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The In-Situ Removal of Menthofuran from Peppermint Oil and Subsequent Reactions of the Solid-Supported Adduct

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THE IN-SITU REMOVAL OF MENTHOFURAN FROM PEPPERMINT OIL AND SUBSEQUENT REACTIONS OF THE SOLID-SUPPORTED ADDUCT

by

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THE IN-SITU REMOVAL OF MENTHOFURAN FROM PEPPERMINT OIL AND SUBSEQUENT REACTIONS OF THE SOLID-SUPPORTED ADDUCT

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Menthofuran is an aromatic heterocyclic compound found naturally in the essential oil of *Mentha piperita* L. or peppermint. Natural peppermint oil may contain between approximately 2 to 8% menthofuran.

Peppermint oil is a complex mixture of over 350 identified chemical compounds; market demands dictate the extent of processing the oil undergoes prior to being introduced into consumer goods. Menthofuran has long been known to readily autoxidize, either alone or within the peppermint oil matrix, leading to a discolored oil with negative organoleptic consequences that adversely affects its commercial viability. Therefore, a facile method for selective removal of menthofuran was developed around 1950. This method has gone largely unchanged for almost 60 years, and is labor-, resource-, and time-intensive.

The purpose of this study was to determine the feasibility of an alternate method of removing menthofuran from peppermint oil which would utilize a new development in the original Diels-Alder (D-A) methodology: a tethered- or anchored-dienophile. The work encompassed in this dissertation demonstrates that an *N*-tethered maleimide is an excellent alternative to the maleic anhydride methodology

developed, and in commercial use, since 1950. A homologous series of maleimide-based dienophiles was employed to demonstrate the efficacy of the iV-tethered dienophile tactic.

A further objective of this study was to investigate the concomitant formation of highly-desirable, economically-valuable derivatives of menthofuran occurring during the Retro-Diels-Alder (RDA) phase of this work. A 2^3 full-factorial experimental design was employed whereby a model Diels-Alder adduct of menthofuran and yV-methylmaleimide was broken with a strong base at variable concentrations and temperatures. Through the use of this methodology, three factors (base [NaOH, Na2CC>3], concentration [2% aqueous, 10% aqueous], and temperature [room temperature, 100°C]) are studied at two different levels or conditions in the course of eight experiments. It was shown that Na2CC>3, aq. 2% at 100°C resulted in the highest concentration of (-)-mintlactone product at >30% of the total yield. The alternative base, NaOH, did not give a lactone product in these trials. In addition, a thermal RDA process was demonstrated as plausible, resulting in quantitative release of the menthofuran with parallel regeneration of the TV-tethered dienophile.

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Robert Joseph Justice II

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CHAPTER 1

INTRODUCTION

History and Origin

Peppermint, *Mentha piperita* L., was first identified botanically in 1696 in Hertfordshire, England, by Dr. Eales.[1] Peppermint is a member of the complex botanical family referred to as Labiatae, meaning "two-lipped." This is a reference to the distinguishing pattern of the flower petals for the 3,200 species of this family.[2] Peppermint belongs to the genus Mentha within the Labiatae family, and is considered a sterile hybrid of *Mentha aquatica* (Water Mint) and *Mentha spicata* (Native Spearmint).[3]

Cultivation

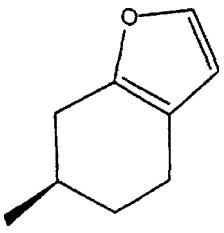
Peppermint cultivation occurred as early as 1000 B.C. and mint leaves have been found in Egyptian tombs from the same era. In addition, Pliny and Hippocrates mentioned mint in their writings as an herb of high utility in relieving digestive maladies as well as being an herb of hospitality.[4] Peppermint came into commercial significance in the mid-eighteenth century in England due to the unique organoleptic (i.e. taste and aroma) qualities the essential oil obtained from the plant possessed.[5] This commercial relevance became apparent when many flavoring and perfumery

applications began using this essential oil. As the subsequent demand for the essential oil of the peppermint plant grew, agricultural production spiked in such a way that production trends began to mimic the movement of population centers: from the Northeastern United States in the late 1700s to early 1800s, eventually migrating westward into the Midwestern region of the United States by the mid-1800s. Cultivation of the plant has now spread around the world, with a large proportion of the global supply of peppermint being grown in the region north of the 41st parallel in the U.S. and primarily in the Pacific Northwest region, including Oregon, Washington, and Idaho. Acreage for peppermint cultivation in the U.S. peaked at 149,000 acres in 1995, and has been in steady decline since then due in large part to cost pressures as a result of peppermint being cultivated abroad.

Isolation of Essential Oil

Essential oil of Mentha piperita L. has been defined by monographs in several compendia, including the pharmacopeia from the United States[6], Great Britain[7], Japan and Europe[8], as well as many National Formulary collections and The Food Chemicals Codex[9]. In these references, peppermint oil is defined as being ".. .obtained from the fresh overground parts of the flowering *Mentha piperita* L. plant via steam distillation..." Work has been conducted to extract this essential oil by other techniques, but the compendia recognize steam distillation as the only acceptable methodology for extraction of the essential oil from the plant. This aspect of isolating the essential oil is critical, as only methodology defined by official

compendia is permissible if the essential oil is going to be used in a formulation designated for consumption. Microwave hydrodiffusion and gravity (MHG) is a recent alternate extraction procedure described by Vian[10] which utilizes only *in situ* water to distend and rupture plant cells, including oil-bearing glands in the plant. This methodology is touted as being "green" or environmentally-friendly, relative to the fossil fuel- and freshwater-intensive conventional steam generation process described in the compendia. Additionally, a supercritical CO2 process has been investigated in which the dried mint hay is extracted with supercritical CO2 at temperatures lower than 320 K, resulting in an oil that is quantitatively extracted from the dried mint hay and experiences no thermal degradation as seen through traditional steam and/or fractional vacuum distillation. There are at least two advantages to this methodology over the traditionally accepted, heat-intensive techniques: the retention of leaf-like character in the final product, and a key component of peppermint oil, menthofuran (1), not being exposed to autoxidation conditions.[11]



1

Figure 1. (+)-Menthofiiran (1)

Chemical Composition of Peppermint Oil

Although non-chromatographic methodologies for examining essential oils have existed for over a century, it was not until 1958 that Purdue University researcher N.K. Ellis began performing experiments with peppermint oil using gas-liquid partition chromatography (GLPC).[12] The implementation of this field of separation science has yielded valuable information relative to the compositions of a vast many essential oils.[13] As a result of the increasingly sophisticated techniques available to the modem analytical chemist, a great deal of research has also been dedicated to assuring the integrity and genuineness of commercial peppermint oil from adulteration and/or dilution with less desirable oils. Common adulterants that have been identified in peppermint oil include camphor oil, cedarwood oil, eucalyptus oil, sandalwood oil, castor oil, mineral oil, paraffin oil, kerosene, anethole, methyl alcohol, a-terpineol, triacetin, benzoate and phthalate esters.[14]

Early utilization of descriptive testing and, much more recently the chromatographic methodologies and mass spectral detection techniques such as GC-MS and HPLC-MS, has allowed researchers to determine that peppermint oil is composed of a very complex mixture of chemical compounds featuring numerous organic functional groups: hydrocarbons, alcohols, esters, aldehydes, ketones, carboxylic acids, phenols, nitrogen heterocycles and miscellaneous compounds (furans, lactones, etc.). The concentrations of these components in the essential oil can vary markedly based on many different factors: agricultural conditions, such as soil composition, sunlight intensity, latitude, nighttime temperatures, rainfall, and

position of plant from which the oil was obtained (flower, leaf tips, leaf, stems, stalk, etc.)[15] For instance, Biggs and Leopold demonstrated that the most important agricultural variable in determining the quality of the essential oil of peppermint was temperature, which greatly influenced growth, flowering, and yield of essential oil.[16]

The bulk of the components found in the essential oil are terpenes, or dipentene compounds, having the general formula C10H16. According to Lawrence, unique components identified in peppermint oil, by functional group and number of compounds of each, are listed in Table 1.[17]

Table 1

Chemical Composition of Peppermint Oil by Functional Group

Organic Functional Group	Number of Compounds
Hydrocarbons	64
Esters	52
Alcohols	70
Aldehydes	34
Ketones	24
Acids	25
Phenols	19
Nitrogen Heterocycles	21
Miscellaneous	53
Total	362

Only 12 components are typically found in peppermint oil at a concentration of >1.0%: menthol, menthone, limonene, 1,8-cineole, menthofuran, d-isomenthone, menthyl acetate, neomenthol, germacrene-D, and (3-caryophyllene.[17]

Table 2

Chemical Composition of Peppermint Oil by Major Constituents

Constituent	Typical Concentration, %
Menthol	43.2
Menthone	20.5
Menthyl Acetate	5.1
1,8-Cineole	4.8
Neomenthol	3.3
d-Isomenthone	2.8
Germacrene-D	2.3
P-Caryophyllene	2.1
Menthofuran	1.7
Limonene	1.3
Total	87.1

Hydrocarbons—measurable quantities

The following hydrocarbon compounds are indentified in peppermint oil: a-pinene, (3-pinene, limonene, sabinene, myrcene, a-terpinene, (£)-|3-ocimene, y-terpinene, p-cymene, camphene, (Z)-(3-ocimene, terpinolene, (3-bourbonene, (3-

caryophyllene, germacrene-D, plus forty-nine other aliphatic mono- and sesquiterpene hydrocarbons. The total concentration of hydrocarbons in peppermint oil typically ranges between 11-13%. (3-caryophyllene (2) is a highly-valued, bicyclic organic intermediate that occurs naturally in peppermint oil and features a 9-carbon ring and a 4-carbon ring. This compound has been investigated for its tendency to facilitate many different biological functions, most notably including an anticarcinogenicity characteristic.[18]

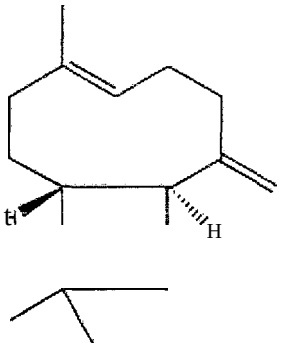


Figure 2. [3-Caryophyllene (2)

Esters

Menthyl acetate, neoisomenthyl acetate, neomenthyl acetate, isomenthyl acetate, plus 48 other aliphatic and monoterpene esters have been identified in peppermint oil. Total ester concentration in peppermint oil is typically 6-8%.[17]

Alcohols

Alcohols constitute the largest single organic functional group by concentration in peppermint oil, and include the following compounds: 3-octanol, trans-sabinene hydrate, linalool, terpinen-4-ol, a-terpineol, menthol, neomenthol, neoisomenthol, viridiflorol, (Z)-3-hexenol, l-octen-3-ol, isomenthol, and fifty-eight • 17 other aliphatic mono- and sesquiterpene alcohols. Viridiflorol **(3)** is a unique tricyclic sesquiterpene alcohol featuring 3-, 5-, and 7-membered rings.[19]

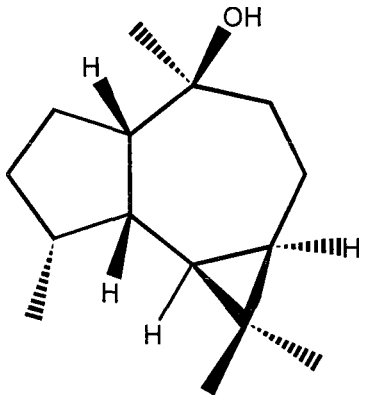


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Figure 3. Viridiflorol **(3)**

Aldehydes

Thirty-four aliphatic, aromatic, and monoterpene (p-menthane-based, see Figure 4.) aldehydes have been identified.[17]

Ketones

Menthone, isomenthone, pulegone, piperitone, carvone, plus nineteen other aliphatic, aromatic, and monoterpene (i.e. p-menthane-based) ketones have been identified. The typical total ketone concentration in peppermint oil is 27-30%.

Acids

Twenty-five aliphatic, aromatic, and monoterpene (i.e. p-menthane-based) acids have been identified in peppermint oil at a combined total concentration of less than 0.2%.[17]

Phenols

Nineteen phenols and phenolic compounds have been identified in peppermint oil at a combined total concentration of less than 0.2%.

Nitrogen Heterocyclic Compounds

Twenty-one nitrogen heterocyclic compounds, all at concentrations less than 100 ppm, have been identified in peppermint oil.[17]

Miscellaneous

Menthofuran, 1,8-cineole, plus fifty-one other miscellaneous compounds have been identified. Relevant to this study, the occurrence of menthofuran will primarily

be investigated. Additionally, the synthesis of conjugate lactone compounds similar in structure to menthofuran will be investigated.

Menthofuran (1), a large focus of this work, is an oxygenated terpene; a bicyclic, aromatic ether or furan, naturally found in peppermint oil at concentrations varying from approximately 2-8%.

The numbering convention used for p-menthane-derived compounds is shown in Figure 4 below. Following IUPAC convention, the name for 1 is 4,5,6,7-tetrahydro-3,6-dimethylbenzofuran. However, for this study, the naming convention proposed by Ferraz[20] for these compounds was employed throughout the work.

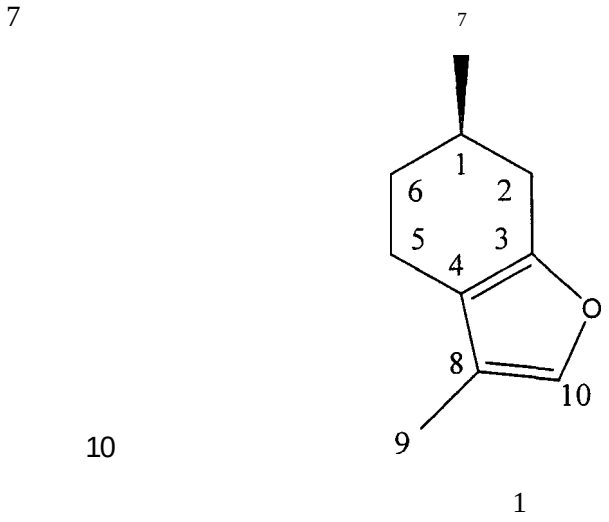

Figure 4. Numbering Convention for p-Menthane **(4)** Terpene Skeleton and p-Menthane Furan [Menthofuran] (1).

Development of Peppermint Varieties

Selective breeding of plants to achieve favored characteristics has occurred for many years. Varieties of peppermint exist for the same reasons: to achieve tangible physical advantages such as higher oil yield per acre, higher plant hardiness and disease resistance, as well as enhanced or suppressed specific compound expression within the essential oil of plants.

The methodology of creating new varieties of peppermint is generalized as follows:

1. Through horticultural practices, idealized plants have tissue cultures removed for cloning.
2. The tissue cultures are incubated in proper media to induce callus and shoot formation.
3. Developed shoots are transferred to greenhouse conditions and grown to allow morphological, botanical, and genetic identification and confirmation of the newly-established plant. '

The use of these practices has provided the varieties of peppermint necessary to allow flavor and fragrance providers to customize commercial products that meet or exceed market expectations with regard to specific taste and/or aroma targets, cost considerations, and yield of essential oil.

Menthofuran

The discovery of menthofuran in peppermint oil

French researcher Charabot[23] discovered that the oil isolated from the flowering heads of the *Mentha piperita* L. plant demonstrated a strong dextrorotatory character, whereas the oil from the remainder of the plant was clearly levorotatory. Subsequent analysis of this same oil years later was unsuccessful in isolating a pure compound but was able to obtain a purified fraction that had an optical rotation of +81° [24] While the strong dextrorotatory quality in this oil was originally believed to

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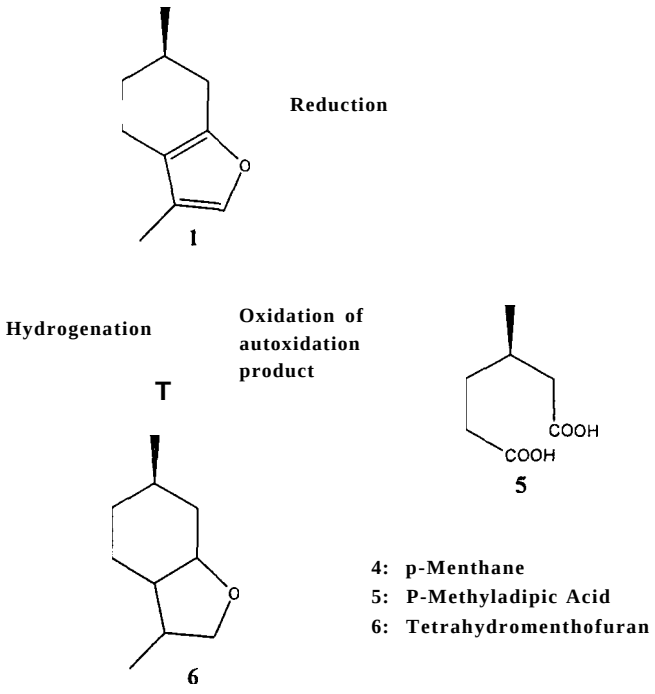
be due to the presence of d-menthone by one researcher, it was later proven to be due to the confirmed presence of 4,5,6,7-tetrahydro-dimethyl-3,5-coumarane (menthofuran) by Weinhaus. This confirmation was achieved through laboratory experiments, such as reduction to p-menthane **(4)** (see Scheme **1),** oxidation of the autoxidation product to P-methyladipic acid **(5),** and hydrogenation to yield the same oxide derived from isopulegol, with an oxygen atom between the 3- and 9-position carbons, (6) [27] Verification of the structure of 1 has been confirmed by spectroscopy.[28]



Scheme 1. Experimental Confirmation of Menthofuran

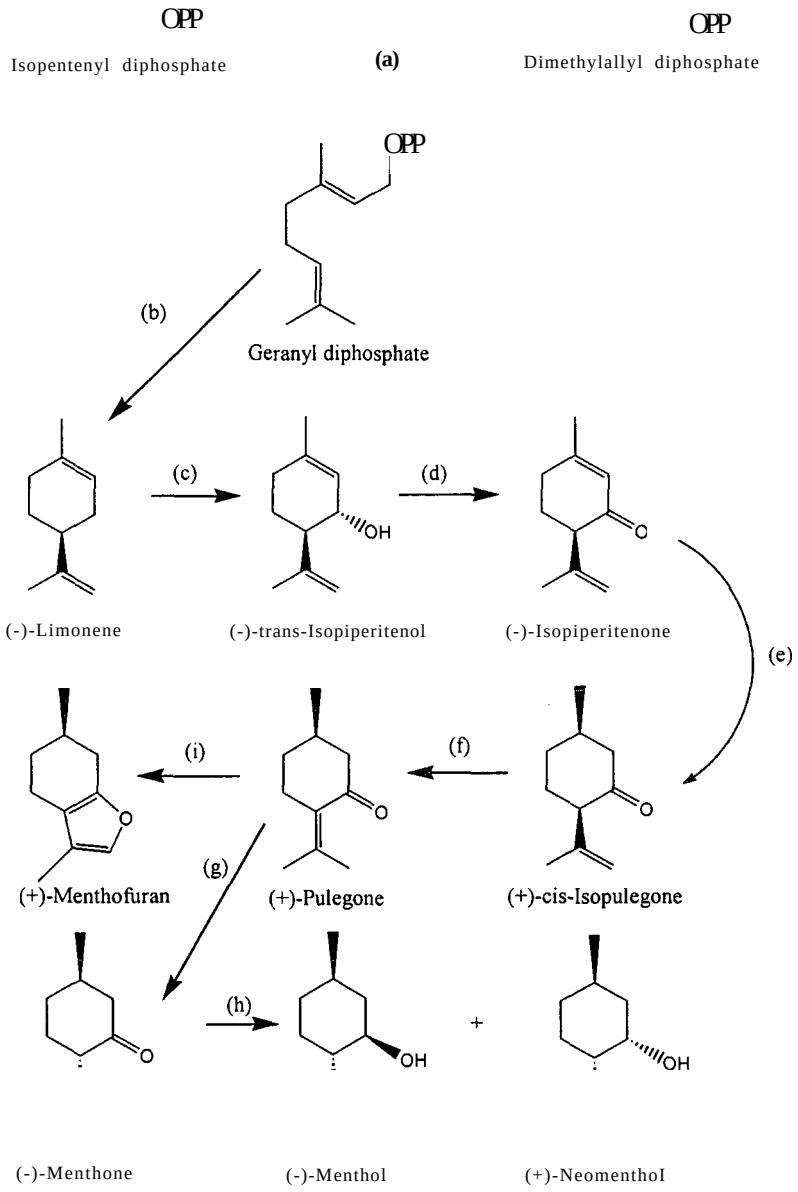
Botanical origin of menthofuran

Menthofuran is a characteristic monoterpene found in species of the Mentha genus that may impart an undesirable quality profile to the essential oils thereof. The oxidative bioconversion of pulegone into menthofuran was theorized by Reitsema [30] and subsequently confirmed by Battaile and Loomis [31] and Clark and Menary and occurs most intensely during the period of flowering of the mature *Mentha piperita* L. plant. *Mentha piperita* L. produces a cytochrome P-450 monooxygenase enzyme, menthofuran synthase, which converts pulegone *in vivo* into menthofuran.

Figure 5. (+)-Pulegone (7)

This work represented a continuation of earlier biosynthetic studies on the oxidation of pulegone to menthofuran *in vivo* conducted by Nelson which suggested that a cytochrome P-450-catalyzed oxidation of the cw-methyl group of the pulegone isopropylidene moiety was integral in this oxidative bioconversion of pulegone to menthofuran.

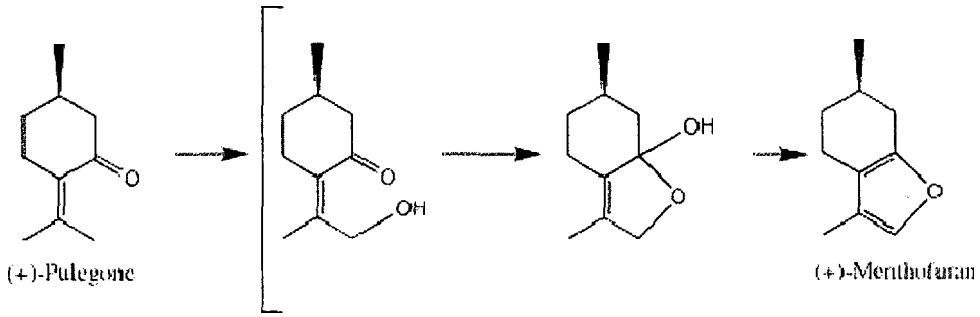
Scheme 2 below delineates the biosynthetic pathway for the synthesis of monoterpenes in peppermint.



Scheme 2. Enzymatic Monoterpenoid Synthesis in *Mentha piperita* L. Enzymes responsible are: geranyl diphosphate synthase (a), (-)-limonene synthase (b), cytochrome P450 (-)-limonene-3-hydroxylase (c), (-)-/ra«5-isopiperitenol dehydrogenase (d), (-)-isopiperitenone reductase (e), (+)-cw-isopulegone isomerase (f), (+)-pulegone reductase (g), (-)-menthone reductase (h), and cytochrome P450 (+)-menthofuran synthase (i). [Nelson, *et. al.*, 1992]

Oil obtained via the steam distillation of flowers exclusively results in a menthofuran-rich essential oil with a very high dextrorotatory character.[34] A correlative relationship is observed between the photoperiod of the *Mentha piperita* L. plants and their tendency to flower. In 1941, Allard published research showing that a photoperiod of 14 hours/day minimum was required to result in flowering of the plants, thereby beginning menthofuran biosynthesis in earnest within the plants.[35] Subsequently, Guenther described a minimum daily photoperiod of 15-16 hours per day was required for peppermint plants in order for the essential oil production to be higher than trace levels.[36] Interestingly, two very close relatives to *Mentha piperita* L., *Mentha arvensis* (Cornmint) and *Mentha spicata* (Spearmint), do not have this enzymatic ability of converting pulegone to menthofuran,[37] even though trace amounts of menthofuran have been reported in *Mentha arvensis* oil.[JO] As a result, very little if any menthofuran is found in the essential oils derived from these two mint species.[39] While this situation is not critical with regard to spearmint oil, it presents a problem with regard to the widespread use of *Mentha arvensis* as a common supplement and diluent of genuine essential oil of *Mentha piperita* L. Blends of *Mentha arvensis* and *Mentha piperita* oils are often enriched with menthofuran in order to impart true *Mentha piperita*-like characteristics to the finished blend.

Elucidation of the biochemical pathway demonstrated by the cytochrome P450 (+)-menthofuran synthase in converting (+)-pulegone to (+)-menthofuran has been achieved.[40]



Scheme 3. Cytochrome P450-regulated Bioconversion of (+)-Pulegone to (+)-Menthofuran

This process is summarized in Scheme 3 above as containing the following steps:

1. There occurs, via a cytochrome P-450, a sy^-methyl hydroxylation of the (+)-pulegone isopropylidene methyl group closest to the carbonyl oxygen. Practically, this is an allylic oxidation.
2. There is a cyclization to form the hemiketal moiety. Radiolabeling experiments[40] in which the pulegone carbonyl oxygen was replaced with $^{18}0$ demonstrated that the carbonyl oxygen does not survive to become the hetero atom in the furan ring. Rather, the syn- hydroxylation product has its oxygen incorporated as the hetero atom in the furan.
3. The hemiketal is dehydrated to complete the furan ring.

Figure 6. Radiolabeled Pulegone Conversion to Menthofuran

Synthetic Mechanisms for Menthofuran

Isopulegol-based methodology

Aside from the biosynthetic pathway leading to menthofuran that has been demonstrated, many conventional laboratory synthetic routes have also been investigated. Using isopulegol as the starting material, researchers have had success in synthesizing menthofuran via a 3-step process as shown in Scheme 4 below.[41]

10

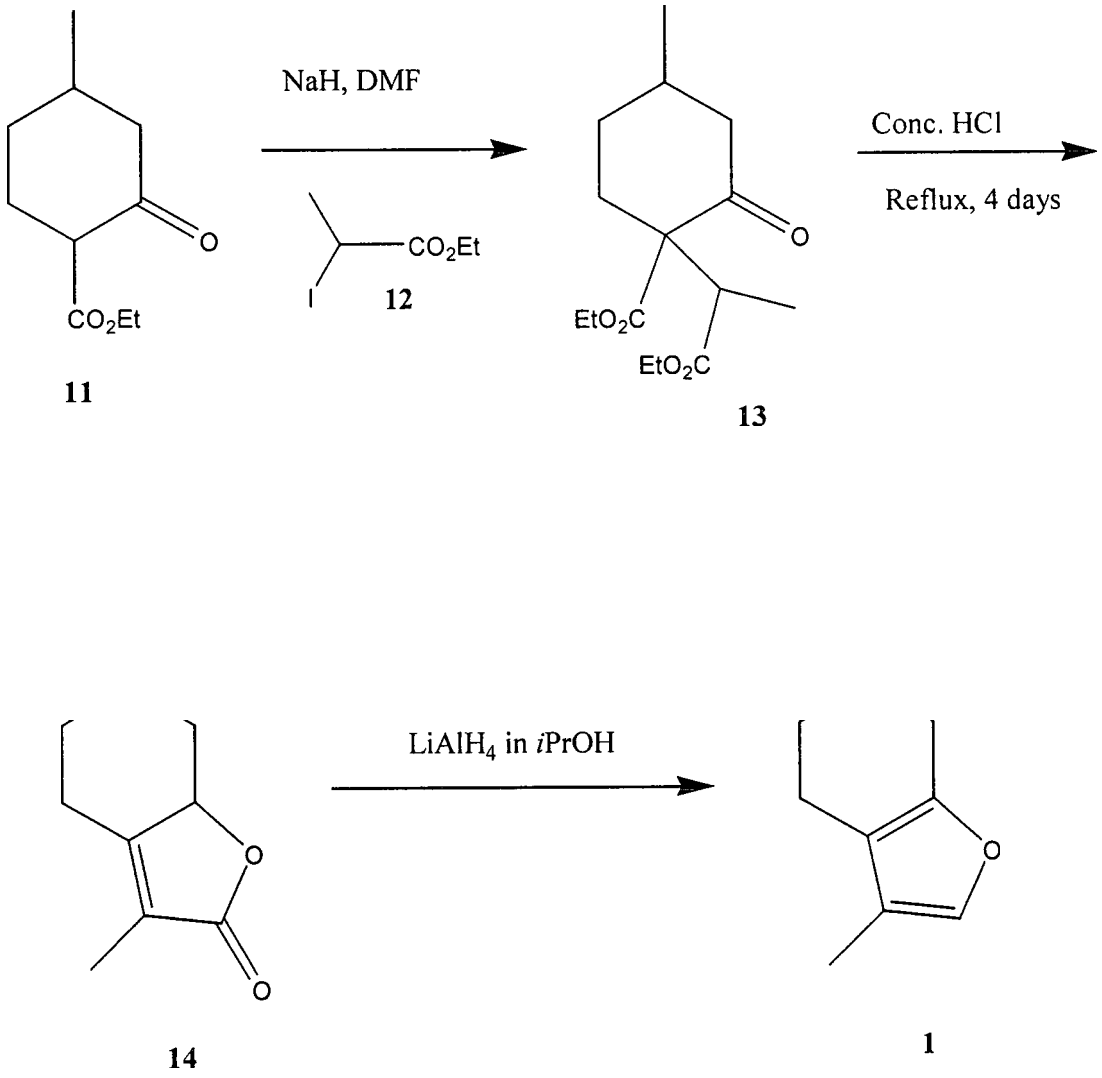
8: (-)-Isopulegol
9: (-)-IsopuIegol epoxide
10: (-)-Isopulegone epoxide

Scheme 4. (+)-Menthofuran Synthesis from (-)-Isopulegol. a.) Acetonitrile:$H20_2$. b.) chlorine/pyridine complex.[42] c.) isomerization with 9% aq. HC1 or spinning-band distillation.

Ethyl-4-methyl-2-oxo-1-cyclohexanecarboxylate (acetoacetic ester) methodology

A three-step process has been described[43] using Ethyl 4-methyl-2-oxo-l-cyclohexanecarboxylate **(11)** as starting material. Direct C-alkylation with ethyl 2-iodopropionate **(12),** followed by hydrolysis of the diester **(13)** with concentrated hydrochloric acid yielded 3,6-dimethyl-2,4,5,6,7,7a-hexahydrobenzofuran-2-one in very good yield. This compound, which will be discussed in depth later, is commonly known as "mintlactone," or (-)-mint lactone, is depicted in Scheme 5 below as

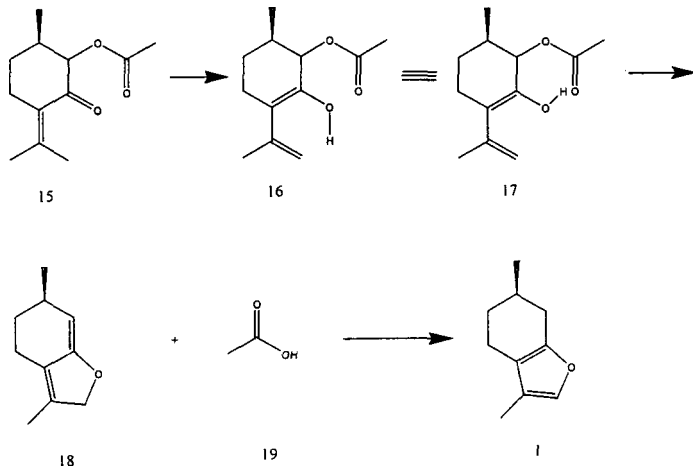
compound **(14).** The concluding step of the synthesis is a $LiAlH_4$ reduction in isopropanol to (±)-Menthofuran, (1).



Scheme 5. Synthesis of (±)-Menthofuran from Ethyl-4-methyl-2-oxo-l-cyclohexanecarboxylate.

Pulegone and pulegone-based methodologies

An alternative process using a derivative of pulegone, 2-acetoxypulegone via pyrolysis to menthofuran has also been reported.[44] The 2-acetoxypulegone **(15)** tautomerizes into the *trans*-znol form of the compound, in which the cyclohexyl ring will exist in the boat conformation, while the *cis*-conformer will preferentially exist as the chair conformer. In the keto tautomer configuration, the carbonyl group of the acetoxy side chain will actually more closely approach an isopropylidene hydrogen than it can a hydrogen atom at the CI-methyl group. This proximity will facilitate the heterocyclic ring closure, leading to menthofuran. Scheme 6 below demonstrates the synthetic approach whereby 2-acetoxypulegone is converted via pyrolysis in benzene at >450 °C into menthofuran with a concomitant generation of acetic acid and an intramolecular rearrangement to complete the conversion.



Scheme 6. (+)-Menthofuran Synthesis from 2-Acetoxypulegone

These three methods represent the only synthetic routes to menthofuran. It should be noted that in these three synthetic methodologies described, the route by which the oxygen atom constituting the hetero atom in the furan ring being incorporated is not consistent with the biosynthetic pathway described earlier, where the oxygen atom in the heterocycle always comes from the action of the (+)-menthofuran synthase cytochrome P450 enzyme occurring as a result of natural respiration of the peppermint plant through the oxidative biosynthetic pathway.

Chemistry of (+)-Menthofuran

Menthofuran fulfills, through the consideration of its furan moiety, all of the requirements to be considered aromatic: 7i-bonds must lie within a planar, cyclic structure; each atom in the cycle must have p-orbitals that form a p-orbital overlap; and Huckel's Rule must be satisfied whereby (4n + *2)-n* electrons must exist within the cycle. As a heterocyclic compound with a conjugated diene configuration, furan achieves aromaticity via a pair of the unshared electrons of the oxygen atom being incorporated into the derealization. The fact that the furan ring in menthofuran is aromatic fulfills the Diels-Alder requirement that the diene be "electron rich."

Autoxidation potential of (+)-Menthofuran

Researchers have long realized[45] the autoxidation tendency of menthofuran. Woodward and Eastman observed that the principle autoxidation product was a

weakly acidic solid compound that melted at 188°. The proposed structure of this autoxidation product is the hemiketal lactone (20):

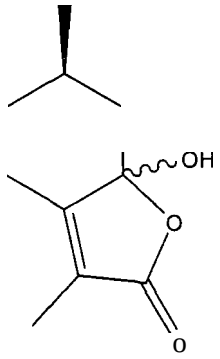


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Figure 7. Menthofuran Hemiketal Lactone (20)

Compound (20) is a 1-step precursor to (-)-mintlactone, requiring only dehydration of the hemiketal hydroxyl group to accomplish the transformation to the lactone (14).[46] Autoxidation of menthofuran is a distinctly exothermic reaction. Production workers involved in the extraction of menthofuran from peppermint oil have reported spontaneous combustion of cloths and towels used to clean up small menthofuran spills after approximately 2 hours in a trash container due to the exothermic nature of the autoxidation of menthofuran.[47]

(+)-Menthofuran exhibits an enhanced reactivity at the 10-position due to several reasons: resonance-induced electron density enhancement at that position, and favorable electron density located at that position due to the induction effects of

the cyclohexyl-ring adjoining the furan ring at the 4- and 5-positions. This enhanced reactivity is critical in subsequent reactions that were studied in this work, especially with regard to the generation of (-)-mint lactone, where the carbon at the 10-position is oxidized to a carbonyl.

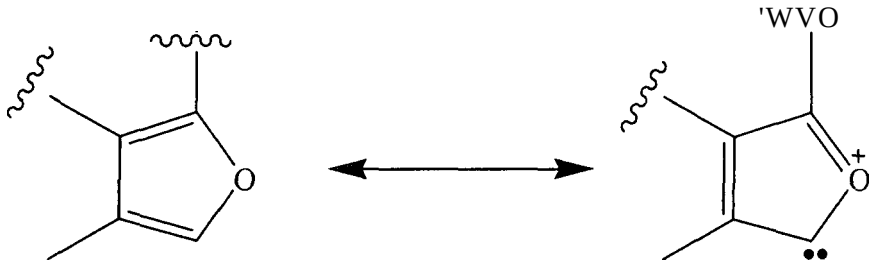


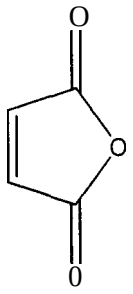
Figure 8. Resonance Structure of Menthofuran

The furan portion of the molecule is shown above with its resonance structure.

Stabilization of Peppermint Oil

It was discovered early[49] that peppermint oil with relatively high levels of menthofuran was unstable. This instability manifested itself through the aforementioned tendency of autoxidation, which would subsequently produce in the oil a dark green color, making the oil commercially unviable. A method of stabilizing the peppermint oil was eagerly desired throughout the flavor and fragrance industries, as this would allow for longer storage periods without adverse side effects occurring over time to the essential oil. As a result, as early as the 1950s,[53] there were documented processes for removing menthofuran from peppermint oils based on the

fact that menthofuran, as a fixed cw-configuration, electron-rich diene, would be an ideal candidate for a Diels-Alder type, [47r+27i] cycloaddition reaction. A likely candidate for the accompanying dienophile was immediately identified as maleic anhydride (21), which was inexpensive, plentiful, and a nearly ideal dienophile.



21

Figure 9. Maleic Anhydride (21)

Maleic anhydride had one additional advantage: when reacted with menthofuran under Diels-Alder conditions the result was a crystalline adduct—easily separated from the balance of the oil. Most peppermint oil manufacturers began using this Diels-Alder methodology to remove menthofuran from peppermint oil, especially from oil that was derived from plants grown in certain agricultural conditions that resulted in a very high concentration of menthofuran, typically >7% (very little rainfall but plenty of irrigation water; long, sunny, hot days; cool nights and harvest during the flowering stage of the plant). This set of extrinsic conditions is replicated ideally in the Kennewick region of Washington State, United States. Oil from this region typically has a menthofuran concentration of between 6 and 9%. Peppermint oil from other growing regions in the United States, especially the Midwestern U.S.,

such as Indiana, Michigan, and Wisconsin, typically have <4% menthofuran. This is primarily due to the vastly different agricultural conditions between the two growing locations. Widespread discussion on the topic of treatment of peppermint oil for the purpose of stabilization began in the literature in the early 1960s, when patented work by Todd discussed at great length several processes for stabilizing peppermint oil, thus making it less susceptible to long-term oxidation.[50] Methodologies employed in this patent included catalytic hydrogenation of the menthofuran component while still in the peppermint oil with Pt, Pd, or Ru, as well as fractional distillation to selectively remove a specific menthone-rich fraction.

The process for selectively removing menthofuran from peppermint oil via the Diels-Alder methodology was patented on December 20, 1982, by The Warner-Lambert Company.[51] The claim to this process, however, was contested by the A.M. Todd Company, Kalamazoo, MI, due to demonstrable evidence of prior use of the same technology and processes to the Warner-Lambert patent. Further, documented evidence of the development of this maleic anhydride process for the removal of menthofuran from peppermint oil existed within the A.M. Todd Company as early as October 1964.[52] Eastman described in 1950, but did not patent, a convenient method for isolating menthofuran from peppermint oil utilizing maleic anhydride as a strong dienophile in forming the Diels-Alder adduct with menthofuran. This crystalline adduct was conveniently isolated from the balance of the peppermint oil, effectively removing large proportions of menthofuran in the process.

Diels-Alder Reaction

History

The Diels-Alder Reaction is considered to be one of the premier carbon-carbon bond-forming reactions available to chemists. For their historic discovery of the pericyclic reaction which bears their names, Otto Diels and Kurt Alder were awarded the 1950 Nobel Prize in Chemistry. Typical reaction conditions include an electron-rich conjugated diene capable of existing in the s-*cis*- configuration and an electron-deficient dienophile which engage in a pericyclic reaction that is believed to proceed via an aromatic transition state wherein 6?r electrons (4n + 2 = 6, where n = 1) are affected.[54]

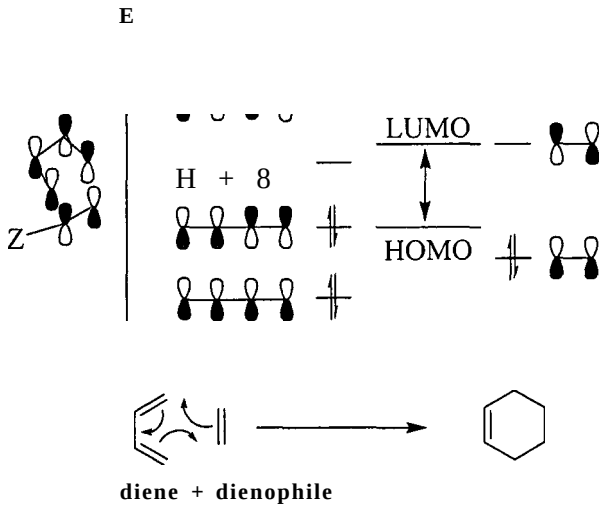
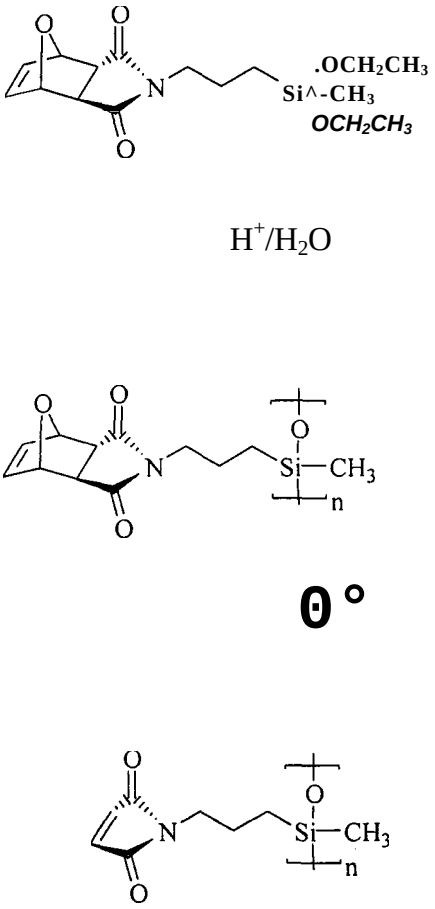


Figure 10. HOMO/LUMO Molecular Orbital (MO) Diagram for Diels-Alder Reaction

Overlap between the highest occupied molecular orbital of the diene (HOMO) and the lowest unoccupied molecular orbital of the dienophile (LUMO) is thermally allowed in the Diels-Alder reaction, provided the orbitals are of similar energy. The reaction is facilitated by electron-withdrawing groups conjugated to the alkene on the dienophile, since this will lower the energy of the LUMO. Good dienophiles often bear one or two of the following substituents: CHO, COR, COOR, CN, C=C, Ph, or halogen. The diene component should be as electron-rich as possible, as this will then raise the energy of the HOMO for the diene; thus, narrowing the energy difference between the dienophile and the diene. This allows the Diels-Alder reaction to proceed very smoothly under moderate reaction conditions.

Despite the mature nature of the Diels-Alder reaction, new applications are being found for its use in many different areas.[55] Liu and colleagues used a concerted Diels-Alder/Retro-Diels-Alder methodology to synthesize thermally-reversible cross-linked polyamides and thermo-responsive polyamide gels.[56] Shaltout and Loy investigated the addition of maleimide functionality to improve mechanical strength of polymeric organosiloxane backbones.[57] Interestingly, it was through the use of the Diels-Alder methodology that Shaltout and Loy protected their maleimide-functionalized siloxane resin prior to polymerization via dilute aqueous acid treatment. It was through Retro-Diels-Alder conditions, after the polymerization had occurred, that the protecting diene, furan, was liberated quantitatively.



Scheme 7. Maleimide Tethered to a Siloxane Backbone with Retro-Diels-Alder Liberation of the Diene and Simultaneous Regeneration of the Dienophile. [Shaltout, 1999]

The work undertaken in this project will be similar to the work of Liu and Shaltout in that the dienophiles are anchored maleimides. The diene in this work, however, is fixed as menthofuran, while Liu's work included polyfunctional furan compounds. Nevertheless, the chemistry and concept are very similar. Further, the solvent system in this work is fixed as peppermint oil, with its myriad of organic functionalities, versus a single-solvent system conventionally chosen for D-A reactions.

As menthofuran is the only fixed *cis*- configured conjugated diene in peppermint oil at a significant (>0.5%) concentration, the Eastman process was quite appropriate for the purpose of removing menthofuran from peppermint oil without concomitant reactions occurring that would result in undesirable co-products, a-Terpinene, a fixed, *cis*- configured conjugated diene, occurs in peppermint oil at a typical concentration of approximately 0.3%.

As previously mentioned, peppermint oil is a very complex mixture of many different organic functional groups. This necessarily makes the idea of selectively removing a single component very tenuous, depending on many factors, including: compatibility of the dienophile selected with the other, non-furan type functional groups, energy of activation in initiating a [47i+27t] cycloaddition reaction between the chosen dienophile and menthofuran, and the feasibility of the reverse reaction, or Retro-Diels-Alder reaction, occurring.

Objectives

This dissertation embodies three objectives:

1. Create a novel, solid-phase bound Diels-Alder reagent model based on *N*-substituted maleimide.
2. Demonstrate equivalent efficiency of this compound in extracting menthofuran from peppermint oil.
3. Concomitantly regenerate the dienophile //-substituted maleimide while liberating the menthofuran via Retro-Diels-Alder reaction conditions.

A Novel Solid-phase Bound Diels-Alder Reagent

While demonstrably effective at this process, maleic anhydride lacks the heterocyclic functionality amenable to tethering to a solid support due to the relative inertness of the ether functional group toward reactivity. Alternatively, maleimide is a prime candidate for tethering at the nitrogen via multiple methodologies that will be discussed in this work.

21 **22**

Figure 11. Maleic Anhydride (21) and Maleimide (22)

In this work, model systems of yV-substituted maleimides were produced to demonstrate the concept of using a tethered dienophile in extracting menthofuran from peppermint oil. This approach to the tethered dienophile homologues demonstrated efficacy of the tactic. The methodologies for achieving the anchoring or tethering of compounds such as those exhibiting Diels-Alder functionality are well

documented.[58,59] An alternative approach to a novel, tethered dienophile based on /-carvone (23) was also considered.

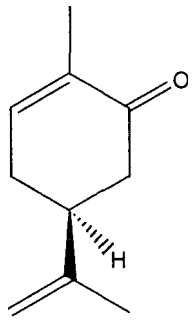


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Figure 12. /-Carvone (23)

Bagnell detailed a novel approach to achieve the conversion of the isopropylidene group in 1-carvone to a tertiary alcohol functionality in which the conversion took place at high temperature in an aqueous media via microwave irradiation.[60] The improvement that this methodology offered was not in the yield, but rather in the duration of the reaction (10 minutes versus 43 hours). In addition, the conventional method of producing the hydroxylated carvone, consisting of long periods of contact with concentrated sulfuric acid followed by multiple extractions, tended to produce as the principle artifact the isomerization product, carvacrol (24).

24

Figure 13. Carvacrol (24)

The Bagnell method, however, would only produce the polymerization product carvacrol at elevated temperatures; at more moderate temperatures, the 8-hydroxy-p-6-menthen-2-one (25) was favored.

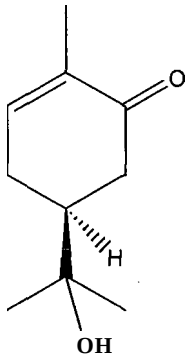

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Figure 14. 8-hydroxy-p-6-menthen-2-one (25)

Comparable efficiency of the ./V-substituted maleimides to the maleic anhydride process for menthofuran extraction

Notwithstanding resonance contributors seen with amide or imide structures, the chemical structure of maleimide differs from maleic anhydride only in the heteroatom. Consequently, objective of determining the degree of equivalence in efficiency between maleic anhydride and iV-substituted maleimide as a model compound for a tethered dienophile will be demonstrated.

Regeneration of solid-phase Diels-Alder reagent with concomitant generation of menthofuran and/or other Retro-Diels-Alder products

The objective of this phase of the dissertation is to identify multiple options in regenerating the Diels-Alder reagent, as well as liberating the menthofuran and/or other RDA products.

The practice of forming the Diels-Alder adduct to extract menthofuran from peppermint oil involves the formation of a crystalline solid, which must be carefully filtered, rinsed, and dried before further processing to isolate menthofuran. The novelty of the approach being proposed in this dissertation is the fact that the dienophile is not a homogeneous component with the peppermint oil, but rather, can be configured as a fixed bed, whereupon the heated peppermint oil is circulated. This allows for the adduct formation to occur *in situ,* while the remaining peppermint oil simply passes to the next processing step. Further, this solid-phase approach would allow single- or multiple-pass processing of peppermint oil for the removal of menthofuran. This would be readily controlled by reaction conditions, and would be

similar in theory to an ion-exchange configuration for a household water softening treatment process. When the solid-phase reagent can extract no further menthofuran from the peppermint oil, the Retro-Diels-Alder phase to liberate menthofuran from the tethered-concept model compound would begin.

CHAPTER 2

RESULTS AND DISCUSSION

Dienophile Design Strategy

In considering the compositional design of the dienophile platform to be used in this project, a significant consideration is that the diene, 1, is electron-rich. This, then, constrains the nature of the dienophile functionality to be very electron-poor, ideally featuring electron-withdrawing groups in the a-position(s) vinylic to the -ene functionality. Further, as the oxygen atom in cyclic ethers is typically unreactive, the groundwork was thus developed for a compound very similar to maleic anhydride to be attempted as the dienophile of choice that also allowed tethering of a "spacer" to both the dienophile and a solid support or a solid support mimic. Maleimide-based compounds constitute a category of chemical compounds that have utility in many different aspects of synthesis: from plastics and biological entities, to pure synthetic chemistry, especially via the Diels-Alder protocol[61] due to the dienophilic nature of this class of compounds.

Alternative synthetic methodologies for achieving N-substituted maleimides

The use of maleimide as the targeted dienophile platform was realized through the substitution of the amine hydrogen via several other methodologies, however. These included a modified Mitsunobu protocol[63,64,63] and a "Two-Component"

methodology wherein maleic anhydride is opened via reflux conditions in diethyl ether to form the maleamic acid; followed by dehydration and ring closure via reflux with acetic anhydride and sodium acetate.[66] The "Two-Component" methodology has been used historically for the synthesis of //-substituted maleimides, but newer research has demonstrated improvements on this methodology.[en] The work undertaken in this project includes the synthesis of a homologous series of *N*-substituted maleimides, with the intention to demonstrate the efficacy of variable-sized "spacers" in the solid-bound dienophile functionality.

The rationale for synthesizing a series of //-functionalized maleimides was twofold: it allowed confirmation that published synthetic protocols would produce equivalent products, and this technique also would allow resolution with regard to inconsistencies in the literature concerning the multiplicity assignments for the maleimide methine protons in NMR. The results of this work unambiguously assign a single NMR peak for these two protons, regardless of the synthetic protocol employed to produce the //-substituted maleimides.

Gabriel Synthesis Approach

As part of the work to synthesize the homologous series of //-substituted maleimide compounds, an initial trial similar to the Gabriel Synthesis of amines was attempted. In this work, however, there were two important variations to the standard Gabriel protocol attempted: the phthalimide component synonymous with the Gabriel Synthesis was replaced with maleimide to allow subsequent access to the electron-

poor 71-bond, and the reaction was not to be taken to the traditional finishing point for Gabriel syntheses—stopping short of generating the free amine. Development of the maleimide-based nucleophile via deprotonation with a strong base was followed by reaction with a halogenated hydrocarbon to complete the coupling, (see Scheme 8 below) This approach produced only unreacted starting compounds,[69] despite attempting the transformation using a well-known Gabriel reaction facilitator: a dipolar aprotic solvent, such as DMF[70].

22

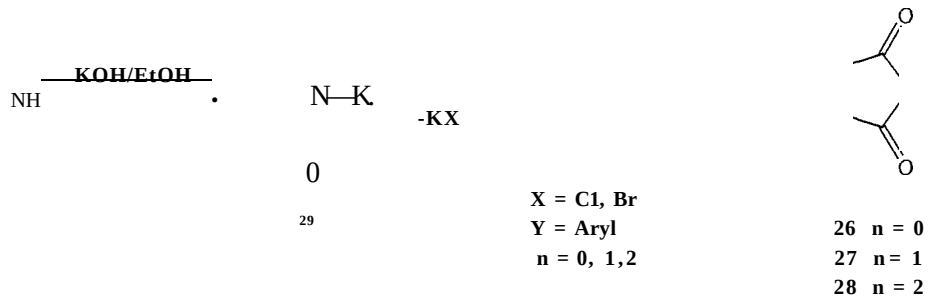
X = CI, Br
Y = Aryl
n = 0, 1,2

26 n = 0
27 n = 1
28 n = 2

Scheme 8. Attempted Gabriel Synthesis of //-Substituted Maleimides. a.) equimolar amounts of maleimide and base (KOH, LiOH) at 20% excess relative to alkyl halide in THF/DMF at RT. This scheme was not successful; only unreacted starting compounds remained; no product was obtained. Product compound names: **(26) 1-**(Phenylmethyl)-1 //-pyrrole-2,5-dione; **(27)** 7V-(2-phenylethyl)-1 //-pyrrole-2,5-dione; **(28)** /V-(3-phenylpropyl)-l//-pyrrole-2,5-dione.

Another Gabriel-type approach was attempted whereby maleimide was treated with an ethanolic KOH solution to affect the potassium salt of the imide.[71] Use of the Salzberg methodology resulted in an initial isolated yield of 36% of the potassium maleimide; harvesting multiple crops of crystals from the filtrate resulted in a very

good isolated yield of 83% of theoretical amount of the potassium maleimide. Following the formation of potassium maleimide, the salt was to be reacted with 1-bromo-3-phenylpropane, a terminally-halogenated compound that is designed to mimic a theoretical reaction between the potassium maleimide and a solid-supported, n-propyl spacer or linker.



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Scheme 9. Gabriel Synthesis of //-Substituted Maleimides per Salzberg & Supniewski. i: equimolar amounts of maleimide and base (KOH) at 20% excess relative to alkyl halide in DMF at reflux.

Despite literature support for successful coupling of a halogenated hydrocarbon to the potassium salt of phthalimide, multiple attempts to couple a terminally-halogenated linker with the potassium salt of maleimide were unsuccessful, resulting in unreacted terminally-halogenated alkyl halide. This reaction was also attempted in a one-pot fashion with the use of LiOH as the base and the *in-situ* generation of the lithium salt of maleimide followed by reaction with an alkyl halide. The outcome of this trial was similar to that of the use of KOH as the base: the only compound identified by GC/MS in the reaction mass was unreacted alkyl halide. There appeared to be no precedence in the literature to support the use of maleimide in the Gabriel Reaction to

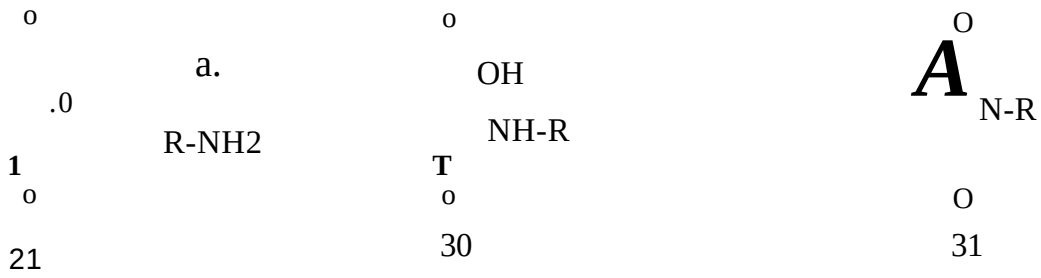
. *T)*

achieve this coupling. Adaptation of the Gabriel methodology to the use of maleimide proved to not be a tenable approach in achieving an ^/-substituted imide.

Development of A'-Tethered Maleimides

Since all attempts to get a Gabriel Synthesis approach to successfully couple a halogenated alkane (or alkylaryl compound) to either a potassium salt of maleimide or an *in situ*-generated potassium maleimide in this work failed, other avenues were pursued in order to successfully create these reaction platforms.

As previously mentioned, two alternative methodologies were identified in the literature: a maleic anhydride:amine methodology (AA) and a modified Mitsunobu protocol (MM), //-tethered maleimides were synthesized using the AA protocol via the indicated amines below with the indicated isolated yields:



Scheme 10. Amine:Anhydride Reaction Protocol, a.) Diethyl ether, reflux, 2 hrs. b.) Acetic anhydride, sodium acetate, reflux, 2 hrs. Product compound names: (30) *N*-substituted maleamic acid; (31) TV-substituted maleimide.

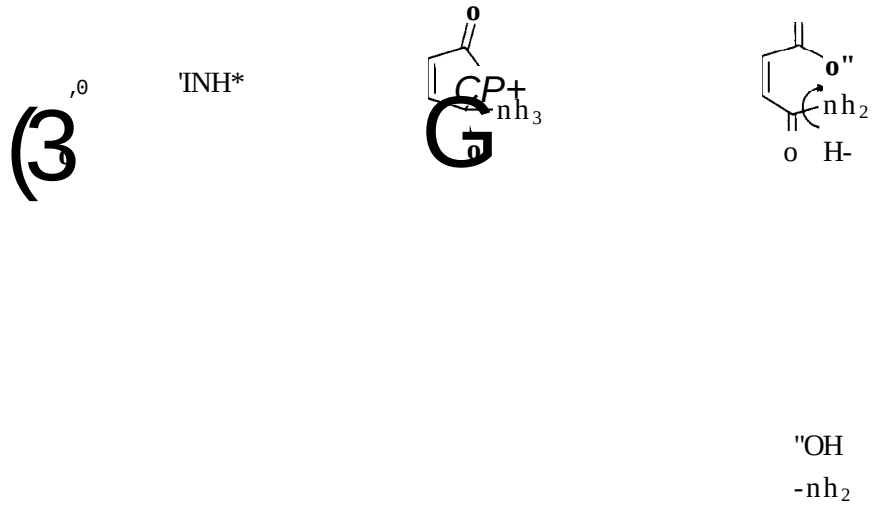
Table 3

Amines Used in the AA Synthetic Protocol with Isolated Yields

Amine Used in AA Reaction	Isolated Yield
1-Phenylmethyl amine	40.72%
3-Phenyl-1-propylamine	23.40%
p-methoxy-1-phenylmethylamine	88.46%
TV-(2-phenylethyl)-amine	73.55%
S-(l)-phenylethylamine	28.58%
TV-pentylamine	38.06%

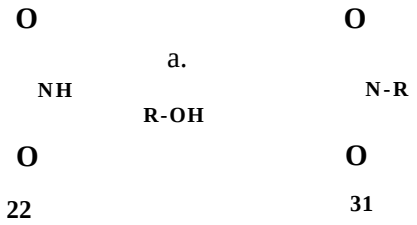
Amines used in the AA synthetic protocol with isolated yields of TV-tethered Maleimides are demonstrated above in Table 3.

With regard to the mechanism of the Amine: Anhydride Reaction, the amine proceeds via nucleophilic attack toward either carbonyl carbon atom with the unshared pair of nitrogen electrons. What follows is the process of ring opening, whereby the anhydride ring is cleaved open to yield, after proton transfer from amine to carboxylate anion, a maleamic acid compound.



Scheme 11. Amine: Anhydride Reaction Mechanism

With regard to the MM methodology, the following alcohols were employed to give the reported yields.



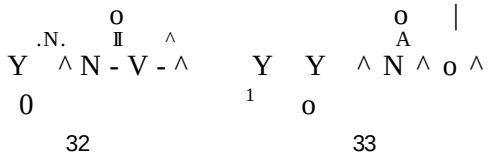
Scheme 12. Modified Mitsunobu Reaction Protocol, a.) Ph_3P, anhydrous THF, -78 °C; DEAD or DIAD; alcohol.

Table 4

Alcohols and Oxidants Used in the MM Synthetic Protocol and Yields

Alcohol	Isolated Yield	Oxidant Used
1-Phenylmethyl alcohol	71.11%	DIAD
3-Phenyl-1-propyl alcohol	54.34%	DIAD
p-methoxy-1-phenylmethyl alcohol	15.50%	DEAD*
A[r]-(2-phenylethyl)-alcohol	4.6%	DEAD*
S-(l)-phenylethyl alcohol	4.5%	DEAD*
pentyl alcohol	13.13%	DIAD

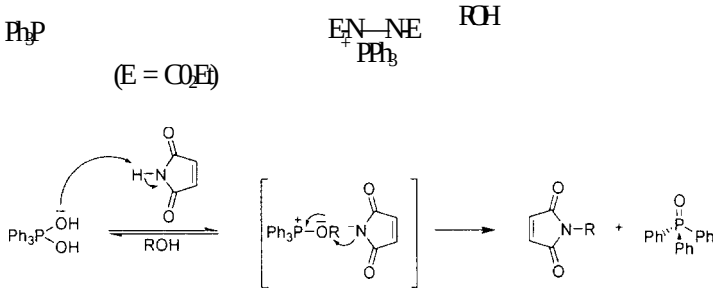
Alcohols and oxidants [DEAD = diethylazodicarboxylate (32); DIAD = Diisopropylazodicarboxylate (33)] used in the MM Synthetic protocol with isolated yields of *N*-tethered maleimides. * Trials with DIAD gave only unreacted alcohol.



32 33

Figure 15. Azodicarboxylate Reagents: DEAD (32) and DIAD (33)

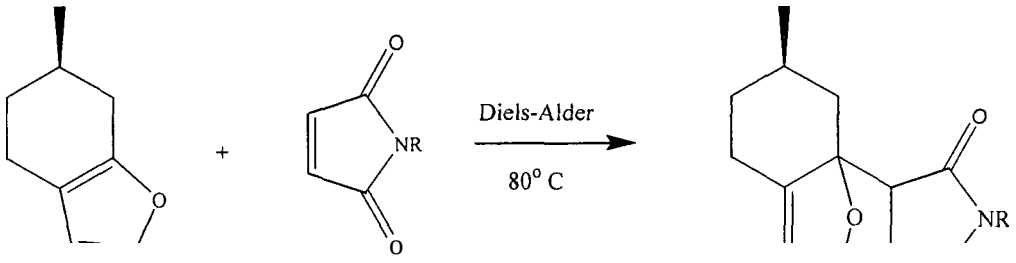
Mechanism for the Mitsunobu Reaction:



Scheme 13. Mechanism for Modified Mitsunobu Reaction.

Diels-Alder Reaction Protocol Development: Menthofuran and Maleimide

Preliminary work to determine the efficacy of a Diels-Alder reaction between menthofuran and maleimide was carried out. Initially, a synthesis experiment was conducted in triplicate using modest temperatures of <65 °C in neat peppermint oil (menthofuran content approximately 7.8%). Results showed that the low temperature was not sufficient to initiate the reaction, and no adduct was produced. Reaction progression was monitored by TLC. It was determined experimentally that pure menthofuran reacted much more readily than peppermint oil at 7.8% menthofuran, proceeding to quantitative completion after 4 hours at 70°C. Kossakowski reported a quantitative yield of the menthofuran and maleimide adduct in refluxing benzene, boiling point 80.1°C, for one hour.[73]



,

22, R = H
34, R = CH_3

o

35, R = H
36, R = CH,

Scheme 14. A Diels-Alder reaction between (+)-Menthofuran and a Maleimide.

The use of Lewis acid catalysis to facilitate a lower-temperature D-A has been described.[74] In this work, the addition of AICI3 followed by heating to 70 °C produced a bright yellow solution, which showed via TLC the disappearance of the maleimide and the appearance of an intense spot just below the menthofuran and above the maleimide (70:30 Ethyl acetate:hexane eluant). This was the adduct, compound 35.

This experiment was repeated with a solvent under reflux (ethyl acetate) at approximately atmospheric pressure overnight. A white solid resulted, which was found to primarily consist of unreacted maleimide via TLC (conditions above). Addition of 5 mL of tetrahydrofuran, followed by an overnight reflux at approximately atmospheric pressure and four days of stirring under argon produced a product via TLC, compound 35. [Rf: menthofuran 0.72; maleimide 0.34; adduct 0.53. Eluant 70:30 EtOAc:Hex].

To investigate a potential novelty in this methodology with regard to using a Lewis acid to facilitate the Diels-Alder reaction at modest temperatures, trials were attempted whereby a stoichiometric amount of a protic Lewis acid to the dienophile was used as catalyst. Three different protic forms were attempted for this reaction: a proton-exchange resin, aqueous HC1, and aqueous H3PO4. All three trials failed to produce product by TLC monitoring, primarily due to the incorrect Lewis Acid being used in H^+. The applicability of the proton to act as a Lewis Acid in complexation with 7t-systems to affect the pericyclic Diels-Alder Reaction is absent.[75]

Confirmation of Diels-Alder Reaction Tactic: Menthofuran and f(3-maleimidopropvD-phenyl-l Functionalized Silica Gel

As the concept of synthesizing and using an //-substituted maleimide as the dienophile in a Diels-Alder reaction with menthofuran had been demonstrated, the confirmation of the Diels-Alder reactivity of menthofuran toward an actual solid-phase tethered //-substituted maleimide was attempted with [(3-maleimidopropyl)-phenyl-] functionalized silica gel. This material is commercially available and was used as received from Sigma-Aldrich. The base peppermint oil, with a menthofuran concentration of approximately 7.8%, was exposed to the above-referenced compound for 60 hours at approximately 70 °C with stirring. Gas chromatography showed that the remaining peppermint oil had a residual level of approximately 0.7% menthofuran.

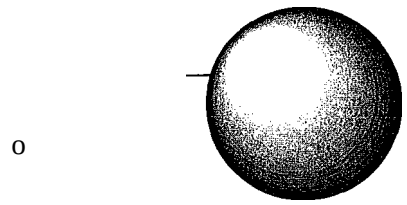


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Figure 16. [3-(maleimidopropyl)-phenyl-] Functionalized Silica Gel with Menthofuran Adduct Attached. (37)

Diels-Alder Reaction Protocol Development: Menthofuran and *N*-Methylmaleimide

The **D**-A adduct between menthofuran and ,/V-methylmaleimide served as the concept platform for this dissertation due to limited availability of an actual tethered substrate. Synthetic protocol development progressed through the use of various solvents at different reflux temperatures to observe the effect, similar to the approach already described for maleimide and menthofuran. Reactions on a 5-mmol scale were attempted in reflux with various organic solvents: hexanes and toluene. After refluxing for 90 minutes, establishing an inert atmosphere of Ar and cooling reactions overnight, TLC (70:30 EtOAc:Hex) demonstrated an adduct formed [R_t 0.56; MF = 0.80; JV-Methylmaleimide = 0.61], Hexanes trial resulted in adduct yield of 60.85%; toluene trial resulted in adduct yield of 26.50%.

A relative bulk trial was conducted on a 25mM-scale. 2.7827 g of *N*-methylmaleimide (2.7827 g, 25.05 mmol) was added to 3.7774 g redistilled menthofuran (94% purity, 23.64 mmol) + 15mL hexanes to reflux for 1 hour and heat off. After subsequent cooling, four crops of crystals were harvested, resulting in an overall total yield of 92.17% (6.5327 g theoretical; 6.0209 g actual). This was the model compound that was used throughout the project to mimic the concept of the tethered dienophiles.

Alternative Dienophile Methodologies

Naturally-Occurring Dienophiles

L-Ascorbic Acid

The attempt was made to produce a D-A adduct with L-ascorbic acid being the dienophile in the D-A reaction with peppermint oil at approximately 7.8% menthofuran.

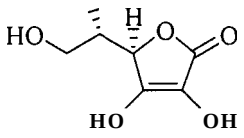

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Figure 17. /-Ascorbic Acid **(38)**

At 65°C, the reaction with menthofuran did not proceed smoothly. After holding at constant temperature over 4 days, the reaction mass appeared dark brown. Crystals were apparent at the headspace interface. Subsequent GC/MS analysis demonstrated that D-A product had not formed, but that the crystals that had formed above the reaction mass were actually /-ascorbic acid.

Pulegone

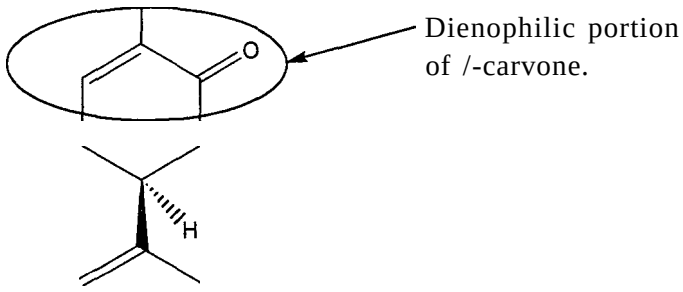
Interestingly, there is a naturally-occurring dienophile in peppermint oil, which has also fallen out-of-favor with consumers and regulatory agencies due to toxicity issues: (+)-pulegone (7).

When compared to maleic anhydride or N-substituted maleimides with two very strong electron-withdrawing groups conjugated with the alkene, pulegone is only a modestly-active dienophile, by virtue of the single electron-withdrawing group a- to the unsaturation, and will typically require the involvement of a Lewis acid to initiate a Diels-Alder reaction. However, in this study, the attempt has been made to synthesize the menthofuran:pulegone adduct. An attempt to remove menthofuran from peppermint oil via Diels-Alder reaction conditions will also likely result in some finite, but minute, quantity of the menthofuran:pulegone adduct being formed concurrently with the preferred adduct obtained via reaction with a more favorable dienophile. This underscores the importance of having a very active, viable dienophile tethered to the solid phase for this project to be successful. Maleimide is a better dienophile in the Diels-Alder reaction than either pulegone or carvone, since the dienophile is typically represented as being "electron-poor" due to strongly electron-withdrawing groups at one or both of the a-positions, or vinylic, to the alkene group. Evidence to support this position becomes clear when consideration is given to the Diels-Alder reaction between maleic anhydride and peppermint oil. GC analysis of the oil before and after the Diels-Alder reaction demonstrates that the pulegone level is consistent: it does not react with menthofuran to form an adduct

and thus reduce the amount of pulegone in the oil matrix. Therefore, pulegone does not compete with maleic anhydride in reacting to form a D-A adduct with menthofuran. It has historically been found that these 'weaker' dienophiles benefit greatly in their activation by complexation with a Lewis acid (*vide supra).*[16] The Lewis acid functions to lower the LUMO energy of the carbonyl substrate portion of the dienophile, thereby depriving the dienophile alkene moiety of electron density. This, in turn, results in the energy gap between the HOMO of the diene and the LUMO of the dienophile decreasing, which ultimately results in thermodynamically-favorable reaction conditions.[77] The consideration of pulegone as an *in situ* dienophile is not implausible, but three issues present hurdles to be overcome. First, activation via Lewis acid complexation may present concerns for this approach. Within the matrix of the peppermint oil, the choice of a Lewis acid candidate must be made very carefully, an obvious choice, aq. HC1, would lead to the acid-catalyzed hydrolysis of the esters and render the peppermint oil virtually worthless except for what could be salvaged as individual components via fractional distillation. Due to residual entrained water as a result of the steam distillation of essential oil from the agricultural hay, anhydrous HC1 would not be effective in this proposal since it would rapidly dissociate and cause the same damage as previously mentioned with aqueous HC1.[78] Second, the typical concentration of pulegone in peppermint oil is < 2.5%. This, then, would present challenges considering the fact that menthofuran almost inevitably exists in a concentration higher than pulegone in the peppermint oil. Third, the Diels-Alder adduct of pulegone and menthofuran is a thick, viscous liquid and

would not be readily amenable to physical separation such as that achieved with a crystalline adduct.

As the essential oils of the genus *Mentha* are abundant in different functional groups, it became of interest to investigate the possibility of using a naturally-derived compound as a dienophile. This concept, if successful, would allow the claim to be made that menthofuran was isolated from peppermint oil solely by reaction with a naturally-derived compound. One idea was to functionalize the terminal methylene double bond at the 8,9-position in the compound /-carvone, which is the most abundant component of the essential oil of the *Mentha spicata* (Native Spearmint) and the *Mentha cardiaca* (Scotch Spearmint) plants.

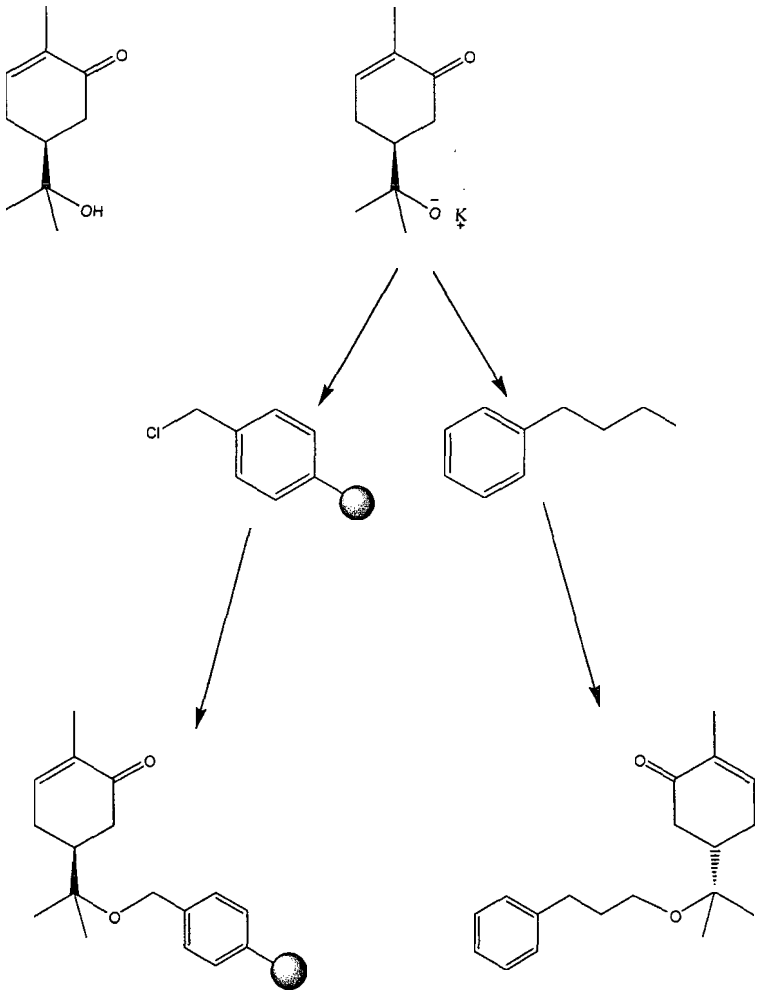


23

Figure 18. Dienophilic Geometry of /-Carvone (23)

The proposed approach was, ultimately, to hydrate the methylene functionality, thereby making a tertiary alcohol group.

Following this conversion, the tertiary alcohol would be deprotonated with either NaH or KH, resulting in a Group I metal salt of the alcohol. Then, via Williamson ether synthesis, a halogenated compound such as a chlorinated Merrifield or Wang resin, would yield a dienophile functionality tethered to a solid support.



Scheme 15. Development of a Tethered, Naturally-Occurring Dienophile. Based on carvone and a similar non-tethered mimic compound: a.) Deprotonation via Group I Metal halide.

Still, the goal of using carvone as the dienophile would be problematic due to reactivity concerns at the cyclic double bond, since there is only one electron-withdrawing group vinylic to the unsaturation.

The literature was scarce in identifying suitably efficient direct techniques for synthesizing the 8-hydroxy-/?-6-menthen-2-one **(25).**[79] Multiple attempts at the procedure of Btichi & Wiiest did not result in final yields reported in the literature. This procedure consisted of mixing /-carvone with 50% H2SO4 at 22 to 24 °C for 40 hours, followed by extraction with pentane:ether (3:1) to remove less polar compounds such as unreacted /-carvone and carvacrol. Subsequently, the aqueous layer was continuously extracted for 24 hours with diethyl ether to collect the target compound. Other researchers have reported difficulty in reliably isolating a viable yield of product, eventually attempting the Btichi & Wiiest method modified to a lower temperature of 0°C instead of the reported condition of 22 to 24°C.[80] This did not significantly improve the yield of the procedure, as Smitt reported that this formulation "... was problematic."[73] Based on literature citations by other researchers and confirmed by results in this work, a large measure of the difficulty encountered in carrying out the full Buchi & Wiiest protocol was due to the 8-hydroxy-p-6-menthen-2-one **(25)** being extremely water soluble. This made the successful separation of the product from the less polar starting compound (/-carvone, **23)** and other by-products such as carvacrol **(24)** complex. Nonetheless, a crude yield of 61.2% (before fractional distillation) was achieved in one trial. Subsequent purification via fractional distillation according to the Buchi & Wiiest method produced only several

drops of product at the anticipated boiling point. Another issue that contributed to the inability to reliably synthesize this compound was the fact that work-up of the Biichi procedure showed a tendency toward the formation of carvacrol **(24)** at variable temperatures.

24

Figure 19. Carvacrol **(24)**

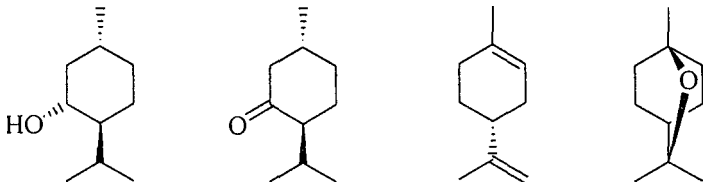
As a result of the difficulty in reliably obtaining 8-hydroxy-p-6-menthene-2-one **(25),** the approach of using /-carvone as a starting point from which to derive a viable tethered dienophile was abandoned.

Retro-Diels-Alder (RDA) Reaction

Thermal

A Retro-Diels-Alder protocol was conducted on menthofuran : *N*-Methylmaleimide adduct at temperatures ranging from 125 to 167 °C for 7 to 12 minutes. The adduct was then promptly quenched in CHCI3 and analyzed via GC/MS. The conclusion was that a much cleaner thermal RDA reaction would be

produced at lower temperatures and for shorter reaction times. Longer reaction times and higher reaction temperatures (>180 °C) resulted in by-products that occur at the expense of menthofuran, including related cyclic and oxygenated terpenes such as menthone, menthol, limonene, and 1,8-cineole (see Figure 19 below). The concentrations of these four thermal by-products were relatively consistent from 180 °C up to a final temperature of 210 °C as follows: Menthone: 0.71% ± 0.09%; Menthol: 1.75% ± 0.08%; Limonene: 0.53% ± 0.07%; 1,8-Cineole: 0.16% ± 0.01%. At temperatures lower than < 180 °C, the RDA reaction was clean, resulting in only iV-methylmaleimide and menthofuran as confirmed by GC/MS.



39 **40** **41** **42**

Figure 20. (-)-Menthol **(39),** (-)-Menthone **(40),** Limonene **(41),** 1,8-Cineole **(42)**

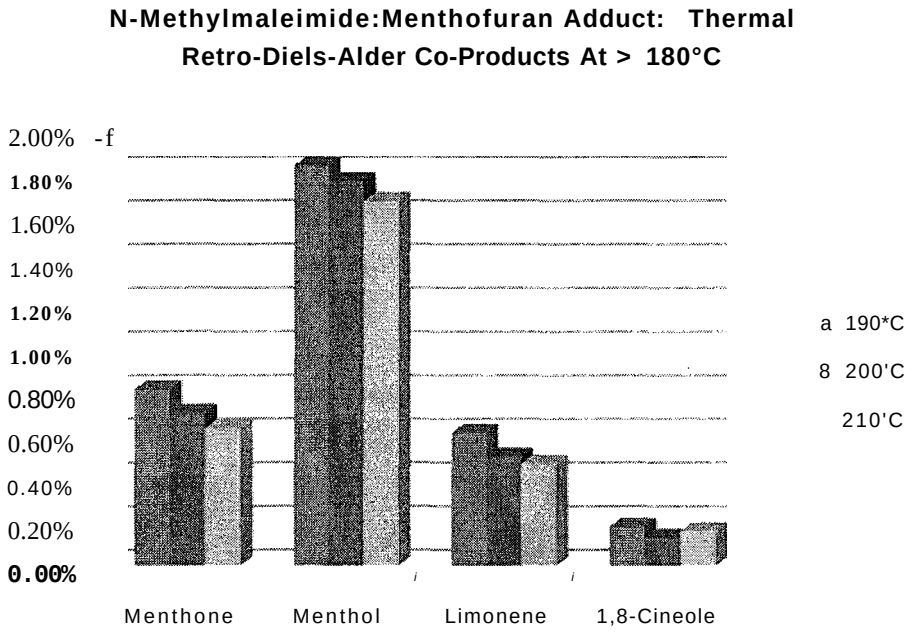


Figure 21. Thermal Retro-Diels-Alder Co-Products at > 180 °C of Menthofuran: *N*-Methylmaleimide Adduct

Conversely, Retro-Diels-Alder reaction conditions were carried out on a sample of the solid-phase bound menthofuran adduct with the [(3-maleimidopropyl)-phenyl-] functionalized silica gel. This reaction was also thermal; with very small amounts of the bound adduct being exposed to temperatures ranging from 165°C to 175°C for 7 minutes. This set of conditions did result in a Retro-Diels-Alder reaction occurring, liberating menthofuran and regenerating the [(3-maleimidopropyl)-phenyl-] functionalized silica gel. Subsequently, the recovered functionalized silica gel was reacted with menthofuran once more and yielded a 98.7% yield of menthofuran.

Generally, when performed for the shortest possible time span, the thermal Retro-Diels-Alder reactions were effective at releasing the diene and, by convention, regenerating the dienophile.

The adduct of menthofuran and [3-(maleimidopropyl)-phenyl-] functionalized silica gel was also subjected to this treatment at longer time intervals. After 15 minutes at 165-170 °C, the solid support was washed with CHCI3 for GC/MS analysis. This analysis showed that a RDA had occurred, but that menthol had been produced in a 10-fold excess relative to the reduced menthofuran yield. With a shorter, 7 minute exposure to the RDA conditions, there was a much cleaner RDA, with only menthofuran being detected via GC/MS.

Aqueous Base

Historically, the Retro Diels-Alder adduct of menthofuran and maleic anhydride has been achieved via base-promoted hydrolysis in dilute basic solutions. This resulted in the menthofuran being liberated, but the maleic anhydride component was hydrolyzed to maleic acid in the water-based process. This process generated a high waste load, and efforts have been expended in finding more environmentally-friendly methodologies to achieve the RDA reaction.

Using the model adduct of jV-methylmaleimide and menthofuran, a 2^3-factorial design of experiments[81] was conducted in which three variables were examined in two conditions, resulting in eight experiments. Table 5 below details the experimental conditions, including the mixture of products generated by the protocol.

[The choice of reaction conditions should be bold, but achievable, and represent a realistic set of experimental conditions in order to accurately assess the effect that

• • 89

changing variables is going to impart to the experiments.] The base that has historically been used to promote the hydrolysis of menthofuran adducts has been NaOH. This material is readily available, relatively inexpensive, and easily neutralized. A less-common option for the choice of base would be Na2CC>3. Considering these two options together, the range has now been set for the variable entitled "Base Used." Similarly, reaction conditions such as temperature and concentration of the aqueous base are spread across a range of values that are feasible and yet challenging. Setting the reaction condition variables allows the researcher to ultimately optimize reaction conditions in order to achieve specific objectives, such as reaction yield efficiencies, reaction time cycles, creation of co-products or by-products, etc.

The reaction as outlined in Table 5 below demonstrates the utility of statistical experimental design. In trial 6, it was found that 2% aqueous Na2CC>3 at 100 °C produced a combination of products that included a significant concentration of (-)-mintlactone at 30.1% of the total yield. Trial 2 most closely approximates the conventional protocol of performing the RDA with regard to menthofuran adducts, especially with maleic anhydride: dilute aqueous (2%) NaOH at a relatively warm temperature (< 100 °C). The results of this work mimic the typical industrial results relative to this set of conditions.

Table 5

Retro-Diels-Alder Experimental Protocol: Conditions, Reactions and Results
//-Methylmaleimide and Menthofuran Adduct

Variable	(-) Condition	(+) Condition
Base Used	Na_2C0_3	NaOH
Temperature	25°C	100°C
Aq. Concentration of Base	2%	10%

Table 5a. Variables

Trial	Base	Temperature	Concentration
1	+	+	+
2	+	+	-
3	+	-	+
4	+	-	-
5	-	+	+
6	-	+	-
7	-	-	+
8	-	-	-

Table 5b. Experiments Performed

Trial	Mint Lactone	Menthone	Mentho-furan	Menthol	Terpinen-4-ol	Pulegone	Menthyl Acetate	P-caryo-phyllene	Germ-acrene-D
1		1.3%	93.4%	5.3%					
2		0.5	97.6	1.9					
3		9.8	0	69.8	2.2	2.5	9.5	3.3	2.0
4		4.0	26.6	58.9	1.9	1.9	4.1	1.6	1.1
5	6.6	1.3	87.5	3.8			0.8		
6*	30.1	1.8	45.2	7.0	0.4			0.1	
7		3.7	0	70.0	2.3	3.0	9.6	3.2	1.9
8J	3.1	3.6	70.5	19.1	0.6		2.5	0.5	

*-Also contained 4.1% Menthofurolactone
J-Also contained 0.1% Menthofurolactone

Table 5c. % Yield of Individual Compounds

Table 5

Retro-Diels-Alder Experimental Protocol: Conditions and Reactions
iV-Methylmaleimide and Menthofuran Adduct (Low base concentration)

Variable	(-) Condition	(+) Condition
Base Used	Na_2C0_3	NaOH
Temperature	25°C	100°C
Aq. Concentration of Base	0.2%	5%

Table 6a. Variables

Trial	Base	Concentration	Temperature
1	+	+	+
2	+	+	-
3	+	-	+
4	+	-	-
5	-	+	+
6	-	+	-
7	-	-	+
8	-	-	-

Table 6b. Experiments Performed

In this set of experiments, the concentration of aqueous base was lowered. As a result, the temperature variable became highly significant: only those trials with the (-) temperature condition (Trials 2, 4, 6, 8) gave clean RDA reactions with only *N*-methylmaleimide and menthofuran present. The remaining four trials in which the temperature was at the (+) condition, 100 °C, resulted in varying combinations of menthofuran, mintlactones, and other co-products that were difficult to characterize

by GC/MS but consisted of primarily of pyrrole-based compounds caused by breakdown of the //-substituted maleimide.

CHAPTER 3

CONCLUSIONS

During the course of this work, it was demonstrated that //-substituted maleimides are readily synthesized via various methodologies as well as being effective dienophiles in the Diels-Alder reaction. As such, it is conceivable to synthesize a reusable "catch-and-release"-type dienophile that is bound to a solid-phase. Further, the Diels-Alder adduct between the iV-substituted maleimides and menthofuran can be reversed via either heat or aqueous basic solutions. The latter option is "tunable" and the Retro-Diels-Alder parameters can be adjusted accordingly to customize the Retro-Diels-Alder product blend. It was demonstrated that, given the proper experimental conditions, (-)-mintlactone can be produced in fair yield during the aqueous Retro-Diels-Alder reaction from a menthofuran and ^/-substituted maleimide adduct, including a maleimide tethered to a solid support, silica gel.

The concept of synthesizing compounds that mimic a solid-phase tethered dienophile was investigated in this work. This tactic demonstrated equivalence in the capacity of an //-substituted maleimide and the single solid-phase tethered maleimide-based dienophile to react with the diene, menthofuran. As such, the demonstration of a tether consisting of three methylene groups was the only possibility in actual comparison between the mimic compounds and the actual tethered compound.

The confirmation of the methine proton equivalence with respect to NMR in the N-substituted maleimides was a fortuitous discovery. While only one refereed journal reference cited these protons as non-equivalent (thus giving a doublet), the experimental results in this study, as well as other literature sources, found that these protons are equivalent and produced a singlet on the NMR spectrum.

CHAPTER 4

EXPERIMENTAL

Isolation of Menthofuran (1)

Menthofuran (1) *(tx-Mentha piperita* L.) was obtained in 83% purity from The A.M. Todd Company, Kalamazoo, MI. Fractional distillation at reduced pressure using a short-path distillation head over a 6-inch Vigreaux column resulted in a 30mL heart cut (representing 31-60% of the distillate volume: following a 30 mL head fraction and preceding a 40 mL tail fraction) with a boiling point of approximately 65°C/4.90 mm. The material was a clear, somewhat viscous liquid with a GC purity of approximately 97% (+)-menthofuran (normalized area %). This material was stored under Ar until further use.

Synthesis of the Diels-Alder Adduct of Maleimide and Menthofuran

Maleimide (22) (0.5609 g, 5.71 mmol) was added slowly to 10 g of peppermint oil (Kennewick District, Washington State, A.M. Todd Company), consisting of approximately 7.8% menthofuran (0.78 g menthofuran, 5.19 mmol). Temperature maintained at 70°C - 80°C overnight in ethyl acetate reflux. Adduct isolated as an oily, crystalline compound.

Synthesis of the Diels-Alder Adduct of A^-Methylmaleimide and Menthofuran

8.5 g of peppermint oil at 7.8% menthofuran (1) (0.663 g menthofuran; 4.41 mmol) was charged to a 25-mL, round-bottom flask with a heating mantle, vertical, water-cooled condenser and argon pad. jV-methylmaleimide (0.5429 g; 4.85 mmol) was added. Heat was applied to affect dissolution of the imide; reaction reached 65°C for 20 minutes and heat removed. Light yellow, clear reaction mass. Cooling slowly did not induce crystallization of adduct.

Reactions on a 5-mmol scale were attempted in reflux with various organic solvents: hexanes and toluene. Each solvent was used at 5 mL under reflux for 90 minutes. Heat was then removed and an Ar balloon added. Cooled reactions overnight at room temperature resulted in white crystals in both reactions. TLC (70:30 EtOAc:Hex) demonstrated an adduct formed (R_t 0.56; MF = 0.80; *N*-Methylmaleimide = 0.61). In the hexanes trial, white crystals were recrystallized *N*-Methylmaleimide and adduct. Rinsing the crystals with cold EtOH 70%) resulted in adduct at a 60.85%) yield (0.7951 g; 1.3065 g theoretical). The toluene trial, however, resulted in very interesting conclusions. Toluene reflux represented the highest temperature that the D-A had been attempted in this work. Toluene was stripped from the reaction mass, resulting in fluffy white crystals. Cold, aqueous 70% ethanol was used to wash the crystals. Some material dissolved in the aqueous ethanol, while some did not. Filtrate was spotted against vV-methylmaleimide on a TLC plate (70:30 EtOAc:Hex); Rt of N-Methylmaleimide = 0.63; Filtrate - 0.58. Clearly, the adduct dissolves in cold 70% EtOH but iV-methylmaleimide only slightly dissolves in this

solvent. Rotovap applied to the filtrate liquor resulted in fluffy white crystals. Cold EtOH 95% was used for a final wash. Theoretical yield of adduct 1.7358 g; isolated 0.4600 g of clear, shiny, pyramidal crystals (26.50% yield). (Melting range 146° - 151°C).

A relative bulk trial was conducted on a 25mM-scale. 2.7827 g of *N*-methylmaleimide (2.7827 g, 25.05 mmol) was added to 3.7774 g redistilled menthofuran (94% purity, 23.64 mmol) + 15mL hexanes to reflux for 1 hour and heat off. After subsequent cooling, four crops of crystals were harvested, resulting in an overall total yield of 92.17% (6.5327 g theoretical; 6.0209 g actual). This was the model compound that was used throughout the project to mimic the tethered dienophiles.

Variations of Gabriel Synthesis to produce N-substituted Maleimides

Use of Lithium Hydroxide

Maleimide **(22)** (0.117 g; 1.2 mmol [1.2 eq relative to alkyl halide]) and $LiOHH_20$ (0.0289 g; 1.2 mmol based on LiOH [1.2 eq relative to alkyl halide]) were added to 1.5 mL dry THF solvent in a 10-mL, round bottom flask with stirring. 1-Bromo-3-phenylpropane (0.199 g; 1.0 mmol) was added and reaction stirred overnight at room temperature. 'H NMR of each reaction isolate was consistent with 1-bromo-3-phenylpropane.

Use of Sodium Hydroxide

Maleimide (22) (0.1234 g; 1.27 mmol [1.27 eq relative to alkyl halide]) and NaOH anhydrous (0.0512 g; 1.28 mmol [1.28 eq relative to alkyl halide]) were added to 2 mL dry THF solvent in a 10-mL, RB flask with stirring. l-Bromo-3-phenylpropane (0.2020 g; 1.01 mmol) was added and the reaction stirred overnight at room temperature. Standard workup of stripping THF, dissolving solid in 9 mL diethyl ether in a 25-mL, 4 water washes (3 mL each) in a small separatory funnel, and rotovap of the ether layer showed a ^{f}H NMR consistent with l-bromo-3-phenylpropane.

Via Salzberg/Supniewski Procedure

Maleimide (22) (0.5240 g; 5.4 mmol) was refluxed with 16.0 mL of absolute ethanol for 15 minutes until maleimide was dissolved. To this solution was added 0.305 g of an ethanolic KOH solution (0.61g KOH, 0.60g H_20, 1.80mL absolute ethanol). Small light crystals precipitated almost immediately from a light yellow ethanolic solution. Filtered crystals on a 4-8 jum fritted-disk funnel with four acetone rinses (3 mL each). Two crops of potassium maleimide crystals were harvested with a total mass of 0.6083 g (83% yield).

Potassium maleimide (29) (0.1365 g; 1.01 mmol) was then combined with 1-bromo-3-phenylpropane (0.2058 g; 1.03 mmol) in 1.5 mL of dry DMF under reflux stirring overnight. 'H NMR was consistent with l-bromo-3-phenylpropane. The

same reaction was attempted in 2.0 mL THF at room temperature with stirring. After 76 hours at room temperature, 2.0mL of THF (due to evaporation of the initial THF) were added and a very slight reflux was affected overnight. Again, despite a cold water condenser, all solvent evaporated and the reaction mass turned brown and sticky. *H NMR demonstrated only l-bromo-3-phenylpropane; no amine produced.

Synthesis of 8-hydroxy-p-6-menthene-2-one (25) from /-carvone (23)

To /-carvone **(23)** (6.0 g; 0.04 mol) was added 40 g of 50% aqueous H_2S0_4; the resulting solution was then stirred for 40 hours at 22-24°C. Following the reaction it was extracted 4x with 3 mL each of 3:1 hexane:diethyl ether (12 mL total). Continuous extraction of the aqueous layer for 24 hours with 25 mL diethyl ether was followed by a brine wash of the diethyl ether layer 3x with 3 mL each (9 mL total) and a wash of the diethyl ether layer with 2x with 5 mL each (10 mL total) of 10% NaHCC>3, and the evaporation of the diethyl ether in the hood produced a clear, slightly yellow-colored thick oil; distilled at full vacuum, short-path head with heating mantle and rheostat. Material was primarily carvone and carvacrol; very little target product by GC/MS.

A second attempt this reaction at 0°C with 5M H2SO4 was tried. In a foam polystyrene cooler filled with ice, /-carvone (15.75 g; 0.1043 mol) was added to 100 mL H2SO4 (5M; approximately 27% H2SO4 aqueous) with vigorous stirring for 78 hours at 0°C. Extraction with 3:1 pentane:ether (3x) to remove unreacted carvone and other less polar by-products produced during this reaction, an intermediate

extraction with diethyl ether showing a moderate yield of 8-hydroxy-/?-6-menthene-2-one. **(25)** (61.2% yield) Subsequent attempts to successfully extract the product from the remainder of the reaction mass via prolonged diethyl ether extraction (24 hours) proved fruitless, as the final step in the Btichi & Wiierst process, which calls for a fractional distillation to isolate the purified product, produced only 5 drops near the boiling range (approximately 88 °C at 0.1 mm).

Synthesis of TV-substituted Maleimides

General Procedure for the Anhydride:Amine (A:A) methodology

Maleic anhydride was added to 10 mL anhydrous diethyl ether in a round bottom flask. The reaction was heated to reflux. Next the amine (5 mmol) in 15 mL of anhydrous diethyl ether was added, drop-wise, to the reaction at reflux. After all the addition of the amine, the reaction was continued at reflux for an additional 2 hours. The diethyl ether was removed under reduced pressure to yield a white powder

ol

reaction mass. Ring closure was accomplished via addition of 15 mL acetic anhydride and 0.15 g sodium acetate to the resulting white powder and refluxing for 2 hours. Strip liquid phase from the reaction mixture by rotary evaporator to near-dryness. The reaction mass was dissolved in 25 mL ethyl acetate, and filtered. The filtrate was washed with 2x 12 mL saturated aqueous sodium chloride, the solvent removed and purified via column chromatography; eluant 40:10 hexane:ethyl acetate.

l-(Phenylmethyl)-li/**-pyrrole-2,5-dione.** White solid mp 68.5-69.5 °C (lit. 69-70 °C)[84]. 'H NMR (400 MHz): 8 4.66 (s, 2H, *-CH_2-)*, 6.70 (s, 2H, -C*H=CH-)*, 7.25 to

7.37 (m, 5H, aromatic). ^{13}C NMR (100 MHz): 5 41.60, 127.94, 128.50, 128.81, 134.30, 136.26, 170.51. MS m/z 187, 104, 106, 130, 91, 78, 54.

7V-benzylmaleamic acid. White solid mp 138.5-139 °C. 'H NMR (400 MHz): 5 1.58 (s, 1H, -NH), 4.54-4.56 (d, 2H, -CH_2-), 6.26-6.29 (d, 1H, H0C(0)CH=), 6.32-6.35 (d, 1H, -NC(0)C//=), 7.25 to 7.37 (m, 5H, aromatic), -15.0 (s, 1H, -COOH). ^{13}C NMR (100 MHz): 8 43.50, 127.32, 127.67, 128.38, 132.44, 132.54, 137.32, 166.28, 166.80.

7V-(3-Phenylpropyl)-liy-pyrrole-2,5-dione. White solid mp 79-80.5 °C. 'HNMR (400 MHz): 8 1.93 (quintuplet, 2H, -CH_2-C//$_2$-CH_2), 2.618 (t, 2H, aromatic-CH_2-), 3.57 (t, 2H, -N-C*H_2-),* 6.64 (s, 2H, *-CH=CH-),* 7.15 to 7.26 (m, 5H, aromatic). ^{13}C NMR (100 MHz): 8 29.89, 33.17, 37.77, 126.04, 128.32, 128.46, 134.08, 141.03, 170.92. MS m/z 117, 111, 215, 91, 82, 105, 65, 77.

JV-(3-Phenylpropyl)-maleamic acid. White solid mp 92-94 °C. 'H NMR (400 MHz): 8 1.59 (s, 1H, *-NH),* 1.95 (quintuplet, 2H, -CH_2-Ctf$_2$-CH_2-), 2.70 (t, 2H, aromatic-*CH_2-),* 3.39 to 3.44 (quartet, 2H, -NH-C//$_2$-), 6.17-6.20 (d, 1H, H0C(0)CH=), 6.29-6.32 (d, 1H, -NC(0)CH=), 7.19 to 7.30 (m, 5H, aromatic), -15.0 (s, 1H, *-COOH).* ^{13}C NMR (100 MHz): 8 30.19,33.31,40.36,128.38,128.75, 131.64, 136.26, 140.90, 165.80, 166.21.

TV-(2-PhenyIethyl)-li/-pyrrole-2,5-dione. Yellow-white solid mp 109.5-110.5 °C (lit. 112 °C). 'H NMR (400 MHz): 8 2.89 (t, 2H, -C//$_2$-aromatic), 3.76 (t, 2H, -N-*CH_2-),* 6.65 (s, 2H, *-CH=CH-),* 7.18 to 7.28 (m, 5H, aromatic). ^{13}C NMR (100 MHz):

5 34.60, 39.20, 126.68, 128.64, 128.91, 134.12, 137.91,170.66. MS m/z 104, 201, 91, 110, 65, 82.

A^{r}-(2-Phenylethyl)-maleamic acid. White solid mp 135.5-136.5 °C. 'H NMR (400 MHz): 5 1.61 (s, 1H, -NH), 2.91 (t, 2H, -C//$_2$-aromatic), 3.65 to 3.68 (quartet, 2H, -NH-C//$_2$-), 6.25-6.28 (d, 1H, H0C(0)CH=), 6.28-6.31 (d, 1H, -NC(0)C//=), 7.20 to 7.32 (m, 5H, aromatic), -15.0 (s, 1H, *-COOH).* ^{13}C NMR (100 MHz): 5 34.85, 41.73,-126, 128.84,-129, 131.22, 134, 137.81, 166.

JV-(p-Methoxybenzyl)-l#-pyrrole-2,5-dione. White solid mp 99.5-102.5 °C (lit. 99 - 102 °C)[85]. 'H NMR (400 MHz): 8 3.76 (s, 3H, -OC//$_3$), 4.59 (s, 2H, *-CH$_2$-* aromatic), 6.67 (s, 2H, *-CH=CH-),* 6.81 to 7.34 (m, 4H, aromatic). ^{13}C NMR (100 MHz): 8 40.97,55.36, 114.05, 114.12, 128.44, 129.99, 130.07, 134.26, 159.3, 170.57. MS m/z 217, 136, 134, 174, 121, 108, 77, 146, 160.

7V=(p-Methoxybenzyl)-maleamic acid. White solid mp 133-134.5°C. 'H NMR (400 MHz): 8 1.58 (s, 1H, *-NH),* 3.80 (s, 3H, -OC*H$_3$),* 4.47-4.49 (d, 2H, -C*H$_2$-),* 6.21-6.25 (d, 1H, H0C(0)C//=), 6.31-6.35 (d, 1H, -NC(0)C//=), 6.88 to 6.90 (t, 2H, aromatic), 7.23 to 7.25 (t, 2H, aromatic), -15.0 (s, 1H, -COOH). ^{13}C NMR (100 MHz): 8 42.50, 54.36, 113.73, 129.10, 132.49, 132.64, 159.42, 166.72.

S-(l)-PhenylethyI-l#-pyrrole-2,5-dione. Thick, oily, clear liquid. 'H NMR (400 MHz): 8 1.79, 1.81 (d, 3H, -C*H$_3$),* 5.36 (q, 1H, -C*H),* 6.62 (s, 2H, *-CH=CH-*\ 7.22 to 7.42 (m, 5H, aromatic). ^{13}C NMR (100 MHz): 8 17.77,49.70, 127.31, 127.80, 128.62, 134.12, 140.40, 170.72. MS m/z 201, 186, 104,77, 120, 158, 144, 131, 172.

S-(l)-Phenylethyl-maleamic acid. White solid mp 118-121 °C. *H NMR (400 MHz): 8 1.57, 1.59 (d, 3H, -CH_3), 5.14 (quintet, 1H, -CH), 6.24, 6.28 (d, 1H, -NC(0)C//=), 6.38-6.42 (d, 1H, -H0C(0)C//=), 7.25 to 7.35 (m, 5H, aromatic), 7.78 (s, lH,-N/f),~15.0(s, 1H, *-COOH).* ^{13}C NMR (100 MHz): 8 21.24,50.46,50.60, 126.39,126.50, 129.01, 131.82,136.41, 141.36, 165.29, 165.80.

iV-pentyl-l//-pyrrole-2,5-dione. Thick, oily, yellow liquid. *H NMR (400 MHz): 8 0.86 (t, 3H, -C*H*$_3$*),* 1.19 to 1.36 (m, 4H, -*CH_2-CH_2-CU_3*),* 1.56 (quintet, 2H, -*CH_2*-CH2-CH2-CH3), 3.48 (t, 2H, -N-C//2-). ^{13}C NMR (100 MHz): 8 14.03, 22.28, 28.30, 28.92,37.97, 134.11, 134.17, 170.99. MS m/z 110, 111,82, 167,99,98,54, 124, 138.

/V-pentyl-maleamic acid. White solid mp 69.5-71.5 °C. 'H NMR (400 MHz): 8 0.87 (t, 3H, *-CH3),* 1.25 to 1.34 (m, 4H, -*CH_2-CH_2-CH_3*),* 1.59 (quintet, 2H, -C*H*$_2$-CH_2-CH_2-CH_3), 3.35 to 3.37 (quartet, 2H, -NH-CH_2-), 6.29-6.32 (d, 1H, -NC(0)C//=), 6.44-6.47 (d, 1H, H0C(0)C//=), 7.80 (s, 1H, -NH), -15.0 (s, 1H, -COOH). ^{13}C NMR (100 MHz): 8 14.00, 22.32, 28.43, 29.02, 40.69, 132.09, 135.96, 166.23.

General Procedure for the Modified Mitsunobu (MM) methodology

Triphenylphosphine (recrystallized: 5 mmol) was added to a 50-mL round bottom flask with 25 mL of anhydrous THF. The reaction flask was cooled to -78°C (acetone/solid CO2). Next the azodicarboxylate (5 mmol) was added over 2-3 minutes. After 5 minutes, the appropriate alcohol was added over 1 minute and

stirred for an additional 5 minutes. Following this, the maleimide (7.5 mmol) was added and again stirred for 5 minutes. The cooling batch is removed and stirring continued overnight. The solvent was then removed and the products purified by column chromatography; eluant was 40:10 hexane:ethyl acetate.

1-(PhenyImethyl)-lJy-pyrrole-2,5-dione. White solid mp 68.5-69.5 °C (lit. 69-70 °C)[78]. 'H NMR (400 MHz): 8 4.66 (s, 2H, -C*H*$_2$-), 6.70 (s, 2H, -*CH=CH~*), 7.25 to 7.34 (m, 5H, aromatic). ^{13}C NMR (100 MHz): 8 41.60, 127.90, 128.50, 128.81, 134.30, 136.20, 170.51. MS m/z 187, 104, 106, 130, 91, 78, 54.

A^{r}-(3-Phenylpropyl)-l//-pyrrole-2,5-dione. White solid mp 79-80.5 °C (lit. 79-80 °C).[79] 'H NMR (400 MHz): 8 1.93 (quintuplet, 2H, -CH$_2$-C//$_2$-CH$_2$), 2.618 (t, 2H, aromatic-C*H*$_2$-), 3.57 (t, 2H, -N-C*H*$_2$-), 6.64 (s, 2H, -*CH=CH-*), 7.15 to 7.26 (m, 5H, aromatic). ^{13}C NMR (100 MHz): 8 29.89, 33.17, 37.78, 126.09, 128.38, 128.51, 134.08, 141.03, 170.91. MS m/z 117, 111,215,91,82, 105,65,77.

2-(Phenylethyl)-l#-pyrrole-2,5-dione. Yellow-white solid mp 109.5-110.5 °C (lit. 112 °C)[4]. 'H NMR (400 MHz): 8 2.89 (t, 2H, -C//$_2$-aromatic), 3.76 (t, 2H, -N-CH$_2$-), *6.64 (s, 2H,-CH=CH-)*, 7.19 to 7.30 (m, 5H, aromatic). ^{,3}C NMR (100 MHz): 8 34.60, 39.20, 126.77, 128.64, 128.91, 134.12, 137.91, 170.65. MS m/z 104, 201, 91, 110, 65, 82.

AHp-MethoxybenzyI)-l#-pyrrole-2,5-dione. White solid mp 99.5-102.5 °C (lit. 99-102 °C).[79] 'H NMR (400 MHz): 8 3.76 (s, 3H, -*OCHj)*, 4.59 (s, 2H, -*CH*$_2$-aromatic), 6.67 (s, 2H, -*CH=CH-*), 6.83 to 7.34 (m, 4H, aromatic). ^{13}C NMR (100

MHz): 8 40.96,55.37, 114.02, 114.14, 128.44, 129.97, 130.08, 134.26, 159.31, 170.56. MS m/z 217, 174, 136, 134, 108, 77, 160, 146.

S-(l)-Phenylethyl-li7-pyrrole-2,5-dione. Thick, oily, clear liquid. 'H NMR (400 MHz): 8 1.81, 1.83 (d, 3H, -C//$_3$), 5.36 (quartet, 1H, -C*H)*, 6.62 (s, 2H, *-CH=CH-),* 7.22 to 7.42 (m, 5H, aromatic). ^{13}C NMR (100 MHz): 8 17.73, 49.73, 127.32, 127.80, 128.60, 134.12, 140.34, 170.69.

TV-pentyl-l//-pyrrole-2,5-dione. Thick, oily, yellow liquid. *H NMR (400 MHz): 8 0.86 (t, 3H, -C//$_3$), 1.19 to 1.36 (m, 4H, -C//$_2$-C//$_2$-CH_3), 1.56 (quintet, 2H, -*CH_2*-CH_2-CH_2-CH_3), 3.48 (t, 2H, -N-CH_2-). 13C NMR (100 MHz): 8 14.03, 22.28, 28.30, 28.92, 37.97, 134.11, 134.17, 170.99. MS m/z 110, 111, 82, 167, 99, 98, 54, 124, 138.

Synthesis of Diels-Alder Adduct of Menthofuran and Pulegone

On a 2-mM scale, (i?)-(+)-Pulegone (7) (98%, Sigma-Aldrich) (0.3112 g; 2.0 mmol) and (+)-Menthofuran (1) (94%, A.M. Todd Company) (0.3336 g; 2.22 mmol) were added to 2.5 mL toluene and refluxed for a total of 133 hours at 111 °C. GC/MS analysis resulted in menthofuran and pulegone peaks being detected due to RDA temperatures being achieved and surpassed in the injection port of the instrument. Product is a heavy, thick, clear, light yellow liquid with a sharp, pungent odor. NMR analysis attached in Appendix B.

Retro-Diels-Alder Reaction: Thermal

Individual samples of the iV-methylmaleimide and menthofuran adduct were subjected to temperatures up to 180 °C in a melting point tube in a melting point apparatus. Each trial resulted in a very clean Retro-Diels-Alder reaction: only menthofuran and TV-methylmaleimide were produced. At temperatures over 185 °C and up to 210 °C, the menthofuran yield dropped approximately 3.5%. This quantity of menthofuran gave rise to a fairly consistent concentration of oxygenated terpenic compounds normally found in peppermint oil, including menthone, menthol, and 1,8-cineole. Limonene, a terpene hydrocarbon also naturally found in peppermint oil, was also present.

Retro-Diels-Alder Reaction: Aqueous base

0.1 g of menthofuran and yV-methylmaleimide adduct was added to a small test tube. Depending experimental conditions required, 3 mL of the appropriate base (Na2CC>3 or NaOH) at a specified concentration (2% or 10% aqueous) was charged to the test tube at either 25°C or 100°C. All reactions were carried out for 24 hours. Extraction procedure: 1 mL CHCI3 (x 3) with 3 moderate shakes after each CHCI3 addition; allow CHCI3 to settle and drain. Analyze via GC/MS.

Another trial was conducted whereby the aqueous base concentrations were reduced to 0.2% to 5%. Each trial conducted with the temperature at 25 °C resulted in a very clean RDA reaction—generating only iV-methylmaleimide and menthofuran.

Appendix A

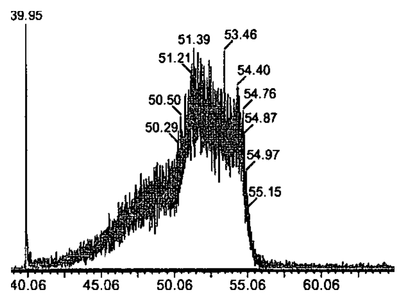
Characterization and Structure Identification Data

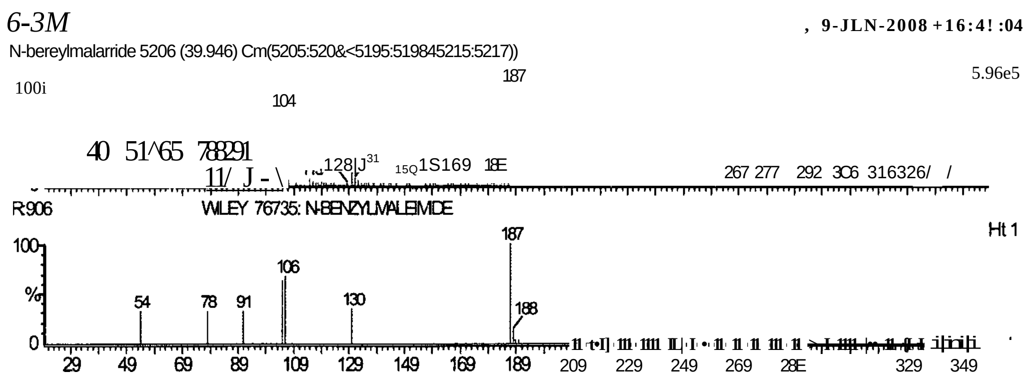
GC/MS Characterization of //-Substituted Maleimides

1. 1 -(Phenylmethyl)-I H-pyrrole-2,5-dione via A.A. Method:

6-3-08
N-benzylmaleimide

9-JUN-2008 + 16:41:04
Scan EI+
187
1.58e6

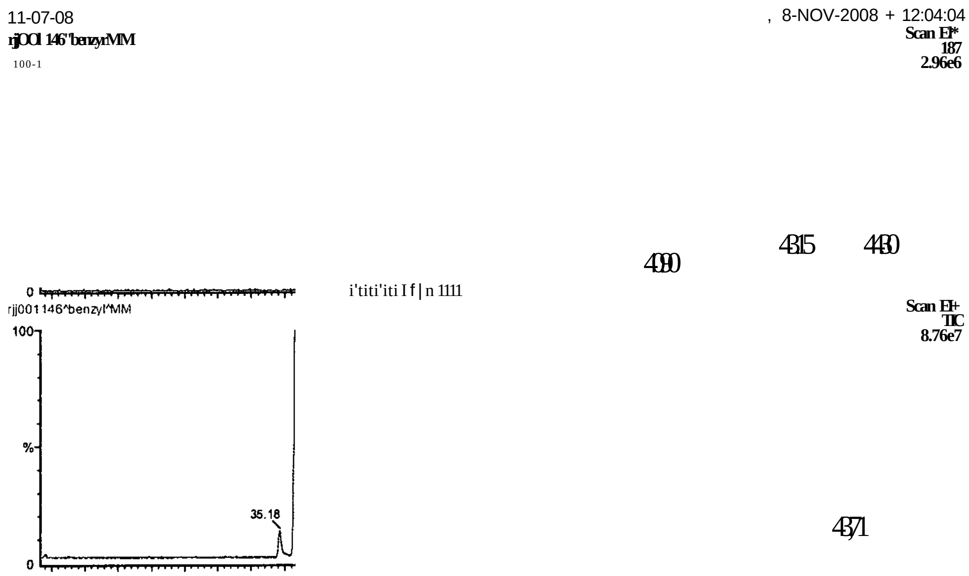


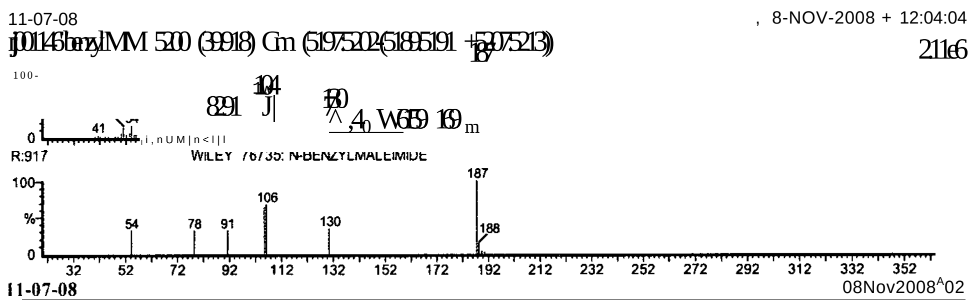


6-3-08 09Jun08a

Hit	REV	For	Compound Name	MW	Formula	CAS
1	906	492	N-BENZYLMALEIMIDE	187	C11H9O2N	1631-26-1
2	840	405	N-PHENYL-4-CHLOROSULFONYL-BENZYLAMINE	337	C13H12ClNO5S	0-00-0
3	802	348	(E)-1-CYANO-2-PHENYLCYCLOPROPANOL $$ CYCLOPROPANECARBONITRIL	159	C10H9ON	50833-33-8
4	769	442	2(1H)-PYRIDINONE, 4-HYDROXY-6-PHENYL- (CAS) $$ 4-HYDROXY-6-PHENYL	187	C11H9O2N	17424-17-8
5	753	327	(Z)-CYANO-2-PHENYLCYCLOPROPANOL $$ CYCLOPROPANECARBONITRIL	159	C10H9OM	53524-53-8
6	744	534	N-BENZYLMALEIMIDE $$ 1H-PYRROLE-2,5-DIONE, 1-(PHENYLMETHYL)	187	C11H9O2N	1631-26-1
7	743	335	BENZENEACETIC ACID, 2-PHENYLETHYL ESTER (CAS) $$ PHENYLETHYL PH	240	C16H16O2	102-20-5
8	730	525	1-(2-PROPENYL)-2,3-DIHYDRO-2,3-DIOXO-1-BENZAZOLE	187	C11H9O2N	0-00-0
9	716	311	1-(4-PYRIDYL)-4-PHENYLBUTANONE $$ 1-BUTANONE, 4-PHENYL-1-(4-PYR	225	C15H15ON	59963-53-7
10	705	378	2-CHLORO-N-PHENETHYLACETAMIDE	197	C10H12ONCl	0-00-0
11	700	324	2-ETHOXY-1,2,3,4-TETRAHYDRONAPHTHALENE $$ 2-ETHOXYTETRALIN	162	C11H14O	0-00-0
12	699	397	2-PHENYL-1-NITROETHANE	151	C8H9O2N	0-00-0
13	690	387	BICYCLCf4.2.0]OCTA-2,4-DIENE-7-CARBONITRILE(CAS)	131	C9H9N	20185-23-3
14	686	312	3-[(3R.7AS)-2-PHENYLPERHYDROPYRROLO[1,2-C]IMIDAZOL-3-YL]-5-PHENYL	449	C26H31O4N3	0-00-0

1-(Phenylmethyl)-1H-pyrrole-2,5-dione via M.M. Method:

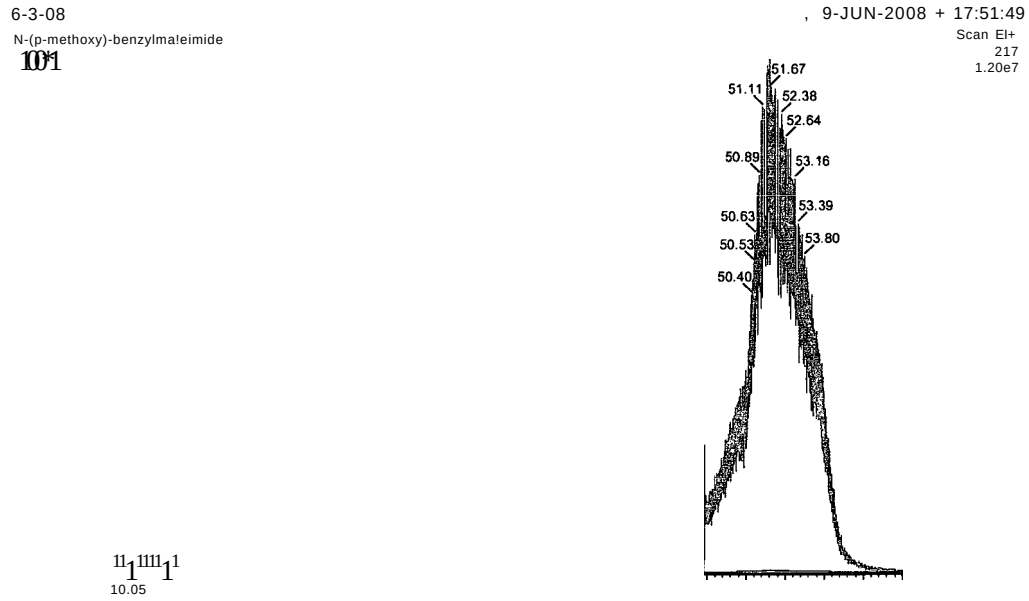


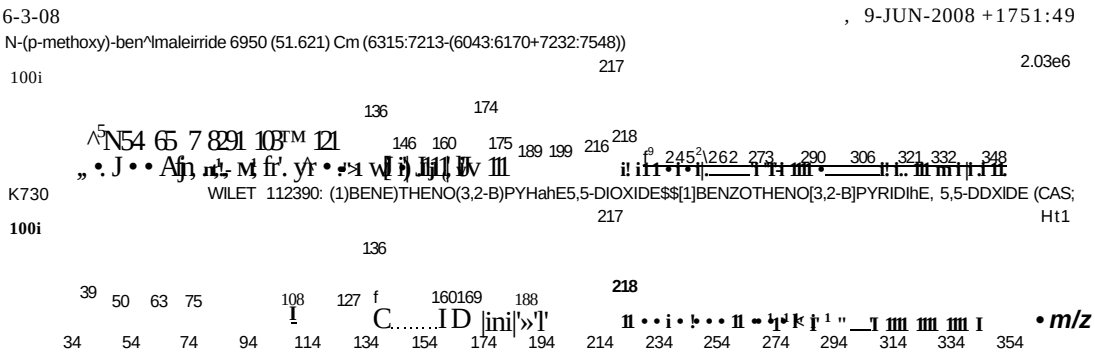


11-07-08 08Nov2008^02

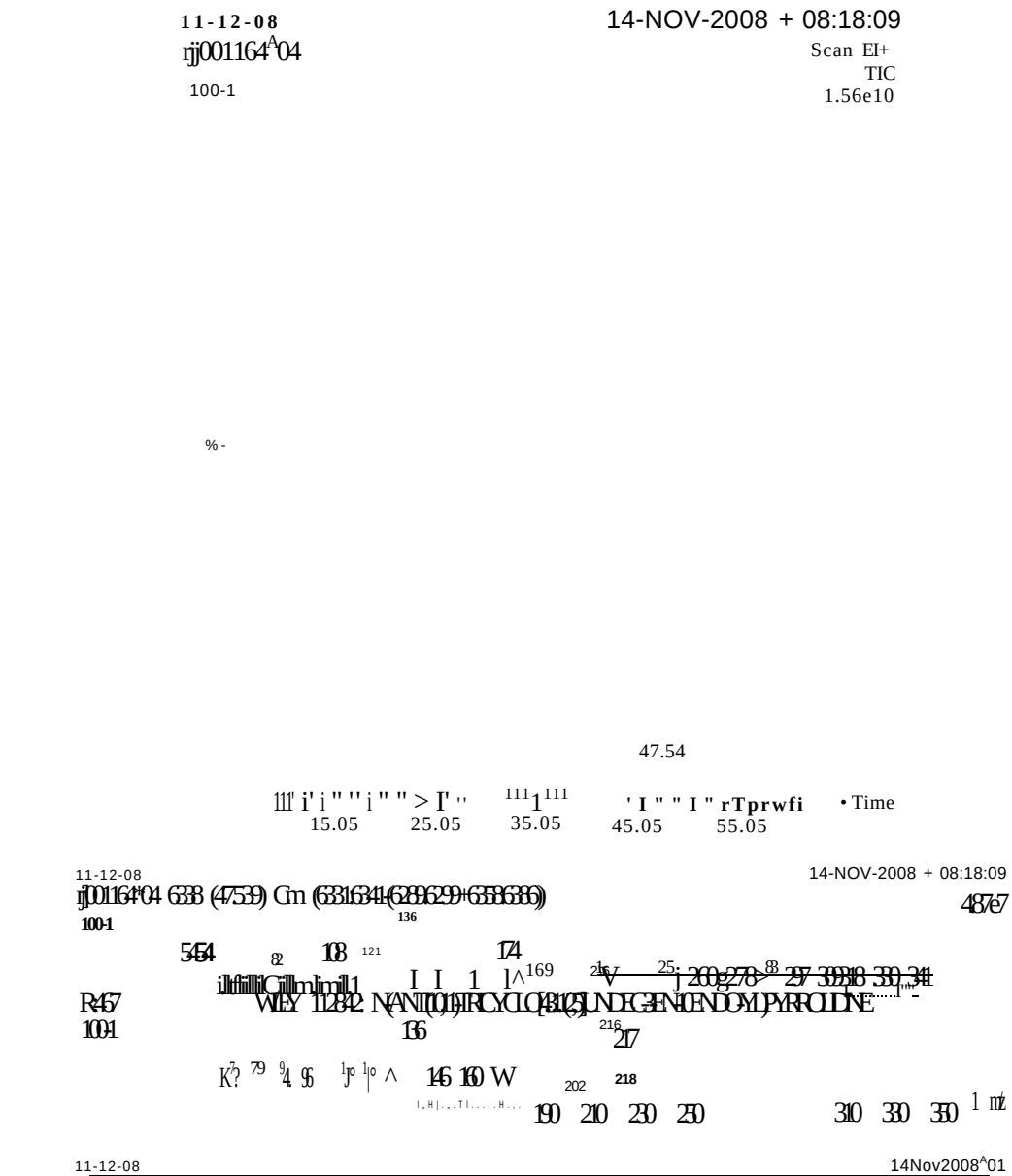
Hit	REV	for	Compound Name	M.W.	Formula	CAS
1	917	506	N-BENZYL MALEIMIDE	187	C11H902N	1631-26-1
2	858	386	N-PENTAFLUOROSULFONYL-BENZYIAMINE	337	C13H802NF5S	0-00-0
3	839	356	(E)-1-CYANO-2-PHENYLCYCLOPROPANOL S$ CYCtOPROPANECARBONITRI	159	C10H90N	5508-33-8
4	790	335	(Z)-1-CYANO-2-PHENYICYCIOPROPANOL SS CYCLOPROPANECARBONITRII	159	C10H90N	5362-45-8
5	76-1	442	2(1 H)-PYRIOINONE, 4-HYDROXr-6-PHENYI- (CAS) S$ 4-HYDROXY-6-PHENYI	187	C11H902N	17424-17-8
6	739	538	1-(2-PROPENYLM ,2.3-TRIHYDRO-2,3-DIOXO-1-BENZAZOLE	187	C11H902N	0-00-0
7	738	369	BENZENEACETIC ACID, 2-PHENYI£THYI ESTER (CAS) SS PHENYIETHYL PH	240	C16H1602	102-20-5
8	721	672	N-(P-TOLYL)MAi.EIMIDE SS 1H-PYRROLE-2.5-DIONE. 1-(4-METHYLPHENYL)-(	187	C11H902N	1631-28-3
9	715	364	2-CHLORO-N-PHENETHYL-ACETAMIOE	197	C10H120NCI	0-00-0
to	709	378	ZINC. BtS(2-PHENYLETHYLy (CAS)	274	C16H18Zn	74685-32-8
11	707	383	2-PHENYLNITROETHANE	151	C8H902N	0-00-0
12	706	364	HEXADECANAMIOE. N-(2-HYDROXYETHYI)- (CAS) SS HYDROXYETHYLPALMIT	299	C18H3702N	544-31-0
13	702	375	BENZOIC ACID. 2-PHENYLETHYI ESTER (CAS) SS PHENETHYLBENZOATE $S	226	C15H1402	94-47-3
14	696	348	IRON, TRIS(1,3,5,7-CYCLOOTATETRAENEJDI- (CAS) SS IRON. TRICYCIOOCTA	424	C24H24Fe2	61279-69-4

2. **W-(p-Methoxybenzyl)-1H-pyrrole-2,5-dione via M.M. method,** [no good match in Wiley 7.0 for this compound...base m/z peak should be 217], Red trace below is the 217 m/z; purple trace is the actual chromatogram. The mass spectral data extract was from across the entire red "blob" area, subtracting for background noise. Therefore, my MS scan is centered at approximately 51.62 minutes.





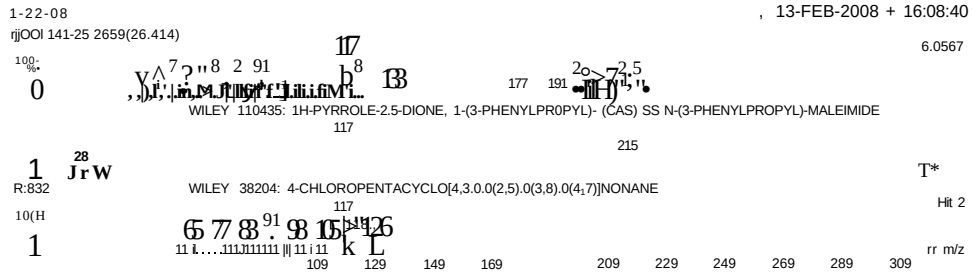
A/-(p-Methoxybenzyl)-1H-pyrrole-2,5-dione by A.A. Method



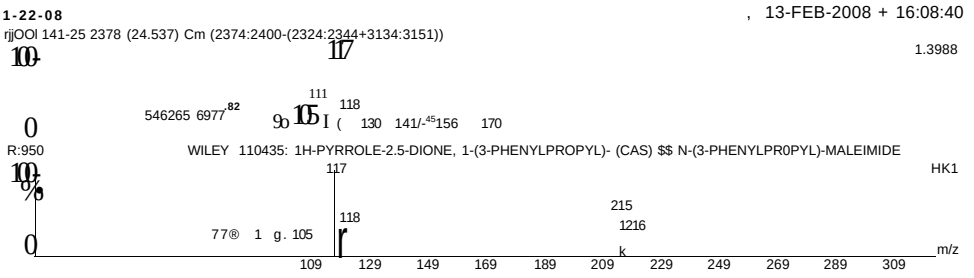
Hit	REV	for	Compound Name	M.W.	Formula	CAS
1	639	336	N2-(4-METHOXYPHENYI)GLYCINE N'-SALICY1_IDEN£HYDRAZIDE	299	C16H1703N3	0-00-0
2	611	312	2-(a-ANISIDINO)-N'-(3-TRiN€THYISILYI-2-PROPYNYLIOENE)ACETHYORAZ!D	303	C15H2102N3S1	0-00-0
3	594	302	BIS(PENTAMETHYICYC10PENTADIENYL)-MAGNESIUM	294	C20H30Mg	0-00-0
4	522	342	1,1-DI8ROMO-2-ISOPROPYV-2-^ETHYL-3-ISOPROPYLIOENECYCLOPROPAN	294	C10H16Br2	35851-46-5
5	467	326	N-{ANTI(10,11>-TRICYCLO[4.3.1.I(2.5))UNDEC-3-EN-10ENOO-YL)PYRROLID!N	217	C15H23N	85523-08-6
6	432	301	2-CYCLOHEXYL-3-(4-METHOXY-PHENYI)-OXAZIRIDINE	233	C14H1902N	0-00-0

MW of 217.

3. A'-(3-Phenylpropyl)-l//-pyrroIe-2,5-dione via M.M. method.



Hit	Rev CAS	For	Compound Name Library	M.W.	Formula
1	951	928	1H-PYRROLE-2,5-DIONE, 1-(3-PHENYLPROPYL)	215	
	C13H1302N		28537-62-4 WILEY		



Hit	Rev CAS	For	Compound Name Library	M.W.	Formula
	950	932	1 H-PYRROLE-2.5-DIONE, 1-(3-PHENYLPROPYL)	215	
	C13H1302N		28537-62-4 WILEY		

A-(3-Phenylpropyl)-l//-pyrrole-2,5-dione via A.A. method.

11-07-08 **8-NOV-2008 + 13:24:52**

rjj001149_11[A]3phenprop[A]AA Scan E1+

100-1 TIC

6.02e8

% -

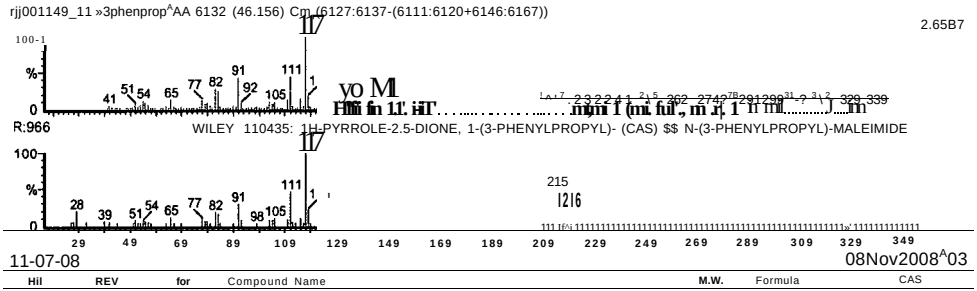
46.16

6.96 51.39

15.13 25!l3 35'. 13 45!13 55.13 • Time

11-07-08 , 8-NOV-2008 + 13:24:52

rjj001149_11 »3phenprop[A]AA 6132 (46.156) Cm (6127:6137-(6111:6120+6146:6167)) 2.65B7

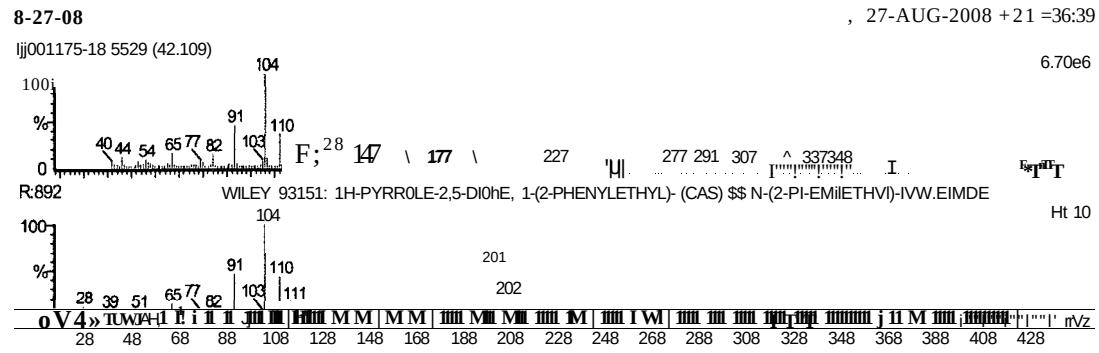


R:966 WILEY 110435: 1H-PYRROLE-2.5-DIONE, 1-(3-PHENYLPROPYL)- (CAS) $$ N-(3-PHENYLPROPYL)-MALEIMIDE

11-07-08 08Nov2008[A]03

Hil	REV	for	Compound Name	M.W.	Formula	CAS
1	966	958	1 H-PYRROLE-2.5-DIONE, 1-(3-PHENYLPROPYI). (CAS) SS N-(3-PHENYLPRO	215	C13H1302N	28537-62-4
2	859	460	4-CHLOROPENTACYCLO(4.3.0.0(2.5).0(3.8).0(4.7)]NONANE	152	C9H9CI	0-00-0
3	758	378	1 •CHLORO-5-CYCIOHEXYI-1,5-DIPHENYLPENTANE	340	C23H29CI	0-00-0
4	756	730	ACRYLIC ACID. 3-[1-HYDROXY-N-(3-PHENYIPROPYL)FORM!MIDOYL]-. CYCLIC	215	C13H1302N	28537-67-9
5	751	725	ACRYLIC ACIO, 3-[1-HYDROXY-N-(3-PHENYLPROPYL)FORMIMIDOYL)-. CYCLIC	215	C13H1302N	28537-67-9
6	666	483	TRICYCLO[4.2.1.12,5]DECA-3.7-DIENE-9.10-OIOL. STEREOISOMER (CAS)	164	C10H1202	65181-89-7
7	633	450	BENZENE, (5-METHYL-1-HEXENYL)-	174	C13H18	86761-76-4
8	632	343	3-PHENYL PROPYL 2,4- DIMETHYL-2-PENTENOATE	246	C16H2202	125427-84-1
9	585	375	1.2.4-METHENO-1 H-CYCLOBUTA(CD]PENTALENE-3.5-OIOL, OCTAHYDRO- (C	164	C1OH1202	54211-08-4
10	584	321	1-(1'-CINNAMYL-3'-METHYLINDOI-2'-YL)ETHANONE	289	C20H190N	0-00-0
11	544	300	2-(0-ISOPROPYLPHENYL)-4H-4,4-DiMETHYL-1.1,3.2-BENZODIOXAPHOSPHO	332	C18H2104P	0-00-0
12	523	331	1.3,2-DIOXABOROLAN-4-ONE, 2-CYCLOHEXYL-5-PHENYL- (CAS) SS MANDELI	244	C14H1703B	54986-49-1
13	510	319	10-METHOXY-TRICYCLO(4.2.1.1 2.5]OECA-3.7-DIEN-9-OL	178	C11H1402	70220-91-6
14	499	320	2,5.5-TRIMETHYL-3-PHSNYL-CYCLOHEXANONE	216	C15H200	0-00-0

4. Af-(2-phenylethyl)-maleimide via A. A. Method.



Ht	REV	for	Compound Name	MW.	FcmnJa	CAS
1	968	610	B-FHBvTrLETHlt FCRW1E	150	C9H10C2	104-62-1
2	946	596	R-ENYLET1-M_ RHENM. /CETATE	240	C16H16C2	102-20-5
3	944	624	FCRMCACID, 2-RWiLETHVt ESTER *(CAS) $$* 2-FHENVLBHVL PCRMOE	150	C9H10CB	104-62-1
4	935	580	®-EEhB3UrANCL (CAS) $$ 4-HHB^LBUT/WL $$ 4PHENYLBUTMRALDBH	148	C10H120	18328-11-5
5	923	597	34VETHvL-2A5-TROO1-FH0Cn-MJMD«XIDINE $$ IMDMXIDINETR	232	C12H12G3N2	67867-430
6	923	597	B-FHBMVLETHVL ACETATE	164	C10H12C2	10345-7
7	922	600	BB^Z&EACEnCACID, 2-FHBM.ETHVL ESTER (OS) $$ FHBMEIHVL FH	240	C16H16C2	102-20-5
8	914	614	PCRMCACID, 2RHENM_ETHM_ ES1ER (CAS) $$ 2-FHENYLETHM FCRMME	150	C9H10C2	10462-1
9	907	585	R-ENETHYLFCRMATE	150	C9H10CE	*OOOO*
10	892	836	1 RPVRRCLE-2,5-DOC, 1 -(2-FHENMETHM)- (CAS) $$ 1^2-FHENYLETHM.)	201	C12H11C2N	6943-904
11	871	518	NKF1-em-2-ETHVL)-^I«EC^Ln^aHE)WW	417	C14H10CNF11	70414-01-6
12	852	561	FRCPAN%10E, 30tCROI^(2-R^IVLei-M.)- (CAS) $$ BETA-CHLCRO	211	C11H14CNQ	306-20-7
13	846	544	**FRCPANWDE 2^,3,3,3-FENTAauCROhH2-R'Y»L£nHM.)- (CAS)**	267	C11H10CNF5	13230-938
14	843	572	ACETAMCE, 222-TRIR-UCRON<2-FHENMETHM.)- (CAS) $S ACETAMDE, 2,	217	C10H10CNF3	45835-5

M.M. Method

2-phenylethanol and maleimide reaction via Mitsunobu Protocol (5mM) using DEAD as oxidant

Mostly unreacted 2-phenylethanol; small amount of product at 42.12 minutes...

10-09-08 14-OCT-2008 + 12:31:37

rjj001184[A]19 Scan EI+

10Q 25.04;561686848 TIC

5.21e9

Area.

%-

25.78 27.83

2628713 13564

269935[36 21]104g892 37.84 41.14[42 12] 437484 91281[67Q4655]

WHWHpHtena I 1111 I 111n1 I

rjj001184[A]19 Scan EI+

100n 42.12 201

1.05e7

%-

42.18

Mi

rjjO01184[A]19 Scan EI+

100-, 2504 TIC

5.21e9

%-

T I i i i I -t Time

22.87 27.87 32.87 37.87 42.87

10-09-08 **, 14-OCT-2008 +12:3137**

rjj00118419 5530 (42.117) Cm (5526:5534-(5504:5510+5550:5564))

104

1.70e7

100i

%

91 110 201

R906 WILEY 93151:1H-FVRROLE-2,5-aOl^E, 1-(2-PhEWLETWL)- (CAS) $$ N-(2-R-EN*IETHYL)-MALEiMDE

100q 104 Ht 14

91 110 2)1

103 111 232

28 39 51

29 49 69 89 109 129 149 169 189 209 229 249 269 289 309 329 349 369 389 409 429

10-09-08 100ct2008[A]12

Hit	REV	fir	Compound Name	M.W.	Formula	CAS
1	990	537	CIS-4.5-EP0XY-1-PHENYL-8-N0NENE SS OXiRANE, 2-{3-BUTENYL)-3-(3-PH£	216	C15H200	127279-18-9
2	989	537	8ENZENEACETIC AC10, 2-PHENYLETHYL ESTER (CAS) SS PHENYIETHYL PH	240	C16H1602	102-20-5
3	983	641	B-PHENYLETHYL FORMATE	150	C9H1002	104-62-1
4	978	598	BHNZENEACETIC ACID. 2-PHENYLETHYL ESTER (CAS) SS PHENYLETHYL PH	240	C16H1602	102-20-5
5	970	303	2-AM1N0-3-BENZYL0XYPYRAZINE SS PYRAZINAMINE. 3-(PHENYLMETHOXY)- (	201	C11H110N3	1 10223-15-9
6	965	627	PHENYLETHYL PHENYL ACETATE	240	C16H1602	102-20-5
7	952	640	FORMIC ACID. 2-PHENYLETHYL ESTER (CAS) SS 2-PHENYLETHYL FORMATE	150	C9H1002	104-62-1
8	949	631	BENZENEACETIC ACID, 2-PHENYLETHYL ESTER (CAS) SS PHENYLETHYL PH	240	C16H1602	102-20-5
9	939	602	BENZENEBUTANAL (CAS) SS 4-PHENYLBUTANAL SS 4-PHENYLBUTYRALDEH	148	C10H120	18328-11-5
10	938	623	B-PHENYLETHYL ACETATE	164	C1 OH1202	103-45-7
11	927	617	3-METHYL-2,4,5-TRIOXO-1-PHENETHYL!MIDAZOLIDINE SS IMIDAZOLIDINETRI	232	C12H1203N2	67867-43-0
12	920	618	FORMIC ACID, 2-PHENYLETHYL ESTER (CAS) SS 2-PHENYLETHYL FORMATE	150	C9H1002	104-62-1
13	914	580	PHENETHYL FORMIATE	150	C9H1002	0000
14	906	895	1H-PYRROLE-2.5-DIONE, !-(2-PHENYLETHYL)- (CAS) SS N-(2-PHENYLETHYL)	201	C12H1102N	6943-90-4

S-(1)-Phenylethyl-1//-2,5-pyrrole via .A. method.

8-11-08 **, 12-AUG-2008 + 03:06:03**

rjjOOl 174[A]30 Scan EI+

100-1 TIC 7.02e8

50.42

50.38

% -

• Time

43.34 45.34 47!34 49.34 5l!34 53.34 55.34

11-12-08 , 18-NQV-2008 +09:01:10

rjjOOl 174[A]S1 phenethylAA 5361 (40.985) Cm (5343:5364-(5308:5317+5392:5410))

100^ 201

104

V I 120

R:813 WILEY 93238: 3A,4,5,6,7,7A-HEXAHYDRO-2-PHENYLBENZOXAZOLE

100-1 158 201

117 130 i I 17*

n,,,t.....t,,Cx m/z

11-12-08 18-Nov-2008 A 01

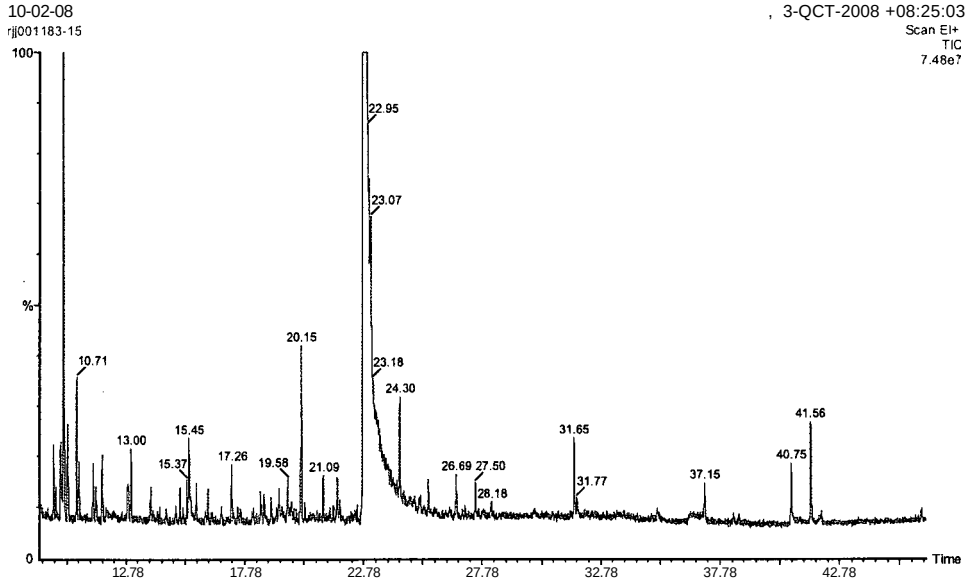
Hit	REV	for	Compound Name	M.W.	Formula	CAS
1	813	425	3A4.5.6.7.7A-HEXAHYDRO-2-PHENYL8ENZOXAZOLE	201	C13H150N	57437-13-5
2	798	319	1-{1-PHENYLVINYL)PYRROLIDIN-2-ONE	187	C12H130N	0-00-0
3	762	324	3,3-DIPHENYL-8-METHOXY-5-METHYL-{2H}-1,4-DiHYDROPYRANO[<I ,3-B]INDO	383	C25H2103N	122946-75-2
4	707	378	CYCLOPENTANECARBOXYUC ACiO, 2-OXO-5-PHENYL-3-PROPYL-, METHYL E	260	C16H20O3	104620-18-0
5	699	359	2,5-DIMETHYI.BENZENESULFONIC ACiO S$ BENZENESULFONIC ACID. 2,5-DI	186	C8H1003S	609-54-1
6	693	355	2,5-DIMETHYLBENZENESULFONIC ACID, AMMONIUM SALT	203	C8H1303NS	0-00-0
7	692	360	2.5-DIMETHYLBENZENESULFONiC ACID $$ BENZENESULFONIC ACID, 2,5-DI	186	C8H1003S	609-54-1
6	685	407	N-(1-PHENYLETHYLIDENE)-2,2-DIMETHYLCYCLOPROPYLAMINE	187	C13H17N	0-00-0
9	662	375	PYRIOINIUM, 3-HYDROXY-1-(4-METHOXYPHENYL)-. CHLORIDE (CAS)	237	C12H1202NCI	42335-70-6
10	642	332	2,5-DIMETHYLBENZENESULFONIC ACID SS BENZENESULFONIC ACID, 2,5-Di	186	C8H1003S	609-54-1
11	622	347	ENDO-2-8ROMO-3-(PHENYLSULONYL)TRICYCLO(3.2.1 0(2.4))OCT-6-ENE	324	C14H1302BfS	0-00-0
12	619	317	2-BROMO-1.3-0IMSTHYLBENZENE SS BENZENE, 2-BROMO-1.3-DIWETHYL- SS	184	C8H9Br	576-22-7
13	618	303	TRANS-2H-PYRAN.TETRAHYDRO-2.6-DIPHENYL-	238	C17H180	55696-68-9
14	606	377	3-DIAZO-1.4.6-TRIMETHYL-1.3-OIHYDRO-[NDOL-2-ONE	201	C11H110N3	0-00-0

No acceptable match in Wiley 7.0 Mass Spectral database. MW of target compound is 201. Mass fragment at 186 a.m.u. is logical due to loss of the chiral methyl group in MS fragmentation.

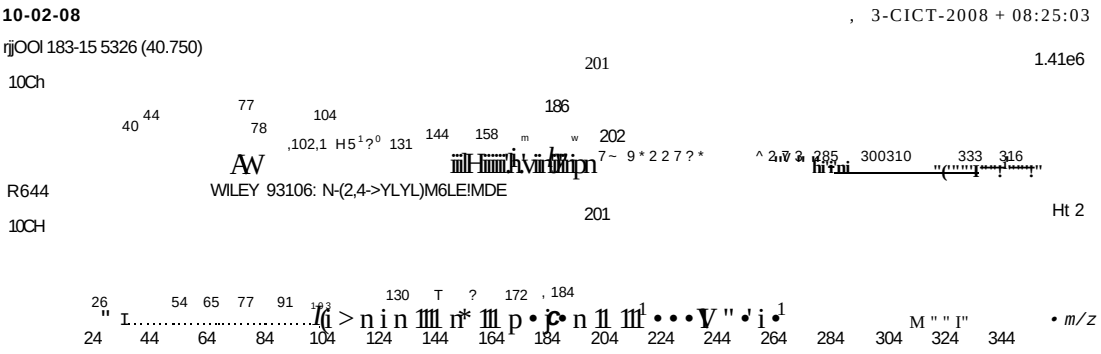
8-11-08 **13Aug2008[A]03**

Hit	REV	for	Compound Name	MW.	Formula	CAS
1	907	460	1,6-HEXANEDICNE, 1,6-DIPHENYL- (CAS) $$ DIBENZOYL-1,4-BUTANE SS 1.4-	266	C18H1802	3375-38-0
2	824	470	1,6-HEXANEDIONE, 1,6-DIPHENYL- (CAS) $$ DIBENZOYL-1,4-BUTANE $$ 1,4-	266	C18H1802	3375-380
3	812	458	1H-ISOINDOLE-1,3(2H)-DI0NE. 2-(4-OXC>4-PH£NYLBlITYL)- (CAS) $$ N-(4-OX	293	C18H1503N	7347-68-4
4	808	325	BENZENE. (1-AZIDOETHYL)- (CAS) $$ .ALPHA-IVETHYLBENZYL AZIDE $$ 1-PH	147	C8H9N3	32366-25-9
5	795	381	22-DIIVETHYL^,5-DIPHENYL-6-OX«r1-AZABICYCLq3.1.0]HE>!ANE	265	C18H190N	89718-50-3
6	790	369	2,2-DIMETHYL-4.5-DIPHENYL-6-0X^-1 -AZABICYCLq3.1.0]HEXANE	265	C18H190N	89718-53-6
7	781	430	WETHANONE, CYCLCPRCPYLPHENYL- (CAS) $$ BENZOYLCYCLOPRCPANE	146	C10H100	3481-02-5
8	768	456	3-PHENYL-3-BUTEN-2-CNE $$ 2-PRCPEN-1-CNE, 2-IvETHYL-1-PHENYL- (CA	146	C10H100	769-60-8
9	768	358	1-FLUORQAZULENE	146	C10H7F	0-00-0
10	760	374	2-PHENYL-2-(TETRAHYDRCfURAN-2-YL)PYRROLIDINE	217	C14H190N	80815-72-1
11	745	344	1H-INDENE-1,3(2H)-DIGNE (CAS) S$ 1,3-INDANDIONE $$ 1,3-DIKETOHYDRIN	146	C9H6Q2	606-23-5
12	744	431	2,4-DIPHENYL-6-(P-NiTROPHENYLSULFINYL(VETVIY1.)-1,3-DIO)^AM	423	C23H2105NS	78020-99-2
13	741	468	ETHANONE, 2-(3,4-DIHYDR0[3]YRIDq2.3-DjPYRIMDINW-YL)-1 -PHENYL- (CAS)	251	C15H130N3	28732-76-5
14	732	494	Z-2-PHENYL-2,3-DIWETHYL-3-ETHO)CCARBONYL-1-0»>rCYCLOPRCPANE	220	C13H1603	0-00-0

S-(l)-Phenylethyl-l//-2,5-pyrrole via M.M. method.



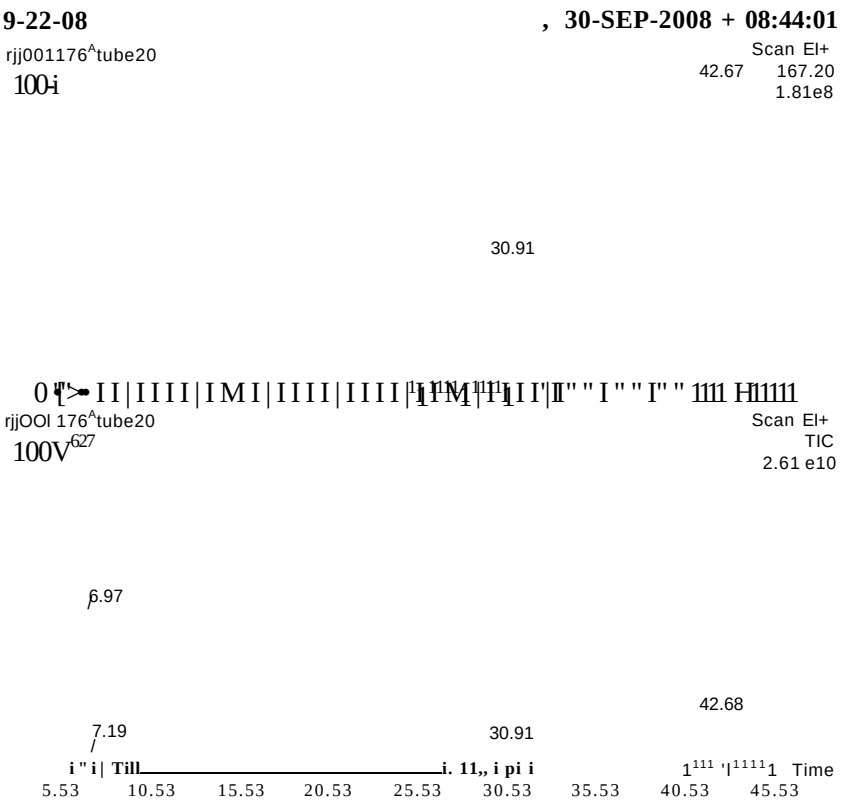
PRODUCT @ 40.75 minutes.

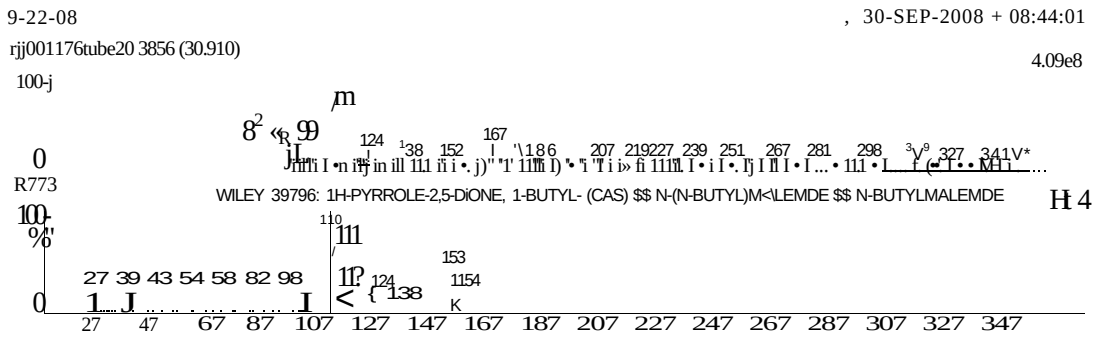


6. N-pentyl-1//-2,5-pyrrole via A.A. Method

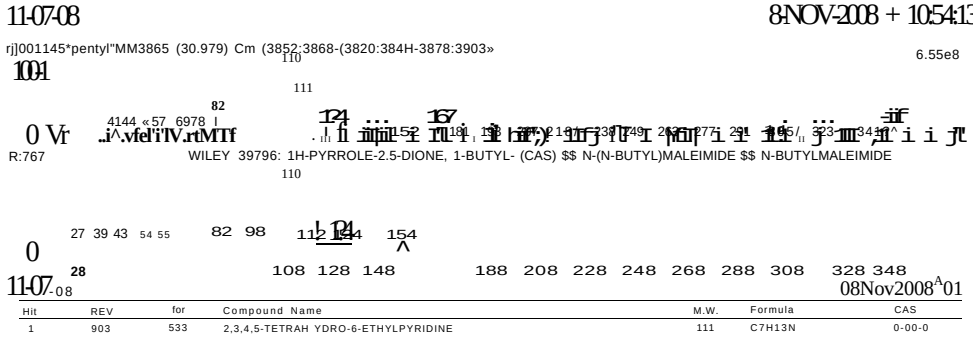
TLC showed a spot that may have been product...active blue fluorescence under black light (spot was bright violet)...

Product should be MW 167, correlating with N-pentylmaleimide. This compound is not in the Wiley 7.0 database, but is consistent with the EI-GC/MS of the corresponding N-butylmaleimide (below), which would have one fewer methylene groups, or 14 a.m.u. less. I believe this is the desired product; produced via the anhydride:amine route...





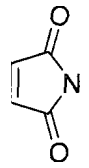
N-pentyl-l//-2,5-pyrrole via M.M. Method



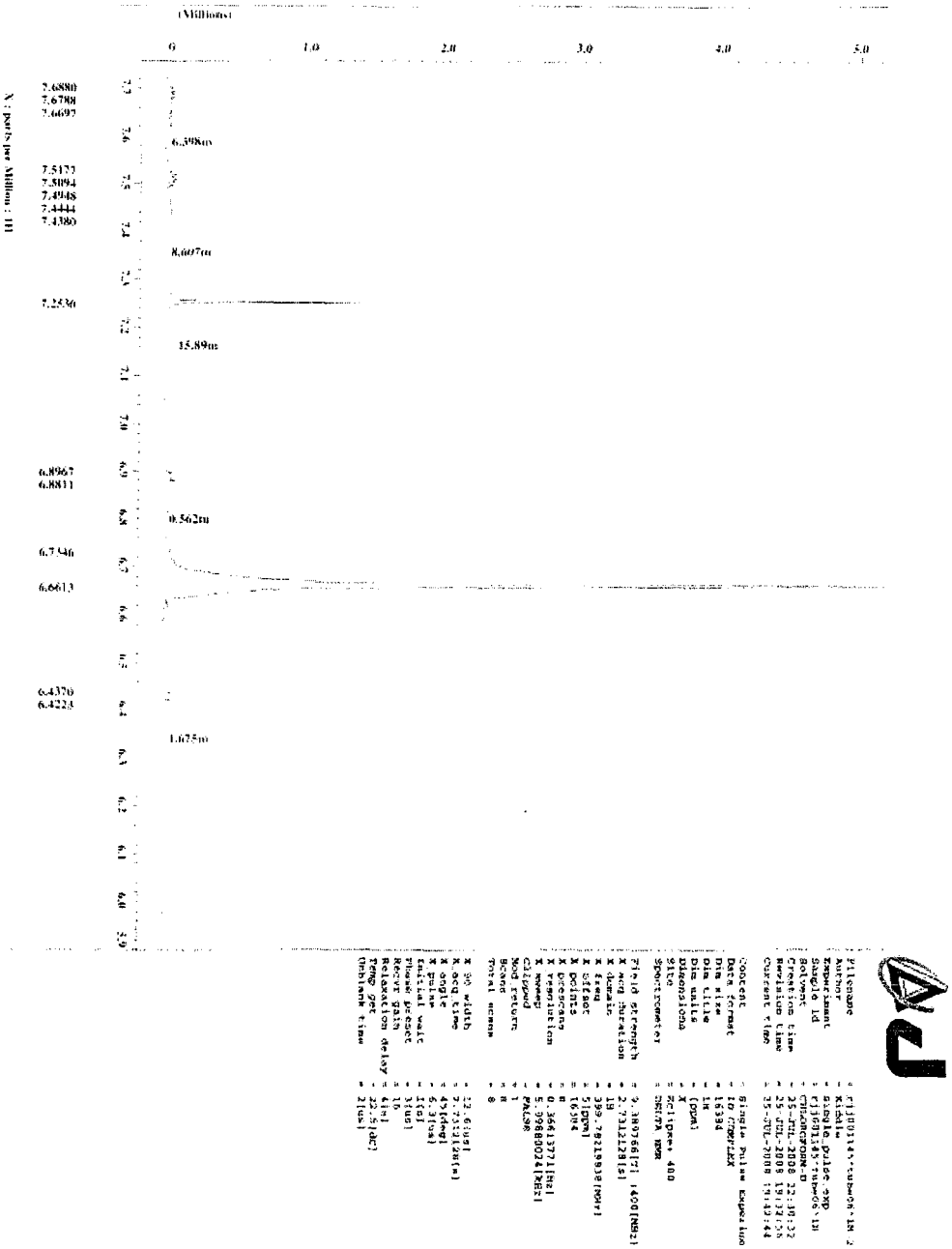
Hit	REV	for	Compound Name	M.W.	Formula	CAS
1	903	533	2,3,4,5-TETRAH YDRO-6-ETHYLPYRIDINE	111	C7H13N	0-00-0
2	817	701	1H-PVRR0LE-2.5-D10NE. 1,1'-[0XYBIS(METHYLENE)1BIS- (CAS)$$ 2-OXAPRO	236	C1QH805N2	15209-14-0
3	814	569	2H-3.4,5,6-TETRAHYDRO-7-N-BUTYLAZEPINE SS 2H-AZEPINE. 7-BUTYL-3.4.5.	153	C10H19N	3338-06-5
4	767	501	QUINOUNE, DECAHYDRO-1,7-DIMETHYL- (CAS) $S N,7-DiMETHYLDECAHYDR	167	C11H21N	32064-85-0
5	767	696	1 H-PYRROLE-2.5-DIONE. 1-8UTYL-(CAS) SS N-(N-8UTYL)MALEIMIDE $S N-BU	153	C8H1102N	2973-09-3
6	766	565	2H-3,4-DIHYDRO-5-(TERT-BUTYL)PYRROLE SS 2H-PYRROLE. 5-(1,1-DIMETHY	125	C8H15N	51269-70-6
7	737	506	2H-3.4.5.6-TETRAHYDRO-7-N-PROPYLAZEPINE SS 2H-AZEPINE. 3.4.5,6-TETR	139	C9H17N	3338-05-4
8	724	629	1H-PYRROLE-2.5-DIONE, 1,1'-(1.7-HEPTANEDIYL)BIS- (CAS) SS 1.7-HEPTAME	290	C15HT804N2	28537-72-6
9	719	451	1-AZIDO-1-SILABICYCLO{2.2.2]OCTANE	167	C7H13N3Si	0-00-0
10	702	341	MYRTINE SS 2H-QUINOLIZIN-2-ONE. OCTAJHYDRO-4-METHYL-, (4R-CIS)- (CAS	167	C10H17ON	66835-10-7
11	697	414	CIS-OCTAHYORO-6-METHYLINODOLIZINE SS INDOLIZINE, OCTAHYDRO-6-ME	139	C9H17N	82255-86-5
12	678	530	1 -AZASPIRO(5.5]UNDECANE SS 1 -AZASPIRO{5.5]UNDECANE (CAS) SS 2.2-PE	153	C10H19N	180-73-4
13	664	580	2H-QUINOLIZIN-1-OL. OCTAHYDRO- (CAS) SS 1-HYDROXYQUINOLIZIDINE	155	C9H170N	22525-60-6
14	659	592	DODECANENITRILE (CAS) SS N-DODECANONITRiLE SS LAURONITRILE $$ LA	181	C12H23N	2437-25-4

Discussion*** The Wiley 7.0 Mass Spectral Database does not have this compound listed The N-butyl homolog of the target compound is listed, and shows a base m/z of 153. Adding an addition -CH2- group to constitute the N-pentyl compound should make the base m/z 167 as demonstrated.

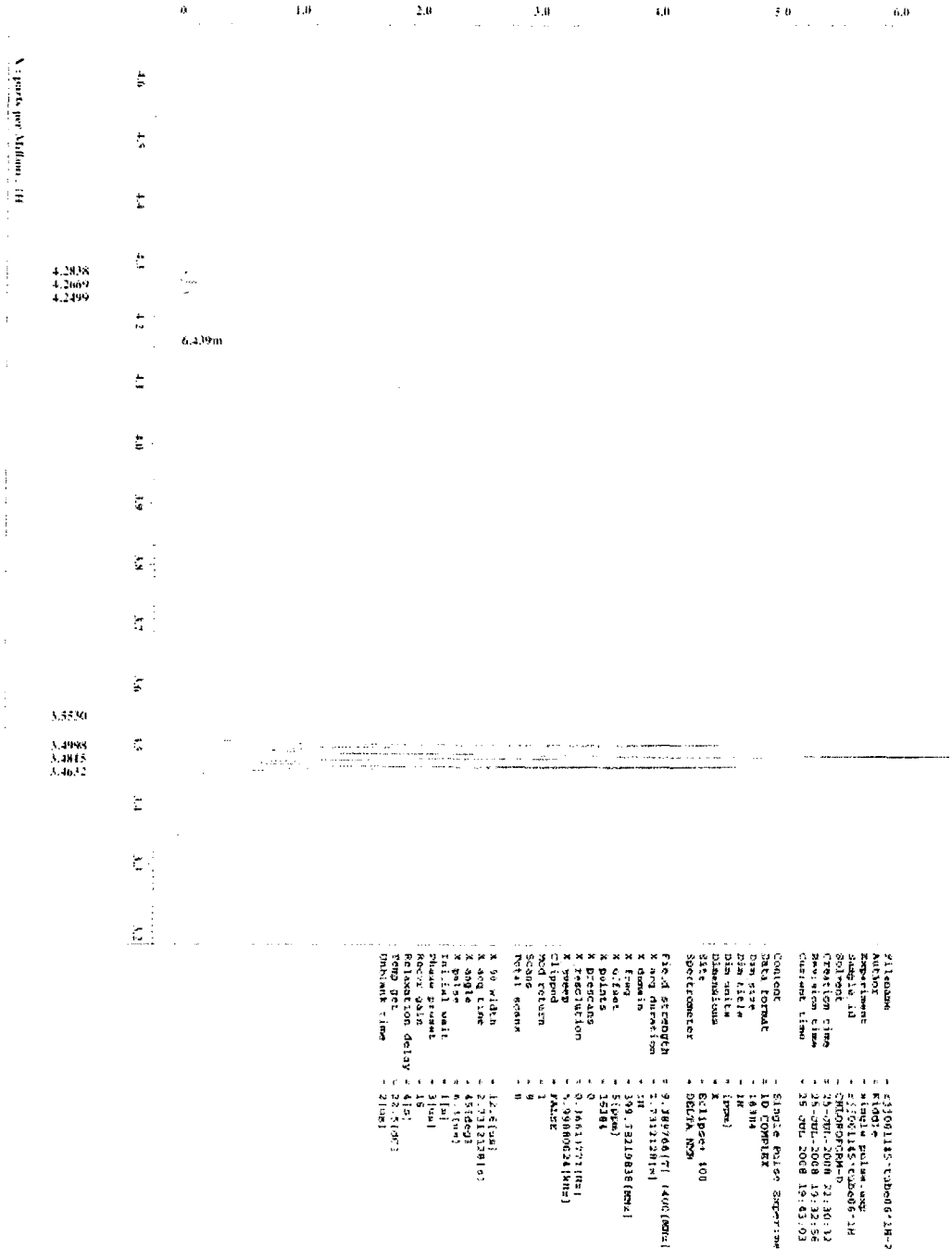
yV-Pentyl-1 //-pyrrole-2,5-dione ^{13}C NMR by M.M. Method



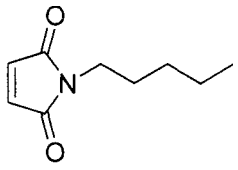
yV-Pentyl-1//-pyrrole-2,5-dione ^{13}C NMR by M.M. Method

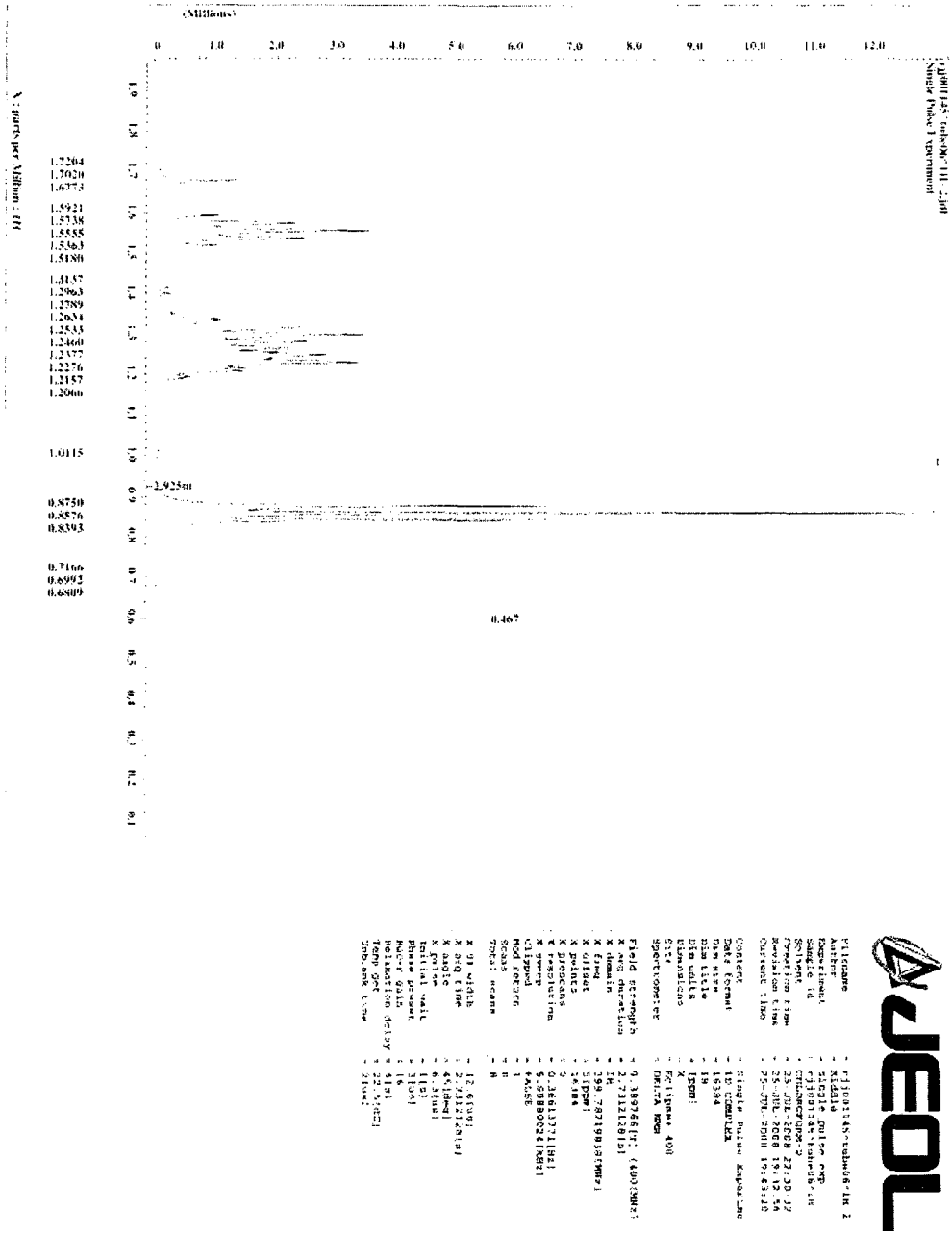


yV-Pentyl-1//-pyrrole-2,5-dione ^{13}C NMR by M.M. Method

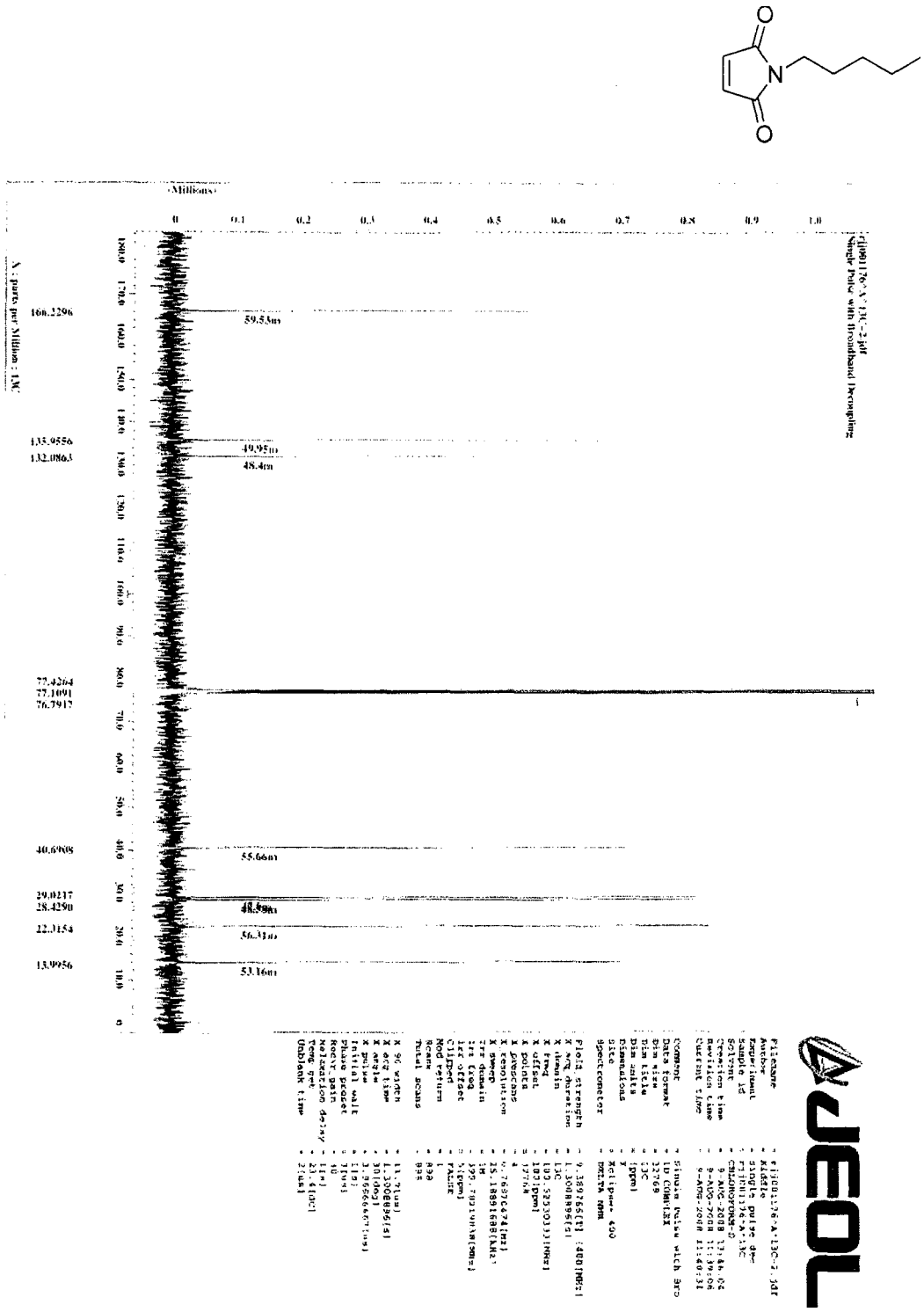


yV-Pentyl-1//-pyrrole-2,5-dione ^{13}C NMR by M.M. Method

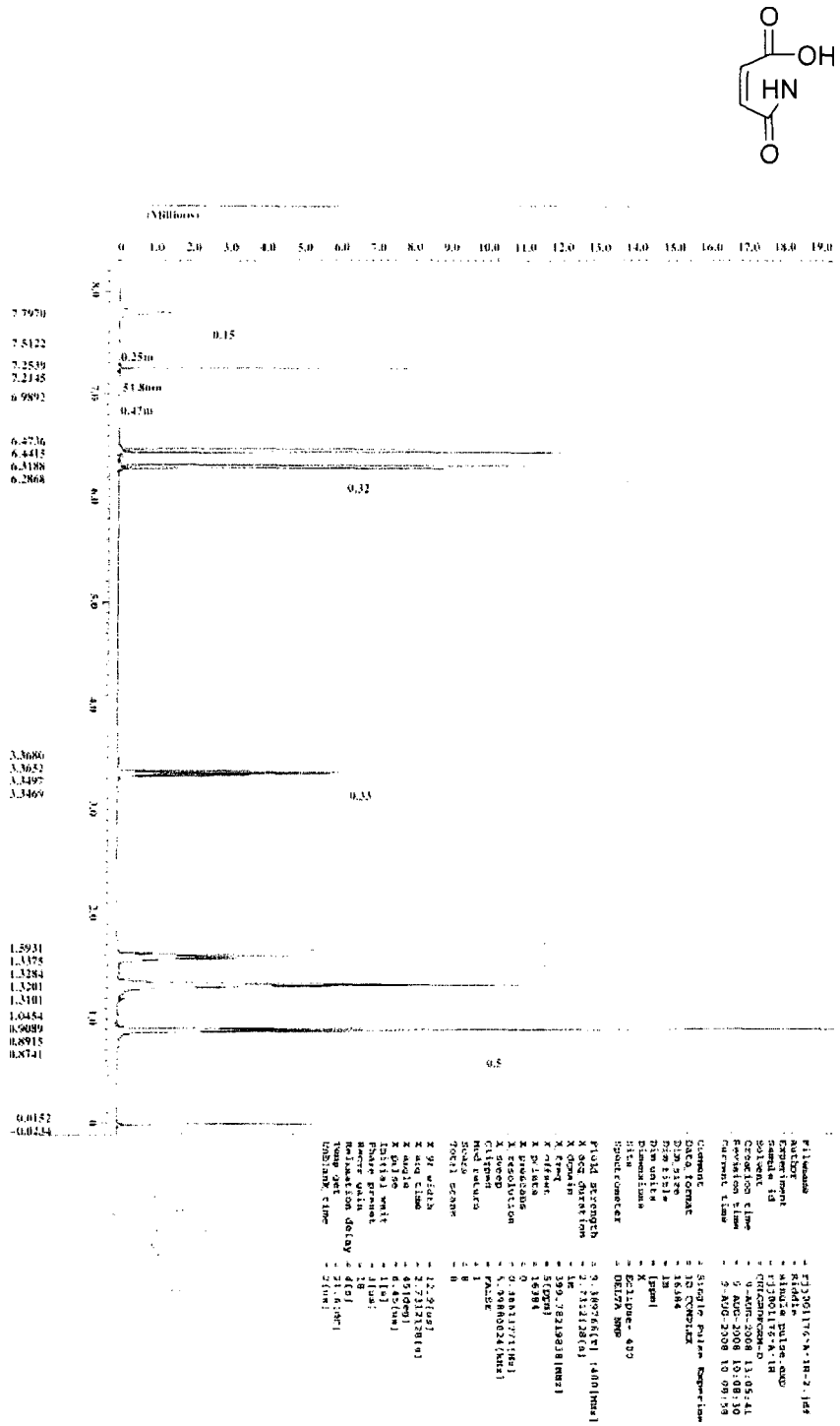




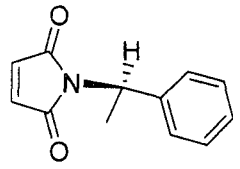
yV-Pentyl-1//-pyrrole-2,5-dione ^{13}C NMR by M.M. Method

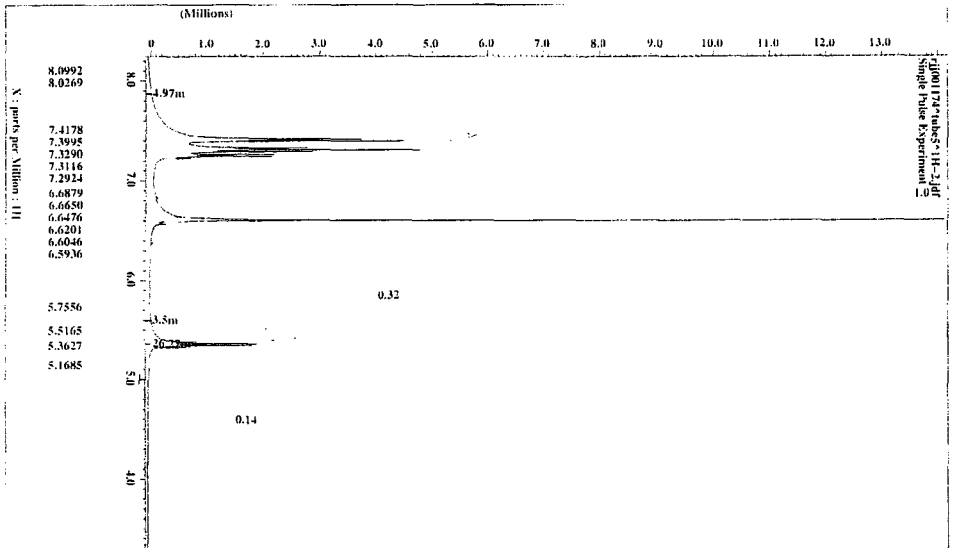


jV-Pentyl-maleamic acid *H NMR by A.A. Method



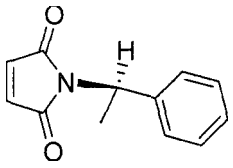
S-(1)-Phenylethyl-1*H*-pyrrole-2,5-dione ^{1}H NMR by A.A. Method

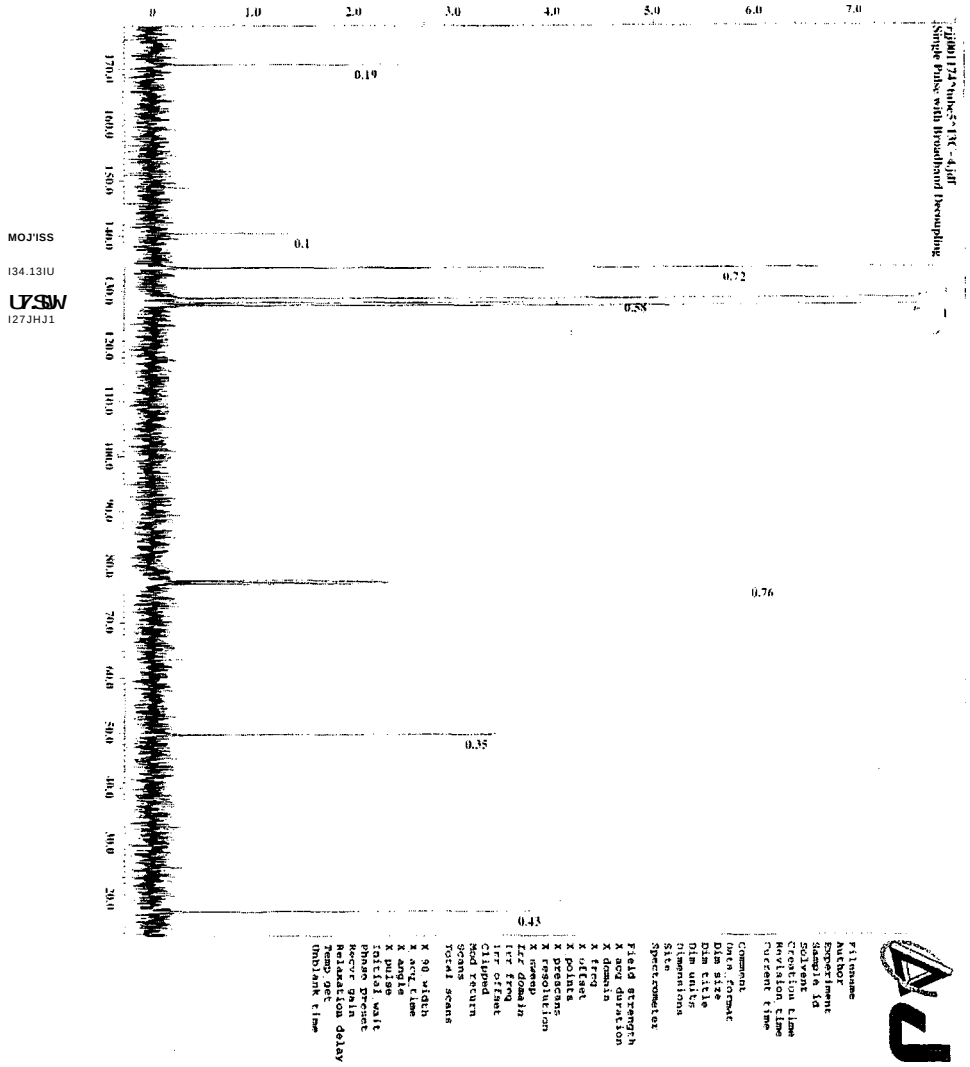




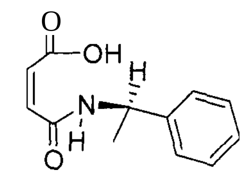
JEOL

jV-(2-Phenylethyl)-l//-pyrrole-2,5-dione ^{13}C NMR by A.A. Method





S-(1)-Phenylethyl-maleamic acid 'H NMR by A.A. Method



(Millim.i

1.0 :.0 y 0 44) 4.0 6.1) i.u xo 11.0 IM UII 151 16i MJ 180 II.

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<J62V
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51245 ii"

15S-7
15445, i
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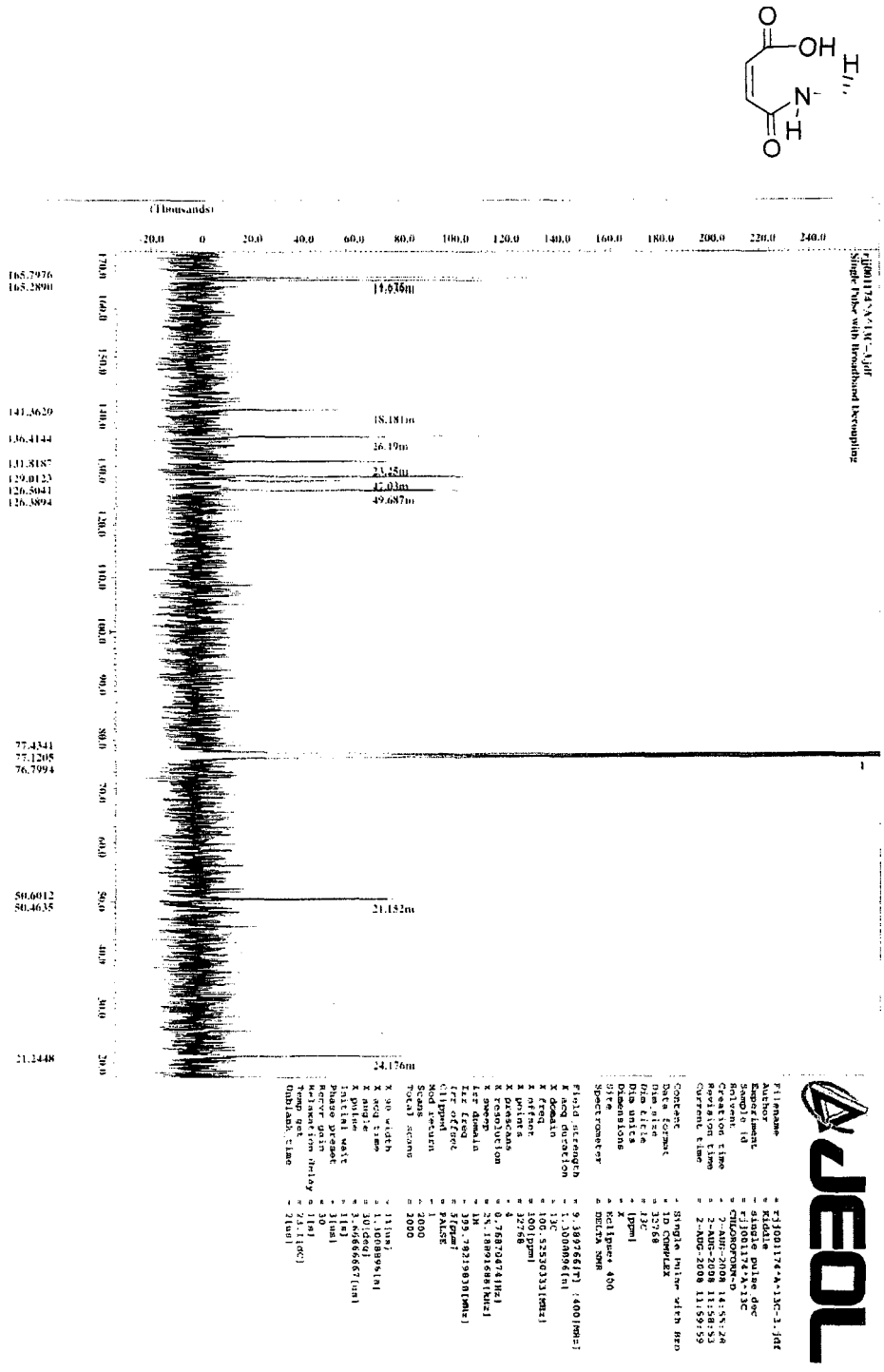
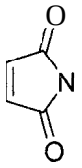
S-(1)-Phenylethyl-maleamic acid ^{13}C NMR by A.A. Method



AK2-Phenylethyl)-l#-pyrcole-2,5-dione 'HNMR by A.A. Method



7.2SU

7.>H2f.

f>AUX

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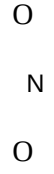
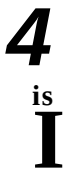
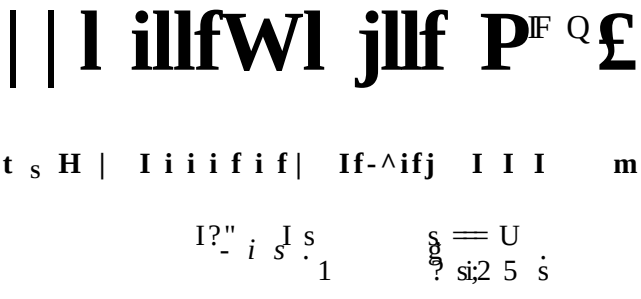
15<74

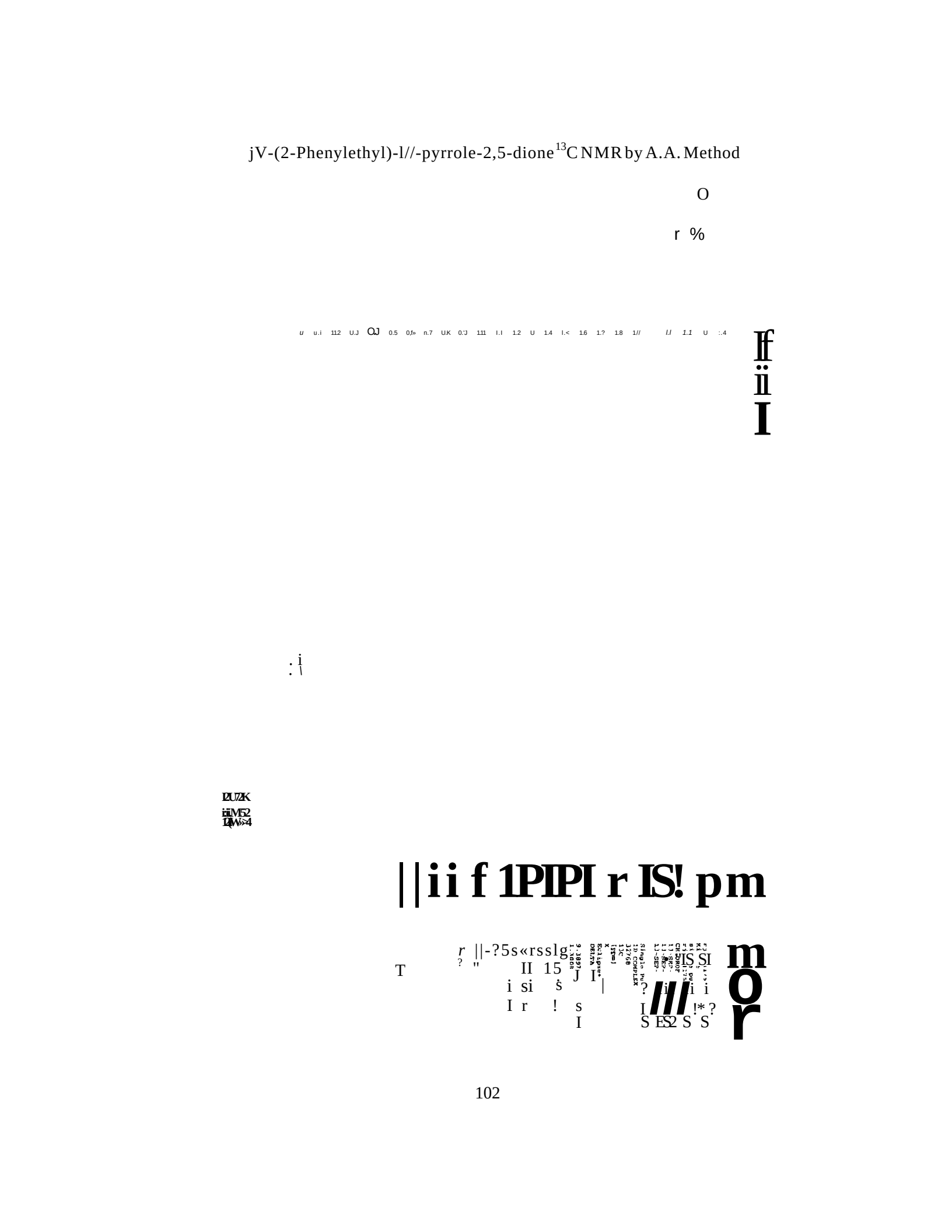
jV-(2-Phenylethyl)-l//-pyrrole-2,5-dione ^{13}C NMR by A.A. Method



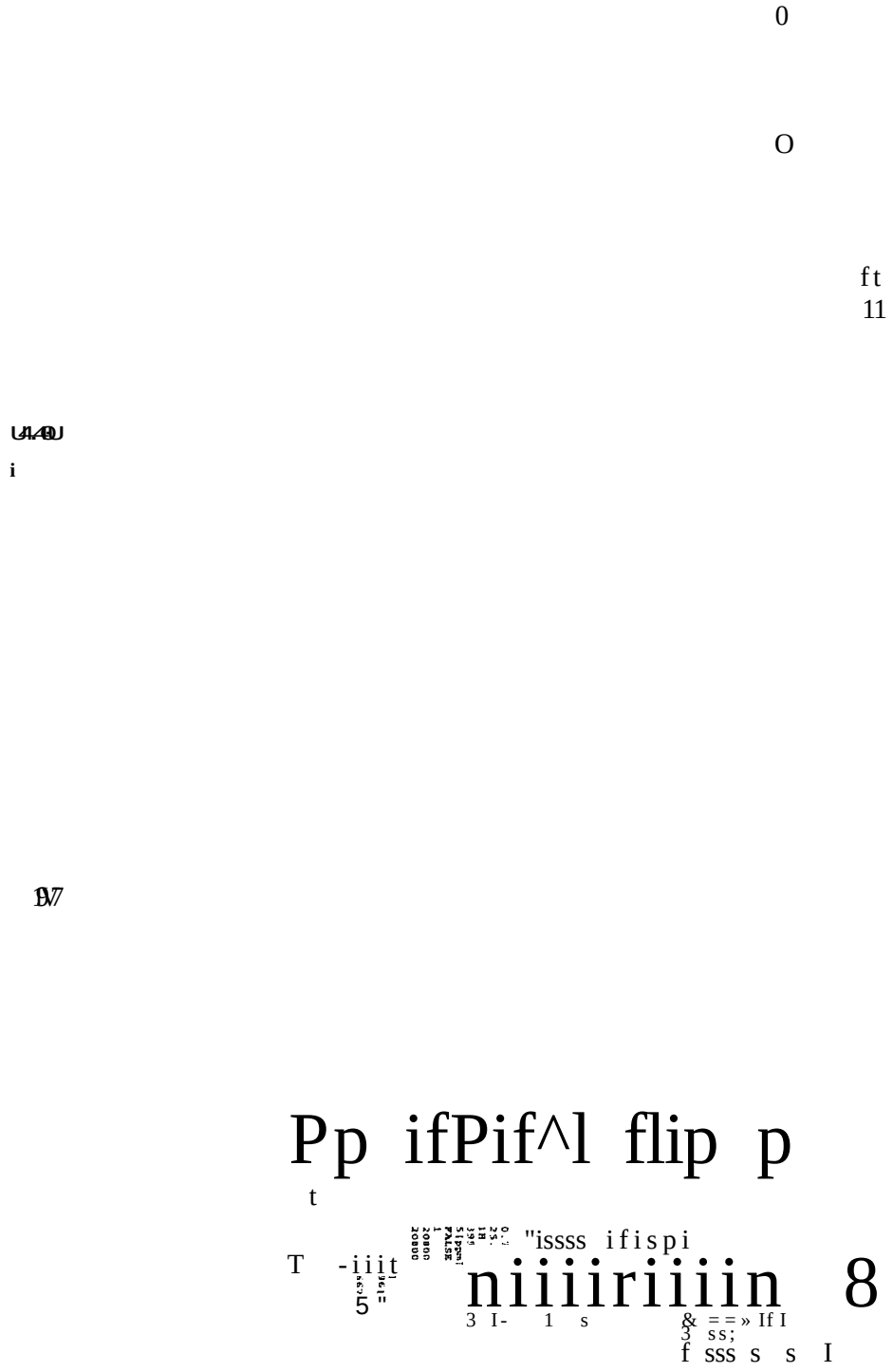




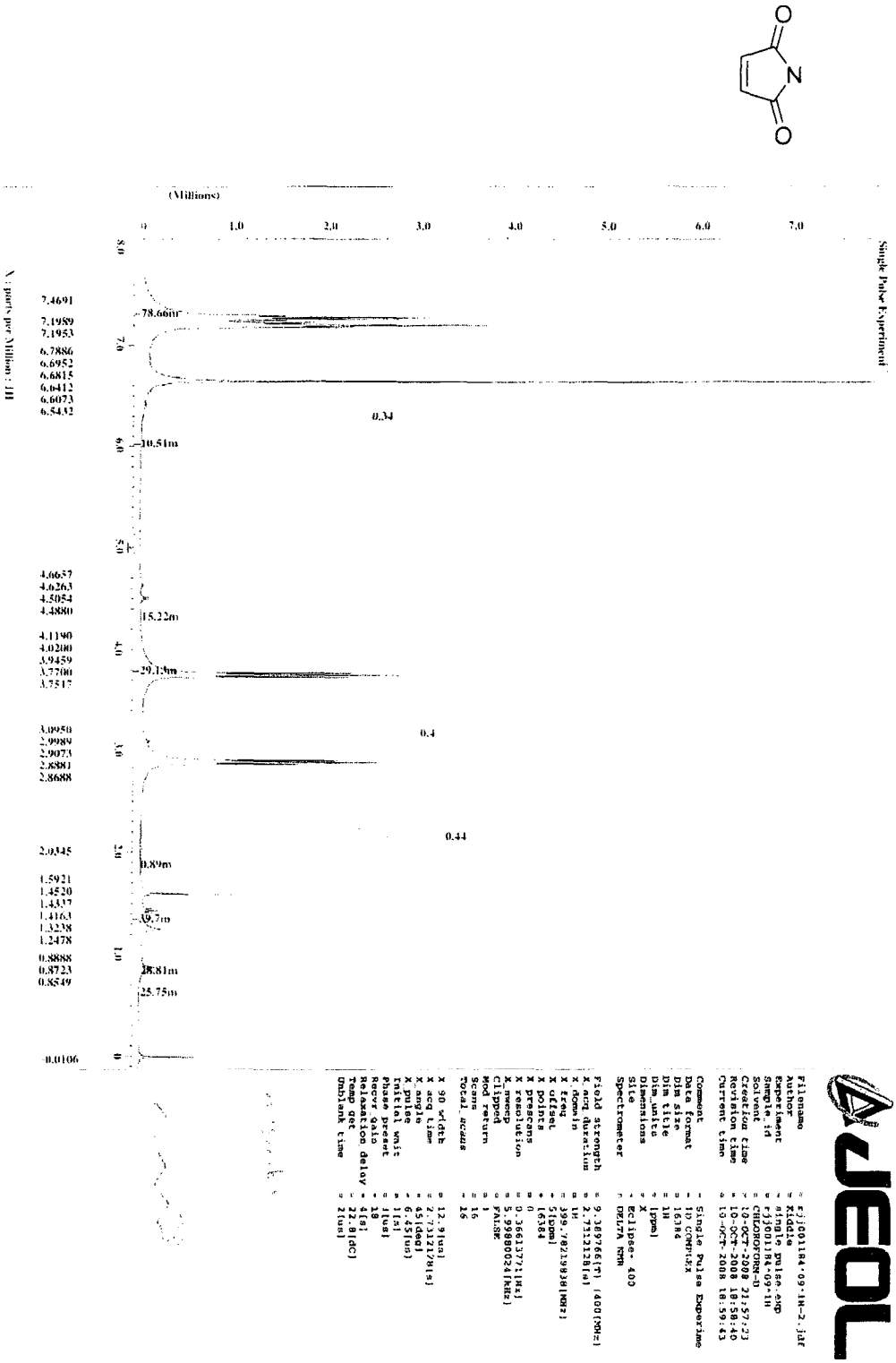
jV-(2-Phenylethyl)-l//-pyrrole-2,5-dione ^{13}C NMR by A.A. Method



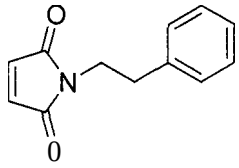
A[r]-(2-Phenylethyl)-l//-pyrrole-2,5-dione ^{13}C NMR by A.A. Method



A/-(3-Phenylpropyl)-l//-pyrrole-2,5-dione ^{13}C NMR by M.M. Method



A/-(3-Phenylpropyl)-l//-pyrrole-2,5-dione ^{13}C NMR by M.M. Method



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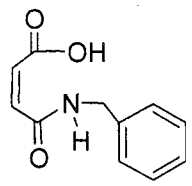
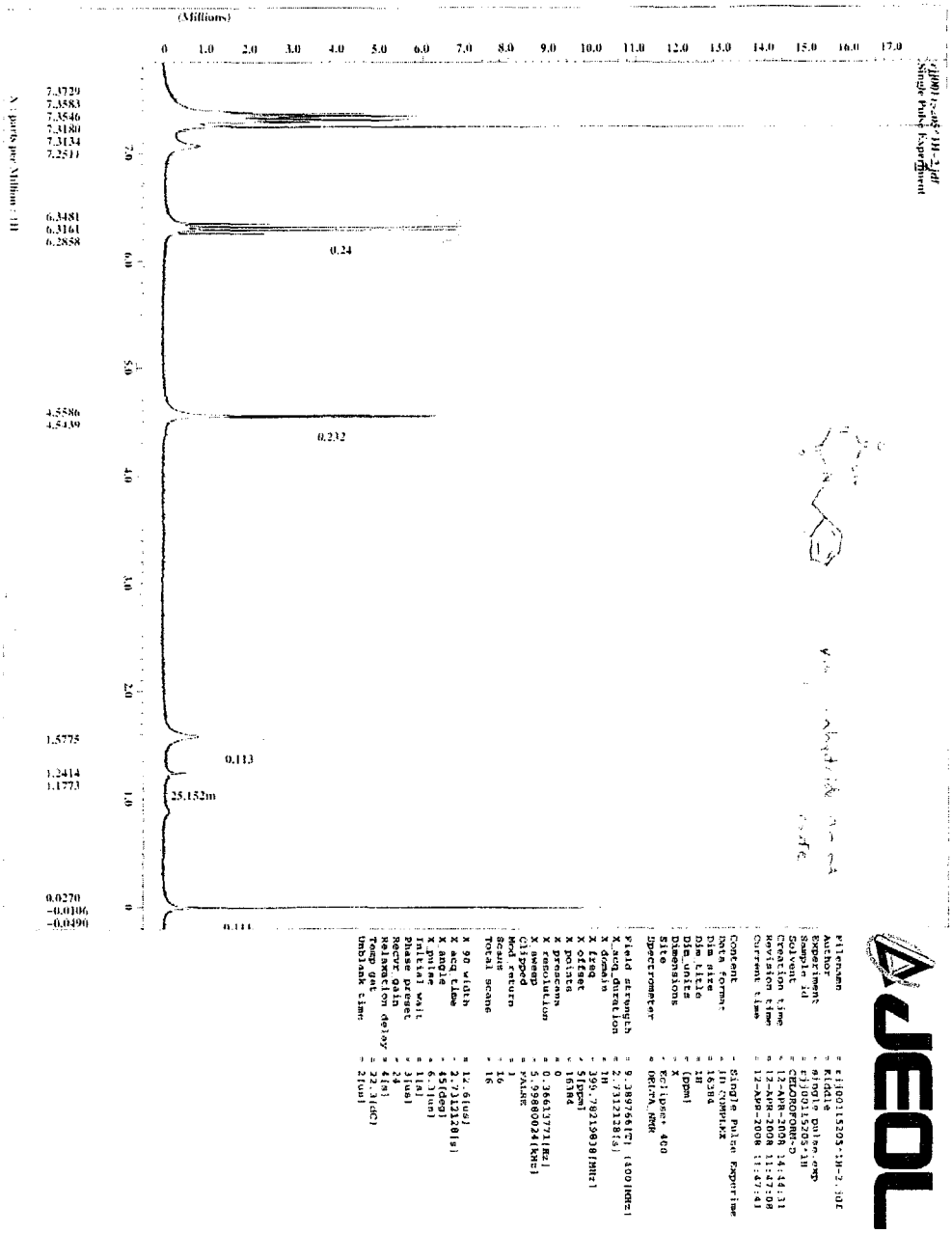
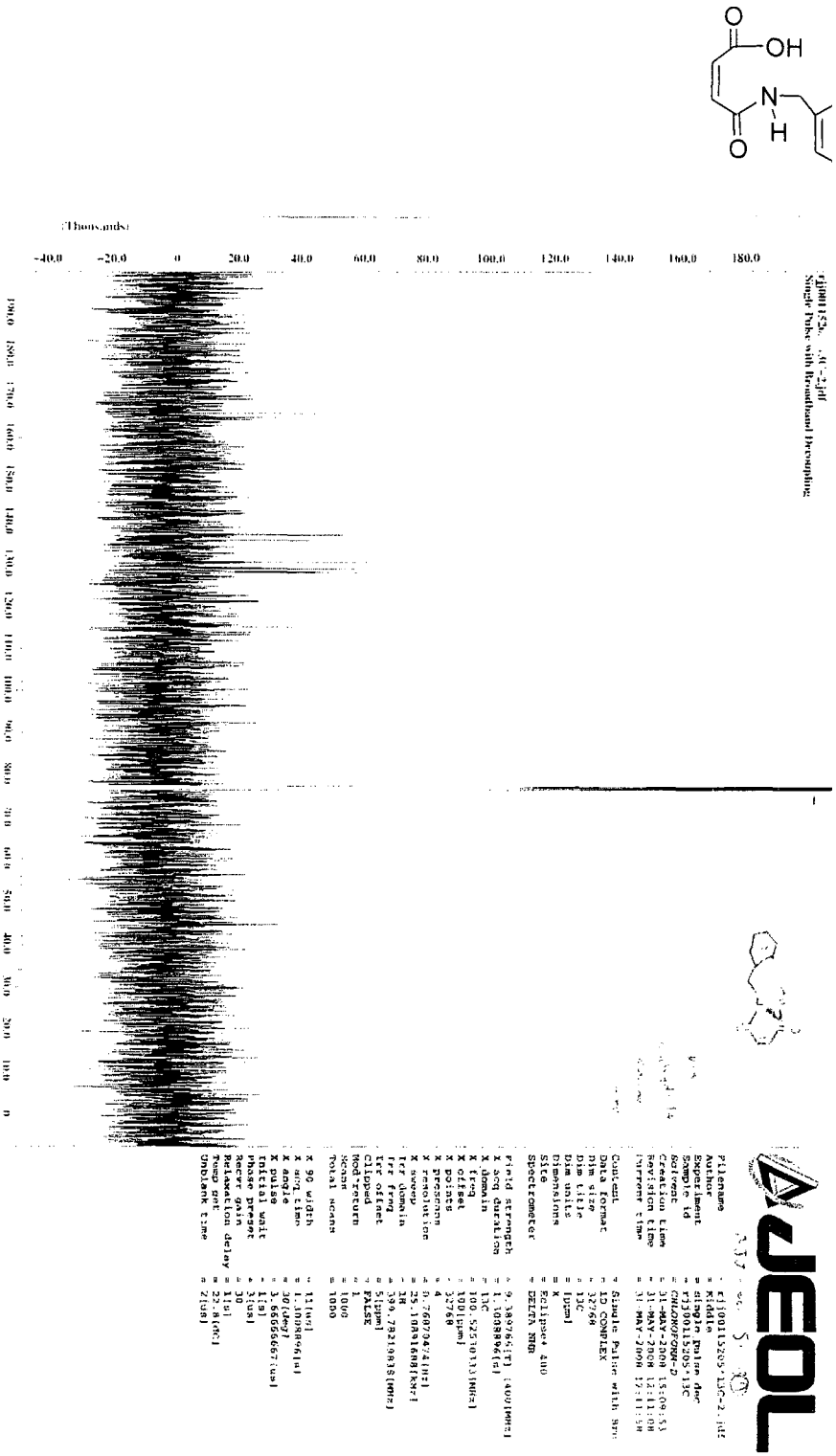
A/-(benzylmaleamic acid) *H NMR by A.A. Method

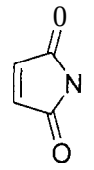


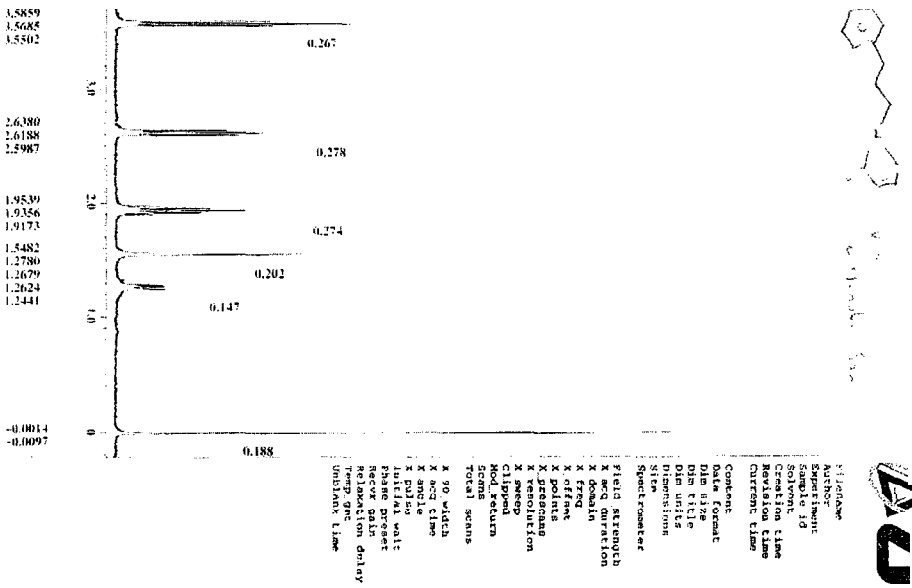


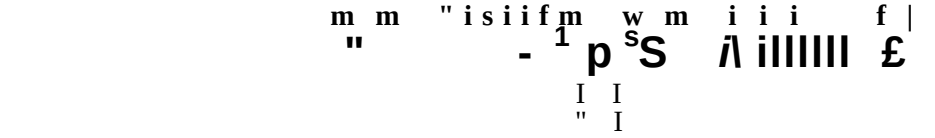
A/-(benzylmaleamic acid) ^{13}C NMR by A.A. Method



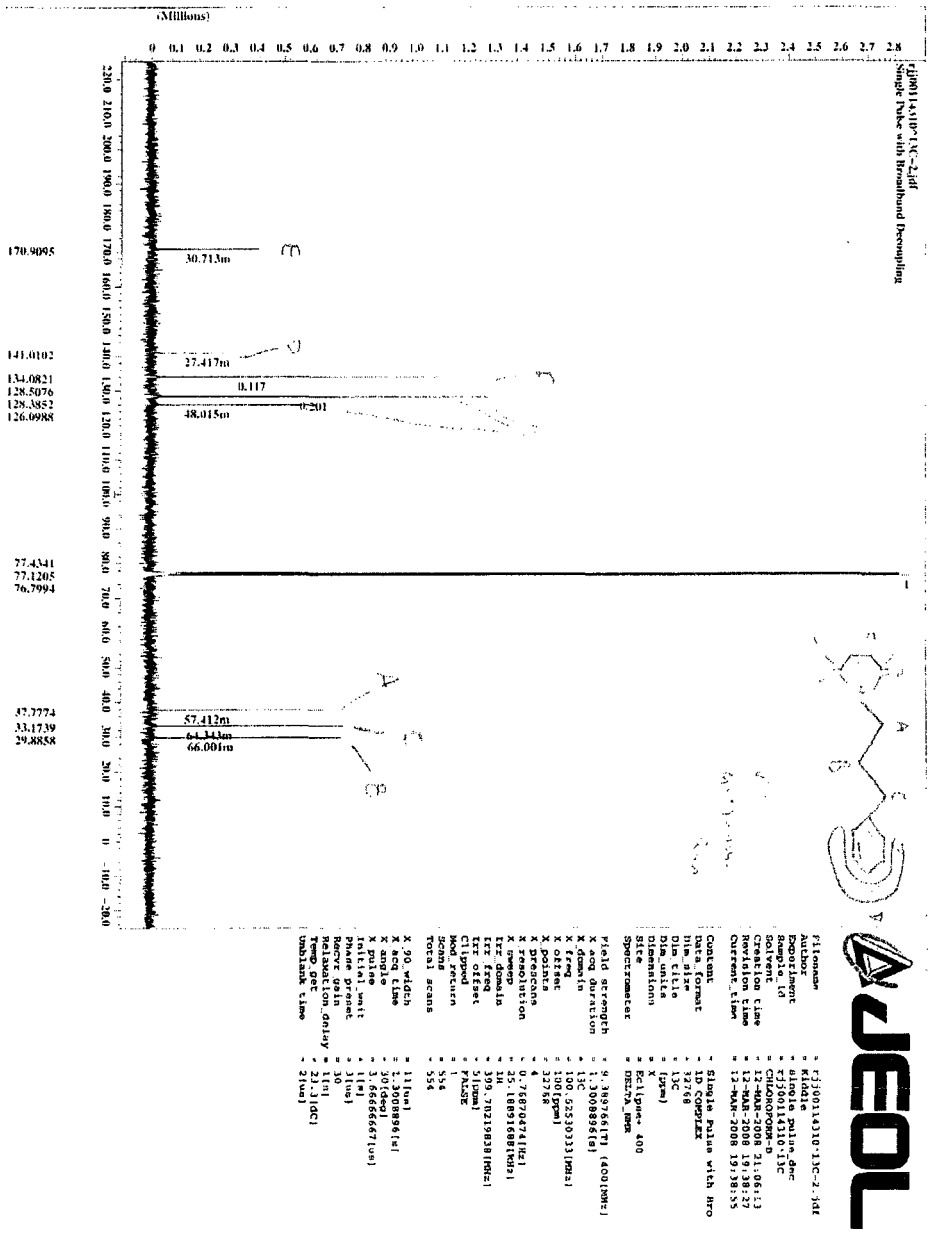
A/-(3-Phenylpropyl)-l//-pyrrole-2,5-dione ^{13}C NMR by M.M. Method



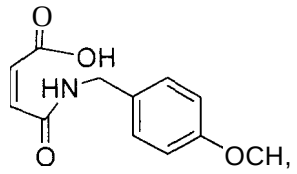




A/-(3-Phenylpropyl)-l//-pyrrole-2,5-dione ^{13}C NMR by M.M. Method



iV-(p-Methoxybenzyl)-maleamic acid H NMR by A.A. Method



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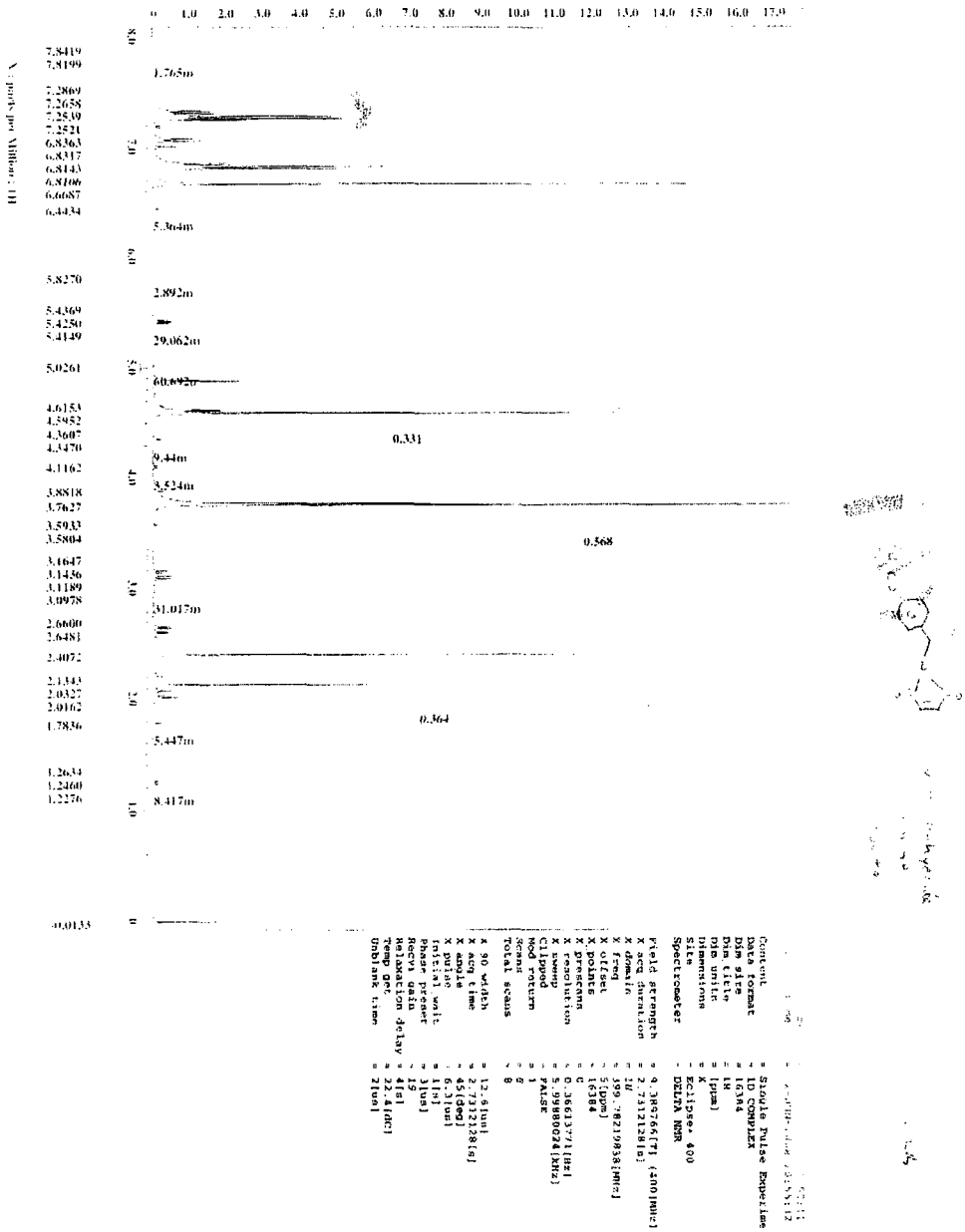
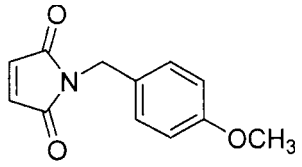
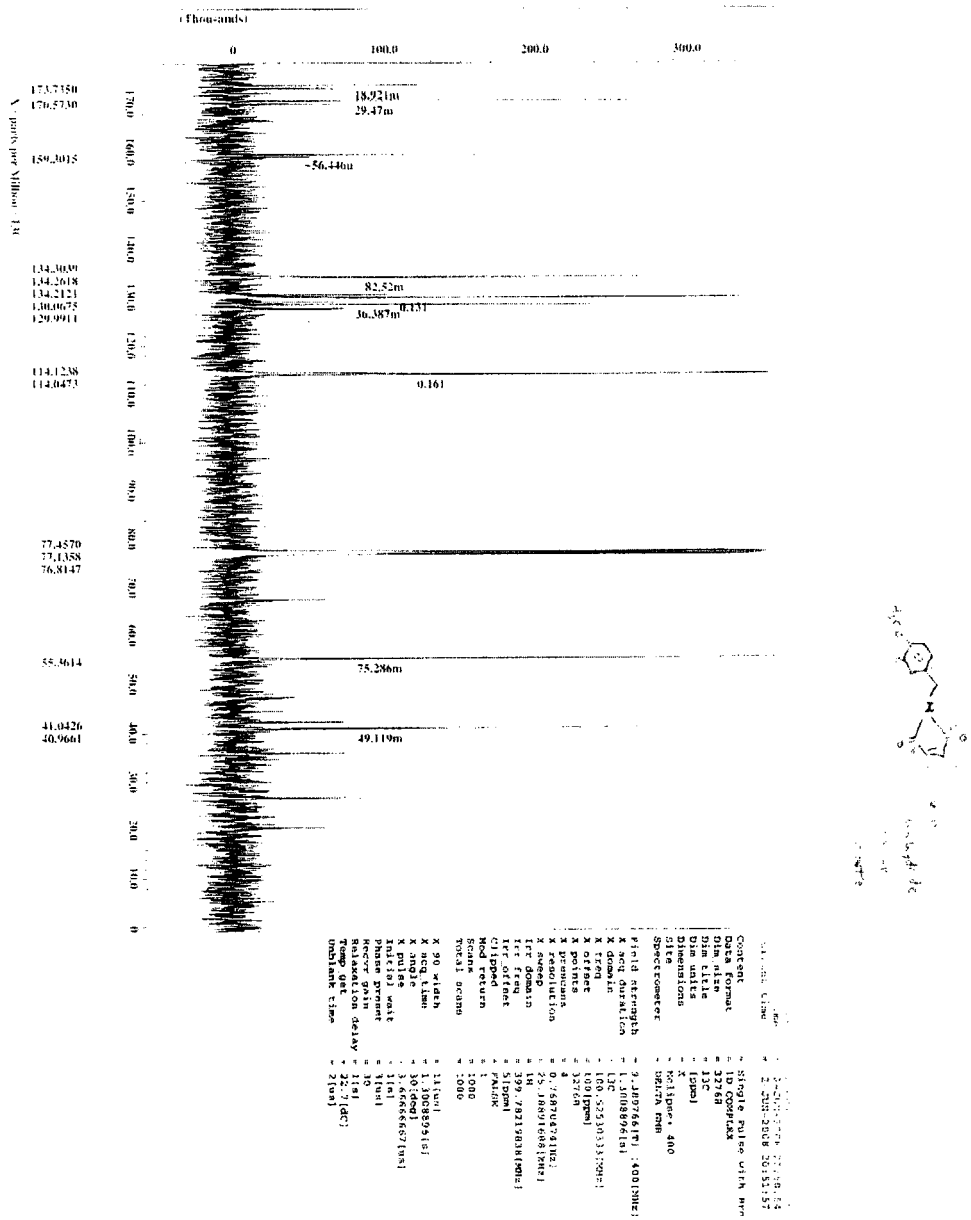
jV-(p-Methoxybenzyl)-1 //-pyrrole-2,5-dione 'H NMR by A.A. Method



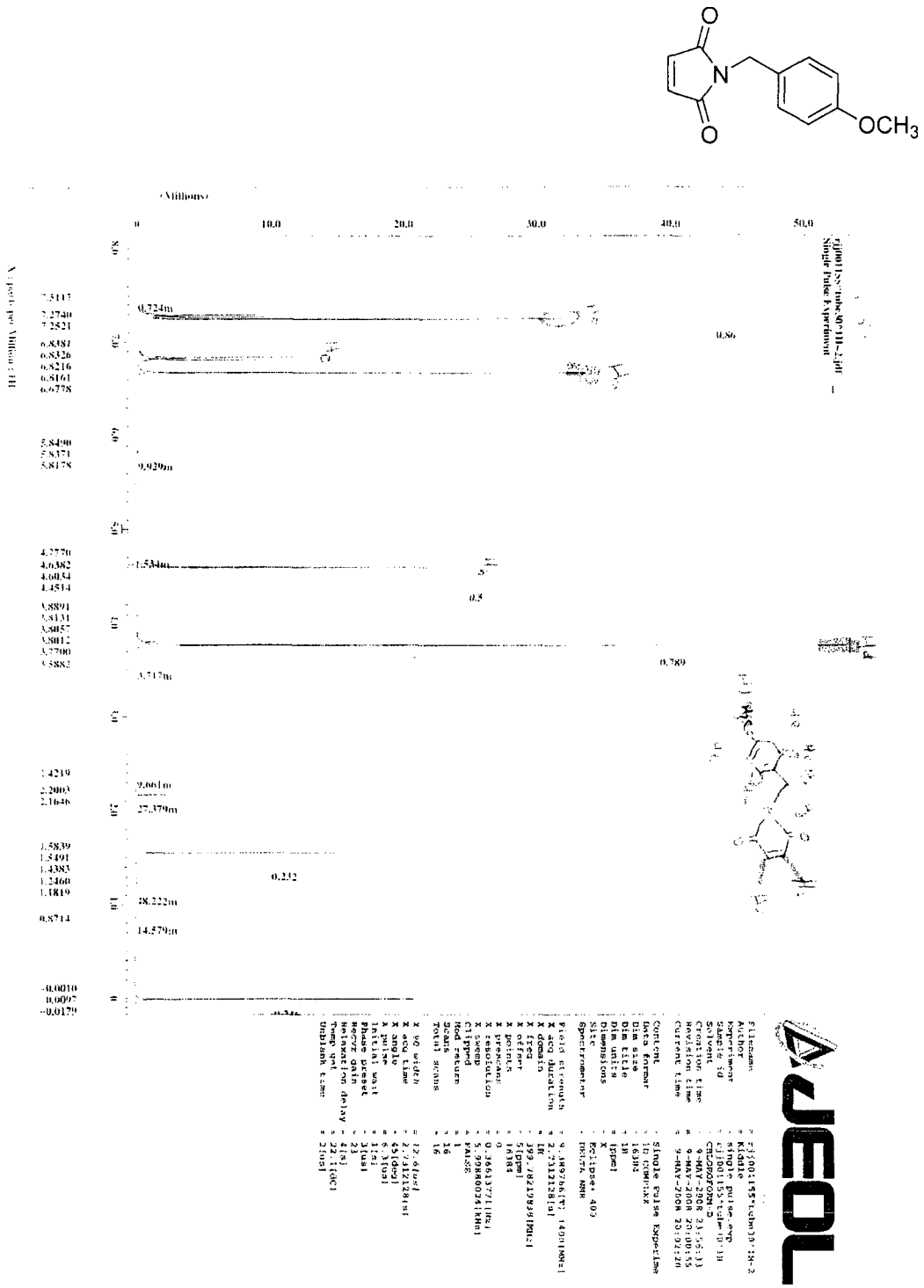
i n

iV-(p-Methoxybenzyl)-1 //-pyrrole-2,5-dione ^{13}C NMR by A.A. Method

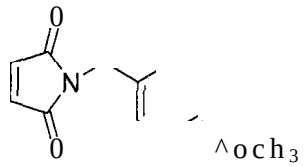




iV-(p-Methoxybenzyl)-1 //-pyrrole-2,5-dione ^{13}C NMR by A.A. Method



iV-(p-Methoxybenzyl)-l//-pyrrole-2,5-dione ^{13}C NMR by M.M. Method



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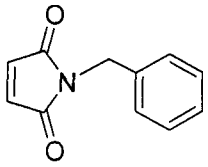
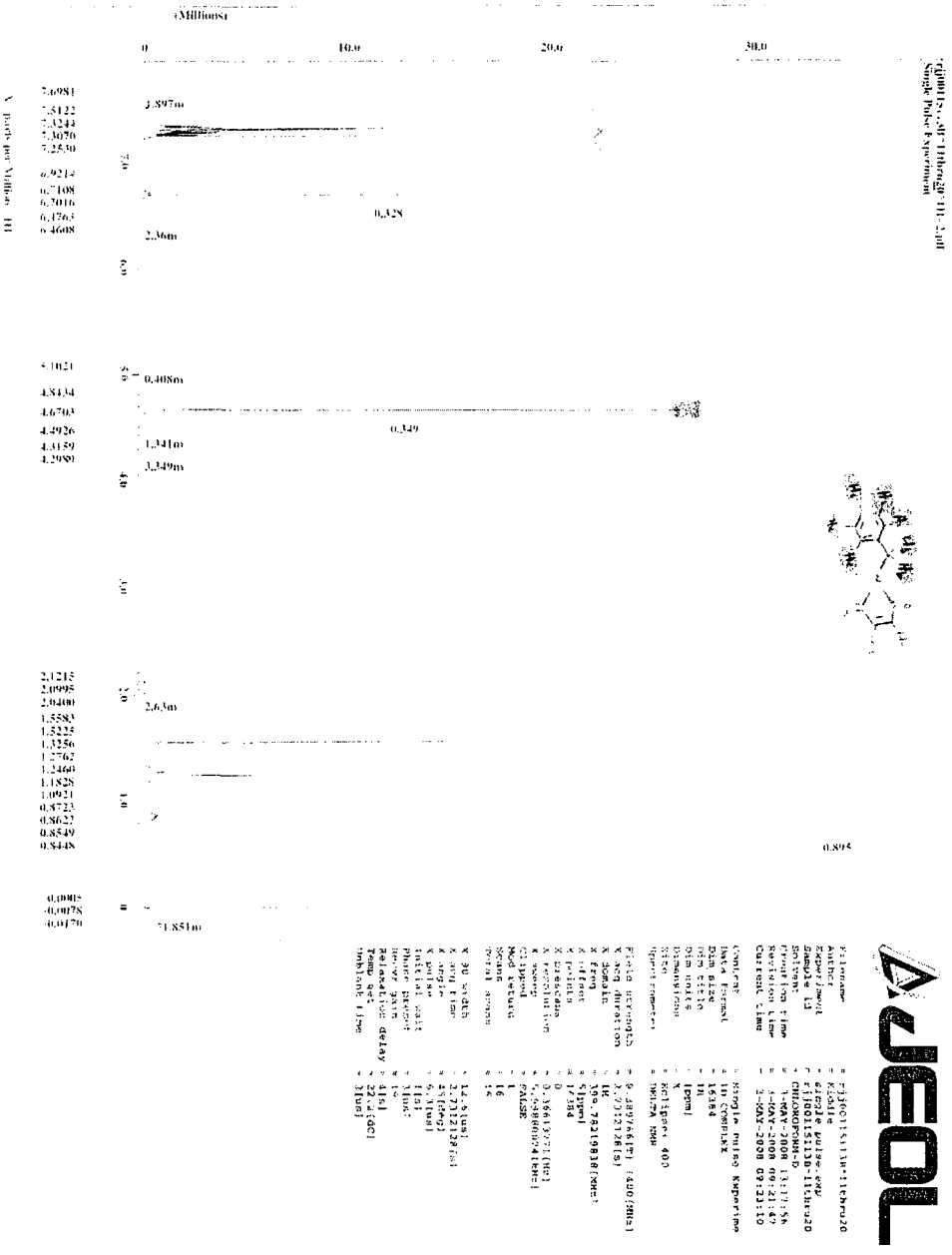
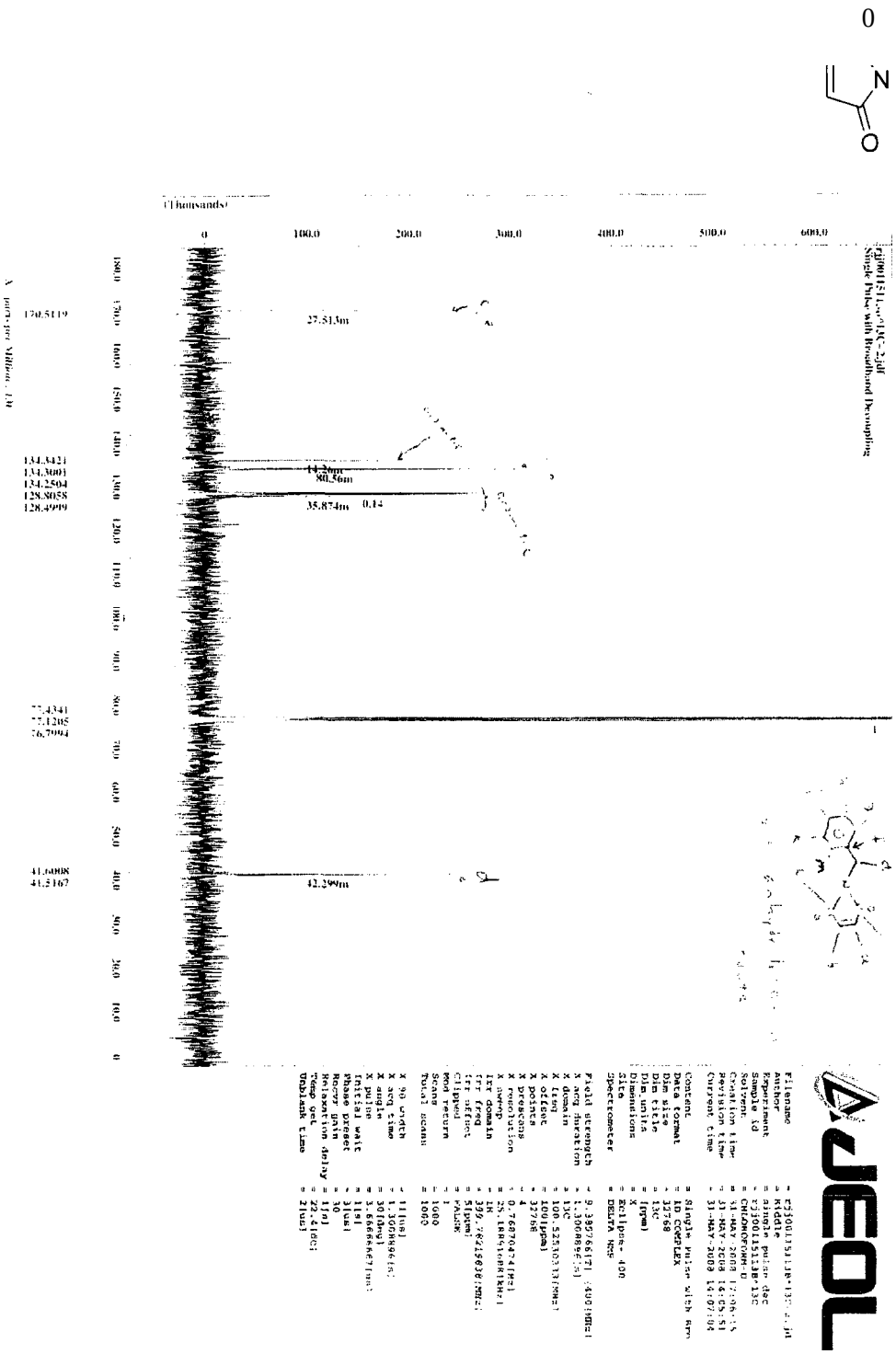
1 -(Phenylmethyl)-1 H-pyrrole-2,5-dione ^{13}C NMR by M.M. Method

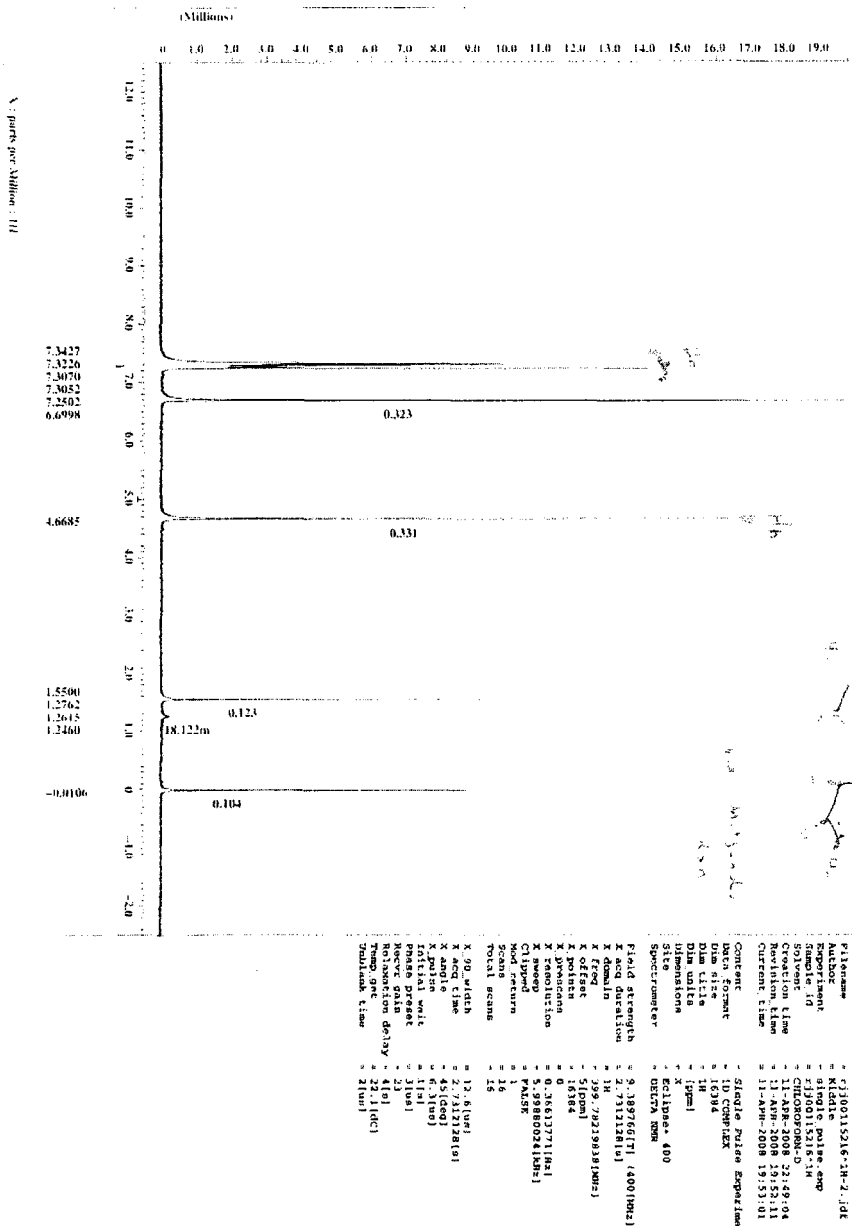




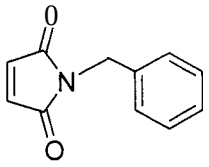
l-(Phenylmethyl)-lH-pyrrole-2,5-dione ^{13}C NMR by A.A. Method

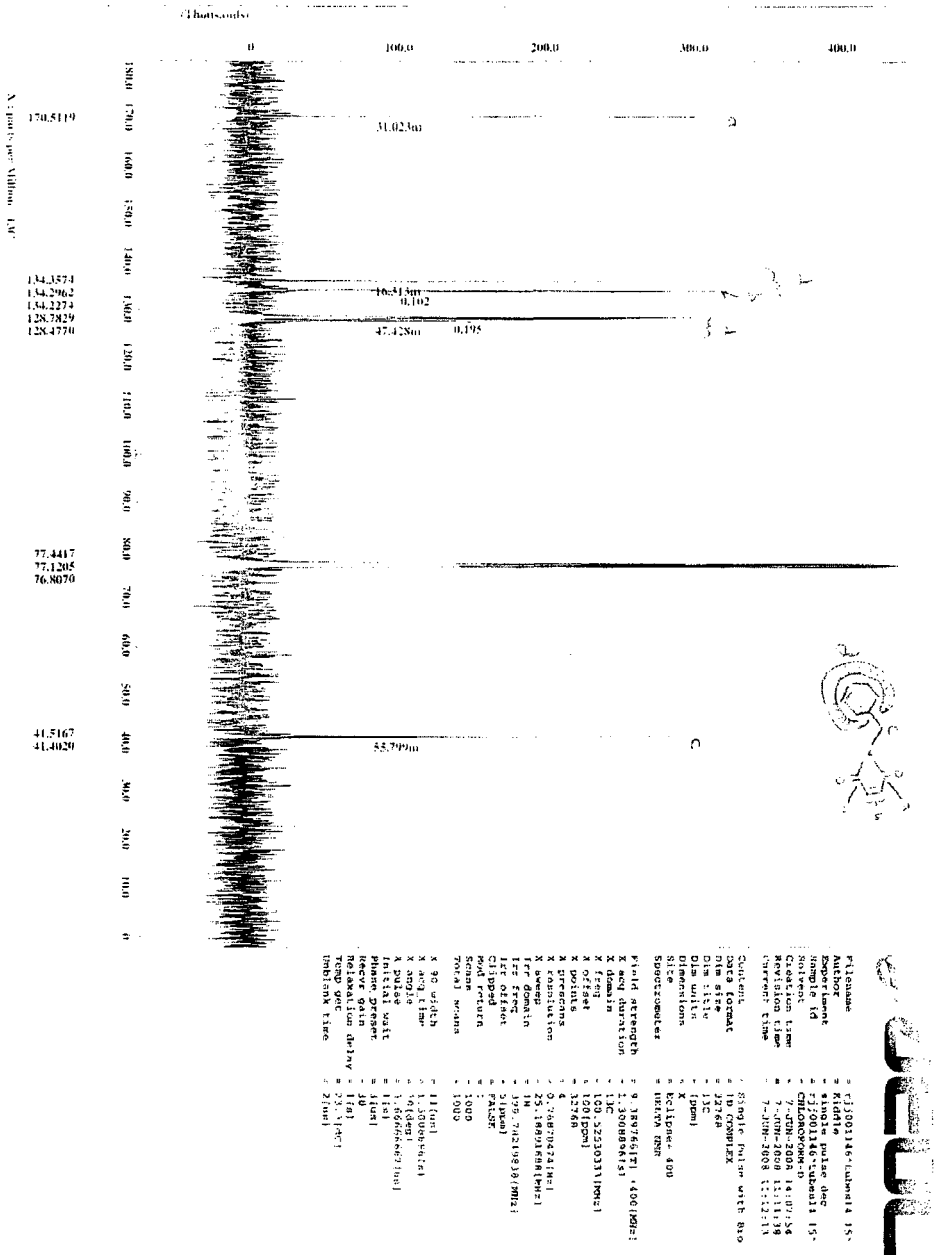


1 -(Phenylmethyl)-1 H-pyrrole-2,5-dione ^{13}C NMR by M.M. Method

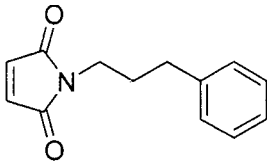


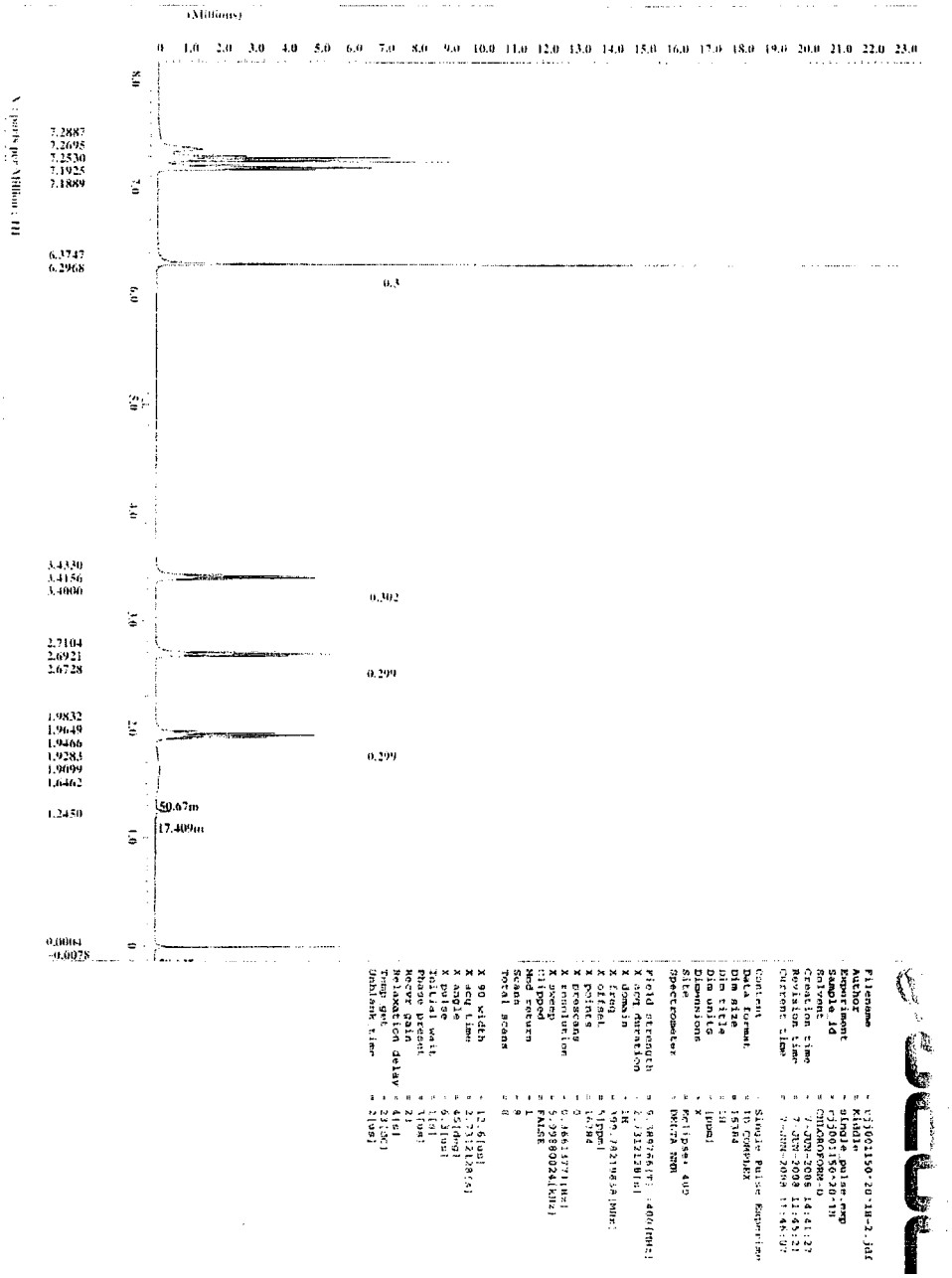
1 -(Phenylmethyl)-1 H-pyrrole-2,5-dione ^{13}C NMR by M.M. Method



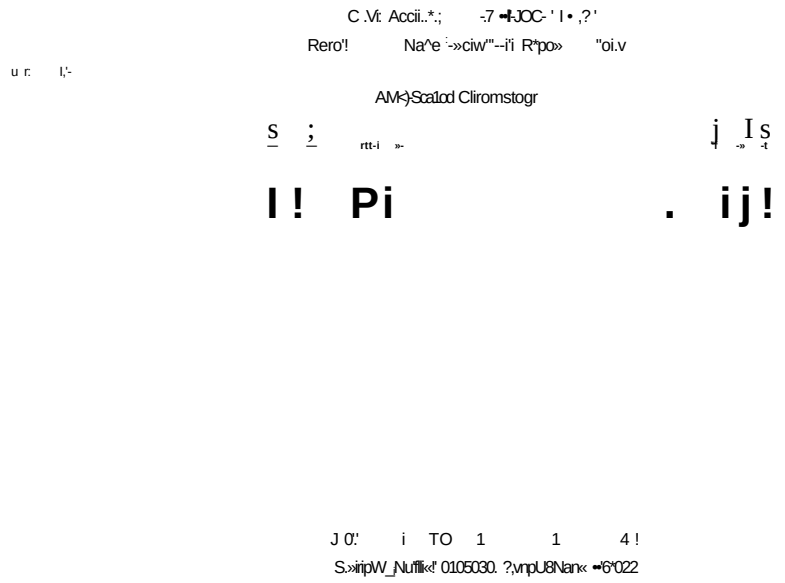


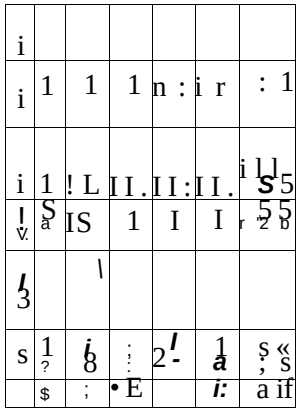
A^-(3-Phenylpropyl)-lH-pyrrole-2,5-dione 'H NMR by A.A. Method





Gas Chromatography (GC) Analysis of Base Peppermint Oil (1 of 2)





Characterization of Commercially Available Mintlactone by GC/MS

Commercial Menthalactone.

(-)-Mintlactone ~ 38.75 min
(-)-Menthofuranolactone (or Mint Furanone) ~ 39.68 min

6-3-08
menthalaclone
100-1

, 4-JUN-2008 + 14:32:01
Scan EI+
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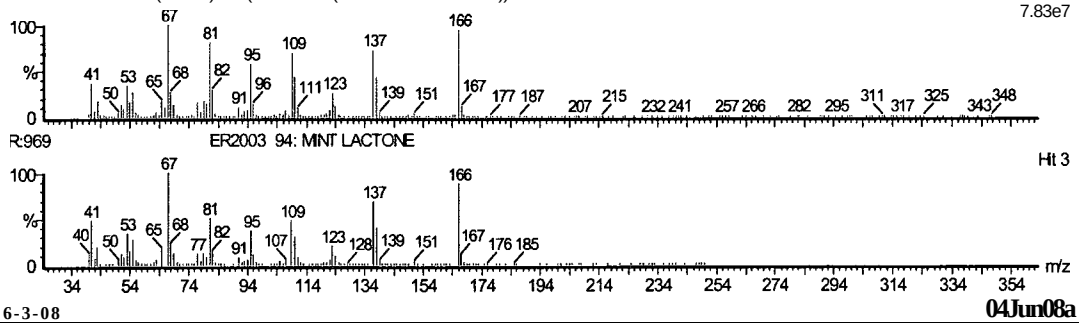
1 84e9

6-3-08 **, 4-JUN-2008 +14:32:01**

rrenthalactone 5028 (38.755) Cm(5012:5033-(4936:4956+5054:5082))

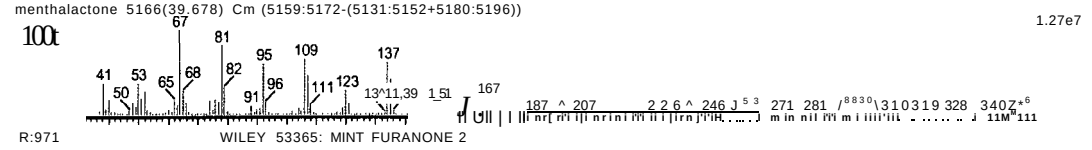
7.83e7



6-3-08 **04Jun08a**

Hit	REV	for	Compound Name	MW	Formula	*CPS*
1	979	568	(-(-ISCMNTUCTCNE	166	C10H14C2	O-OOO
2	974	969	MNTFUR«NONE2	166	C10H14C8	O-OOO
3	969	953	MWL»CTCNE	0		0-00-0
4	966	952	MNTFUFWJONE1	166	C10H14C8	oco-o
5	946	606	3-^ET>^^.5$_1$6,7.8$_1$8AAJ^{3}HA-HEX^MDRO-2H-CVCLCHEFT/^]FUR^N-2-CN	166	C10H1402	107115-58-5
6	945	548	(-J-MNTUCTCNE	166	C10H14C2	0-00-0
7	920	482	SP!Rq2.6]NCWN04-CNE	138	C9H140	ooo-o
8	906	600	2-PENT(L-2-CVCLCHE)<Eisl-1-CNE $$!SOJ/«fiOJE I $$ PEt^TYL CvCLCHEXE	166	C11H180	25435-63-6
9	302	681	3-N-PENTVL-2-CVCLCHE>EN-1-aME	166	C11H180	0-00-0
10	885	398	3.4-DIETHM_-2.5-DIIVETHM.-2,4-HEXCIIENE	166	C12H22	133795-40-1
11	876	618	3-PHENM.-1,4(E)-DCOEGaOIBNE	236	C17H32	0-00-0
12	874	402	1,2-DI-NCPRCPVLCVa.CHJTENE	138	C10H18	0«H)
13	870	499	5-ISCFRCPM_-8-IVETHM_SPIRC(3.4)OCTA^-1-CNE	180	C12H200	57760-25-5
14	865	460	EPOXVHNENE	154	C10H180	OOOO

menthalactone 5166(39.678) Cm (5159:5172-(5131:5152+5180:5196))

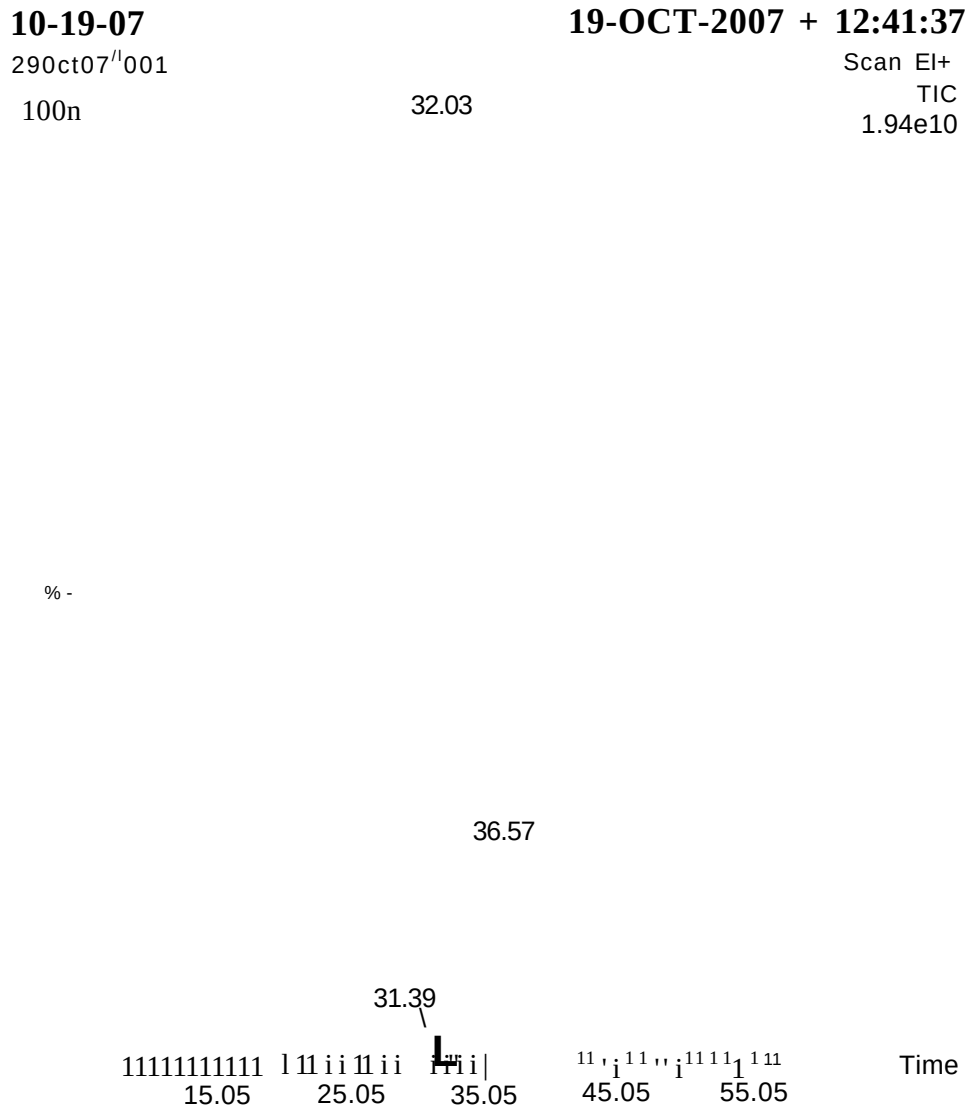


6-3-08 **04Jun08a**

Hit	REV	for	Compound Name	M.W.	Formula	CAS
1	973	549	(-)-ISOMNTUCTONE	166	C10H1402	o-oo-o
2	971	966	MNTFURANONE2	166	C10H1402	0-00-0
3	966	950	MNT LACTONE	0		O-uO-O
4	960	946	MNTFUFWNONE 1	166	C10H1402	0-00-0
5	946	595	3-lvETHVL ^1,5.6,7.8,8AALPHA-HEX/HYDRO-2H-CYCl.OHEPT4(B]FURAN-2-ON	166	C10H1402	107115-58-2
6	938	530	(-(-MNTIJCTONE	166	C10H14Q2	0-00-0
7	925	478	SPIRC(2.61NONAN04-ONE	138	C9H140	0-00-0
8	913	597	2-PENTYL-2-CYCLOHEXEN-1-ONE SS ISOWSM3NEI SS PENTYL CYCLCHEXE	166	C11H180	25435-63-6
9	910	683	3-N-PENTYL-2-CYCLOHEXEN-1 -ONE	166	C11H180	0-00-0
10	882	623	3-PHENYL-1,4(E)-DCOECADIENE	236	C17H32	0-00-0
11	876	385	3,4-DIETHYL-2,5-DIWETHYL-2,4-HEXmiENE	166	C12H22	133795-40-1
12	872	576	(Z)-1,5-DIIYETHYLSPIRO(3.5)NONAN-(Z)-7-ONE	166	C11H180	56063-27-5
13	871	497	5-ISOPRCFYl-8-lvETHYLSPIRO(3.4)OCT/*N-1-ONE	180	C12H200	57760-25-5
14	868	412	(Z)-3-(1-HOHYLETHYL)-1.3-NONADIENE	166	C12H22	OOO-O

Characterization of 8-hydroxy-p-6-menthene-2-one (25) by GC/MS

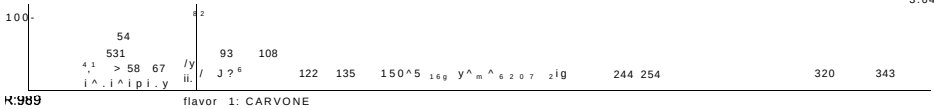
Peak at 36.57 minutes is 8-hydroxy-p-6-menthene-2-one at a yield of approximately 17%. Carvacrol present at 81%.



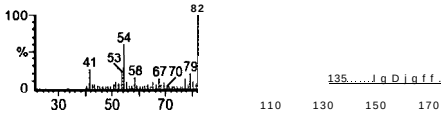
10-19-07 19-OCT-2007 + 12:41:37

290ct07*001 3747 (30.181) Cm (3742:3755-(3728:3736+3765:3775))

3.64e7



R:989 flavor 1: CARVONE



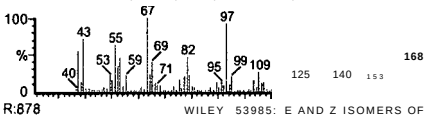
135.....J g D j g f f .

110 130 150 170 190 210 230 250 270 290 310 330 350

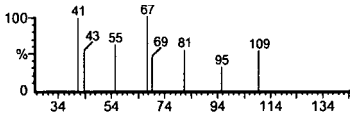
10-19-07 , 19-OCT-2007 + 12:41:37

290ct07'001 3928 (31.392) Cm (3918:3939-(3890:3908*3947:3959»

2.6107



R:878 WILEY 53985: E AND Z ISOMERS OF 2.6-DIMETHYL-2.5-DECADIENE



'|""!""!""!"

10-19-07 rij001095A

Hit	REV	for	Compound Nome	M.W.	Formula	CAS
1	878	411	E AND Z ISOMERS OF 2.6-DIMETHYL-2.5-DECADIENE	166	C12H22	68965-65-1
2	858	545	(1 RS,5SR.6SR)-6-PENTYI-2-OXABICYCIO(3.3.0]OCTAN-3-ONE	196	C 12H2002	82934-95.0
3	856	406	8-PENTADECENOI S$ 8-PENTADECEN-1-OL 5$ 8-PENTADECEN-1-OL. (2)- (C	226	C15H300	64437-36-1
4	851	536	(+)-<1S,2'S)-3-(2'-ISOPROPYLCYCLOPROPYL)-1-PROPANOL	142	C9H180	0-00-0
5	846	594	(2S,5R)-2-ISOPROPYL--5METHYLHEPT-6-EN-1-OL	170	C11H220	126580-59-4
6	838	439	DAUANONE EPOXIDE	252	C15H2403	0-00-0
7	838	379	(3AR.4R,7ARH+M.7A-DIMETHYI-TRANS-HEXAHYDROBENZOFURAN-2(3H)-0	168	C10H1602	104575-83-9
8	836	437	(E)-3,7-DIMETHYL-6-OXO-2-OCTENAJ. SS 2-OCTENAL, 3.7-D1METHYI-6-0X0-,!	168	C10H1602	70856-12-1
9	833	528	(Z)-CIS-9.1O-EPOXYHEPTADEC-6-ENE	252	C17H320	0-00-0
10	825	699	VALERIANSAEURE. 10-UNDECENYLESTER	254	C16H3002	0-00-0
11	824	687	1.19-EiCOSADIENE	278	C20H38	14811-95-1
12	822	686	1-EICOSYNE (CAS) $S EICOSYNE-1	278	C20H38	765-27-5
13	818	473	CITRONELIYI ACETATE $S 6-OCTEN-1-OL, 3,7-DIMETHYU ACETATE (CAS) S	198	C12H2202	150-84-5
14	815	694	3-EICOSYNE (CAS)	278	C20H38	61866-66-6

10-19-07 19-OCT-2007 + 12:41:37

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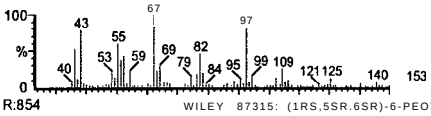
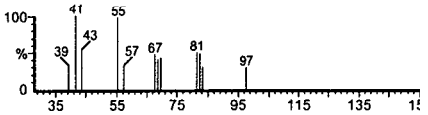
8.07e6



178 189197 208 219 233

R:854 WILEY 87315: (1RS,5SR.6SR)-6-PEOTYL-2-OXABICYCLO[3.3.0]OCTAN-3-ONE



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10-19-07 riioo 1095A

Hit	REV	for	Compound Name	M.W.	i-ormula	CAS
1	854	574	(1RS,5SR.6SR)-6-PENTYI-2-OXABICYCLO[3.3.0]OCTAN-3-ONE	196	C12H2002	82934-95-0
2	845	560	(•)-(1S,2'S)-3-(2'-ISOPROPYICYCLOPROPYL)-1-PROPANOL	142	C9H180	0-00-0
3	838	407	(3AR.4R,7AR)-(+)-4,7A-DIMETHYI-TRANS-HEXAHYDR06ENZ0FURAW-2(3H).0	168	C1OH1602	104575-83-9
4	832	620	BiCYCLO[4.1.0]HEPTANE, 7-BUTYL- (CAS) SS NORCARANE. 7-BUTYL-	152	C11H20	18645-10-8
5	824	599	(2S.5R)-2-ISOPROPYL--5METHYIHEPT-6.£N.1-OL	170	C11H220	126580-59-4
6	818	721	3-EICOSYNE (CAS)	278	C20H38	61886-66-6
7	816	724	ERYTHRO-CIS(1,4),TRANS(1'.4')-4,4'-OIHYDROXYB!CYCLOOCTYL	254	C16H3002	0-00-0
8	816	532	(Z)-CIS-9.10-EPOXYHEPTADEC-6-ENE	252	C17H320	0-00-0
9	815	467	Z-3-HEXENYL ACETATE	142	C8H1402	3681-71-8
10	812	718	9-0CTADECEN-1-0L (Z)- (CAS) $S CIS-9-OCTAOECEN-1-OL SS OLEOL $S SAT	268	C18H360	143-28-2
11	811	699	1-EICOSYNE (CAS) SS EICOSYNE-1	278	C20H38	765-27-5
12	801	706	3-HEXADECYNE (CAS)	222	C16H30	61886-62-2
13	800	596	Z-6-NONEN-1-OL; CIS-6-NCNENOL	142	C9H180	35854-86-5
14	800	697	ERYTHRO-TRANS(1,4).TRANS(1',4')-4,4'-DIHYDROXYBIC YCLOOCTYL	254	C16H3002	0-00-0

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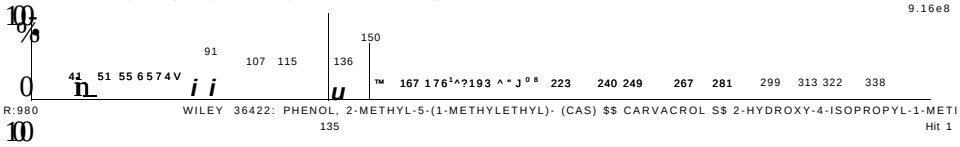

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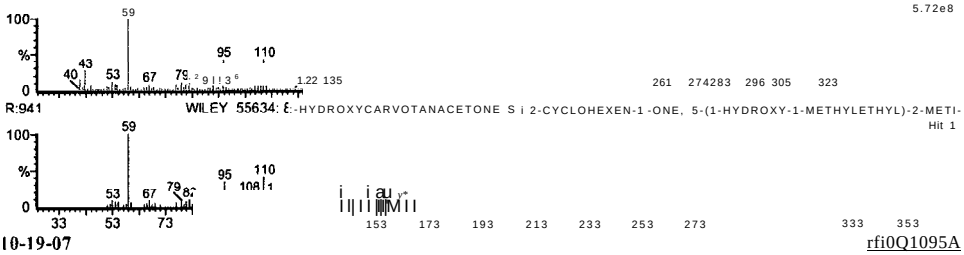

10-19-07 rfi0Q1095A

	for	Compound Name	M.W.	Formula	CAS
941	806	B-HYDROXYCARVOTANACETONE SS 2-CYCLOHEXEN-1-ONE. 5-(1-HYDROXY-	168	C10H1602	7712-46-1
915	323	(+-)GYMNOMITROI	220	C15H240	71564-38-0
866	601	8-HYDROXY-P-MENTH-1-EN-7-AL	168	C10H1602	0-0-0-0
	358	4,4-DtMETHYL-8-OXABfCYCLO(3.2.1)OCT-6-EN-3-ONE-2-SPIRO-1'-CYCLOHEX	220	C14H2002	122166-46-5
	302	5.6-SECOCHOLESTAN-6-OIC ACID. 3-(ACETYLOXY)-5-OXO-, (3.BETA)- (CAS)	476	C29H4805	10473-42-4
	428	3-{3.3-OIMETHYI-2-EXO-NORBRNYI_>-2-METHYIPROP-2-EN-1-OL	194	C13H220	113159-68-5
710	450	PiPERITONE	152	C10H160	6091-50-5
710	314	2-(2'.2'-DIMETHYI-6'-METHYLIDENECYCL0HEXYI)-1-METHYL-1-CYCL08UTA	208	C14H240	95530-25-9
710	314	1-(5'.5'-DIMETHYL-6-VINYL-r-CYCLOHEXENYL)-2-METHYL-2-PROPANOL	208	C14H240	95452-18-9
703	462	TRtCYCIO(2.2.1 02.6]HEPTAN-3-OI. 4,5.5-TRIMETHYI-(CAS)	152	C10H160	62560-53-6
701	337	TR1CYCLO[4.4.0.0 2,8]DEC-3-EN-5-OL	150	C10H 140	0-0-0-0
698	346	4-(2,2,6-TRIMETHYL-BICYCIO|4.1.0]HEPT-1-YL)-BUTAN-2-ONE	208	C14H240	7 7143-20-5
697	309	2-(2',2'-DIMETHYL-6'-METHYLIDENECYCLOHEXYL>-1-METHYL-1-CYCLOBUTA	208	CUH240	95530-24-0
696	352	ACETIC ACID 7.7-DIMETHYL-2-OXO-BICYCLO(2.2.1]HEPT-1-YIfwETHYI ESTER	210	C12H1803	108266-83-7

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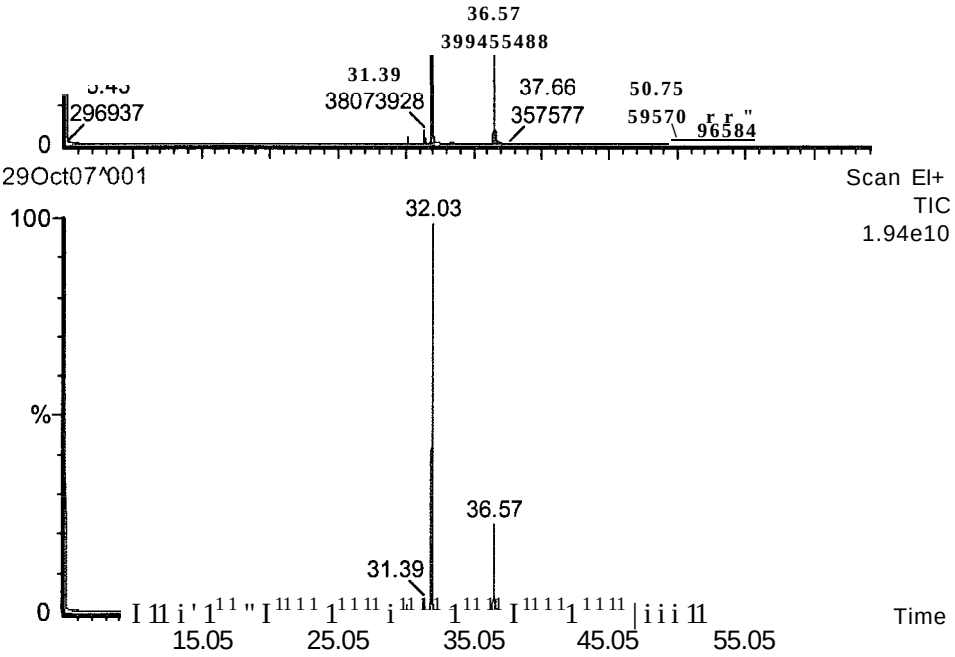
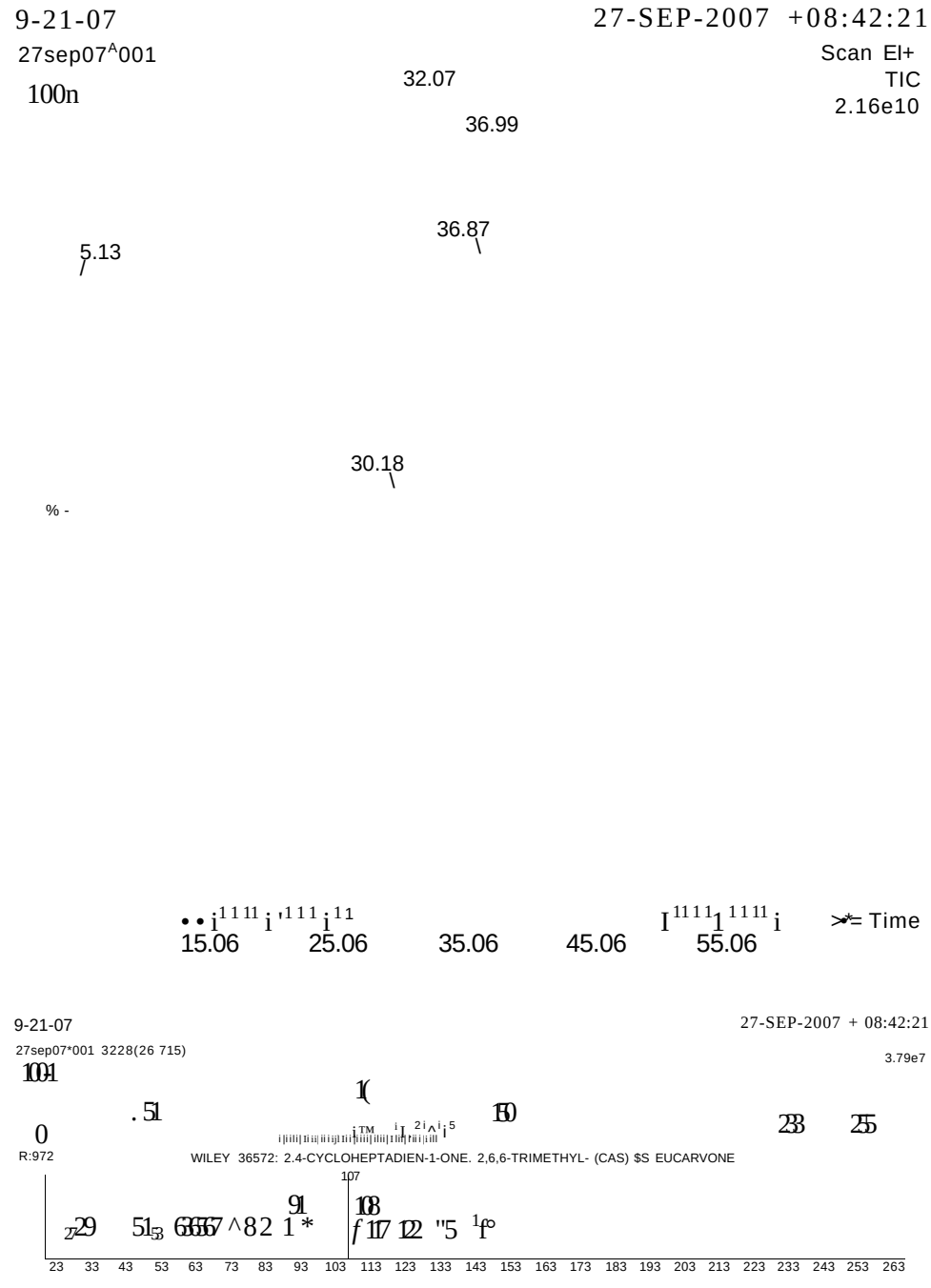


Appendix B

Reaction Characterization

GC/MS Characterization of Synthesis of 8-hydroxy-p-6-menthene-2-one 25 from 23

Summary: Approximately 61 % yield of 25.



9-21-07 i-jjOOI 10621

Hit	REV	for	Compound Name	M W.	Formula	CAS
1	972	954	2.4-CYCLOHEPTADIEN- 1-ONE. 2.6.6-TRIMETHYL- (CAS) SS EUCAfiRVONE	150	C10H 140	503-93-5
2	963	942	2.4-CYCL0HEPTADIEN-1-0NE. 2,6.6-TRIMETHYL- (CAS) SS EUCARVONE	150	C10H140	503-93-5
3	962	942	2 4-CYCL0HEPTA0IEN-1-0NE. 2,6,6-TRIMETHYL- (CAS) SS EUCARVONE	150	C10H 140	503-93-5
4	944	536	(+ 1-CAR-2-EN-4-ONE $$ 3.7.7-TRIMETHYLBICYCL0[4.1,0)HEPT-3-ENE	150	C10H140	28226-49-5
5	940	920	2.4-CYCLOHEPTADIEN-1-ONE. 2.6.6-TRIMETHYL-(CAS) SS EUCARVONE	150	C10H 140	503-93-5
6	933	622	CHRYSANTHENONE SS BICYCLO[3.1 1]HEPT-2-EN-6-ONE. 2,7,7-TRIMETHYI-	150	C 10H 140	473-0G-3
7	924	776	BIC YCL0[3.1 0|HEX-3-EN-2-ONE. 4-METHYI-1-(1 -METHYLETHYL)- (CAS) SS U	150	C10H140	24545-81-1
8	922	520	5-(1-C HLOR-1-METHYLETHYL)-3.5-DIMETHYL-2-C YC LOPENTEN-1-ONE	186	C10H150CI	85620-34-4
9	920	794	1,3-CYCLOPENTADIEN. 5.5-DIMETHYL-2-ETHYI-	122	C9H14	0-00-0
10	916	883	CHRYSANTHENONE $S 8ICYCL0[3.1.1)HEPT-2-EN-6-ONE. 2,7.7-TRIMETHYI-	150	C10H 140	473-06-3
11	913	864	BICYCLO[3.1 OJHEX-3-EN-2-ONE. 4-METHYL-1 •(1 -METHYLETHYL)- (CAS) SS U	150	C10H140	24545-81-1
12	913	778	1.3-CYCLOPENTADIEN, 5.5-DIWETHYL-1-ETHYL-	122	C9H14	0-00-0
13	910	818	3.3-DIMETHYL-6-METHYLENE-CYCLOHEXENE	122	C9H14	0-00-0
14	906	828	3.5-HEPTADIEN-2-OL. 2 6-DIMETHYL- ?$ 3.4-DIHYDRO-2H.1'H-(2.2]B!PYRROL	140	C9H160	7741 1-76-8

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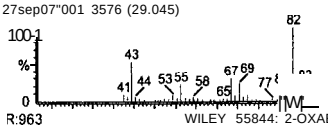
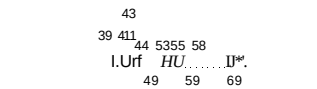
27sep07"001 3576 (29.045) 6.1Be7



T ^ 153

R:963 WILEY 55844: 2-OXABICYCLO[2.2.2]OCTAN-6-ONE, 1,3,3-TRIMETHYL- (CAS)



9-21-07 IiiOO 110621

Hit	REV	for	Compound Name	M.W.	Formula	CAS
1	963	944	2-OXABICYCLO[2.2.2]OCTAN-6-ONE. 1,3,3-TRIMETHYL- (CAS)	168	C10H1602	107598-08-3
2	829	790	2(3H)-BENZ0FURAN0NE, HEXAHYDRO-3A.7A-DIMETHYL-, CIS- (CAS)	168	C1 OH 1602	38110-72-4
3	807	758	5-OCTEN-2-ON, 5-METHYL-	140	C9H160	121986-29-6
4	783	687	CYCLOHEXANE. (1 -METHYLBUTYL)-	154	C11H22	61208-94-4
5	782	701	CYCLOHEXANE. (1,3-OIMETHYLBUm)- (CAS)	168	C12H24	61142-19-6
6	781	716	2.6-DIMETHYL HEPT-5-EN-1-AL	140	C9H1SO	106-72-9
7	776	551	1.3.3-TRIMETHYL-2-OXABIC YCLO{2.2.2]OCTAN-5-ONE	168	C10H1602	81781-25-1
8	772	722	DECANE 2-C YCLOHEXYL-, 2-C YCLOHEXYL- (CAS)	224	C16H32	13151-73-0
9	765	700	2.6-DIMETHYL HEPT-5-1-AL	140	C9H160	106-72-9
10	762	678	MELON ALDEHYDE: 2.6-DIMETHYL-5-HEPTENAL	140	C9H160	106-72-9
11	755	654	EICOSANE, 2-CYCLOHEXYL- (CAS) SS 2-CYC10HEXYLEIC0SANE $S CYCLOH	364	C26H52	4443-56-5
12	751	657	UNOECANE 2-CYCLOHEXYL-. (CAS) SS UNDECANE. 2-CYCLOHEXYL-	238	C17H34	13151-77-4
13	745	458	1,4-CINEOLE	154	C10H180	470-67-/
14	745	700	DODECANE, 2-CYCLOHEXYL-	252	C18H36	13151-82-1

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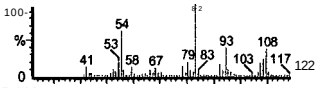
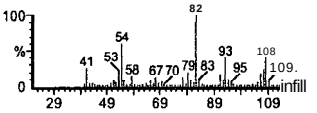


R:992 flavor 1: CARVONE



9-21-07 rjjOOI 10621

		Compound Name	Formula	CAS
992	985	CARVONE	C10H140	6485-40-1
987	948	2-CYCLOHEXEN-1 -ONE. 2-METHYL-5-(1 •METHYLETHENYI)-,(R>- (CAS)	C10H140	6485-40-1
979	973	2-CYCLOHEXEN-1-ONE. 2-METH YL-5-(1•METHYLETHENYL)•(CAS) SS 2-METH	C10H140	99-49-0
971	953	CARVONE: ISOMER NOT SPECIFIED	C10H14O	0-00-0
968	959	2-CYCLOHEXEN-1-ONE, 2-METH YL-5-(1-METHYLETHENYL)- (CAS) SS 2-METH	C10H140	99-49-0
967	952	2-CYCLOHEXEN-1-ONE, 2-METH YL-5-0 •METHYLETHENYL)- (CAS) $5 2-METH	C10H140	99-49-0
967	944	2-CYCLOHEXEN-1 -ONE. 2-METH YL-5-(1 METHYLETHENYL)- . (S)- (CAS) 0-	C10H140	2244-16-8
966	943	2-CYCLOHEXEN-1-ONE. 2-METHYL-5-0 METHYLETHENYL)- (CAS) SS 2-METH	C10H 140	99-49-0
965	956	2-CYCLOHEXEN-1-ONE. 2-METHYL-5-(1•METHYLETHENYL)•(CAS) SS 2-METH	C10H140	99-49-0
	942	2-CYCLOHEXEN-1-ONE. 2-\itTHYL-5-(1 METHYLETHENYL)- . (S)- (CAS) 3* U-	C10H140	2244-16-8
	926	2-CYCLOHEXEN-1-ONE. 2-METHYI-5-(1 METHYLETHENYL)- (CAS) SS 2-METH	C10H 140	99-49-0
964	948	2-CYCLOHEXEN-1-ONE. 2-METHYI-5-(1 •METHYLETHENYL)- (CAS) SS 2-METH	C10H140	99-49-0
964	950	2-CYCLOHEXEN-1-ONE. 2-METHYI-5-(1 METHYLETHENYL)- . (S)- (CAS) SS D-	C10H140	2244-16-8
	953	2-CYCLOHEXEN-1-ONE. 2-METHYI-5-(1 METHYLETHENYL)- .(S)- (CAS) SS D-	C10H140	2244-16-8

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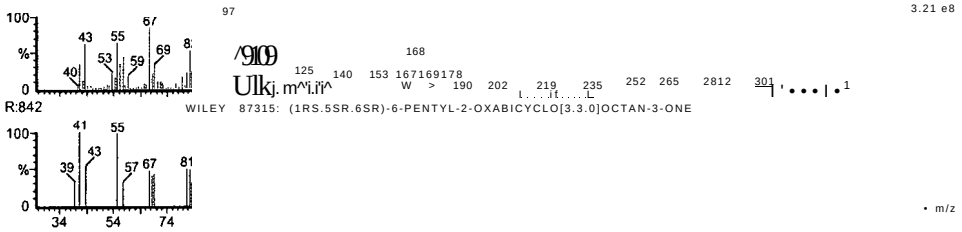

9-21-07 riiooi 1Q621

Hit	REV	for	Compound Name	M.VV.	Formula	CAS
1	842	508	(1RS.5SR.6SR)-6-PENTYL-2-OXA6ICYCLOI3.3.0]OCTAN-3-ONE	196	C12H2002	82934-95-0
2	842	383	(3AR,4R.7AR)-(+)-4,7A-DIMETHYL-TRANS-HEXAHYDR08ENZ0FURAN-2(3H)-0	168	C10H1602	104575-83-9
3	842	596	BIC YCLO[4.1 O]HEPTANE. 7-BUTYL- (CAS) SS NORCARANE. 7-BUTYL-	152	C11H20	18645-10-8
4	824	522	{Z)-CIS-9.IO-EPOXYHEPTADEC-6-ENE	252	C17H320	0-00-0
5	820	414	2.2-DIMETHYL-3-HYDROXYCYCLOHEXYLACETIC ACID	186	C1OH 1803	132216-30-9
6	818	652	(Z) 14-TRICOSENYL FORMATE	366	C24H4602	77899-10-6
7	816	519	CYCLOHEXANOL. 2-(1-METHYLETHYL)- (CAS) SS 2-ISOPROPYLCYCLOHEXAN	142	C9H180	96-07-1
8	813	667	1-EICOSYNE (CAS) SS EICOSYNE-1	278	C20H38	765-27-5
9	813	675	9-OCTADECENAL. (Z)- (CAS) SS C(S-OCTADEC-9-ENAL SS OLEALOEHYDE SS	266	C18H340	2423-10-1
10	812	544	(2S.5R)-2-ISOPROPYL-5METHYLHEPT-6-EN-1 -OL	170	C11H220	126580-59-4
11	809	668	5H-INOEN-5-ONE. OCTAHYDRO-1-HYDROXY-7A-METHYL- (CAS)	168	C10H1RQ2	42199-04-2
12	809	668	7-HYDROXY-6-METHYL-BIC YCLO[4.3.0]NONAN-3-ONE	168	C10H1602	0-00-0
13	799	471	(+)-(1S.2'S)-3-(2'-ISOPROPYLCYCLOPROPYL)-1-PROPANOL	142	C9H180	0-00-0
14	791	657	3-EICOSYNE *(CAS)*	278	C20H38	6)886-66-6

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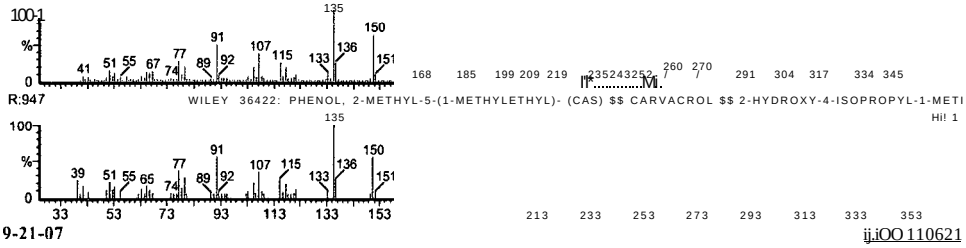

9-21-07 ij.iOO 110621

		Compound Name		Formula	CAS
947	928	PHENOL, 2-METHYI-5-(1-METHYLETHYI)- (CAS) SS CARVACROL SS 2-HYDRO	150	C10H 140	499-75-2
944	881	PHENOL. 2-METHYL-5-(1-METHYIETHYL)- (CAS) SS CARVACROL S$ 2-HYDRO	150	C10H 140	499-75-2
944	904	PHENOL, 5-METHYI_-2-(1-METHYLETHYL)- (CAS) SS THYMOL S$ M-THYMOL SS	150	C10H 140	89-83-8
938	897	PHENOL, 2-METHYL-5-(1-METHYLETHYI)- (CAS) SS CARVACROL SS 2-HYDRO	150	C10H140	499-75-2
926	906	PHENOL. 2-METHYL-5-(1-METHYLETHYL)- (CAS) SS CARVACROL SS 2-HYDRO		C10H140	499-75-2
920	892	PHENOL, 5-METHYL-2-(1-METHYLETHYL)- *(CAS)* SS THYMOL SS M-THYMOL $S		C10H 140	89-33-8
916	790	PHENOL, 5-METHYI-2-(1-METHYIETHYI.)- (CAS) SS THYMOL SS M-THYMOL 5$		C10H140	89-83-8
903	863	PHENOL. 2-METHYL-5-(1-METHYLETHYL)- (CAS) $$ CARVACROL SS 2-HYDRO	150	C10H140	499-75-2
903	819	PHENOL. 5-METHYL-2-(1-METHYLETHYL>- (CAS) SS THYMOL SS M-THYMOL SS	150	C10H140	89-33-8
902	840	PHENOL, 5-METHYL-2-0-METHYIETHYL)- (CAS) $$ THYMOL SS M-THYMOL SS		C10H14O	89-83-8
895	856	THYMOL		C10H140	89-83-8
894	859	PHENOL. 5-METHYL-2-(1-METHYLETHYL)- (CAS) SS THYMOL SS M-THYMOL SS		C10H140	89-83-8
891	856	PHENOL, 2.3.5,6-TETRAWETHYI- (CAS) SS DURENOL SS PHENOL. TETRAMET	150	C10H14O	527-35-5
890	836	2-CYCLOHEXEN-1-ONE. 2-METHYL-5-(1 -METHYLETHENYL)-(CAS) SS 2-METH	150	C10H140	99-49-0

9-21-07 27-SEP-2007 + 08:42:21

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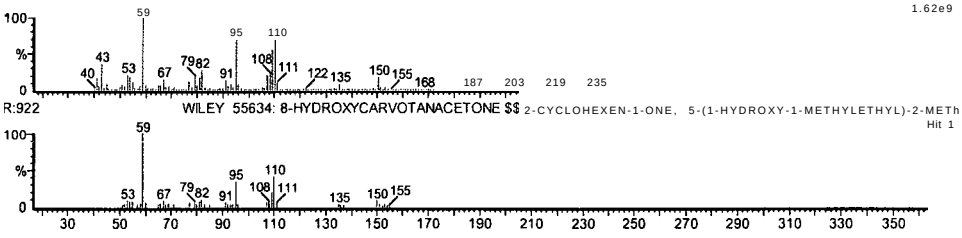

REV	for	Compound Name		Formula	CAS
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866	533	8-HYDR0XY-P-MENTH-1-EN-7-AL		C1 OH1602	0000
785	504	14-ETHANONAPHTHALENE-5.3-DIONE. 1.4.4A.8A-TETRAHYDR0-1 -METHOXY-		C13H1403	91910-07-5
753	365	2-(2'.2'-OIWETHYI-6'-METHYlIOENECYCLOHEXYL>-1-METHYI-1-CYCIOBUTA	208	C14H240	95530-25-9
753	385	1-(5'.5'-DIMETHYL-6-VINYL-1'-CYCLOHEXENYL)-2-ME THYL-2-PROPANOL	208	CMH240	95452-18-9
749	437	4-(2.2.6-TRIMETHYI-BtC YCLO(4.1,0]HEPT-1-YI)-BUT/AN-2-ONE	208	C14H240	77143-20-5
739	372	4,4-OIMETHYL-8-OXA6ICYCLO(3.2.1]OCT-6-EN-3-ONE-2-SPIRO-r-CYCLOHEX	220	C14H2002	122166-46-5
738	436	ACETIC ACID 7.7-DfMETHYL-2-OXO-BICYCLO(2.2.1iHEPT-1-YLMETHYI ESTER	210	C12H1803	108266-83-7
736	575	5-H-BROMO-1-METHYL-ETHYL)-2-METHYI-CYCL0HEX-2-EN0NE	230	C 10H150Br	71697-85-3
729	3 50	CIS-12-NOR-CARYOPHYLL-5-EN-2-ON	206	C14H220	60362-44-9
724	423	TRICYCLO[4 4.0.0 2.8JDEC-3-EN-5-OL		C10H140	0000
716	323	A-NOR-8-HOMO-5.BETA-CHOIESTAN-6-ONE		C21H36C	0000
713	611	2-METHYLISOBORNEOL SS 2-BORNANOL. 2-METHYL-		C11H200	91278-70-5
713	375	2-(3'-HYDR0XY-3'-METHYLBUTYL)-3-METHYLFURAN SS 2-FURANPROPANOL.		C1OH 1602	92356-07-5

9-21-07 27-SEP-2007 + 08:42:21

27sep07/X301 Scan EI+

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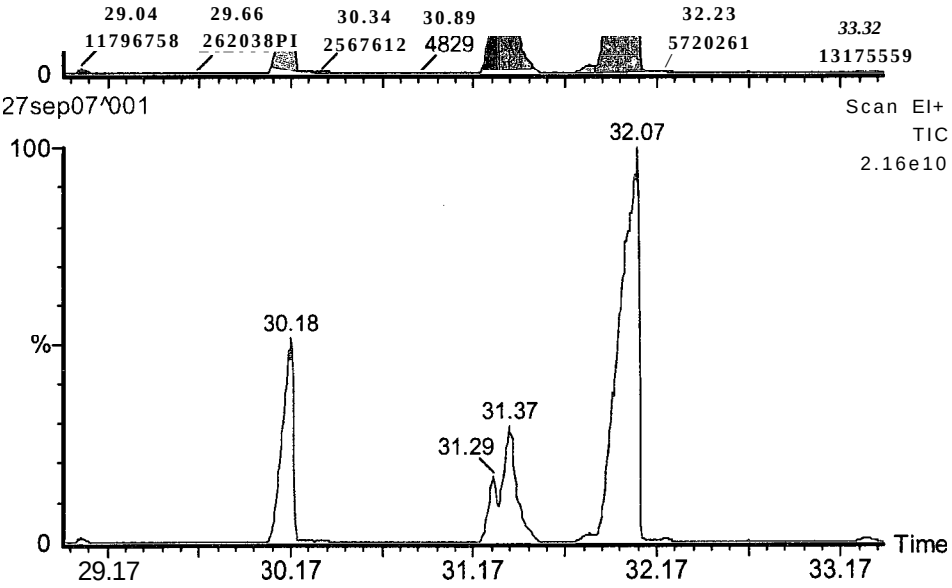

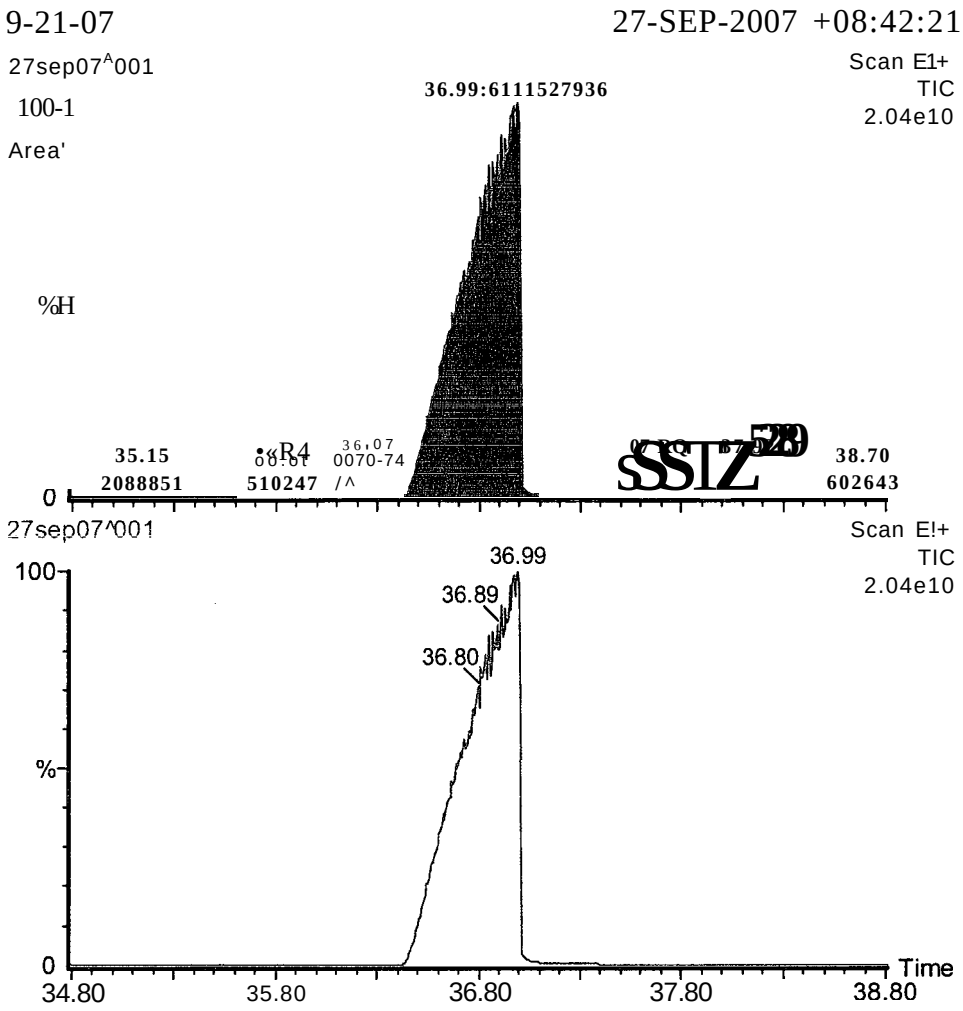
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36.99
36.89
36.80
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Time
34.80
35.80
36.80
37.80
38.80

Characterization of Extraction of (+)-Menthofuran from Peppermint Oil by GC/MS by [3-(maleimido)-propyl] Functionalized Silica Gel under D-A Conditions

Base Peppermint Oil post treatment w/ [3-(maleimidopropyl)-phenyl-] functionalized silica gel: Original menthofuran content ~ 7.5%.

15-meter Supelcowax 10 GC-FID shows a negligible amount of menthofuran remaining (0.07%) in the oil.

60-meter DB-5 GC/MS also shows a negligible amount of menthofuran remaining (see chromatogram and selected ion extracts below)...

1. From top to bottom below:

a.) the purple ion extract is 150 m/z, which is the base molecular weight for menthofuran;

b.) the green ion extract is 108 m/z, which is the principal fragment for menthofuran;

c.) the red trace below is the raw chromatogram.

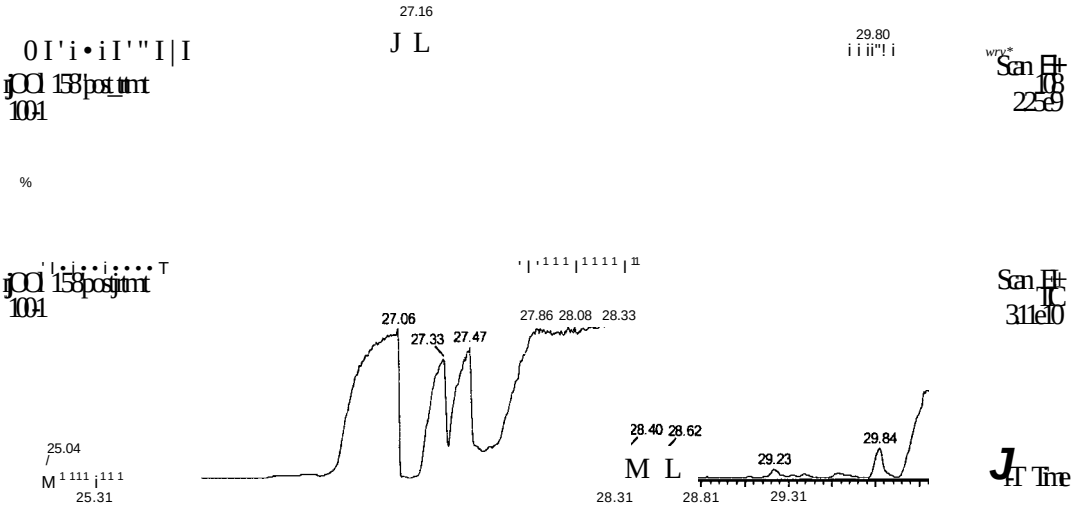
2. As can be seen, menthofuran elutes at approximately 27.15 minutes...

6-3-08 **20JUN-2008 + 11:38:01**

rjjOOl 158\post_ttmt Scan EI+

100-1 150

1.42e8



6-3-08 , 20-JUN-2008 + 1 1:38:01

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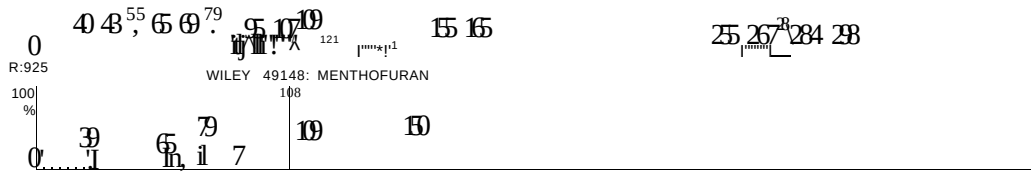
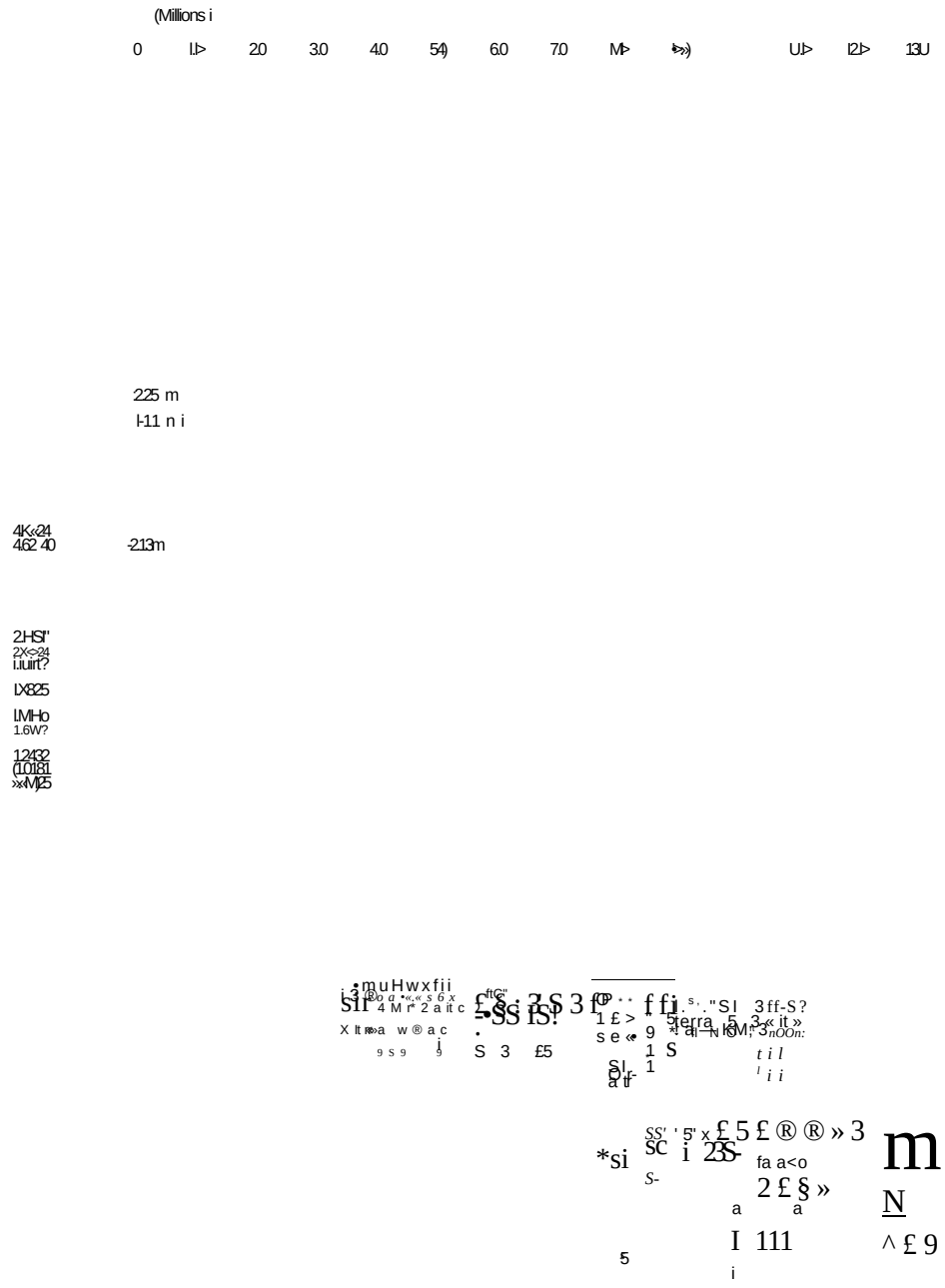
100-1



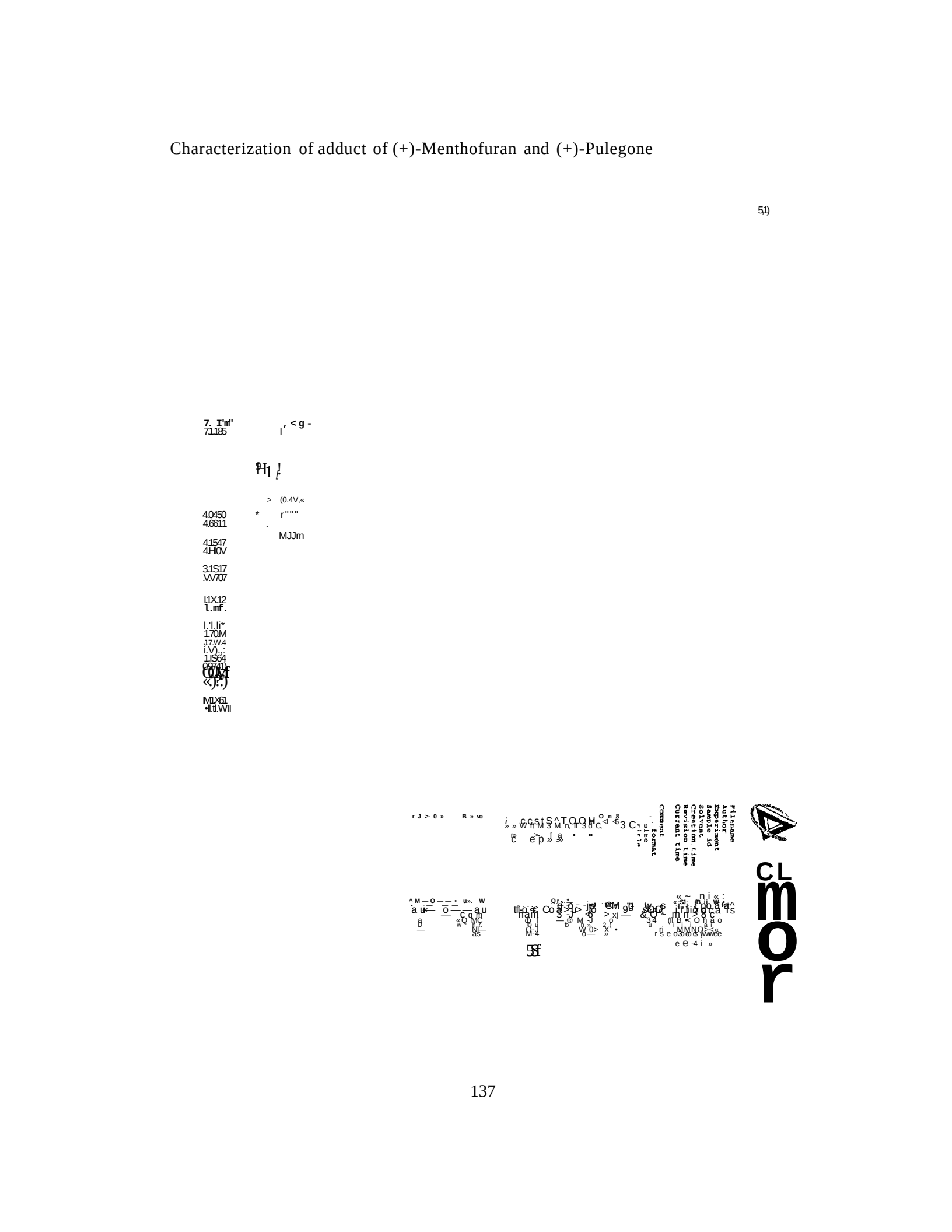
6-3-08 20Jun08

Hit	REV	(or	Compound Name	MW.	Formula	CAS
1	925	469	MENTHOFURAN	162	C11H140	0-00-0
2	859	420	ACETIC ACID, 3*ETHYIPHENYL ESTER SS ACETIC ACID. M-TOLYI ESTER SS	150	C9H10O2	122-46-3
3	854	407	3-OXO-.ALPHA-IONONE	206	C13H1802	0-00-0
4	837	338	1-(3'-BUTENYL)-1,2-EPOXYCYCLOPENTANE SS 6-0XAB!CYCL0(3.1 .OjHEXANE.	138	C9H140	119681-01-5
5	832	541	NENTHOFURAN	150	C10H140	494-90-6
6	825	573	(uENTHOFURAN	150	C10H14O	0-00-0
7	814	595	BENZOFURAN. 4.5.6.7-TETRAHYDRO-3.6-DIIVETHYL- (CAS) SS fcENTHOFURA	150	C10H140	494-90-6
8	812	593	fcENTHOFURAN	150	C10H140	494-90-6
9	811	638	BENZOFURAN, 4.5.6.7-TETRAHYDR0-3.6-DIMETHYL- (CAS) SS MENTHOFURA	150	C10H14O	494-90-6
10	809	617	BENZOFURAN. 4,5.6.7-TE"mAHYDR0-3,6-DIf»ETHYI- (CAS) SS MENTHOFURA	150	CI0H14O	494-90-6
11	808	328	BIS((8R.12R)-8.12-EPOXY-LABD-13E-ENE-15-YL|l\/£RCURY	782	C40H68O2Hg	0-00-0
12	807	590	BENZOFURAN. 4,5,6.7-TETRAHYDR0-3,6-DI[kETHYL- (CAS) SS MENTHOFURA	150	C10H140	494-90-6
13	802	594	MENTHOFURAN	150	C10H140	494-90-6
14	801	479	BICYCLO[3.1.0]HEX-3-EN-2-ONE. 4-METHYL-1-(1-METHYLETHYL)- (CAS)SSU	150	C10H140	24545-81-1

Characterization of (+)-Pulegone (7)



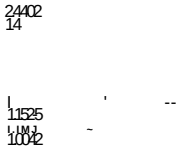
Characterization of adduct of (+)-Menthofuran and (+)-Pulegone



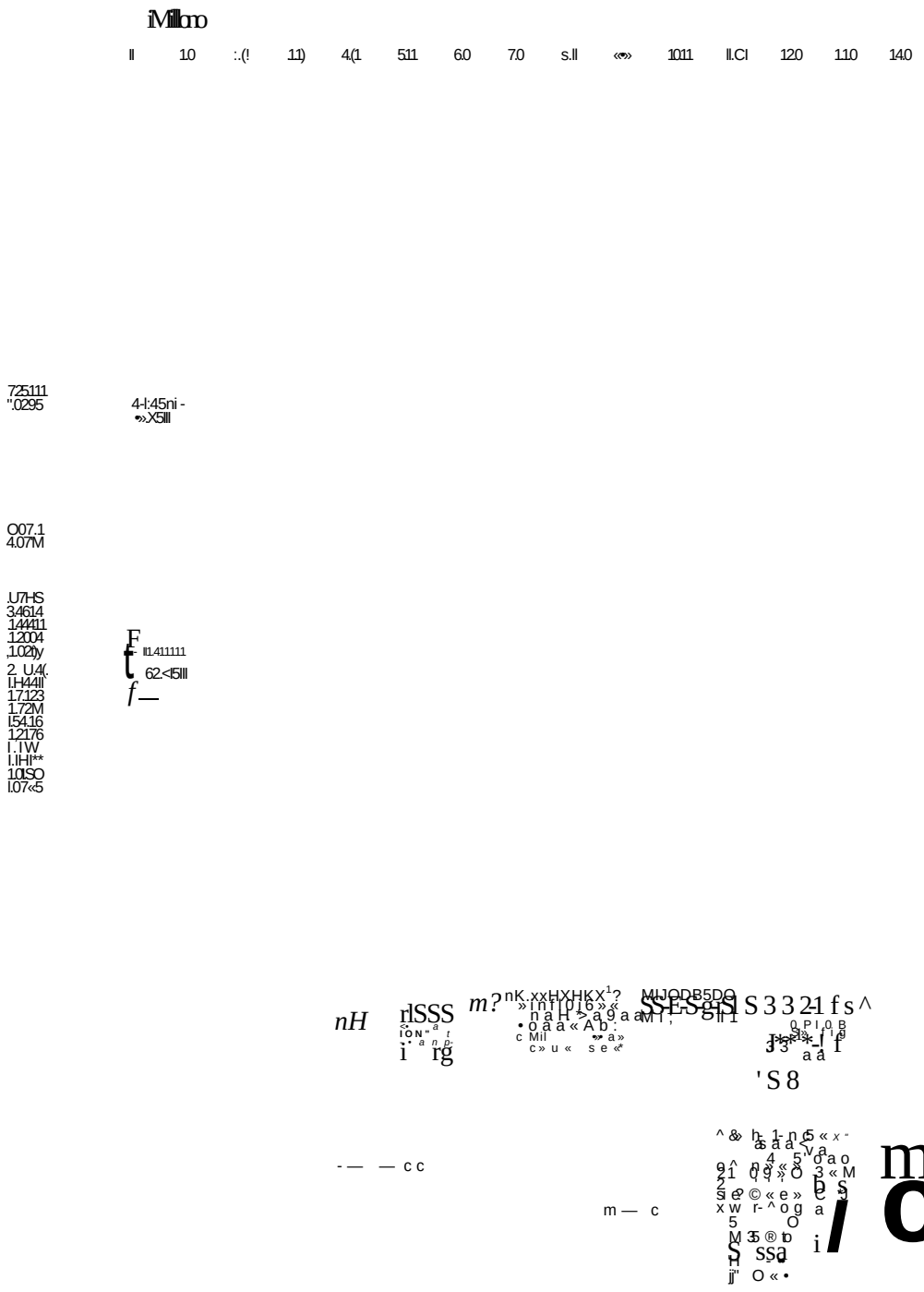
Characterization of (+)-Menthofuran (1)

II

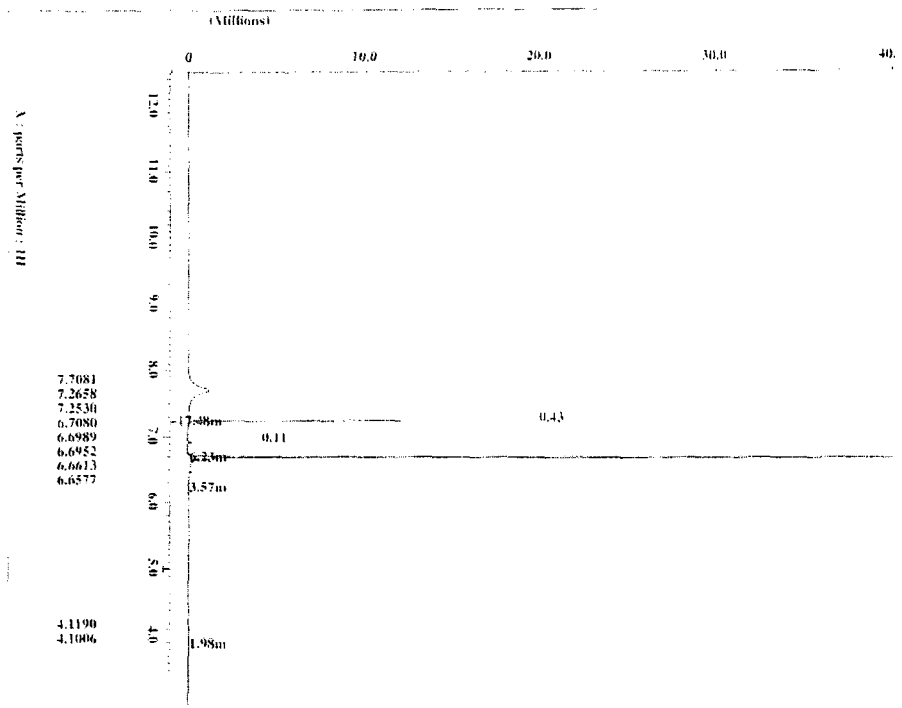
: !



Characterization of (+)-Menthofuran and Maleic Anhydride Adduct (38)



Characterization of Maleimide (**22**)



cJEOL

rilennoe	•	rjj00.107{>D~2.jd*
Author	»	Kiddle
Kxperim«?nt	-	single pu > ai?. ewp
s*«oj>ln..id	=	maleimide
aoivftnc	»	CHLCRCKCKKCO
Creation time	~	9-MAY-2007 19:42:39
Revision time	=	lfl-PEB-2010 18:38:15
current _time	=	18-FE9-20l0 ia:3Bil«

Data, format	-	ID COMPLEX
OS		I fis H a
I>i». title	=	1H
Diss uuits	s	Cppai)
ftimonsi ons	=	X
Sice	=	Scl.i.p#*+ 400
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Field strength		9.389766(TJ (400(MH2l
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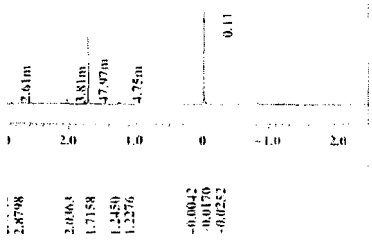

rjOOl 082A-2.jtlf
Single PULsc Experiment

J l l k

120 II.0

X : parts per Millinn : III

JEOL

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Author	=	Riddle
Experiment		single jiulse.exp
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Revieion_time	=	18-FEB-2010 18:39:43
Current_time	=	18-FEB-2010 18:39:45
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Oia~title		
Dim_units		
Dimensions		
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Spectrometer	=	DELTA_NHR

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X.Error3	s	399.782198381MHz J
X.offset	s	Slpgnnl
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x.resolution	·	0.36613771[Hz.]
X_sweep		5.99880024[kHz]
Clipped		FALSE
Mod_retura	o	1
Scans		8
Total.scans		8
X_90_width		12.6(us]
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X.angle	=	45[deg]
X.jmtse	=	6.3(us]
initial_wait	s	KB)
Phase_preset		3 (us]
Recvx-gain		6
Relaxation.delay		Ms)
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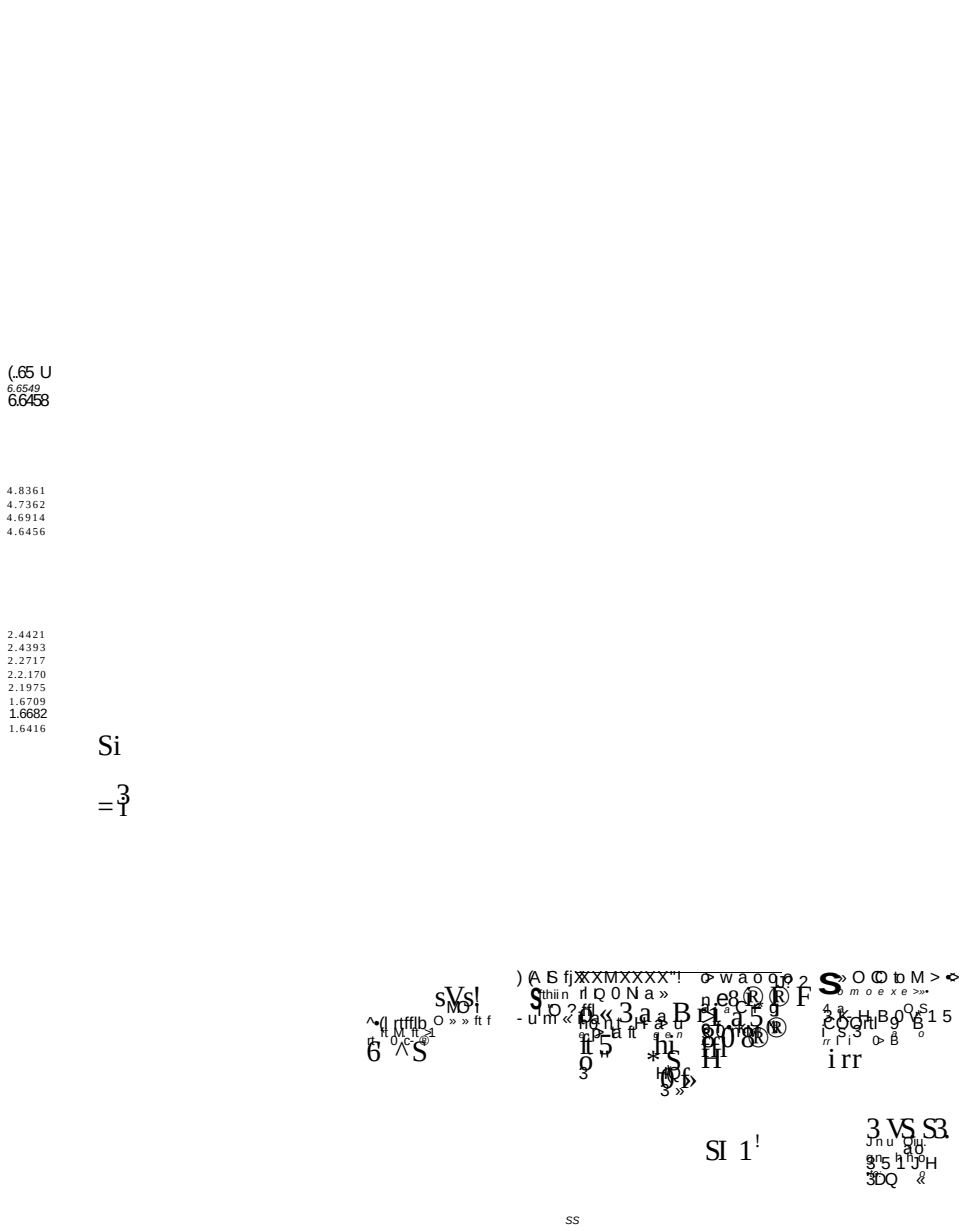
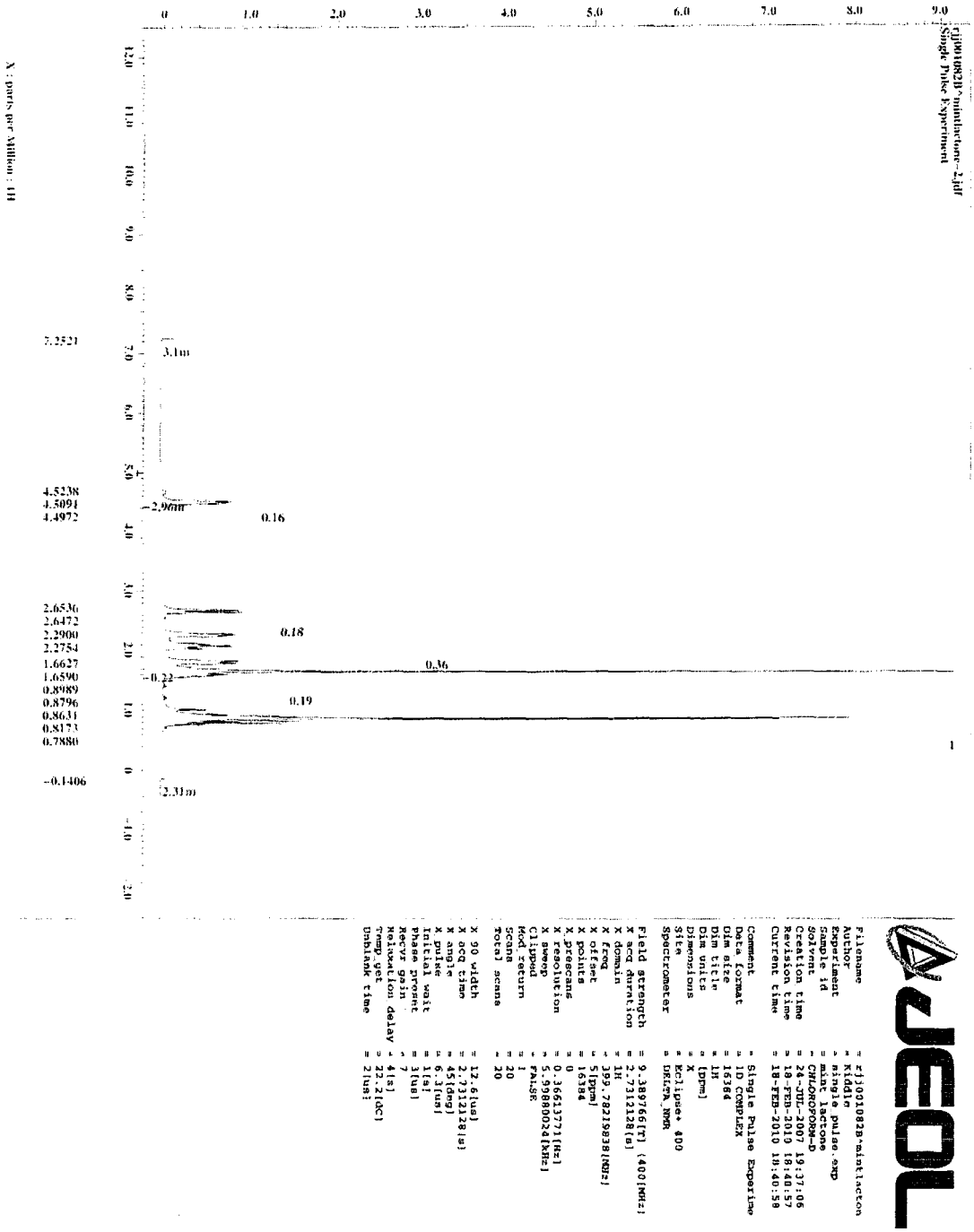
Unblank.tiree		2 [us]

Characterization of /-Carvone (23)

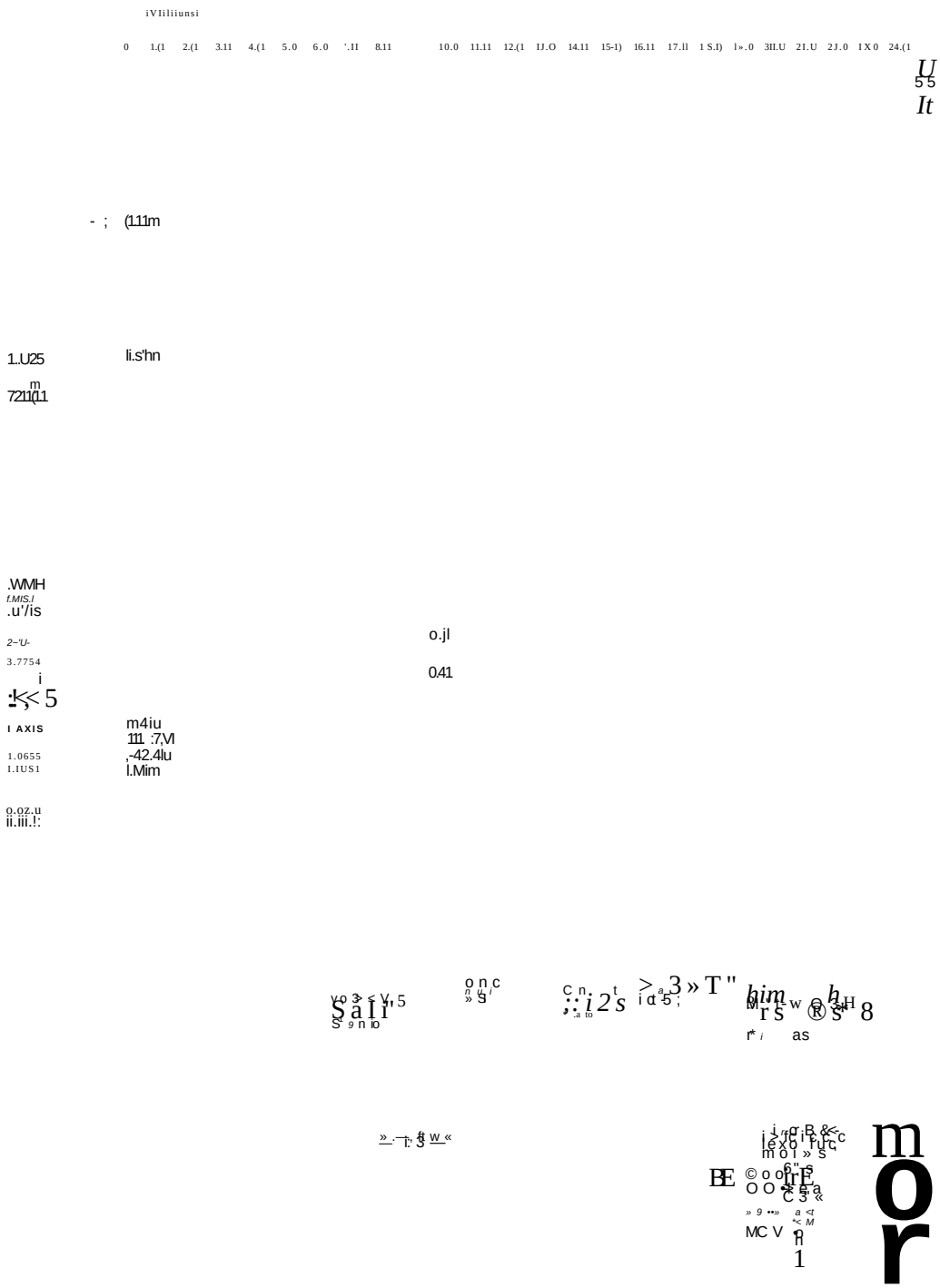
(Millions)



Characterization of (-)-mintlactone **(14)**



Characterization of l-bromo-3-phenylpropane



Characterization of freshly-distilled (+)-Menthofuran (1)

rjj!M)Jll)7l7-2.jdf
Single Pulse Experiment

1111 1410

X : parts per Million : III

JEOL

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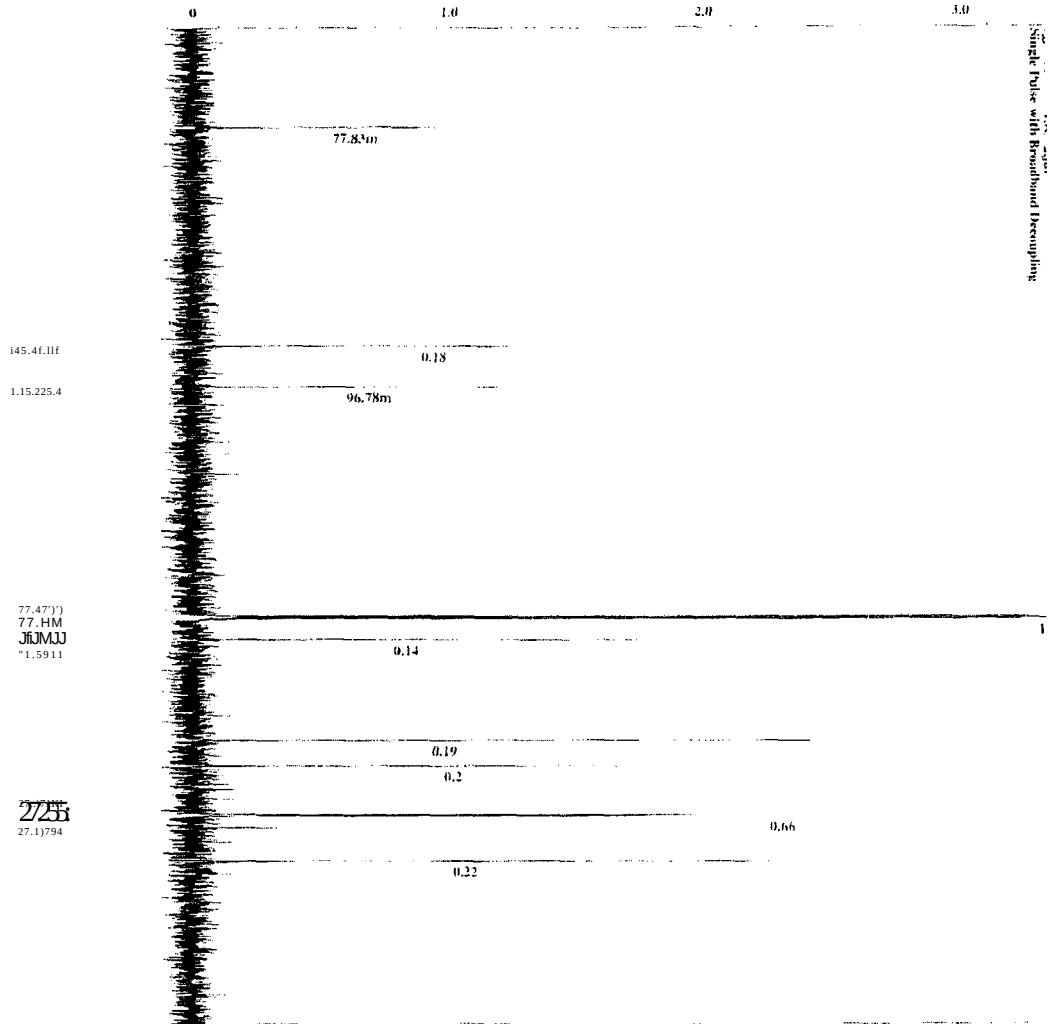
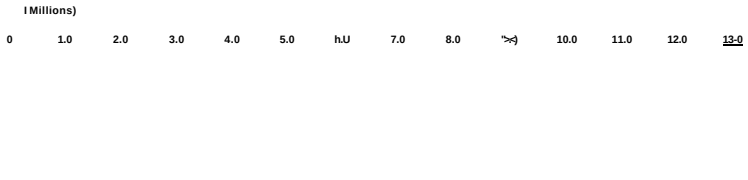
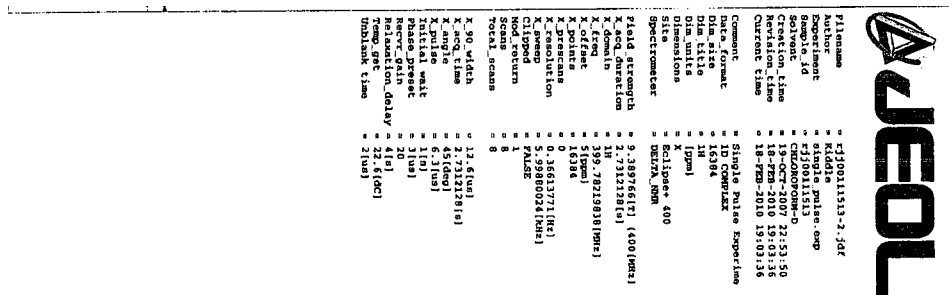
Characterization of Reaction Product 8-hydroxy-p-6-menthene-2-one **(25)**



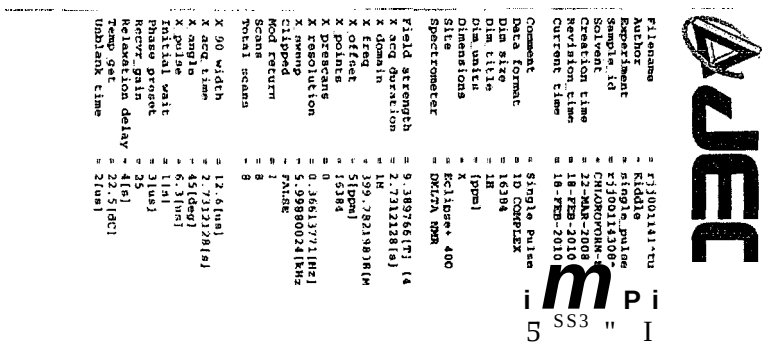
Characterization of Attempt at Gabriel Reaction with Potassium Maleimide and 1-bromo-3-phenylpropane





Absent from the 'H NMR is the methine singlet (2H); no product produced.

Characterization of yV-(3-Phenylpropyl)-1 //-pyrrole-2,5-dione



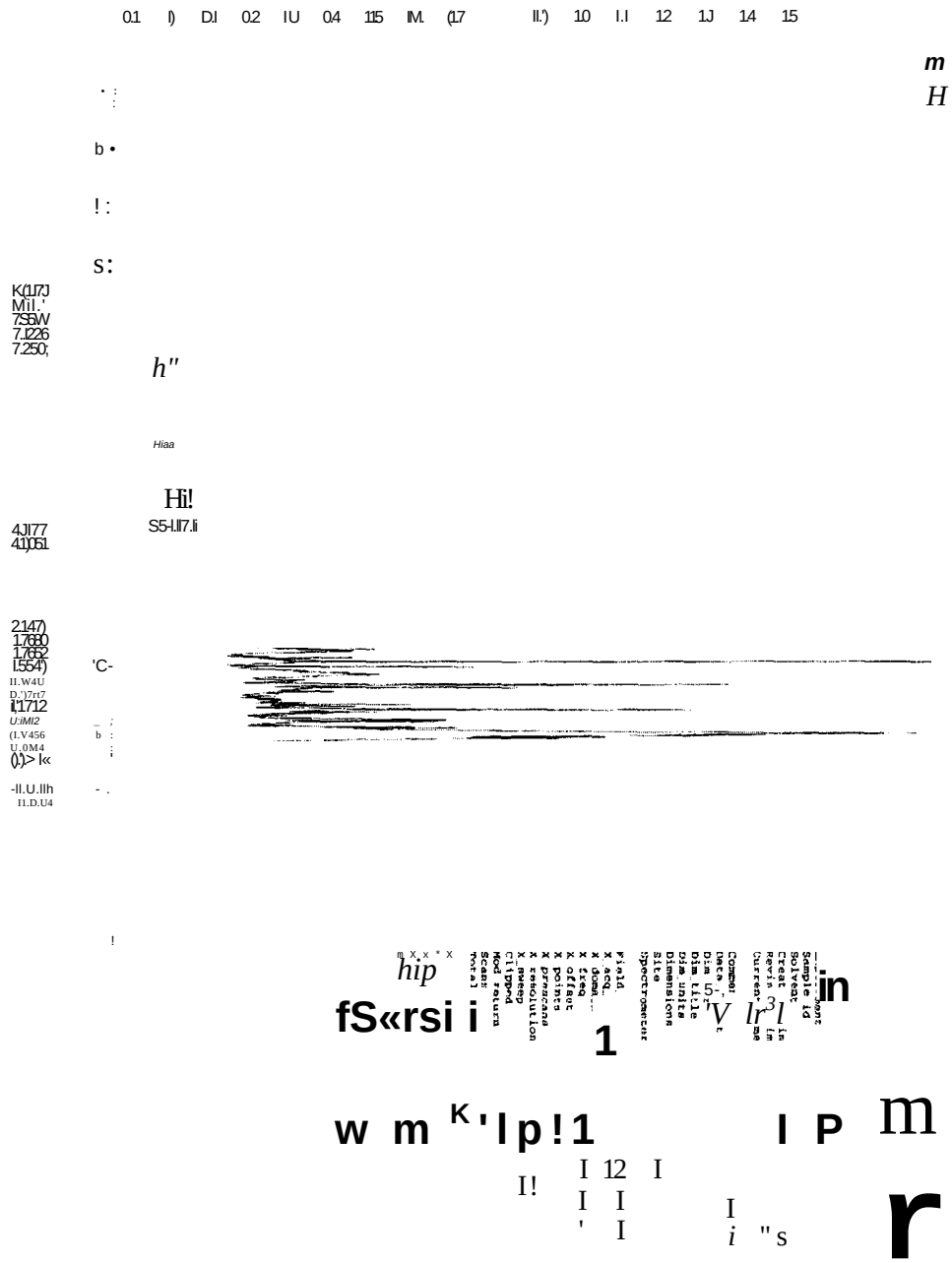
^{13}C NMR Characterization of 8-hydroxy-/?-6-menthene-2-one **(25)** [Redistilled]

Characterization of Adduct of TV-methylmaleimide and (+)-Menthofuran (36) (^{1}H NMR)

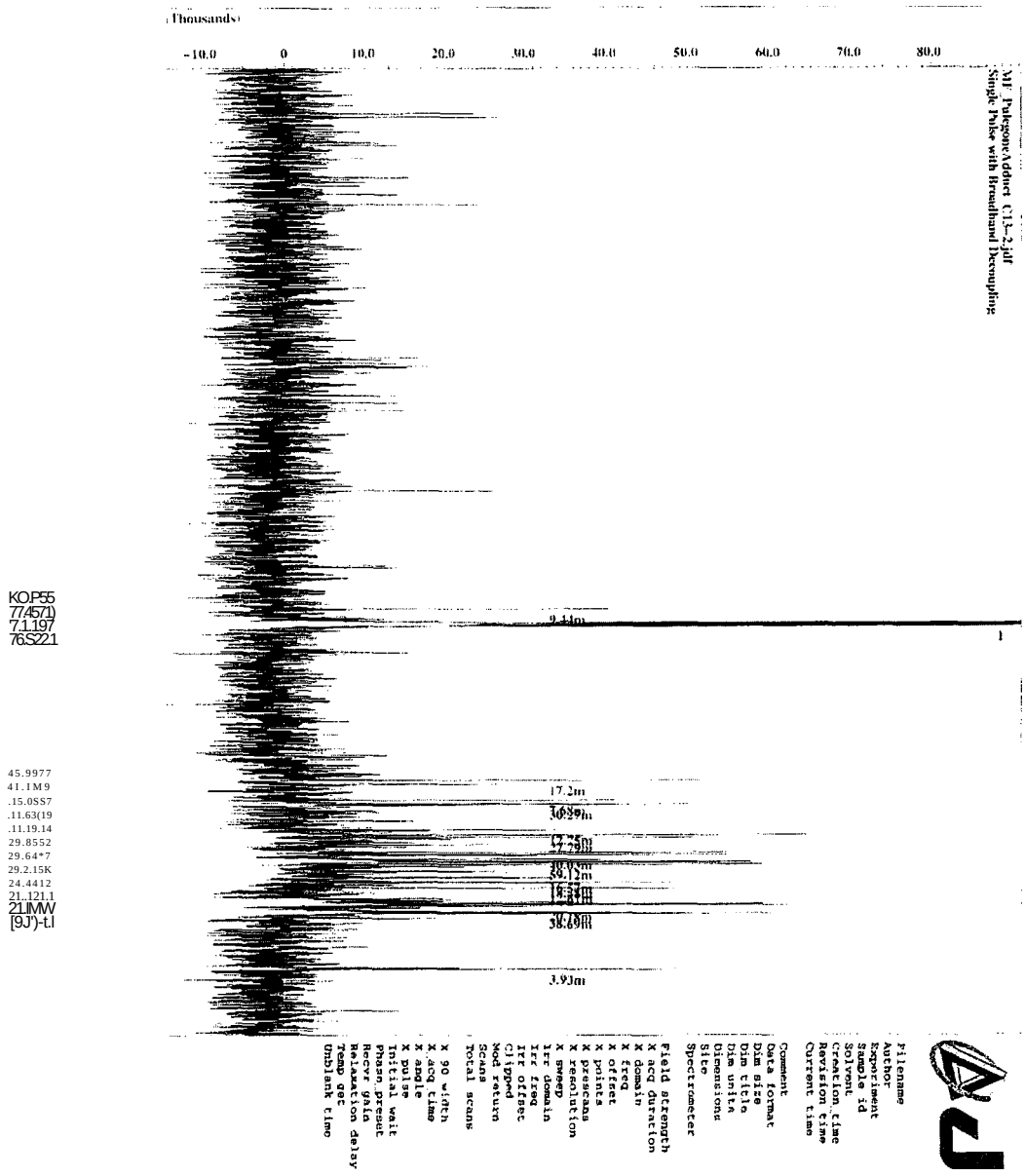
Characterization of Adduct of JV-methylmaleimide and (+)-Menthofuran (^{13}C NMR)

Filename
Author
Experiment
Sample id
Solvent
Creation time
Revision time
Current time
Comment
Data format
Dim size
Dim title
Dim units
Dimensions
Site
Spectrometer
Field strength
X acq duration
X domain
X freq
X off
X poi
X pre
X res
X swe

Characterization of Adduct of Pulegone (7) and (+)-Menthofuran (*H NMR)



Characterization of Adduct of Pulegone (7) and (+)-Menthofuran (^{13}C NMR)



irgssss.-sssgrr HgBi}g<

T lift" 1 f! 11 jl p ^{1}11llSffl

f I- s I
I s =« a

Characterization of 2^3 Experimental Design for RDA in Aqueous Base by GC/MS

Trial 1

10-09-08

rjjOOl 185*01

100-1

10-OCT-2008 + 10:14:26

Scan EI+
TIC
2.09e9

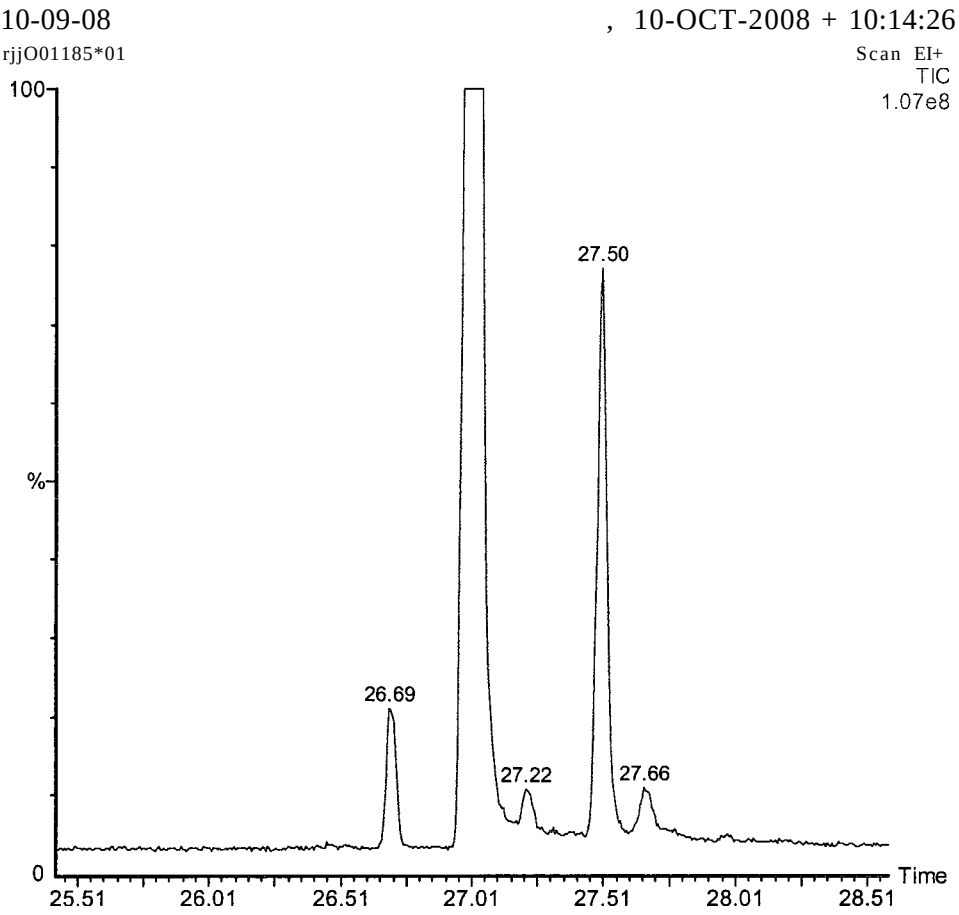
27.02

%H

27.50
/

'|''''|''' T¹ T T¹ IIII|IMI|I T¹ T¹ T* • i • • • • Time

6.40 11.40 16.40 21.40 26.40 31.40 36.40 41.40 46.40


10-09-08
, 10-OCT-2008 + 10:14:26
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Scan EI+
TIC
1.07e8
100
%
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26.69
27.22
27.50
27.66
25.51
26.01
26.51
27.01
27.51
28.01
28.51
Time

10-09-08 10-OCT-2008 + 10:14:26

rjjO01185*01 Scan EI+

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Area-

26 45 26 53 26.69 26.87 27.22 27.32 27.50 27.66 27.78

29637 x3388 804754 10402 422135 61004 3398415 40369846617

0 / FfWFi

rjjO01185*01 Scan EI+

27.02 TIC

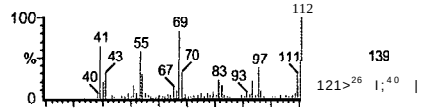
100- 1,36e9

1[11] " i " ı – / v 27.50

26.53 26.73 26.93 27.13 27.33 2753 2773 Time

10-09-08 , IO-OCT-2OO8 +10:14:26

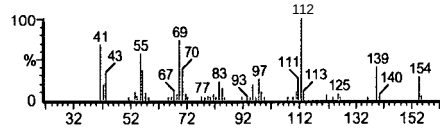
rjj001185'01 3225 (26.694) Cm(3222:3230-(3212:3217+3235:3240)) 1.72e6



121>26 I;40 | 174182191 206 223232 247 257 267 280 293 307 317 330 341 /

|fniijn«|ii'<f|l.....1

R:982 WILEY 41492: P-MENTHONE $$ CYCLOHEXANONE, 5-METHYL-2-{1-METHYLETHYL)-, TRANS- (CAS) $$ TRANS-MENTh Hit 2



192 212 232 252 272 292 332 352 m/z

10-09-08 100ct2008A01

Hit	REV	for	Compound Name	MW.	Formula	CAS
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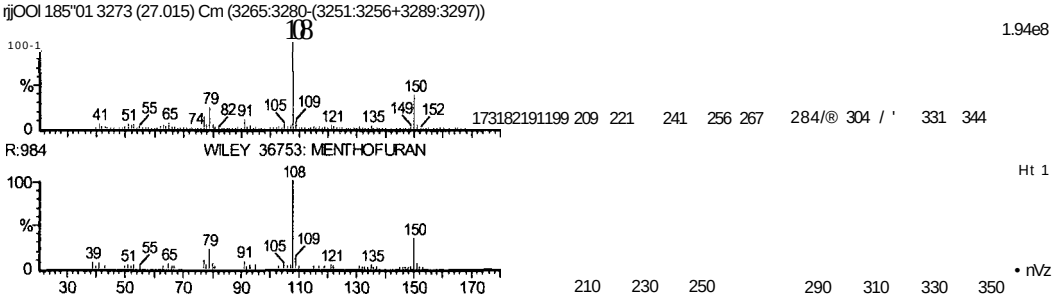
2	982	973	P-MENTHONE SS CYCLOHEXANONE. 5-METHYL-2-(1-METHYLETHYL)-. TRANS	154	CI0H18O	89-80-5
3	981	816	L-WNTHONE	154	C10H180	10458-14-7
4	979	967	CYCLOHEXANONE. 5-METHYL-2-(1-METHYLETHYL)-, CIS- (CAS) SS ISOfcENT	154	CI OH180	491-07-6
5	979	967	CYCLOHEXANONE, 5-METHYL-2-0 .METHYLETHYL)-, CIS- (CAS) SS ISOIVENT	154	C10H180	491-07-6
6	976	967	CYCLOHEXANONE. 5-METHYL-2-(1-METHYLETHYL)-. CIS- (CAS) SS ISOfcENT	154	C10H180	491-07-6
7	974	956	CYCLOHEXANONE. 5-METHYL-2-(1-METHYLETHYL)-. (2R-CIS)- (CAS) SS P-ME	154	C10H180	1196-31-2
3	972	953	(»ENTri0NE-D3 SS CYCLOHEXANONE. 5-IVETHYL-2-(1 -IVETHYLETHYL)-. (2S-T	154	C10H180	14073-97-3
9	972	960	P-MENTHONE SS CYCLOHEXANONE, 5-METHYL-2-(1-lvETHYLETHYL)-. TRANS	154	C10H180	89-80-5
10	972	963	P-MENTHONE SS CYCLOHEXANONE. 5-hETHYL-2-<1-fcETHYLETHYL)-, TRANS	154	C10H180	89-80-5
11	971	949	fcENTHONE	154	C10H180	89-80-5
12	971	953	P-MENTHONE SS CYCLOHEXANONE, 5-kETHYL-2-(1-IVETHYLETHYL)-. TRANS	154	C10H180	89-80-5
13	971	953	CYCLOHEXANONE. 5-METHYL-2-(1-METHYLETHYL)-(CAS) SS 5-IVETHYL-2-IS	154	C10H180	10458-14-7
14	971	965	CYCLOHEXANONE. 5-METHYI-2-(1 -METHYLETHYL)-, CIS- (CAS) SS ISOMENT	154	C10H180	491-07-6

10-09-08 , IO-OCT-2008 +10:14:26

rjjOOl 185"01 3273 (27.015) Cm (3265:3280-(3251:3256+3289:3297))

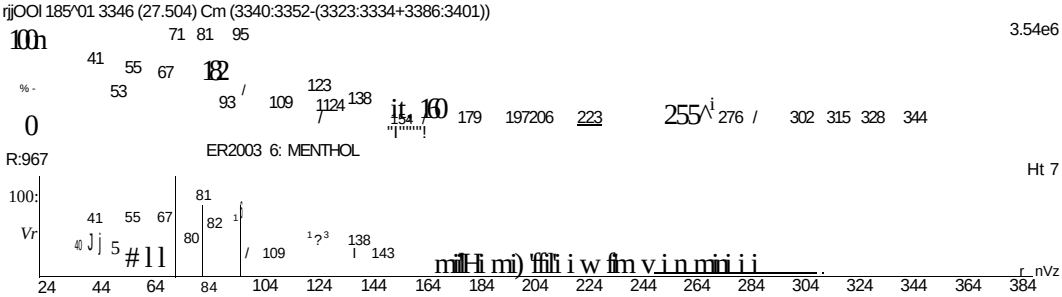


10-09-08 10Qct2008^A01

Hit	REV	lor	Compound Name	MW.	Formula	CAS
1	984	975	MENTHOFURAN	150	C10H140	494-90-6
2	980	941	MENTHOFURAN	150	C10H14O	•194-90-6
3	971	944	MENTHOFURAN	150	C10H140	0-00-0
4	965	950	BENZOFURAN. 4.5.6.7-TETRAHYDR0-3.6-DIMETHYL- (CAS) SS MENTHOFURA	150	C10H140	494-90-6
5	965	953	BENZOFURAN, 4.5.6.7-TETRAHYDRO-3.6-DIMETHYL- (CAS) SS MENTHOFURA	150	C10H140	494-90-6
6	962	945	MENTHOFURAN	150	C10H140	494-90-6
7	940	923	BENZOFURAN. 4.5.6.7-TETRAHYDRO-3.6-DIMETHYL- (CAS) SS MENTHOFURA	150	C10H140	494-90-6
8	935	910	BENZOFURAN, 4,5.6.7-TETRAHYDRO-3,6-DIMETHYL- (CAS) SS MENTHOFURA	150	C10H140	494-90-6
9	918	717	MENTHOFURAN	162	C11H140	0-00-0
10	911	868	4 5.6.7-TETRAHYDRO-3.6-DIMETHYLBENZOFURAN	150	C10H140	0-00-0
11	869	592	4-ISOPROPOXYTOLUENE SS BENZENE. I-METHYL-4-(1-METHYLETHOXY)- (C	150	C10H140	22921-10-4
12	834	647	ISOSERICENINE	260	C16H2003	19912-86-8
13	833	590	ACETIC ACID. PHENYLMETHYL ESTER (CAS) SS BENZYL ACETATE SS ETHAN	150	C9H1002	140-11-4
14	828	643	P-TOLYL HYDROCINNAMATE	240	C16H1602	0-00-0

10-09-08 10-QCT-2008 +10:14:26

rjjOOl 185^01 3346 (27.504) Cm (3340:3352-(3323:3334+3386:3401))



10-09-08 100ct2008^A01

Hit	REV	tor	Compound Name	M.W.	Formula	CAS
1	981	967	(-VfcETHOL	156	C10H200	89-78-1
2	976	959	L-(->.fcENTHOI. SS CYCLOHEXANOL, 5-fcETHYL-2-(1-IVETHYLETHYL)-, [1R-(1 .A	156	C10H200	2216-51-5
3	973	955	CYCLOHEXANOL, 1-METHYL-4-(1-METHYLETHYL)- SS 1-IVETHYL-4-(1-IVETHYL	156	C10H200	21129-27-1
4	972	942	CYCLOHEX0NOL. 5-N/ETHYL-2-(1-(/ETHYLETHYL)-. (1 S-(1 ALPHA.2.ALPHA.5.	156	C10H200	2216-52-6
5	970	598	CITRONELLYL ISOBUTYRATE SS ISOBUTANOIC ACID 3.7-D«vETHYL-6-OCTEN	226	C14H2602	97-89-2
6	968	914	CYCLOHEXANOL. 5-WETHYL-2-(1 -NiETHYLETHYL)- (CAS) SS 3-P-IvENTHANOL	156	C10H200	1490-04-6
7	967	941	MENTHOL	0		89-78-1
8	967	947	NEO-MENTHOL	156	C10H200	491-01-0
9	966	935	CYCLOHEXANOL. 5-^ETHYL-2-(1-IVETHY1-ETHYL)- (CAS) SS 3-P-WENTHANOL	156	C10H200	1490-04-6
10	965	938	D-NEOISOfr/ENTHOL	156	C10H200	0-00-0
11	964	813	L-(-)^ENTHOL SS CYCLOHEXANOL, 5-IVETHYL-2-(1-IVETHYLETHYL)-, [1R-(1 A	156	C10H200	2216-51-5
12	964	935	CYCLOHEXANOL. 5-METHYL-2-(1-IvETHYLETHYL)-. (1 .ALPHA.2.B6TA.5.ALPH	156	C10H200	15356-70-4
13	963	933	(•)-NEOISOMENTHOL	156	C10H200	0-00-0
14	963	928	NEO-fcENTHOL SS CYCLOHEXANOL. 5-METHYL-2-(1-METHYLETHYL)-, (1 ALP	156	C10H200	491-01-0

Trial 2

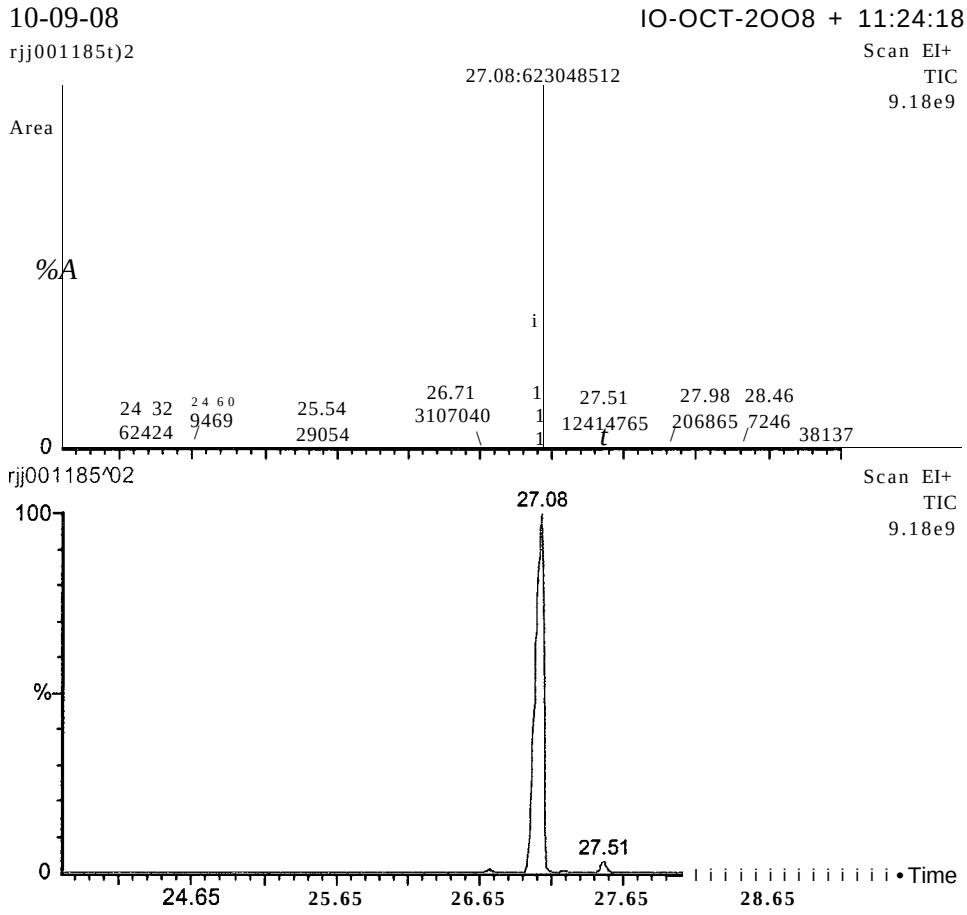
10-09-08
rjjO01185*02
100n

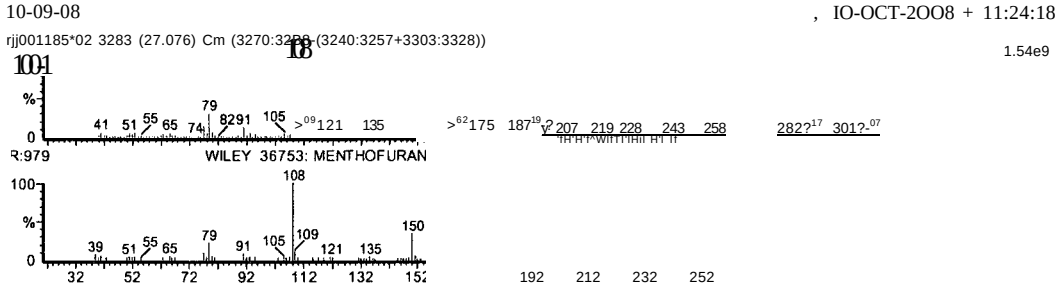
, IO-0CT-2008 +11:24:18
Scan EI+
TIC
4.83e8

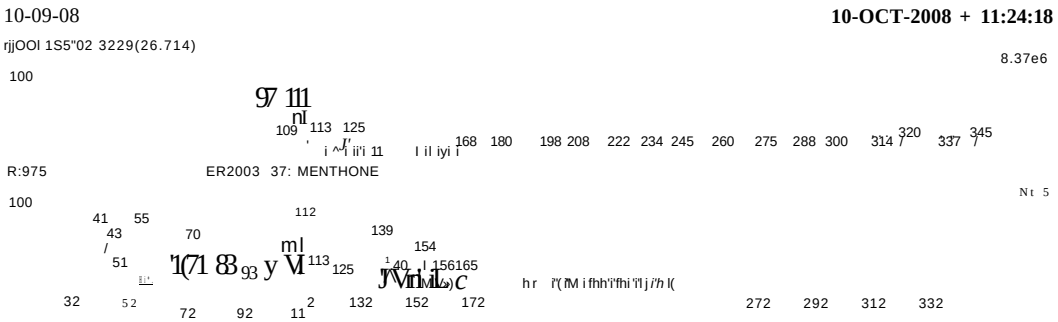
27.51

26.71

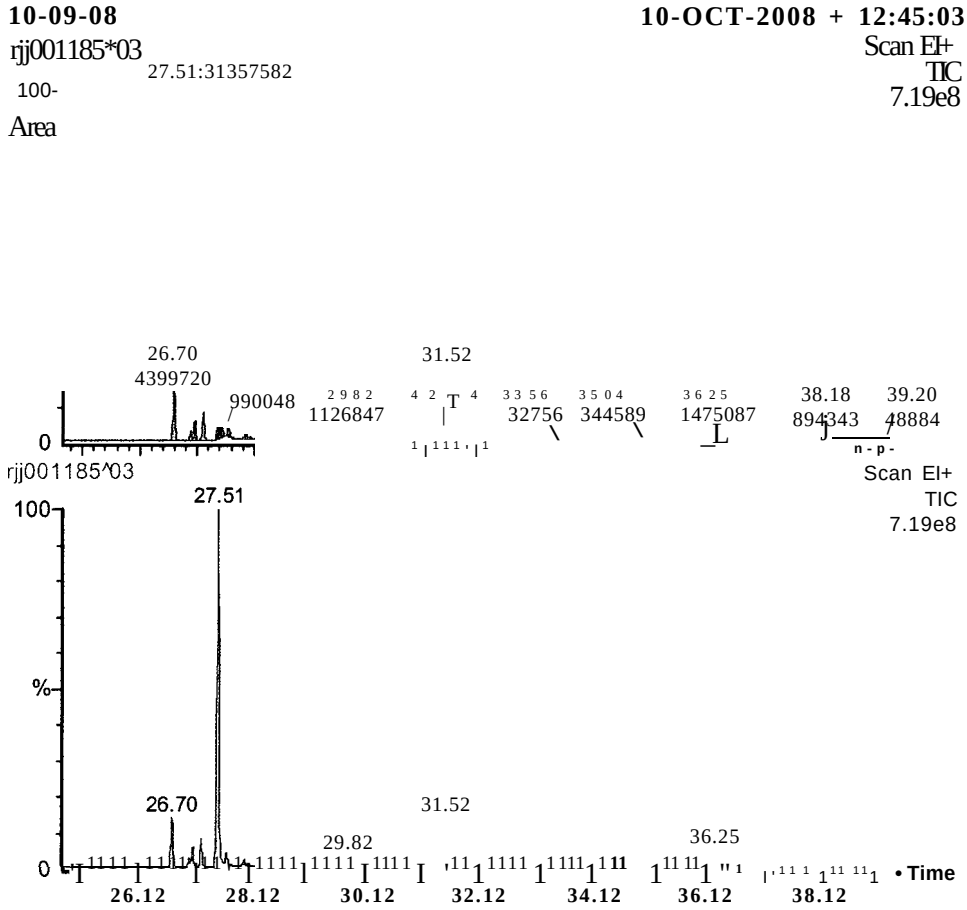
24.65 ' 25.65 ' 2$_{6}$:$_{6}$5 ^ S S ' ' ' ' 28.65. . . . . ^


10-09-08
IO-OCT-2OO8 + 11:24:18
rjj001185t)2
Scan EI+
TIC
9.18e9
27.08:623048512
Area
%A
i
24 32
62424
24 60
9469
25.54
29054
26.71
3107040
27.51
12414765
27.98 28.46
206865 7246
38137
t
rjj001185^02
Scan EI+
TIC
9.18e9
100
%
0
27.08
27.51
24.65
25.65
26.65
27.65
28.65
Time


10-09-08
, IO-OCT-2OO8 + 11:24:18
rjj001185*02 3283 (27.076) Cm (3270:3288) (3240:3257+3303:3328))
1.54e9
WILEY 36753: MENTHOFURAN
R:979
108
79
91
105
109
121
135
150
39
51
55
65
32
52
72
92
112
132
192
212
232
252


10-09-08
10-OCT-2008 + 11:24:18
rjjOOI 1S5"02 3229(26.714)
8.37e6
100
R:975
ER2003 37: MENTHONE
100

Trial 3

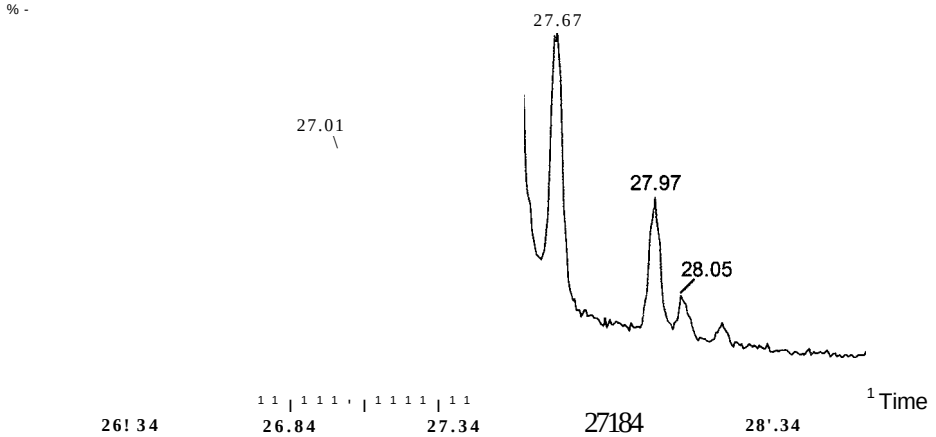

10-09-08
10-OCT-2008 + 12:45:03
rjj001185*03
27.51:31357582
Scan EI+
TIC
7.19e8
100-
Area
26.70
4399720
990048
31.52
1126847
32756
344589
1475087
38.18
894343
39.20
48884
0
rjj001185^03
Scan EI+
TIC
7.19e8
100
27.51
%
26.70
31.52
29.82
36.25
0
26.12
28.12
30.12
32.12
34.12
36.12
38.12
• Time

10-09-08
rjjOOl 185t)3
100-

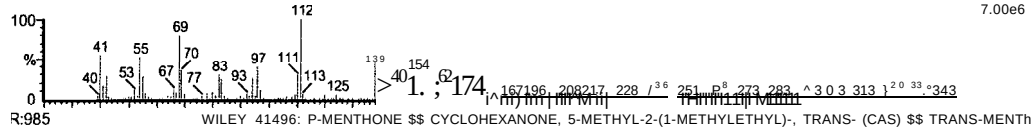
10-OCT-2008 + 12:45:03
Scan EH+
TIC
7.15e7

27.22

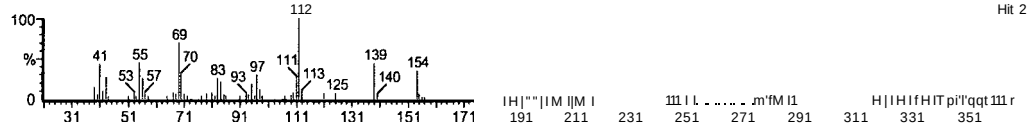
27.07



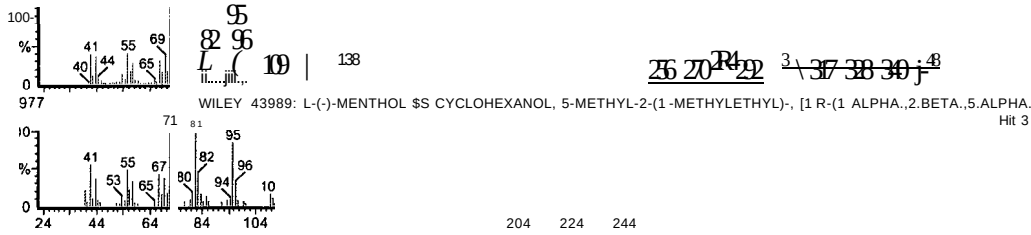
10-09-08 , IO-OCT-2OO8 +12:45:03
rjjOOl 185D3 3227 (26.701) Cm (3222:3233-(3202:3215+3247:3261))
7.00e6



R:985 WILEY 41496: P-MENTHONE $$ CYCLOHEXANONE, 5-METHYL-2-(1-METHYLETHYL)-, TRANS- (CAS) $$ TRANS-MENTh
Hit 2



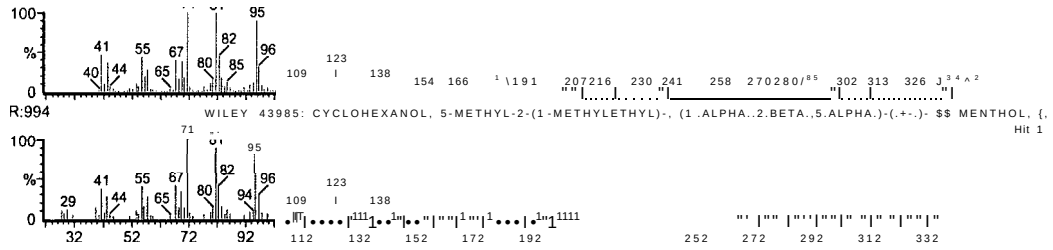
10-09-08 lQ-OCT-2008 + 12:45:03
rjj001185"03 3305 (27.223)



977 WILEY 43989: L-(-)-MENTHOL $S CYCLOHEXANOL, 5-METHYL-2-(1 -METHYLETHYL)-, [1 R-(1 ALPHA.,2.BETA.,5.ALPHA.;
Hit 3

10-09-08 , 10-OCT-2008 + 12:45:03

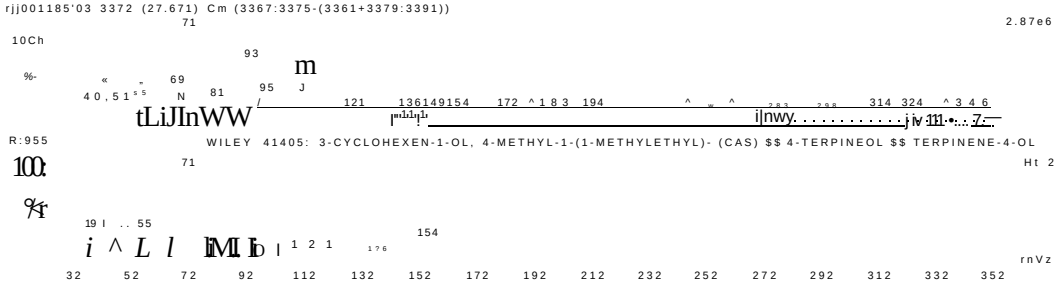
rjjO011 S S W 3348 (27.511) Cm (3342:3352-(3324:3330+3360:3366))



R:994 WILEY 43985: CYCLOHEXANOL, 5-METHYL-2-(1-METHYLETHYL)-, (1 .ALPHA..2.BETA.,5.ALPHA.)-(.+-.)- $$ MENTHOL, {, Hit 1

10-09-08 , 10-QCT-2008 +12:45:03

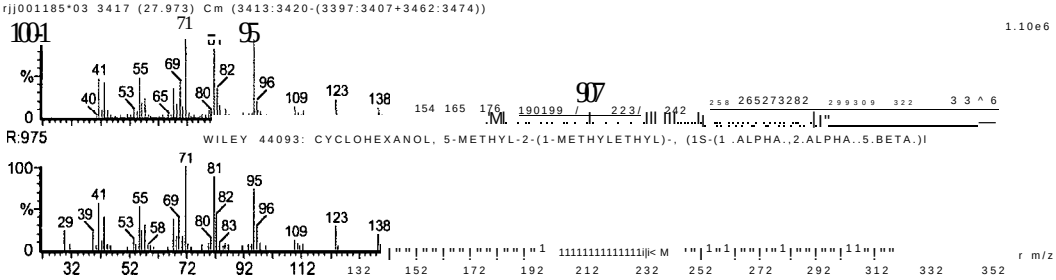
rjj001185'03 3372 (27.671) Cm (3367:3375-(3361+3379:3391))



R:955 WILEY 41405: 3-CYCLOHEXEN-1-OL, 4-METHYL-1-(1-METHYLETHYL)- (CAS) $$ 4-TERPINEOL $$ TERPINENE-4-OL Ht 2

10-09-08 10-QCT-2008+ 12:45:03

rjj001185*03 3417 (27.973) Cm (3413:3420-(3397:3407+3462:3474))



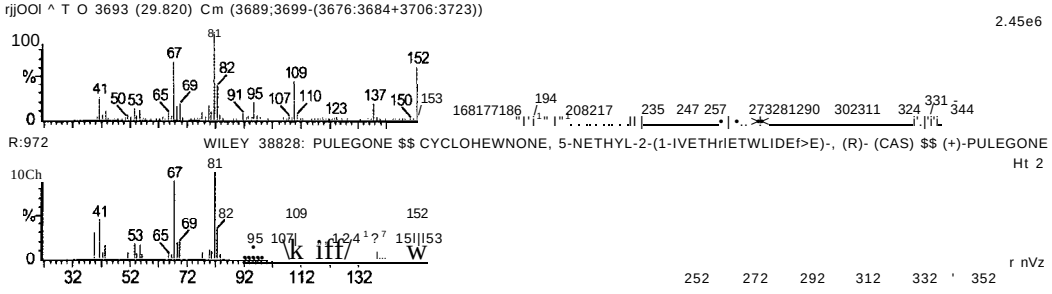
R:975 WILEY 44093: CYCLOHEXANOL, 5-METHYL-2-(1-METHYLETHYL)-, (1S-(1 .ALPHA.,2.ALPHA..5.BETA.)I

10-09-08 10Oct2008[A]03

Hit	REV	tor	Compound Name	M.W.	Formula	CAS
t	975	967	NEO-MENTHOL	156	C10H200	491-01-0
2	975	953	CYCLOHEXANOL. 5-METHYL-2-(1-METHYLETHYL)-. [1S-(1 .ALPHA..2.ALPHA.5.	156	C10H200	2216-52-6
3	975	957	L-(-)-MENTHOL S$ CYCLOHEXANOL. 5-HiETHYL-2-(1-METHYLETHYL)-. J1R-(1 .A	156	C10H200	2216-51-5
4	974	966	(-)-METHOL	156	C10H200	89-78-1
5	974	945	CYCLOHEXANOL, 5-METHYL-2-{1 -METHYLETHYL)- (CAS) SS 3-P-MENTHANOL	156	C10H200	1490-04-6
6	973	955	(•1-ISOMENTHOL	156	C10H200	23283-97-8
7	973	950	CYCLOHEXANOL, 5-METHYL-2-(1-METHYLETHYL)-. (1 ALPHA.2.BETA,5.BETA	156	C10H200	490-99-3
8	973	953	CYCLOHEXANOL. 1-METHYL-4-(1-METHYLETHYL)-SS 1-METHYL-4-(1-METHYL	156	C10H200	21129-27-1
9	971	953	(+J-NEOISOMENTHOL	156	C10H200	0-00-0
10	971	953	CYCLOHEXANOL, 5-METHYL-2-(1-METHYLETHYL)- (CAS) SS 3-P-MENTHANOL	156	C10H200	1490-04-6
11	970	943	D-NEOISOHENTHOL	156	CIQH200	0-00-0
12	970	948	CYCLOHEXANOL. 5-METHYL-2-(1-METHYLETHYL}- (CAS) SS 3-P-MENTHANOL	156	CIQH20O	1490-04-6
13	970	948	MENTHOL SS CYCLOHEXANOL, 5-METHYL-2-(1-METHYLETHYL)-, (1 ALPHA,2.	156	C10H200	89-78-1
14	969	942	CYCLOHEXANOL. 5-METHYL-2-(1-METHYLETHYL)- (CAS) SS 3-P-MENTHANOL	156	C10H200	1490-04-6

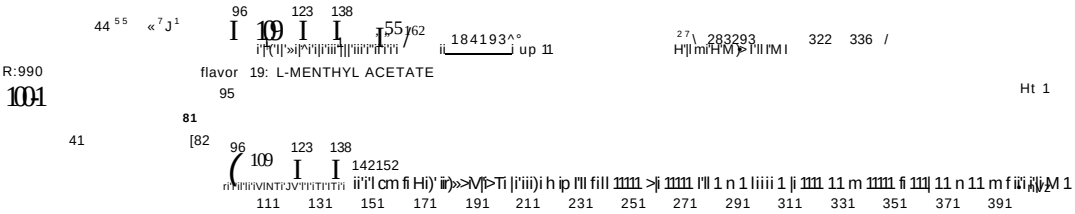
10-09-08 **, 10-QCT-2008 + 12:45:03**

rjjOOl ^ T O 3693 (29.820) Cm (3689;3699-(3676:3684+3706:3723))



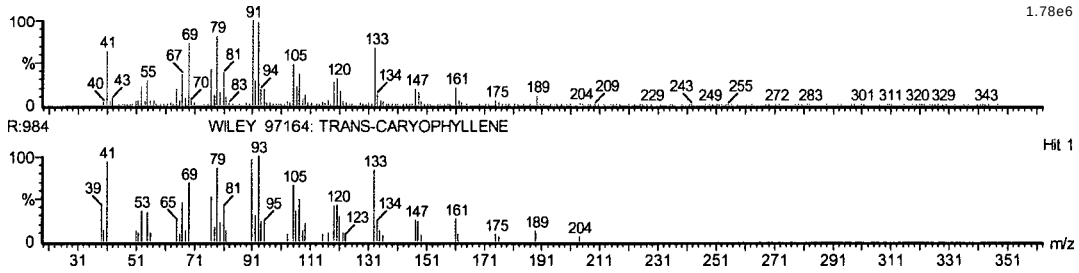
10-09-08 IO-OCT-2008 + 12:45:03

rjjOOl 185*03 3947 (31.520) Cm(3941:3954-(3910:3920+397B:3994))



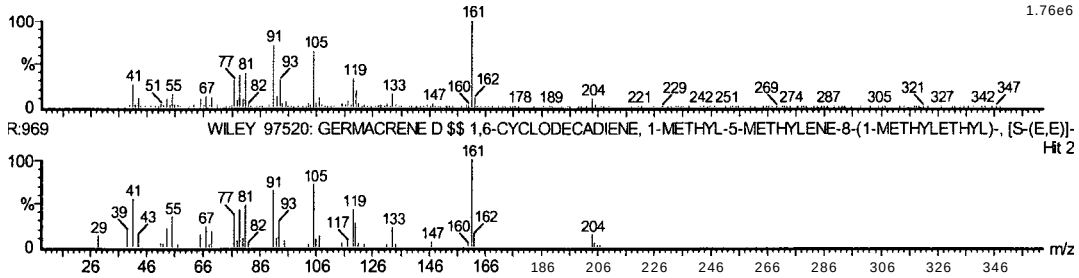
10-09-08 10-OCT-2OO8 + 12:45:03

rjj001185'03 4654 (36.253) Cm(4649:4658-(4619:4630+4667:4686))

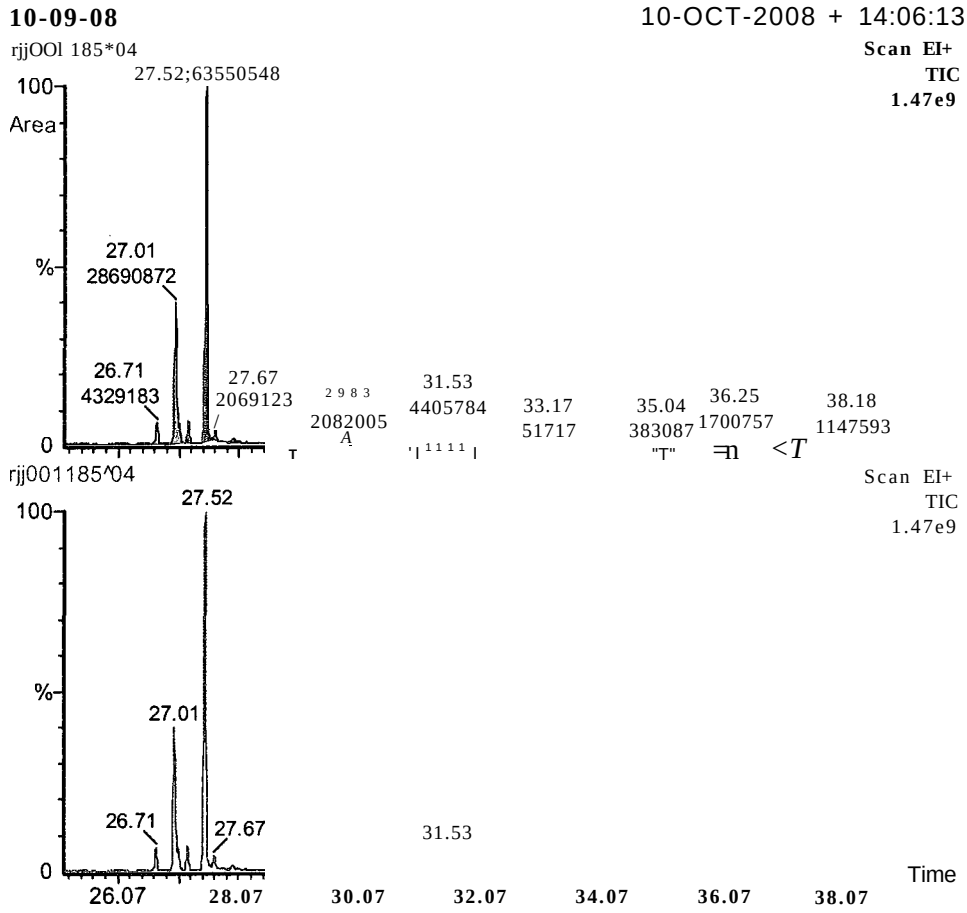


10-09-08 , IO-OCT-2OO8 +12:45:03

rjjOOl 185^03 4942 (38.181) Cm (4937:4946-(4912:4925+4961:4970))



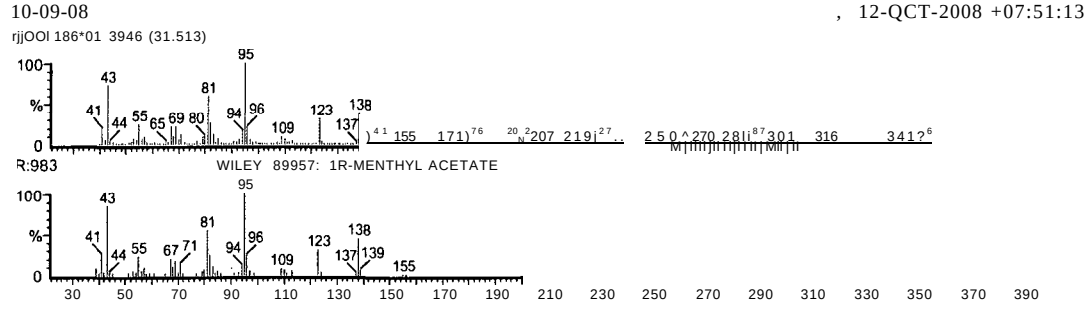
Trial 4



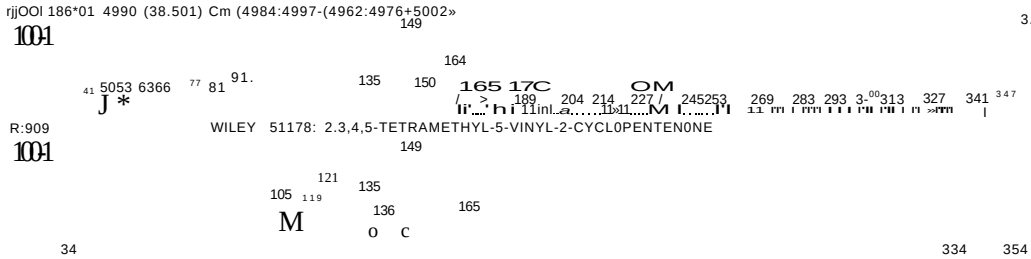
(peaks at approximately same retention times as rjjOOl 185[A]03)

Trial 5

26.70 minutes = menthone
27.06 minutes = menthofuran
27.50 minutes = menthol



10-09-08 **, 10-QCT-2008 + 12:45:03**

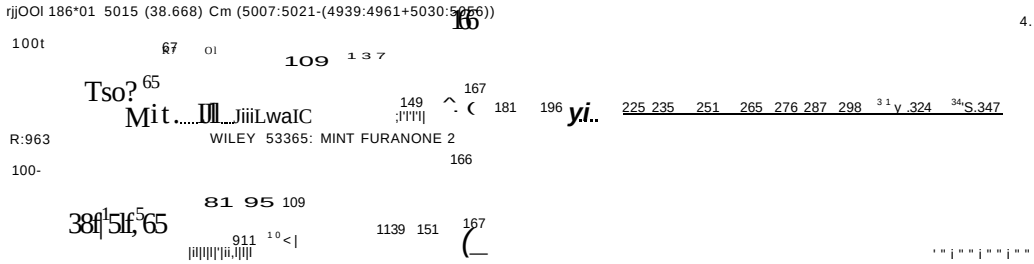


10-09-08 **100ct2008[A]05**

Hit	REV	for	Compound Name	MW.	Formula	CAS
1	909	682	2.3.4.5-TETRAH/ETHYL-5-V1NYL-2-CYCLOPENTENONE	164	C11H160	54277-22-4
2	892	563	2H-BENZIMDAZ0L-2-0NE, 1,3-OiHYDRO-5-luETHOXY- (CAS) $$ 5-WETHOXYB	164	C8H802N2	2080-75-3
3	875	499	1-.ALPHA.9-.ALPHA-DIH/ETHYL-CIS-BICYCLO(4.3.0lNON-7-EN-2-ONE	164	C11H160	77494-84-9
4	842	491	2'-HYDROXY-4',6'-DHVETHYL/CETOPHENONE IS 2-HYDROXY-4.6-DIHIETHYLA	164	C10H1202	16108-50-2
5	838	541	TRICYCLO[3.3.1.1 (3,7)]DECAN0NE, 4-IODO-, (1 .ALPHA.3.BETA.4.BETA.5.ALP	276	C10H130I	56781-86-3
6	835	520	TRICYCL0(3.3.1.1(3.7)]DECAN0NE. 440D0-. (1 ALPHA,3.BETA,4.ALPHA,5.AL	276	C10H130I	56781-85-2
7	834	655	BENZENE, 1-BUTYL-4-METH0XY- (CAS) SS BUTANE, P-ANISYL-	164	C11H160	18272-84-9
8	821	404	1-[2'-ETHENYL-1'-CYCLOHEXENYL]PROPANONE SS ETHANONE, 1-(2-ETHENY	150	C10H140	115692-14-3
9	815	776	2,5-CYCLOHEXADIENE-1,4-OIONE, 2-(1,1 -OIIVETHYLETHYL)- (CAS) SS T-BUTY	164	C10H1202	3602-55-9
10	814	721	2-ETHYL-5-N-PROPYLPHENOL SS PHENOL. 2-ETHYL-5-PROPYL- (CAS) SS 2-	164	C11H160	72386-20-0
11	813	639	BENZENE, 1-(1.1-DIN«THYLETHY1.H-METHOXY- (CAS)$$ P-TERT-BUTYLANI	164	C11H160	5396-38-3
12	809	527	3,4-DIIVETHOXYSTYRENE	164	C10H1202	0-00-0
13	805	755	1H-INDENE, 1-ETHYUDENE0CTAHYDR0-7AIVETHYL-, (1Z.3AALPHA,7ABET	164	C12H20	56324-69-7
14	802	518	TRICYCLO[3.3.1.1 (3,7)]DECANONE, 4-BROM3-, (1.ALPHA.3.BETA.4.BETA.5.A	228	C10H130Br	32456-48-7

Mintlactone

10-09-08 , 12-OCT-2008 +07:51:13

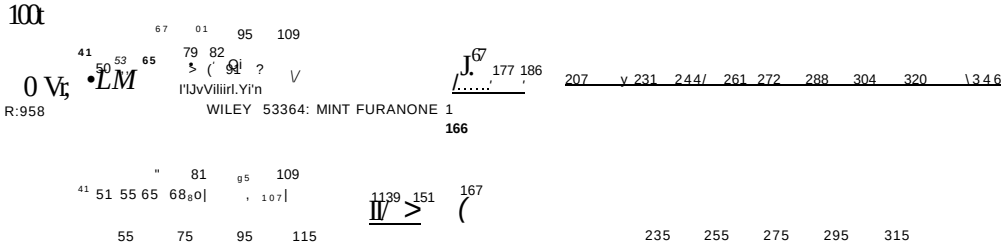


10-09-08 **100ct2008[A]05**

Hit	REV	for	Compound Name	MW.	Formula	*CPS*
1	979	568	(-HSCMNTIACTCNE	166	C10H14C2	0-00-0
2	964	621	3-IVETlHYL-4,5,6,7,8,8AALPHA-HEXfiHYORO-2H-CYCLCHEPTA{BjFURAN-2-CN	166	C10H14C2	107115-58-2
3	963	947	MNT FURANONE 2	166	C10H14C2	O-OO-O
4	962	945	MNTFURANONE1	166	C10H14C2	000-0
5	944	920	MNT LACTONE	0		0-00-0
6	944	548	(-)-MNTIACTONE	166	C10H14Q2	0-00-0
7	912	608	2-PENTYL-2-CYCL0HEXEN-1-0NE $$ ISQJASMCNEI SS PENTYL OCLCHEXE	166	C11H180	25435-63-6
8	909	459	SP!RC(2.6]NCNAN04-GNE	138	C9H140	0-00-0
9	895	669	3-N-PENTYL-2-CYCLCHEXEN-1-0NE	166	C11H180	0-00-0
10	878	597	3-PHENYL-1,4(E)-DODECADIENE	236	C17H32	0-00-0
11	878	487	5-ISCPROPYL-8-lvETHYLSPIRO(3.4)OCTAN-1-CNE	180	C12H200	57760-25-5
12	872	394	1,2-DI-NOPROPYLCYCLCBUTENE	138	C10H18	0-00-0
13	864	562	(Z)-1,5-DIMETHYLSPIRO(3.5)NCNAN-(Z)-7-ONE	166	C11H180	56063-27-5
14	858	412	3.4-DIETHYL-2.5-DIIYETHYL-2,4-HEXOIENE	166	C12H22	133795-40-1

10-09-08 12-OCT-2008 +07:51:13

rjj001186^01 5160 (39.639) 8.05e6



10-09-08 100ct2008^A05

Hit	REV	for	Compound Name	M.W.	Formula	CAS
1	981	561	(-)-ISOMINTLACTONE	166	C10H1402	0-00-0
2	964	957	MINT FURANONE 2	166	C10H1402	0-00-0
3	958	940	MINT FURANONE 1	166	C10H1402	0-00-0
4	957	605	3-METHYL-4.5.6.7.8.8A.ALPHA.-HEXAHYDRO-2H-CYCLOHEPTA1B1FURAN-2-ON	166	C10H1402	107115-58-2
5	956	547	(-)-MINTLACTONE	166	C10H1402	0-00-0
6	951	935	MINT LACTONE	0		0-00-0
7	907	590	2-PENTYL-2-CYCLOHEXEN-1-ONE 51ISOJASMONE 1 S$ PENTYL CYCLOHEXE	166	C11H180	25435-63-6
8	900	657	3-N-PENTYL-2-CYCLOHEXEN-1-ONE	166	C11H180	0-00-0
9	899	423	3.4-DIETHYL-2.5-DIMETHYL-2.4-HEXADIENE	166	C12H22	133795-40-1
10	898	437	SPIRO(2.6]NONAN04-ONE	138	C9H140	0-00-0
11	883	485	5-ISOPROPYL-8-METHYLSPIRO(3.4)OCTAN-1-ONE	180	C12H20O	57760-25-5
12	874	596	3-PHENYL-1.4(E)-DODECADIENE	236	C17H32	0-00-0
13	865	558	(Z)-1.5-DIMETHYLSPIRO(3.5)NONAN-(Z)-7-ONE	166	C11H180	56063-27-5
14	854	367	1,2-DI-NOPROPYLCYCLOBUTENE	138	C10H18	0-00-0

Trial 6

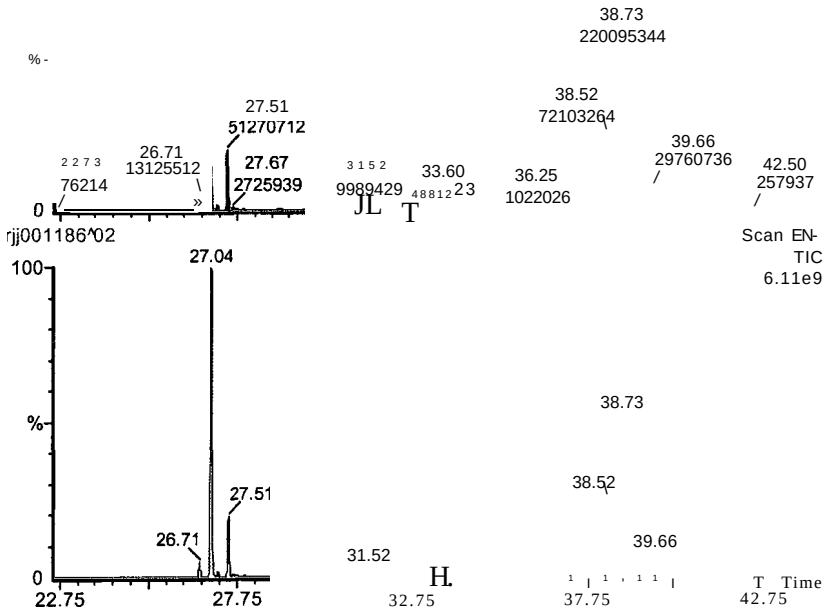
10-09-08 **12-OCT-2008 +09:01:01**

rjjO01186"02 Scan EI+

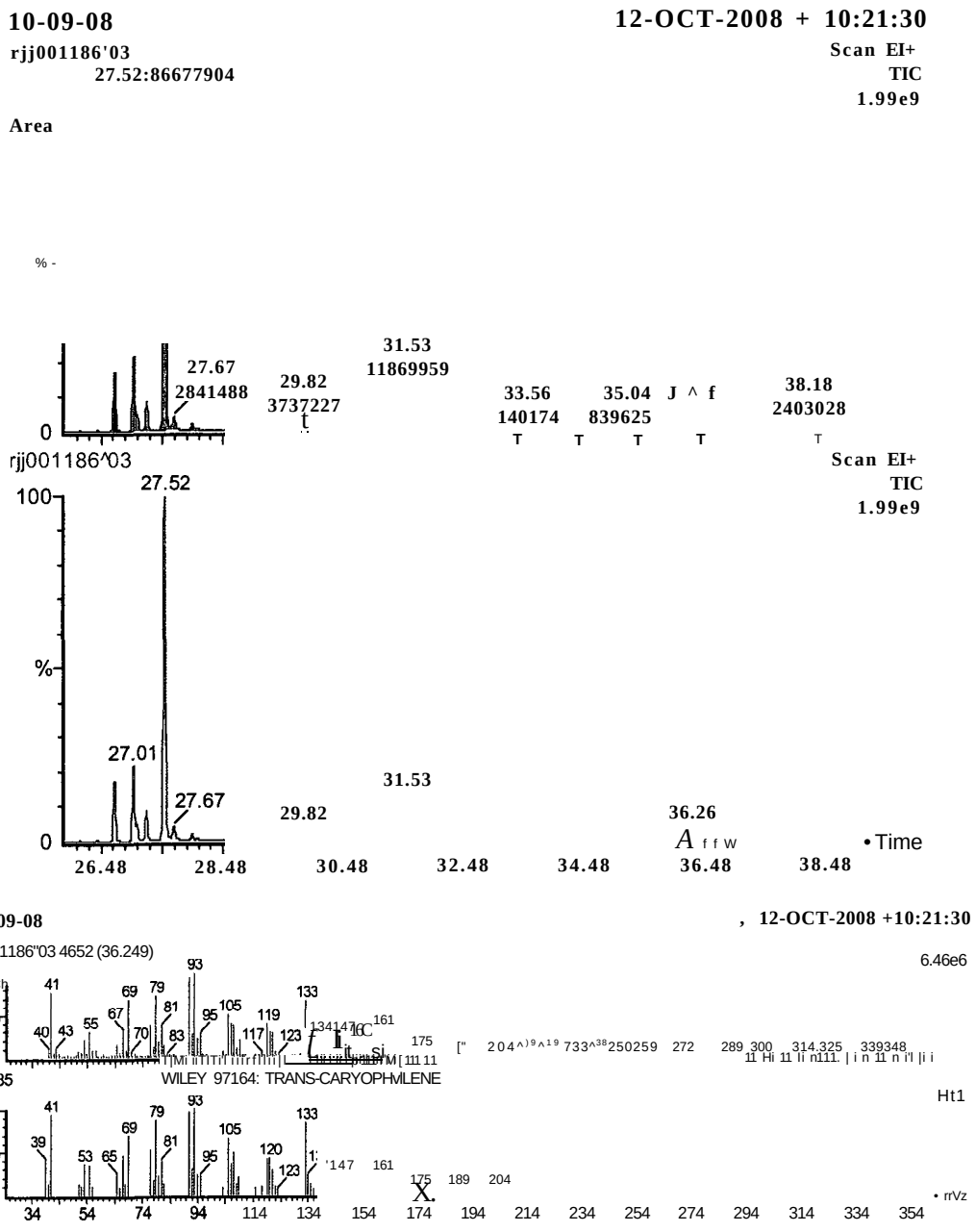
27.04;329495296 TIC

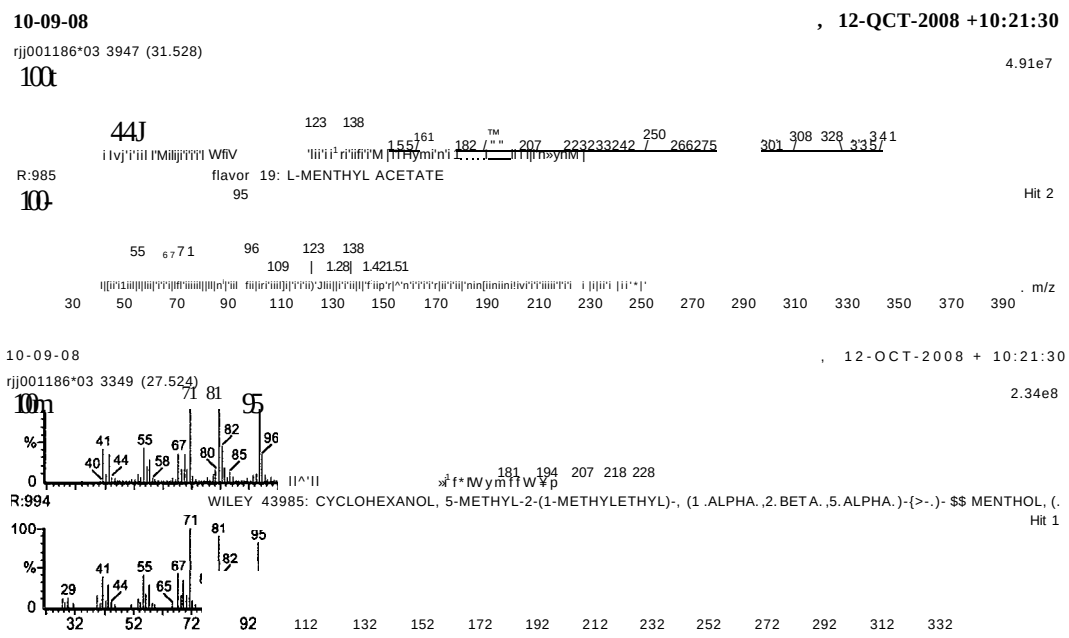
100-| 6.11e9

Area

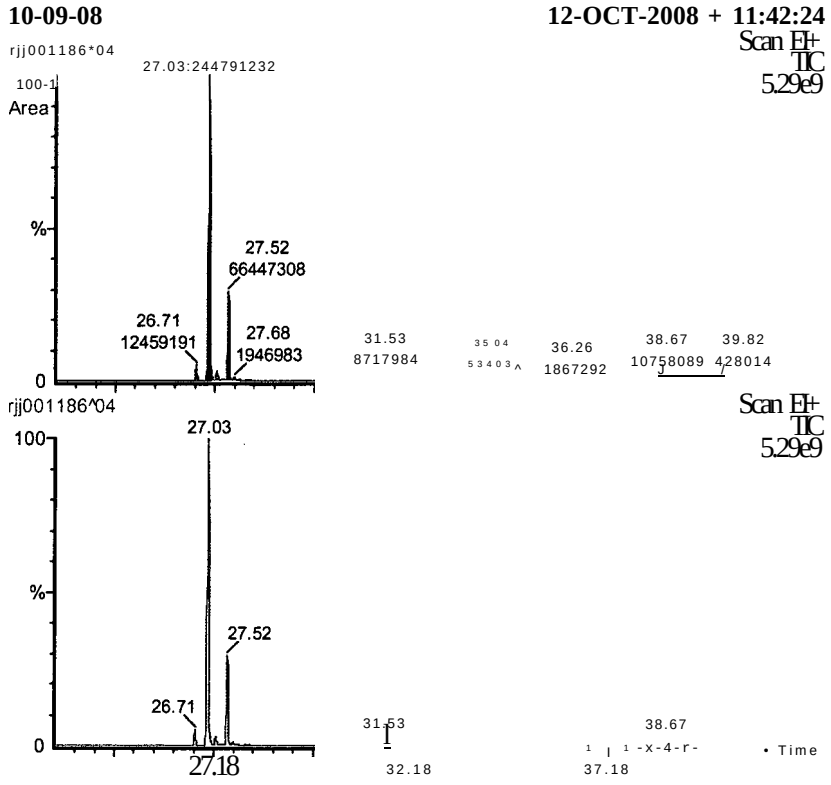


Trial 7


10-09-08
12-OCT-2008 + 10:21:30
rjj001186'03
Scan EI+
27.52:86677904
TIC
1.99e9
Area
% -
27.67
2841488
29.82
3737227
31.53
11869959
33.56
140174
35.04
839625
38.18
2403028
rjj001186^03
Scan EI+
TIC
1.99e9
100
%
0
27.52
27.01
27.67
31.53
29.82
36.26
• Time
26.48
28.48
30.48
32.48
34.48
36.48
38.48
10-09-08
, 12-OCT-2008 +10:21:30
rjj001186"03 4652 (36.249)
6.46e6
WILEY 97164: TRANS-CARYOPHMLENE
Ht1
R:985
• rrVz


10-09-08
, 12-QCT-2008 +10:21:30
rjj001186*03 3947 (31.528)
4.91e7
R:985
flavor 19: L-MENTHYL ACETATE
Hit 2
. m/z
10-09-08
, 12-OCT-2008 + 10:21:30
rjj001186*03 3349 (27.524)
2.34e8
R:994
WILEY 43985: CYCLOHEXANOL, 5-METHYL-2-(1-METHYLETHYL)-, (1 .ALPHA.,2.BETA.,5.ALPHA.)-{>-.)- $$ MENTHOL, (.
Hit 1

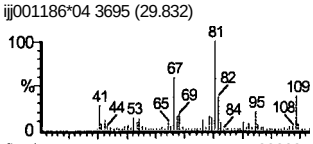
Trial 8


10-09-08
12-OCT-2008 + 11:42:24
rjj001186*04
Scan EI+
TIC
5.29e9
27.03:244791232
Area
27.52
66447308
26.71
12459191
27.68
1946983
31.53
8717984
36.26
1867292
38.67
39.82
10758089
428014
rjj001186^04
Scan EI+
TIC
5.29e9
27.03
27.52
26.71
31.53
38.67
27.18
32.18
37.18
Time

10-09-08 **, 10-QCT-2008 + 12:45:03**

ijj001186*04 3695 (29.832)

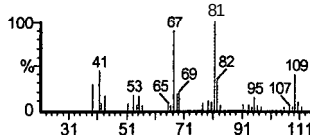
1.05e7



175 191 n a f 226 237 ^264 281 i ^ 310 327 338 z*6

R:968 WILEY 38828: PULEGONE $$ CYCLOHEXANOL, 5-IVETHyL-2-(1-WEIH»T.ETHYLIDENE)-, (R)- (CAS) $$ (+)-PULEGONE

Ht2



31 51 71 91 111 131 151 171 191 211 231 251 271 291 311 331 351

Characterization of 2^3 Experimental Design for RDA in Low Concentration Aqueous Base by GC/MS

rjjOOl 188

General Retention Times:
17.44 min N-methylmaleimide
27.10 min Menthofuran

-001. Mostly MF; some pyrrole-based by-products...

11-07-08 **11-NOV-2008 + 10:14:39**

rjj001188y01

Scan El+
TIC
1.96e10

100-1

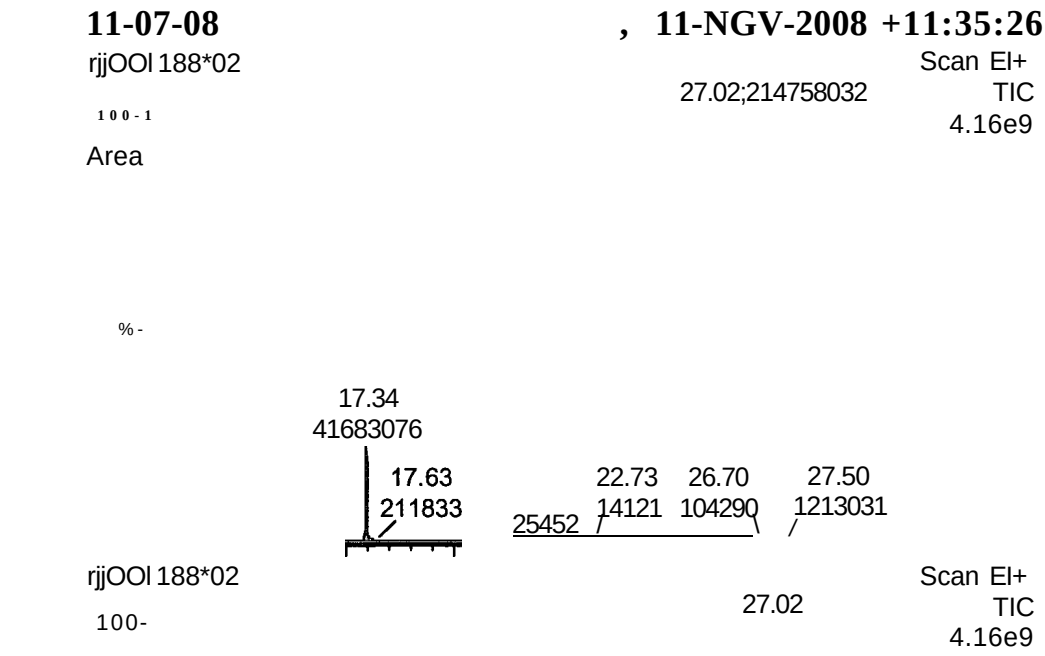
6.28
!/

27.11

% -

1111 • • <1 1 < < ii• 1111 1 1 111 1 111 1 1 1 1 1 111 1 111 111 M M |. i. i Time
15.05 25.05 35.05 45.05 55.05

-002. Clean RDA reaction.



-003. Not as clean RDA as -002.

11-07-08 **, 11-NGV-2008 + 12:56:32**

rjjOOl 188*03 Scan El+

TIC

100t 1.97e10

Area

27.09
1064919872

%H

17.43
356005920

38.67
76234896

54.27
50002172

13.53
8898046l

0 i •• i i 11 11 i[8]JL^a

rjjOOl 188*03 Scan El+

TIC

100t 1.97e10

27.09

%H

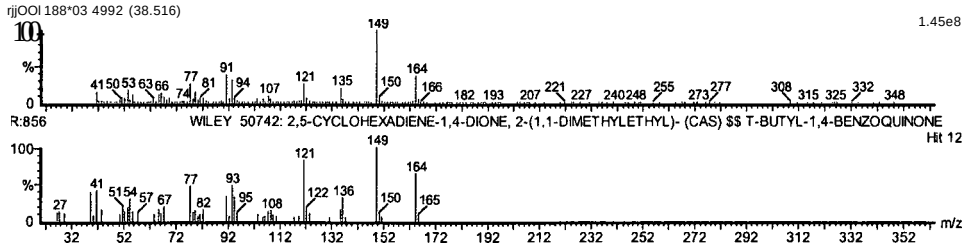
17.43

38.67 54.27

Time

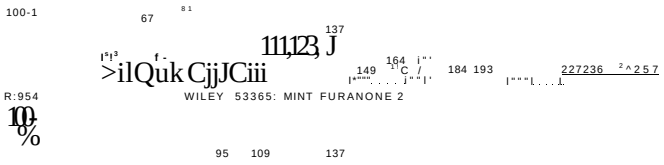
15.06 25.06 35.06 45^06 55T06

11-07-08 , ll-i\OV-2008 + 12:56:32



11-07-08 11-NOV-2008 + 12:56:32

rjj001188"03 5017 (38.683)



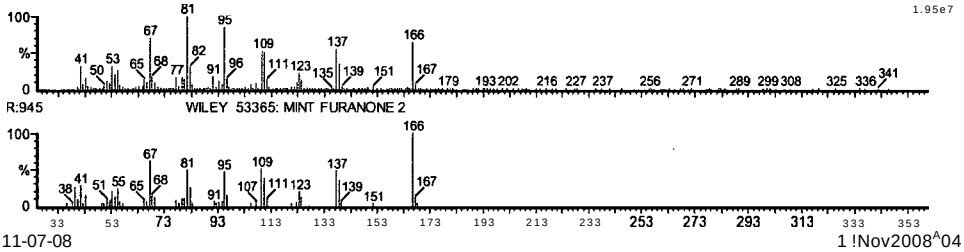
0 .A^iLM.,,*, ' j f c t k - '

11-07-08 IINov2008^04

Hit	REV	for	Compound Name	M.W.	Formula	CAS
1	955	604	3-MEtHYL-4.5,6,7,8,8A.ALPHA.-HEXAHYDR0-2H-C YCLOHEPTA[B]FURAN-2-ON	166	C1 OH1402	107115-58-2
2	954	940	MINT FURANONE 2	166	C10H1402	0-00-0
3	951	531	(-HSOMINTLACTONE	166	C10H1402	0-00-0
4	939	916	MINT FURANONE 1	166	C10H1402	0-00-0
5	933	912	MINT LACTONE			0-00-0
6	929	518	(->-MINTIACTONE	166	C10H1402	0-00-0
7	928	605	2-PENTYL-2-CYCLOHEXEN-1-ONE $S ISOJASMONE I SS PENTYI. CYCLOHEXE	166	C11H180	25435-63-6
8	906	660	3-N-PENTYI-2-CYCL0HEXEN-1-0NE	166	C11H180	0-00-0
9	900	455	(Z)-3-(1-METHYLETHYLH,3-NONADIENE	166	C12H22	0-00-0
10	899	510	5-ISOPROPYL-8-METH YLSPIR 0(3.4)OCTAN-1-ONE	180	C12H200	57760-25-S
11	895	640	3-PHENYI-1.4(E)-OODECADIENE	236	C17H32	0-00-0
12	895	453	(E)-3-(1 -ME"mYLETHYI_)-1,3-NONADIENE	166	C12H22	0-00-0
13	877	448	SPIRO{2.6]NONANQ4-ONE	138	C9H140	0-00-0
14	872	567	(Z)-1,5-DIMETHYLSPIRO{3.5)NONAN-(Z)-7-ONE	166	C11H180	56063-27-5

11-07-08 , 11-NOV-2008 + 12:56:32

rjj001188^03 5162 (39.654)

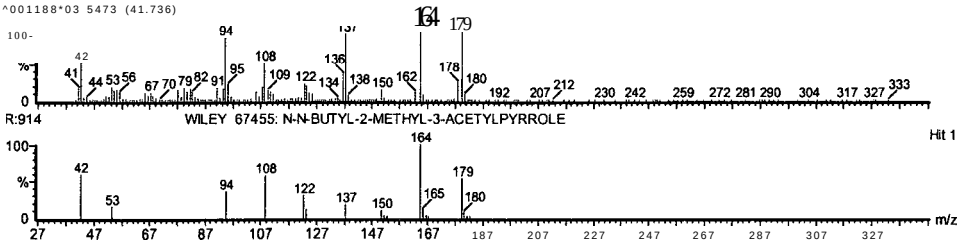


11-07-08 1 !Nov2008^04

Hit	REV	(or	Compound Name	M.W.	Formula	CAS
1	947	597	3-METHYt-4.5.67.8.8AAJ.PHA.-HEXAHYDRO-2H-CYCLOHEPTAIB]FURAN-2-ON	166	C1 OH1402	107115-58-2
2	945	923	MINT FURANONE 2	166	C10H1402	0-00-0
3	937	512	(-MSOMINTLACTONE	166	C1 OH1402	0-00-0
4	928	898	MINT LACTONE	0		0-00-0
5	928	899	MINT FURANONE 1	166	C1 OH1402	0-00-0
6	916	596	2-PENTYL-2-CYCLOHEXEN-1-ONE $S ISOJASMONE I$$ PENTYL CYCLOHEXE	166	C11H180	25435-63-6
7	905	495	(-)-MINTLACTONE	166	C1OH1402	0-00-0
8	902	660	3-N-PENTYL-2-CYCLOHEXEN-1-ONE	166	C11H180	0-00-0
9	899	646	3-PHENYL-1,4(E)-DODECADIENE	236	C17H32	0-00-0
10	885	856	2-ETHYLOECALIN	166	C12H22	0-00-0
11	879	516	54SOPROPYI-8-METHYLSPIRO(3.4)OCTAN-1-ONE	180	C12H200	57760-25-5
12	878	477	SPIRO(2.6]NONAN04-ONE	138	C9H140	0-00-0
13	872	339	2-N-BUTYL-4-VINYLCYCLOPENTANONE $S CYCLOPENTANONE, 2-BUTYL-4-E	166	C11H180	54973-10-3
14	870	421	{Z)-3-<1-METHYL ETHYL y 1.3-NONADIENE	166	C12H22	0-00-0

11-07-08 11-NQV-2008 + 12:56:32

^001188*03 5473 (41.736)



Hit	REV	for	Compound Name	M.W.	Formula	CAS
1	914	575	N-N-BUTYL-2-METHYL-3-ACETYLPYRROLE	179	C11H170N	O-OO-O
2	905	408	(1E)-2-[6'.6'-OIMETHYLCYCLOHEX-1'-ENYI}-N,N-DIWETHVLETHEN-1-YLAMINE	179	C12H21N	105962-05-8
3	894	352	(1E)-2-[2'.6'-OIMETHYICYCLOHEX-r-ENYL)-N.N-DIMETHVLETHEN-1-YIAWINE	179	C12H21N	126090-67-3
4	882	546	6,7-OIMETHYL-2.3.4,5,6.7-HEXAHVDROCYCLOPENT(B)AZEPIN-8(1H)-ONE	179	C11H170N	0-00-0
5	8/3	469	3-ETHYL-2-(1-PYRROUDINYL}-2-CYCLOPENTEN-1-ONE	179	C11H170N	0-00-0
6	799	514	2,5-DIMETHYL-1-PROPYIPYRROIE	137	C9H15N	20282-39-7
7	793	351	3,9-OIMETHYL-1.2.3,8,9,9A-HEXAHYDRO-4H-QUINOLIZIN-4-ONE	179	C11H170N	96791-39-8
6	781	407	TRANS-4,5-OiMETHYI-2-(1-PVRROLIDINYI)-2-CYCLOPENTEN-1-ONE	179	C11H170N	0-00-0
9	771	346	(3AALPHA.6AALPHA,9A6ETA)-DODECAJHYDROPYRIOO{2,1,6-DEJQUINOUZI	179	C12H21N	57194-67-9
10	757	493	3,4-OIMETHYL-2-<-J-PYRROLIDINYL)-2-CYCLOPENTEN-1-ONE	179	C11H170N	0-00-0
11	750	443	7-METHYL-2.3.4,5,6,7-HEXAHYDROPENT(B)AZEPINE-8{1H>-ONE	165	C10H150N	0-00-0
12	744	457	7-ETHYL-2.3,4.5,6.7-HEXAHYDROCYCIOPENT(B)AZEPIN-8(1H)-ONE	179	C11H170N	0-00-0
13	735	334	(1./iJ.PHA,4.ALPHA.7S>2',2 -DfMETHYLSPIRO{BICYCLO[2.2.1IHEPT-5-ENE-7,	194	C11H1403	67237-20-1
14	726	316	(2.ALPHA.3ABETA,6A8ETA,9ABETA)-DOOECAh(YDROPYRIDO[2.1.6-DE}QUI	207	C13H210N	89959-69-3

Late eluting compounds do not match anything in Wiley 7.0

-004. Very clean RDA.

11-07-08 , 11-NOV-2008 + 14:17:29

rjjOOl 188*04 Scan EI+

100-1 TIC

Area' 2.04e10

27.09
907579648

%-

17.42
335679424

6.96
7288272

28.49
4021204

52.69
1671458

0 | i i r i | i i i i | i f i i | i i i i | i i i i | i i i i |) i i i | i) i i | i i i i] 'i i M [

rjjOOl 188*04 Scan EI+

100-| 6.29 TIC

2.04e10

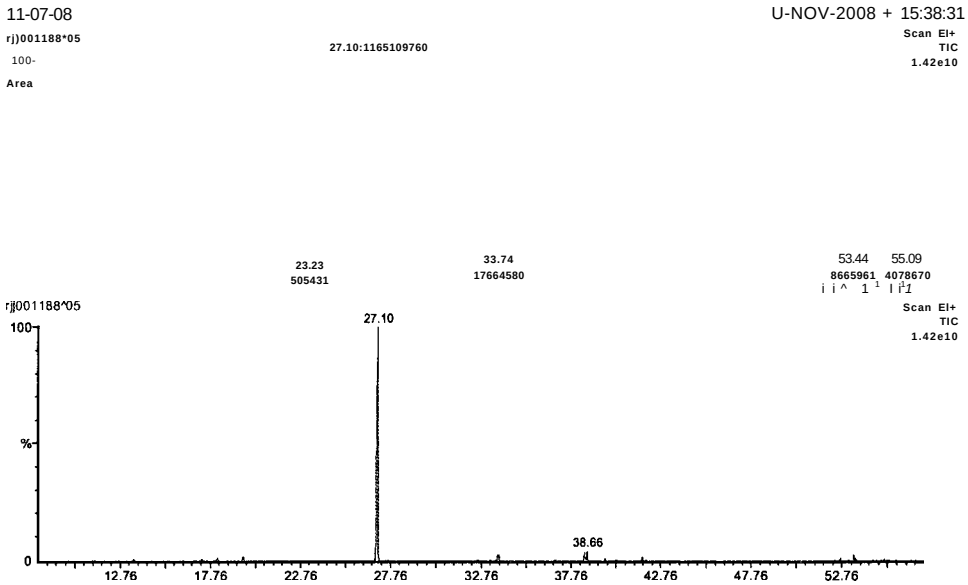
27.09

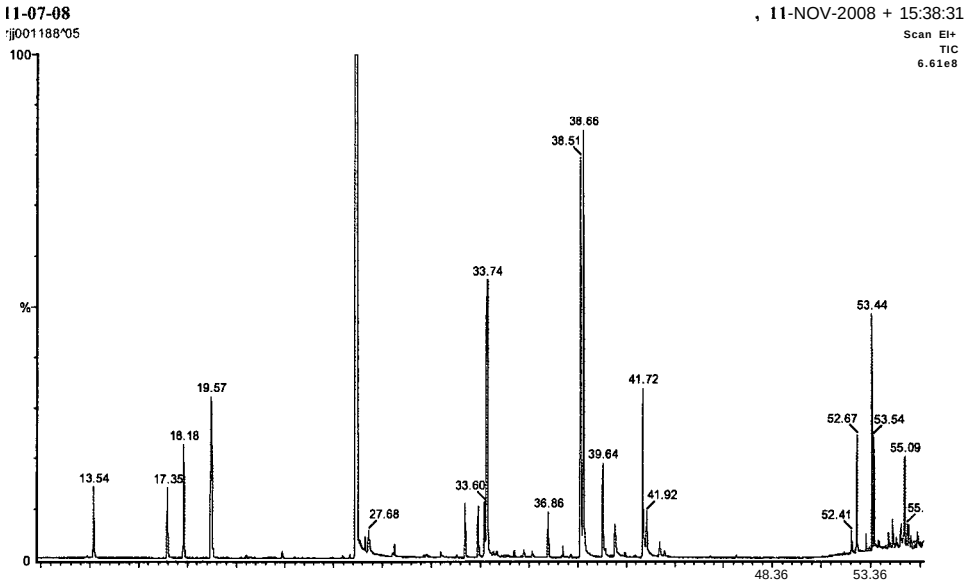
%-

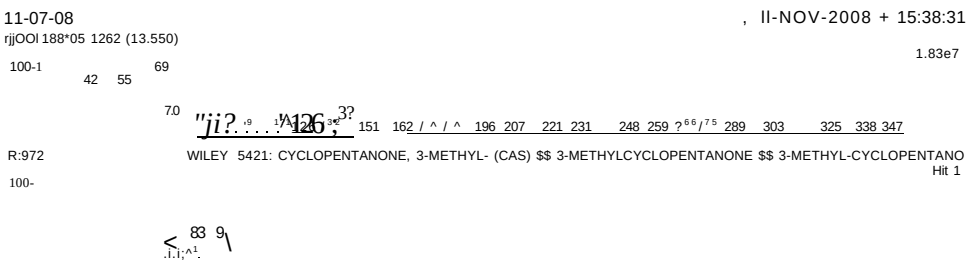
17.42

o'r.M,.., 15.05 25.05 35.05 45.05 55.05 Time

-005. Product mostly menthofuran. Lots of other pyrrole-type side products...



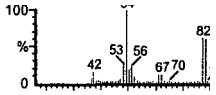




11-07-08 , ll-NOV-2008 + 15:38:31

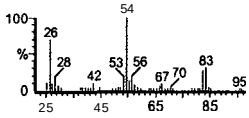
rjjOOl 188*05 1831 (17.360)

1,32e7



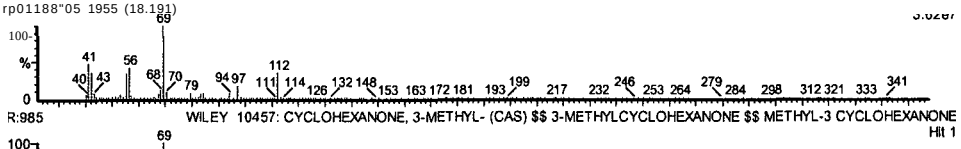
R:957 WILEY 9715: N-METHYLMALEIMIDE $$ 1H-PYRROLE-2.5-DIONE, 1-METHYL- (CAS) SS MALEIMIDE, N-METHYL-

Hit 1



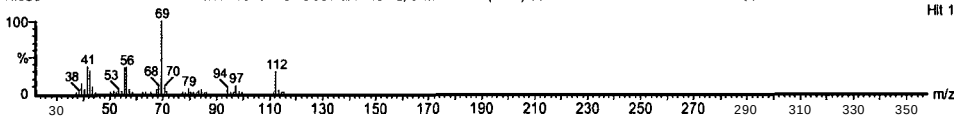
11-07-08 , 11-NQV-2008 + 15:38:31

rp01188"05 1955 (18.191)



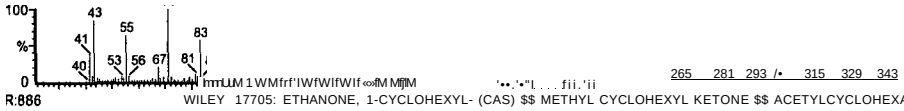
R:985 WILEY 10457: CYCLOHEXANONE, 3-METHYL- (CAS) $$ 3-METHYLCYCLOHEXANONE $$ METHYL-3 CYCLOHEXANONE

Hit 1

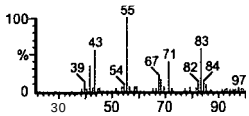


11-07-08 , 11-NQV-2008 + 15:38:31

rjjOOl 188*05 2161 (19.570)



R:886 WILEY 17705: ETHANONE, 1-CYCLOHEXYL- (CAS) $$ METHYL CYCLOHEXYL KETONE $$ ACETYLCYCLOHEXANE



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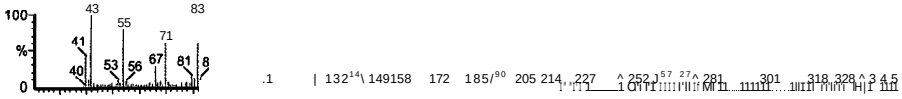
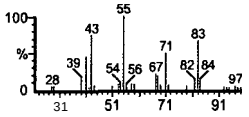
rjj001188*05 2170 (19.630)



R:942 WILEY 17707: ETHANONE, 1-CYCLOHEXYL- (CAS) $$ METHYL CYCLOHEXYL KETONE $$ ACETYLCYCLOHEXANE



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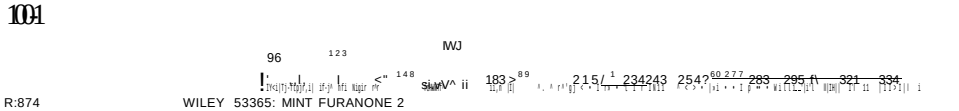
rjJ001188*05 4281 (33.765)



R:874 WILEY 53365: MINT FURANONE 2

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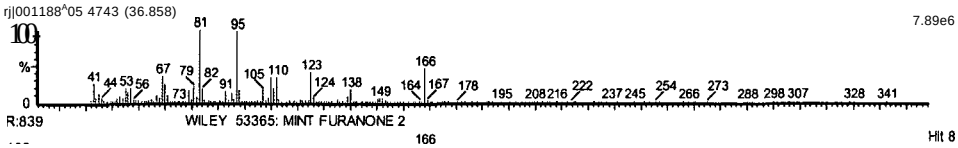
rjl001188^05 4743 (36.858) 7.89e6



11-07-08 1 INov2008^06

Hit	REV	for	Compound Name	M.W.	Formula	CAS
7	842	660	7-METHYLSPWCHS.4) DECAN-3-ONE	166	c i A m a o	0-00-0
8	839	748	MINT FURANONE 2	166	C10H14O2	0-00-0
9	837	478	(1S,3S)-2,2,3-TRIMETHYL-6-M€THYLIOENECYCLOHEXANE-1-CARBALOEHYD	166	C11H180	0-00-0
10	835	733	NAPHTHALENE, DECAHYDRO-1,6-DIMETHYL- (CAS) SS 1,6-DIMETHYL DECALI	166	C12H22	1750-51-2
11	826	556	3-N-PENTYL-2-CYCL0HEXEN-1-0NE	166	C11H180	0-00-0
12	826	486	2-PENTYI-2-CYCL0HEXEN-1-0NE $$ iSOJASMONE I $$ PENTYL CYCLOHEXE	166	C11H180	25435-63-6
13	825	418	2-METHYL-2-CYCLOOCTENONE S$ 2-CYCLOOCTEN-1-ONE, 2-METHYI- (CAS)	138	C9H140	70527-95-6
14	819	538	DEHYDROIRIDOOiAL S$ 2-CYCLOPENTENE-1-ACETALDEHYDE, 2-FORMYL-.A	166	C10H14O2	66884-89-7
15	817	434	3-METHYLENE-1-UNDECENE	166	C12H22	0-00-0
16	816	728	MINT LACTONE	0		0-00-0
17	815	727	MINT FURANONE 1	166	C1OH1402	0-00-0
18	814	721	{4R,5R,9S)-5,9-DIMETHYISPIRO(3.5)NONAN-1-ONE	166	C11H180	64070-08-2
19	811	446	5-ISOPROPYL-8-METHYLSPIRO(3.4)OCTAN-1-ONE	180	C12H200	57760-25-5
20	811	447	(E)-2.4.4-TRIMETHYL-2.5-HEPTADIENE	138	C10H18	116786-15-3

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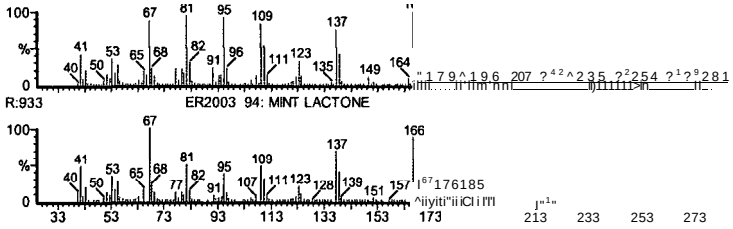
rjJOOl 188*05 5012 (38.659) Cm (5006:5018-(4960:4970+5039:5051)) 2.41 e7



11-07-08 IINov2008^06

Hit	REV	for	Compound Name	M.W.	Formula	CAS
1	963	535	(-)-ISOMINTLACTONE	166	C10H1402	0-00-0
2	961	599	3-METHYT.-4,5,6,7.8,8A.ALPHA-HEXAHYDRO-2H-CYCLOHEPTA{BIFURAN-2-ON	166	C10H1402	107115-58-2
3	949	919	MINT FURANONE 2	166	C1OH1402	0-00-0
4	946	916	MINT FURANONE 1	166	C10H1402	0-00-0
S	936	520	(-)-MINTLACTONE	166	C10H1402	0-00-0
6	933	893	MINT LACTONE	0		0-00-0
7	918	590	2-PENTYL-2-CYCLOHEXEN-1-ONE $$ ISOJASMONE I $S PENTYL CYCLOHEXE	166	C11H180	25435-63-6
8	899	647	3-N-PENTYL-2-CYCLOHEXEN-1-ONE	166	C11H180	0-00-0
9	897	458	SPIRO(2.6]NONAN04-ONE	138	C9H140	0-00-0
10	896	507	5-ISOPROPYL-8-METHYLSPIRO(3.4)OCTAN-1-ONE	180	C12H200	57760-25-5
11	882	609	3-PHENYL-1,4(E)-DODECADIENE	236	C17H32	0-00-0
12	874	557	(Z)-1.5-DIMETHYLSPIRO(3.5)NONAN-(Z)-7-ONE	166	C11H180	56063-27-5
13	868	432	(Z)-3-(1-METHYLETHYL)-1.3-NONADIENE	166	C12H22	0-00-0
14	864	450	EPOXYPINENE	154	C10H180	0-00-0

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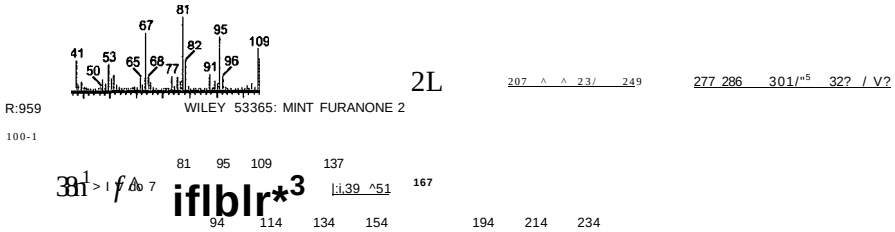
rjj001188*05 5159 (39.643) 1.30e7



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Hit	REV	for	Compound Name	M.W.	Formula	CAS
1	963	553	(-HSOMINTIACTONE	166	C10H1402	0-00-0
2	959	946	MINT FURANONE 2	166	C1OH1402	0-00-0
3	954	620	3-METHYL-4,5.6,7.8.8AALPHA-HEXAHYDRO-2H-CYCLOHEPTA(B]FURAN-2-ON	166	C10H1402	107115-58-2
4	946	926	MINT FURANONE 1	166	C10H1402	0-00-0
5	941	922	MINT LACTONE	0		0-00-0
6	929	534	{-}-MINTLACTONE	166	C1OH1402	0-00-0
7	916	615	2-PENTM-2-CYCLOHEXEN-1-ONE SS ISOJASMONE I SS PENTYL CYCLOHEXE	166	C11H180	25435-63-6
8	897	670	3-N-PENTYL-2-CYCL0HEXEN-1-ONE	166	C11H180	0-00-0
9	895	456	SP!RO[2.6JNQNAN04-ONE	138	C9H140	0-00-0
10	888	506	5-ISOPROPYL-8-METHYLSP!RO{3.4)OCTAN-1-ONE	180	C12H200	57760-25-5
11	878	610	3-PHENYL-1,4(E)-OODECADIENE	236	C17H32	0-00-0
12	876	444	(Z)-3-{1-METHYL ETHYL M.3-NONADIENE	166	C12H22	0-00-0
13	872	442	(E)-3-(1-METHYLETHYL)-1.3-NONAOIENE	166	C12H22	0-00-0
14	868	408	1,2-OI-NOPROPYLCYCLOBUTENE	138	C10H18	0-00-0

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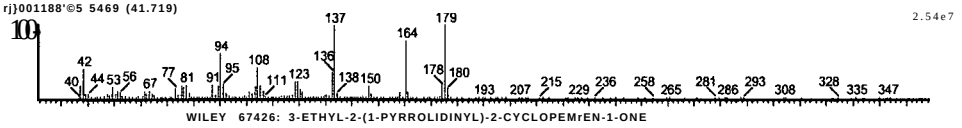
rj}001188'©5 5469 (41.719)



WILEY 67426: 3-ETHYL-2-(1-PYRROLIDINYL)-2-CYCLOPEMrEN-1-ONE

136

164 179

70 150

J c

34 54 334 354

11-07-08 11NOV2008^06

Hit	REV	for	Compound Name	M.W.	Formula	CAS
1	892	478	3-ETHYL-2-(1-PYRR0LIDINYL)-2-CYCL0PENTEN-1-0NE	179	C11H170N	0-00-0
2	891	558	6,7-D!METHYL-2,3,4.5,6.7-HEXAHYDROCYCLOPENT(B)AZEPIN-8(1H)-ON£	179	C11H170N	0-00-0
3	887	573	N-N-SUTYL-2-METHYL-3-ACETYLPYRROLE	179	C11H170N	0-00-0
4	868	393	3,9-DIMETHYL-1,2.3,8,9,9A-HEXAHYDRO-4H-QUINOLIZiN-4-ONE	179	C11H170N	96791-39-8
5	813	505	7-ETHYL-2,3,4,5,6.7-HEXAHYDROCYCLOPENT(B)AZEPIN-8(1H)-ONE	179	C11H170N	0-00-0
6	796	397	(3AALPHA,6AALPHA,9ABETA.)-DODECAHYDROPYRIOO[2,1.6.0EjOUINOLIZI	179	C12H21N	57194-67-9
7	791	404	TRANS-4.5-DIMETHYL-2-(1-PYRROLIDINYL)-2-CYCLOPENTEN-1-ONE	179	C11H170N	0-00-0
8	755	503	3.4-D!METHYL-2-(1-PYRROL IDINYL)-2-CYCLOPENTEN-1-ONE	179	C11H170N	0-00-0
9	746	356	3-METHYL-2-(1-PYRROLIDINYL)-2-CYCLOPENTEN-1-ONE	165	C10H150N	0-00-0
10	738	611	1H-AZEPINE-2.5-010NE. 4-IS0PR0PYL-7-METHYL- (CAS)	179	C10H1302N	10315-42-1
11	733	426	7-METHYL-2,3.4,5.6,7-HEXAHYDROPENT(B)AZEPINE-8(1H)-ONE	165	C10H150N	0-00-0
12	728	348	(2.ALPHA,3ABETA.6ABETA,9A.BETA)-DODECAHYDROPYRIDO[2,1,6-DE]QUI	207	C13H210N	89959-69-3
13	700	337	(1.ALPHA.4ALPHA,7S*)-2',2'-DIMETHYLSPIRO[BICYCLO(2.2.1]HEPT-5-ENE-7.	194	C11H1403	67237-20-1
14	694	428	MALTOXAZINE SS 8-OXO-1,2,3,3A,5,6,7.8-OCTAHYDRO-CYCLOPENTAJD]PYRR	179	C10H1302N	80933-73-9

-006. Very clean RDA reaction.

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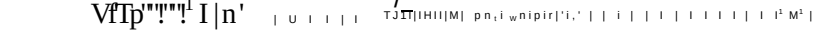

rjj001188*06 Scan El+
6.28 TIC
100-1 2.05e10

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15.05 25.05 35.05 45.05 55.05

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