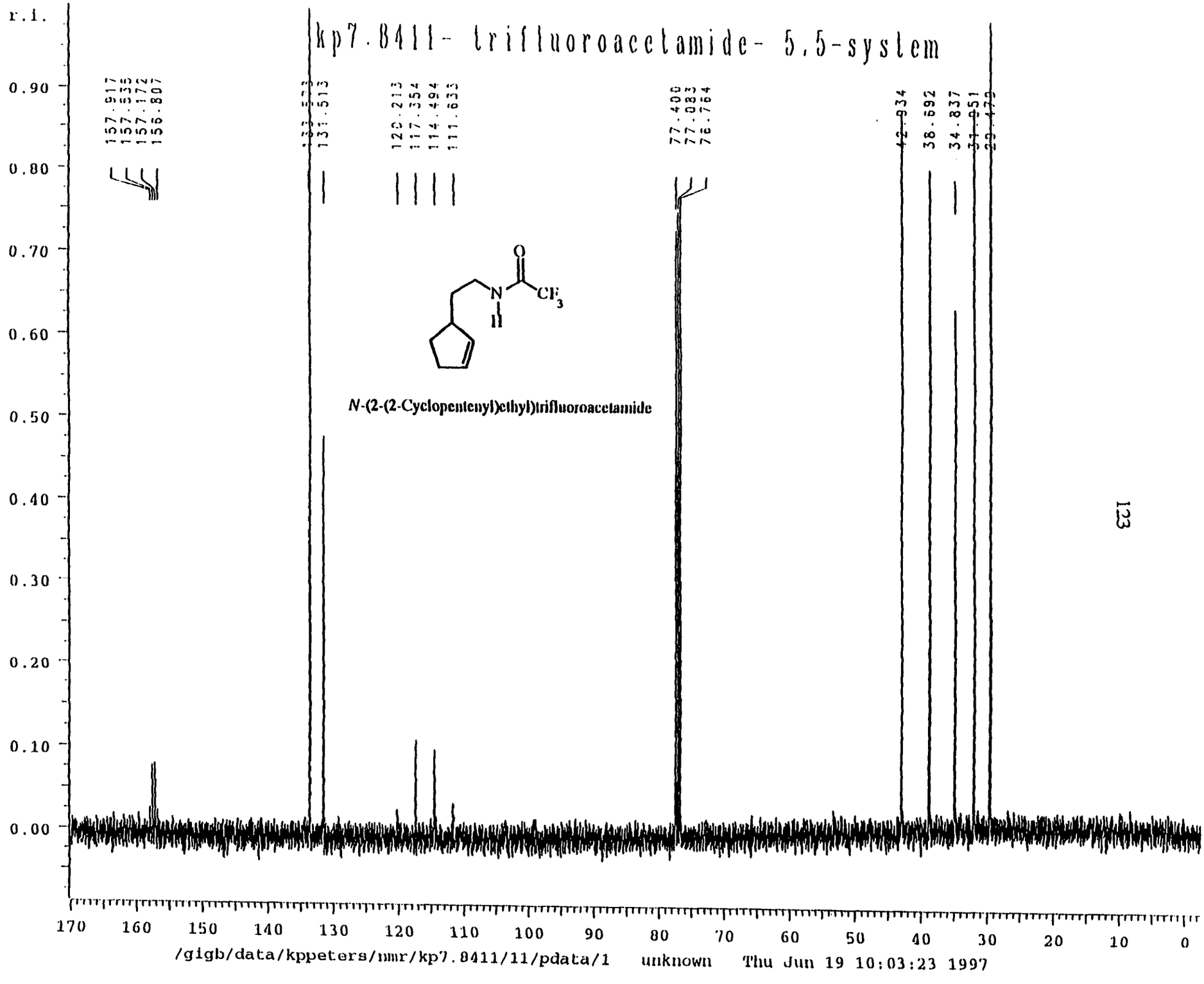


N-(2-(2-Cyclopentenyl)ethyl)benzamide


kp7.7723- benzamide- 5,5-system
r.i.
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
167.763
134.805
134.336
131.251
129.944
128.487
127.042
77.564
77.245
76.926
43.281
38.871
35.721
32.016
29.713
O
N
H
N-(2-(2-Cyclopentenyl)ethyl)benzamide
121
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
/gigb/data/kppeters/nmr/kp7.7723/11/pdata/1 unknown Thu Jun 19 11:26:35 1997

kp7.8511- trifluoroacetamide- 5.5-system

N-(2-(2-Cyclopentenyl)ethyl)trifluoroacetamide


kp7.8411- trifluoroacetamide- 5.5-system
r.1.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
157.917
157.533
157.172
156.807
131.513
129.213
117.354
114.494
111.633
77.400
77.083
76.764
42.934
38.692
34.837
31.951
29.479
O
N
CF3
N-(2-(2-Cyclopentenyl)ethyl)trifluoroacetamide
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
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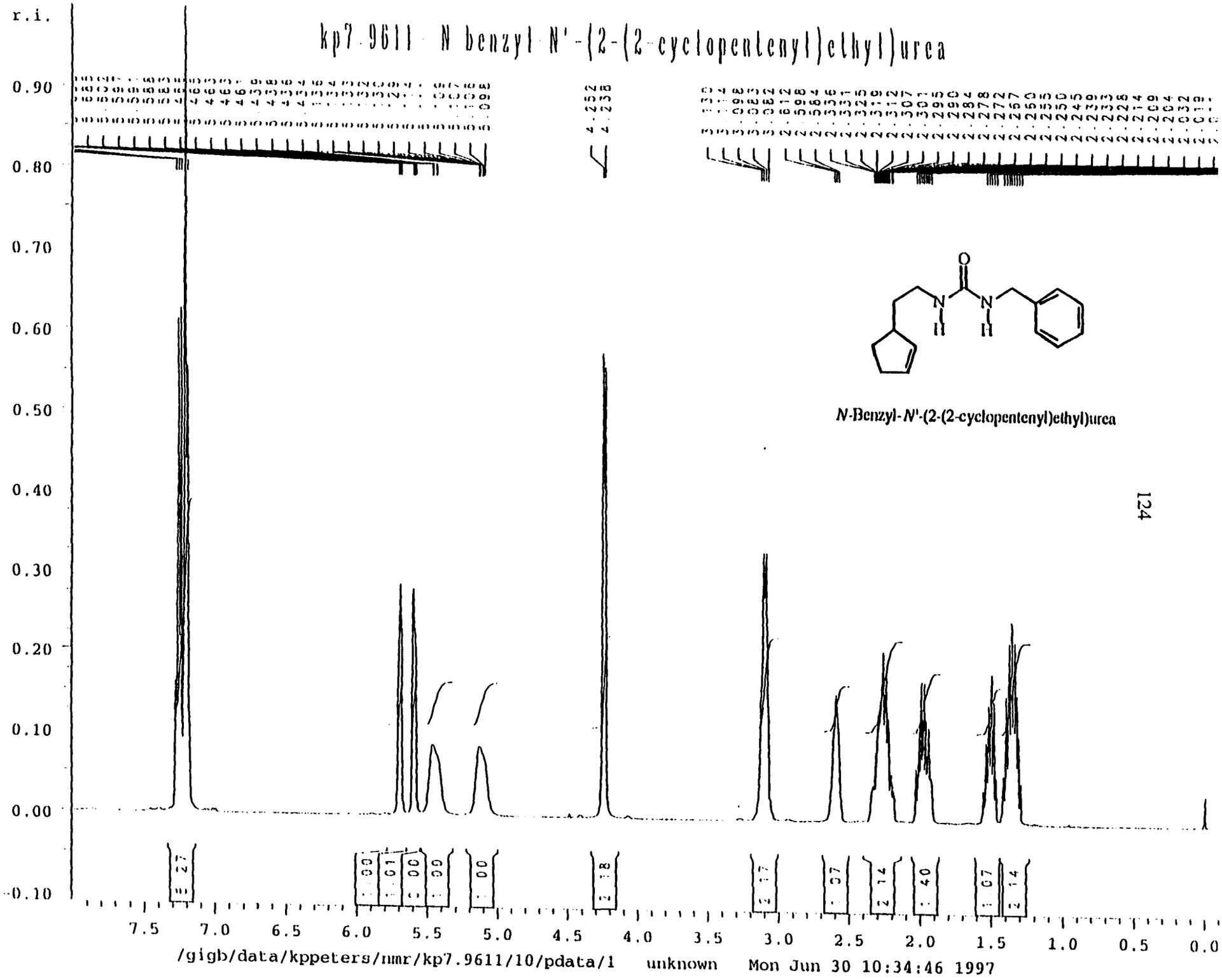
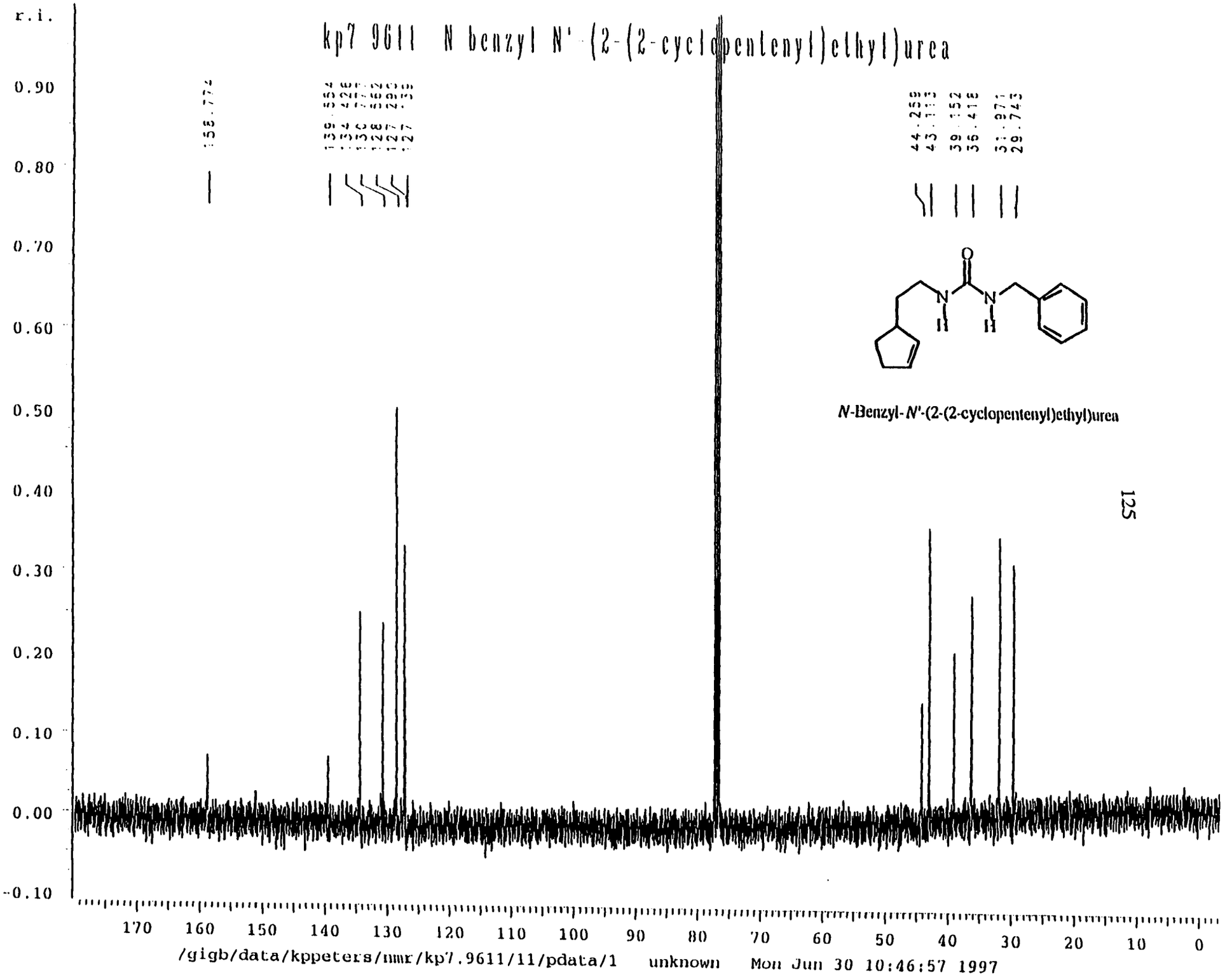
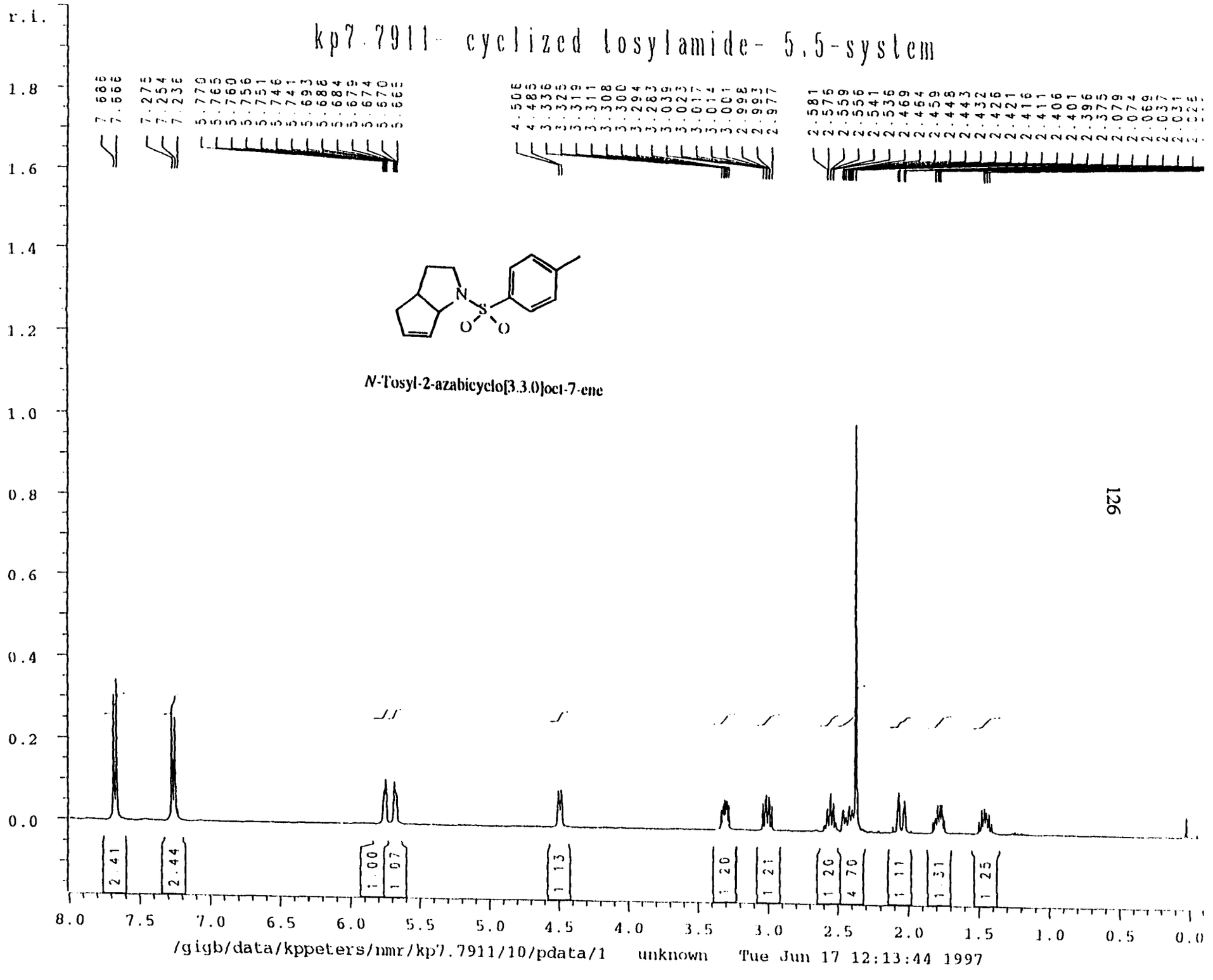


N-Benzyl-*N*'-(2-(2-cyclopentenyl)ethyl)urea


kp7 9611 N benzyl N' (2-(2-cyclopentenyl)ethyl)urea
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
158.772
139.554
134.426
128.562
127.291
127.133
44.259
43.113
39.152
36.418
31.971
29.743
O
N
H
N
H
N-Benzyl-N'-(2-(2-cyclopentenyl)ethyl)urea
125
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
/gigb/data/kppeters/nmr/kp7.9611/11/pdata/1 unknown Mon Jun 30 10:46:57 1997


kp7.7911- cyclized tosylamide- 5,5-system
r.i.
7.686
7.666
7.275
7.254
7.236
5.779
5.765
5.760
5.756
5.751
5.746
5.741
5.693
5.686
5.684
5.679
5.674
5.670
5.665
4.506
4.485
3.336
3.325
3.319
3.311
3.308
3.300
3.294
3.283
3.039
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3.014
3.001
2.998
2.993
2.977
2.581
2.576
2.559
2.556
2.541
2.536
2.469
2.464
2.459
2.448
2.443
2.432
2.426
2.421
2.416
2.411
2.406
2.401
2.396
2.375
2.079
2.074
2.069
2.037
2.031
N
S
O
O
N-Tosyl-2-azabicyclo[3.3.0]oct-7-ene
2.41
2.44
1.00
1.07
1.13
1.20
1.21
1.26
4.70
1.11
1.31
1.25
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
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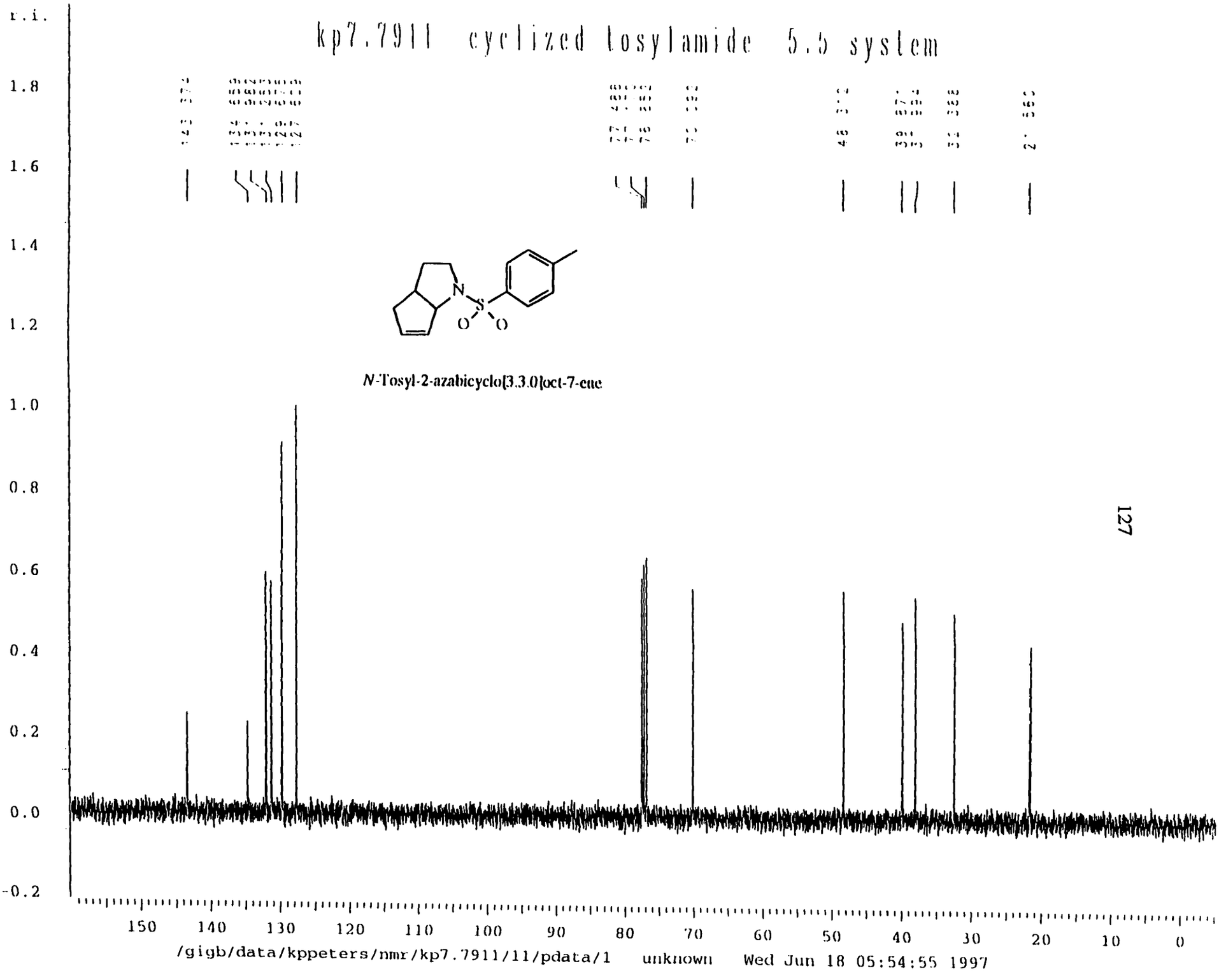
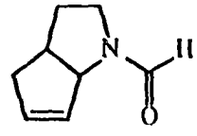
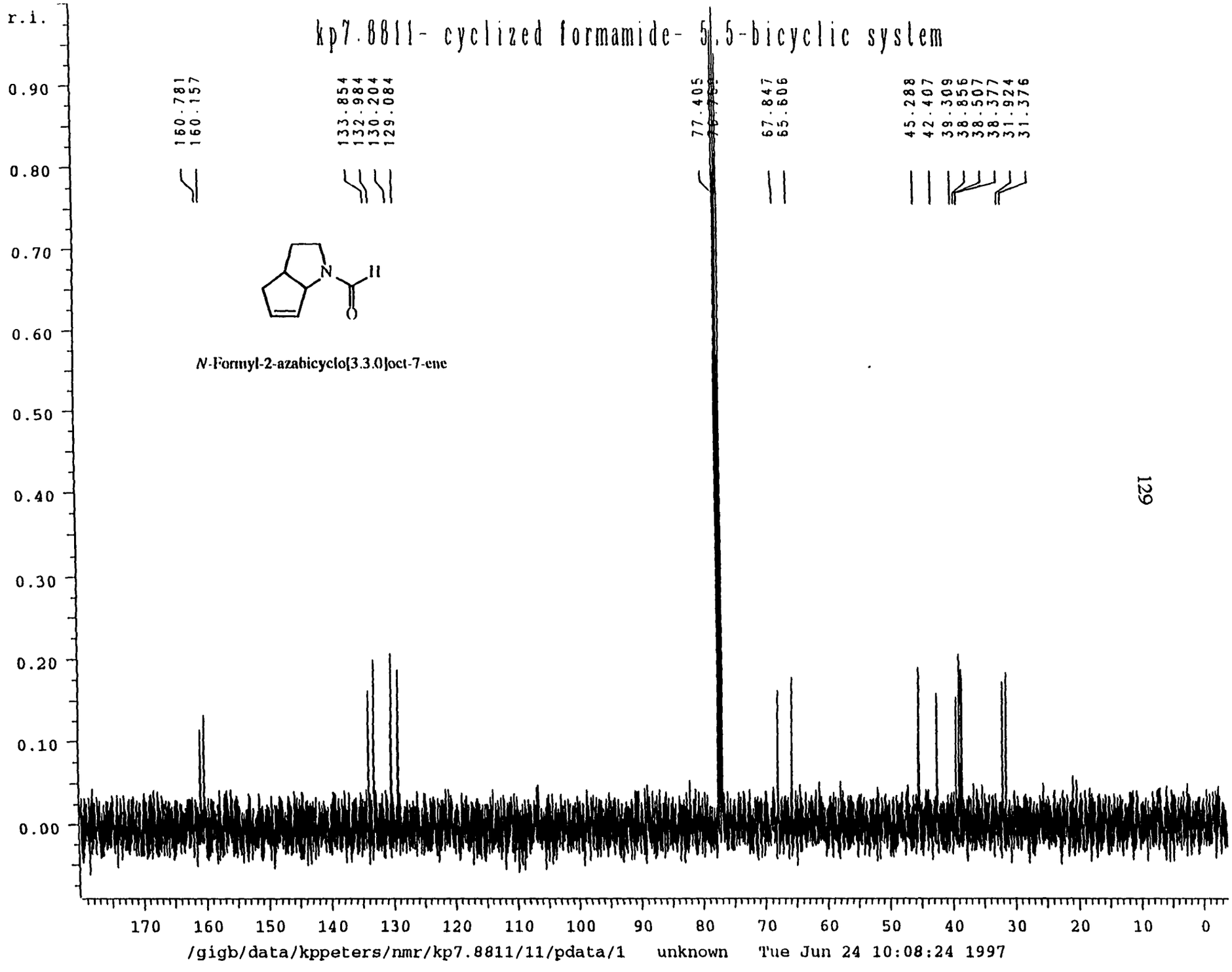

kp7.7911 cyclized tosylamide 5.5 system
r.i.
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
N
S
O
O
N-Tosyl-2-azabicyclo[3.3.0]oct-7-ene
127
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
/gigb/data/kppeters/nmr/kp7.7911/11/pdata/1 unknown Wed Jun 18 05:54:55 1997

kp7.8811 - cyclized formamide - 5,5-bicyclic system



N-Formyl-2-azabicyclo[3.3.0]oct-7-ene


kp7.8811- cyclized formamide- 5,5-bicyclic system
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
160.781
160.157
133.854
132.984
130.204
129.084
77.405
67.847
65.606
45.288
42.407
39.309
38.856
38.507
38.377
31.924
31.376
N
H
O
N-Formyl-2-azabicyclo[3.3.0]oct-7-ene
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
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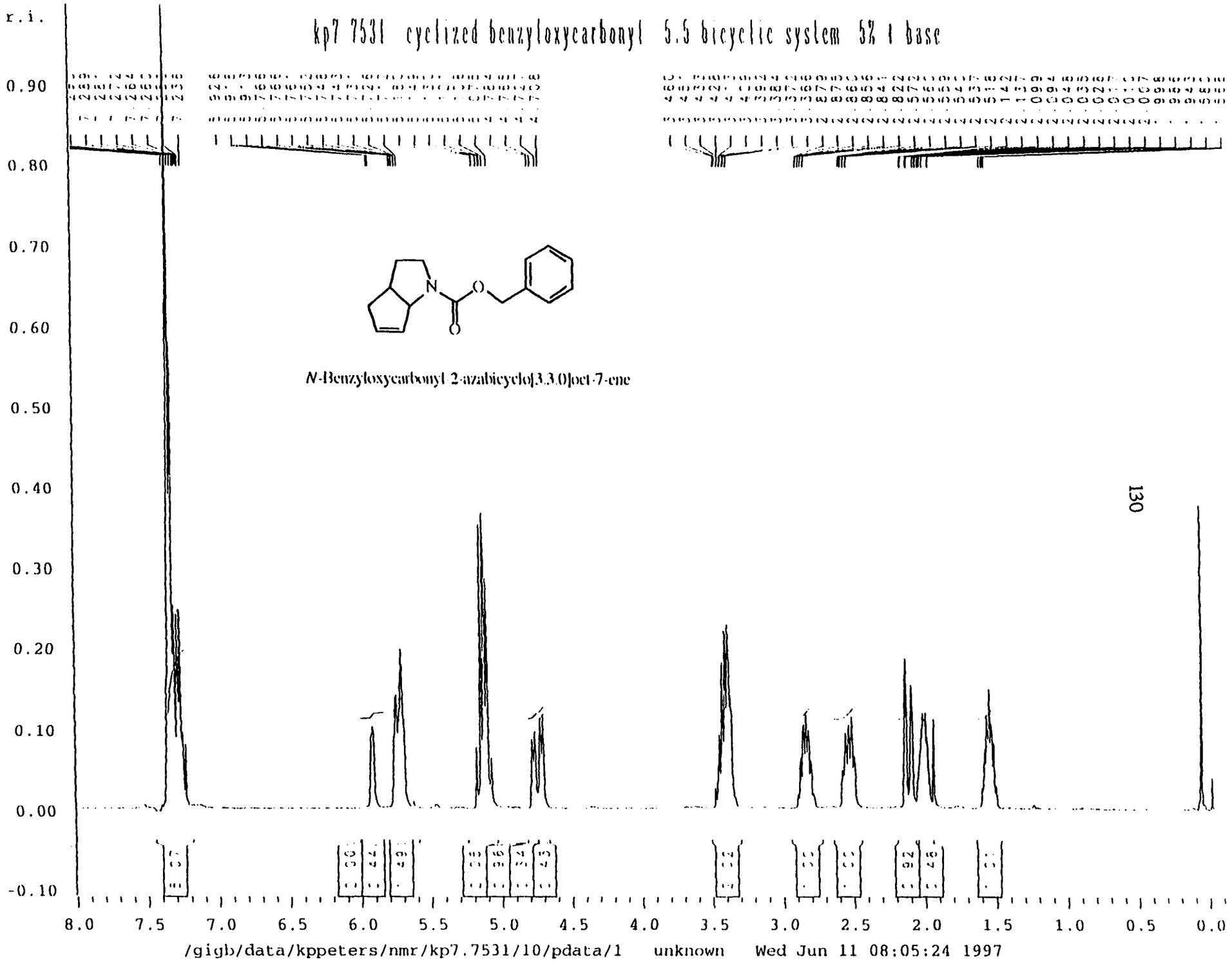
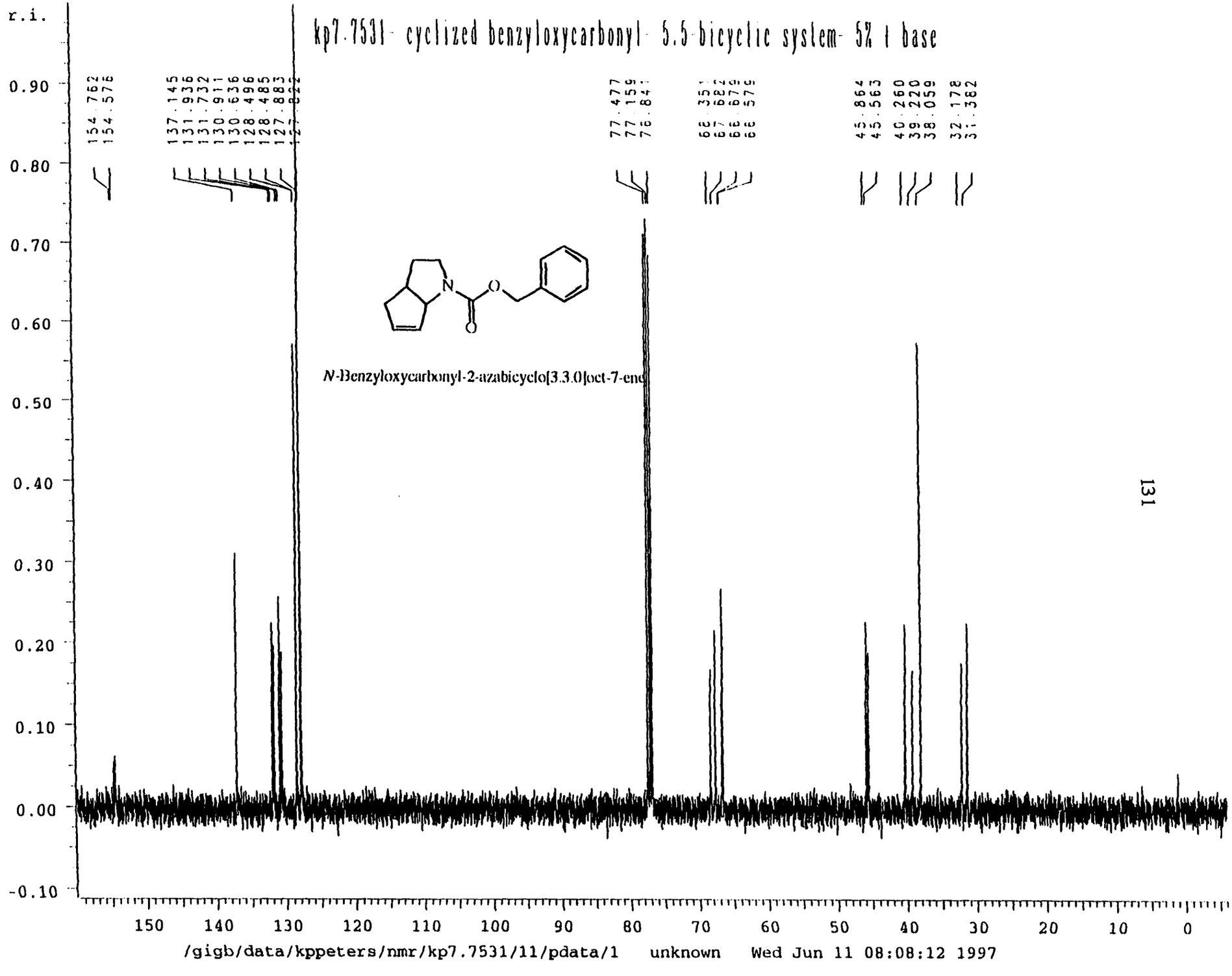
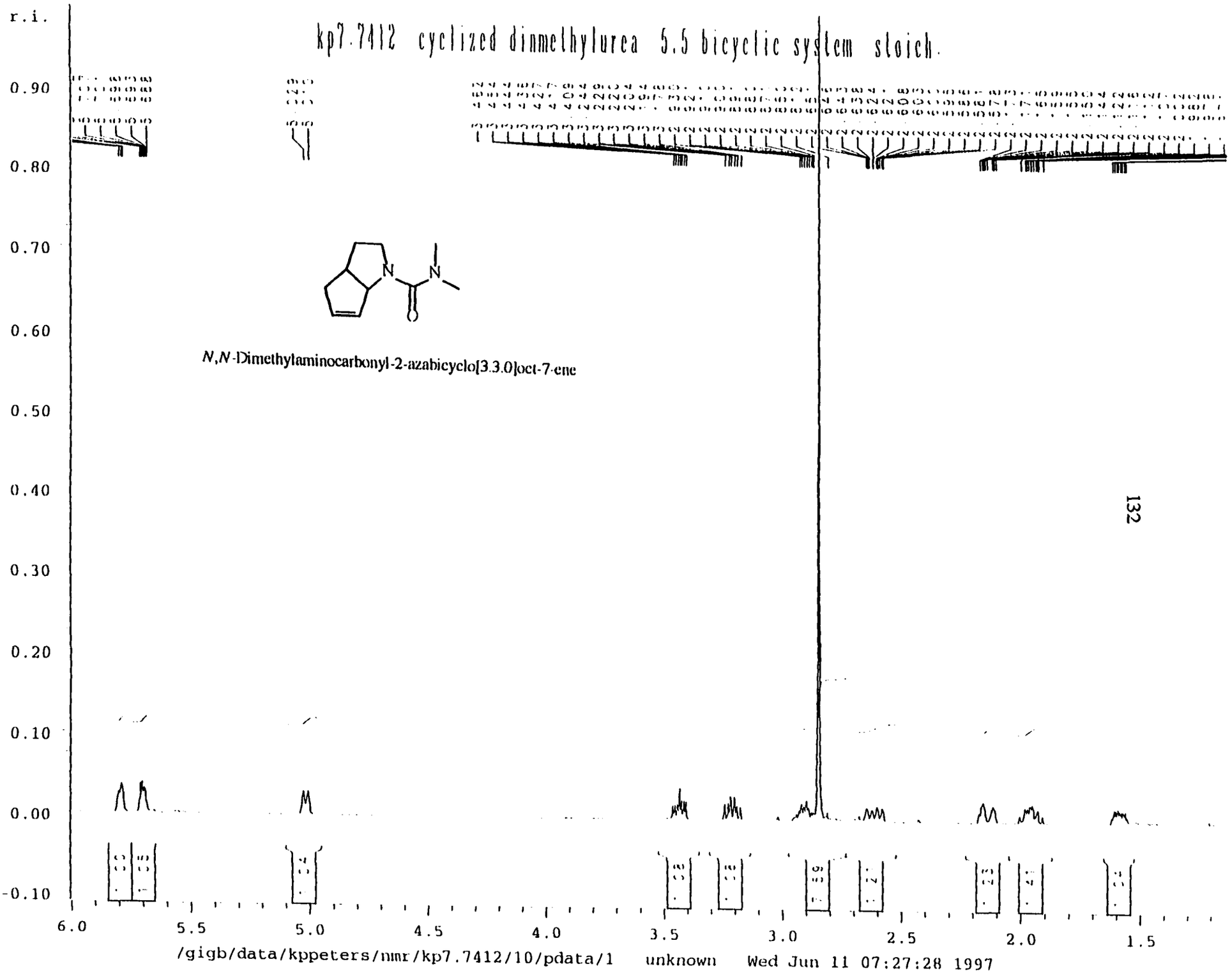


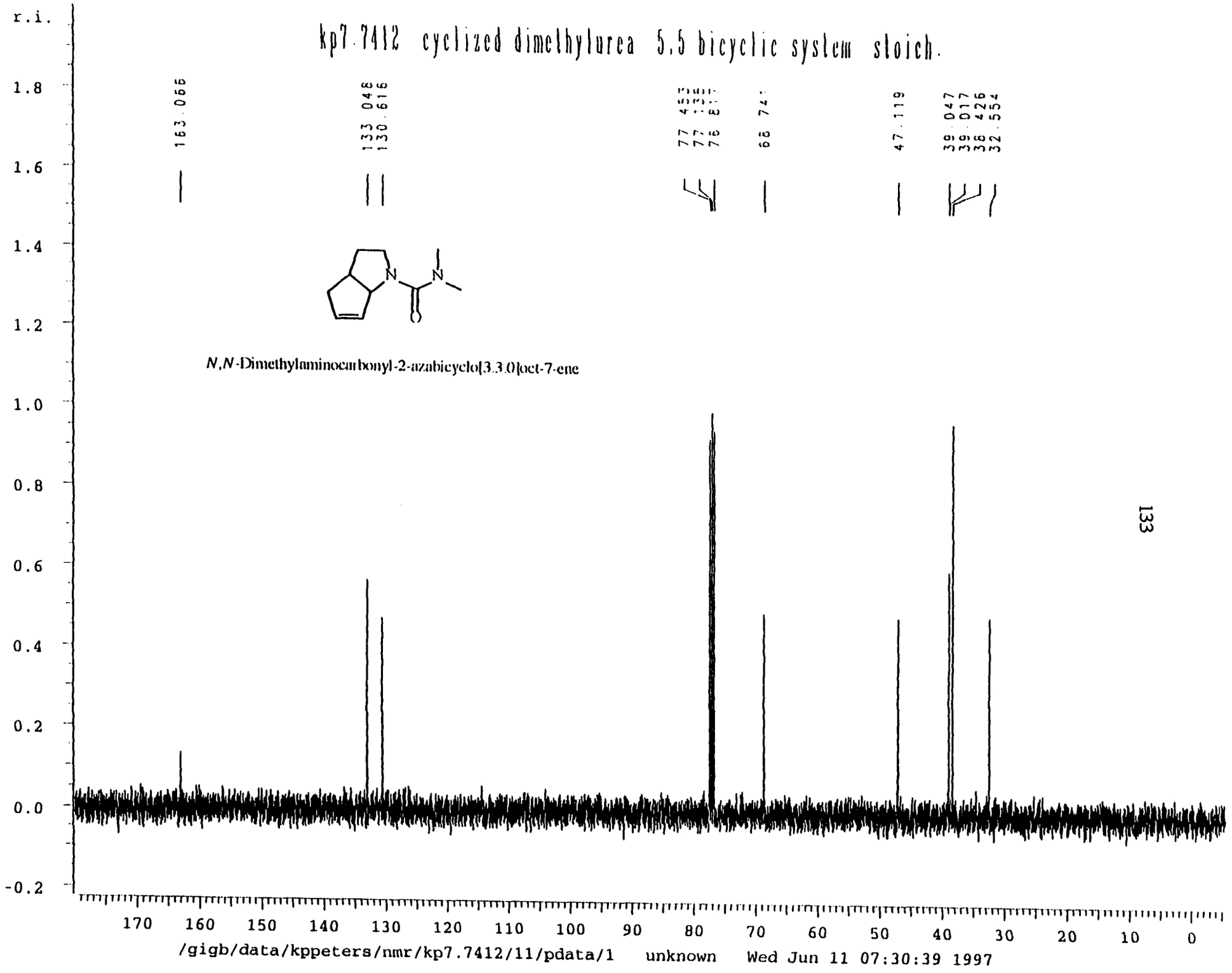
N-Benzyloxycarbonyl-2-azabicyclo[3.3.0]oct-7-ene

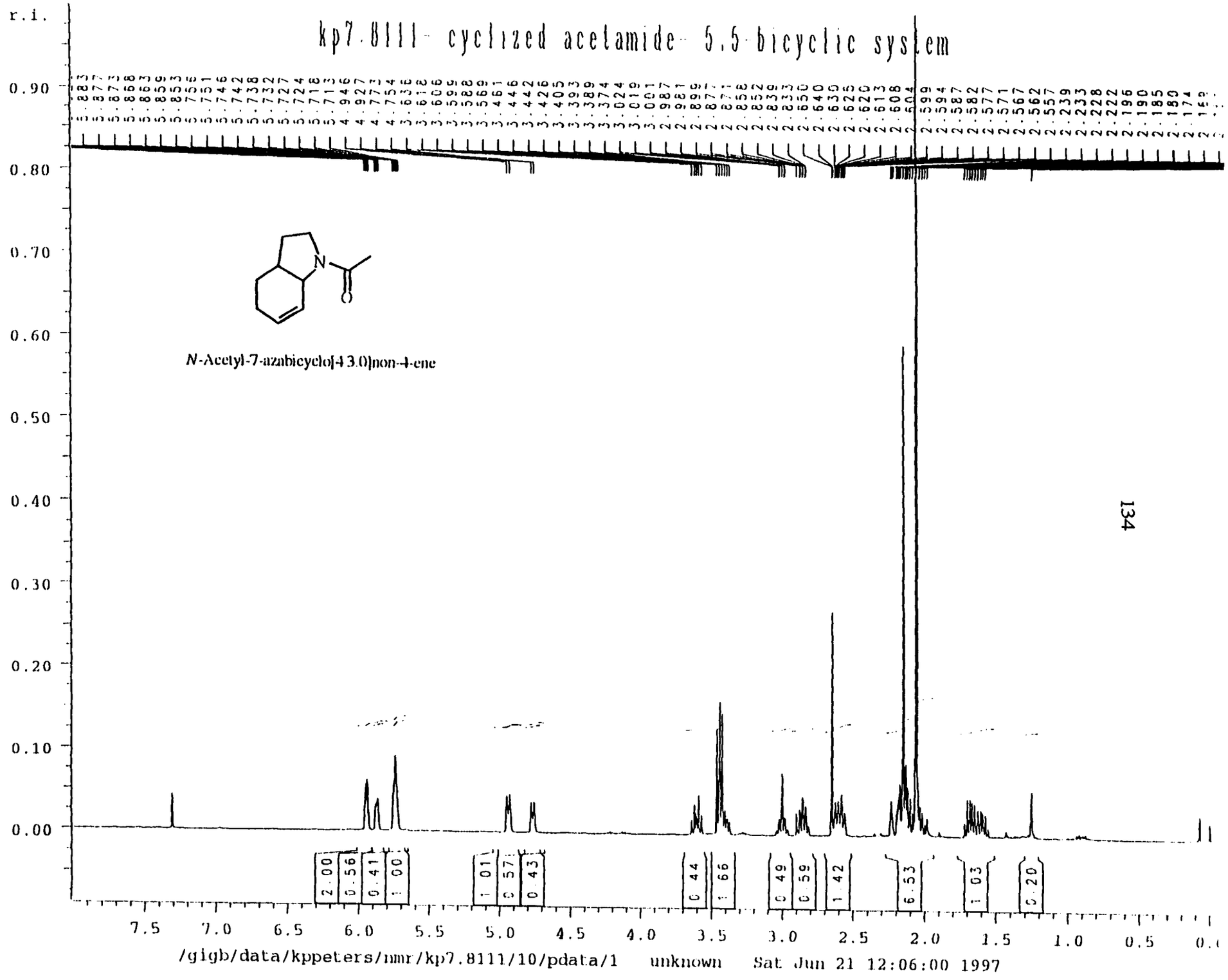


N-Benzyloxycarbonyl-2-azabicyclo[3.3.0]oct-7-ene



N,N-Dimethylaminocarbonyl-2-azabicyclo[3.3.0]oct-7-ene


kp7.7412 cyclized dimethylurea 5.5 bicyclic system stoich.
163.066
133.048
130.616
77.453
77.135
76.817
68.741
47.119
39.047
39.017
38.426
32.554
r.i.
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
N,N-Dimethylaminocarbonyl-2-azabicyclo[3.3.0]oct-7-ene
133
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
/gigb/data/kppeters/nmr/kp7.7412/11/pdata/1 unknown Wed Jun 11 07:30:39 1997


kp7.8111- cyclized acetamide- 5,5-bicyclic system
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
N
O
N-Acetyl-7-azabicyclo[4.3.0]non-4-ene
2.00
0.56
0.41
1.00
1.01
0.57
0.43
0.44
1.66
0.49
0.59
1.42
6.53
1.03
0.20
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
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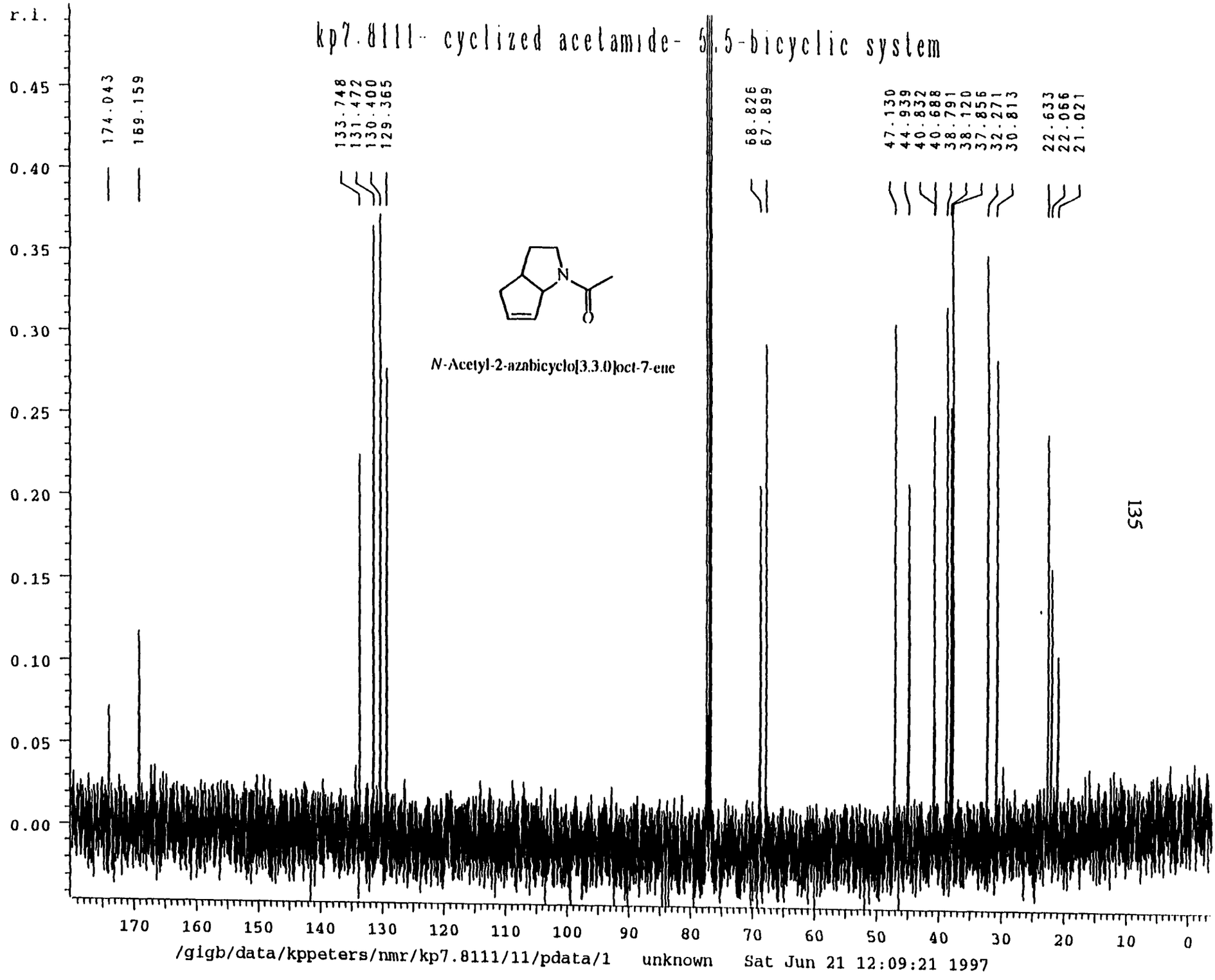
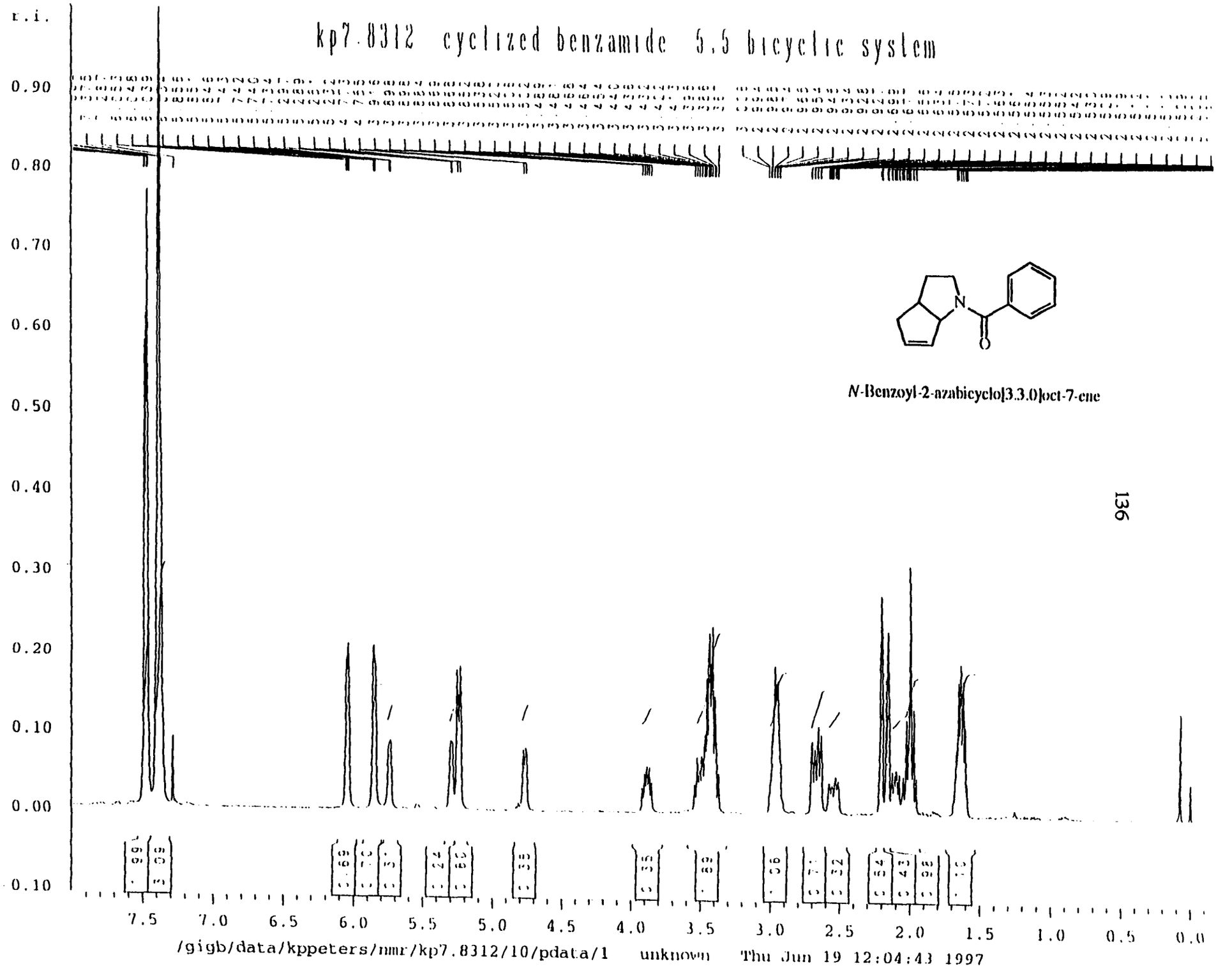
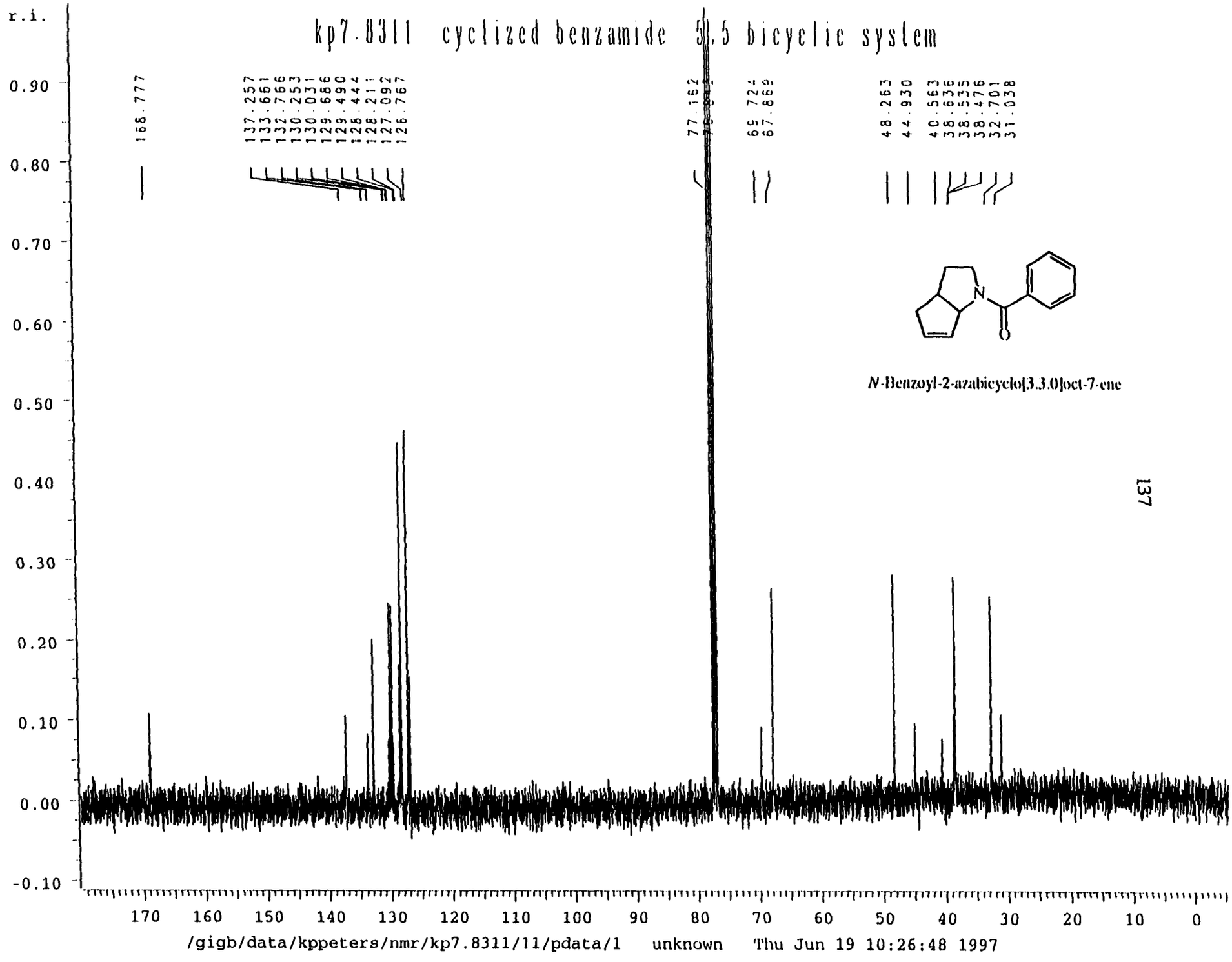

kp7.8111- cyclized acetamide- 5,5-bicyclic system
r.i.
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
174.043
169.159
133.748
131.472
130.400
129.365
68.826
67.899
47.130
44.939
40.832
40.688
38.791
38.120
37.856
32.271
30.813
22.633
22.066
21.021
N
O
N-Acetyl-2-azabicyclo[3.3.0]oct-7-ene
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
/gigb/data/kppeters/nmr/kp7.8111/11/pdata/1 unknown Sat Jun 21 12:09:21 1997
135



N-Benzoyl-2-azabicyclo[3.3.0]oct-7-ene


kp7.8311 cyclized benzamide 5,5 bicyclic system
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
168.777
137.257
133.661
132.766
130.253
130.031
129.686
129.490
128.444
128.211
127.092
126.767
77.162
69.724
67.869
48.263
44.930
40.563
38.636
38.535
38.476
32.701
31.038
N
O
N-Benzoyl-2-azabicyclo[3.3.0]oct-7-ene
137
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
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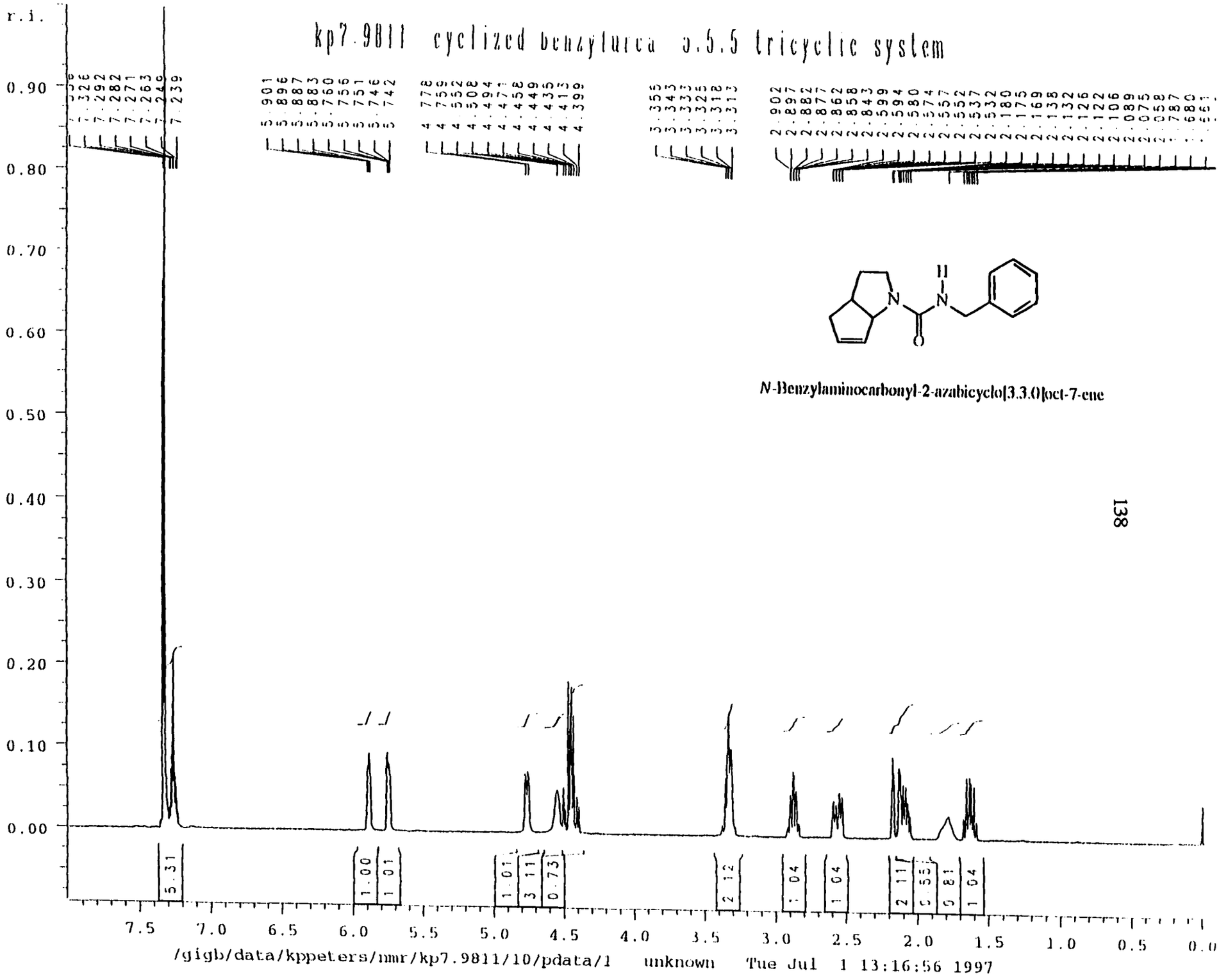
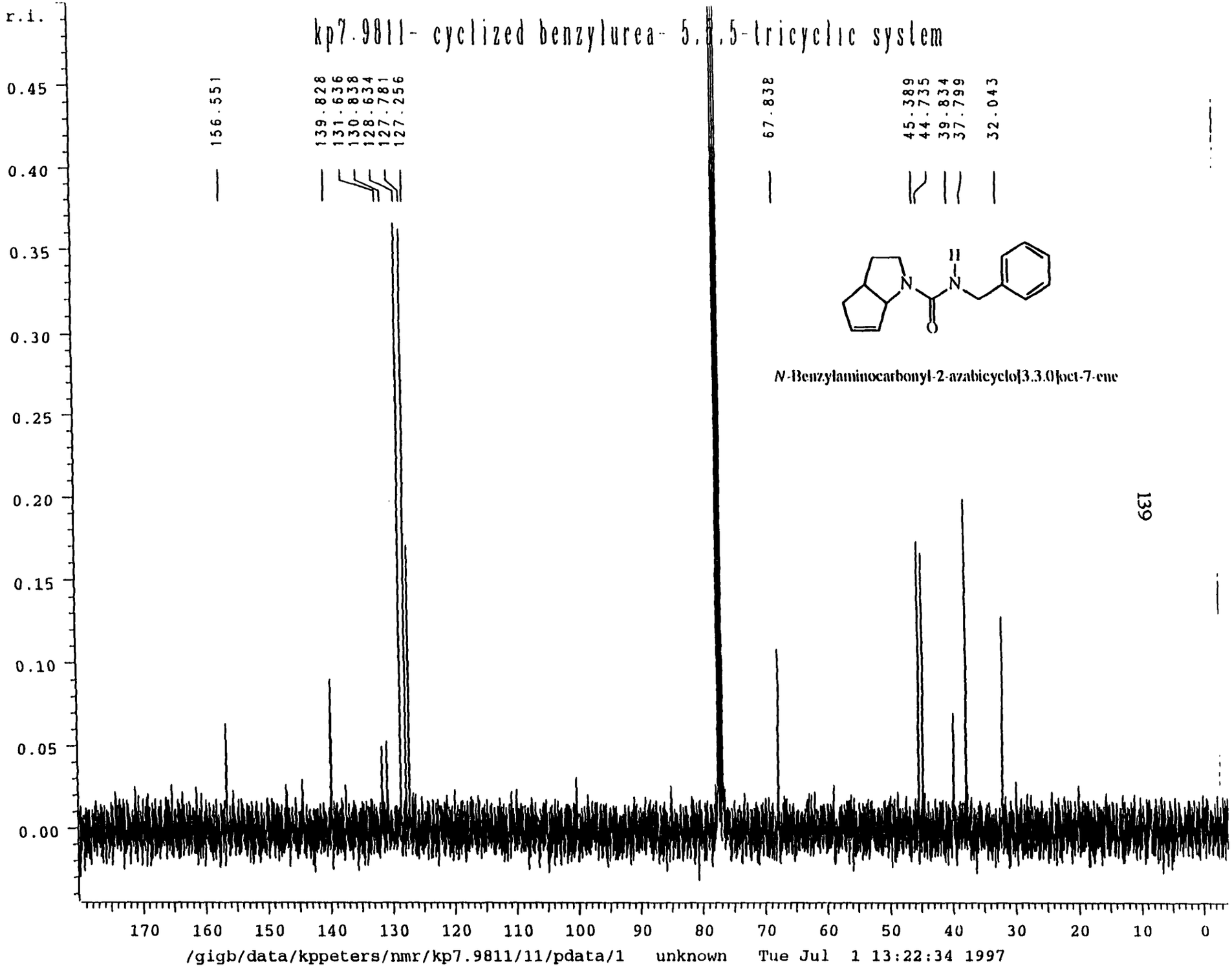


N-Benzylaminocarbonyl-2-azabicyclo[3.3.0]oct-7-ene


kp7.9811- cyclized benzylurea- 5.[illegible].5-tricyclic system
r.i.
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
156.551
139.828
131.636
130.838
128.634
127.781
127.256
67.838
45.389
44.735
39.834
37.799
32.043
N-Benzylaminocarbonyl-2-azabicyclo[3.3.0]oct-7-ene
139
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
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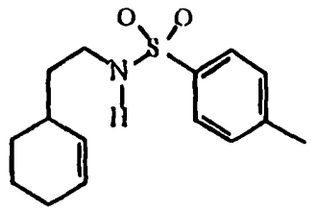
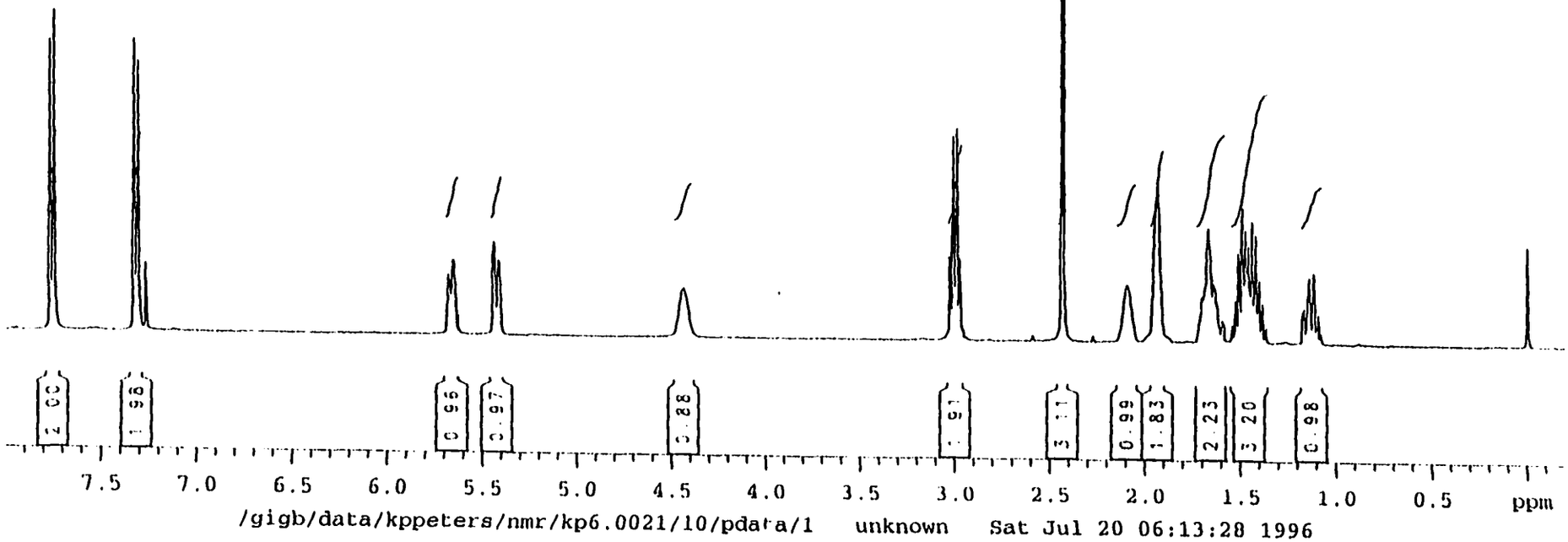
kp6.0021 - tosyl derivative



2-(2-Cyclohexenyl)-*N*-tosylethanamine



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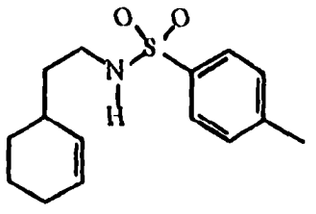
kp6.0021 tosyl derivative



2-(2-Cyclohexenyl)-*N*-tosylethanamine

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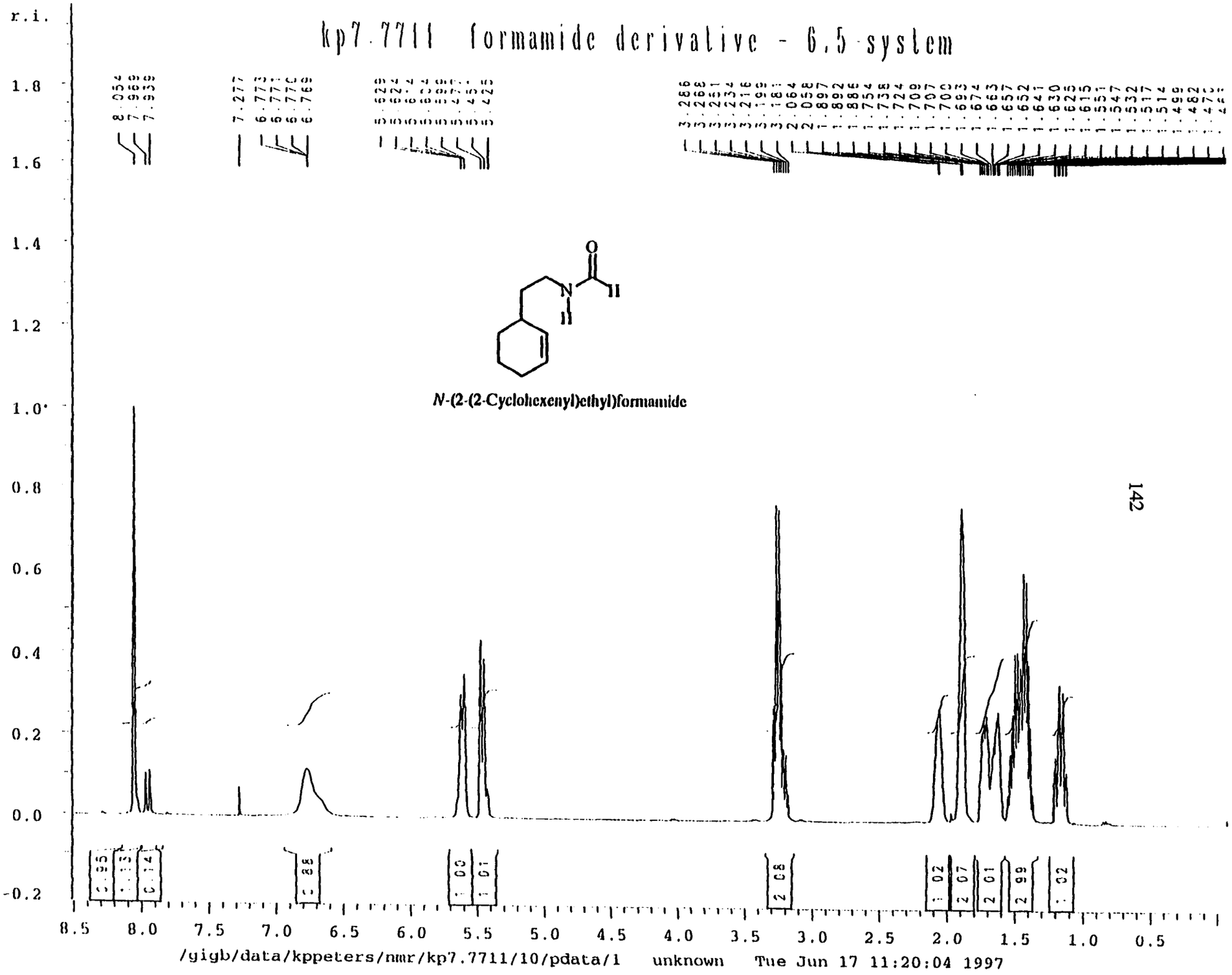
kp7.7711 formamide derivative - 6.5 system
r.i.
8.054
7.969
7.939
7.277
6.773
6.771
6.770
6.768
5.626
5.624
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0.704
0.702
0.700
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0.472
0.470
0.468
0.466
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0.462
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0.450
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0.424
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0.310
0.308
0.306
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0.300
0.298
0.296
0.294
0.292
0.290
0.288
0.286
0.284
0.282
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0.278
0.276
0.274
0.272
0.270
0.268
0.266
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0.260
0.258
0.256
0.254
0.252
0.250
0.248
0.246
0.244
0.242
0.240
0.238
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0.234
0.232
0.230
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0.224
0.222
0.220
0.218
0.216
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0.212
0.210
0.208
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0.202
0.200
0.198
0.196
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0.192
0.190
0.188
0.186
0.184
0.182
0.180
0.178
0.176
0.174
0.172
0.170
0.168
0.166
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0.162
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0.154
0.152
0.150
0.148
0.146
0.144
0.142
0.140
0.138
0.136
0.134
0.132
0.130
0.128
0.126
0.124
0.122
0.120
0.118
0.116
0.114
0.112
0.110
0.108
0.106
0.104
0.102
0.100
0.098
0.096
0.094
0.092
0.090
0.088
0.086
0.084
0.082
0.080
0.078
0.076
0.074
0.072
0.070
0.068
0.066
0.064
0.062
0.060
0.058
0.056
0.054
0.052
0.050
0.048
0.046
0.044
0.042
0.040
0.038
0.036
0.034
0.032
0.030
0.028
0.026
0.024
0.022
0.020
0.018
0.016
0.014
0.012
0.010
0.008
0.006
0.004
0.002
0.000
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
O
N
N-(2-(2-Cyclohexenyl)ethyl)formamide
1.95
1.13
1.14
0.88
1.00
1.01
2.08
1.02
2.07
2.01
2.99
1.02
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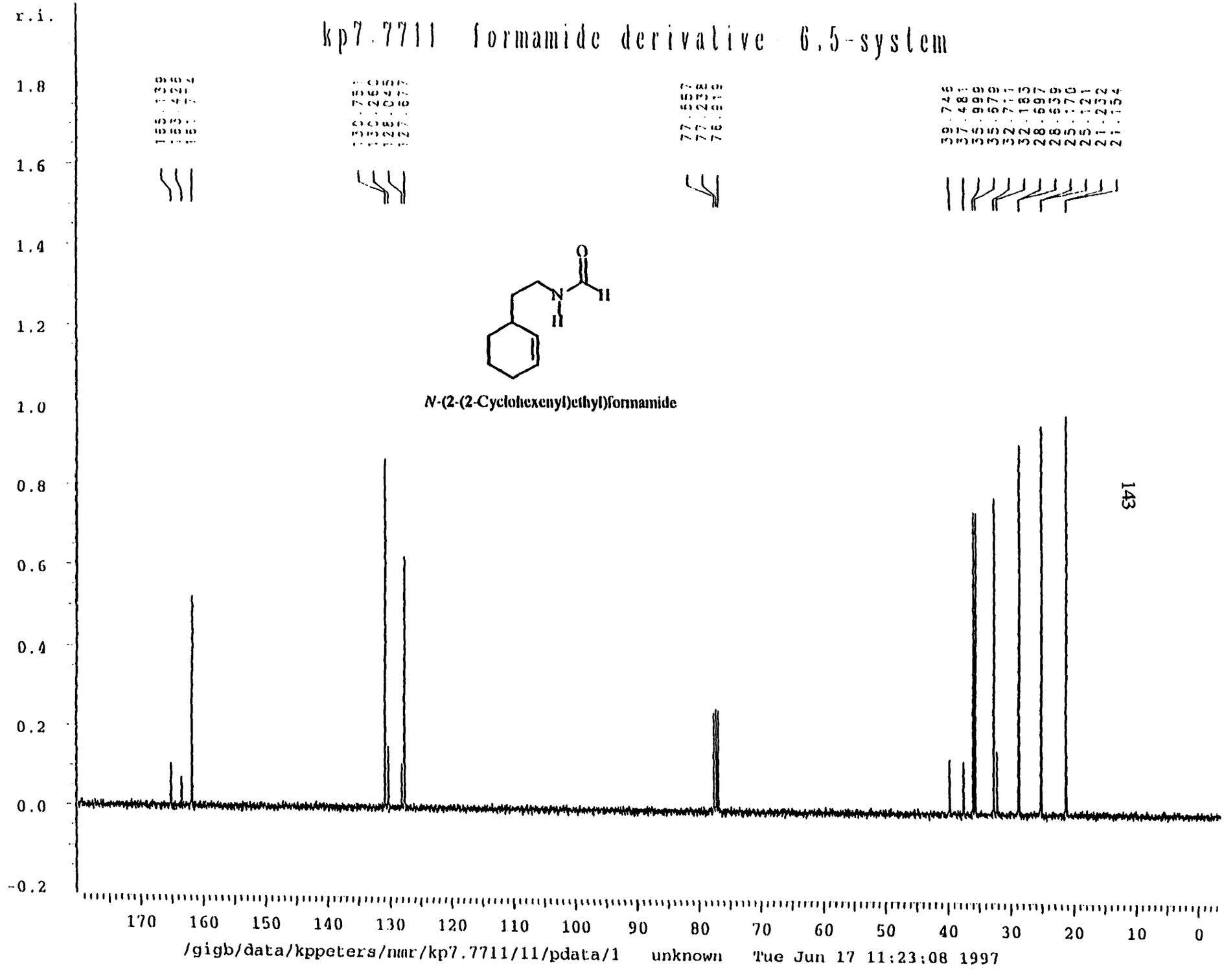
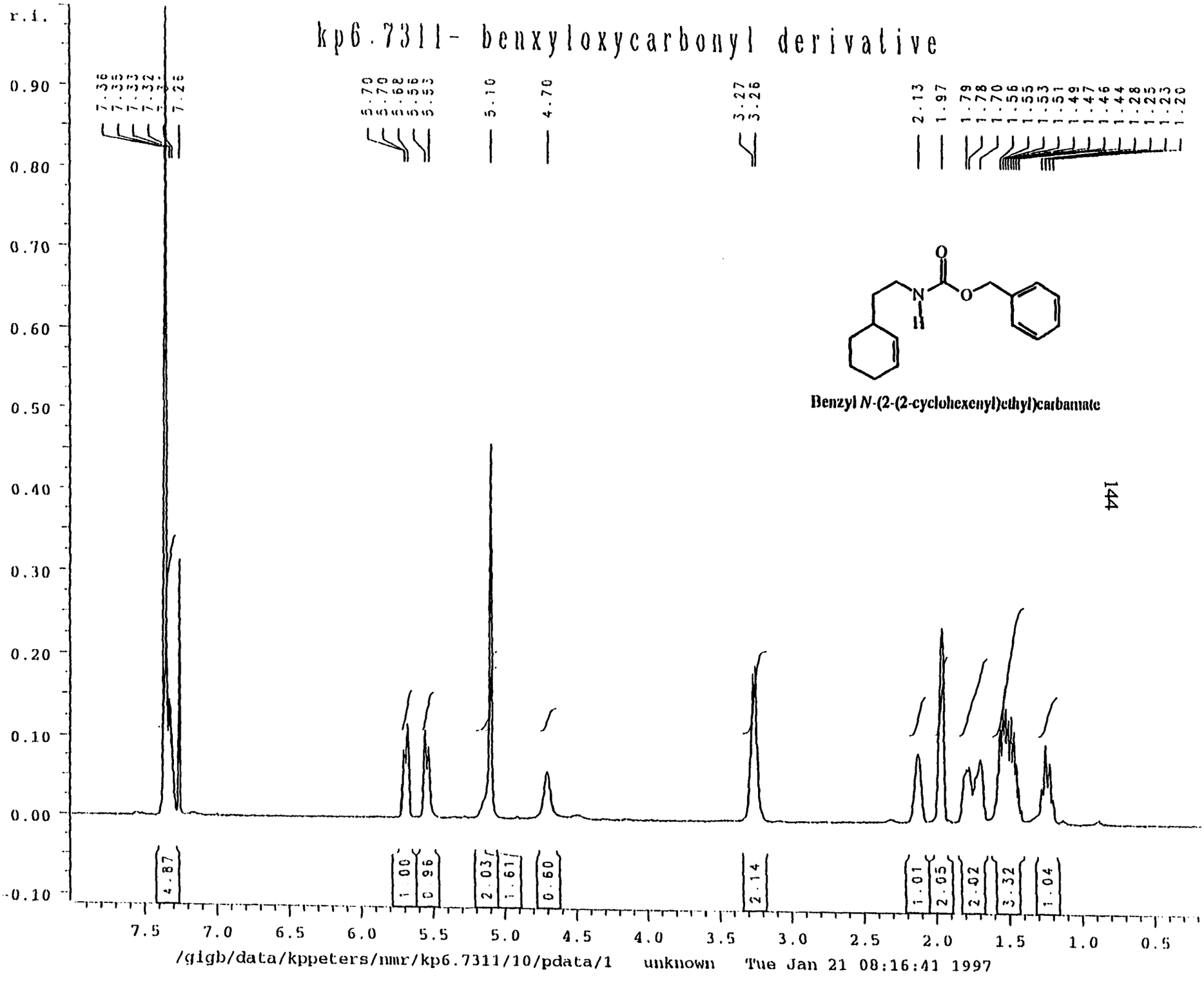
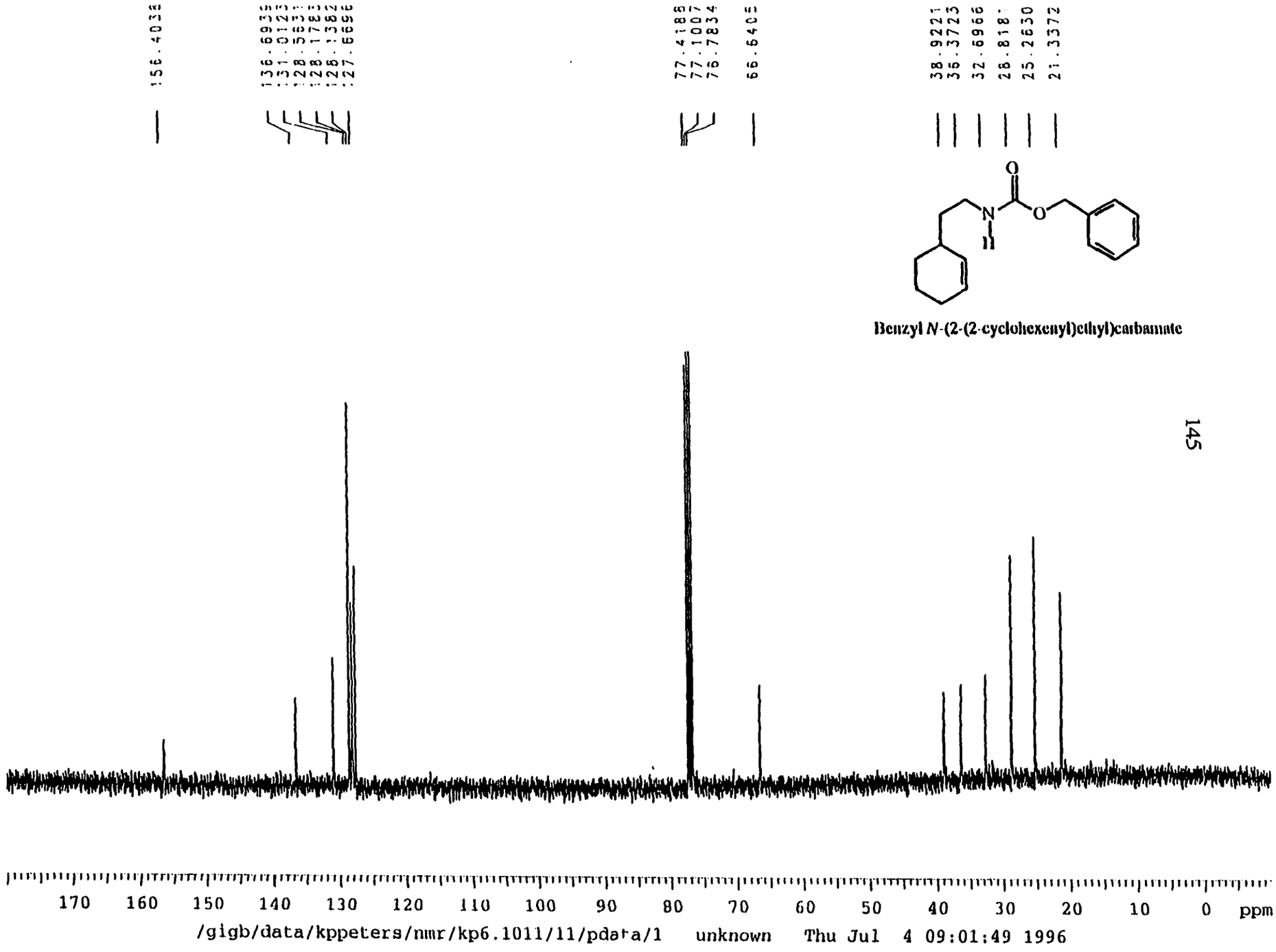

kp7.7711 formamide derivative 6.5-system
r.i.
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
N-(2-(2-Cyclohexenyl)ethyl)formamide
143
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
/gigb/data/kppeters/nmr/kp7.7711/11/pdata/1 unknown Tue Jun 17 11:23:08 1997

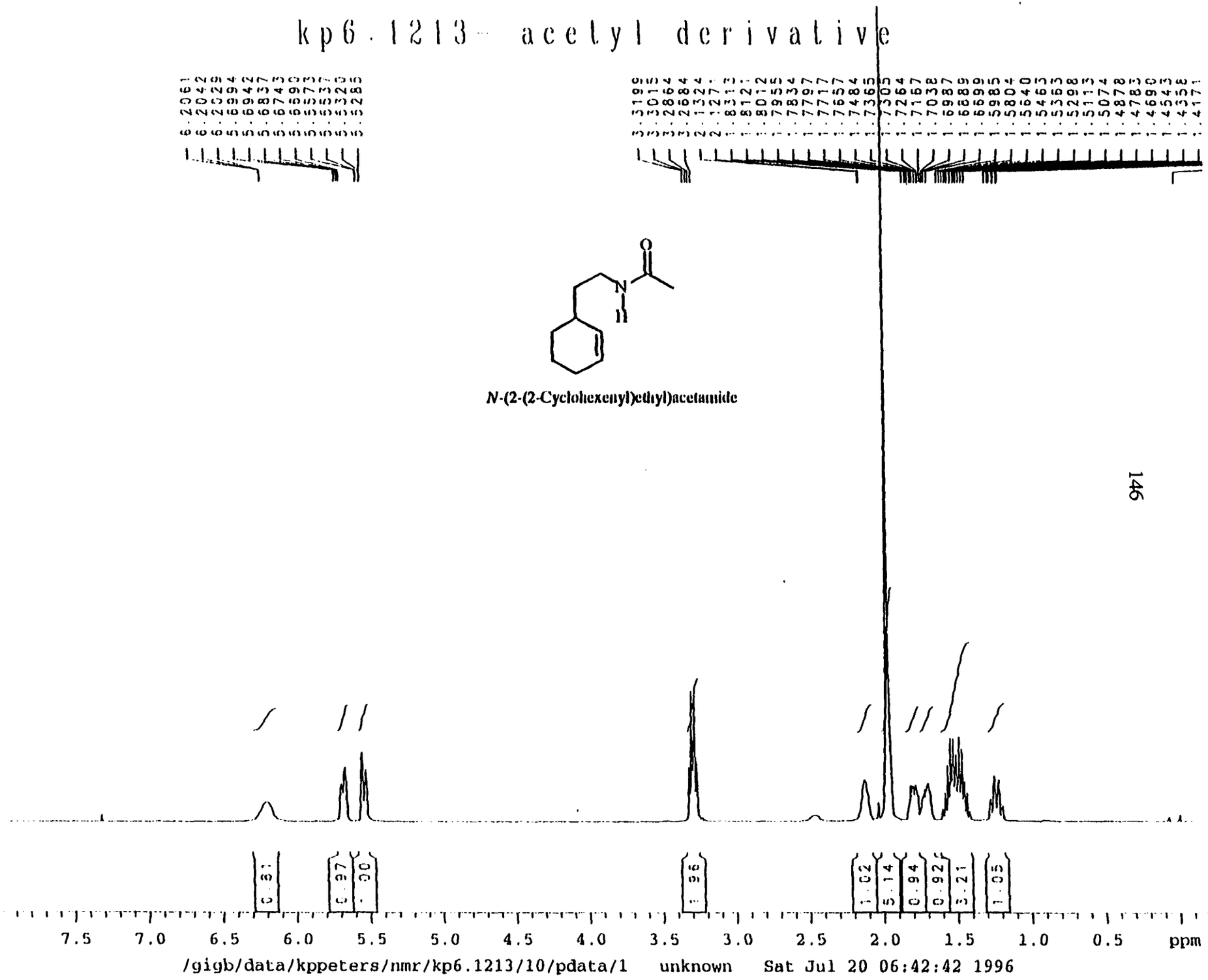


Benzyl *N*-(2-(2-cyclohexenyl)ethyl)carbamate

kp6.1011 benzyloxycarbonyl derivative

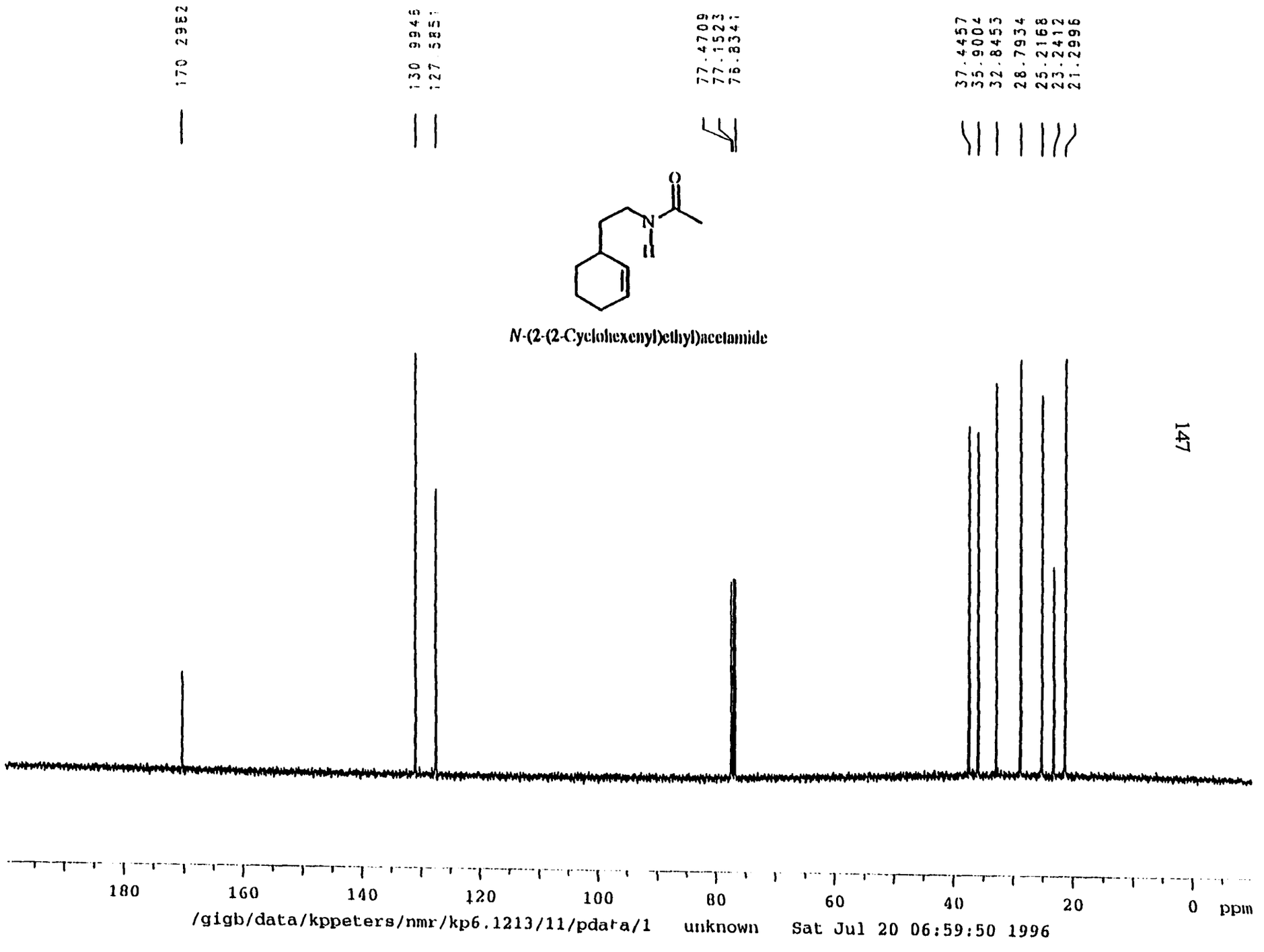


kp6.1213 - acetyl derivative

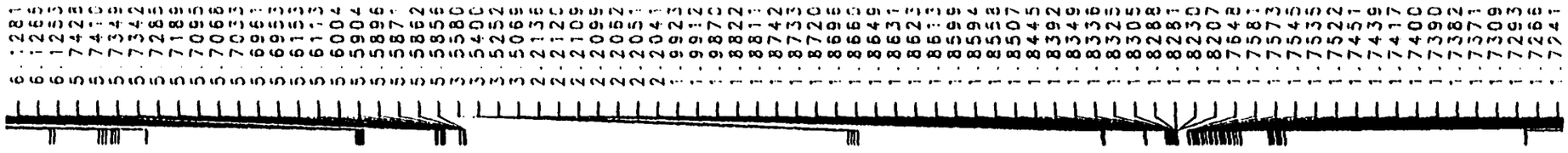


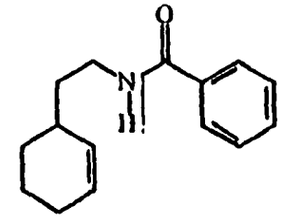
N-(2-(2-Cyclohexenyl)ethyl)acetamide

kp6.1213 acetyl derivative

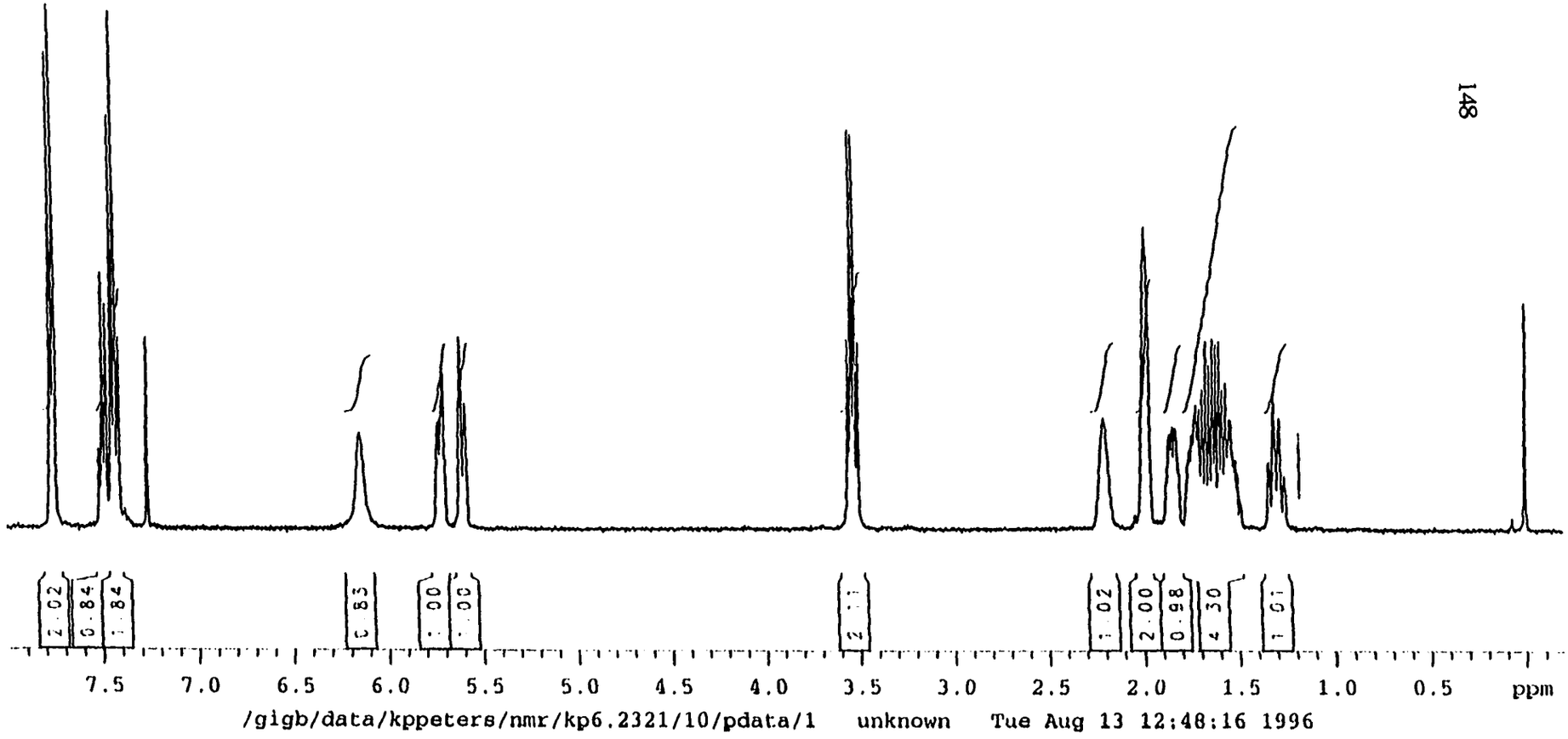


kp6.2321 - benzamide derivative





N-(2-(2-Cyclohexenyl)ethyl)benzamide



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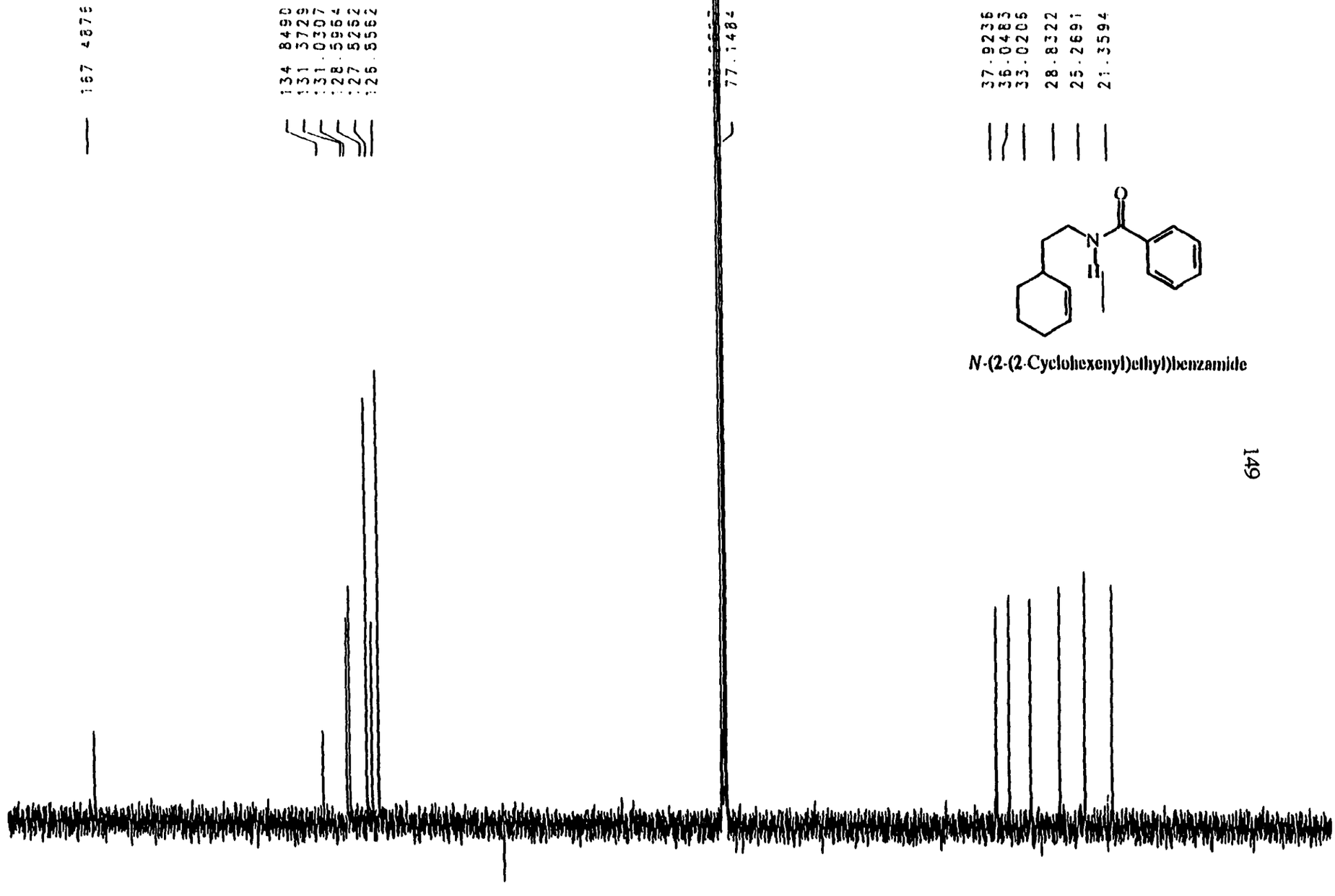
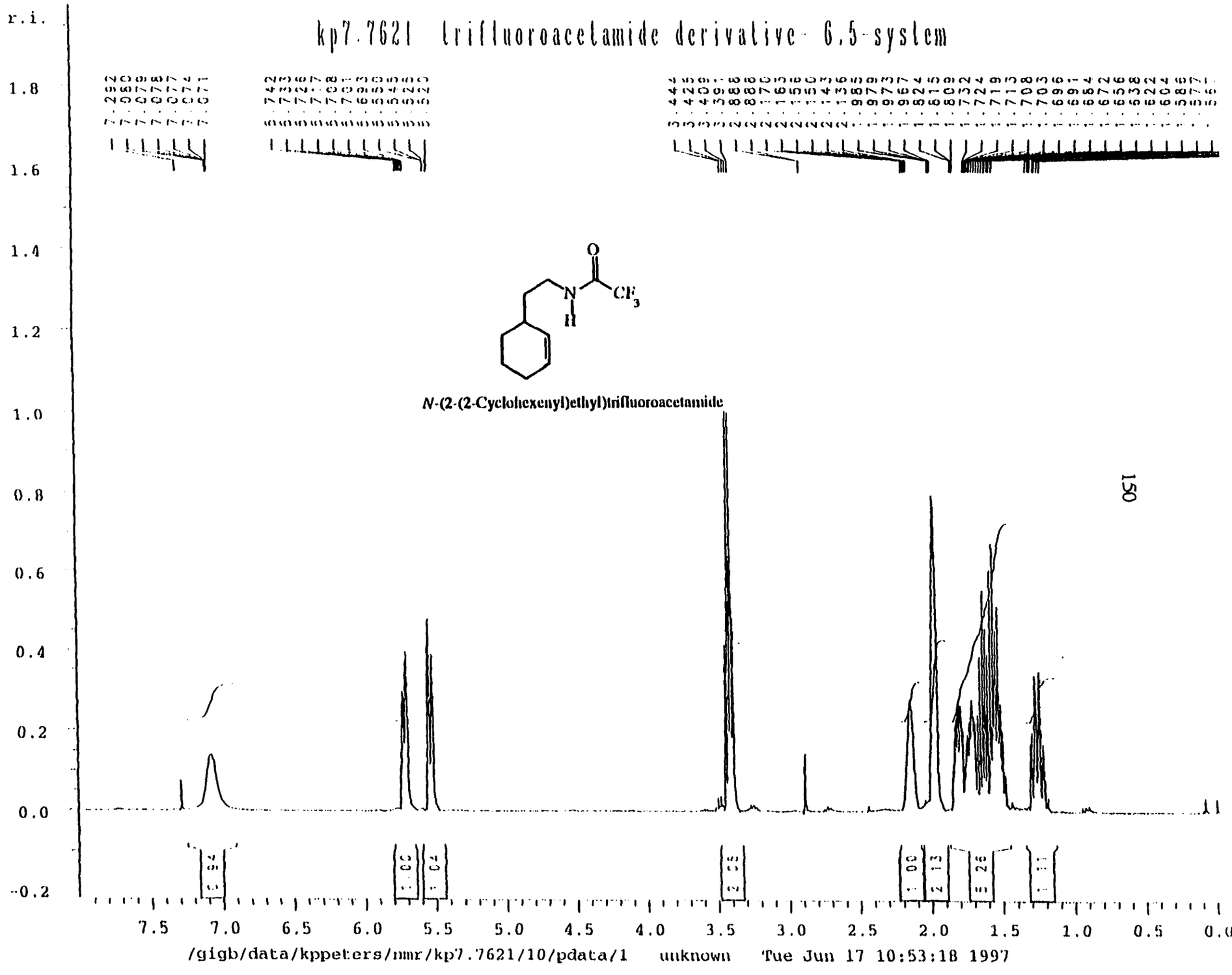
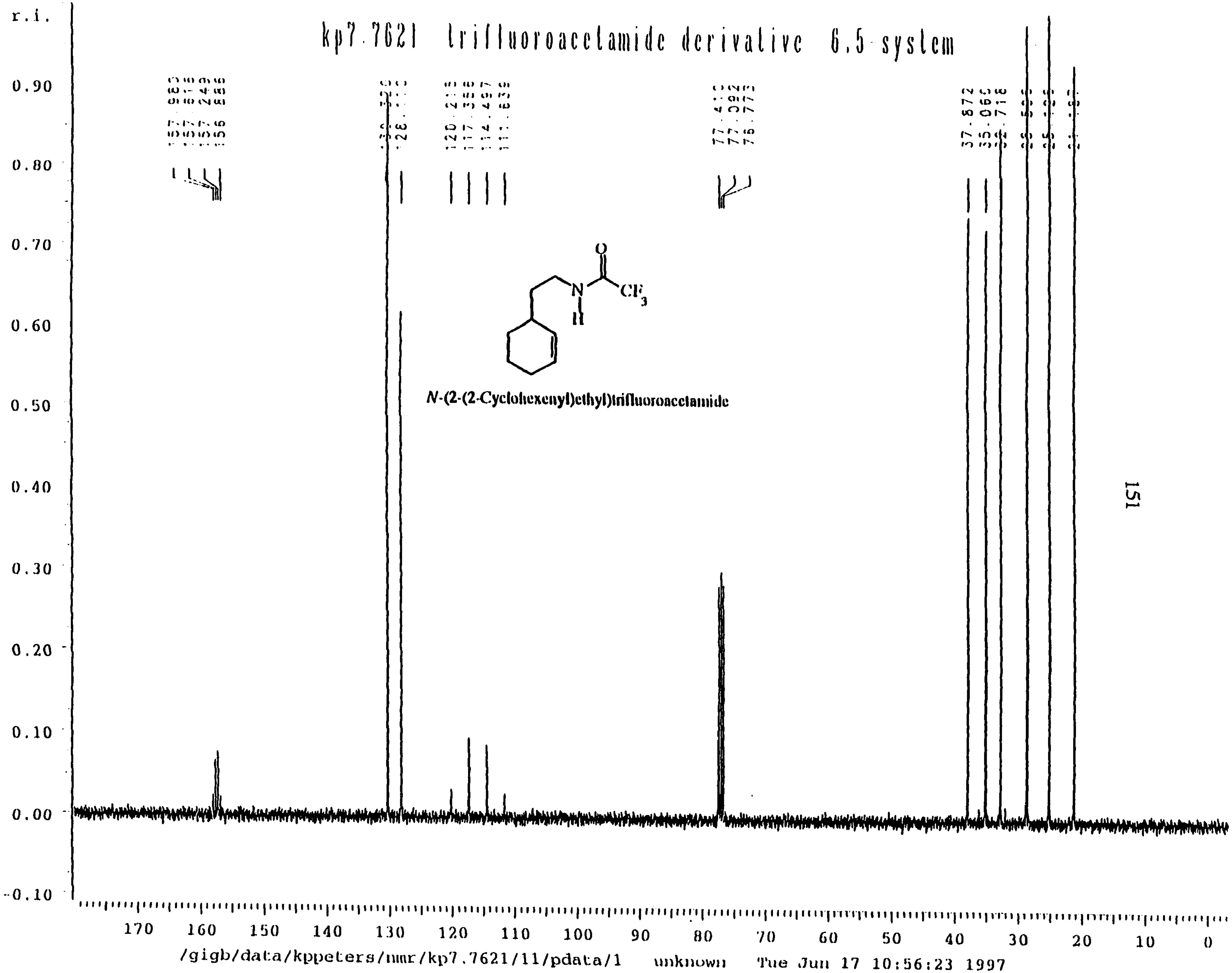
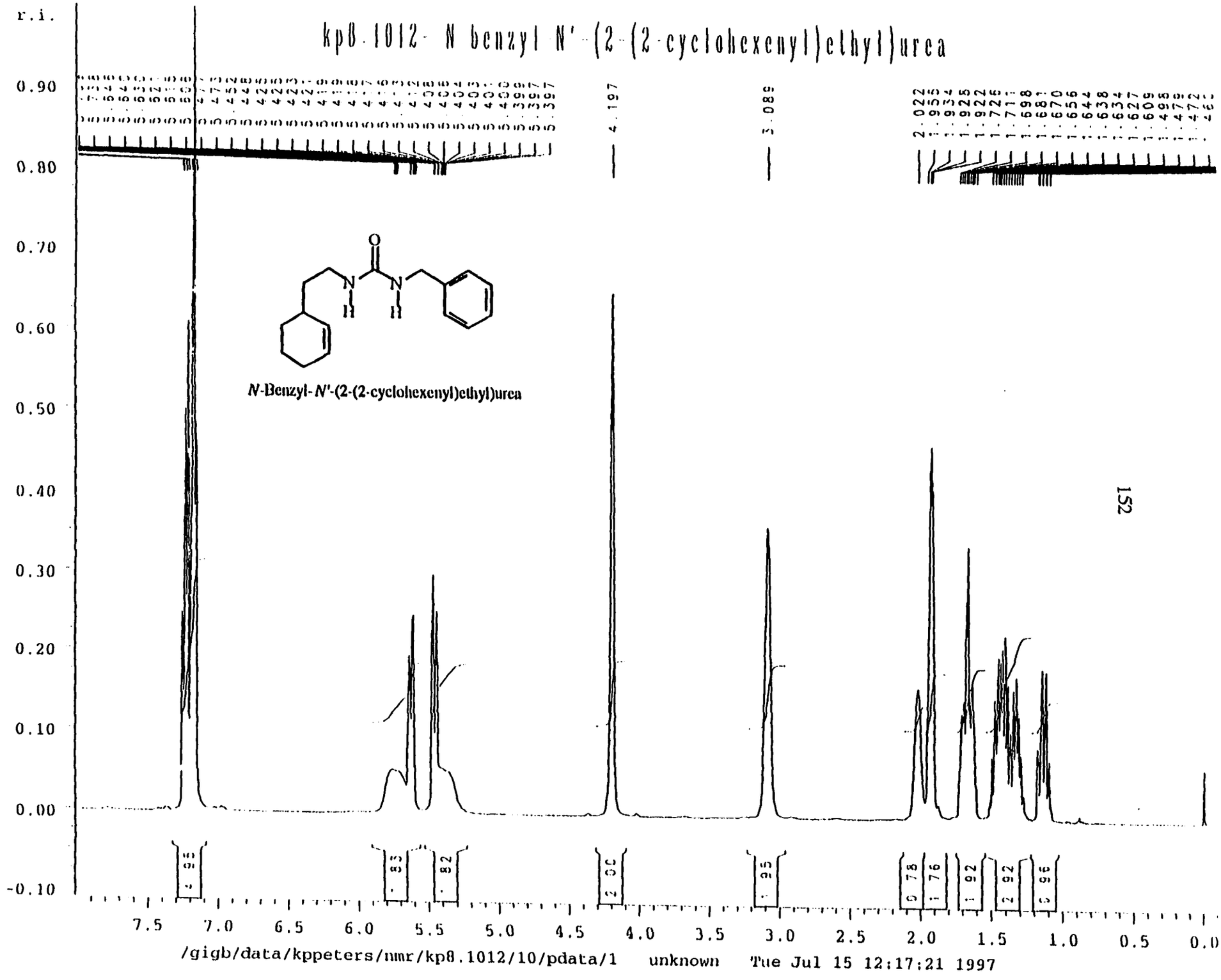
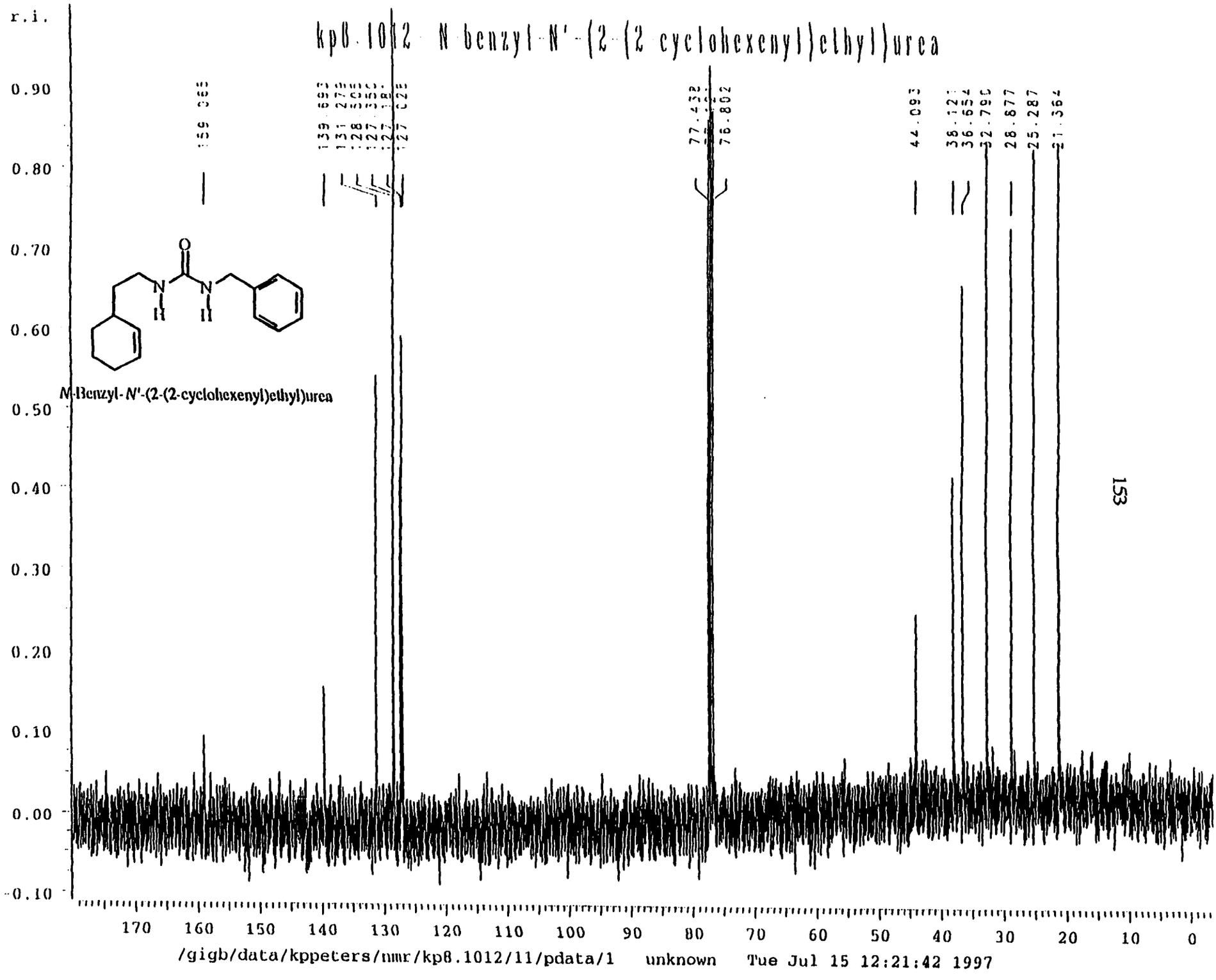
kp6.2312 benzamide derivative



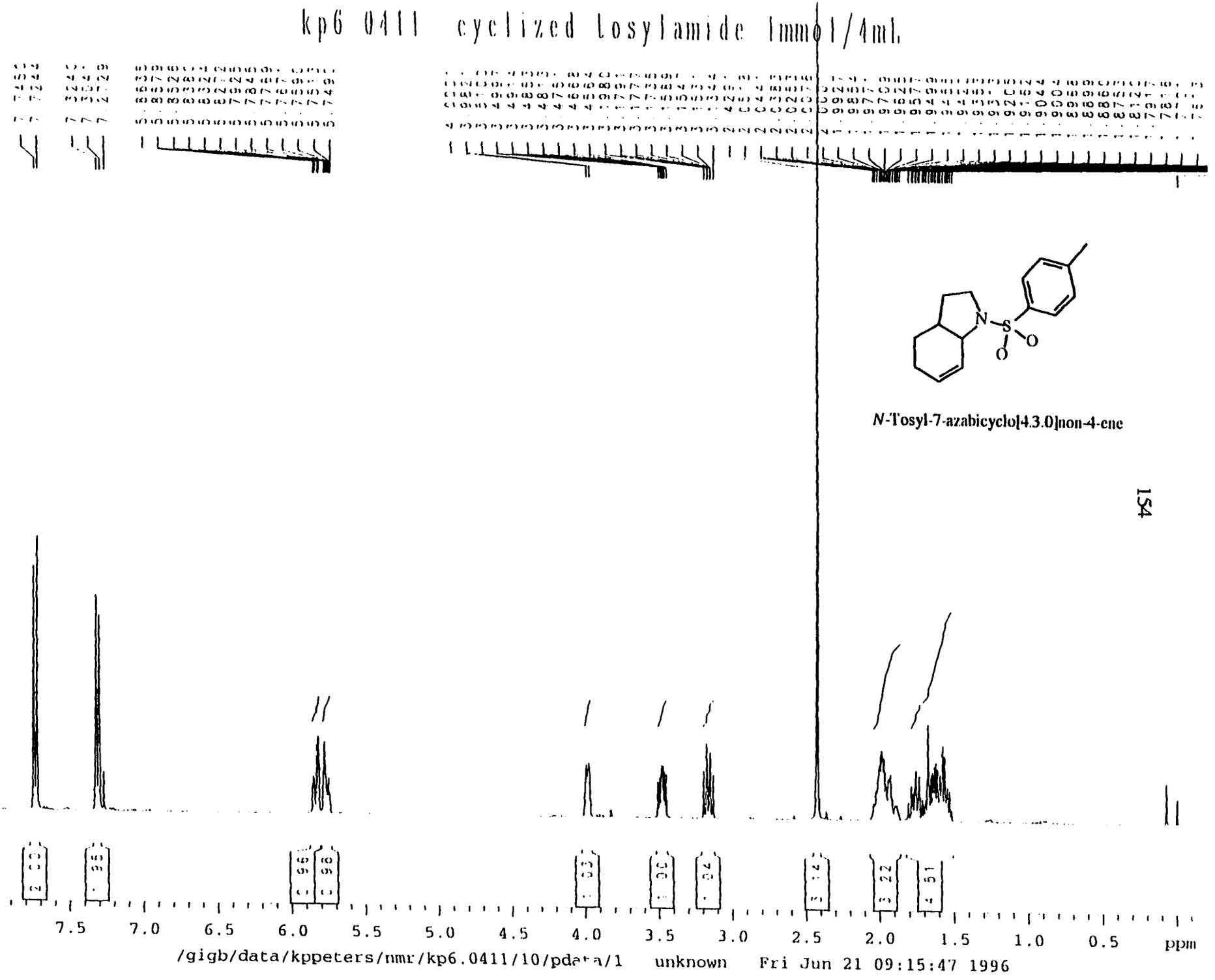

kp7.7621 trifluoroacetamide derivative- 6.5-system
r.i.
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
O
N
H
CF3
N-(2-(2-Cyclohexenyl)ethyl)trifluoroacetamide
150
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
/gigb/data/kppeters/nmr/kp7.7621/10/pdata/1 unknown Tue Jun 17 10:53:18 1997


kp7.7621 trifluoroacetamide derivative 6.5 system
r.i.
N-(2-(2-Cyclohexenyl)ethyl)trifluoroacetamide
/gigb/data/kppeters/nmr/kp7.7621/11/pdata/1 unknown Tue Jun 17 10:56:23 1997


kp8.1012- N benzyl N'-(2-(2-cyclohexenyl)ethyl)urea
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
4.197
3.089
2.022
1.955
1.934
1.925
1.922
1.726
1.711
1.698
1.681
1.670
1.656
1.644
1.638
1.634
1.627
1.609
1.498
1.479
1.472
N-Benzyl-N'-(2-(2-cyclohexenyl)ethyl)urea
152
1.95
1.83
1.82
2.00
1.95
5.78
1.76
1.92
2.92
3.96
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
/gigb/data/kppeters/nmr/kp8.1012/10/pdata/1 unknown Tue Jul 15 12:17:21 1997


kp8.1012 N benzyl-N'-(2-(2 cyclohexenyl)ethyl)urea
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
159.365
139.693
131.278
128.505
127.355
127.118
127.028
77.432
76.862
44.093
38.121
36.654
32.795
28.877
25.287
21.364
N-Benzyl-N'-(2-(2-cyclohexenyl)ethyl)urea
153
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
/gigb/data/kppeters/nmr/kp8.1012/11/pdata/1 unknown Tue Jul 15 12:21:42 1997

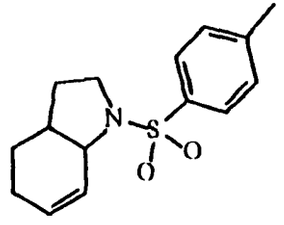
kp6 0411 cyclized tosylamide 1mmol/4ml



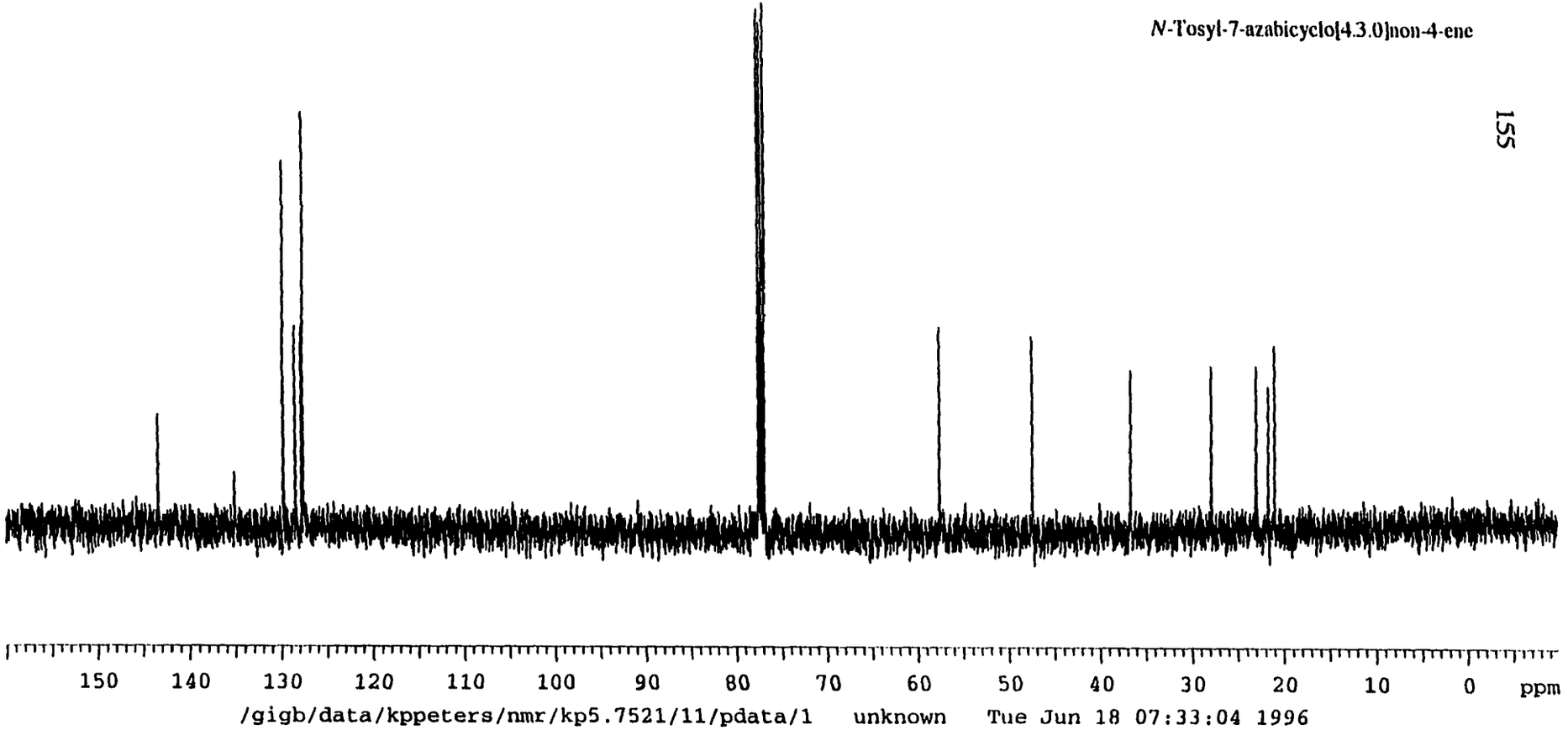
N-Tosyl-7-azabicyclo[4.3.0]non-4-ene

kp5.7521 - cyclized tosyl derivative

143.2523
134.9732
129.6711
128.3257
127.6612
127.5070
77.4271
77.3114
77.1088
76.7914
57.4945
47.3388
36.5284
27.7418
22.8698
21.5585
20.8606



N-Tosyl-7-azabicyclo[4.3.0]non-4-ene



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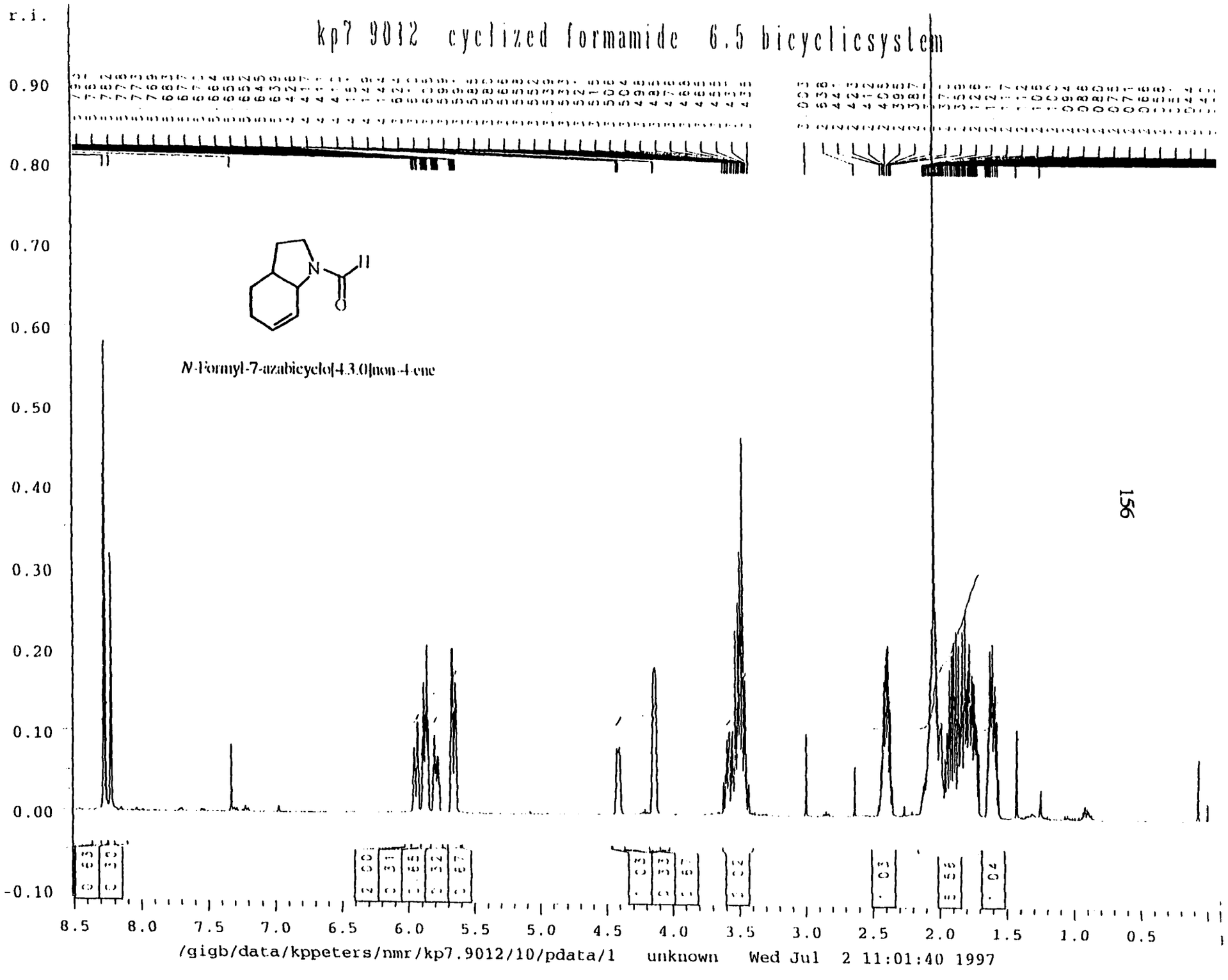
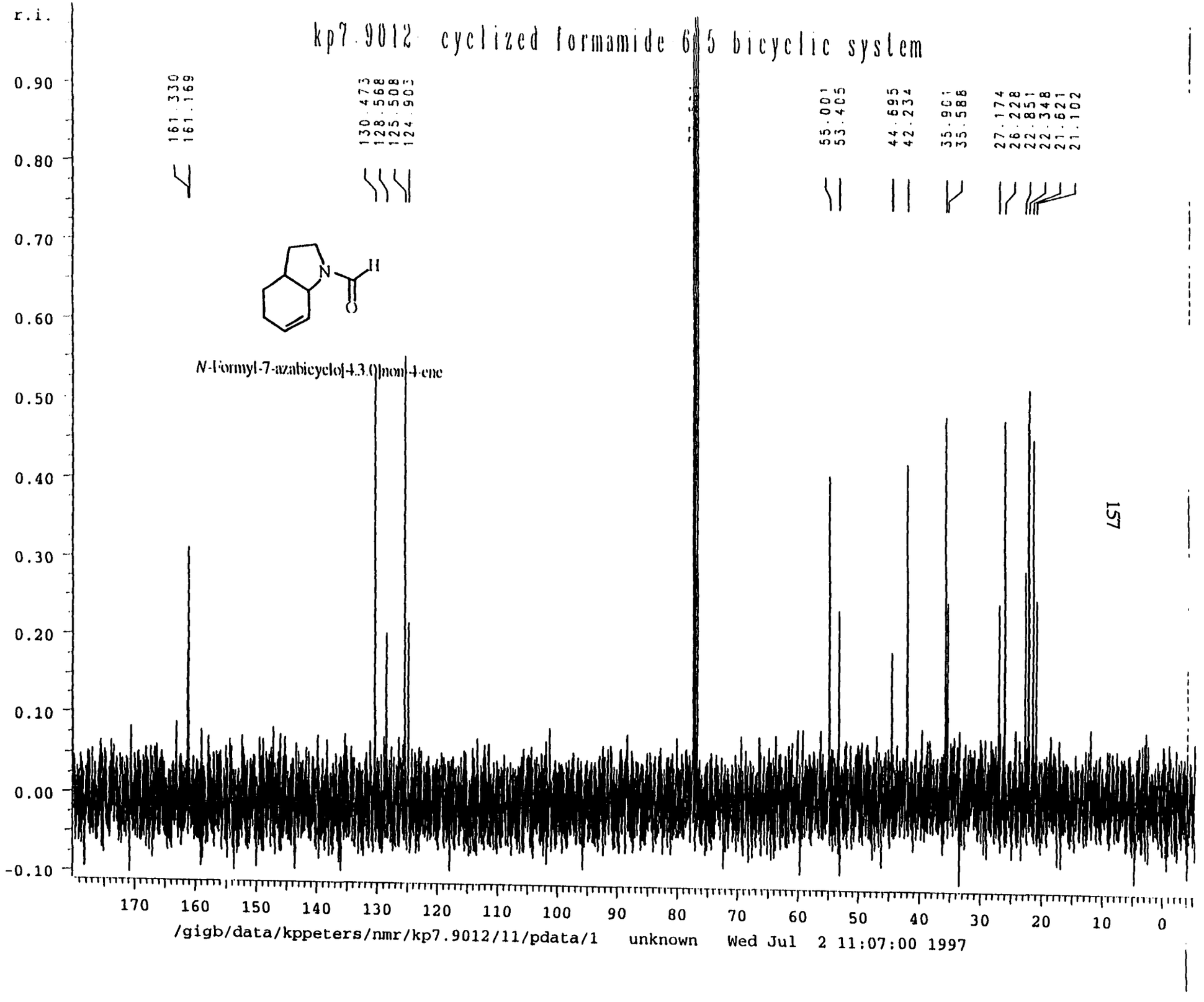
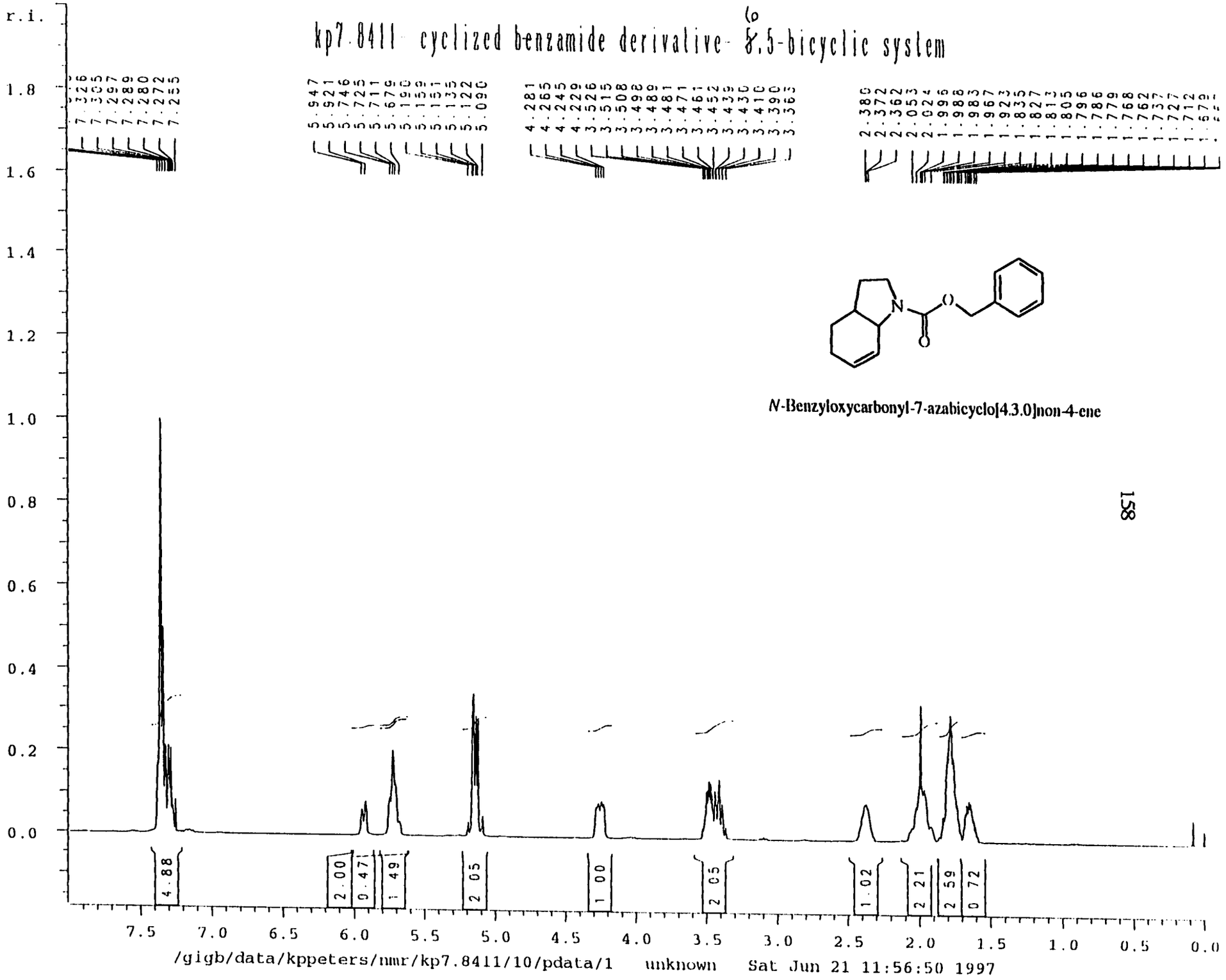
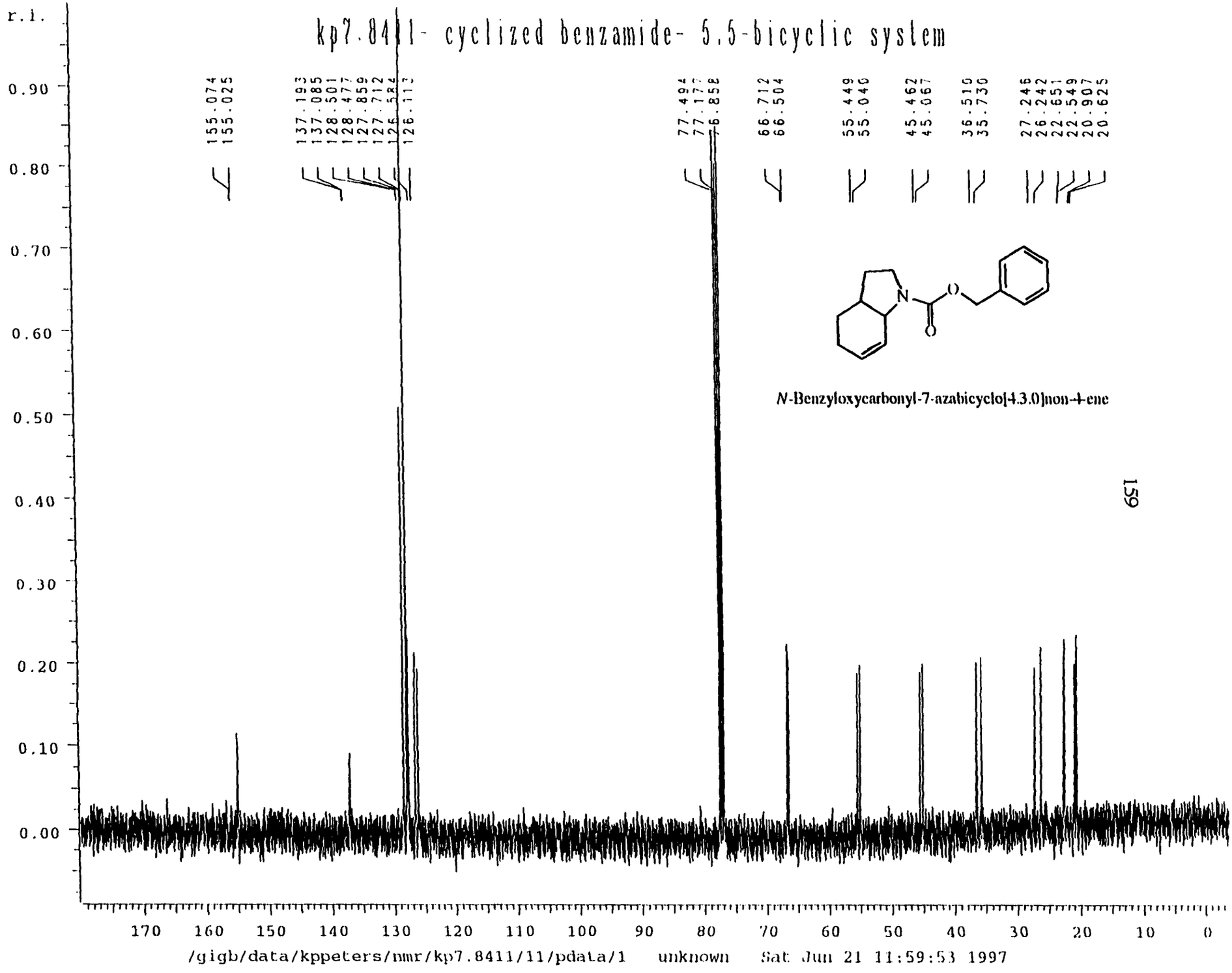

kp7 9012 cyclized formamide 6.5 bicyclicsystem
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
N
O
N-Formyl-7-azabicyclo[4.3.0]non-4-ene
156
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
/gigb/data/kppeters/nmr/kp7.9012/10/pdata/1 unknown Wed Jul 2 11:01:40 1997


kp7.9012 cyclized formamide 6 5 bicyclic system
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
161.330
161.169
130.473
128.568
125.508
124.903
55.001
53.405
44.695
42.234
35.901
35.588
27.174
26.228
22.851
22.348
21.621
21.102
N
H
O
N-Formyl-7-azabicyclo[4.3.0]non-4-ene
157
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
/gigb/data/kppeters/nmr/kp7.9012/11/pdata/1 unknown Wed Jul 2 11:07:00 1997

kp7.8411 cyclized benzamide derivative- 6,5-bicyclic system



N-Benzyloxycarbonyl-7-azabicyclo[4.3.0]non-4-ene


kp7.8411- cyclized benzamide- 5.5-bicyclic system
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
155.074
155.025
137.193
137.085
128.501
128.477
127.859
127.712
126.584
126.113
77.494
77.177
76.858
66.712
66.504
55.449
55.040
45.462
45.067
36.510
35.730
27.246
26.242
22.651
22.549
20.907
20.625
N
O
O
N-Benzyloxycarbonyl-7-azabicyclo[4.3.0]non-4-ene
159
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
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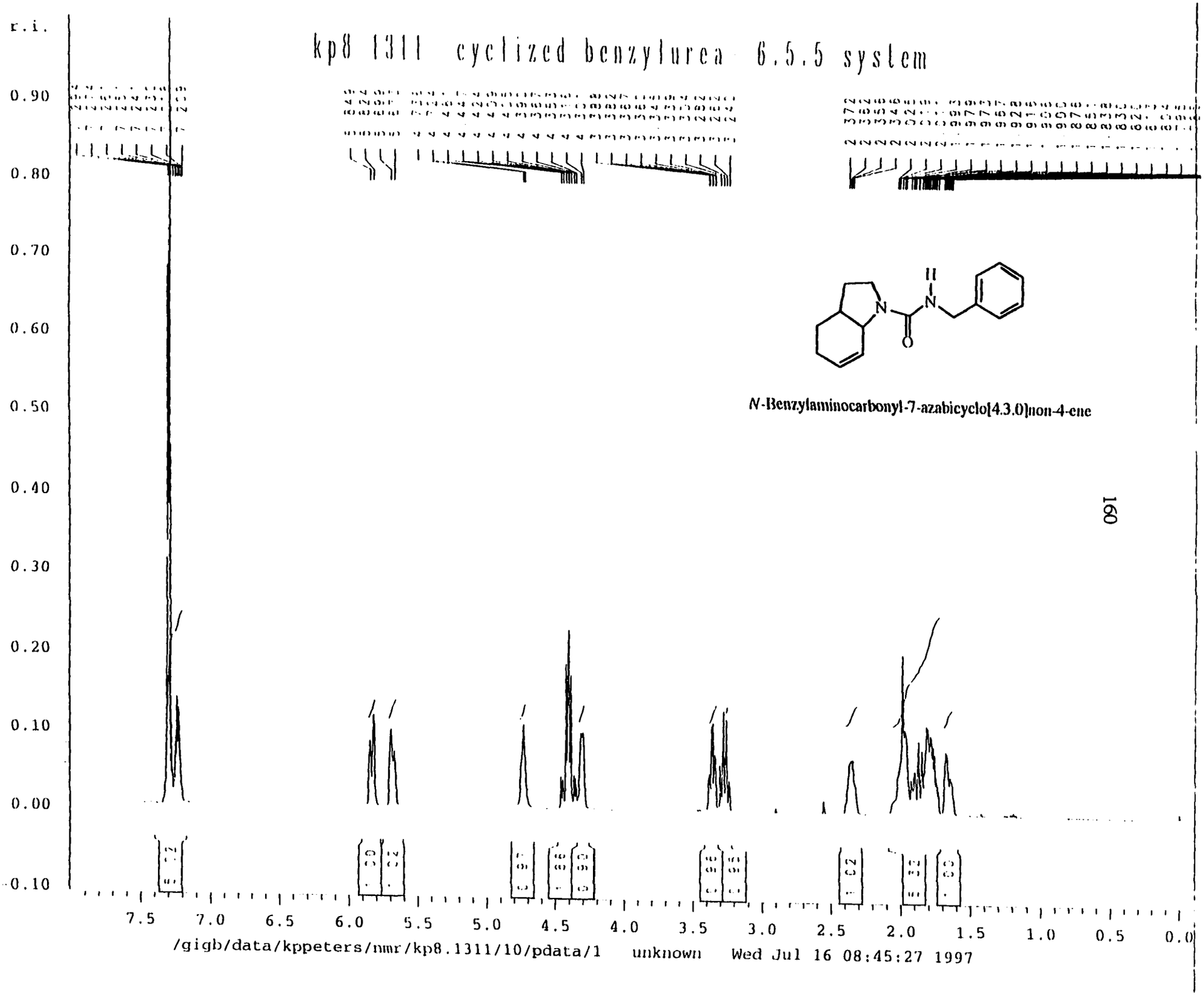
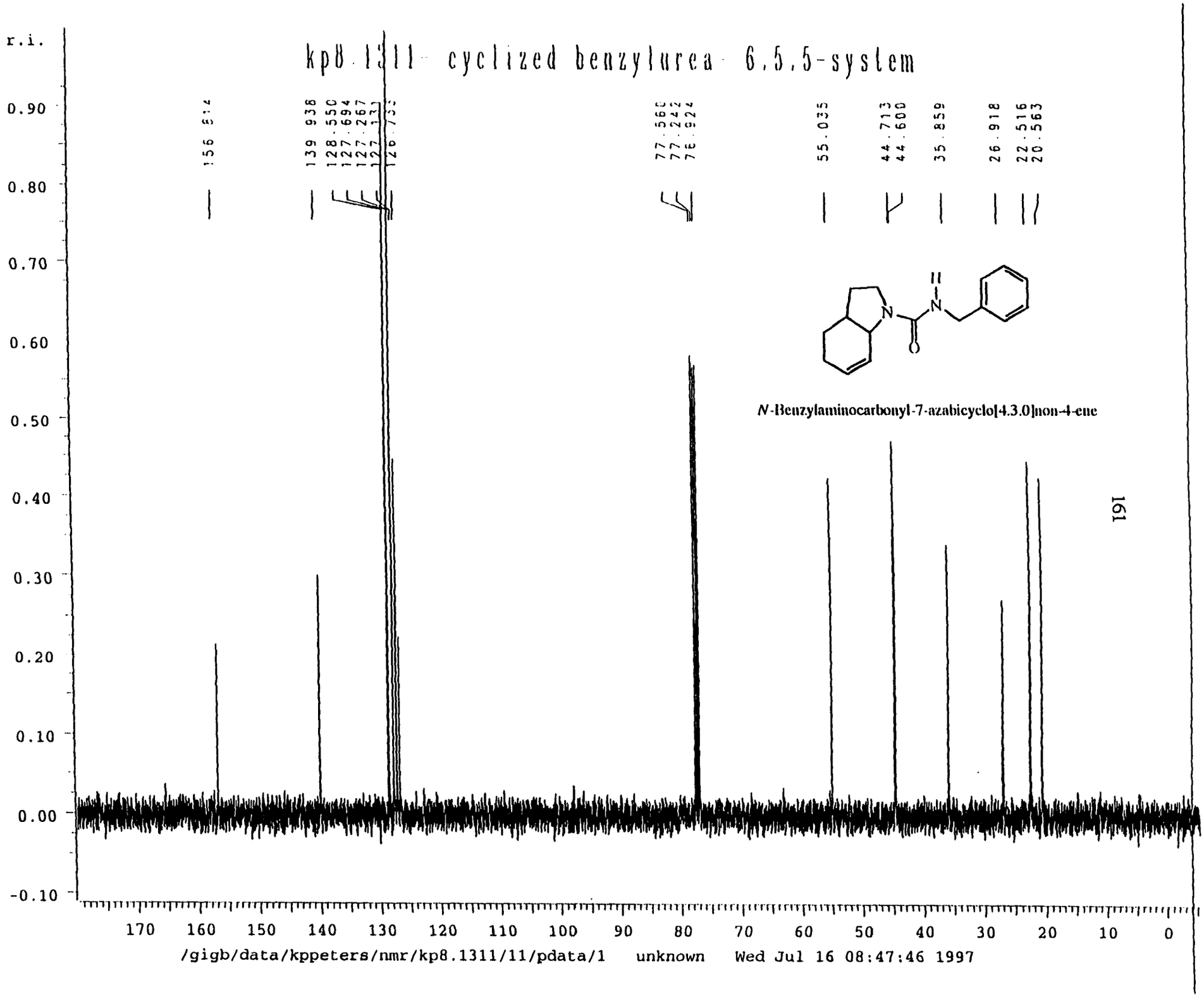
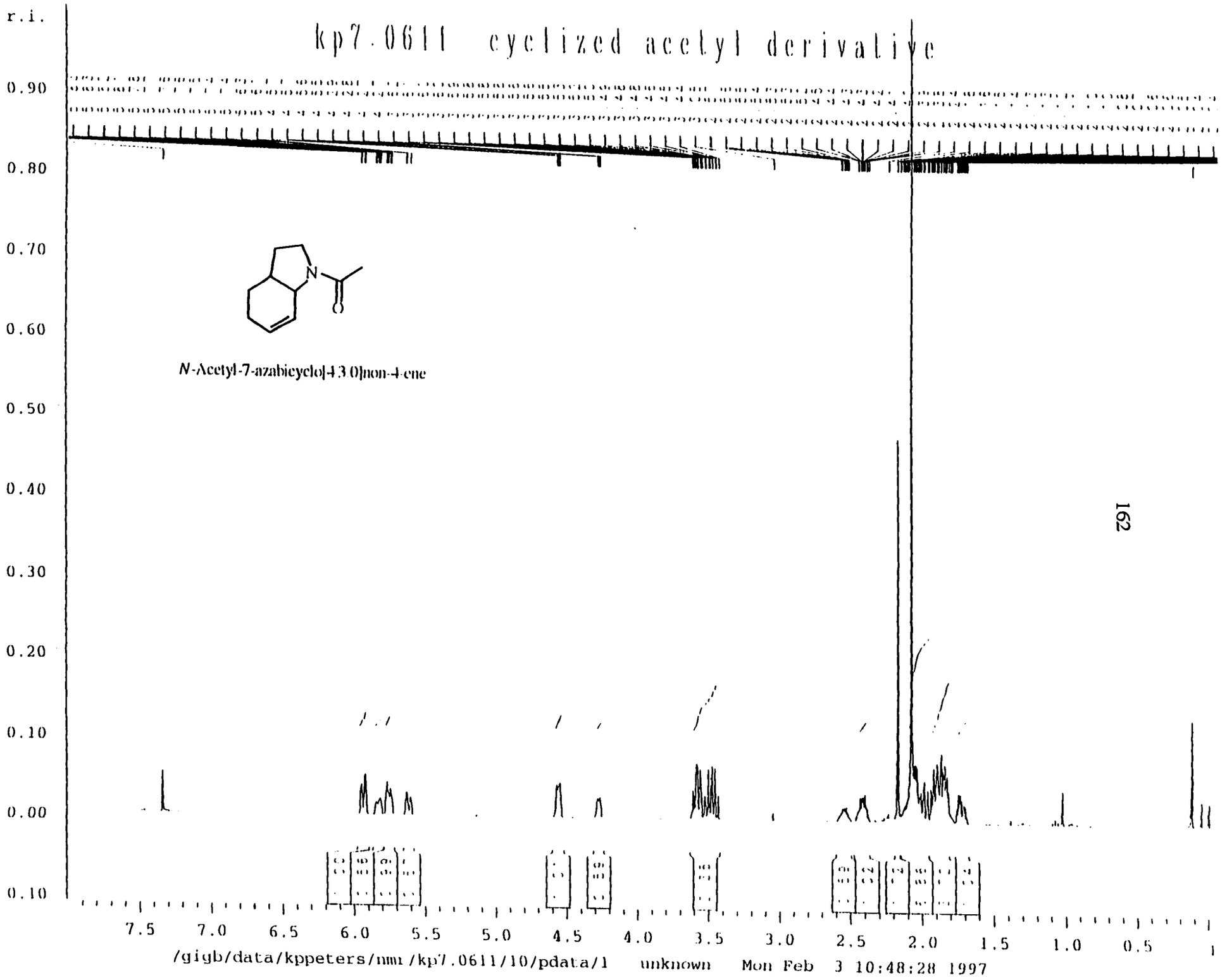


N-Benzylaminocarbonyl-7-azabicyclo[4.3.0]non-4-ene


kp8.1311 cyclized benzylurea 6,5,5-system
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
156.814
139.938
128.550
127.694
127.267
127.131
126.733
77.566
77.242
76.924
55.035
44.713
44.600
35.859
26.918
22.516
20.563
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
/gigb/data/kppeters/nmr/kp8.1311/11/pdata/1 unknown Wed Jul 16 08:47:46 1997
N-Benzylaminocarbonyl-7-azabicyclo[4.3.0]non-4-ene
161


kp7.0611 cyclized acetyl derivative
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0.10
N
O
N-Acetyl-7-azabicyclo[4.3.0]non-4-ene
162
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
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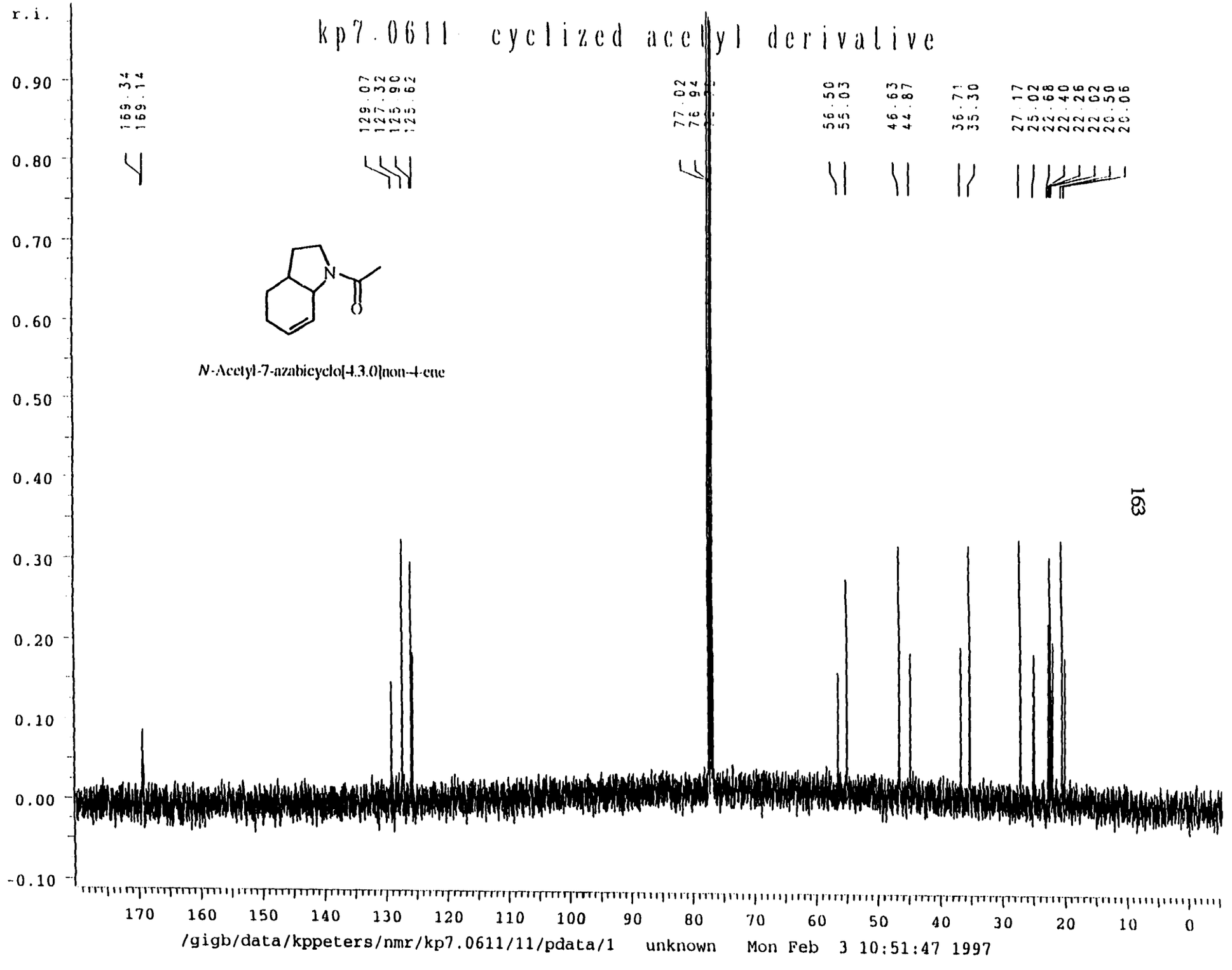
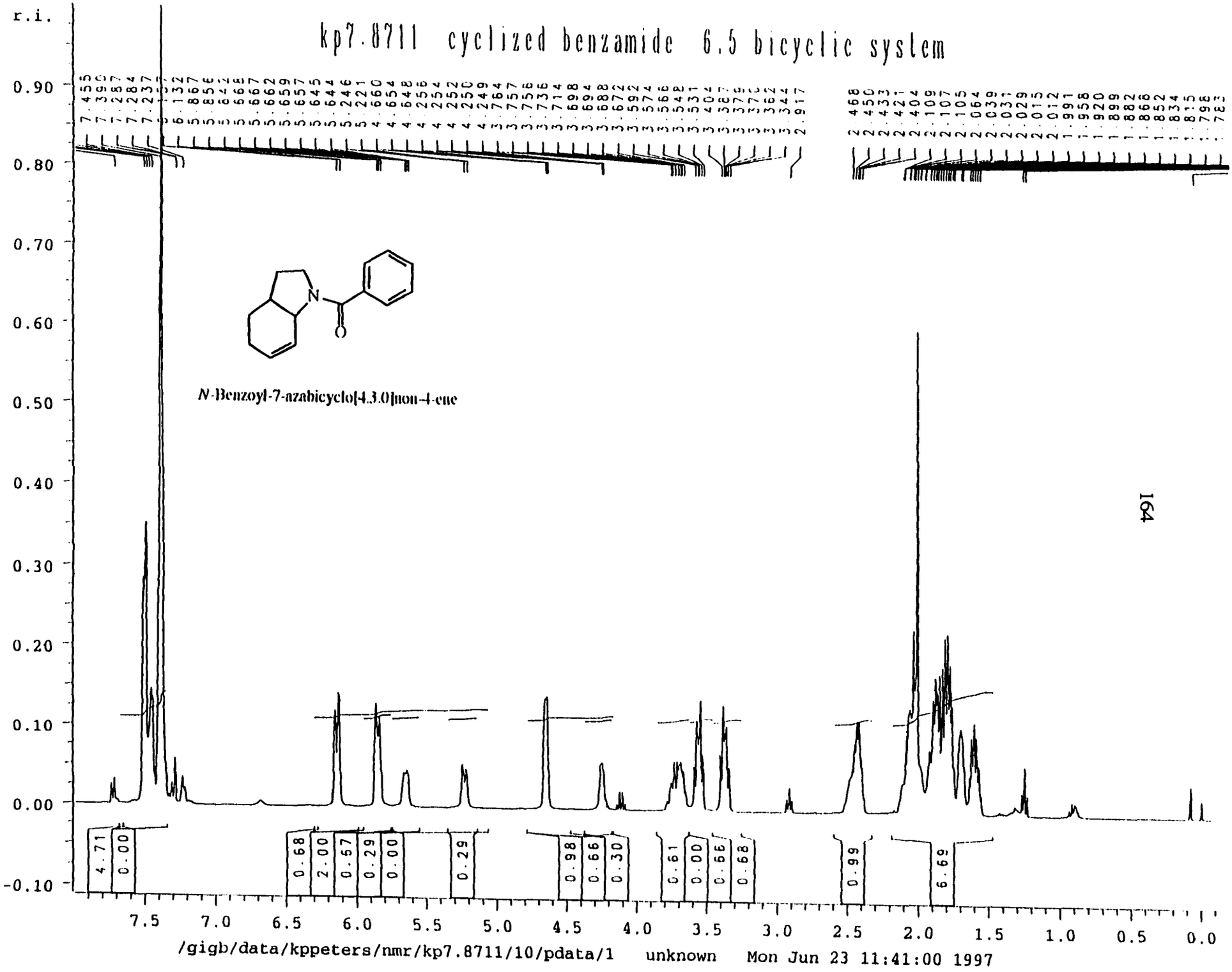

kp7.0611 cyclized acetyl derivative
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
169.34
169.14
129.07
127.32
125.90
125.62
77.02
76.94
56.50
55.03
46.63
44.87
36.71
35.30
27.17
25.02
22.68
22.40
22.26
22.02
20.50
20.06
N
O
N-Acetyl-7-azabicyclo[4.3.0]non-4-ene
163
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
/gigb/data/kppeters/nmr/kp7.0611/11/pdata/1 unknown Mon Feb 3 10:51:47 1997


kp7.8711 cyclized benzamide 6.5 bicyclic system
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
N
O
N-Benzoyl-7-azabicyclo[4.3.0]non-4-ene
4.71
0.00
0.68
2.00
0.67
0.29
0.00
0.29
0.98
0.66
0.30
0.61
0.00
0.66
0.68
0.99
6.69
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
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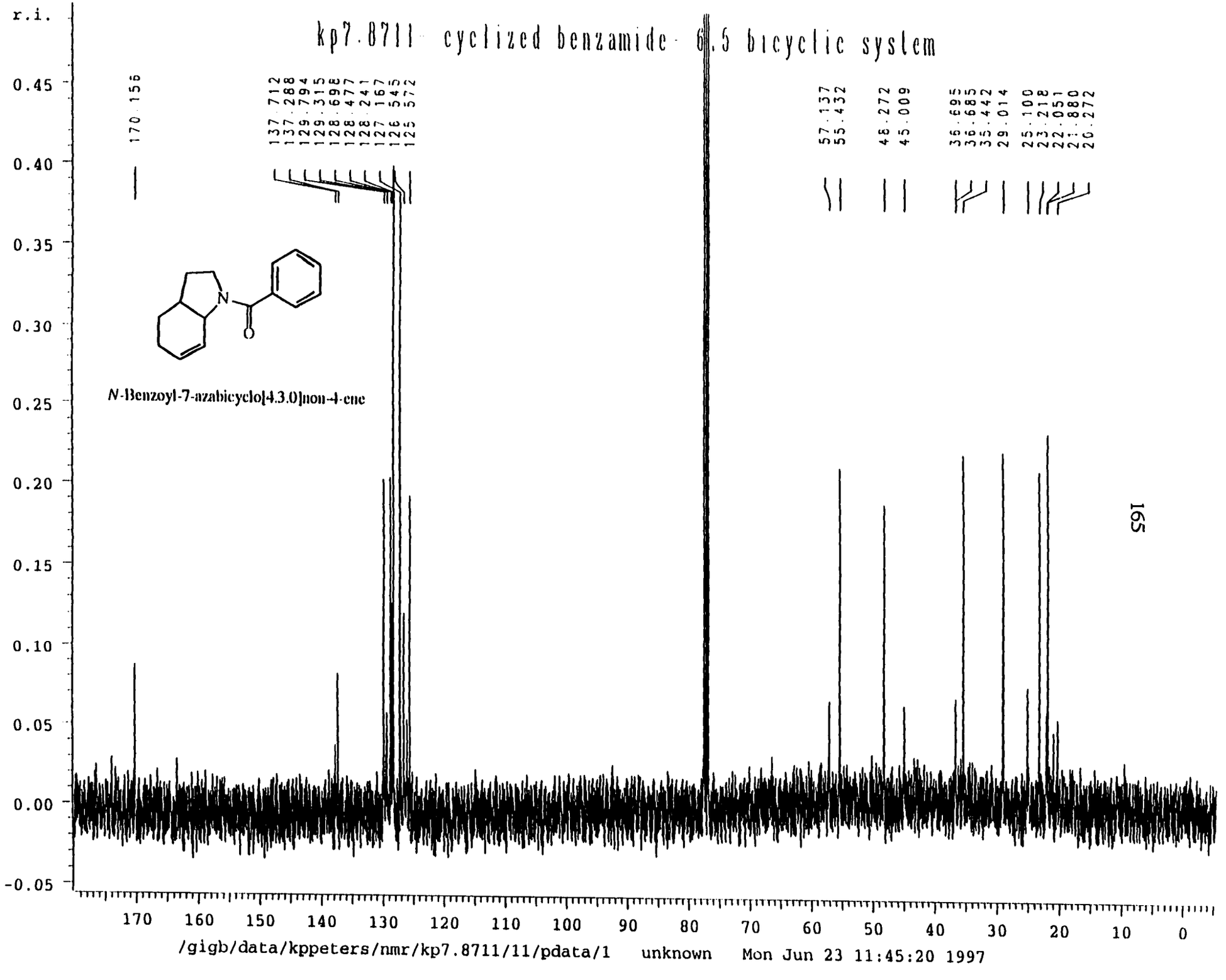
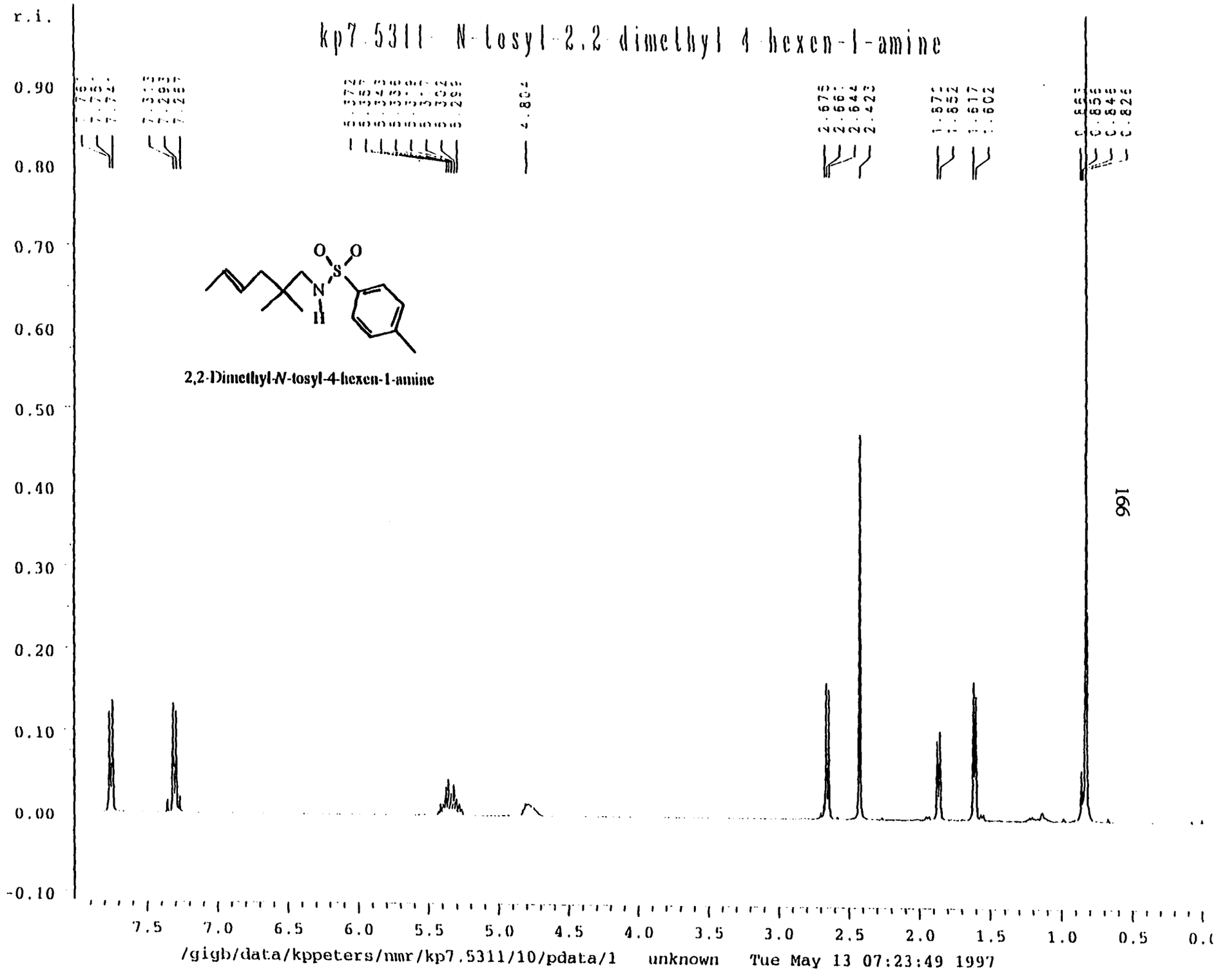
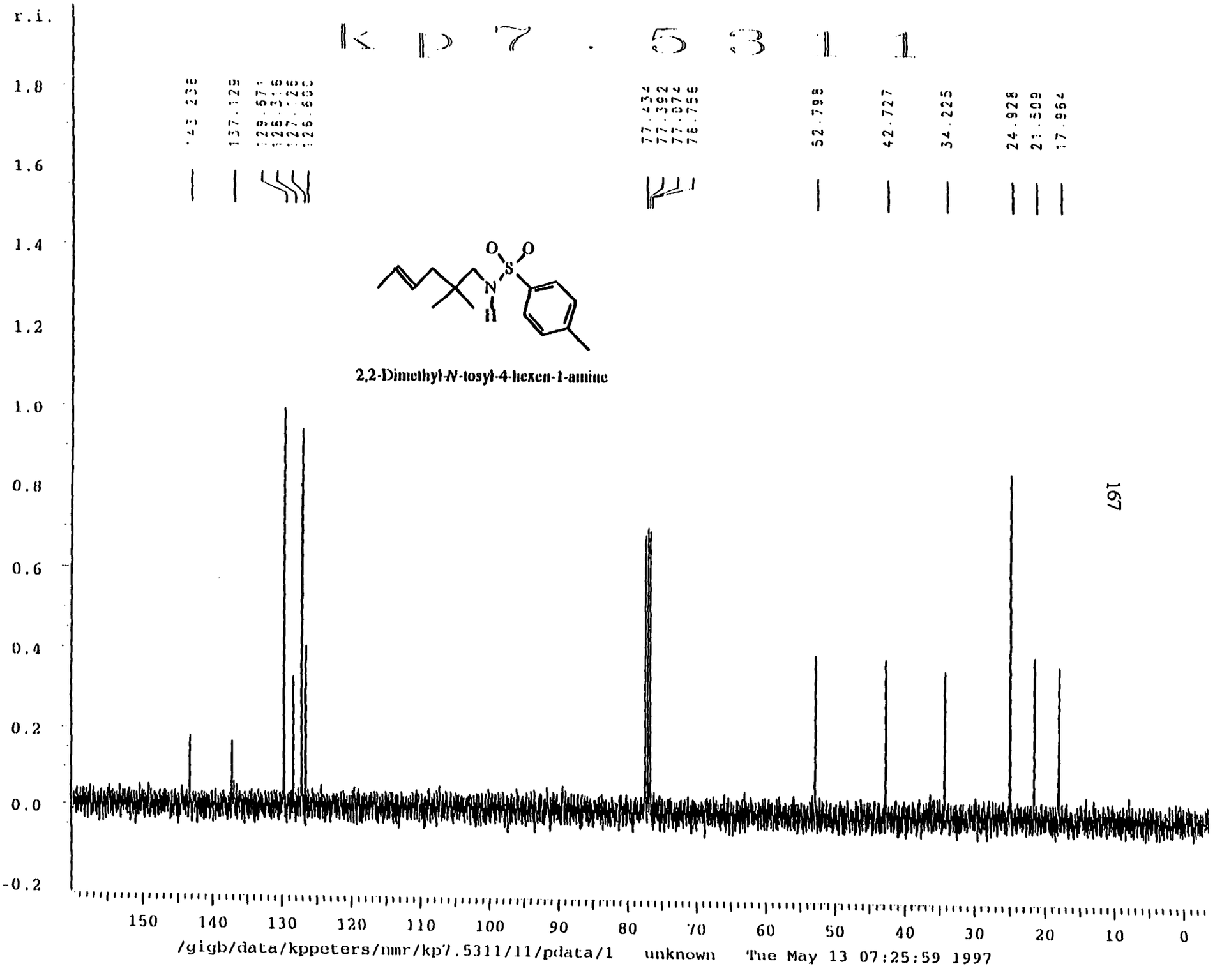
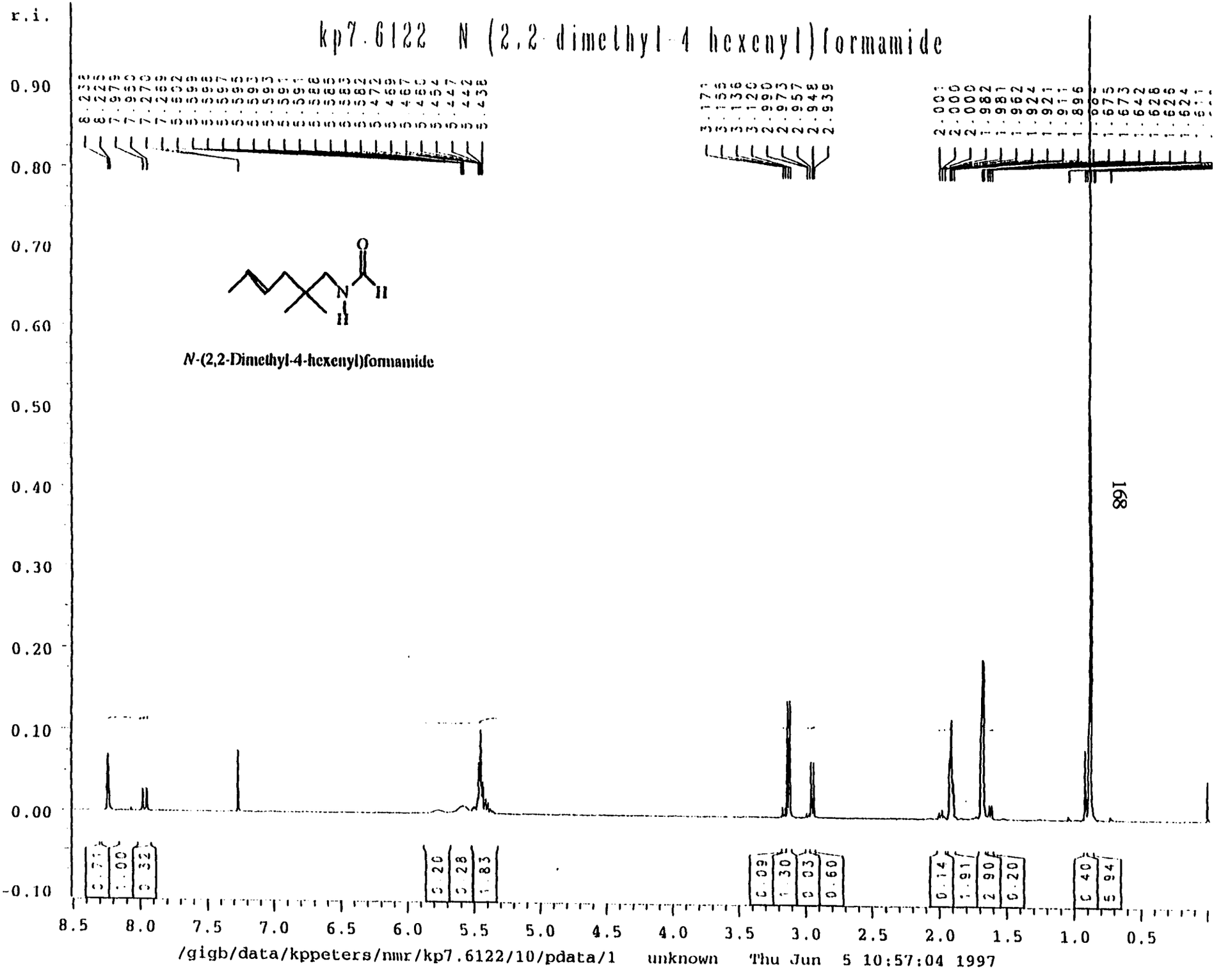
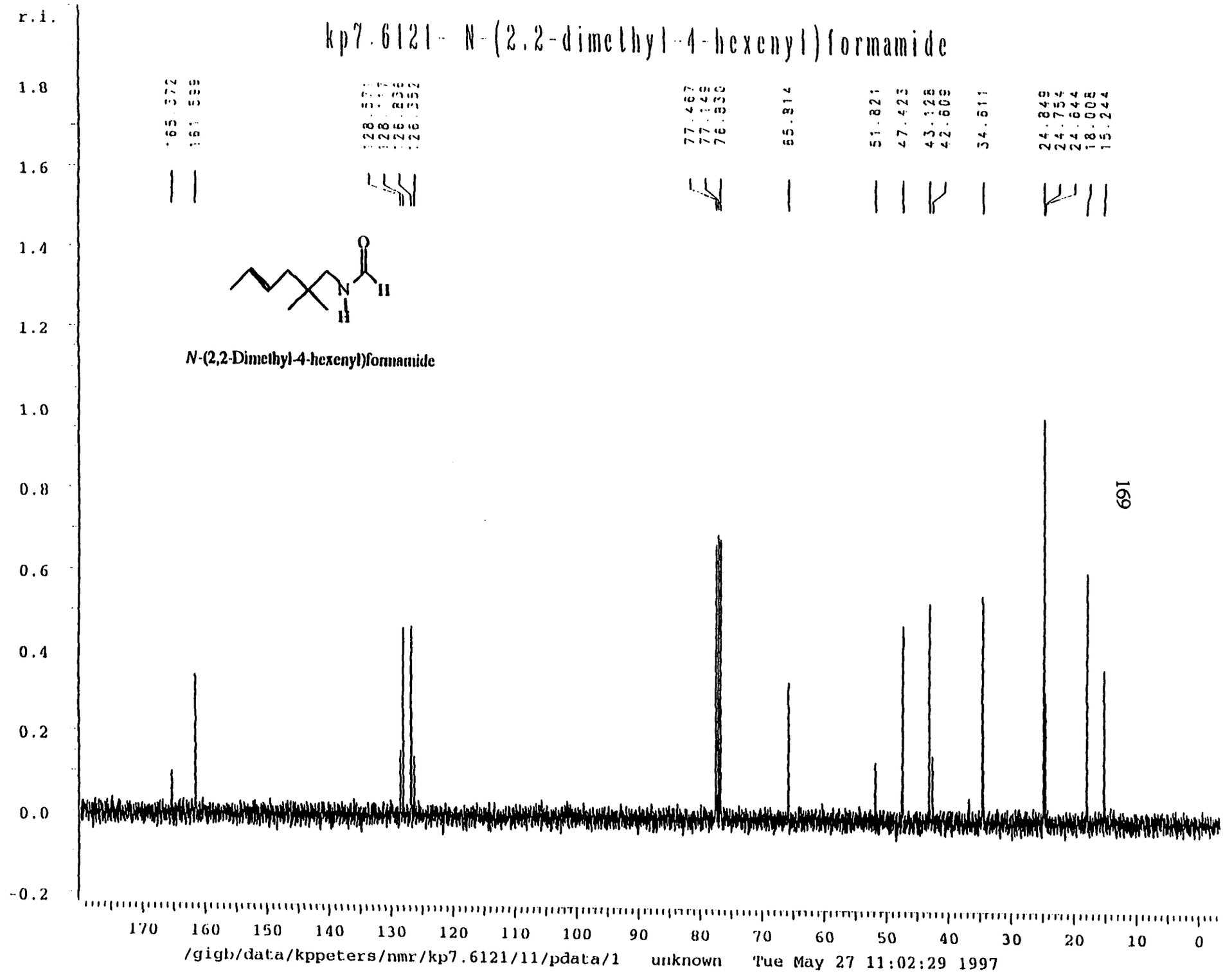

kp7.8711 cyclized benzamide 6,5 bicyclic system
r.i.
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
170.156
137.712
137.288
129.794
129.315
128.698
128.477
128.241
127.167
126.545
125.572
57.137
55.432
48.272
45.009
36.695
36.685
35.442
29.014
25.100
23.218
22.051
21.880
20.272
N
O
N-Benzoyl-7-azabicyclo[4.3.0]non-4-ene
165
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
/gigb/data/kppeters/nmr/kp7.8711/11/pdata/1 unknown Mon Jun 23 11:45:20 1997

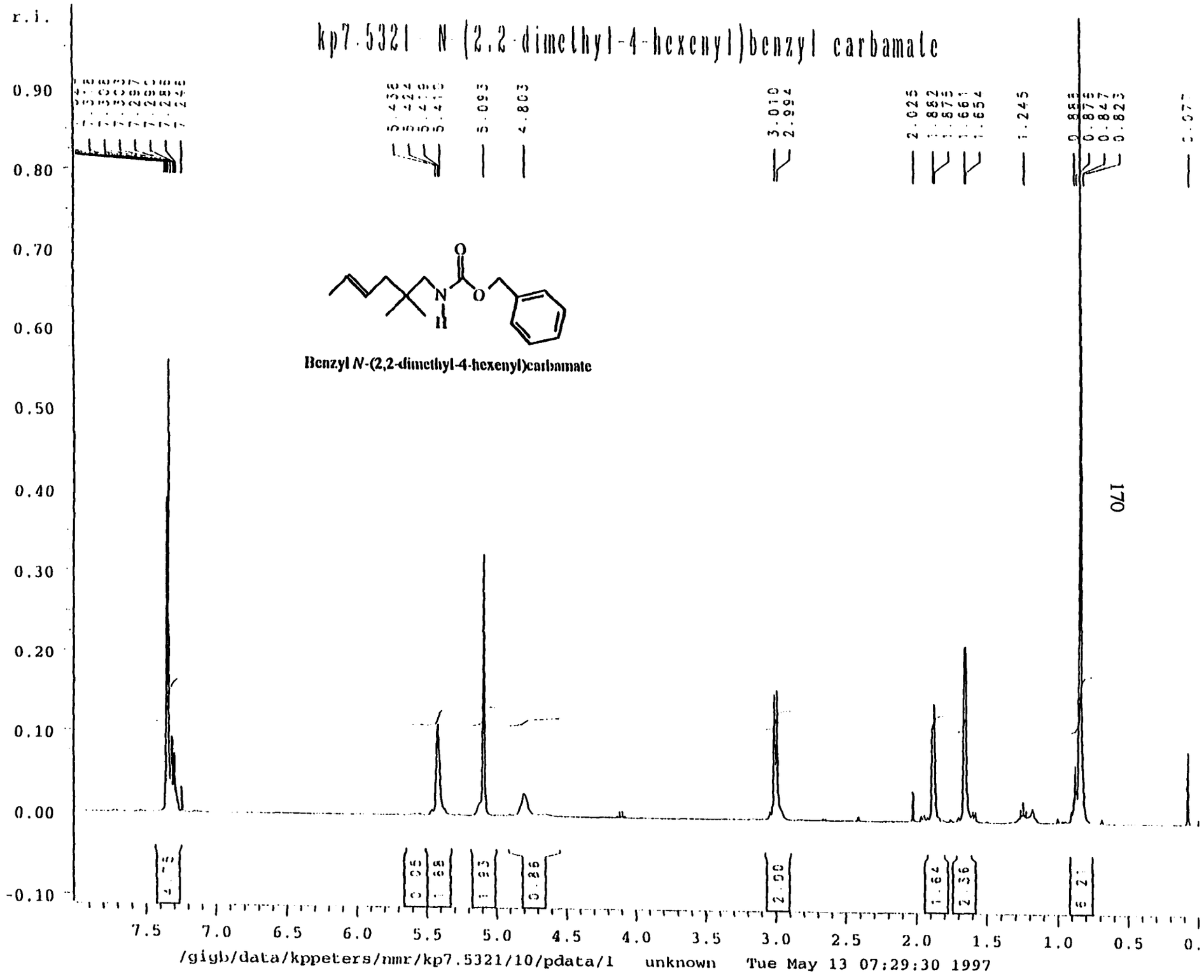

kp7.5311 N-tosyl-2,2-dimethyl-4-hexen-1-amine
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
4.804
2.675
2.661
2.644
2.423
1.671
1.652
1.617
1.602
0.865
0.856
0.848
0.826
O
S
O
N
H
2,2-Dimethyl-N-tosyl-4-hexen-1-amine
166
/gigb/data/kppeters/nmr/kp7.5311/10/pdata/1 unknown Tue May 13 07:23:49 1997



2,2-Dimethyl-*N*-tosyl-4-hexen-1-amine

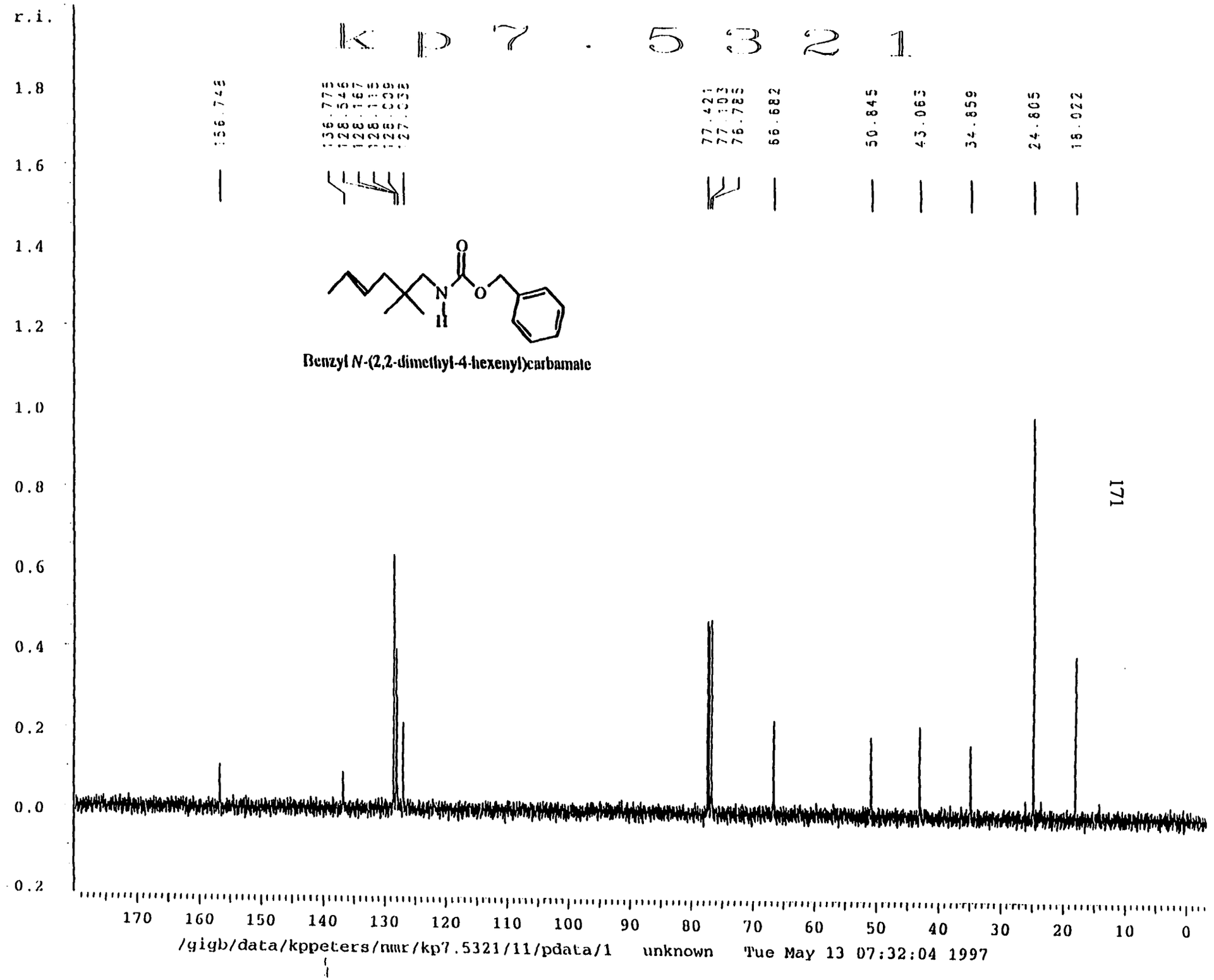

kp7.6122 N (2,2-dimethyl-4 hexenyl)formamide
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
N-(2,2-Dimethyl-4-hexenyl)formamide
168
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
/gigb/data/kppeters/nmr/kp7.6122/10/pdata/1 unknown Thu Jun 5 10:57:04 1997

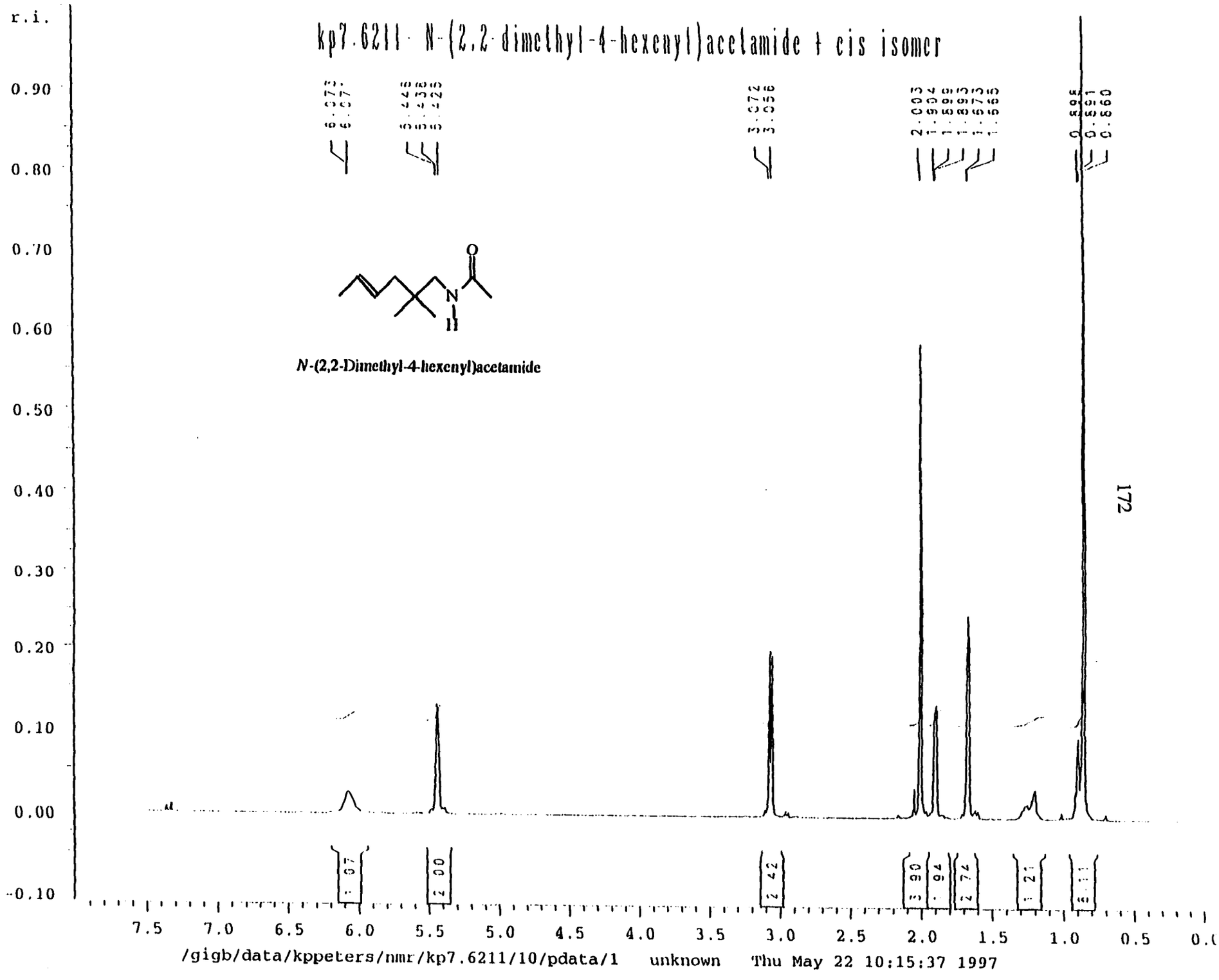

kp7.6121 - N-(2,2-dimethyl-4-hexenyl)formamide
r.i.
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
165.372
161.599
128.571
128.117
126.838
126.352
77.467
77.146
76.838
65.814
51.821
47.423
43.128
42.609
34.611
24.849
24.754
24.644
18.008
15.244
169
N-(2,2-Dimethyl-4-hexenyl)formamide
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
/gigb/data/kppeters/nmr/kp7.6121/11/pdata/1 unknown Tue May 27 11:02:29 1997



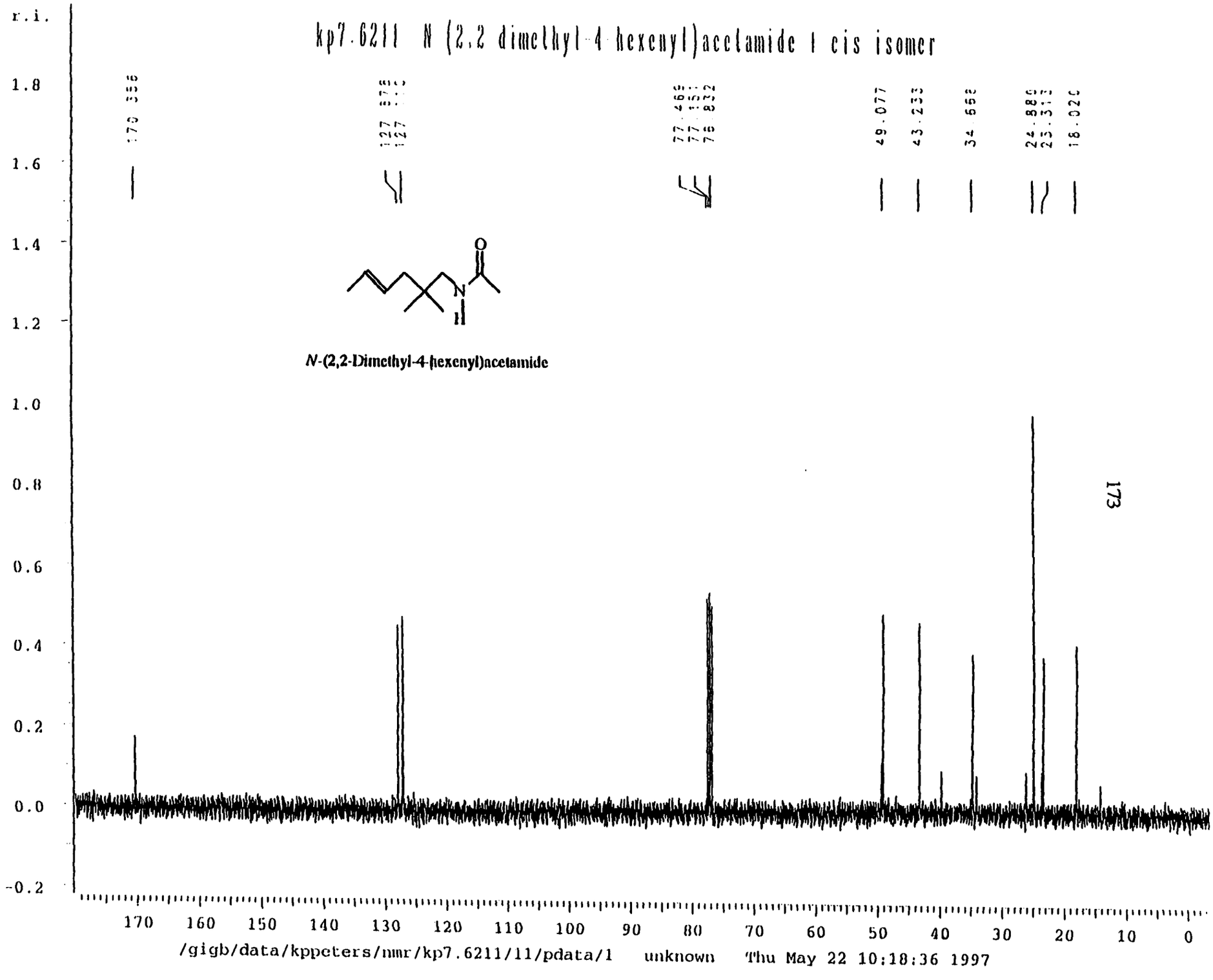
Benzyl *N*-(2,2-dimethyl-4-hexenyl)carbamate

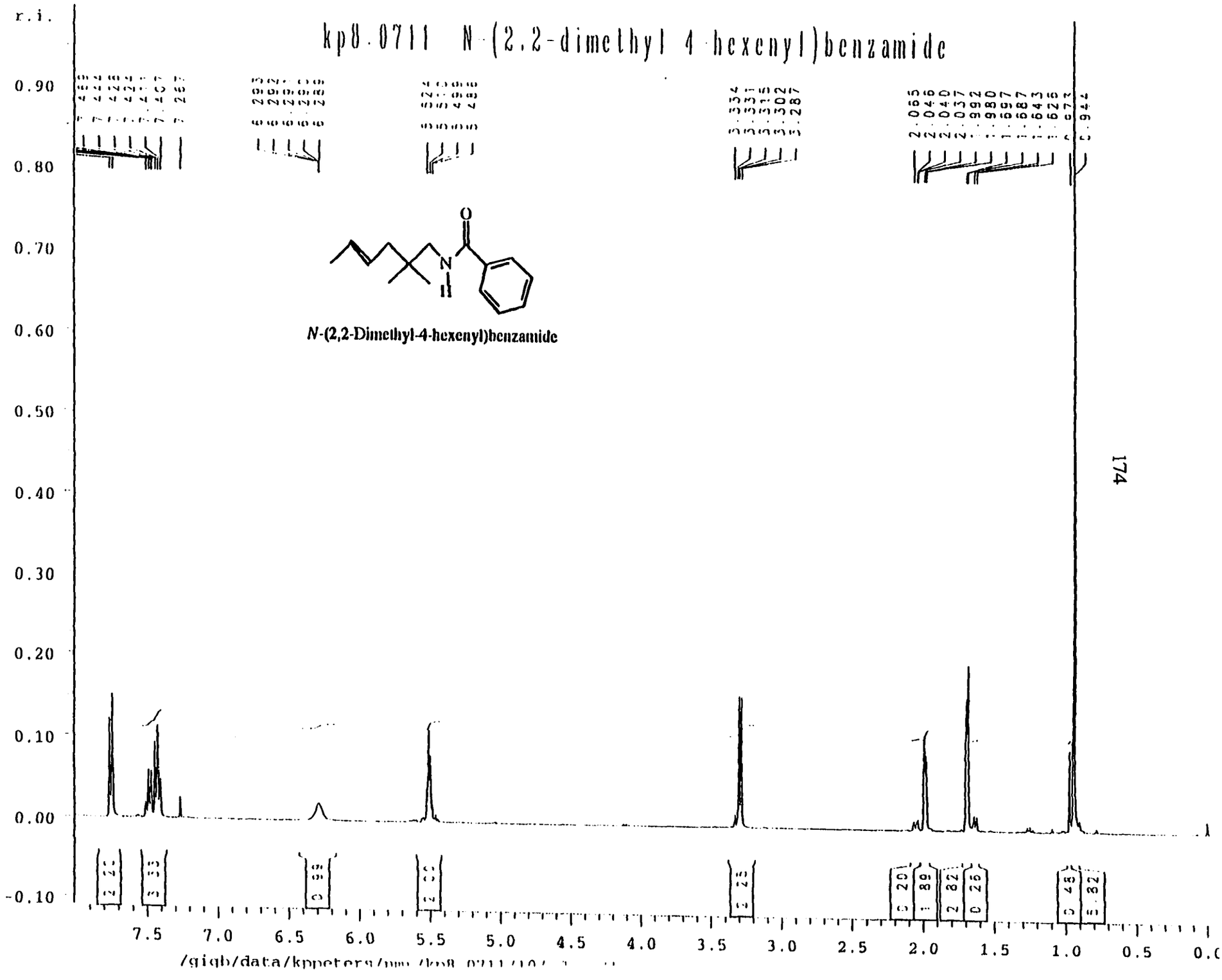
kp7.5321

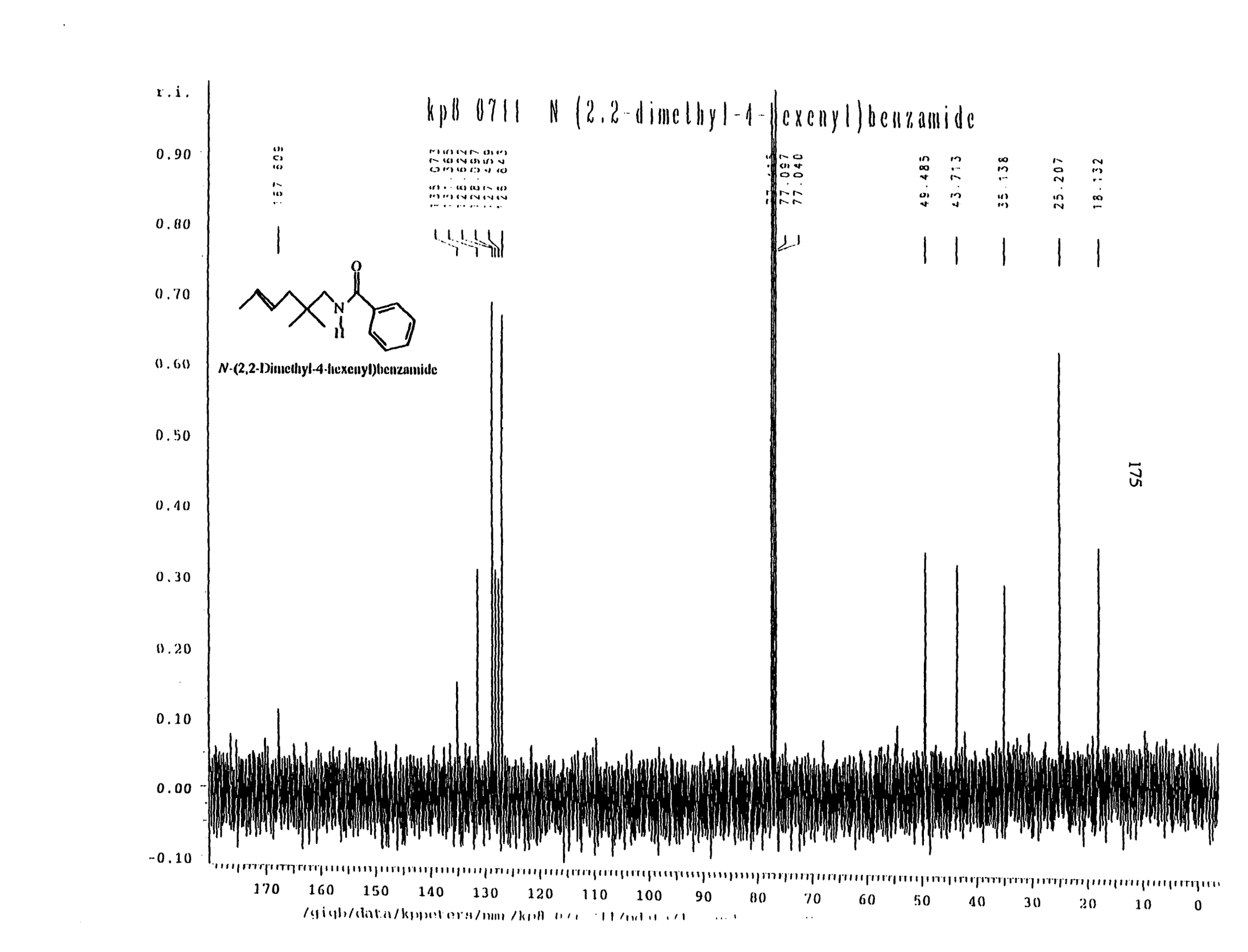

r.i.
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
0.2
156.748
136.775
128.546
128.167
128.133
128.039
127.838
77.421
77.103
76.785
66.682
50.845
43.063
34.859
24.805
18.022
O
N
H
O
Benzyl N-(2,2-dimethyl-4-hexenyl)carbamate
171
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
/gigb/data/kppeters/nmr/kp7.5321/11/pdata/1 unknown Tue May 13 07:32:04 1997

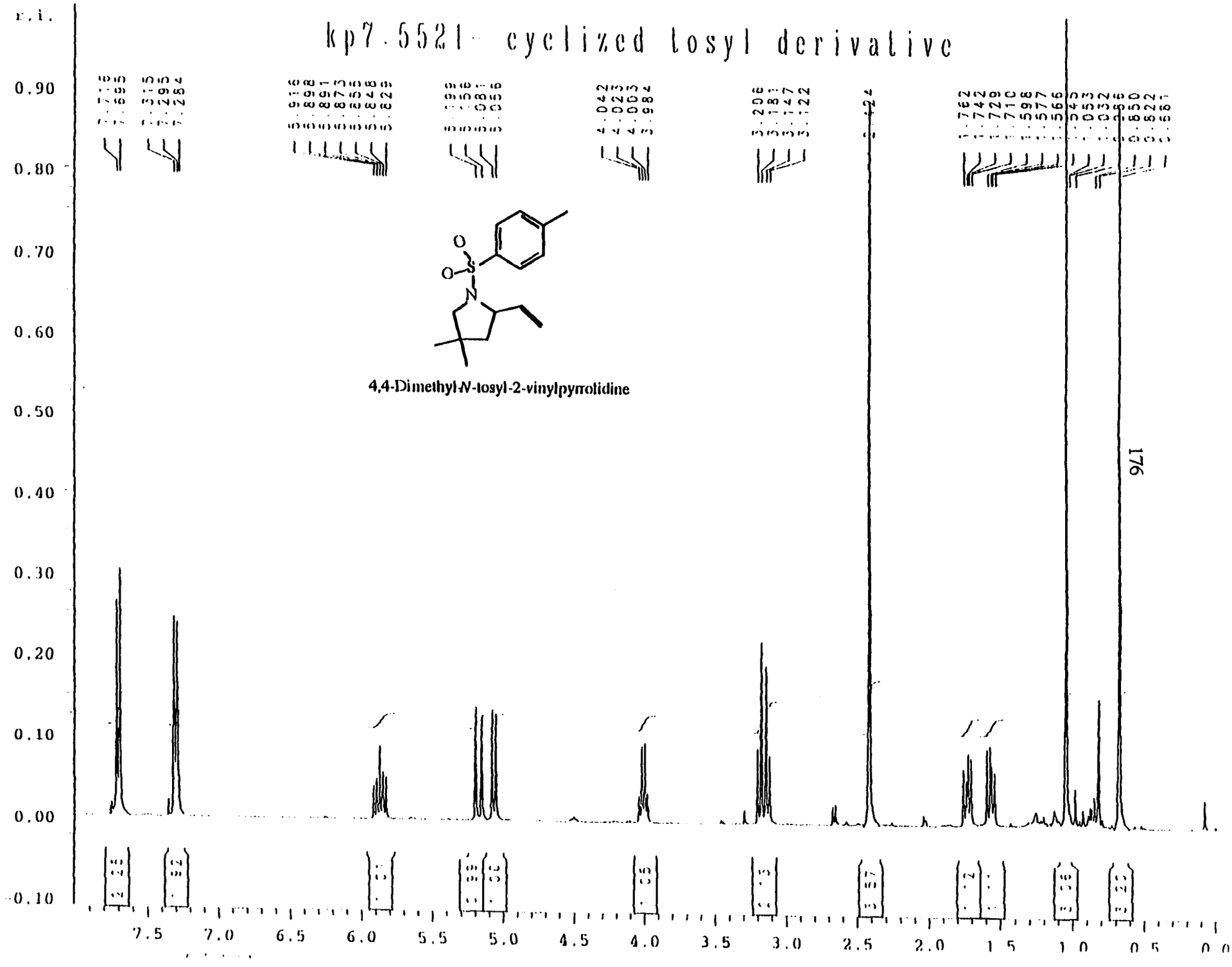


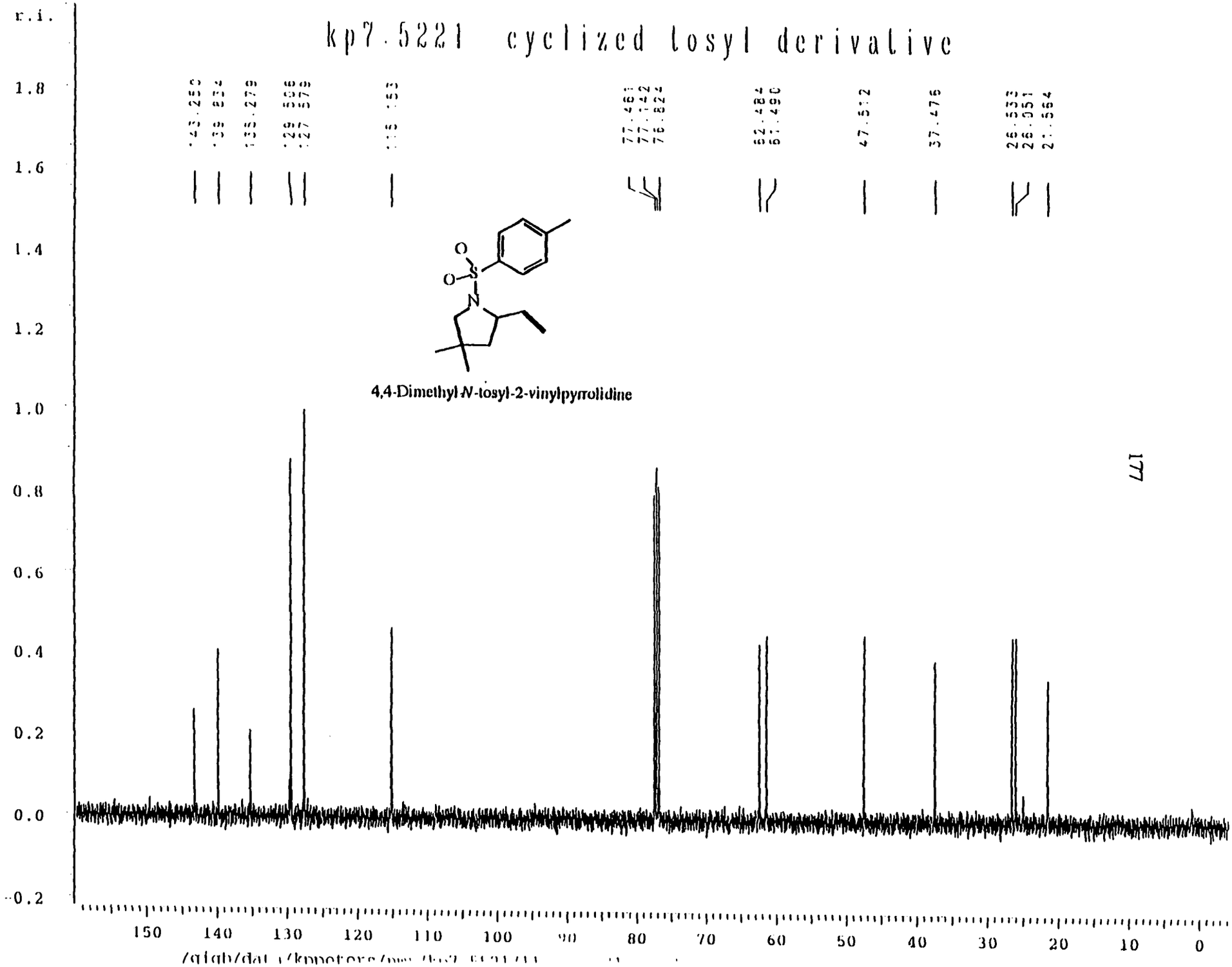
N-(2,2-Dimethyl-4-hexenyl)acetamide

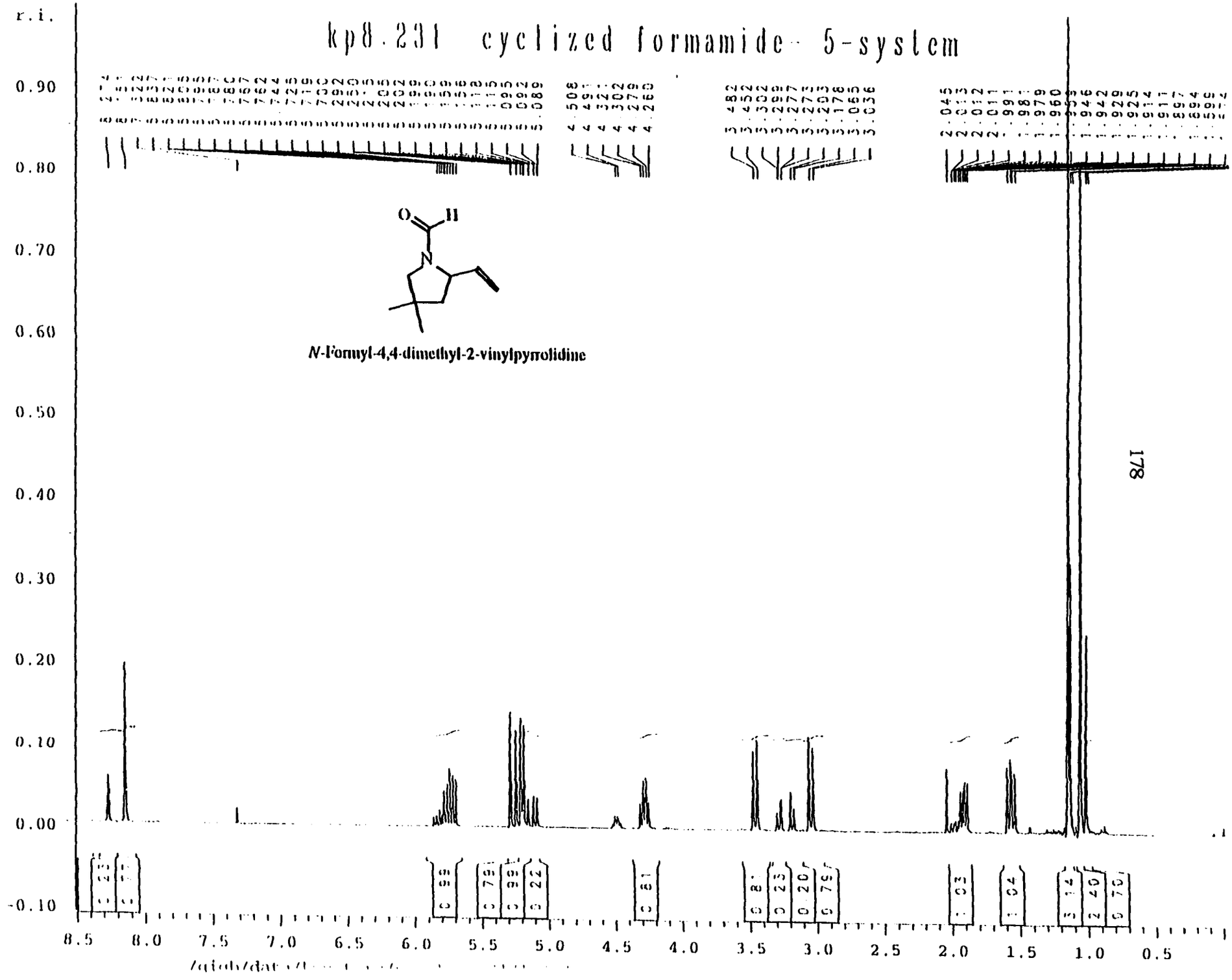

kp7.6211 N (2,2 dimethyl-4 hexenyl)acetamide I cis isomer
r.i.
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
170.336
127.878
127.
77.466
77.151
76.832
49.077
43.233
34.668
24.886
23.313
18.020
O
N
H
N-(2,2-Dimethyl-4-hexenyl)acetamide
173
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
/gigb/data/kppeters/nmr/kp7.6211/11/pdata/1 unknown Thu May 22 10:18:36 1997

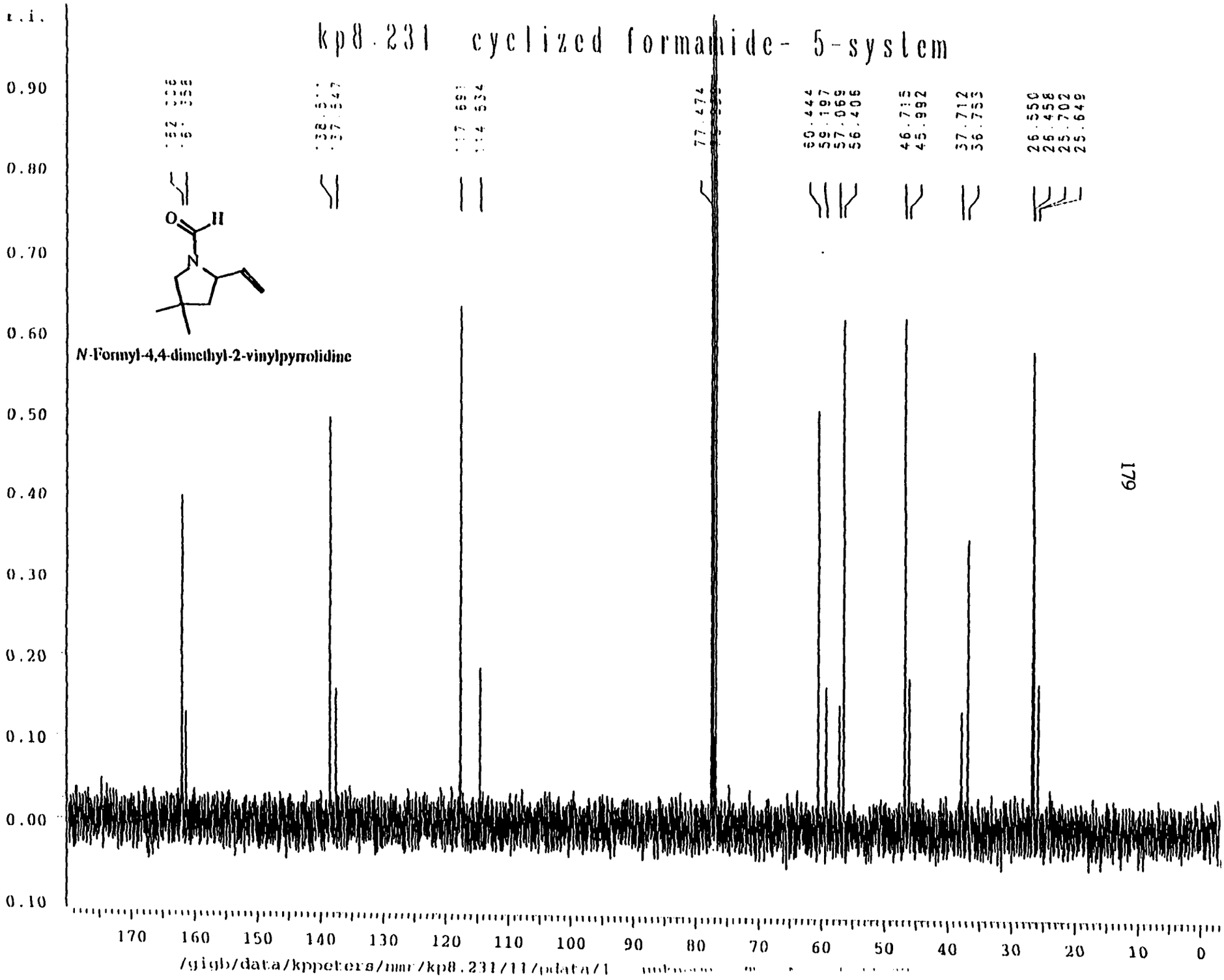

kp8.0711 N-(2,2-dimethyl 4-hexenyl)benzamide
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
/giqb/data/kppeters/nmr/kp8_0711/10/
N-(2,2-Dimethyl-4-hexenyl)benzamide
174

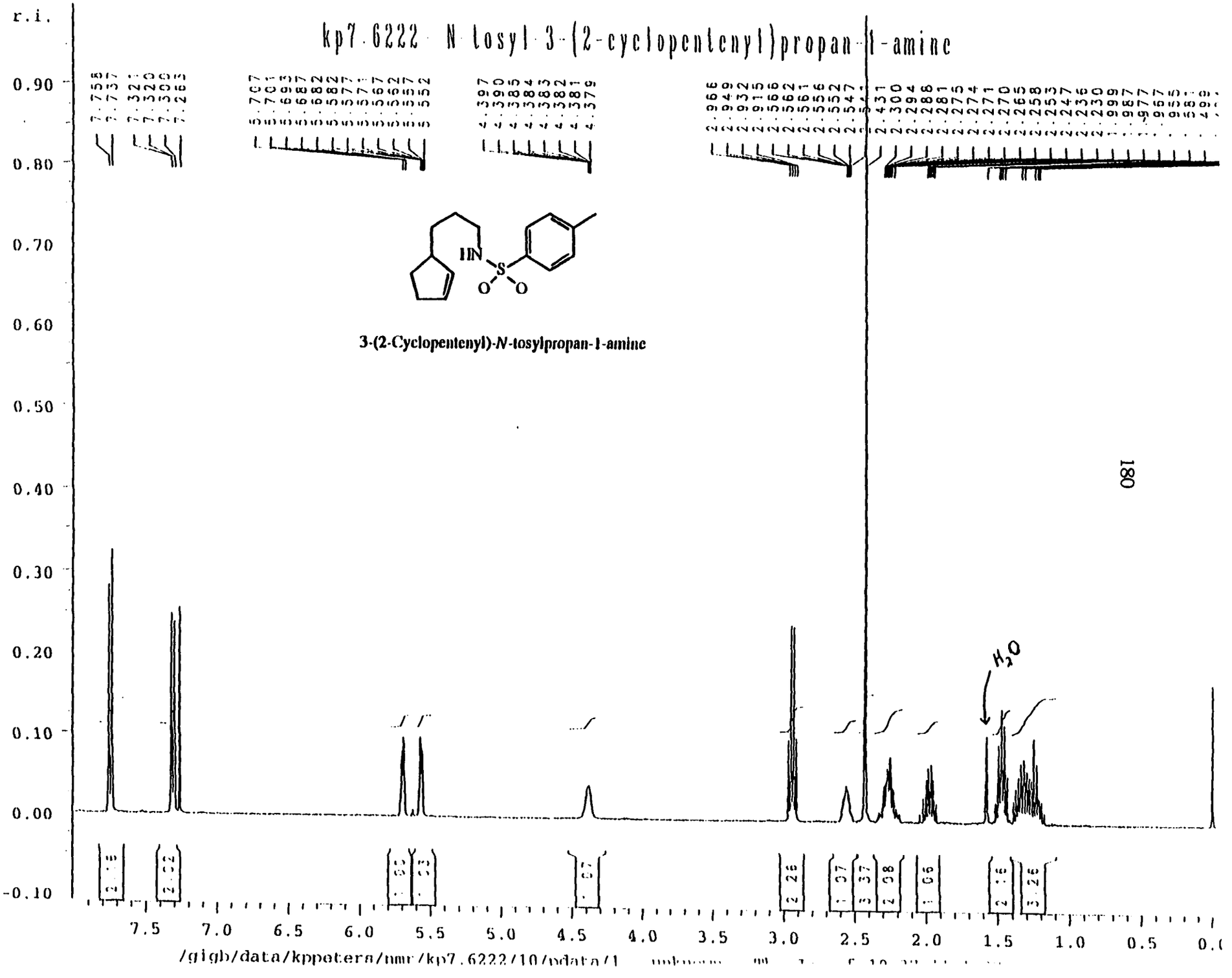

kp8 0711 N (2,2-dimethyl-4-hexenyl)benzamide
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
167.809
135.073
131.366
128.622
128.097
127.459
126.843
77.097
77.040
49.485
43.713
35.138
25.207
18.132
N-(2,2-Dimethyl-4-hexenyl)benzamide
175
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
/giqb/data/kppeters/nmr/kp8


kp7.5521- cyclized tosyl derivative
4,4-Dimethyl-N-tosyl-2-vinylpyrrolidine
176

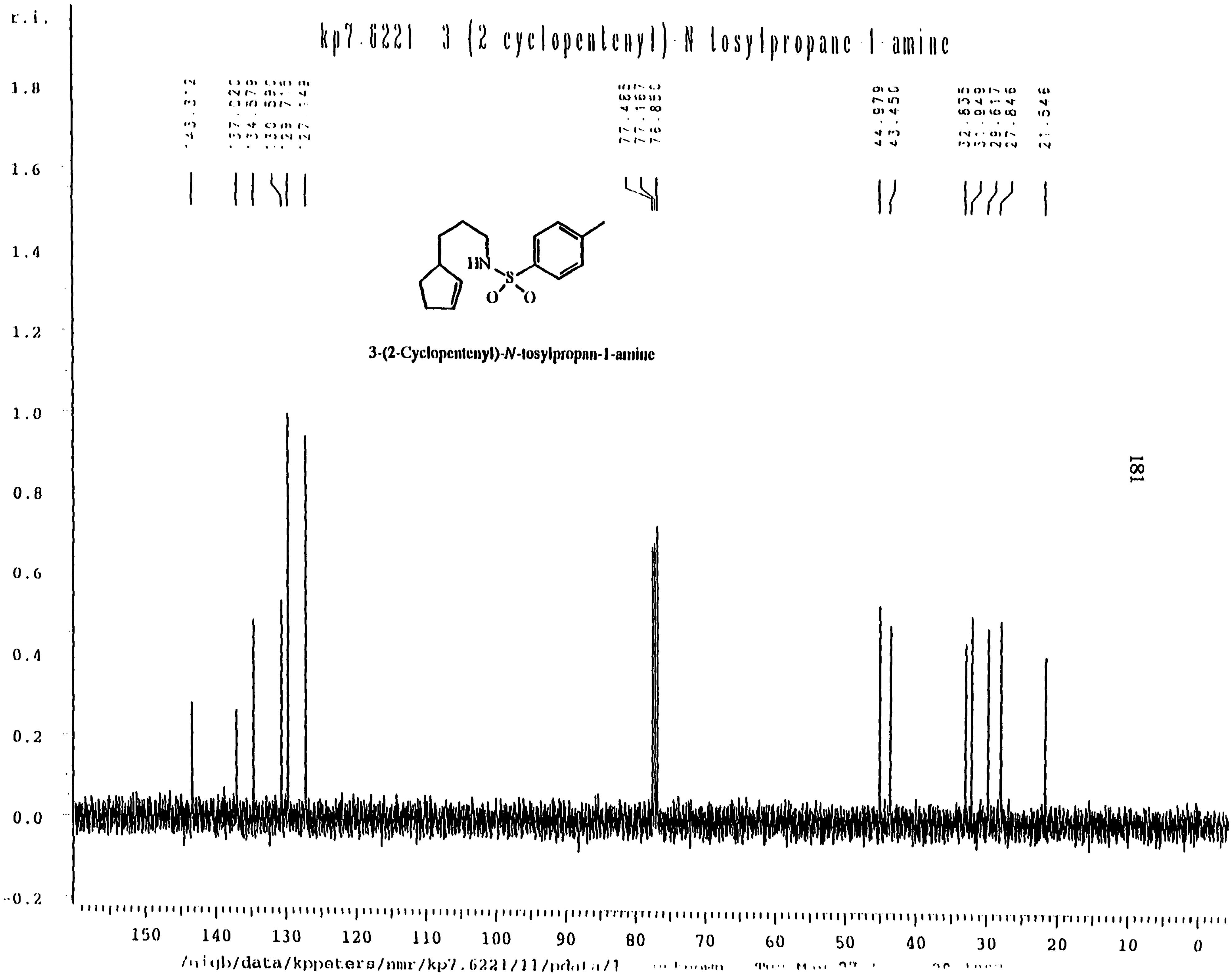

kp7.5221 cyclized tosyl derivative
r.i.
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
143.253
139.834
135.279
129.556
127.579
118.153
77.461
77.142
76.824
62.484
57.490
47.512
37.476
26.533
26.051
21.564
O
O
S
N
4,4-Dimethyl-N-tosyl-2-vinylpyrrolidine
177
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0


kp8.231 cyclized formamide - 5-system
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
O
H
N
N-Formyl-4,4-dimethyl-2-vinylpyrrolidine
178

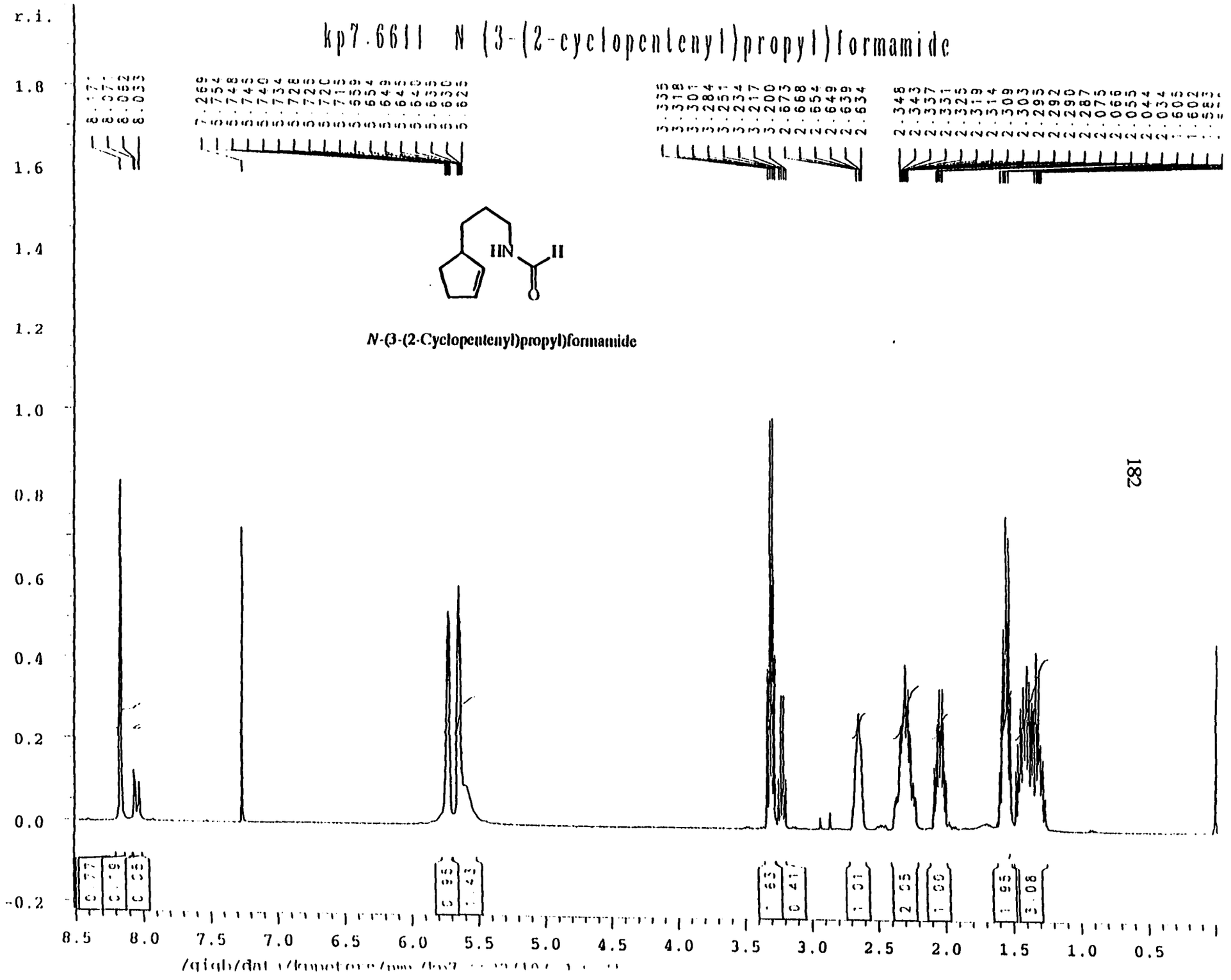

kp8.231 cyclized formamide- 5-system
N-Formyl-4,4-dimethyl-2-vinylpyrrolidine
O
H
N
132.338
131.358
138.511
137.347
117.681
114.534
77.474
60.444
59.197
57.069
56.406
46.715
45.992
37.712
36.753
26.550
26.458
25.702
25.649
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
0.10
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
/gigb/data/kppeters/nmr/kp8.231/11/pdata/1
179

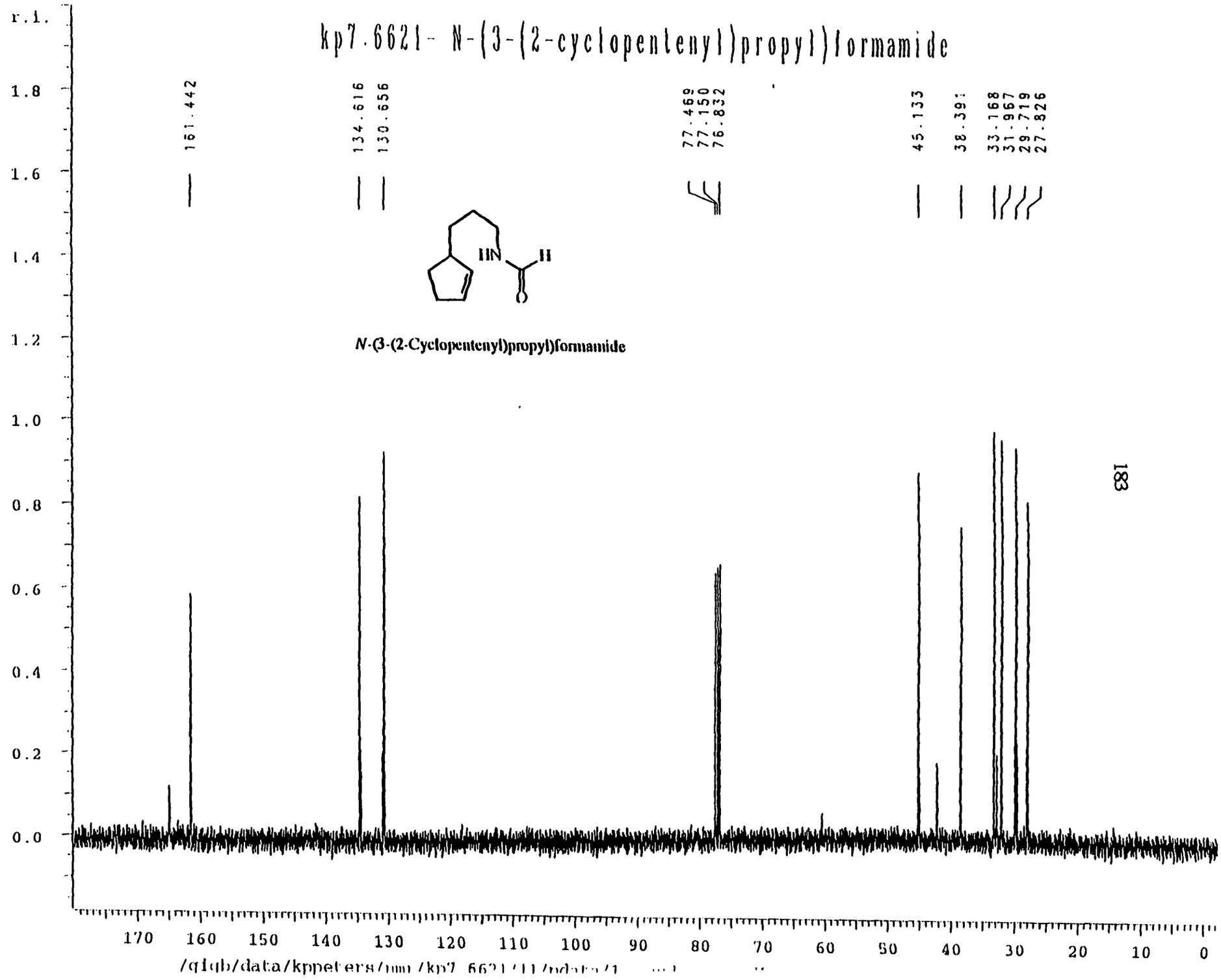


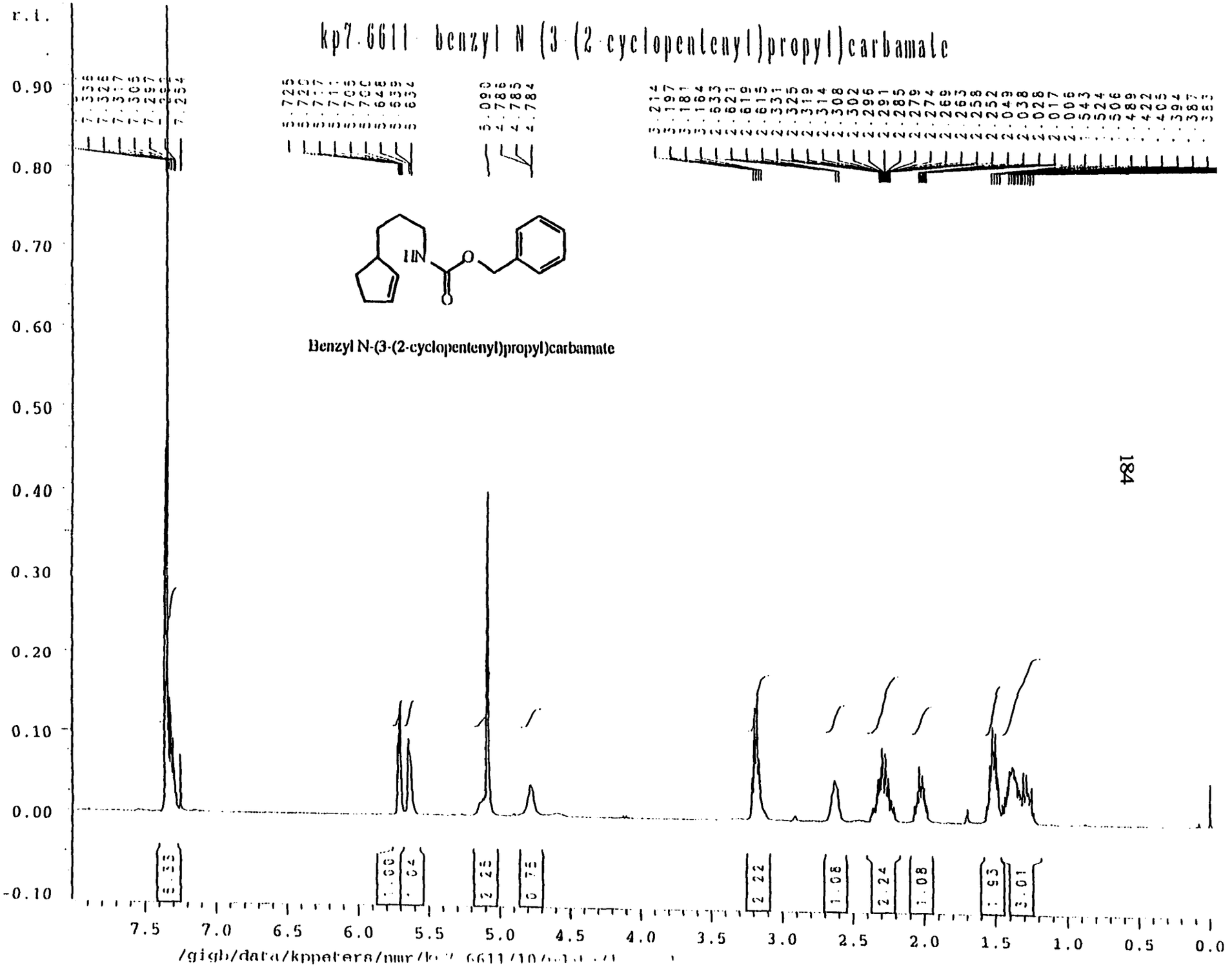
3-(2-Cyclopentenyl)-*N*-tosylpropan-1-amine

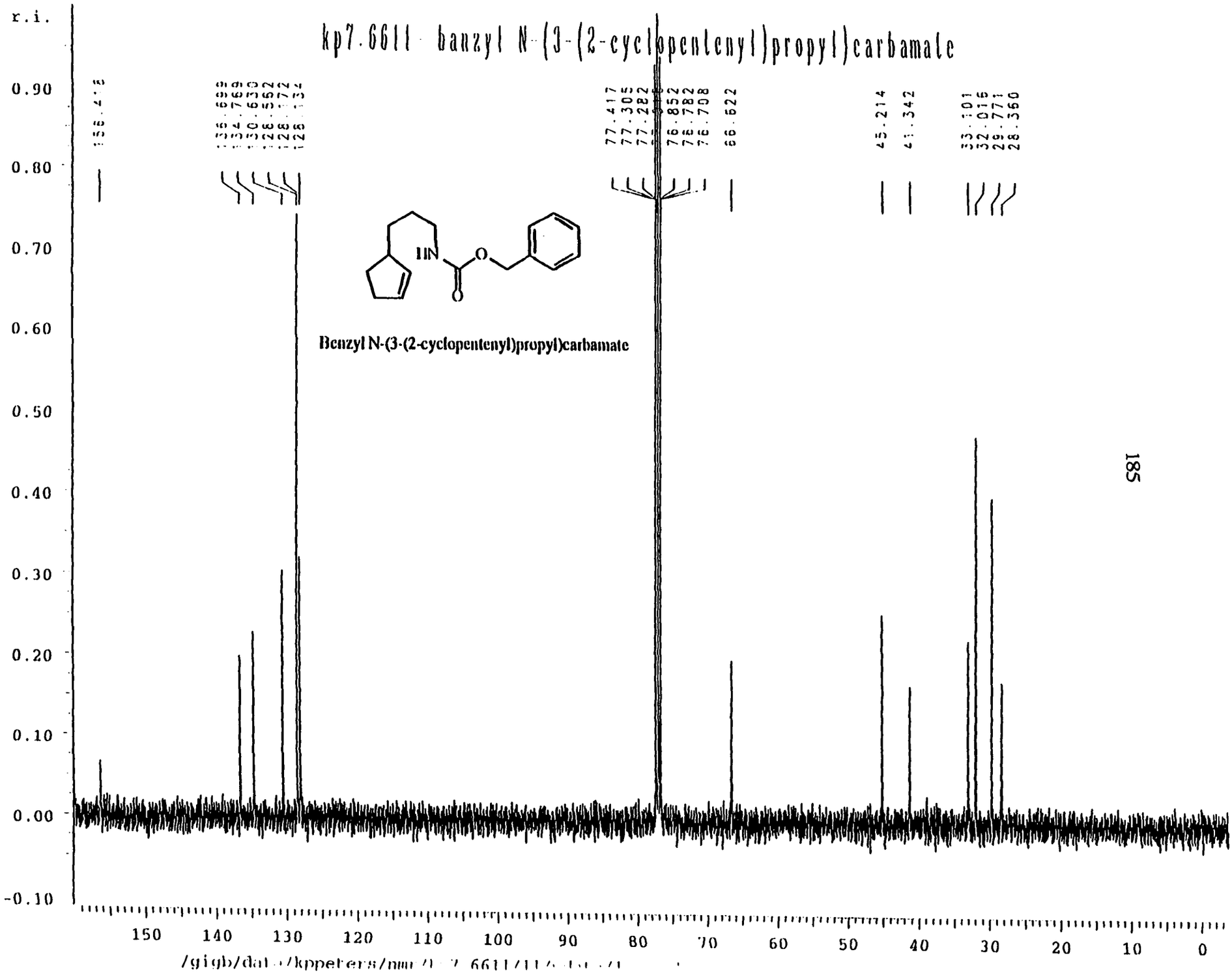


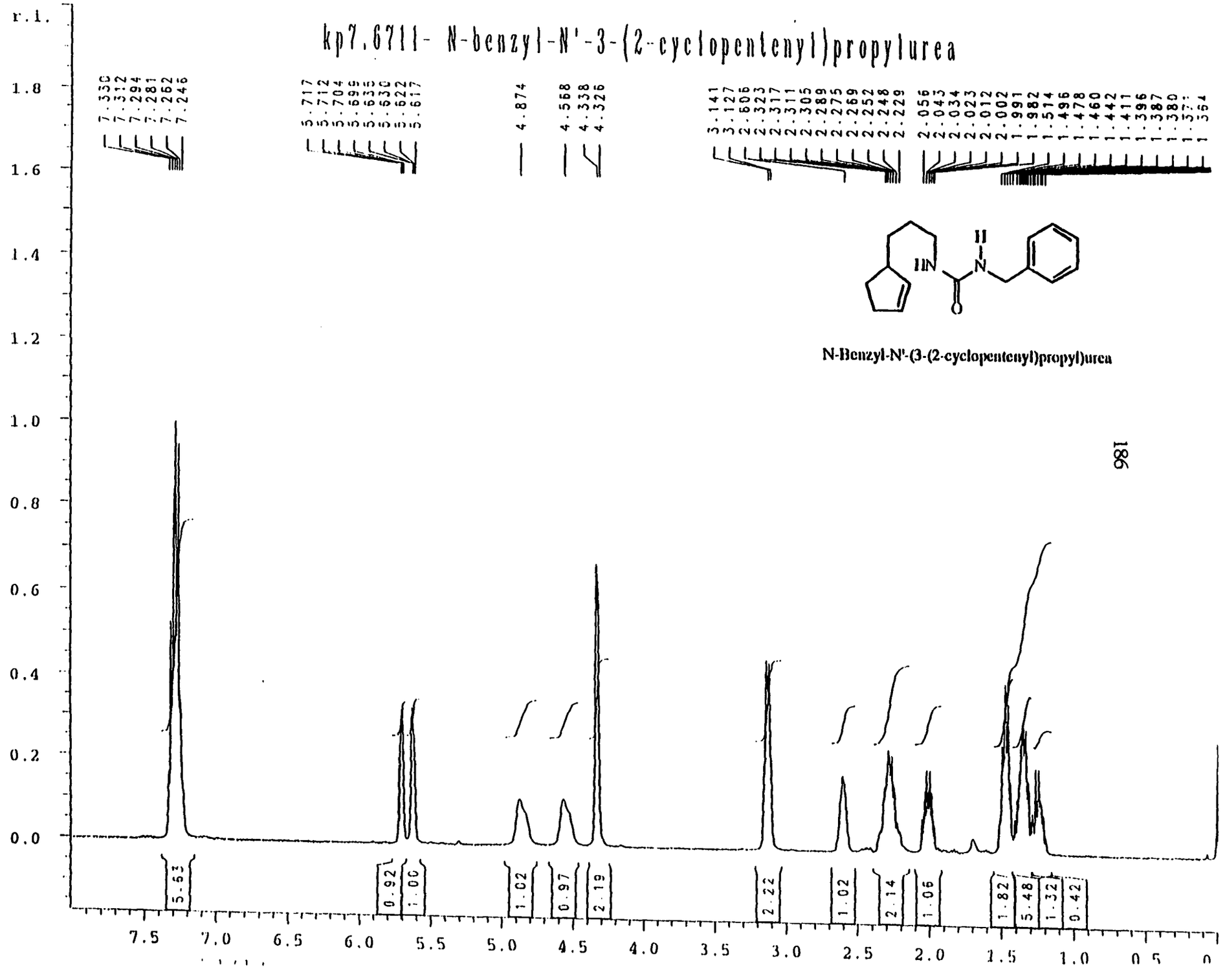
kp7.6221 3 (2 cyclopentenyl) N tosylpropane 1 amine
3-(2-Cyclopentenyl)-*N*-tosylpropan-1-amine
HN
S
O
O
77.485
77.165
76.855
44.979
43.450
21.546
r.i.
/nigb/data/kppeters/nmr/kp7.6221/11/pdata/1

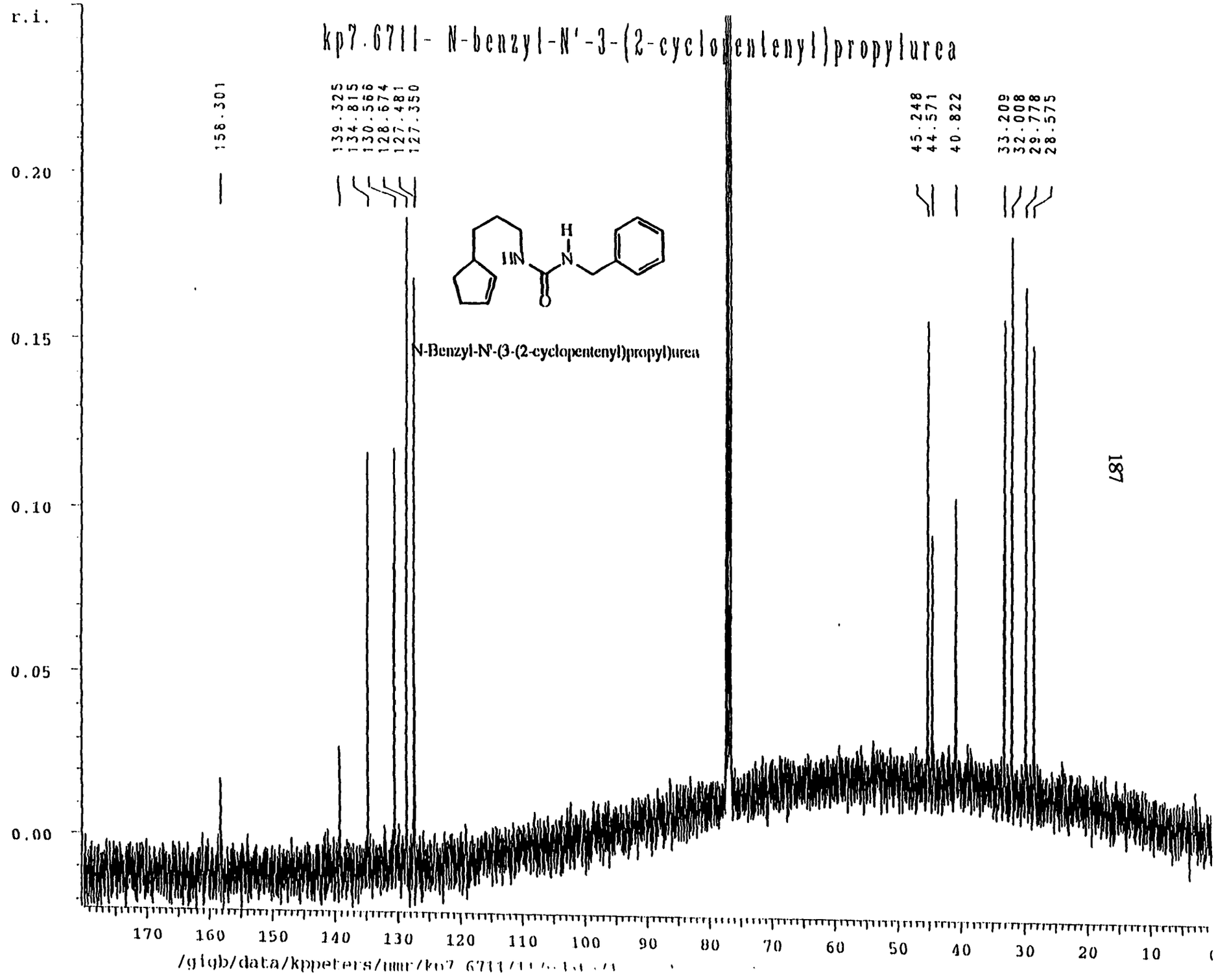

r.i.
kp7.6611 N (3-(2-cyclopentenyl)propyl)formamide
HN
H
O
N-(3-(2-Cyclopentenyl)propyl)formamide
182
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

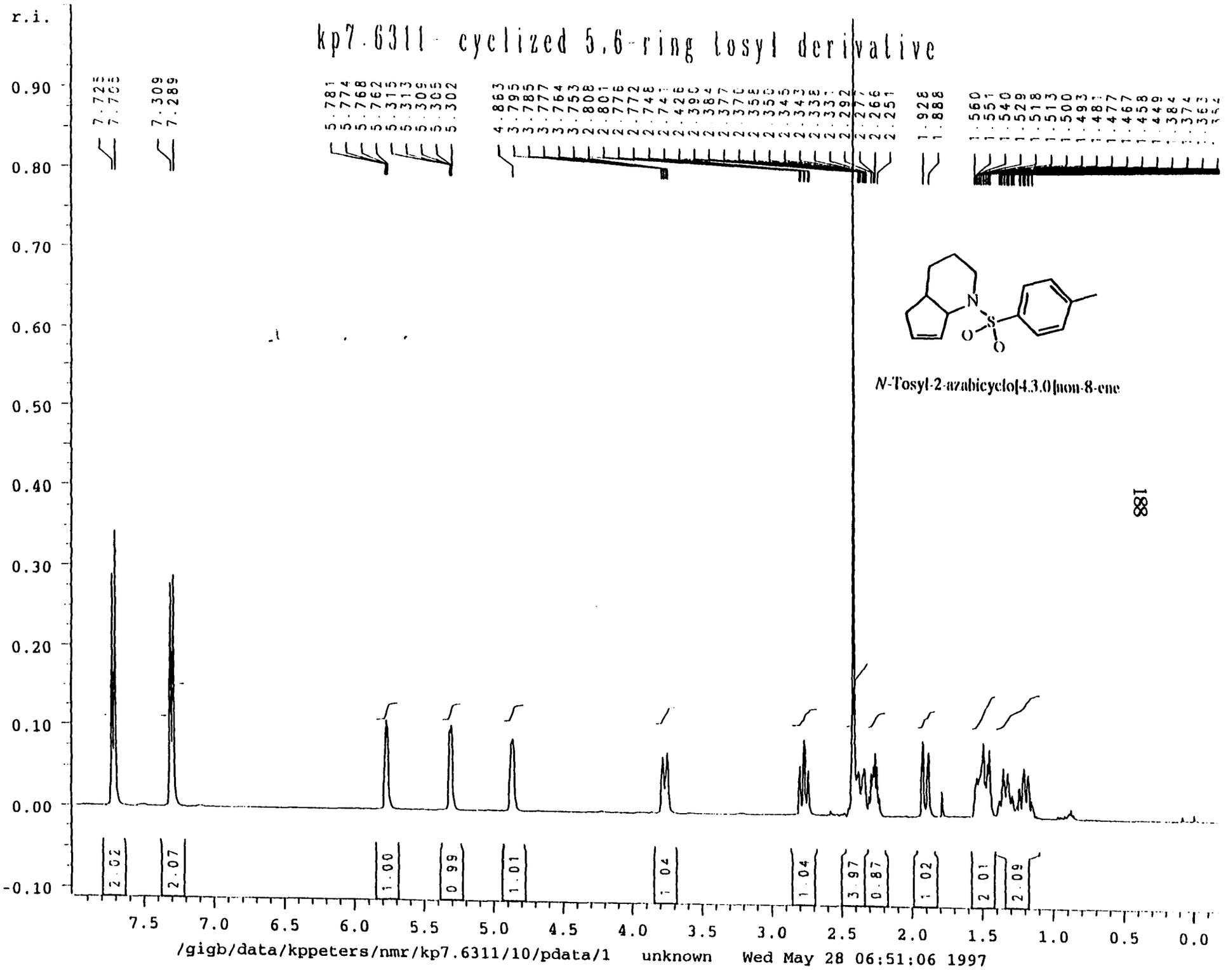

kp7.6621- N-(3-(2-cyclopentenyl)propyl)formamide
161.442
134.616
130.656
77.469
77.150
76.832
45.133
38.391
33.168
31.967
29.719
27.826
N-(3-(2-Cyclopentenyl)propyl)formamide
r.i.
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
183


kp7.6611 benzyl N (3 (2 cyclopentenyl)propyl)carbamate
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
HN
O
O
Benzyl N-(3-(2-cyclopentenyl)propyl)carbamate

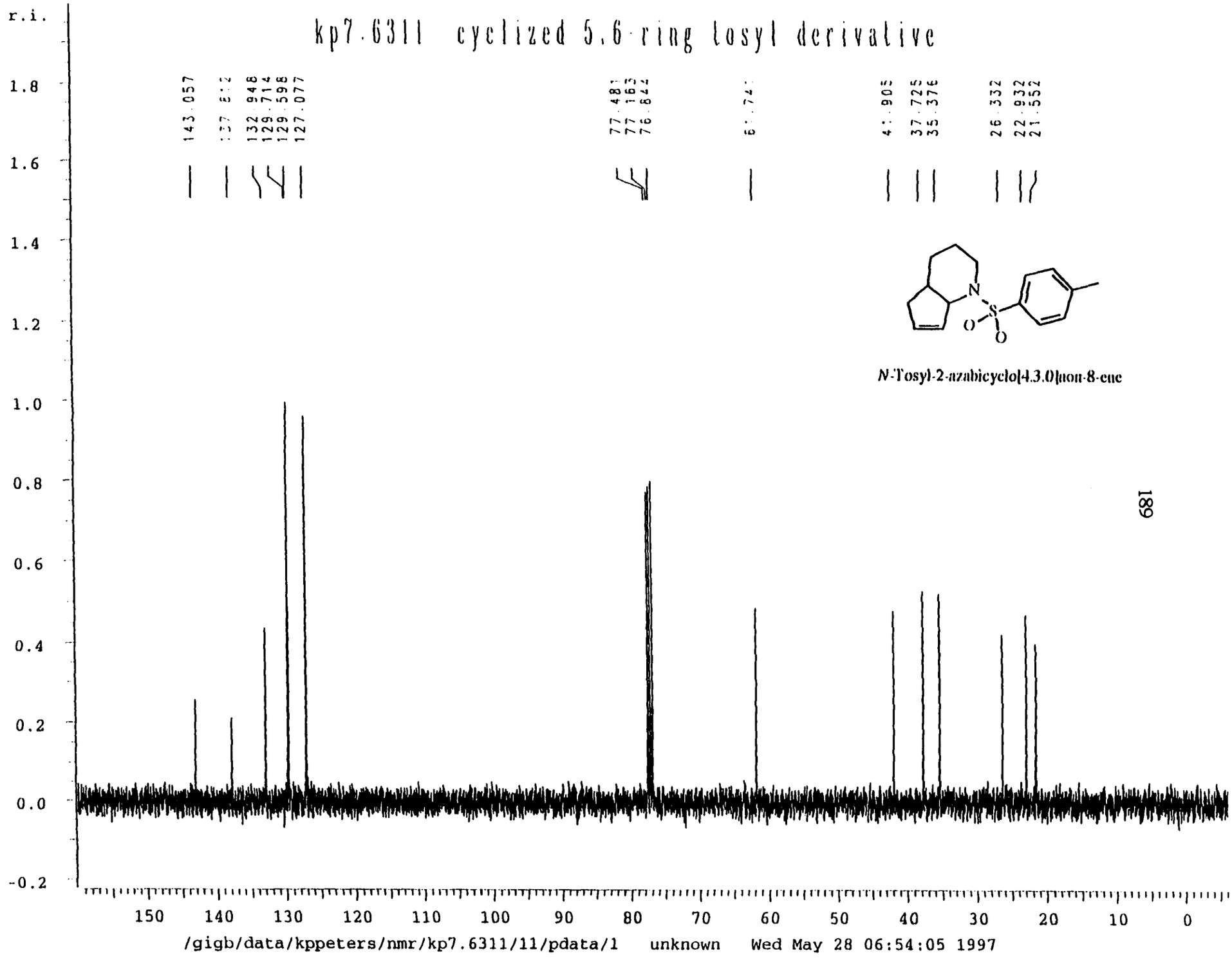

kp7.6611 benzyl N-(3-(2-cyclopentenyl)propyl)carbamate
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
156.418
136.699
134.769
130.630
128.562
128.172
128.134
77.417
77.305
77.282
76.852
76.782
76.708
66.622
45.214
41.342
33.101
32.016
29.771
28.360
HN
O
O
Benzyl N-(3-(2-cyclopentenyl)propyl)carbamate
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
/gigb/dat

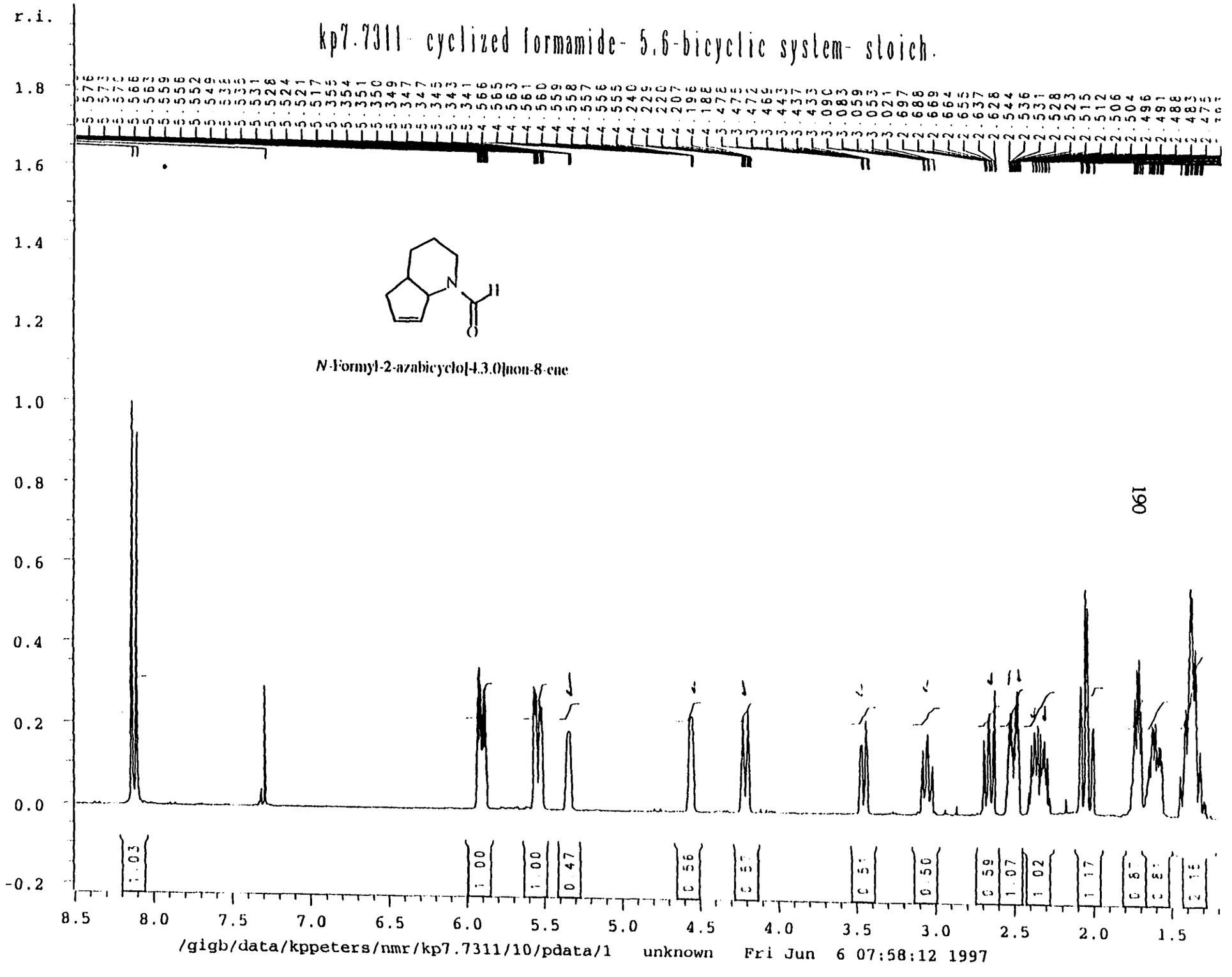

kp7.6711- N-benzyl-N'-3-(2-cyclopentenyl)propylurea
r.i.
7.336
7.312
7.294
7.281
7.262
7.246
5.717
5.712
5.704
5.699
5.635
5.630
5.622
5.617
4.874
4.568
4.338
4.326
3.141
3.127
2.606
2.323
2.317
2.311
2.305
2.289
2.275
2.269
2.252
2.248
2.229
2.056
2.043
2.034
2.023
2.012
2.002
1.991
1.982
1.514
1.496
1.478
1.460
1.442
1.411
1.396
1.387
1.380
1.364
HN
N
O
N-Benzyl-N'-(3-(2-cyclopentenyl)propyl)urea
5.63
0.92
1.06
1.02
0.97
2.19
2.22
1.02
2.14
1.06
1.82
5.48
1.32
0.42
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0.2
0.4
0.6
0.8
1.0
1.2
1.4
1.6
1.8


kp7.6711- N-benzyl-N'-3-(2-cyclopentenyl)propylurea
r.i.
0.20
0.15
0.10
0.05
0.00
158.301
139.325
134.815
130.566
128.674
127.481
127.350
45.248
44.571
40.822
33.209
32.008
29.778
28.575
N-Benzyl-N'-(3-(2-cyclopentenyl)propyl)urea
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
/g1gb/data/kppeters/nmr/kp7.6711/



N-Tosyl-2-azabicyclo[4.3.0]non-8-ene


kp7.6311 cyclized 5.6-ring tosyl derivative
r.i.
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
143.057
132.948
129.714
129.598
127.077
77.481
77.163
76.842
37.725
35.376
26.332
22.932
21.552
N
S
O
O
N-Tosyl-2-azabicyclo[4.3.0]non-8-ene
189
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
/gigb/data/kppeters/nmr/kp7.6311/11/pdata/1 unknown Wed May 28 06:54:05 1997


kp7.7311- cyclized formamide- 5,6-bicyclic system- stoich.
r.i.
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
-0.2
N-Formyl-2-azabicyclo[4.3.0]non-8-ene
190
1.03
1.00
1.00
0.47
0.56
0.55
0.51
0.50
0.59
1.07
1.02
1.17
0.87
0.81
2.13
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
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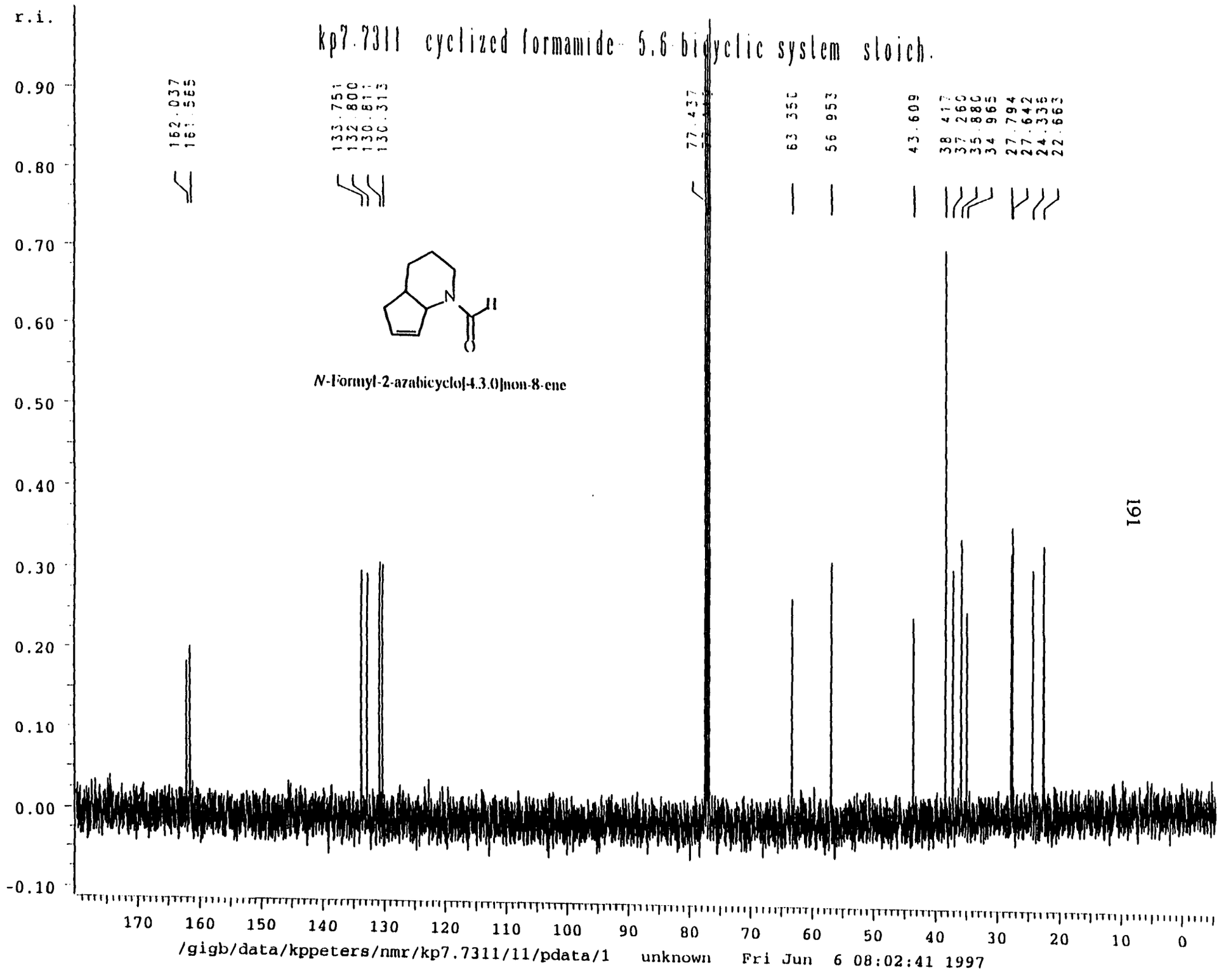
kp7.7311 cyclized formamide 5,6 bicyclic system sloich.
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
162.037
161.585
133.751
132.800
130.811
130.313
77.437
63.351
56.953
43.609
38.417
37.260
35.880
34.965
27.794
27.642
24.336
22.663
N-Formyl-2-azabicyclo[4.3.0]non-8-ene
191
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
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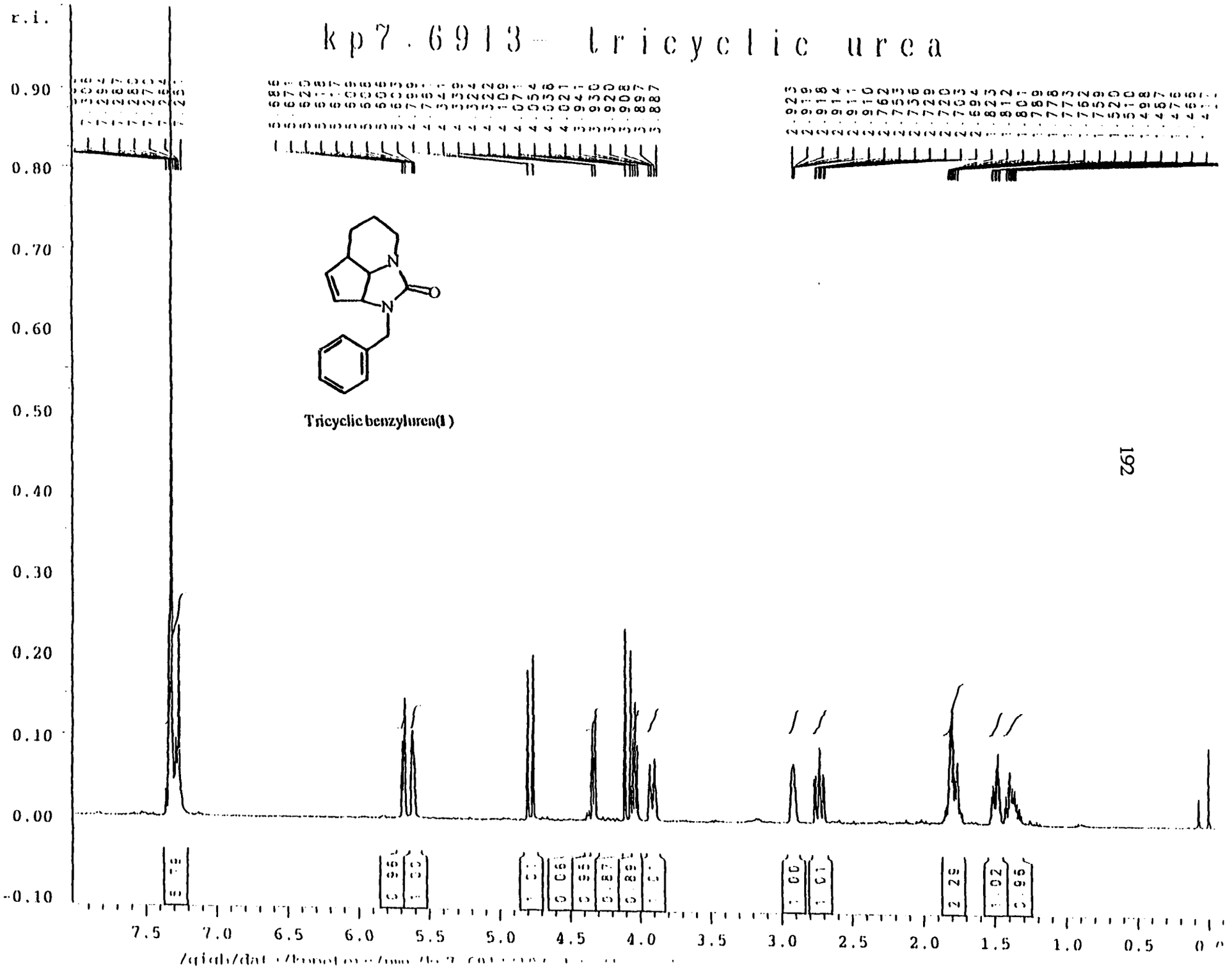
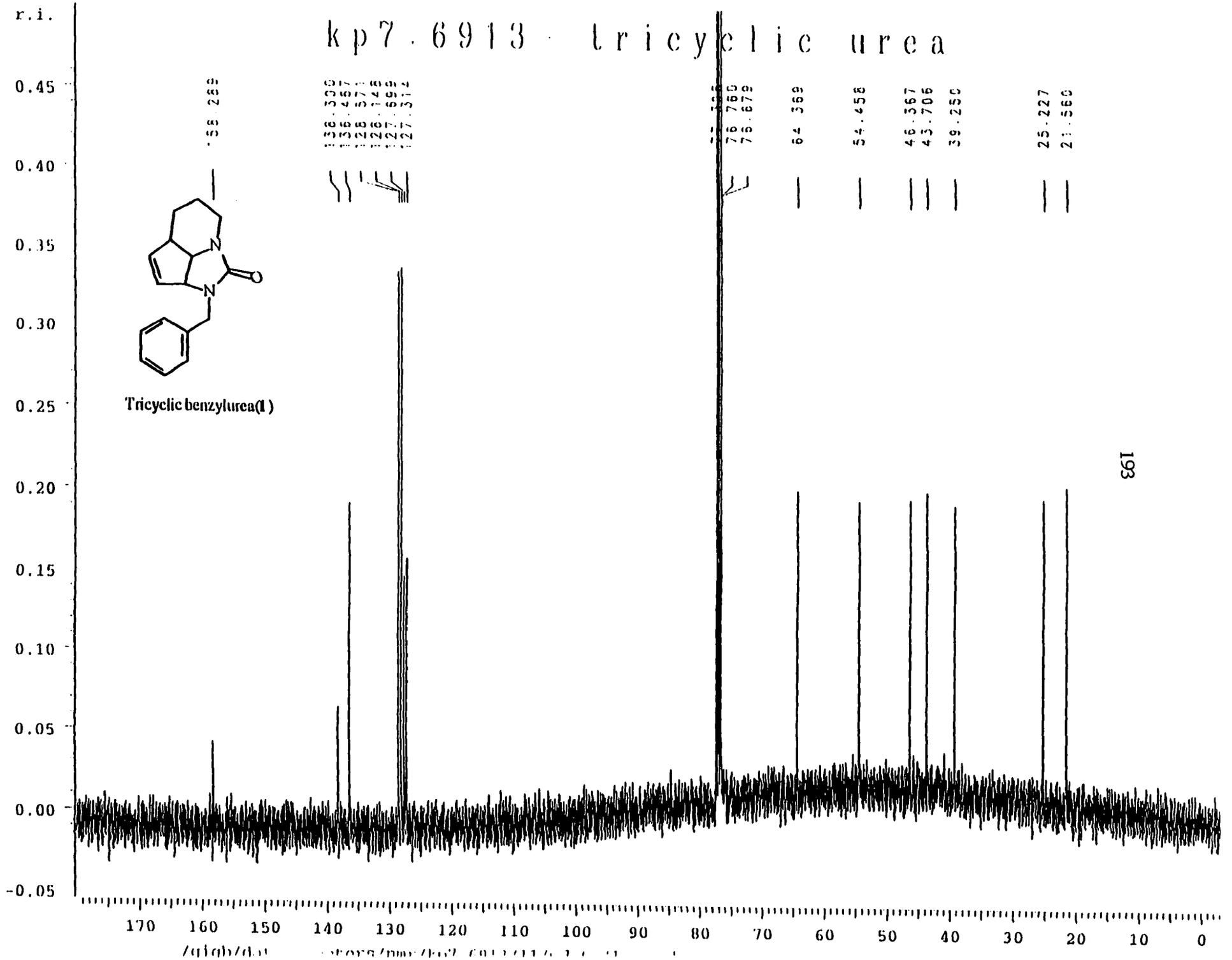

kp7.6913- tricyclic urea
r.i.
0.90
0.80
0.70
0.60
0.50
0.40
0.30
0.20
0.10
0.00
-0.10
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Tricyclic benzylurea(1)


kp7.6913 - tricyclic urea
r.i.
0.45
0.40
0.35
0.30
0.25
0.20
0.15
0.10
0.05
0.00
-0.05
58.288
136.355
136.467
128.577
128.148
127.698
127.312
76.760
76.679
64.369
54.458
46.367
43.706
39.250
25.227
21.560
Tricyclic benzylurea(1)
193
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

ACKNOWLEDEMENTS

I would like to thank Professor Richard C. Larock for his support, advice and flexibility in allowing me to pursue this degree with my career goals in mind. He truely exemplifies the term 'mentor' in my mind.

I would like to thank Professor Glen A. Russell, Professor William S. Jenks, Professor L. Keith Woo and Professor James A. Thomas for their time, effort and constructive criticisms in service on my Program of Study Committee.

I would like to thank Professor Martha E. Russell and Professor Kathleen Trahanovsky for their confidence in my abilities as an instructor and their invaluable council in my experiences as an instructor at Iowa State University.

I would like to thank Steve Vander Louw, Kristi Berst and Jason Harp for being there to keep my mind on chemistry when it needed to be and to get my mind off of chemistry when it needed to be.

I would like to thank the past and present members of the Larock group with whom I have worked and socialized for the past five years. In particular, I would like to thank Tim Hightower, Hoseok Yang, Mark Doty, Lisa Hasvold, John Zenner and Steve Gagnier.