INVESTIGATIONS

INTO

THE

REACTIONS

OF

ENAMINES AND IMINES

by

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DECLARATION

The experimental work described in this thesis was carried out in the Department of Chemistry, University of Natal, Durban on a full–time basis from February 1985 to December 1986 and on a part–time basis from then until December 1990 under the supervision of Prof. P.W. Hickmott.

These studies represent original work by the author and have not been submitted in any other form to another University. Where use was made of the work of others it has been duly acknowledged in the text.

Signed: 

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I hereby certify that the above statement is correct.

Signed: 

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ABSTRACT

The alkylation of 2–methylcyclohexanone imines using methyl acrylate has been investigated with a view to optimising the reaction conditions.
The mechanism of this alkylation reaction has been investigated and it has been shown that the alkylation does not proceed *via* a 2,6–intermediate which subsequently undergoes a rearrangement to the 2,2–product, but rather proceeds directly to the 2,2–product.

As it had been shown that the alkylation of 2–substituted cyclohexanone imines in dry methanol occurred at the more substituted position, it was decided, in the light of certain apparently anomolous patent work, to investigate the alkylation of unsubstituted cyclohexanone imines using a variety of electrophilic alkenes. The results show that in certain instances, 2,2–bis–alkylation occurs and in others, mono–alkylation and that it is the strength of the electron–withdrawing group attached to the alkene which determines whether 2,2–bis–alkylation occurs or not. The reasons for this are discussed in the text. The preparation of a number of novel 2,2–bis–cyclohexanones and an octahydroquinoline are described.

The reaction of 1–phenyl–2–propen–1–one (phenyl vinyl ketone) with the benzylamine imines of 2–butanone and 1–phenyl–2–propanone in methanol gave gave two novel bicyclic diones, whereas the reaction between the benzylamine imine of 3–pentanone with 1–phenyl–2–propen–1–one gave only mono–cyclic products only even though there appeared to be no

impediment to the formation of the bicyclic compound. The structures were determined using nuclear magnetic resonance and confirmed by X–ray crystallography. The reaction between 1–phenyl–2–propen–1–one and N–(1–phenyl–1–ethylidene)benzylamine gave after hydrolysis only the mono–substituted product, 1,5–diphenyl–1,5–pentandione.

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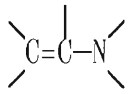
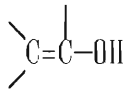
CHAPTER 1

1. INTRODUCTION

Since Stork's[1,2,3] papers on the preparation and reactions of enamines, considerable attention has been paid to the field of enamine chemistry. Enamine reactivity had been known since 1883 when first Collie,[4] then Benary[5] and later Robinson[6] described the C–alkylation or acylation of aminocrotonic esters, but it is without doubt the pioneering work of Gilbert Stork which made researchers the world over aware of the potential of this reaction of enamines with a wide variety of electrophilic reagents. Reviews[7,8] on enamines and their chemistry have been published in the past. To date the most comprehensive reviews on the field have been those of Hickmott.[9,10,11] The term enamine was introduced by Wittig and Blumenthal,[12] in 1927, to refer to the unsaturated amine structure which is analogous to an enol.



enamine



enol

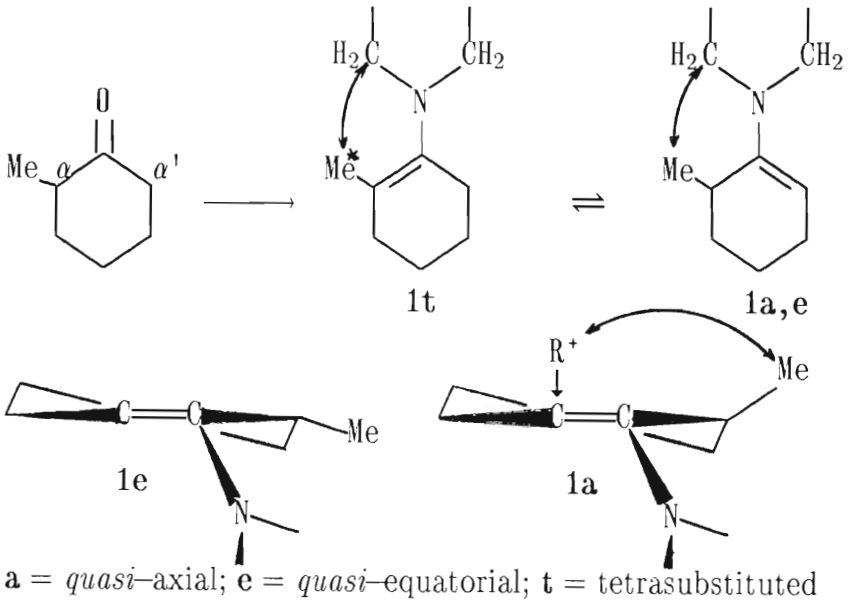
The amino–group may be primary, secondary or tertiary. Until recently the latter has been by far the most important of the three to synthetic organic chemistry. This is because the primary and secondary enamines normally exist as the imine or Schiff base, unless they are further stabilised by conjugation. A permanent polarisation of the enamine molecule results from interaction between the lone–pair orbital of the nitrogen and the π–electrons of the double bond, thus increasing the electron density at the β–carbon:

This may be clearly seen in the proton nuclear magnetic spectra of the various cyclohexanone enamines. The proton attached to the α–carbon is

shielded and because of this appears up–field (δ 4,1 – 4,6) compared to the olefinic proton signal of cyclohexene (δ 5,6). The enamine is thus an ambident nucleophile and as a result of this permanent polarisation, may be attacked both at the β–position and the nitrogen (to varying degrees). The Stork alkylation, as this reaction has become known, refers to the C–alkylation and acylation of a carbonyl carbon via an enamine intermediate. The enamine reaction provides a remarkable synthetic method which provides both a mild and reliable method for the mono–alkylation and mono-acylation of carbonyl compounds. One of the major advantages of the enamine synthesis over other methods for carbon–carbon bond formation, is that it nearly always produces the mono–alkylated/ acylated product and is relatively free of O–substituted and di-substituted impurities. The scope of the Stork reaction has been greatly expanded since Stork's initial publication.[1] Further publications by Stork *et al.* alone cover tosylation of enamines,[13] the synthesis of bridged bicyclic compounds and ring enlargement,[14] heterocyclic synthesis,[15,16] natural product synthesis,[17] and the formation and reaction of metallo–enamines.[18] It has been shown that the Stork reaction is critically dependent on the conditions under which the reaction is carried out. Factors such as: changes in solvent, amine moiety in the enamine, temperature and catalysts, to name but a few, may affect the path taken by the reaction. Because such changes produce such a diversity of products, Hickmott[9] has proposed an extension to the definition of the Stork reaction to include "**conversion of an aldehyde or ketone into a C–alkylated, acylated, carbocyclic or heterocyclic derivative by reaction of an electrophile with an enamine intermediate.**" The stereoselectivity or regioselectivity of an enamine reaction may also be altered by changes in the experimental conditions. Before the factors affecting stereo– and regioselectivity may fully be understood, it is necessary to consider certain aspects concerning the structure of enamines in general.

2. Structure and Reactivity

Before one can fully appreciate the significance of this work, it is essential to consider the *normal* enamine reaction in more detail. Unsymmetrical ketones, such as the 2–alkylcyclonones and branched acyclic ketones, produce mixtures of structurally isomeric enamines. These isomers have been shown to undergo rapid acid catalysed equilibration. Neither purely thermal or purely base catalysed equilibration has been observed, even after one week in pyrrolidine at 80°.[19]



a = *quasi*–axial; **e** = *quasi*–equatorial; **t** = tetrasubstituted

Scheme 1.

The amine used determines the isomeric distribution. Pyrrolidine enamines of 2–methylcyclohexanones occur < 10% in the more substituted form **1t**, whereas morpholine enamines occur from 30 – 65% in the more substituted form **1t** in the enamine mixture.[19] Only isomer **1t** resulted when optically active (+)–methylpiperidine formed the enamine with 2–methylcyclohexanone. Similar differences are noted between the enamines formed from pyrrolidine and morpholine with both 2–alkoxycyclohexanones and 3–alkoxy–*trans*–decal–2–ones.[20] Such differences can be attributed to the

different conjugating and steric requirements of the amine moiety. This must be larger than that of a phenyl group because the enamines of 1–phenylindan–2–one[21] and propiophenone[22] have the phenyl group twisted out of the plane of the double bond. (The latter has the E-configuration). The fact that the equilibrium:

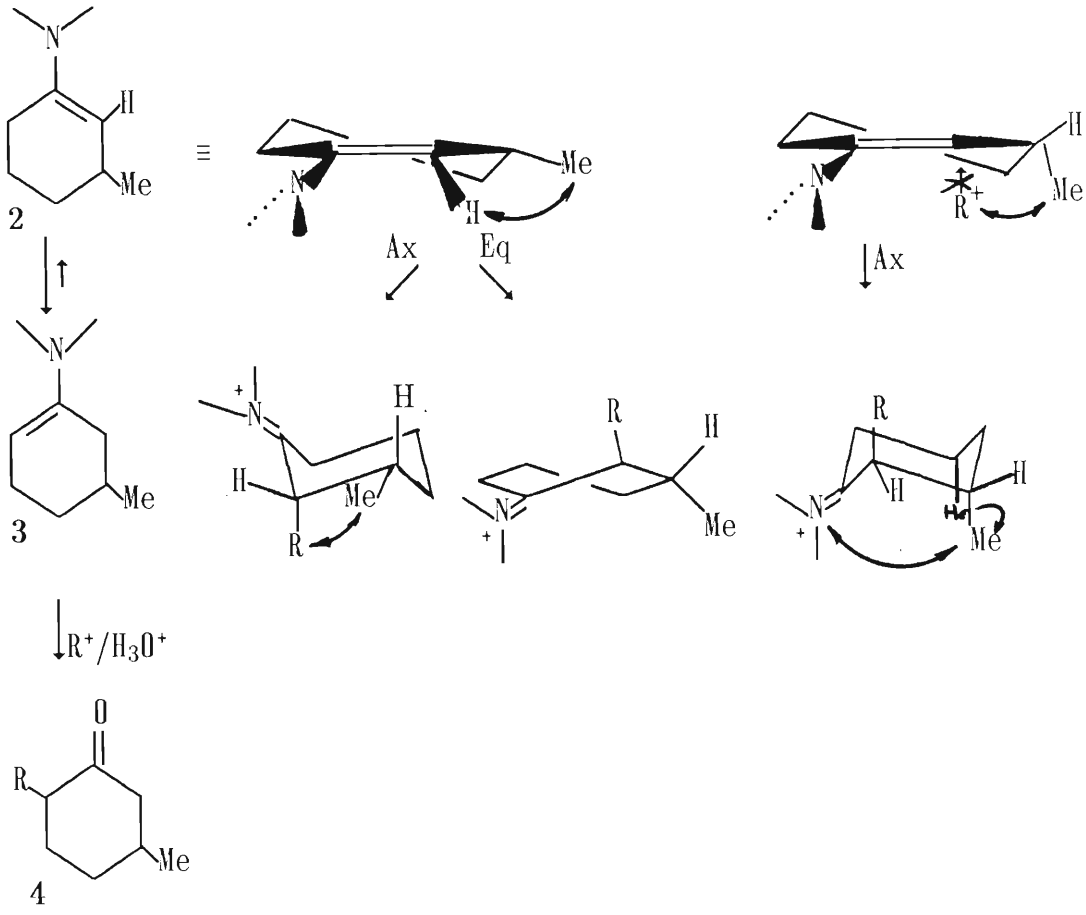
$$trans\text{–}C_6H_5CH{=}CHCH_2NMe_2 \rightleftharpoons trans\text{–}C_6H_5CH_2CH{=}CHNMe_2$$

lies 90% towards the enamine illustrates this point very well. This study also showed that the dimethylamino substituent stabilised the double bond more effectively than did either the acetyl or n–butylsulphonyl substituents. The isomer in the more substituted form **1t** contains a tetrasubstituted double bond and hence is destabilised by large steric interactions. This interaction was termed allylic strain ($A^{1,3}$) by Johnson.[23] The steric interference between the methyl group and the α–methylene groups arises if the groups are coplanar. This means that the interaction could be reduced if there were rotation about the N–C(sp^2) bond. This however would reduce the orbital interaction between the nitrogen lone pair and the π–electrons of the double bond. Clearly, a compromise situation must be achieved in order to balance the condition for such interaction between the lone pair and the double bond and the requirement of lowest energy. The less substituted form of the enamine can exist in two possible conformations which may be termed quasi–axial and quasi–equatorial (**Scheme** 1: **1a** and **1e** respectively). Conformer **1e** is destabilised by the less severe allylic ($A^{1,2}$) strain[23] and so the most stable isomer is **1a** provided all other factors remain the same. This has several important consequences.

α,α–Disubstitution of ketones *via* their enamines is not usually observed because the methylene group of the amine moiety and the methyl group in **1t** (marked with an asterisk in **Scheme** 1: **1t**) must become coplanar[3] in order for maximum interaction between the lone pair orbital on the nitrogen and the π–orbital of the double bond to occur. A product–like transition

state would thus be destabilised by increasing $A^{1,3}$–interactions. The net result is that further alkylation or acylation of such a system occurs at the less substituted α'–position of the ketone *via* **1a**. As would be expected, the rate of substitution is reduced because of the development of 1,3–diaxial interactions, as shown in **1a**. If attack occurs from the equatorial direction towards the double bond, then the development of steric interactions associated with a boat or twist conformation may also reduce the rate of substitution. Hickmott[24] considers that axial attack on the quasi–equatorial conformer **1e** is a higher energy process than such attack on the quasi–axial conformer **1a** because of the developing $A^{1,3}$–interactions. It also appears the equatorial attack is less favoured.

With compounds such as *cis*–4–t–butyl–2–methylcyclohexanone, the equatorial 2–substituent cannot be converted into the axial conformer by ring–flipping, due to the 1,3–diaxial strain, and as a result epimerisation to the *trans*–isomer occurs, which provides a method for the conversion of the more stable *cis*–diequatorial 2,4–disubstituted cyclohexanone to the less stable *trans*–isomer.[19] However, this is not the case with the 2,6–di-substituted cyclohexanones, since protonation of the resulting enamine is non-stereoselective and a *cis–trans* mixture of ketones results on hydrolysis. Allylic strain also accounts for the fact that the enamines of 3–methyl-cyclohexanones exist mainly as isomer **3** in **Scheme 2** overpage.[25]

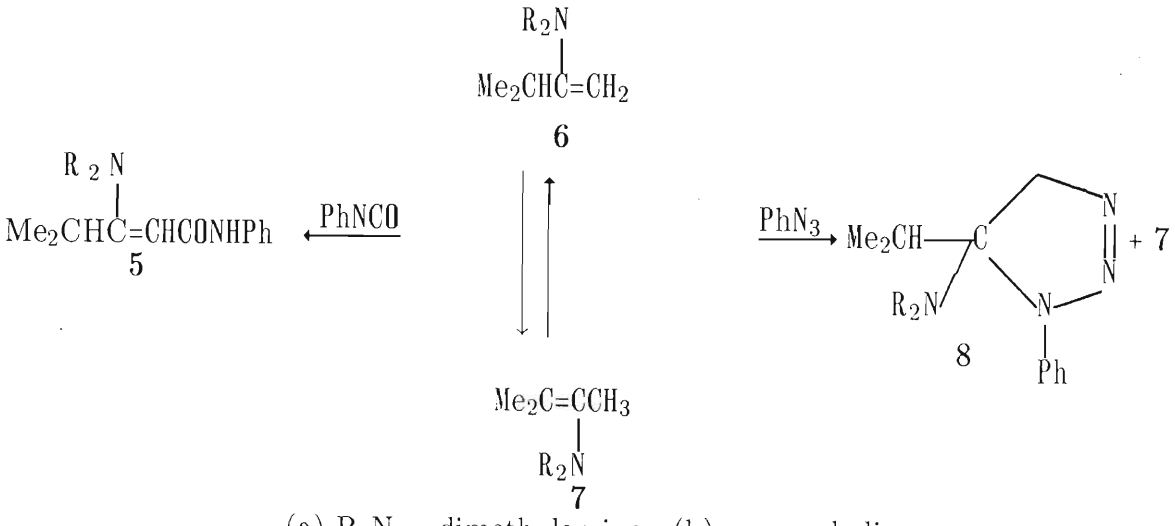


Ax = axial attack of electrophile R^+; Eq = equatorial attack.

Scheme 2.

Of course, the regioselectivity of the enamine reactions cannot be attributed to the isomer distribution of the enamines *per se*. From the Curtin-Hammett principle,[26] it follows that if the activation energy of the reaction is larger than the barrier to isomer interconversion, the product distribution must reflect the transition state energies rather than the ground–state isomer populations. For example, the 2,5–disubstituted cyclohexanones have been obtained in yields much higher than the percentages of the isomer **3** present[3] in the parent enamines,[27] which clearly demonstrates the rapid equilibrium between the enamine isomers. Certainly, in the case of reactions which involve product–like transition states, the formation of 2–substituted 3–methylcyclohexanones *via* isomer **2** will be inhibited by the developing steric interactions shown in **Scheme 2.**

Acyclic enamines also show the same trends. Pocar *et al.*[28] demonstrated unequivocally that the less substituted enamine is the more reactive of the two and that interconversion of enamine isomers may or may not occur during a reaction, depending upon the reagent and experimental conditions used. An example of this is the dimethylamine enamine of methyl isopropyl ketone which exists as a 50:50 mixture of **6** and **7** (**Scheme 3**). However reaction with phenylisocyanate gives only the 3–dimethylamino–4-methyl-2-pentenoic acid anilide **5** in 100% yield. In the given circumstances, the more substituted isomer **7** is deactivated by $A^{1,3}$–strain and rearranges to the more reactive less substituted form **6**. If however an equilibrium mixture of **6** and **7** is treated with 4–nitrophenylazide at room temperature, in an amount equivalent to the less substituted isomer **6**, only the triazoline **8** is obtained, and the isomer **7** may be isolated unchanged, by rapid distillation.[29]



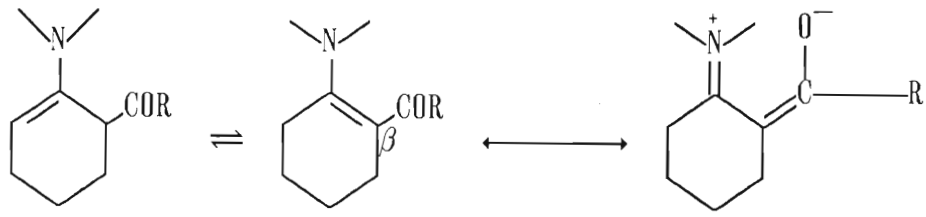
(a) R_2N = dimethylamino; (b) = morpholino

SCHEME 3

It is thus surprising that bromination of unsymmetrical enamines occurs at the more and the less substituted positions. This tends to suggest that the bromination reaction has a reactant–like transition state in which the

aforementioned steric interactions are less strongly developed.[30]

Cyclopropyl methyl ketone enamines exist only in the less substituted form[31] whereas cyclohexyl methyl ketone enamines exist as a 25:75 mixture of the more and less substituted forms, respectively.[32] It is interesting to note that only the less substituted forms react with diethyl azodicarboxylate, phenylisocyanate, mesyl chloride and β–nitrostyrene,[33] as would be expected for a reaction involving a product–like transition state.



9 10 11

SCHEME 4

R = Me, OMe, OEt, Ph, NHPh

In the case of acylated enamines an equilibrium mixture of the more and the less substituted forms (**10** and **9** respectively) again results, with the isomer distribution again being dependent on the amine moiety in the enamine. In this instance, it is the pyrrolidine enamine which exists mainly in the more substituted (or conjugated) form, **10**. The converse is true for the morpholine and piperidine enamines, which usually exist in the less substituted (or non-conjugated) form, **9**.[34,35] An important difference with the more substituted acyl enamine **10** is that further reaction with electrophiles tends not to take place at the β–carbon, but at the oxygen atom (as **11**).[36,37]

The main factors which appear to determine the reactivity of an enamine are the amine moiety and the degree of substitution at the α– and β–positions. Alkyl substituents at the C–α position increase the electron

density[38] and also the reactivity at the C–β position, *via* hyperconjugative and inductive effects, unless steric interactions prevent or reduce the lone pair interaction. On the other hand, steric and electronic effects of β–substituents decrease the reactivity at C–β. The order of reactivity therefore is normally:

$R_2NC(R)=CH_2 > R_2NC(R)=CHR > R_2NCH=CHR > R_2NCH=CR_2$.

Aldehyde enamines, which tend to react preferentially at the nitrogen, are thus less readily C–alkylated than cyclic and acyclic ketone enamines, and the enamine of acetone was considered to be too reactive to be isolated until relatively mild methods of enamine synthesis were developed recently.[9]

It would appear from spectroscopic evidence[39] that the reactivity varies with ring size of the ketone in the order 5 > 12 > 8 > 6 > 7.

Pyrrolidine enamines are markedly more reactive that the enamines of other secondary amines[3,40,41] This is attributed to the increased orbital interaction of the nitrogen lone–pair in the enamine. Reduced stereo-selectivity of the pyrrolidine enamines, spectroscopic and X–ray crystallographic evidence[42,43,44] all provide further evidence for this interaction. Attempts to increase this reactivity still further by introducing additional heteroatoms into the amine moieties within the enamines, was without success.[9]

3. SPECTROSCOPIC DATA

3.1 INFRA–RED SPECTRA

Enamines show medium to strong absorptions in the region 1 610 – 1 675 cm^{-1}. Should the enamine be protonated to give the iminium salt, then the absorption shifts to higher wave numbers (1 640 – 1 690 cm^{-1}).[45]

With 2–methylcyclohexanone enamines, the more substituted double bond isomer absorbs at longer wave numbers (1 668 – 1 675 cm^{-1})[19] than the less

substituted isomers (1 635 – 1 640 cm^{-1}).

3.2 ULTRAVIOLET SPECTRA

Ultraviolet (UV) absorption occurs in the range 220 – 230 nm (ϵ 4 000 – 10 000)[45] for both the free enamines and their iminium salts. N–Protonation results in a hypsochromic shift to shorter wavelengths (*i.e.* 198 nm).

3.3 MASS SPECTRA

Enamines show M – 1, M^+ and M + 1 ions, but the base peak is usually that of the eniminium ion[46] which forms as follows:

$$R_2\overset{+}{N}\text{–}CH\text{=}CH\text{–}CH_2\text{–}R \longrightarrow R_2\overset{+}{N}\text{=}CH\text{–}CH\text{=}CH_2 + R^{\cdot}$$

3.4 PROTON NUCLEAR MAGNETIC RESONANCE

The β–olefinic ^{1}H–NMR chemical shifts (δ) of a number of cyclic and acyclic ketone enamines (60 MHz) in various solvents are listed in **Table 1**.[47,48] From this table, it can be seen that the chemical shifts in carbon tetrachloride are similar to those of the neat liquid, whereas those in deuteriochloroform, occur to higher field values. A measure of the amount of charge delocalisation due to pπ-conjugation, may be obtained from these values since the β–vinyl proton is shielded because of the increased electron density at the β–carbon. Should the steric factors be identical or at least similar, it is expected that there should be some form of correlation between enamine reactivity and chemical shift, provided that the spatial direct shielding effects are negligible or at least identical. Clearly, before such a correlation may exist, two factors must apply: (1) the enamines must have similar structures; and (2) the chemical shift differences must be appreciable.

TABLE 1[47,48]

Table of olefinic ^{1}H–NMR chemical shifts of cyclic ketone enamines.

Enamine		Chemical Shift (δ)		
Amine	Ketone ring size	Solvent		
		CCl_4	$CDCl_3$	neat
Pyrrolidine	5	3,91	4,02	–
Pyrrolidine	6	4,13	4,28	4,16
Pyrrolidine	7	4,36	–	–
Pyrrolidine	8	4,08	–	–
Piperidine	5	4,25	4,37	–
Piperidine	6	4,53	4,66	–
Piperidine	7	4,75	–	–
Piperidine	8	4,48	–	–
Piperidine	12	4,30	–	–
Morpholine	5	4,35	4,43	–
Morpholine	6	4,56	4,64	4,55
$C_6H_{12}NH$	6	4,25	4,35	–
Me_2NH	6	–	–	4,37
Et_2NH	6	–	–	4,43
Ph(Me)NH	6	–	–	5,27

Table 2,[47,48] below, shows the thermodynamically controlled isomeric distribution of a number of enamines derived from 2–methylcyclohexanone as well as substituted double bond isomers.

TABLE 2:

Isomeric distribution and olefinic chemical shifts for less substituted isomer of 2–methylcyclohexanone.

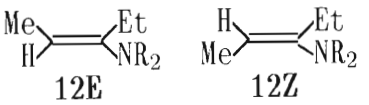
Amine moiety	Percentage less substituted form	Chemical shift (δ) [neat liquid]
pyrrolidine	90	4,18
dimethylamine	60	4,45
morpholine	52	4,6
piperidine	46	4,62
diethylamine	25	4,55
2,5–dimethylpyrrolidine	60	4,53

Gurowitz and Joseph,[49] pointed out that the proportion of the less substituted isomer increases with increasing pπ–conjugation between the amine moiety and the enamine double bond.

Stradi and Pocar[50] have determined the configuration of a number of acyclic enamines as well as discussing the factors affecting their stability, reactivity and spectroscopic properties. **Table 3** summarises their results and shows that the olefinic proton signals of the E–isomer appear to higher field than those of the corresponding Z–isomer. In addition, there is no observable allylic coupling between H and Et in the E–isomers, except for # **11**. They attribute the difference in chemical shifts between the two isomers to the $A^{1,3}$–strain between the Me and amine moieties in the Z–isomer which reduces the pπ–conjugation. The same reason is cited for the greater thermodynamic stability of the E–isomer, except for # **10** where there is conjugation between the nitrogen lone pair and the aromatic π–system. When such pπ–conjugation with the benzene ring is prevented, as in # **11**, which has an ortho methyl group, the E–isomer is again favoured because of the increased pπ–conjugation between the double bond of the enamine and the nitrogen lone–pair. Proceeding down the series (# **1** – **4**; **6** – **7**), there is a decrease in the contribution of the E–isomer to the mixture, which reflects the increase in $A^{1,2}$–strain due to the ethyl group. One observes reductions in pπ–conjugation in the downfield shift of the olefinic proton (δ 4,13 – 5,24).

TABLE 3[52]

Percentage composition and olefinic proton chemical shifts (δ) for acyclic ketone enamines



12E 12Z

No.	%	δ_H	%	δ_H	NR_2
1	97	4,13	3	4,54	Me_2N
2	86	4,25	14	5,00	Et_2N
3	80	4,35	20	4,90	n–Pr_2N
4	55	5,25	45	5,34	i–Pr_2N
5	88	4,34	12	4,72	morpholino
6	90	4,35	10	4,70	piperidino
7	65	4,37	35	5,00	2–methylpiperidino
8	98	3,92	2	4,24	pyrrolidino
9	83	4,19	17	4,81	$C_6H_{11}(Me)N$
10	20	4,45	80	4,84	Ph(Me)N
11	83	5,09	17	5,20	o–$MeC_6H_4(Me)N$

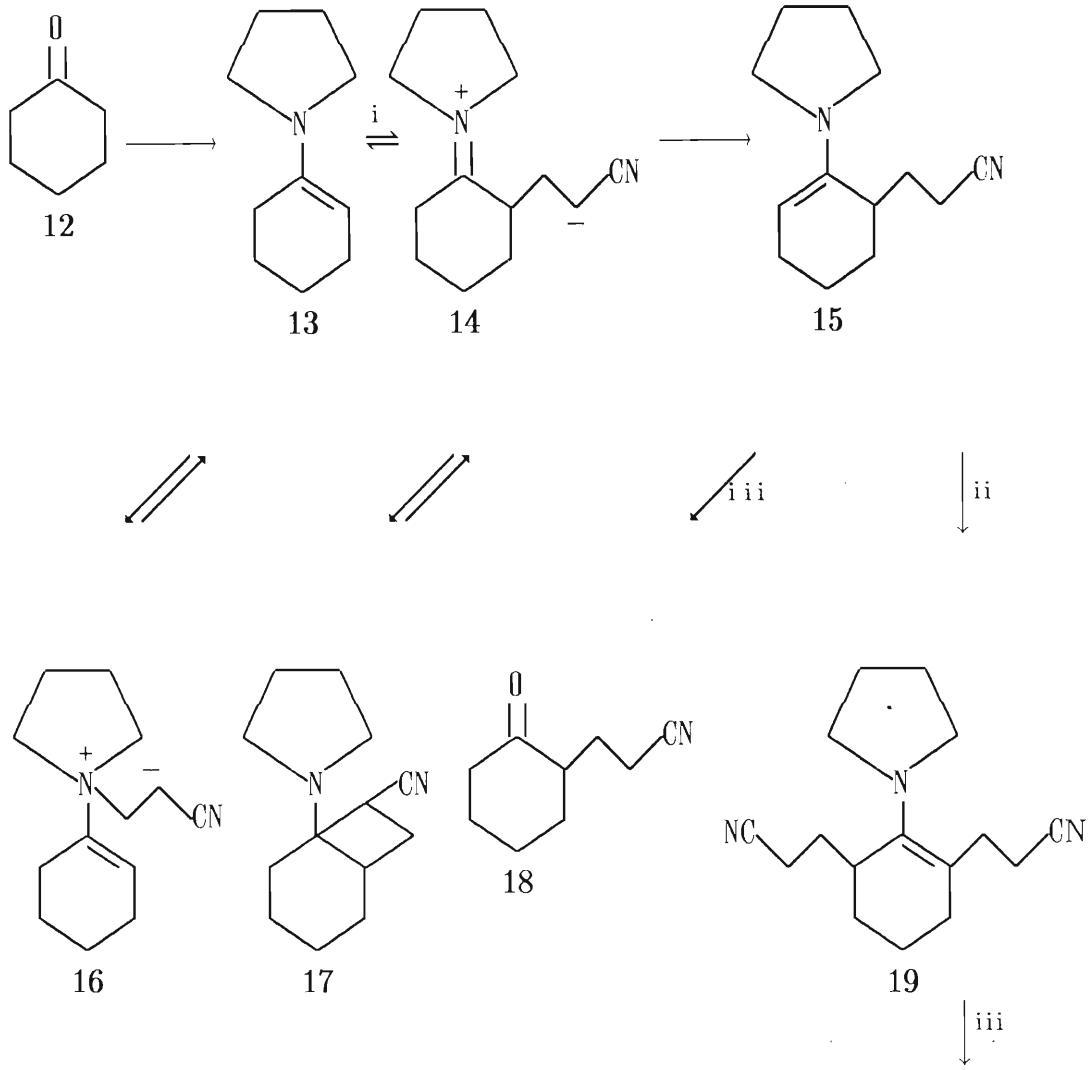
3.5 ^{13}C–Nuclear Magnetic Resonance Spectra

Much work has been carried out in the areas of cyclic and acyclic enamines.[53-59] The C–1 olefinic carbon produces a signal between 124 and 156 ppm (downfield from TMS) and the C–2 signals appear in the range from 79 to 131 ppm. The olefinic carbons tend to be deshielded by substituents attached to them (α–effect), the size of which varies markedly. Ahmed and Hickmott[56] have attributed this to an alteration in the electronic contribution of the amine moiety ($\Delta\delta$C) [corrected for variation in α– and β–effects of alkyl substituents with increasing substitution] to the chemical shift of the olefinic carbons by the steric and electronic effects of introducing an alkyl substituent [$\Delta\delta C = \delta_{enamine} - \delta_{alkene}$]. Since the α–effect of the amine moiety is expected to be mainly determined by electronegativity, the amine contribution to the chemical shift of C–1 ($\Delta\delta$C–1) is relatively constant. The shift caused by the amine moiety (morpholine 26 ppm and pyrrolidine 23 ppm) is however surprisingly similar

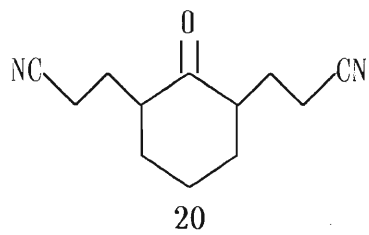
to the deshielding effect of an isopropyl group attached to an olefinic carbon, which is of the order of 23 ppm, despite the higher electronegativity of the nitrogen atom in the amine moiety.[60] This is an anomaly which has not yet been explained satisfactorily. The C–2 chemical shift in the enamine ($\Delta\delta$C–2) is variable due to the amine contribution, which causes high field shifts of between 5 and 43 ppm relative to the chemical shift of the β–carbon of the corresponding alkene in which the amine has been replaced by hydrogen.

4. ALKYLATION OF ENAMINES WITH ELECTROPHILIC ALKENES

The C–alkylation of enamines is successful only because the N-alkylation step is essentially reversible[3] (**Scheme 5**: **13** $\rightleftharpoons$ **16**), whereas the C–alkylation is normally rendered irreversible *via* proton transfer (**13** → **14** → **15**).



Reagents:
i acrylonitrile (benzene or dioxane)
ii acrylonitrile (ethanol)
iii water



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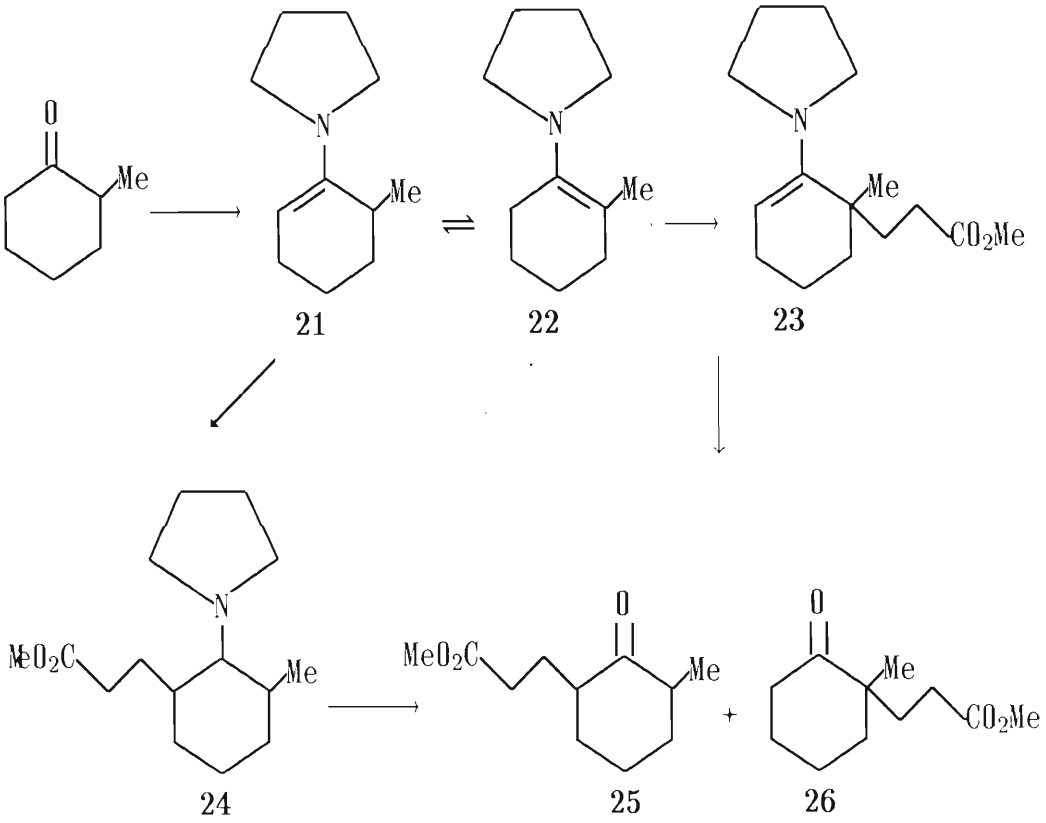
SCHEME 5

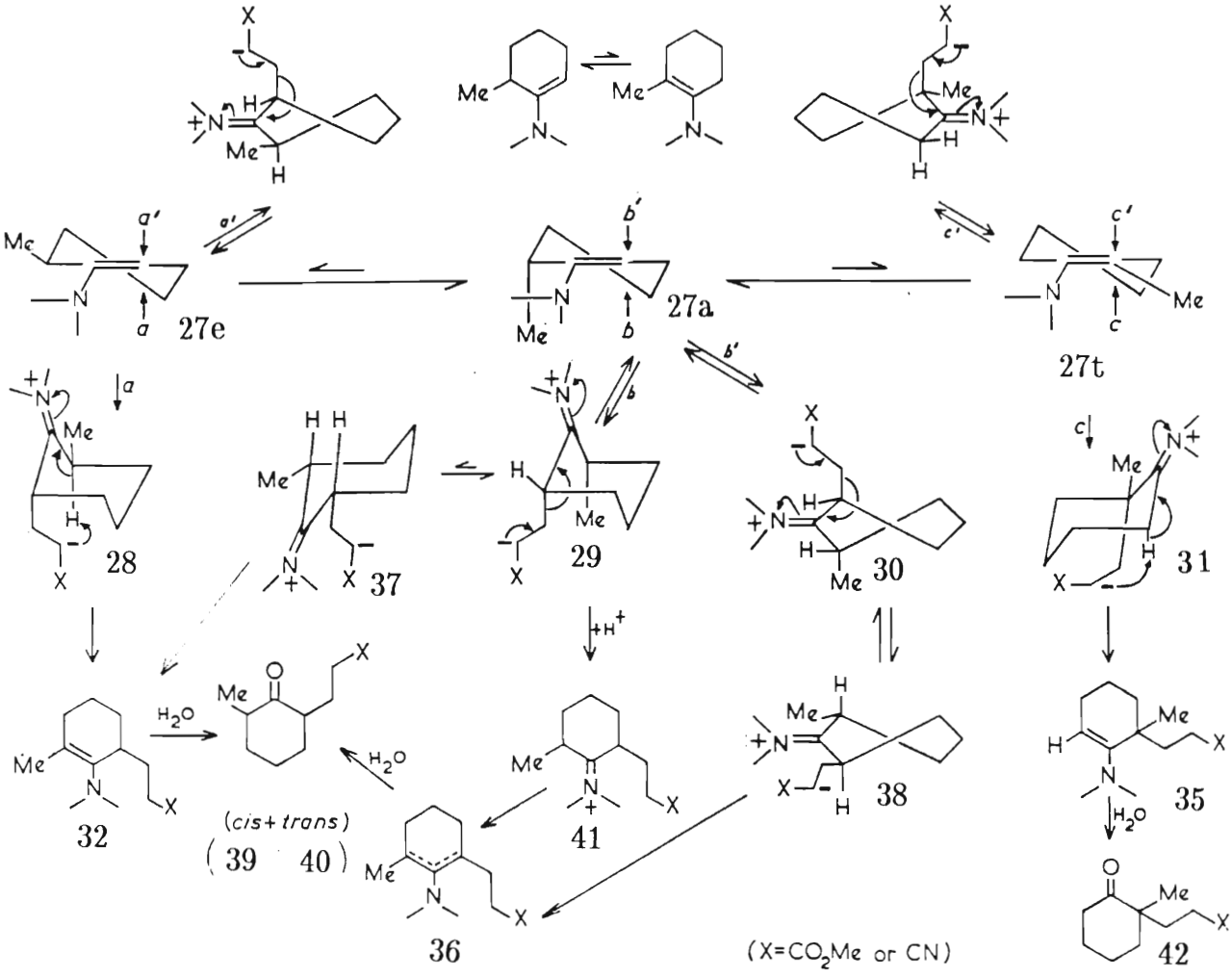
Exceptions do however exist, where the C–alkylation step is reversible even after proton transfer.[60,61] Using this method, ketone and aldehyde enamines can thus be alkylated in high yield. The zwitterionic intermediate (**14**) may collapse, at low temperature, to the cyclobutane adduct **17**.[62] The experimental conditions may be altered in order to produce either the mono– (**15**, **18**) or dialkylated (**19**, **20**) products. The latter product is referred to, in the case of six–membered rings, as 2,6–disubstitution of the original ketone. In aprotic solvents, the reaction of morpholine enamines normally stops at the monosubstituted stage. However an exception to this is the conversion of 1–morpholinocyclohexene to 2,6–bis(*β*–nitroethyl)cyclohexanone with nitropropene in benzene at 10° C.[63] As previously discussed, steric interactions in the monosubstituted enamine, and in the transition state of the reaction, favour reaction at the least substituted *β*–position of an isomeric mixture of enamines. However, House and Schellenbaum[62] reported that prolonged reaction (66 h) of the pyrrolidine enamine of 2–methylcyclohexanone with methyl acrylate in dioxan under reflux produced a 1:1 mixture of 2,2– and 2,6–disubstituted cyclohexanones (**Scheme 6**: **25** and **26**).



SCHEME 6

This leads to the conclusion that attack at the least substituted position (**21**) was not as favourable as had been thought. This observation seemed to undermine the theoretical foundations upon which enamine chemistry had been based. However Malhotra and Johnson[63] (1985) proposed that the formation of the 2,2–disubstituted product **26** occurred in the hydrolysis step, *via* a Michael reaction between the methyl acrylate and 2–methylcyclohexanone, catalysed by the pyrrolidine. Some doubt as to whether this was in fact the case still existed however, since no experimental

evidence was given and also the conditions were very mild for an enolate–anion mechanism. House's work has been repeated and it was shown[66] unequivocally that the 2,2–disubstituted product **26** was derived from enamine **22**, since the disubstituted enamine **23** was shown to be present [methyl singlet at δ 1,17 and the CH= triplet at 4,75] in the crude reaction mixture prior to hydrolysis. Observations that products **25** and **26** were formed in approximately equal amounts may erroneously lead one to assume that reaction at the more and less substituted β–positions of enamines (**22** and **21** respectively) occur with equal ease. One needs just to consider that enamine **21** always has lower energy pathways open to it but in some cases these are reversible and may not lead to products. The course of the reaction is determined by higher energy routes which means that reactions of enamine **22** will contribute to the product distribution. Consider **Scheme 7** below, which shows the theoretical basis for this statement, showing the high and low energy pathways: (**Table 4**:[67] provides the experimental basis upon which **Scheme 7** is based).



SCHEME 7

Hickmott[9] provides the following explanation which is applicable to those electrophilic alkene reactions which may be considered essentially irreversible once the anionic centre of the intermediate zwitterion has been protonated. Only one exception to this reasoning was cited – the strange reactivity of dibenzoyldi–imide.[66,67] However there is now evidence to suggest that reactions with methyl vinyl ketone are reversible even after protonation of the anionic centre of the zwitterion, in which case thermodynamic (i.e. product stability) rather than kinetic (i.e. transition state stability) considerations may govern the outcome of the reaction. Nevertheless it is pertinent to deal with this explanation in some detail since it will highlight the differences in the reaction pathway followed by the alkylation of imines using electrophilic alkenes which will be dealt with in Chapter 2.

1. ***Energetics and reversibility of competing reaction pathways.***

The low energy pathways referred to previously involve paths **b** and **b'** in **Scheme 7** above, which are respectively axial and equatorial attack by the electrophile on the enamine conformer which has the methyl substituent quasi–axially oriented (i.e. **27a**). These two pathways may be expected to involve similar energetics since the main steric interactions are 1,3–diaxial methylene–methyl interactions (≈15 $kJ.mol^{-1}$)[68] in **29** and the nonbonded twist interactions (≈11 $kJ.mol^{-1}$)[69] in **30**. These two pathways do not lead to products if the dilution is high, provided aprotic solvents of low dielectric constant are used, since both pathways are rendered reversible under such conditions. (Refer to **Table 4**; # 1). Although it is possible to prevent reversion to the starting enamine by protonating the anionic centre provided the dilution is high and also bearing in mind that the lifetimes of the zwitterionic intermediates produced (**29** and **30**) are very short, the process

would involve the intramolecular transfer of the equatorially oriented hydrogen. As this is a high energy process owing to the unfavourable stereoelectronic factors[70] which involve a four–membered transition state and also the negligible overlap of the C–H orbital with the p–orbital of the iminium group. As the charge is neutralised on formation of the cyclobutane structure, strain is introduced into the structure, which has been shown to result in ring opening even at room temperature.[71] Similar arguments may be applied to pathways **a'** and **c'**, but there are the additional $A^{1,3}$–interactions in the iminium salts formed which will produce even higher energy pathways than **b** or **b'**. This leaves only pathways **a** and **c**, both of which involve axial attack of the electrophilic alkene on **27e** and **27t**. Both the iminium salts formed (**28** and **31**) are destabilised *via* $A^{1,3}$– strain between the α–methylene groups of the amine ring and the methyl ($\approx$23 kJ.mol^{-1} for a methyl–methyl interaction[23]). Although these two routes are also high energy processes, they may be rendered irreversible *via* stereo-electronically controlled intramolecular proton transfer *via* a six–membered cyclic transition state (**28** $\longrightarrow$ **32**; and **31** $\longrightarrow$ **35**). This means that as the destabilising steric factors are the same for both pathways, their activation energies should be similar as well, which should lead to approximately equal amounts of the 2,2– and 2,6– disubstituted products. This is indeed what is observed under conditions of high dilution in which intermolecular interactions are reduced to a minimum (**Table 4**; # 1). As expected the yields of both products are lower (for the same reaction times) since the dilution results in a reduction in the concentration of starting reagents. Despite the fact that the energy differences among the pathways is small, it only requires $\approx$13 kJ free energy to alter a 9:1 product ratio to a 1:9 ratio under conditions of thermodynamic control.

TABLE 4[65]

Effect of reaction conditions on the ratio of 2,2– to 2,6–disubstitution.[a]

No	Electrophilic alkene	Solvent	Reaction time (h) (reflux)	Yield (%)	Disubstituted cyclohexanone (% composition) trans–2,6 38	cis–2,6 39	2,2– 41
1	methyl acrylate	Dioxan	66[b]	10	28	20	52
2	methyl acrylate	Dioxan	66	65	45	20	35
3	methyl acrylate	Dioxan	66[c]	70	46	36	18
4	methyl acrylate	Acetonitrile	66	65	65	30	5
5	methyl acrylate	Methanol	3	70	70	30	0
6	methyl acrylate	Methanol	66	50	56	44	0
7	methyl acrylate	Benzene	66[d]	60	55	25	20
8	methyl acrylate	Mesitylene	66[e]	65	43	24	33
9	methyl acrylate	Mesitylene	66[f]	40	30	20	50
10	acrylonitrile	Dioxan	66	70	32	20	48
11	acrylonitrile	Methanol	66	70	69	31	0
12	methyl acrylate	None	66[d]	80	52	33	15

[a]Enamine concentration 2,3 mol.l^{-1} unless otherwise stated.

[b]Enamine concentration 36,5 mol.l^{-1}.

[c]Enamine concentration 0,11 mol.l^{-1}.
[d]Temperature: 80° C.
[e]Temperature: 100° C.
[f]Temperature: 160° C, under pressure.

2. ***Effect of concentration and solvent.***

Intermolecular proton exchange may increase as the enamine concentration increases. When the anionic centres of molecules **29** and **30** have been protonated, the products are stable iminium salts, which can undergo stereo-electronically controlled deprotonation to the enamines, **32** and **36** *via* conformations **37**, **38** and **41**.

As the enamine concentration increases (0,11 ⟶ 2,3 ⟶ 36,5 mol.l^{-1}) [**Table 4**] the percentage 2,6–disubstitution increases (48 ⟶ 65 ⟶ 82 %) and in the absence of solvent, reaches a maximum (85 %) [**Table 4**: # **12**]. It is surprising that at high enamine concentration 2,2–disubstitution still occurs. This Hickmott attributes to the short lifetime of the zwitterionic

intermediates **29** and **30** in solvents having low dielectric constants, which will cause reductions in the rates of product formation *via* routes **b** and **b'** which allows pathways **a** and **c** still to compete. On the other hand, in polar solvents of high dielectric constants (**Table 4**: # **4**), the lifetimes of the zwitterions **29** and **30** increase sufficiently to allow intermolecular protonation even at lower enamine concentration. Thus increased product formation is seen *via* pathways **b** and **b'**. In protic solvents, the formation of **29** and **30** are rendered irreversible due to the increased dielectric constant and the solvating power of the solvent. Coupled to this is the fact that the protic solvent provides a direct method of protonation of the zwitterions. Under such conditions (**Table 4**: **5**, **6** and **11**) no 2,2-disubstitution is observed and the low energy pathways **b** and/or **b'** give rise only to 2,6–disubstitution.

3. *Evidence for the intermediacy and reversible formation of zwitterionic intermediates.*

When the enamine mixture **27a**, **e** and **t** with methyl acrylate was heated under reflux in monodeuteriomethanol and hydrolysed, the proton NMR spectrum of the 2,6–disubstituted cyclohexanones (**39** and **40**) showed the axial and equatorial methyl signals as doublets because no deuterium had been incorporated into the enamine. However, mass spectroscopy showed that about 70 % deuteriation had occurred at the α–position of the methoxycarbonyl side–chain which shows that **29** and **30** were zwitterions. Further, Risaliti *et al.*[71] have shown that the formation of these zwitterions is reversible because maleate esters were isomerised to fumarate esters when catalysed by enamines – a process which did not occur when tertiary amines were used. Further evidence was provided by Fleming and Harley-Mason[60] who showed that the cyclobutanes formed by cycloaddition of electrophilic alkenes to enamines reverted to starting materials on heating and some even

at ambient temperature. Yoxall[72] has even used the reversibility of zwitterion formation to develop conditions for changing the regioselectivity of reaction of certain dienamines.

4. ***Other factors affecting the lifetime of the zwitterion intermediates.***

The lifetime of the zwitterionic intermediate formed is affected as already seen, by the dielectric constant and solvating ability of the solvent, but it is also affected by temperature, the stabilisation of the anionic centre and the ease of charge neutralisation by cyclisation. As can be seen from **Table 4** (# **2** and **7**), the relative amounts of 2,6– *vs* 2,2–disubstitution in dioxan (2:1) and benzene (4:1) is highly likely to be a temperature effect. In benzene (lower temperature) the lifetimes of the zwitterionic intermediates will be increased which will enhance the chances of intermolecular protonation of the anionic centres. The results will be product formation *via* routes **b** and **b'**, the low energy routes in **Scheme 7**, which results in an increased yield of the 2,6–disubstituted product. Further confirmation of the temperature effect are the reactions in mesitylene at the same concentrations but at two different temperatures. At 100 °C the ratio of 2,6– to 2,2–disubstitution is around 2:1, whereas at 160 °C the ratio changes to 1:1 (**Table 4**: # **8** and **9**). At the higher temperature, the lifetime of the zwitterionic intermediates **29** and **30** (**Scheme 7**) will be decreased. This theory is further enhanced by the fact that in the absence of solvent, and at ambient temperature, only the 2,6–product is obtained, even if in very low yield. This must be due to the fact that the lifetimes of the zwitterionic intermediates **29** and **30** are now longer and in equilibrium with the cyclobutane adducts and also because of the inability of the molecules to overcome the higher energy barriers, at the low temperature, which would lead to the zwitterionic intermediates **28** and **31**.

Another factor which will increase the lifetime of the zwitterionic intermediate may be attributed to factors which increase the stability of the

anionic centre, such as the electronegativity of the atom bearing the negative charge (O > N > C) and also the stabilising effect of substituent groups – the stabilising effect of which appears to increase in the order[73] $NO_2 > C{=}O > SO_2 > CO_2H > CO_2R > CN > CONH_2$.

This can be clearly seen by comparing # **2** and # **10** in **Table 4**, where at the same enamine concentration (2,3 $mol.l^{-1}$) acrylonitrile gave more of the 2,2–disubstituted product than methyl acrylate, which may be attributed to the fact that the cyano–group provided less stabilisation of the anionic centre of the zwitterionic intermediates than did the alkoxycarbonyl substituent.

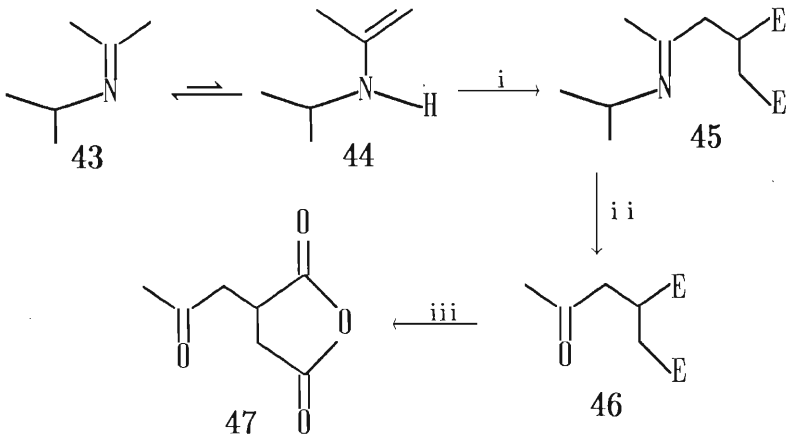
A further point worth noting is that where a zwitterionic intermediate is not generated, the problem of 2,2–disubstitution does not arise. A good example is the reaction with acryloyl chloride.[65,21]

5. IMINES

5.1 IMINE–ENAMINE TAUTOMERISM

There is much chemical[76,77,78] and spectroscopic[71,79] evidence for imine–enamine tautomerism. This tautomerism which has many applications to chemical synthesis will be considered in detail as it is of direct relevance to the direction of this research project. The imine–enamine equilibrium is displaced almost completely toward the imine form for simple aldehydes and ketones – a fact amply demonstrated by spectroscopic studies. An exception is found where further conjugation stabilises the enamine form as with a carbonyl[79,80] or imine group,[81] or with an aromatic system.[82,83] Even though this imine–enamine tautomerism favours the imine form in almost all cases, there are many reactions which clearly show that the enamine form reacts with a variety of electrophilic reagents at the

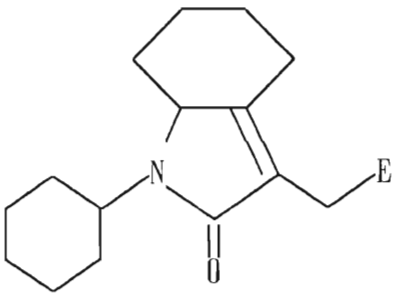
α–position to the original carbonyl function (C–β of the enamine). Pfau and Ribieri[84] convincingly demonstrated the enamine–imine tautomerism in the reaction of N–isopropylideneisopropylamine (**Scheme 8**: **43**) and dimethyl maleate to give products **45** – **47** in high yield.



SCHEME 8

Reagents: (i) *cis*–$MeO_2CCH{=}CHCO_2Me$, PhH, Δ; (ii) H_2O, dioxan, 20° C
(iii) Δ, E = CO_2Me.

In methanol, no olefinic signals were observed in the proton NMR spectrum for **43**, but in deuteriomethanol, the signals corresponding to the two methyls (which are magnetically non–equivalent) attached to the imine double bond (δ 1,94 and 2,01) rapidly disappear. This shows that even though the imine form (**43**) predominates, the exchange of the six hydrogens occur rapidly *via* the enamine form (**44**) This result is extremely useful, since it provides a method for preparing the enamine of acetone *in situ*.[9] This reaction when applied to the imine of cyclohexanone gave the lactam **48**, *via* the C–alkylated enamine **49**.[84,85]



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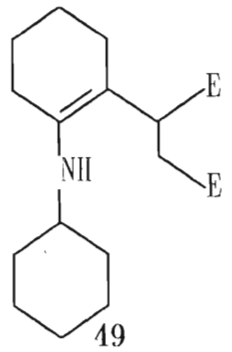

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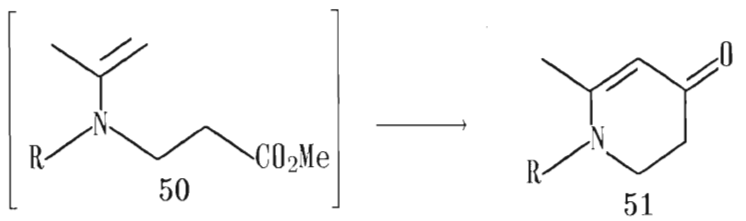
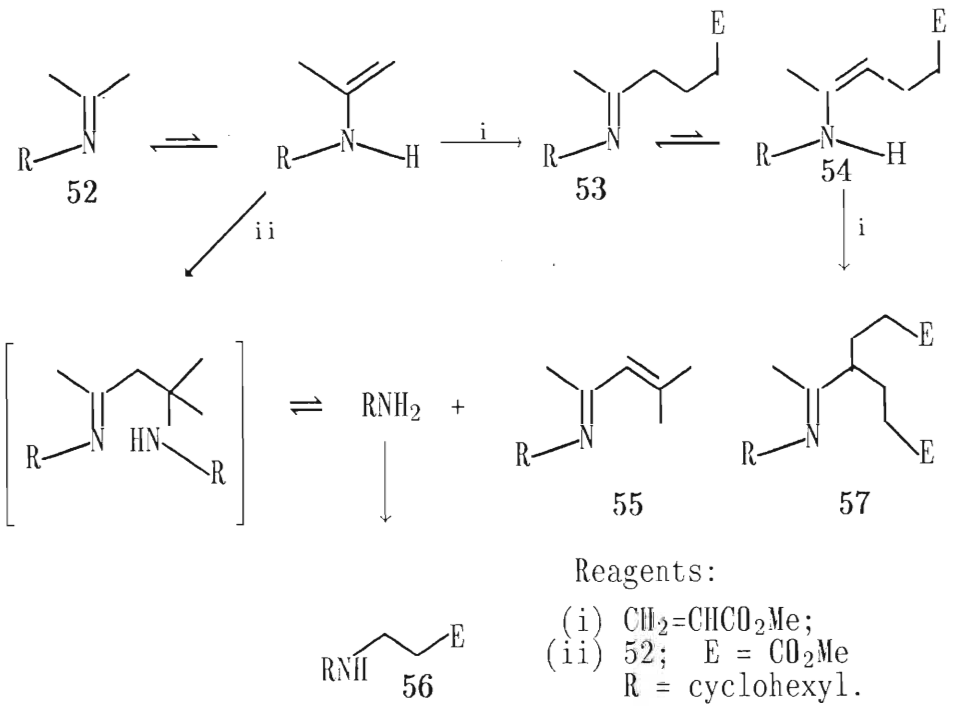


SCHEME 9

5.2 REGIOSELECTIVITY OF THE IMINE REACTION WITH ELECTROPHILIC ALKENES

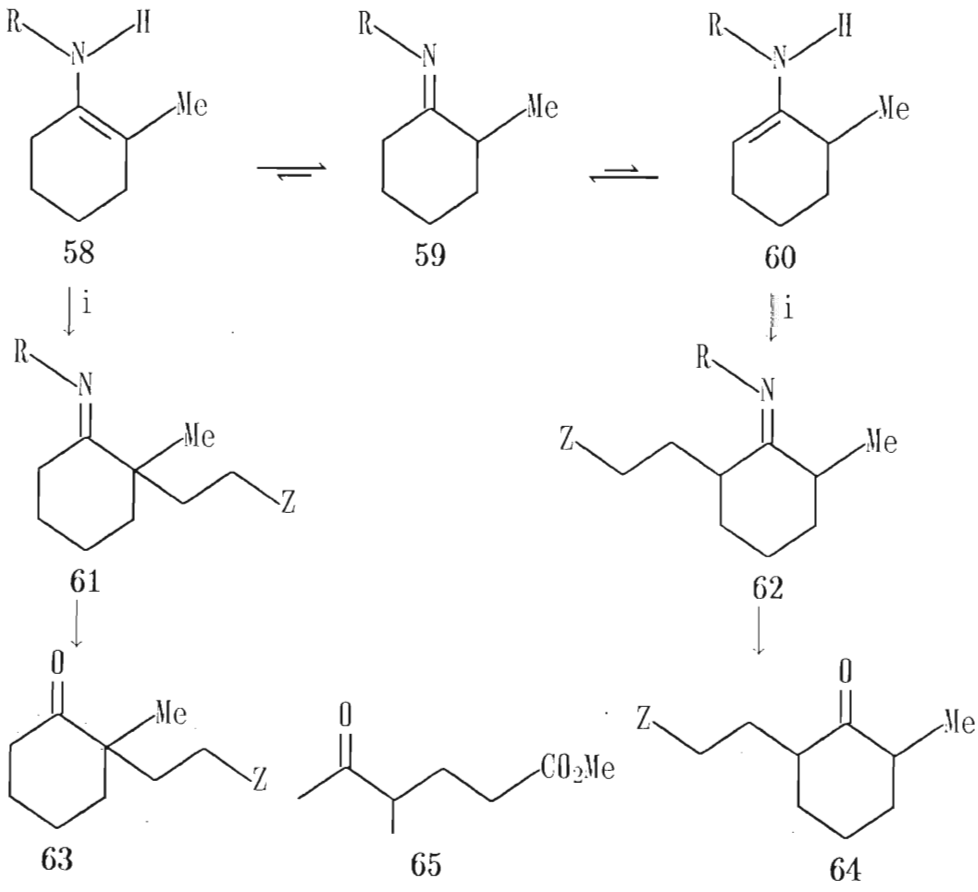
It was recently claimed[86] that only N–alkylation of N–isopropylidenecyclohexylamine occurred with methyl acrylate, which is in direct contradiction of Pfau and Ribieri's work. This is not correct.[87] Pfau *et al.* have shown that with these reagents absolutely no N–alkylation occurs, not even reversibly, since the N–alkylated product **50** (**Scheme 9**) cyclised spontaneously to the enaminoketone **51**, none of which was present in the product mixture from the reaction of methyl acrylate with N–isopropylidenecyclohexylamine (**Scheme 10**). The only products isolated were **53**, **55**, **56** and **57**.



SCHEME 10

The formation of the α,α–bisalkylated product **57** is interesting, in that when two equivalents of methyl acrylate were used, it was produced in 86% yield, which is a result in sharp contrast to the reaction of tertiary enamines derived from unsymmetrical ketones.[9] Here reaction occurs preferentially at the least substituted position. What must be occurring is that the enamine takes up a conformation in which $A^{1,3}$–interactions[23] are minimal both in the ground and transition states, namely **54**. Thus the steric interactions which have been used[9] to predict the products of tertiary enamine reactions are therefore not applicable to primary or secondary enamines. Preliminary investigations by Hickmott and Davison[10] showed that 2–methylcyclohexanone imines reacted preferentially with electrophilic alkenes *via* the more substituted enamine tautomer to give the 2,2–disubstituted cyclohexanone exclusively, in both protic and aprotic solvents. The attempted bis–alkylation with the more bulky dimethyl maleate failed on steric grounds.[87] Similarly, aldimines undergo mono– and bis–C–alkylation with methyl acrylate.

Reaction of the isopropylamine imine of acetone with methylvinylketone gives a good method for the preparation of 3–methylcyclohex–3–enone.[88] The intermediate stages may be hydrolysed or further alkylated (α,α'-di-alkylation in this case !) to give heptane–2,6–dione or undecane–2,6,10–tri-one respectively. The acetophenone imine was also α,α–dialkylated and isobutyraldehyde imine was mono–alkylated. It was predicted that alkylation of 2–substituted cyclohexanone imines would occur at C(2), in contrast to tertiary enamines where alkylation occurs preferentially at the less substituted C(6) position of the 2–substituted cyclohexanone. Hickmott and Rae[89] showed showed that this was indeed the case. The regioselectivity of the reaction of acrylonitrile, methyl acrylate and phenyl vinyl ketone with imines of unsymmetrical ketones was investigated.



Reagents: (i) CH_2=CH–Z ($-H^+$); (ii) H_2O, Δ; Z = CO_2Me, CN, SO_2Ph

SCHEME 11

The reasoning behind this work was that the imine of 2–methylcyclohexanone **59** (**Scheme 11**) would be in equilibrium mainly with the more substituted secondary enamine **58** rather than the less substituted double bond isomer **60**. This is because enamine **58** is stabilised over enamine **60** by the hyperconjugative interaction of the methyl group without being affected by $A^{1,3}$–interactions[23] which are normally present in tertiary enamines, because the bulky N–alkyl substituent or ring residue in the latter is replaced by a hydrogen atom (in **58** and **60**). Also imine **61** which is produced by alkylation of enamine **58**, contains no $A^{1,3}$–strain and minimal $A^{1,3}$–strain in the transition state leading to it. On the basis of this, it was predicted that alkylation would provide mainly the 2,2–disubstituted cyclohexanone **63** after hydrolysis, in preference to the 2,6–disubstituted cyclohexanone. This work was a preliminary study of the reaction and as such, the reaction between methyl acrylate and various imines of 2–methylcyclohexanone were carried out. The results of this work appear in **Table 5** overpage.

TABLE 5[89]

Reactions of imines of 2–methylcyclohexanone with methyl acrylate.[a]

No	Imine	Equivalent of methyl acrylate	Solvent	Reaction time (h)	Other additives	% Yield[b]	
						2,2–	2,6–[c]
1	benzylamine	1	MeOH	4	–	13	2
2	benzylamine	2	MeOH	4	–	46	4
3	benzylamine	2	MeOH	24[d]	–	45	3
4	benzylamine	5	MeOH	4	–	64	4
5	cyclohexylamine	2	MeOH	4	–	42	9
6	aniline[e]	2	MeOH	4	–	3	trace
7	benzylamine	2	benzene	68	–	3	0
8	benzylamine	2	toluene	68	–	3	0
9	benzylamine	2	CH_3CN	95	–	50	2
10	benzylamine	2	benzene	68	$Me_2NH.HCl$[f]	32	0
11	benzylamine	2	benzene	68	Et_3N[f]	32	0
12	benzylamine	2	benzene	24	4–DMAP[f g]	40	1
13	benzylamine	2	benzene	24	4–DMAP[f g]	49	1
14	benzylamine	2	MeOH	4	4–DMAP[f g]	59	5

[a]At the boiling point of the dry solvent unless stated otherwise.
[b]Analysed by gas–liquid chromatography.
[c]Mixture of stereoisomers.
[d]Room temperature, stirred.
[e]Mostly unreacted starting 2–methylcyclohexanone recovered.
[f]1,0 Equivalents.
[g]4–Dimethylaminopyridine.
[h]0,1 Equivalents.

Under all conditions the 2,2–disubstituted ketone **63**, (Z = CO_2Me) was the main product. It was decided that since the benzylamine imine produced less of the 2,6–disubstituted product than did the cyclohexylamine imine and the yields of the 2,2–disubstituted products were similar (**Table 5**: # **2** and **5**) the remainder of the preliminary investigation would be carried out using the benzylamine imine of 2–methylcyclohexanone. The aniline imine gave a very low yield (**Table 5**: # 6) which may be due to the stabilising effect of the phenyl group on the imine and/or the low reactivity of the enamine tautomer. A preliminary attempt was made to optimise the reaction conditions. The highest yield achieved occurred when the alkylating agent

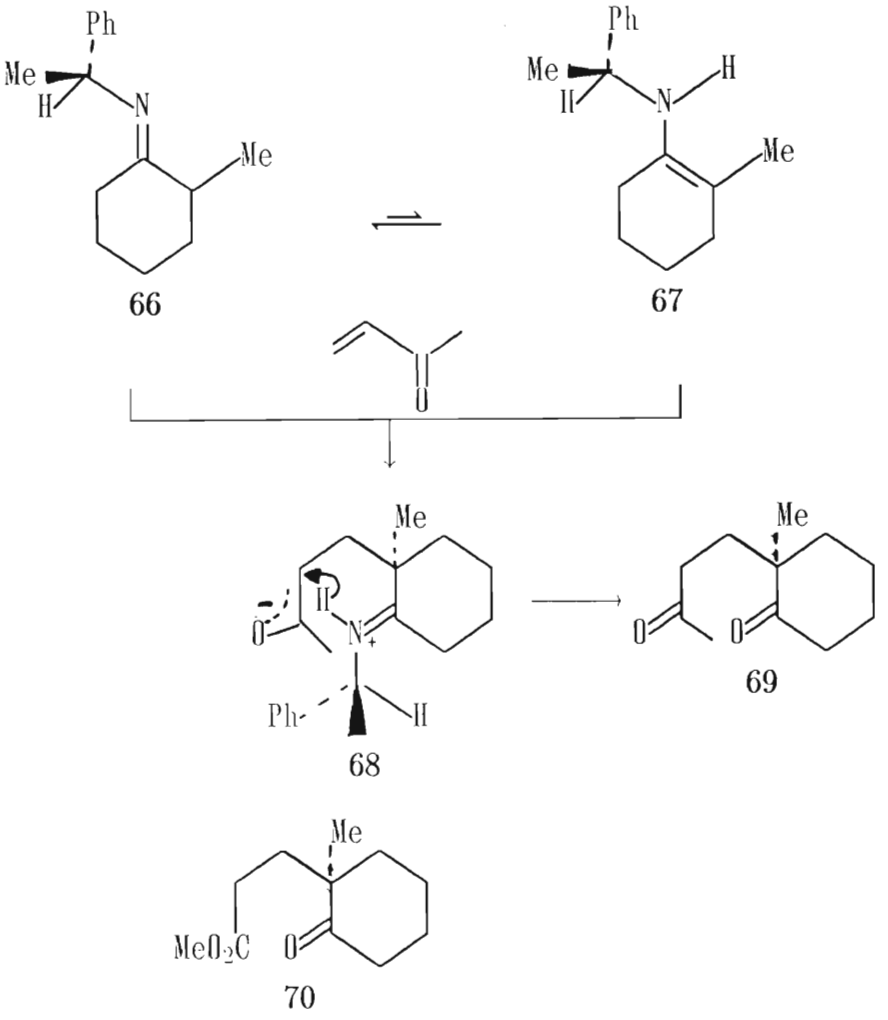
was present in large excess and the solvent was 'super dry'[90] methanol (**Table 5**: # 4), the reasons for which have not been determined. Further, the investigation showed that the use of aprotic solvents of low dielectric constant (toluene and benzene) gave very low yields even after prolonged reaction times (# 7 and 8). The use of acetonitrile, which has a high dielectric constant (# 9) gave a marked increase in yield relative to that obtained in benzene, as did the addition of weakly acid (# 10) or base (# 11 – 14) catalysts (again relative to benzene). This was presumably due to the effect of the catalysts on the enamine–imine equilibrium.

It was further shown that when acrylonitrile and phenyl vinyl sulphone were reacted with N–(2–methylcyclohexylidene)benzylamine (**Scheme 11**: # **59**; R = $PhCH_2$) in methanol, the spectroscopic evidence showed clearly that reaction had occurred in the more substituted position to give the 2,2–disubstituted ketone **63** (Z = CN or SO_2Ph, respectively) after hydrolysis.

When N–(2–butylidene)benzylamine was treated under the same conditions with methyl acrylate in 'super dry' methanol, the product was methyl 4–methyl–4–oxohexanoate (**65**). This result is very important, since it indicated that the methodology of this study may be extended to give direct reaction to the more substituted position of acyclic as well as cyclic ketones.

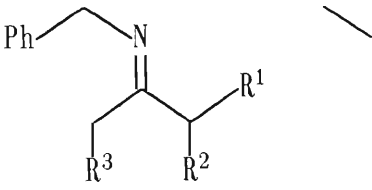
Pfau et al.[91] recently described the alkylation of the imine formed from *rac*–2–methylcyclohexanone and (*S*)–(–)–1–phenylethylamine ($[\alpha]_D^{20}$ = –39,4°) with methyl vinyl ketone (MVK). The reaction was carried out in THF at 20 °C for 3 days and gave the adduct **68** (**Scheme 12**). Hydrolysis of this reaction mixture using acetic acid (10 %) at 20 °C for 1 hour gave the (*R*)–(+)–diketone (**Scheme 12**: **69**) in 88,6 % yield, again demonstrating the regioselective nature of this reaction as well as the stereoselective nature of this particular reaction. Pfau also reports the reaction of methyl acrylate with imine **66** which gave, after the same hydrolysis, the (*R*)–(+)–keto ester

70, in 81 % yield ($[\alpha]_D^{20}$ = 33,8°; [EtOH] = 2,95) (!) – a result which the author will comment on later in Chapter 2.

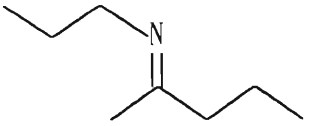


SCHEME 12

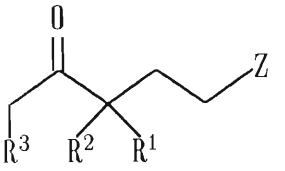
Brookes[92] in an extension of the work of Hickmott[89] and Pfau[91] investigated the reactions of electrophilic alkenes with imines of acyclic ketones. Using the benzylamine or n–propylamine imines (**Scheme 13**: **71** and **72** respectively) of butanone, pentan–2–one, pentan–3–one, 3–methylbutanone, 2–methylpentanone and 4–methylpentanone (**Scheme 13**: **71 a–f** and **72** respectively), they alkylated them using various electrophilic alkenes (viz. acrylonitrile, methyl acrylate, and phenyl vinyl sulphone).



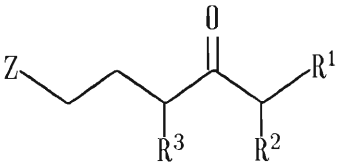
71



72



73



74

	R^1	R^2	R^3
(a)	Me	H	H
(b)	Et	H	H
(c)	Me	Me	H
(d)	Me	Me	H
(e)	Me	Me	Me
(f)	*i*–Pr	H	H

SCHEME 13

They found that the reaction was not as regioselective as the corresponding alkylation of 2–substituted imines,[89,93] and only **71d** gave 100 % alkylation at the more substituted position and then only with acrylonitrile and methyl acrylate; phenyl vinyl sulphone gave the less substituted regioisomer (**74d**; Z = SO_2Ph) and in very low yield. Imine **71f** with phenyl vinyl sulphone produce the less substituted regioisomer (**74f**; Z = SO_2Ph) as the main component of the reaction mixture. **Table 6** shows a summary of the the relative amount of attack at the more and the less substituted positions expressed as a percentage.

TABLE 6[92]

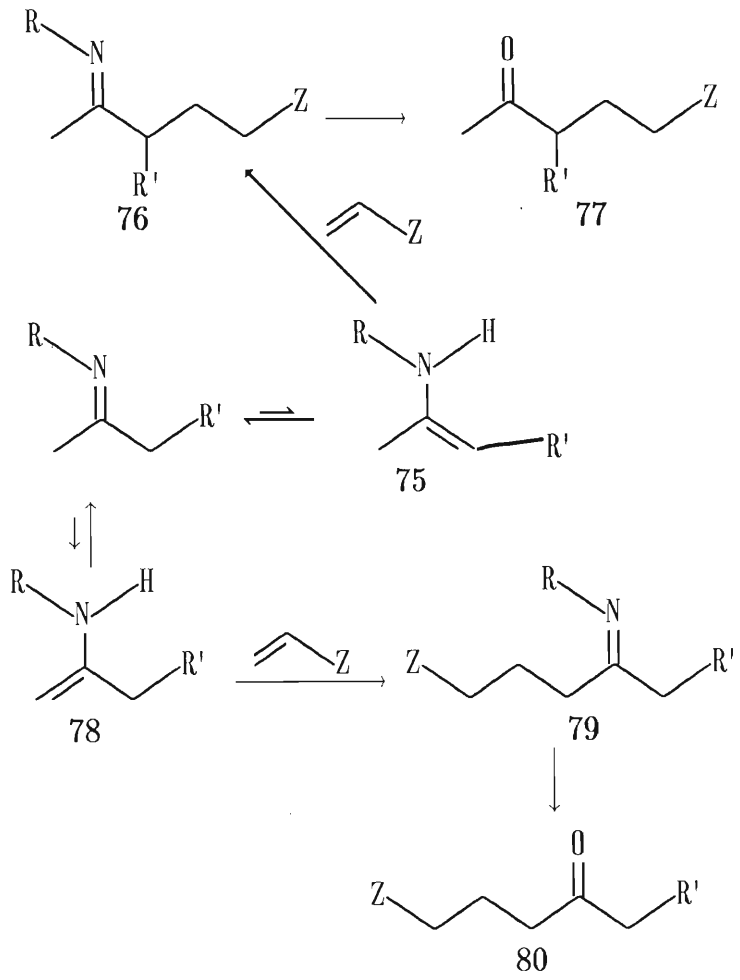
Regioselective alkylation of acyclic imines with electrophilic alkenes

Imine	Substituents			Relative (%) attack at the: more substituted	less substituted
	R^1	R^2	R^3	β–position[a]	β'–position[a]
3b	Me	H	H	95	5
3b				92	8[b]
4	Et	H	H	90	10
3d	Me	Me	H	100	0
3d				97	3[b]
3e	Me	Me	Me	80	20
3e				78	22[b]
3f	*i*–Pr	H	H	50	50
3f				30	70[b]

[a] β or β' refer to the reacting secondary enamine tautomer and corresponds to the α– or α'–position of the imine precursor.
[b] Z = SO_2Ph

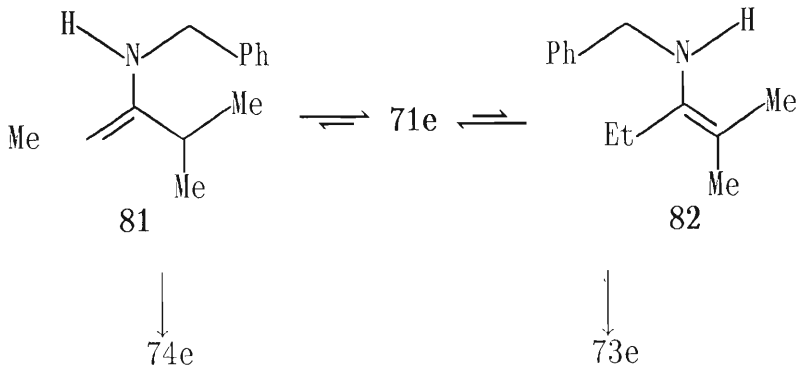
The explanation offered for the above results is analogous to the reasoning used to explain the regioselective 2,2–disubstitution of imines.[89,93] Normally it is not possible to observe secondary enamine tautomers in the proton NMR spectra of imines even though this has been clearly demonstrated as already discussed. If one considers the unsymmetrical acyclic methyl ketones, the imine may be in equilibrium with two secondary enamine tautomers (**Scheme 14**: **75** and **78**). It is, however the more substituted double–bond isomer (**75**) which is thermodynamically favoured since it is able to adopt a conformation in which no $A^{1,3}$–strain exists between the R and R^1 substituents. So when R is relatively small (i.e. Me), the steric impediment is zero or very small, and reaction occurs with the major enamine tautomer (**75**), which gives the more substituted ketone (**77**). But as the size of the R^1 substituent increases (**Scheme 13**: Imines **72** and **71f**) where R' = ethyl or *iso*–propyl respectively, the steric impediment preventing reaction with **75** becomes evident and the reaction proceeds *via*

the less substituted enamine tautomer **78**, which in turn leads to the less substituted ketone (**80**: **Scheme 14**).



SCHEME 14

For imine **71e**, the less substituted enamine tautomer **81** (**Scheme 15**) is possibly more thermodynamically stable than **78** (**Scheme 14**), because of the stabilising effect of the methyl substituent at the β'–position. This means that **81** will be present in greater concentration than **82** (**Scheme 14**) [**81** $\rightleftharpoons$ **71** $\rightleftharpoons$ **82**].



SCHEME 15

Because of this the ratio of attack at the more substituted to less substituted position falls from 9:1 for **75** (R' = ethyl) and **78** (R' = ethyl) to 4:1 for **82** and **81**. Attack at the less substituted β'–carbon of imine **71f** results in the ratio decreasing further to 1:1 or even 3:7 in favour of such attack, because of the steric impediment of the bulky *iso*–propyl group at the the more substituted β–carbon of **75** (R' = *i*–Pr), and more reaction is channeled through the less substituted tautomer (**78**; R' = *i*–Pr), even though the latter is present to a much smaller extent.

The fact that phenyl vinyl sulphone attacks more readily at the less substituted β'–position than either methyl acrylate or acrylonitrile is probably due to steric interactions between the bulky phenyl group and the imine.

It was not possible to say whether the formation of **76** or **79** occurred *via* the normal enamine reaction mechanism or *via* a one–step aza–ene reaction, but as a result of Hickmott and Rae's work[89] the prospect of a rearrangement, after initial reaction with **78**, to **76** may be ruled out. These authors note that no bis–alkylation took place even when 5 equivalents of the electrophilic alkenes were used as in the alkylation of the symmetrical imine **71c**.

This survey of the literature lays the foundation for the work carried out by the author.

The work carried out by Brookes[92] and fully described above was a continuation of the work of Rae, where during his work towards a Masters degree,[94] it was shown that the alkylation of N–(2–butylidene)benzylamine occurred at the more substituted position.

SECTION 2

2.1 FOREWORD TO EXPERIMENTAL

This section is situated in this position since the following four sections each has an experimental section attached immediately following the discussion sections, and also as the information below applies to all four experimental sections.

2.1.1 NUCLEAR MAGNETIC RESONANCE:

The ^{13}C nuclear magnetic resonance spectra were recorded in deuteriochloroform solution, unless otherwise stated, using the carbon probe of a Varian Associates CFT–20 or CFT–20A nuclear magnetic resonance spectrometer operating at 20 MHz, a Bruker Instrument operating at 125 MHz, and a Varian Gemini 200 Instrument operating at 50 MHz, using the central line of the deuteriochloroform triplet at δ 77,09 or trimethylsilane (TMS) singlet at δ 0,00 as reference peak.

The ^{1}H nuclear magnetic resonance spectra were recorded in deuteriochloroform on a Varian Associates T–60 spectrometer operating at 60 MHz; a Varian CFT–20, CFT–20A or Varian Gemini 200 operating at 80, 80 or 200 MHz respectively. The remainder of the ^{1}H nuclear magnetic resonance spectra were run on a Bruker instrument operating at 500 MHz.

Unless otherwise stated the internal standard was tetramethylsilane (TMS).

The following abbreviations were used when assigning the spectra:

s : singlet;	d : doublet;	q : quartet;
m : multiplet;	c : complex;	br : broad;
o : overlaid;	J : coupling constant (Hz);	
dd: doublet of doublets.		

2.1.2 INFRA–RED SPECTROSCOPY

The infra–red (IR) spectra were recorded on a Perkin Elmer SP–1000 infra–red spectrometer.

The Fourier Transform infra–red (FTIR) spectra were recorded on a Nicolet 5SXC FTIR spectrometer.

Spectra were calibrated with the 1 601 cm^{-1} peak of a polystyrene film. Nujol, $CHBr_3$ or dry KBr were used as dispersing agents for solids. The spectra of oils were recorded neat, as a thin film between two KBr flats. The solvent used in liquid cells is indicated where pertinent.

2.1.3 GAS CHROMATOGRAPHY

The gas–liquid chromatography (GC) was performed on a Perkin Elmer, or Varian Associates 6000 chromatograph, using flame ionisation detection. The capillary gas chromatography (CGC) was performed on the Varian 3400 gas chromatograph. The columns used will be indicated in the text.

2.1.4 MASS SPECTROSCOPY

Mass spectra and accurate mass measurements were recorded by the Council for Scientific and Industrial Research (CSIR) in Pretoria, on a Varian Associates MAT–212 spectrometer operating at 70 eV.

2.1.5 C/H/N ANALYSES

Micro–analyses were carried out by the Department of Chemistry of the Natal University in Pietermaritzburg, by the National Chemical Research Laboratory of the CSIR in Pretoria or at Glaxo in Weir.

2.1.6 MELTING POINTS

Melting points were measured on a Kofler hot–stage melting point apparatus and are uncorrected.

2.1.7 GENERAL CHROMATOGRAPHY

Analytical thin layer chromatography (TLC) was carried out on Merck : Art. 5554 aluminium–backed silica gel (0,2 mm) plates, the silica gel containing a fluorescent indicator (F254).

All flash chromatography was carried out on Merck : Art. 9385 silica gel.

Unless specifically stated, all reagents and solvents were dried and distilled before use.

2.2 General abbreviations:

satd.	=	saturated	aq.	=	aqueous
dil.	=	dilute	conc.	=	concentrated

2.3 PURIFICATION AND DRYING OF SOLVENTS:

Where molecular sieves were used for drying solvents, between 50 and 70 g of the activated sieves were added per litre of solvent.

The electrophilic alkenes used were dried as follows:

Methyl acrylate was shaken with anhydrous magnesium sulphate, filtered, distilled (BP 80 °C) from quinol and stood over molecular sieves (4A) for 12 h. before use.

Acrylonitrile was stood over molecular sieves (4A) and distilled from quinol into a receptacle containing quinol.

Methyl vinyl ketone was treated in the same manner as acrylonitrile.

Phenyl vinyl ketone was steam distilled from the vessel in which it was prepared, extracted into methylene chloride, dried over anhydrous magnesium sulphate and finally after removal of the solvent on a rotary evaporator, it was stored over molecular sieves (3A), with a trace of quinol to prevent polymerisation.

The solvents were dried as follows:

Methanol was dried following the method in Vogel[90] used for drying ethanol. The "super–dry" methanol was prepared by heating magnesium (2,6 g), iodine (0,26 g) and methanol (50 ml) under reflux, the condenser being fitted with a drying tube. After all the magnesium had been consumed, methanol (450 ml) was added and the mixture refluxed for a further hour. The methanol was then fractionally distilled *via* a Claisen head (BP 64,5 °C) onto molecular sieves (3A; BDH Bead Type).

Benzene was distilled, collecting the fraction between 78 and 80 °C, which was stood over anhydrous calcium chloride for 24 h prior to being distilled onto molecular sieves (5A).

Acetonitrile (HPLC grade) was used without distillation and was dried over molecular sieves (4A bead type) for 24 h prior to use.

Dimethylsulphoxide (DMSO) was distilled and stored over molecular sieves (Type 3A).

Tetrahydrofuran (THF) (Aldrich Chemical Company) was used directly and was removed from the bottle *via* a septum using dry nitrogen to replace the solvent removed.

Hexane was distilled and dried over sodium wire for 24 hours prior to use.

Dioxane was allowed to stand over powdered KOH for 4 days, prior to distillation into a flask containing dry molecular sieves (4A; 50 g/l).

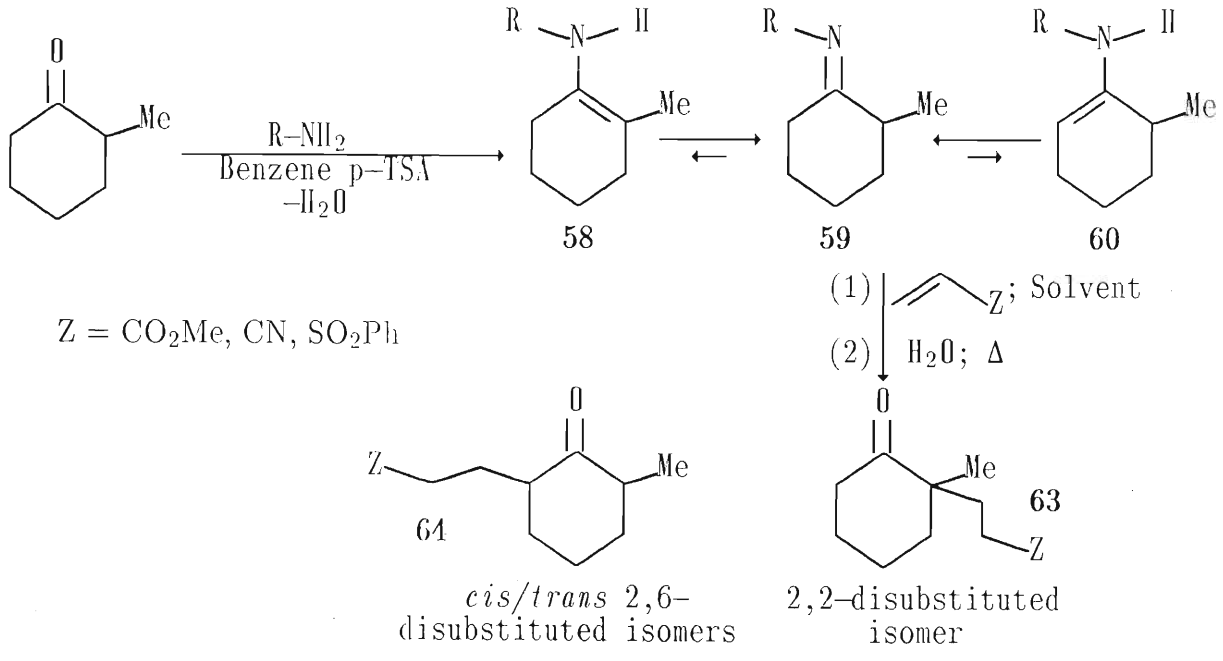
Ethyl acetate was heated under reflux over P_2O_5 for 30 minutes and then distilled onto molecular sieves (4A; 50 g/l).

2.2 ALKYLATION OF 2–METHYLCYCLOHEXANONE IMINES WITH ELECTROPHILIC ALKENES.

2.2.1 DISCUSSION

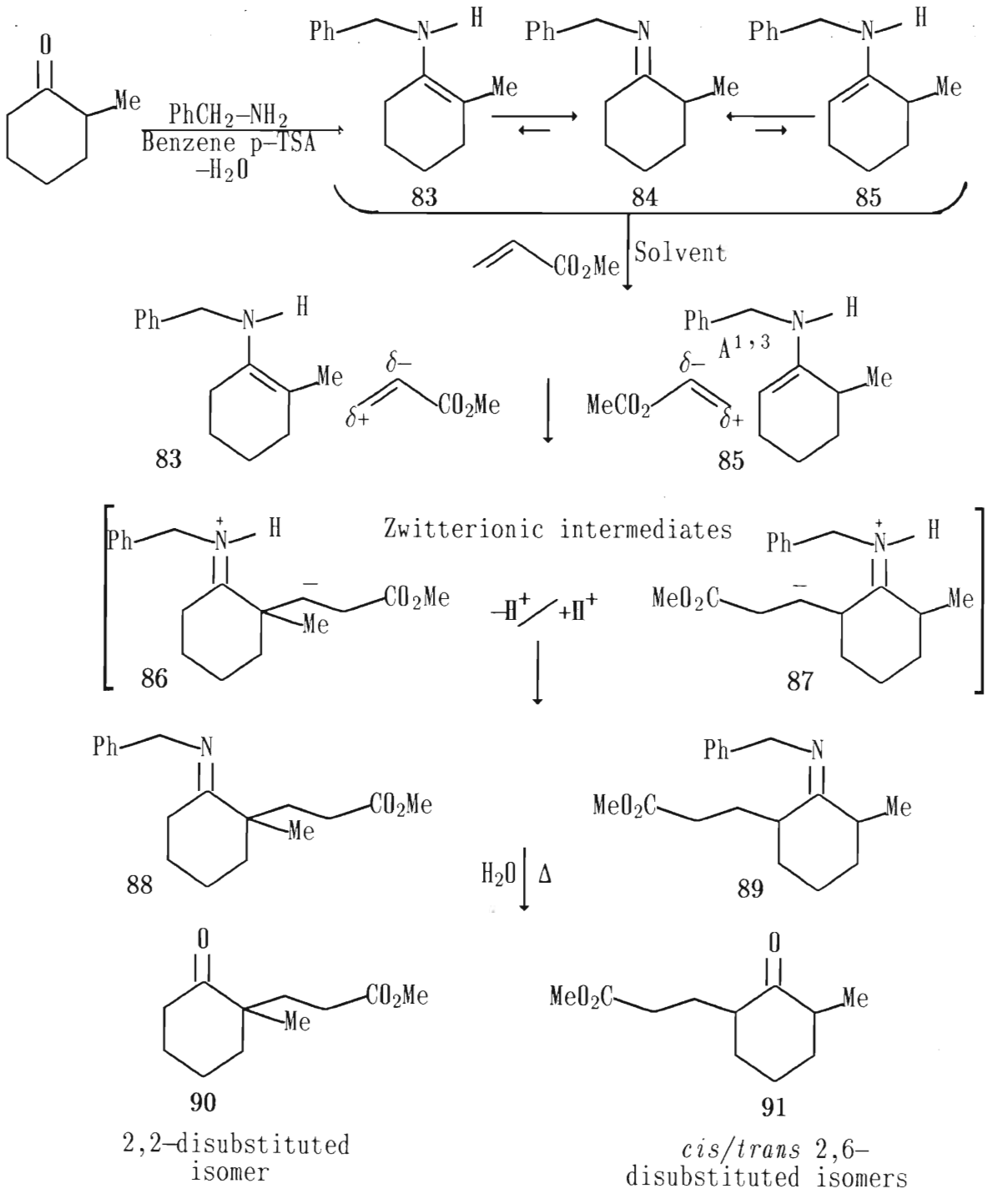
The first part of this study is a direct continuation of the pilot project presented in partial fulfillment of the requirements for the degree of Master of Science, in the Department of Chemistry, University of Natal, Durban, in 1984. The pilot study revealed that the alkylation of 2–methylcyclohexanone using various electrophilic alkenes was highly regioselective[89] and that the major products, in all cases, were the 2,2–disubstituted cyclohexanones. The aim of the first part of this work was to optimise of the reaction conditions in an attempt to maximize the yield of the 2,2–disubstituted product.

The reaction in outline is as follows:



SCHEME 16

The reaction proceeds because imine (**Scheme 16: 59**) is in tautomeric equilibrium with the enamine forms (**Scheme 16: 58, 60**). However, the enamine forms cannot be observed in either the infra-red spectrum or in the proton or carbon nmr spectra due to the very low concentrations present.



SCHEME 17

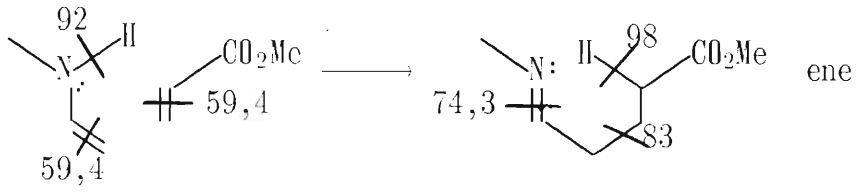
REACTION MECHANISM

Referring to **Scheme 17** above, the direction of attack of the methyl acrylate is determined by the fact that the imine of 2–methylcyclohexanone (**84**) is in equilibrium mainly with the more substituted secondary enamine (**83**) rather than with the less substituted double bond isomer (**85**). This is because enamine (**83**) is stabilised over enamine (**85**) by the hyperconjugative interaction of the methyl group without incurring the allylic destabilisation ($A^{1,3}$–strain[23]) which is normally associated with a tertiary enamine,[3,10] since the bulky N–alkyl substituent has been replaced by a hydrogen atom in **83** and **85**. Imine (**88**) which is produced by alkylation of enamine (**83**) has no $A^{1,3}$–strain and minimal $A^{1,3}$–strain in the transition state leading to it, and so the major product should be the 2,2–disubstituted cyclohexanone after hydrolysis of the imine. This was verified fully in the pilot project[94] previously mentioned. In Section 2.2, it will be shown that the step from enamine (**85**) to imine (**89**) is irreversible in that no 2,2–disubstituted product (**90**) is formed when imine (**89**) is exposed to the same reaction conditions with or without the presence of the methyl acrylate. Thus there is no question of imine (**89**) being formed preferentially and then undergoing a rearrangement to imine (**88**).

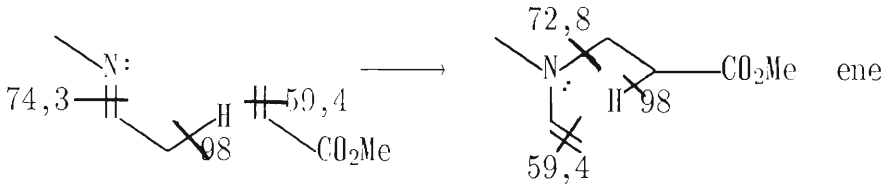
It is difficult to imagine enamine (**83**) reacting appreciably faster than enamine (**85**) regardless of whether the reaction proceeds *via* a reactant–like or product–like transition state. The fact that imine (**88**) forms preferentially over imine (**89**) can most likely be attributed to the very small amount of enamine (**85**) present at equilibrium.

At this stage more needs to be said concerning the mechanism of this reaction. In 1986 Lin *et al.* [97] state quite categorically that simple imines, in contrast to either alkenes or even carbonyl compounds,[98] do not participate in the ene reaction. However, the retro–ene reaction of allyl imines and

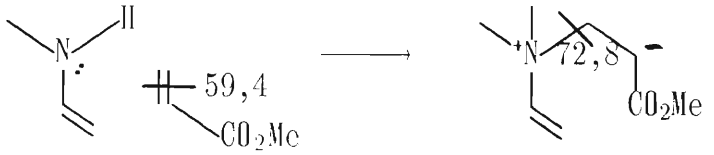
alkenes is well–known.[99] Successful ene reactions have only been reported for strained imines,[100] iminium ions,[101] and a few N–sulphonyl imines.[102] Consider the following bond energy and enthalpy calculations for the enamine and ene reactions: (based on bond energies given by Lin.[97])

(a) 

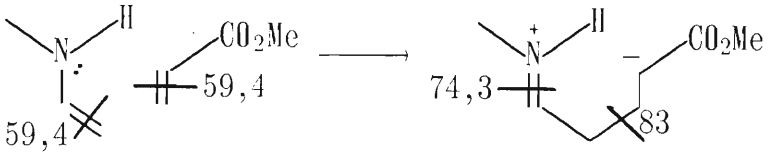
$\Delta H = 92 + 59{,}4 + 59{,}4 - 74{,}3 - 98 - 83 = -44{,}5$ kcal/mol (Very Exothermic)

(b) 

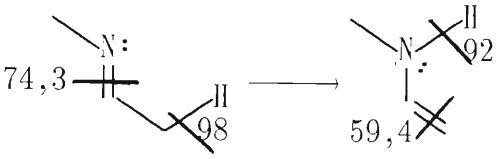
$\Delta H = 74{,}3 + 98 + 59{,}4 - 72{,}8 - 98 - 59{,}4 = +1{,}5$ kcal/mol (Slightly Endothermic)

(c) 

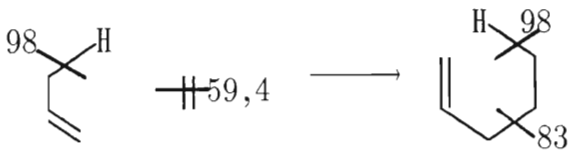
$\Delta H = +59{,}4 - 72{,}8 = -13{,}4$ kcal/mol (Exothermic)

(d) 

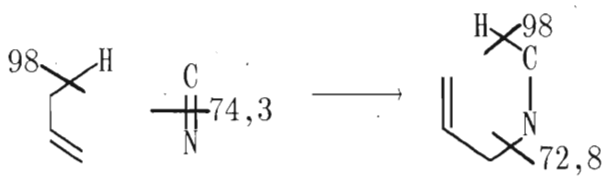
$\Delta H = +59{,}4 + 59{,}4 - 74{,}3 - 83 = -38{,}5$ kcal/mol(Exothermic)

(e) 

$\Delta H = 74{,}3 + 98 - 92 - 59{,}4 = +20{,}9$ kcal/mol (Endothermic)

(f) 

$\Delta H = +98 + 59{,}4 - 83 - 98 = -23{,}6$ kcal/mol (Exothermic)

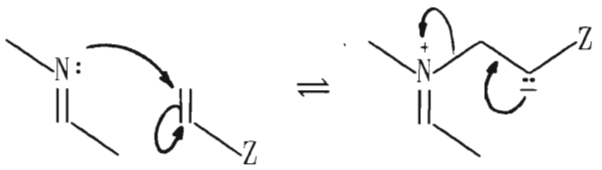
(g) 

$\Delta H = +98 + 74{,}3 - 98 - 72{,}8 = +1{,}5$ kcal/mol (Slightly Endothermic)

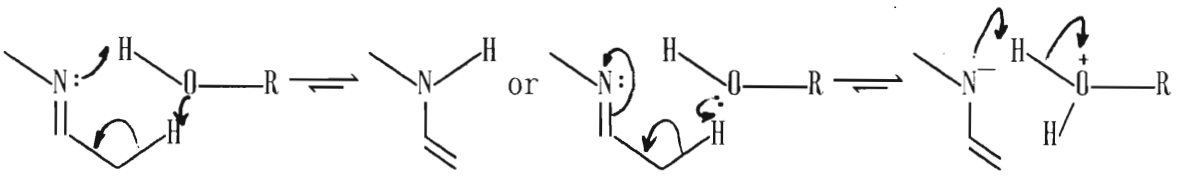
(i) From the bond energy consideration and enthalpies of competing reactions, N–alkylation by the ene–reaction [reaction (b)] seems to be energetically more favourable than enamine formation [reaction (e)]. It is thus surprising that C–alkylation occurs at all. However three factors presumably compensate for this:

Firstly, the enamine C–alkylation, and to a lesser extent N–alkylation, is an appreciably exothermic reaction whether *via* the ene–reaction (a) or the zwitterionic pathway (d) (ΔH = –44,5 and –38,5 kcal/mol respectively), so the secondary enamine tautomer is likely to be rapidly removed, and the equilibrium displaced.

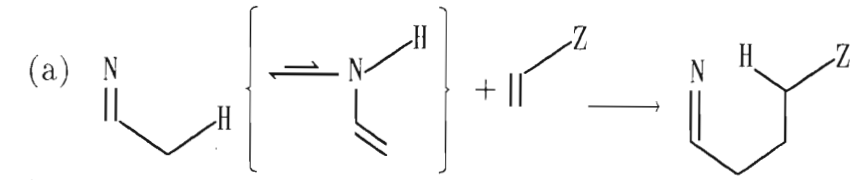
Secondly, interaction with the nitrogen lone–pair is more likely than C=N bond fission (bond energy: 74,3 *versus* 59,4 kcal/mol for a C=C bond fission) giving a zwitterion, the formation of which would be reversible, *i.e.*



Thirdly, enamine formation will be favoured by protic or oxygen containing solvents or solvents of high dielectric constant such as acetonitrile, thus lowering the activation energy for the tautomeric shift.

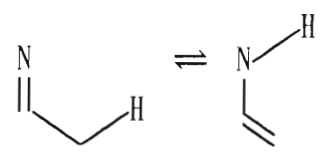


(ii) Since the enthalpy of formation of the C–alkylated product from the imine *via* the ene–reaction ($\Delta H = -23{,}6$ kcal/mol) *i.e.*



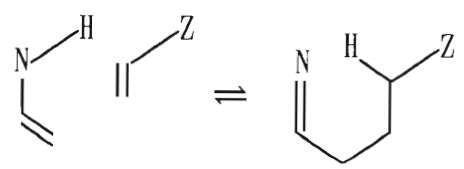
$\Delta H = 59{,}4 - 83$ kcal/mol
$= -23{,}6$ kcal/mol.

i.e.

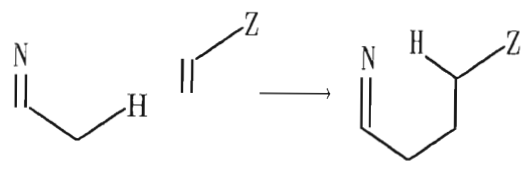


$\Delta H = +20{,}9$ kcal/mol

\+

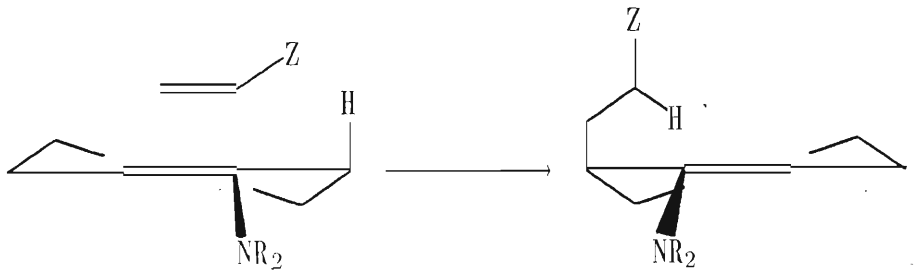


$\Delta H = -44{,}5$ kcal/mol



$\Delta H = -23{,}6$ kcal/mol

is the same as that from the tertiary enamine *via* ene–reaction:

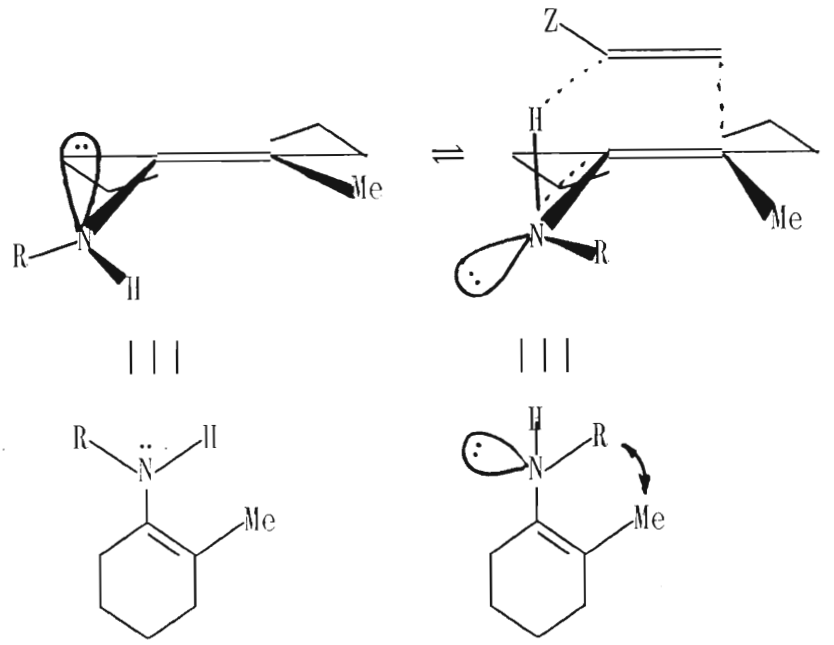


$$\Delta H = +59{,}4\ (C{=}C) - 83\ (C{-}C) = -23{,}6\ \text{kcal/mol.}$$

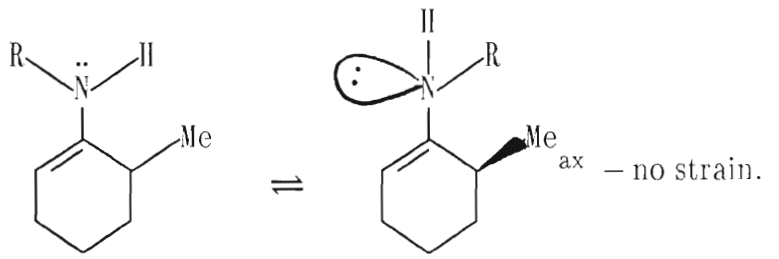
And, since tertiary enamines are well known to react with electrophilic alkenes *via* a two–step zwitterionic pathway, it was reasonable to assume that secondary enamines react in the same way.

The rate determining step is likely to be the formation of the secondary enamine, so the fact that the reaction goes better in methanol, than say benzene, is irrelevant to the mechanism. It does not in itself rule out the ene–pathway, which should be unaffected by the solvent *vis–a–vis* the two–step zwitterionic route.

Finally for the ene–reaction to occur, the conjugation of the enamine system has to be disrupted by rotation about the C–N bond, *viz.*



This clearly re–introduces an element of allylic strain* and if this mechanism appertained, alkylation of the less substituted enamine tautomer would be expected, *viz.*:

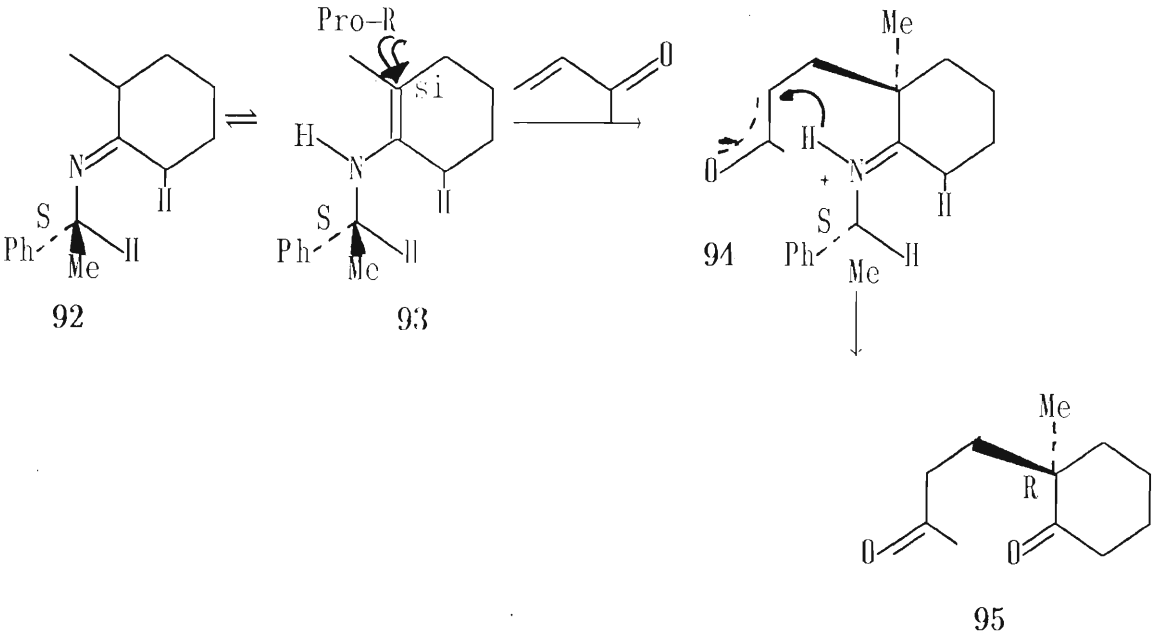


– no strain.

(*This can be removed by pyramidal inversion but both this and the rotation process requires energy (≈ 10 kcal/mol for vinylamine) where steric effects are minimal, with the consequent increase in activation energy.)

The enthalpy of alkylation of the imine has been shown to be the same as that for the tertiary enamine. For the ene–reaction (a) on page 47 the enthalpy of reaction is more negative than the enthalpy for the reaction (d) which involves a zwitterionic intermediate i.e. the classical enamine reaction. This is borne out by the recent work of Sevin *et al.* [103], Pfau *et al.* [104,105] and d'Angelo *et al.* [106,107,108] which indicates that the reaction mechanism proceeds *via* the ene–mechanism. The theories of Sevin *et al.* in their molecular orbital study[103] will be examined in some detail because they use the techniques of quantum mechanical calculations and molecular orbital theory to elucidate the reaction mechanisms.

Pfau *et al.* [91] observed high diastereofacial selectivity (≈90 %) for the reaction:



SCHEME 18

and both high chemical and optical yields were obtained.

Sevin, Pfau and Tortajada[103] adopted a different strategy to Seebach *et al.*[109] to arrive at the structure of the transition state. Instead of using a model for the transition state which was deduced from the reaction products, their work was based on a quantum mechanical study of the reactants which leads to the composition of the transition state. Using various geometric arrangements of model compounds, they attempted to define the electronic and steric aspects in order to propose a simple model which would be used for actual testing.

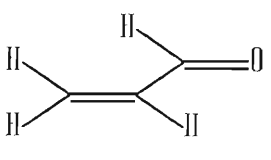
From **Scheme 18**, certain salient features were extracted in order that a simple enough reaction model could be defined which could be subjected to numerical testing via quantum mechanics.
The imine **92**, N–(2–methylcyclohexylidene)–(S)–(–)–1–phenylethylamine is in tautomeric equilibrium with enamine **93**. Enamine **93** reacts with methyl vinyl ketone (MVK) to give the zwitterion **94** which undergoes intramolecular proton transfer, and after hydrolysis gives the (R)–(+)–diketone **95** with enantiomeric excess of 91 %. This means that alkylation takes place mainly at the pro–R face of **93** in a quasi–axial manner. The proton transfer in **94** is assumed to be rapid unless the zwitterion has an unfavourable geometry. This observation is borne out by the fact that Michael additions to cyclohexenones proceed mainly *via* axial attack.[110]

Sevin *et al.*[103] then examined the nature of the reactants. Enamine **93** has a π–system comprising 2 electron pairs located on 3 atomic centres (N–C–C).

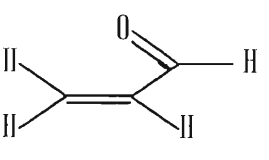
This system is isoelectronic with an allylic anion with 2 electrons in a molecular orbital (MO) of high energy. In terms of the theory governing hard and soft acids and bases[111] this moiety is then a 'soft' nucleophile which means that if it interacts with the soft acid centre of the conjugated ketone, such interaction will in all probability involve frontier orbital interactions.[112]

On this evidence, Sevin *et al.* propose that the transition state will have largely the same geometry as the optimal approach of the reactants, which will be governed by both MO interactions and steric (non–bonded) effects.

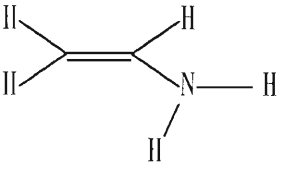
As molecules of the complexity of those appearing in **Scheme 18** cannot be used in an *ab initio* quantum mechanical calculation, simpler molecules with structures **96(a)**, **96(b)** and **97** were selected to investigate the various reaction possibilities:



96(a)



96(b)



97

Initially consideration was given to the formation of a carbon–carbon bond between the terminal carbons of molecules **96** and **97**. As both molecules are virtually planar, MO overlap is favoured when each molecule occupies a plane parallel to the other. (Refer: **Figure 1**).

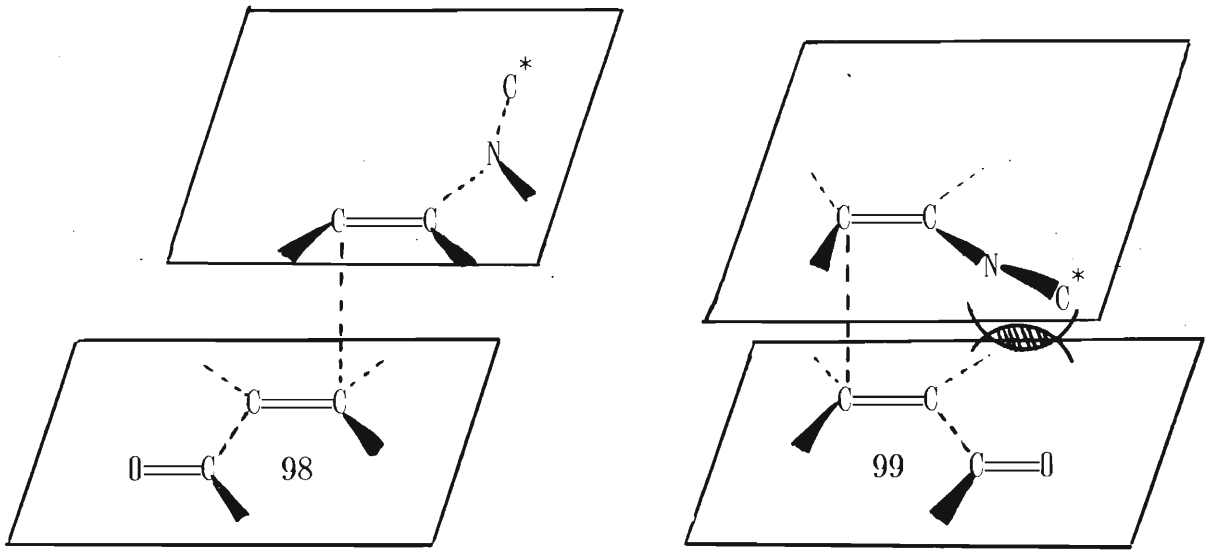
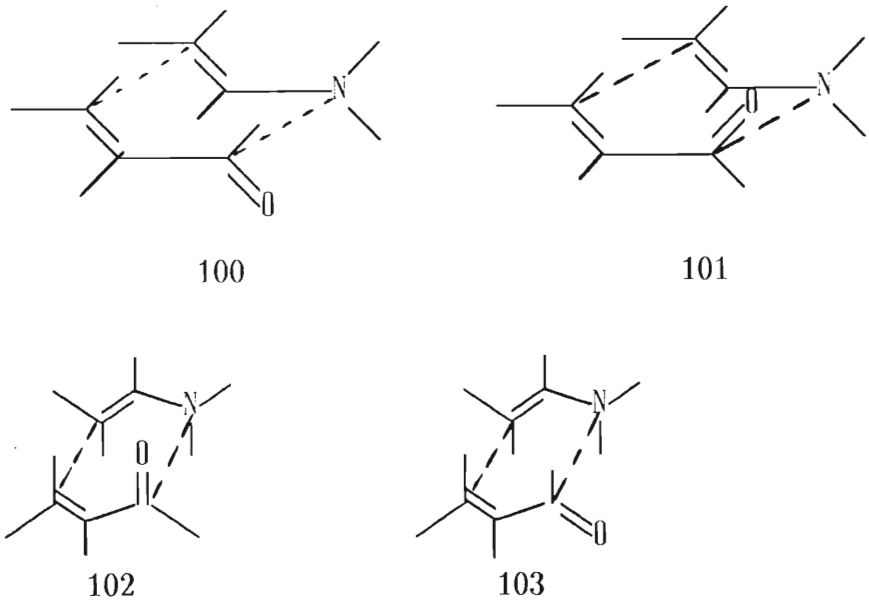


FIGURE 1

Diagrams **98** and **99** (**Figure 1**) are the limiting structures. In structure **98**, which represents the loose approach between reactants **96** and **97**, the steric interactions are at a minimum but the chiral centre α to the N–atom is far from the other atoms that it would not be possible for asymmetric induction to occur.

In the close or compact structure represented by structure **99** (**Figure 1**), the chiral centre lies much closer to the rest of the system and may well result in the induction of chiral interactions. The authors point out that the structure is sterically congested and will not be favoured unless of course favourable MO interactions occur.

They studied five types of structures: the all–trans, loose structure **98**, and the four compact geometries **100** – **103**, depicted in **Figure 2**:



100 **101**

102 **103**

FIGURE 2

The molecules in **Figure 2** comprise two sets:

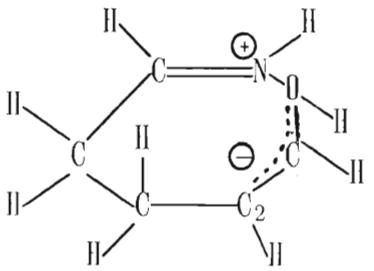
The three atoms of **97** (N–C–C) and the three carbons of **96** may be arranged so as to form a pseudo–six–membered ring, which has a boat-conformation in **100** and **101** and a chair–conformation in **102** and **103**. The difference between **100** and **101** is the relative position of the carbonyl with respect to the concavity of the ring. In **102**, the carbonyl is pseudo–axial and in **103** it is pseudo–equatorial.

Their *ab initio* calculations were carried out using standard procedures,[113] and all geometries were optimized, using two levels of optimization.

The first involved the optimization of all the geometrical parameters of **96(a)**, **96(b)** and **97**. The second involved maintaining the reactant molecules (**100** – **103**) in parallel planes and freezing the CH and NH bond lengths,

with all the other parameters optimised. A preliminary scan and calculation revealed a suitable interplanar displacement 27,5 nm, at which displacement the overlap of the π–systems is noticeable. Any decrease in interplanar displacement results in an increase in the potential energy of the system. The related π–overlap was calculated to be of the order if $\approx$ 0,1 and the overall repulsion energy to be $>$ 10 kcal/mol with respect to infinite separation, and it was concluded that such values are suitable for the perturbation theory analysis.

Sevin *et al.* also attempted to optimize the zwitterionic intermediate **104**:



104

which caused them to encounter many technical difficulties. A minimum energy could not be obtained, but in the vicinity of the molecule depicted in **104** the potential energy was found to change smoothly, indicating that the system has a stable conformation. This is perhaps the most important discovery of this paper, in that although zwitterion **104** may be regarded as a local energy minimum, the zwitterion is unlikely to form because of its high potential energy. Sevin *et al.* proposed that a "facile proton transfer from NH_2 to C_2, occurring more or less concomitantly with the C–C bond formation, would indeed prevent the system from passing through a high energy zwitterionic transient species."

TABLE 7

Compound	Energy (au)	Relative Energy (kcal/mol)
97	-132,326444	
96(a)	-189,689880	
96(b)	-189,689884	
96+97(∞)	-322,016324	0,00
100	-321,995306	13,19
101	-321,996254	12,59
102	-322,002313	8,79
103	-322,000934	9,65
98	-322,003870	7,81
104	-321,873685	89,50

The data calculated by Sevin *et al.* is given above in **Table 7.**

From these data, it is clear that the lowest energy structure is the all–trans loose arrangement **98**. The compact chair structures **102** and **103** have approximately the same energy.

The compact boat structures **100** and **101** are less stable but the difference between the energy of **98** and these structures is very small. From this it is concluded that the compact structures will be highly favoured with respect to the structure (**98**) in which all steric effects are absent. Also, in structures **100** and **101** the maximum number of bonds are in the eclipsed conformation and hence one would expect the non–bonded repulsive interactions to be a maximum which would account for the higher energy of these structures, compared with **98**. The remainder of this work involved the use of MO theory to account for the further stabilisation of the compact structures.

Consider **Figure 3** below:

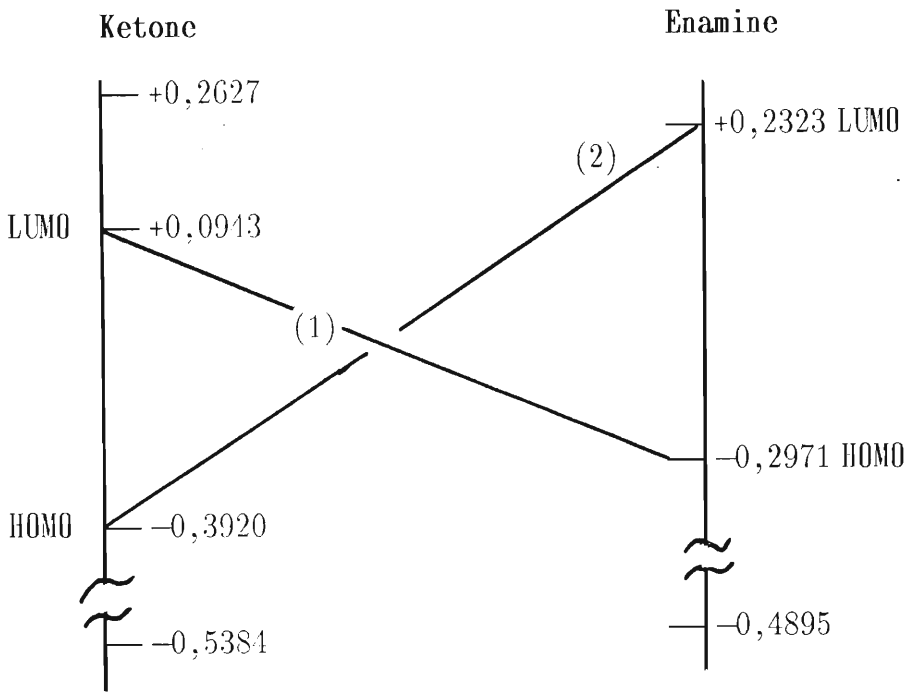
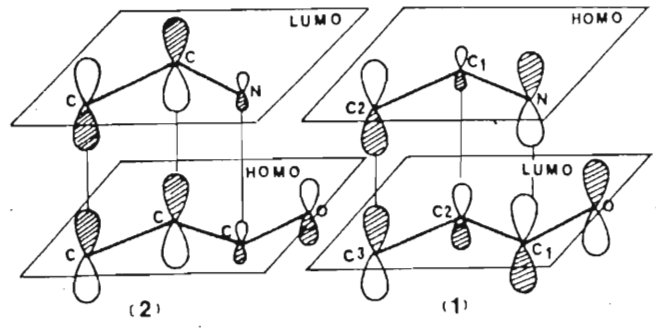


FIGURE 3:

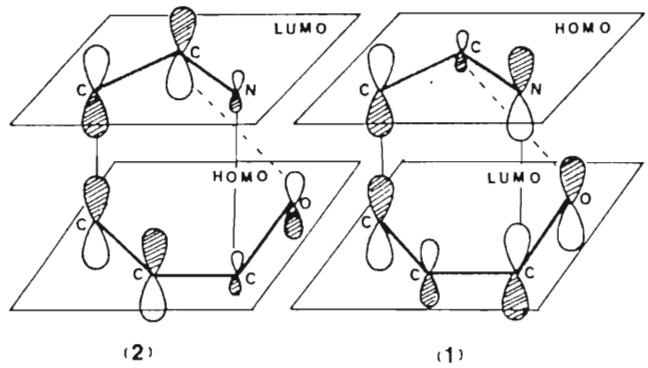
Calculated energies (au) for the frontier orbitals of **96** and **97**.

HOMO = Highest occupied molecular orbital
LUMO = Lowest unoccupied molecular orbital.

As the terminal carbon atoms approach to form a bond, two stabilising two–electron interactions must be considered, *viz.* between the HOMO and the LUMO of each system, respectively. These two interactions are shown as (1) and (2) in Figure 3. The perturbation interaction which arises from two non–degenerate MO's is $\approx S^2/\Delta E$, where S is the degree of overlap and ΔE is the energy difference between the two levels. To a first approximation, the overlap of the MO's of the two terminal carbon atoms is approximately the same for both cases. This means that interaction (1) will be more important as it is of lower energy. However, other overlaps must be considered.



BOAT 100



CHAIR 102

FIGURE 4:

Figure 4 above shows the representation of Sevin *et al.* of the MO arrangement for molecules **100** and **102**. The lobes have been drawn by the authors to be approximately proportional to their calculated coefficients and, because C–C bond formation was desired, the overlap was taken as positive, which fixed the relative signs of the other contributions. The numbers in **Figure 4** correspond to the numbers in **Figure 3**.

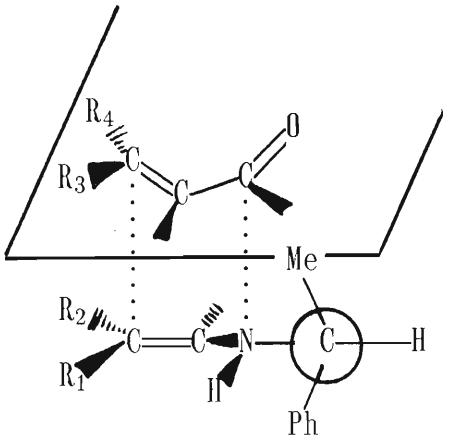
There will be an attraction between the terminal carbon lobes as well as an attraction between the nitrogen of the enamine and the carbonyl carbon of the propenal in both diagrams marked (1) in **Figure 4**. However, in Figure 4: Boat (1), C_1 of the enamine and C_2 of the propenal will form a repulsive interaction which is not present in Figure 4: Chair (1) because the two

carbon atoms are not coincident. So the favoured structure is Figure 4: Chair (1). A further effect results from the position of the oxygen atom in the s–cis configuration, shown by the dotted lines in Figure 4. This interaction provides an additional stabilisation for both Chair (1) and (2) but is not present in either of the s–trans structures.

These attractive interactions in the chair structures of the compact systems are likely to compensate for the non–bonded repulsions which occur in such systems.

Sevin *et al.* discuss asymmetric induction using their compact model. Consideration of enamine **93** (**Scheme 18**) identifies two series of problems concerning the N–substitutents. Firstly, the N–ethene unit is assumed to be very nearly planar which implies that the most stable geometry corresponds to the smallest interaction between the ethylenic methyl and the smallest substituent on the N, which in this case is H. Secondly, the conformation around the N and the asymmetric carbon, where this carbon is linked to the conjugated N–C–C chain. It may be inferred that the preferred conformation is where the CH lies in the nodal plane of the unsaturated system, which is the type of conformation usually observed in α–substituted ketones or alkenes.[114]

Further, if one examines enamine **93** (**Scheme 18**), this situation provides the minimum steric congestion when one considers the pseudo–equatorial H borne by the nearest saturated carbon of the cyclic structure. The conformation is shown below:



105

The flexibility of this structure is important but it may be frozen in a compact activated complex. The conformation creates two diastereotopic faces, one having a methyl group pointing into the superior half–space and the second having a phenyl group pointing into the inferior half–space (in the case of an S–carbon). As the methyl and phenyl groups are of significantly different sizes, any rotation of the two groups will result in the methyl group occupying the less hindered face.

Considering two cases:

(i) R_3 and R_4 on the ketone in **105** are identical (eg. in MVK), resulting in the formation of one new asymmetric centre, i.e. the ethylenic centre of the former enamine. This has been established experimentally;

(ii) where R_3 and R_4 are not the same, probably resulting in the formation of a second asymmetric centre, provided the structure of the reaction transition state remains unaltered.

Sevin *et al.* provide a further argument in favour of the compact activated complex in examining the evolution of the zwitterion which results in the formation of the initial C–C bond. In the structure **104**, obtained from the

least motion path starting from the boat geometry of **102**, proton transfer from NH_2 to C_2 is facile since they are close together. A comparison of the energy of **104** and **96** + **97** (**Table 7**) may not represent accurately what happens in the reaction mixture, where solvation is likely to play a major role in the stabilisation of any ionic species formed. However the high calculated endothermicity indicates that proton transfer is likely to be concerted with the addition step which would avoid the high energy incurred in the formation of the zwitterion.

Sevin *et al.* conclude that Michael–type additions might proceed *via* a compact activated complex an observation which is enhanced by the observed asymmetric induction of Pfau *et al.*'s reaction[91] which could not have occurred if the approach had involved an all–trans loose structure. Further, the proposed structure of the transition state allows for the prediction of the synchronous formation of two asymmetric centres using the same (or similar) enamine (**Scheme 18: 93**) and a 3–substituted enone. The latter has now been tested experimentally several times[91,104,105,106,107,108] and has been shown to be true.

It now becomes clear why imine alkylations attempted by the author using N–(2–methylcyclohexylidene)benzylamine and alkylating agents such as methyl iodide, dimethyl sulphate, benzyl chloride and benzoyl chloride in a wide range of solvents failed. The cyclic transition state required by the ene reaction would not have been able to form, and the preferred mode of reaction then presumably becomes one of initial N–alkylation.[9]

Further investigations on the effect of reaction time, imine concentration, other solvents, Lewis acid catalysts, weak acid and base catalysts, and the concentration of methyl acrylate, were carried out and the results are

summarised in **Table 8** (a) and (b) with some of the important results from the pilot project.[94]

The use of capillary gas–liquid chromatography with very polar columns enhanced previous experimental work such that it became possible to quantify not only the 2,2–disubstituted isomer, but also the *cis*– and *trans*–2,6–disubstituted isomers produced in the reaction. The order of elution is assumed to be: cis–2,6–, then trans–2,6– and finally the 2,2–disubstituted product. This order of elution was determined by Firrell[96] using preparative gas chromatography. It was not possible to verify whether the cis– and trans–2,6–isomers eluted from the column used in the same order as discovered by Firrell, but it was confirmed that the 2,6–isomers eluted before the 2,2–disubstituted product, by comparison against authentic materials prepared using Stork's method.[14]

The quantification of these compounds was extremely difficult as it was not possible to separate the isomers from one another in order to obtain single standards, since preparative gas chromatography was not available to the author.

Repeated attempts were made to form crystalline derivatives of the mixture of isomers, all of which failed. The rationale behind these attempts was that recrystallisation of the solid derivatives would result in the derivative of the 2,2–disubstituted isomer being obtained in a pure form, which could then be hydrolysed back to the ketone and used as a standard for the quantification of the various reaction mixtures. The failure to form a crystalline derivative was undoubtedly due to the isomeric nature of the product mixture. It was decided that the simplest way to quantify the reaction mixtures

would be to inject repeatedly the mixture of the 2,2– and 2,6–compounds, obtained after vacuum distillation, into a gas chromatograph. An auto-sampler was used to reduce injection errors. It was assumed that the response factors of the various isomers at the flame ionisation detector, because of their similar chemical composition, would be the same.

Repeated injections of the mixture of 2,2– and 2,6–isomers showed that the 2,2–isomer, the cis– and trans–2,6–isomers were present in the ratio of 57,9 : 20,1 : 22,0 respectively, with a standard deviation of 0,41 (n = 12) When the composition of the isomeric standard had been determined it was necessary to find an internal standard which had a similar general structure to the components of interest. A compound, 2–cyanoethylcyclohexanone, prepared using Stork's method,[14] was chosen since, under the chromatographic conditions cited, it eluted approximately 1 minute after the 2,2–peak. Selected chromatograms are included after the experimental section.

Reaction mixtures from various experiments were then injected onto the same column under the same instrumental conditions and, using a calibration graph, the percentage compositions of the various crude reaction mixtures were estimated.

These results are given in **Tables 8** (a) and (b). The hypothesis that 2,2–disubstitution occurs when imines of 2–methylcyclohexanone react with electrophilic alkenes was proven in the pilot project[94] previously mentioned. This provides an extremely valuable extension to the Stork alkylation reaction. It means that the regioselectivity of the reaction can be changed completely from α,α'–disubstitution to α,α–disubstitution merely by changing the amine moiety from a secondary to a primary amine. Further it was shown by the author that this reaction proceeds with either methyl acrylate, acrylonitrile,[94] or phenyl vinyl sulphone.[89]

TABLE 8 (a):

Reaction of N–(2–methylcyclohexylidene [a])benzylamine with methyl acrylate. [b]

Effect of temperature, concentration of methyl acrylate, solvent and reaction time on the yield of 2,2– and 2,6–dialkylated cyclohexanones.

No	Imine conc. ($mol.l^{-1}$)	Equiv. methyl acrylate	Solvent	Reaction time (h)	Yield[c](%)		
					2,2–	*cis*–2,6	*trans*–2,6
1	0,4	1	MeOH	4	13[d]	2	< 0,1
2	0,4	2	MeOH	4	46[d e]	2	3
3	0,4	2	MeOH	16	34[d]	2	3
4	0,4	2	MeOH	68	38[d]	2	2
5	0,8	2	MeOH	24	45[d e]	1,5	1,5
6	0,4	5	MeOH	4	64[d]	1	3
7	0,4[f]	2	MeOH	4	42[d]	3	6
8	0,4[g h]	2	MeOH	4	3[d]	< 0,1	< 0,1
9	0,4	2	benzene	4	16[d]	< 0,1	0,5
10	0,4	2	benzene	68	3[d]	0	0
11	0,2	2	benzene	96	3[d]	0	0
12	0,2	2	toluene	68	3[d]	0	0
13	0,2	2	CH_3CN	95	50[d]	1	1
14	0,4	5	CH_3CN	4	66	< 0,1	< 0,1
15	0,4	2	THF	3	54	< 0,1	< 0,1
16	0,25	5	THF	72	42[e]	< 0,1	< 0,1
17	0,4	5	THF	72	52[e]	< 0,1	0,2
18	0,4	2	DMSO	3	37	1	< 0,1

[a] Unless otherwise stated.
[b] At the boiling point of dry solvent unless otherwise stated.
[c] Analysed using GC; Mixture of stereoisomers.
[d] See reference.[94] [e] At room temperature.
[f] N–(2–methylcyclohexylidene)cyclohexylamine.
[g] N–2–methylcyclohexylidene)aniline.
[h] Mostly unreacted 2–methylcyclohexanone recovered.

TABLE 8 (b):

Reaction of N–(2–methylcyclohexylidene [a])benzylamine with methyl acrylate. [b]

Effect of solvent, concentration of methyl acrylate, reaction time, and other additives on the yield of 2,2– and 2,6–dialkylated cyclohexanones.

No	Imine conc. ($mol.l^{-1}$)	Equiv. methyl acrylate	Solvent	Reaction time (h)	Other additives	Yield[c](%)		
						2,2–	*cis*–2,6	*trans*–2,6
20	0,4	2	benzene	68	$Me_2NH.HCl$ [i]	32[d]	0	0
21	0,4	2	benzene	68	Et_3N [i]	49	< 0,1	< 0,1
22	0,4	2	benzene	24	4–DMAP [i j]	40[d]	< 0,1	1
23	0,4	2	benzene	24	4–DMAP [j k]	49[d]	< 0,5	0
24	0,4	5	benzene	24	4–DMAP [j k]	51	< 0,1	< 0,1
25	0,4	5	benzene	4	$AlCl_3$ [k]	50	0,6	2
26	0,4	5	benzene	4	BF_3 [l k]	65	0,7	1
27	0,4	2	benzene	4	$ZnBr_2$ [k]	48	< 0,1	< 0,1
28	0,4	5	benzene	24	$ZnBr_2$ [k]	44[e]	< 0,1	< 0,1
29	0,4	5	CH_3CN	4	4–DMAP [j k]	63	< 0,1	1
30	0,5	5	THF	72	$ZnBr_2$ [k]	64[e]	0,2	0,3
31	0,5	2	MeOH	4	4–DMAP [j i]	59[d]	5	1
32	0,4	5	MeOH	3	4–DMAP [j i]	90	5	3

[a] Unless otherwise stated.
[b] At the boiling point of dry solvent unless otherwise stated.
[c] Analysed using GC; Mixture of stereoisomers.
[d] See reference.[94] [e] At room temperature.
[j] 4–Dimethylaminopyridine.
[i] 1 Equivalent.
[k] 0,1 Equivalents.
[l] BF_3–diethyl etherate.

The imine, N–(2–methylcyclohexylidene)benzylamine, was prepared using the method outlined by Hickmott and Sheppard.[95] A mixture of primary amine, trace 4–toluenesulphonic acid, 2–methylcyclohexanone and benzene was heated under reflux using a Dean and Stark head to remove the water

formed azeotropically.

It was shown in the pilot study that the aniline imine of 2–methylcyclohexanone gave a very low yield of 2,2–disubstituted product which was probably due to resonance stabilisation of the imine tautomer and/or low reactivity of the enamine tautomer owing to the $p\pi$–conjugation of the nitrogen lone pair with the benzene ring. (**Table 8 (a)**: 8).

It was thus decided to use benzylamine as the primary amine although cyclohexylamine could equally well have been used as it produced very similar results to the benzylamine imine (**Table 8 (a)**: 7).

Further reasons for using benzylamine are: (1) in the proton nmr, the benzyl–CH_2 signal is usually clearly visible; (2) the aromatic region provided an easy means of determining the completeness of the reaction; (3) it gives the 2–methylcyclohexanone imine formed a sufficiently high boiling point that the imine is not removed on the rotary evaporator when the benzene is removed; (4) the imine is simple to fractionally distill in *vacuo*.

When the imine had been fractionally vacuum distilled, the purity of the fractions was determined easily using the infra–red spectra (of the various fractions.) The ketone peak is clearly seen even if a trace of the ketone is present in the imine.

It was found that the imine is very stable at room temperature in darkness, provided the flask is well sealed. In fact one imine fraction remained pure, without any decomposition to the ketone, for more than one year, the flask being stored in a cupboard.

When the concentration of methyl acrylate is increased from 1 to 2 equivalents in "super–dry" methanol dried following Vogel's[90] method for drying ethanol, the yield of the 2,2–disubstituted cyclohexanone **90**

increased from 13 to 46 % (**Table 8(a)**: **1**, **2**). Increasing the quantity of methyl acrylate from 2 to 5 equivalents (**Table 8(a)**: **6**), led to an increase in the yield of the 2,2–product from 46 to 64 %.

Doubling the concentration of the imine and carrying out the reaction at room temperature (**Table 8 (a)**: **5**) gave a similar result to reaction **2** (**Table 8 (a)**) although the yield of 2,6–isomers decreased slightly.
However an increase in the reaction time alone (**Table 8 (a)**: **3**, **4**) resulted in a decrease in the yield of the 2,2–product without effecting an increase in the yield of the 2,6–isomers.

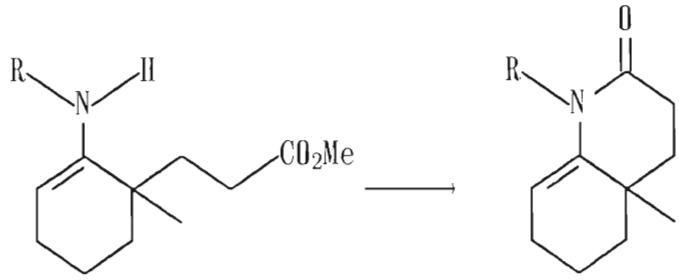
In general, enamine alkylation reactions carried out in benzene require much longer reaction times than those in methanol. It was only towards the end of the this project that it was discovered that the yield of the 2,2–product was increased in benzene when the reaction time was reduced (vide infra) !

On changing the solvent to benzene the yield of the 2,2–product is much lower than in methanol for equivalent reaction conditions. The reaction between methyl acrylate (2 equivalents) and the imine (0,4 M) in benzene gave a low yield of compound 90 of 16 %. (Cf. **Table 8 (a)**: **2**, **9**). Increasing the reaction time (normal for enamines) to 68 hours at the boil, (**Table 8(a)**: **10**) reduced the yield to 3 %, with no trace of any 2,6–isomers. This was verified on the gas chromatograph by injecting a very concentrated solution of the reaction mixture; no 2,6–peaks were observed.

The reaction was also carried out in toluene during the pilot project and

because of the low yield of 2,2–product it was decided not to investigate this solvent further. (**Table 8 (a)**: **12**). Toluene was used because its boiling point is higher than the solvents previously used and it was hoped that this might increase the yield of the reaction products.

Both benzene and toluene have low solvating abilities and this may be responsible for the low yields obtained in these solvents. It is noted that the yield of the reaction decreased on increasing the reaction time or increasing the reaction temperature. This has subsequently been found to be due to cyclisation of the intermediate: [126]i.e.



Acetonitrile has a relatively high dielectric constant and, in contrast to methanol, is aprotic. Methanol is capable of protonating the anionic intermediates (**Scheme 17**: **86** and **87**) directly, whereas in aprotic solvents the proton must be transferred either *inter*– or *intra*–molecularly. Benzene and toluene are poor solvents for this reaction because of their poor solvating ability, whereas solvents with excellent solvating characteristics may well facilitate or promote the formation of the transition state complex. This is evidenced by the fact that tetrahydrofuran (THF) is also a good solvent for this reaction though it has a much lower dielectric constant than methanol or acetonitrile.

Acetonitrile proved to be a very good solvent for this reaction. An acceptable yield of 2,2–product was obtained and the yield of 2,6–isomers was also low (**Table 8 (a)**: **14**) compared to that in other solvents. The yield of the 2,2–product was approximately the same as that when the reaction

was carried out in methanol (**Table 8 (a): 6**).

Halving the imine concentration and using an extended reaction time in acetonitrile at the boil, gave a reduced yield of the 2,2–product (50 %), and the yield of the 2,6–isomers was significant (**Table 8 (a): 13**).

Many organic reactions are carried out in THF due to its excellent solvating ability. Though is has a dielectric constant similar to that of toluene and benzene it can solvate polar species. In the two experiments carried out in THF at room temperature, fair yields of the desired 2,2–product were obtained (**Table 8 (a): 16**: 42 %, **17**: 52 %). For equal reaction times, a higher concentration of imine gave a higher yield of 2,2–product (**Table 8 (a): 17** and **16** respectively).

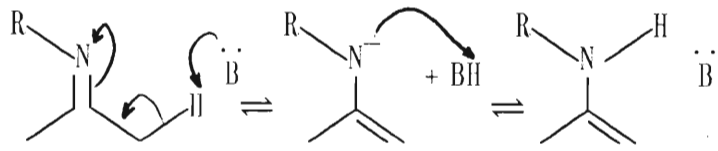
Again it is noted that the shortest reaction time at the boil resulted in the best yield for this solvent and a better yield than the yield in methanol at equivalent concentrations.

At this point it is important to note that considerable losses appear to occur during the course of this reaction. After hydrolysis, removal of the solvent on the rotary evaporator, acid workup and ether extractions, the neutralised aqueous phases were extracted with ether (and in some cases also with dichloromethane) and, apart from a small amount of alkylated imine, no other organic compounds could be isolated. Examination of the reaction mixture by gas chromatography, prior to hydrolysis, showed the presence of 2–methylcyclohexanone. It was shown that the removal of the solvent on the rotary evaporator also azeotroped off all the 2–methylcyclohexanone, and so it was not possible to determine the yields taking into account the amount of unreacted 2–methylcyclohexanone.

Reaction in dimethylsulphoxide (DMSO) (**Table 8 (a)**: 18) gave a disappointing yield of 39 % 2,2–disubstituted cyclohexanone, which may have been due to the difficulty in removing all the water from the DMSO.

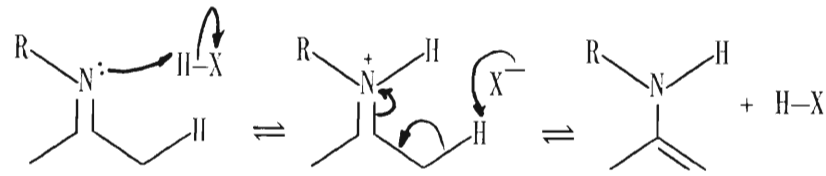
Although hydrolysis of the imine proceeds rapidly (<1 hour) at the boil, it was shown that at room temperature, even with stirring the hydrolysis proceeds very slowly.

It is known that acids and bases catalyse the conversion of imine to enamine:



The rate of both the forward and reverse reaction will be increased, but the enamine will be removed by reaction with the electrophilic alkene and so the equilibrium will be displaced to the right more rapidly.

Similar considerations also apply to catalysis using acids:



The addition of various Lewis acids and bases, and other weak acids and

bases, dramatically increased the yield of the reactions carried out in benzene (**Table 8 (b): 20 – 32**). Dimethylamine hydrochloride (1 equivalent) produced no 2,6–isomers, but, at the same concentrations, the addition of triethylamine (1 equivalent) gave a higher yield of the 2,2–disubstituted product together with traces of the 2,6–impurities.

Reducing the reaction time to 24 hours and using 4–dimethylaminopyridine (4–DAP; 1 equivalent) reduced the yield of the 2,2–product and again produced some 2,6–impurities (**Table 8 (b): 22**). However when the reaction conditions were held constant and the quantity of 4–dimethylaminopyridine was reduced to 0,1 equivalents, the yield of the 2,2–product was the same (**Table 8 (b): 23**) as that provided by the reaction in benzene with triethylamine (**Table 8 (b): 21**). When the reaction conditions were held constant and the quantity of methyl acrylate was increased to 5 equivalents, the yield of 2,2–product increased to 51 % (**Table 8 (b): 24**). A marginal increase in the yield of the 2,2–product was observed on decreasing the number of equivalents of weak base and decreasing the reaction time (**Table 8(b): 22; 23**).

When the reaction time was decreased to 4 hours (**Table 8(b): 25**) and aluminium chloride (0,1 equivalents) was used, the yield increased to 50 %, although the quantity of 2,6–isomers also increased.

Boron trifluoride diethyl etherate (0,1 equivalents), under the same reaction conditions produced the best yield of the 2,2–product in benzene (**Table 8(b): 26**), although the 2,6–isomers were still present.

Zinc bromide (0,1 equivalents) with methyl acrylate (2 equivalents) gave a 48 % yield of 2,2–product, with only trace amounts of the 2,6–isomers being produced (**Table 8(b)**: **27**). When the concentration of methyl acrylate was increased to 5 equivalents, and the reaction time increased to 24 hours, the yield decreased marginally (**Table 8(b)**: **28**). This again shows the importance of a shorter reaction time.

In acetonitrile (**Table 8(b)**: **29**), with 4–dimethylaminopyridine (0,1 equivalents) at the boil, a yield of 63 % 2,2–product was realised, which is a marginal decrease when compared to the same reaction conditions without the addition of 4–dimethylaminopyridine (**Table 8(a)**: **14**).

Reaction **16** (**Table 8(a)**) was repeated with zinc bromide (0,1 equivalents) and at higher imine concentration, which improved the yield from 42 to 64 % (**Table 8(b)**: **30**). A similar increase in yield was observed when reaction **2** (**Table 8(a)**) was repeated with the addition of 4–dimethylamino-pyridine (1 equivalent) using "super–dry" methanol as the solvent (**Table 8(b)**: **31**). When the number of equivalents of methyl acrylate was increased to 5, the concentration of imine increased slightly, the reaction time decreased to 3 hours and 1 equivalent of 4–dimethylaminopyridine added, there was a dramatic increase in the yield of the desired 2,2–product to 90 % (**Table 8 (b)**: **32**). There was however an increase in the quantity of the 2,6 isomers which may have arisen because of the increase in the concentration of the methyl acrylate. At this stage it was decided to call a halt to the optimisation of this reaction since these conditions gave an very acceptable yield except for the 2,6–impurities produced.

Finally it should be pointed out that the the effects of increasing the concentration of the imine in the reaction with both 2 and 5 equivalents of methyl acrylate were investigated. No quantification of these reaction mixtures was attempted since the yield of the 2,6–impurities had increased dramatically to a point where the reaction was synthetically useless. Further evidence for the fact that this discovery was not new appears in the work of Krimm,[77] who reported that when refluxing neat acrylonitrile with the (N–cyclohexylidene)cyclohexylamine and subsequent hydrolysis of the reaction mixture, only the 2,6–bis(2–cyanoethyl)cyclohexanone was obtained. As will be more fully described in Section 2.4, this reaction was repeated and verified. It would appear that as the concentration of imine increases, the yield of the 2,6–product also increases.

A final comment is required prior to concluding this section of the work. Pfau[91] claimed that a yield of 81 % 2,2–disubstituted product was obtained when the imine formed from (S)–(–)–1–phenylethylamine and *rac*–2-methylcyclohexanone was reacted with methyl acrylate in THF for 3 days at room temperature. It was decided to repeat the reaction under similar conditions using benzylamine in place of (S)–(–)–1-phenylethylamine. Despite several attempts, the author was unable to obtain the very high yield claimed by Pfau. It seems unlikely that the imine moiety could have such a dramatic effect on the yield of the desired 2,2–product. It is possible that salient points may not have appeared in the communication from which we worked, and this could account for the difficulty we experienced. The THF used by the author was purchased from Aldrich and was removed

under dry nitrogen via a septum which discounts the possibility that the THF was not dry.

The discovery that imines of cyclohexanone underwent 2,2–disubstitution with methyl acrylate amongst other electrophilic alkenes,[93] (**Section 2.4**) also prompted the termination of further investigations into this reaction. [This does not mean that further investigations could not have been carried out on this reaction.]

Suggestions for further investigation include:

(1). shorter reaction times using methanol, THF, acetonitrile and other solvents;

(2) reaction in benzene with BF_3–diethyl etherate at various concentrations.

(3) reaction **32** (**Table 8(b)**) with other acid and base additives at various concentrations, to determine whether the yield of the 2,6–isomers could be decreased.

(4) reaction in THF at low reaction times (2 – 3 hours) with 4–dimethylaminopyridine at various concentrations at room temperature and at the boil in an attempt to determine whether the same kind of yield could be achieved as was obtained in methanol (Reaction **32**: **Table 8 (b)**).

CONCLUSION:

From the work carried out so far, it is obvious that the best conditions for the production of the 2,2–disubstituted product are reaction **32** (**Table 8(b)**). Methyl acrylate (5 equivalents), N–(2–methylcyclohexylidene)-benzylamine (0,4 M), and 4–dimethylaminopyridine (1 equivalent) were heated in "super–dry" methanol under reflux for 3 hours.

2.2.2 EXPERIMENTAL

General method for the preparation of imines:

The imines were prepared using the method of Hickmott and Sheppard.[95] The imine used through out this section was N–(2–methylcyclohexylidene)-benzylamine which has previously been fully described.[94] The imine shows a characteristic C=N absorption at ν 1661 cm^{-1} and has a boiling point of 102 – 104° C/0,30 mm Hg (Lit.: 120 – 135° C/0,7 mm Hg).[95] The proton nmr spectrum shows three main regions: the aromatic region appears as a broad singlet centered on δ 7,18 (5H); the benzyl $-CH_2-$ occurs as a singlet at δ 4,50 (2H); the methylene/methine envelope (9H) occurs as a broad signal between δ 1,3 and 2,8 and finally the methyl group appears as a doublet (J = 7,2 Hz) at δ 1,14 (3H).

For completeness one of the preparations carried out during this phase of the work is presented:

A mixture of 2–methylcyclohexanone (56,08 g; 0,500 mol), benzylamine (58,94 g; 0,550 mol), toluene–4–sulphonic acid (0,11 g) and benzene (100 ml) was heated under reflux under a Dean and Stark head until no further water was liberated. The benzene was removed on a rotary evaporator and the crude residue fractionally distilled to give N–(2–methylcyclohexylidene)-benzylamine (85,32 g; 85%). The boiling point was constant at 102,5° C/ 0,30 mm Hg.

A repeat preparation gave yield of 87% (104,20 g; bp 102 – 105° C/0,18 mm Hg).

Accurate mass:

Found for $C_{14}H_{19}N$:	201,1517
Requires:	201,1521

Analysis of the reaction products using capillary gas chromatography:

All the analyses carried out using a 25 m , BP20 capillary column having an internal diameter of 0,25 mm. The carrier gas was helium using a flow rate of 17,1 $cm.s^{-1}$.

Instrumental Parameters:

Detector: Flame ionisation detector (FID)

Attenuation: 256 Range: 10

Injector Temperature: 210° C

Detector Temperature: 240° C

Column temperature: 100° C, isothermal for 4 minutes.

Column Ramp: 15° C/minute from 4 minutes to 200° C

Uncorrected retention times:

Cis–2,6–product[a]:	13,7 min.
Trans–2,6–product[b]:	13,8 min
2,2–product[c]:	14,3 min
Internal Standard[d]:	15,6 min.

[a]methyl 3–(*cis*–3–methyl–2–oxocyclohexyl)propanoate
[b]methyl 3–(*trans*–3–methyl–2–oxocyclohexyl)propanoate
[c]methyl 3–(1–methyl–2–oxocyclohexyl)propanoate
[d]3–(2–oxocyclohexyl)propanenitrile

General method for the reaction between methyl acrylate and N–(2–methyl-cyclohexylidene)benzylamine:

The solvents were dried and distilled (where appropriate) according to the methods outlined in the Foreword to the Experimental. All glassware was heated in an oven (100° C) and assembled whilst still hot. The reflux apparatus was sealed with a drying tube containing silica gel and allowed to cool prior to the introduction of the the reagents.

A mixture of the N–(2–methylcyclohexylidene)benzylamine, methyl acrylate and dry solvent was either heated under reflux or stirred at room temperature for the required time. A quantity of water (1 – 10 ml) was added and the mixture boiled for a period of 1 hour to effect the hydrolysis. The solvent and any residual methyl acrylate was removed on a rotary evaporator and after cooling, extracted with diethyl ether (2 x 50 ml). The ether extract was washed with dilute hydrochloric acid (2 M; 4 x 25 ml), satd. aq. sodium hydrogen carbonate (25 ml), water (25 ml), and finally with satd. aq. sodium chloride (25 ml). The ether extract was dried over anhydrous magnesium sulphate, with stirring, for 1 hour. After filtration, the ether was removed on a rotary evaporator and the residue weighed.

As was reported previously,[94] the proton nmr of the residues showed, in all cases, that the methyl doublet at δ 1,14 had collapsed to a singlet which indicated that 2,2–disubstitution had taken place.

The outline of the reactions will now be given, using the same numbering system for the reactions that appears in Tables 8 (a) and (b) in Section 1.1:

Reaction 14: Table 8 (a)

N–(2–methylcyclohexylidene)benzylamine (2,00 g; 10 mmol), methyl acrylate (4,28 g; 49,8 mmol) in dry acetonitrile (25 ml) was heated under reflux for 4 hours. Water (1 ml) was added and boiled for a further hour. After the extraction, aqueous workup, drying of the extract, and removal of the solvent, as described above, an oil (1,70 g) was obtained.

Analysis of this product using CGC showed the reaction to yield methyl 3–(*cis*–3–methyl–2–oxocyclohexyl)propanoate (<2 mg; <0,1%); methyl 3–(*trans*–3–methyl–2–oxocyclohexyl)propanoate (<2 mg; <0,1%); and methyl 3–(1–methyl–2–oxocyclohexyl)propanoate (1,29 g: 66%).

Reaction 15: Table 8 (a)

N–(2–methylcyclohexylidene)benzylamine (10,00 g; 49,7 mmol), methyl acrylate (8,54 g; 99,4 mmol) in dry THF (125 ml) was heated under reflux for 3 hours. Water (5 ml) was added and boiled for a further hour. The volatiles were removed on a rotary evaporator and to the residue was added dil. hydrochloric acid (2 M; 50 ml). After the extraction, the normal aqueous workup, drying of the extract, and removal of the solvent, as described above, an oil (6,99 g) was obtained. The acidified mother liquors were allowed to stand for approximately one hour and were then extracted with diethyl ether (100 ml). The extract was dried over anhydrous magnesium sulphate and the ether removed. This gave a further 0,79 g product.

Analysis of this product using CGC showed the reaction to yield 2–methylcyclohexanone (1,01 g;); methyl 3–(*cis*–3-methyl-2-oxo-cyclohexyl)propanoate (<9,2 mg; <0,1%); methyl 3–(*trans*–3–methyl–2-oxocyclohexyl)propanoate (<9,2 mg; <0,1%); and methyl 3–(1–methyl–2-oxocyclohexyl)propanoate (5,02 g; 54%).

Reaction 16: Table 8 (a)

N–(2–methylcyclohexylidene)benzylamine (2,50 g; 12,4 mmol), methyl acrylate (5,34 g; 62,1 mmol) in dry THF (50 ml) was stirred at room temperature for 3 days. Water (1 ml) was added and heated under reflux for an hour. After the extraction, aqueous workup, drying of the extract, and removal of the solvent, as described above, a yellow oil (1,46 g) was obtained.

Analysis of this product using CGC showed the reaction to yield methyl 3–(*cis*–3–methyl–2–oxocyclohexyl)propanoate (<2,5 mg: <0,1 %); methyl 3–(*trans*–3–methyl–2–oxocyclohexyl)propanoate (<2,5 mg; <0,1 %); and methyl 3–(1–methyl–2–oxocyclohexyl)propanoate (1,02 g; 42 %).

Reaction 17: Table 8 (a)

N–(2–methylcyclohexylidene)benzylamine (5,00 g; 24,8 mmol), methyl acrylate (10,68 g; 124 mmol) in dry tetrahydrofuran (60 ml) was stirred at room temperature for 3 days. Water (1 ml) was added and heated under reflux for an hour. After the extraction, aqueous workup, drying of the extract, and removal of the solvent, as described above, a yellow oil (3,29 g) was obtained.

Analysis of this product using CGC showed the reaction to yield methyl 3–(*cis*–3–methyl–2–oxocyclohexyl)propanoate (<4,6 mg: <0,1 %); methyl 3–(*trans*–3–methyl–2–oxocyclohexyl)propanoate (9,3 mg; 0,2 %); and methyl 3–(1–methyl–2–oxocyclohexyl)propanoate (2,41 g; 52 %).

Reaction 18: Table 8 (a)

N–(2–methylcyclohexylidene)benzylamine (1,61 g; 8 mmol), methyl acrylate (1,38 g; 16 mmol) in dry dimethylsulphoxide (DMSO) (20 ml) was heated under reflux for 3 hours. Water (1 ml) was added and heated under reflux for an hour. After the extraction, aqueous workup, drying of the extract, and removal of the solvent, as described above, a pale brown oil (1,62 g) was obtained.

Analysis of this product using CGC showed the reaction to yield methyl 3–(*cis*–3–methyl–2–oxocyclohexyl)propanoate (<15,8 mg: 1 %); methyl 3–(*trans*–3–methyl–2–oxocyclohexyl)propanoate (<1,6 mg; <0,1 %); and methyl 3–(1–methyl–2–oxocyclohexyl)propanoate (0,58 g; 37 %).

Reaction 21: Table 8 (b)

N–(2–methylcyclohexylidene)benzylamine (2,00 g; 10 mmol), methyl acrylate (1,71 g; 19,9 mmol), triethylamine (1,00 g; 10 mmol) in dry benzene (25 ml) was heated under reflux for 68 hours. Water (1 ml) was added and heated under reflux for an hour. After the extraction, aqueous workup, drying of the extract, and removal of the solvent, as described above, a yellow oil (1,66 g) was obtained.

Analysis of this product using CGC showed the reaction to yield methyl 3–(*cis*-methyl–2–oxocyclohexyl)propanoate (<2 mg: <0,1 %); methyl 3–(*trans*–3-ethyl–2–oxocyclohexyl)propanoate (<2 mg; <0,1 %); and methyl 3–(1-ethyl–2–oxocyclohexyl)propanoate (0,97 g; 49 %).

Reaction 24: Table 8 (b)

N–(2–methylcyclohexylidene)benzylamine (2,50 g; 10 mmol), methyl acrylate (4,28 g; 50 mmol), 4–dimethylaminopyridine (0,12g; 1 mmol) in dry benzene (25 ml) was heated under reflux for 24 hours. Water (1 ml) was added and heated under reflux for an hour. After the extraction, aqueous workup, drying of the extract, and removal of the solvent, as described above, a yellow oil (1,63 g) was obtained.

Analysis of this product using CGC showed the reaction to yield methyl 3–(*cis*–3–methyl–2–oxocyclohexyl)propanoate (<2 mg: <0,1 %); methyl 3–(*trans*–3–methyl–2–oxocyclohexyl)propanoate (<2 mg; <0,1 %); and methyl 3–(1–methyl–2–oxocyclohexyl)propanoate (1,01 g; 51 %).

Reaction 25: Table 8 (b)

N–(2–methylcyclohexylidene)benzylamine (5,00 g; 24,8 mmol), methyl acrylate (10,22 g; 119 mmol), aluminium chloride (0,33 g; 2,5 mmol) in dry benzene (60 ml) was heated under reflux for 4 hours. Water (1 ml) was added and heated under reflux for an hour. After the extraction, aqueous workup, drying of the extract, and removal of the solvent, as described above, a yellow oil (4,13 g) was obtained.

Analysis of this product using CGC showed the reaction to yield methyl 3–(*cis*–3–methyl–2–oxocyclohexyl)propanoate (29 mg: 0,6 %); methyl 3–(*trans*–3–methyl–2–oxocyclohexyl)propanoate (98 mg; 2 %); and methyl 3–(1–methyl–2–oxocyclohexyl)propanoate (2,46 g; 50 %).

Reaction 26: Table 8 (b)

N–(2–methylcyclohexylidene)benzylamine (5,00 g; 24,8 mmol), methyl acrylate (10,68 g; 124 mmol), boron trifluoride diethyl etherate (0,35 g) in dry benzene (60 ml) was heated under reflux for 4 hours. Water (1 ml) was added and heated under reflux for an hour. After the extraction, aqueous workup, drying of the extract, and removal of the solvent, as described above, a yellow oil (4,06 g) was obtained.

Analysis of this product using CGC showed the reaction to yield methyl 3–(*cis*–3–methyl–2–oxocyclohexyl)propanoate (0,34 mg: 0,7 %); methyl 3–(*trans*–3–methyl–2–oxocyclohexyl)propanoate (0,49 mg; 1 %); and methyl 3–(1–methyl–2–oxocyclohexyl)propanoate (3,19 g; 65 %).

Reaction 27: Table 8 (b)

N–(2–methylcyclohexylidene)benzylamine (5,00 g; 24,8 mmol), methyl acrylate (4,27 g; 50 mmol), zinc bromide (0,56 g; 0,25 mmol) in dry benzene (60 ml) were heated under reflux for 4 hours. Water (20 ml) was added and heated under reflux for an hour. After the extraction, aqueous workup, drying of the extract, and removal of the solvent, as described above, an yellow oil (3,59 g) was obtained.

Analysis of this product using CGC showed the reaction to yield methyl 3–(*cis*—methyl–2–oxocyclohexyl)propanoate (<5 mg: <0,1 %); methyl 3–(*trans*-methyl–2–oxocyclohexyl)propanoate (<5 mg; <0,1 %); and methyl 3–(1-methyl–2–oxocyclohexyl)propanoate (2,41 g; 48 %).

Reaction 28: Table 8 (b)

N–(2–methylcyclohexylidene)benzylamine (5,00 g; 24,8 mmol), methyl acrylate (10,68 g; 124 mmol), zinc bromide (0,56 g; 2,48 mmol) in dry benzene (60 ml) were stirred at room temperature for 24 hours. Dil. acetic acid (10%; 20 ml) was added and stirred for 10 hours. After the extraction, aqueous workup, drying of the extract, and removal of the solvent, as described above, an yellow oil (2,88 g) was obtained.

Analysis of this product using CGC showed the reaction to yield methyl 3–(*cis*—methyl–2–oxocyclohexyl)propanoate (<5 mg: <0,1 %); methyl 3–(*trans*-methyl–2–oxocyclohexyl)propanoate (<5 mg; <0,1 %); and methyl 3–(1-methyl–2–oxocyclohexyl)propanoate (2,16 g; 44 %).

Reaction 29: Table 8 (b)

N–(2–methylcyclohexylidene)benzylamine (2,00 g; 9,9 mmol), methyl acrylate (4,28 g; 50 mmol), 4–dimethylaminopyridine (0,12 g; 1 mmol) in dry acetonitrile (25 ml) were heated under reflux for 4 hours. Water (1 ml) was added and the mixture boiled for a further hour. After the extraction, aqueous workup, drying of the extract, and removal of the solvent, as described above, an yellow oil (1,66 g) was obtained.

Analysis of this product using CGC showed the reaction to yield methyl 3–(*cis*—methyl–2–oxocyclohexyl)propanoate (<2 mg; <0,1 %); methyl 3–(*trans*-methyl–2–oxocyclohexyl)propanoate (20 mg; 1 %); and methyl 3–(1-methyl–2–oxocyclohexyl)propanoate (1,24 g; 63 %).

Reaction 30: Table 8 (b)

N–(2–methylcyclohexylidene)benzylamine (6,32 g; 31 mmol), methyl acrylate (4,28 g; 157 mmol), zinc bromide (0,70 g; 3 mmol) in dry tetrahydrofuran (60 ml) were stirred at room temperature for 3 days. Water (1 ml) was added and the mixture heated under reflux for an hour. After the extraction, aqueous workup, drying of the extract, and removal of the solvent, as described above, an yellow oil (5,27 g) was obtained.

Analysis of this product using CGC showed the reaction to yield methyl 3–(*cis*—methyl–2–oxocyclohexyl)propanoate (12 mg; 0,2 %); methyl 3–(*trans*-methyl–2–oxocyclohexyl)propanoate (19 mg; 0,3 %); and methyl 3–(1-methyl–2–oxocyclohexyl)propanoate (3,98 g; 64 %).

Reaction 31: Table 8 (b)

N–(2–methylcyclohexylidene)benzylamine (25,00 g; 124 mmol), methyl acrylate (53,49 g; 621 mmol), 4–dimethylaminopyridine (1,52 g; 12 mmol) in dry methanol (31,6 ml) were heated under reflux for 4 hours. Water (20 ml) was added and the mixture boiled for a further hour. After the extraction (ether; 3 x 100 ml), aqueous workup (2M HCl, 4 X 50 ml; Water, 2 X 50 ml; Satd.$NaHCO_3$, 50 ml; Satd. NaCl, 50 ml), drying of the extract, and removal of the solvent, as described above, a yellow oil (27,48 g) was obtained.

Analysis of this product using CGC showed the reaction to yield methyl 3–(*cis*—methyl–2–oxocyclohexyl)propanoate (1,23 g; 5 %); methyl 3–(*trans*-methyl–2–oxocyclohexyl)propanoate (0,24 g; 1 %); and methyl 3–(1-methyl–2–oxocyclohexyl)propanoate (14,51 g; 59 %).

Reaction 32: Table 8 (b)

N–(2–methylcyclohexylidene)benzylamine (3,99 g; 20 mmol), methyl acrylate (8,52 g; 99,1 mmol), 4–dimethylaminopyridine (2,42 g; 20 mmol) in dry methanol (50 ml) were heated under reflux for 3 hours. Water (1 ml) was added and the mixture boiled for a further hour. After the extraction, aqueous workup, drying of the extract, and removal of the solvent, as described above, an yellow oil (3,93 g) was obtained.

Analysis of this product using CGC showed the reaction to yield methyl 3–(*cis*—methyl–2–oxocyclohexyl)propanoate (196 mg; 5 %); methyl 3–(*trans*-methyl–2–oxocyclohexyl)propanoate (118 mg; 3 %); and methyl 3–(1-methyl–2–oxocyclohexyl)propanoate (3,52 g; 90 %).

2.3 INVESTIGATION INTO THE MECHANISM OF THE ALKYLATION OF N–(2–METHYLCYCLOHEXYLIDENE) BENZYLAMINE WITH METHYL ACRYLATE:

2.3.1 DISCUSSION:

The referees of a paper we submitted to Tetrahedron Letters[89] suggested that imine **89** (**Scheme 19**) could form preferentially and subsequently undergo a rearrangement to imine **88** to give the 2,2–product on hydrolysis. It was suggested that we attempt to verify (or disprove) this possibility.

Firstly it was necessary to prepare the ketone **91** (**Scheme 19**) and from it imine **89**. This imine would be heated under reflux together with methyl acrylate in dry methanol, and after hydrolysis and the usual workup, the product would be analysed on capillary gas chromatography to determine whether any of the 2,6–starting ketone had undergone the suggested conversion to the 2,2–ketone (**Scheme 19**: **90**).
Secondly, imine **89** would alone be subjected to the reaction conditions without methyl acrylate because it was possible (though unlikely) that the imine may have undergone this rearrangement to the 2,2–imine without the presence of the alkylating agent.

It was decided that several further experiments be carried out which would make it easier to identify whether any rearrangement had taken place and also to determine whether the electrophilic alkene played a part in the suggested rearrangement:

Firstly, the pyrrolidine enamine of 2–methylcyclohexanone was to be alkylated with acrylonitrile to give 3–(3–methyl–2–oxocyclohexyl)-propanenitrile (**106**) and from it the benzylamine imine (**107**) would be prepared.

Imine **107** would then to be subjected to the following reaction conditions

(1) methyl acrylate in methanol heated under reflux for 4 hours;

(2) methanol alone heated under reflux for 4 hours;

(3) 4–dimethylaminopyridine (0,1 equivalents) in methanol heated under reflux for 4 hours;

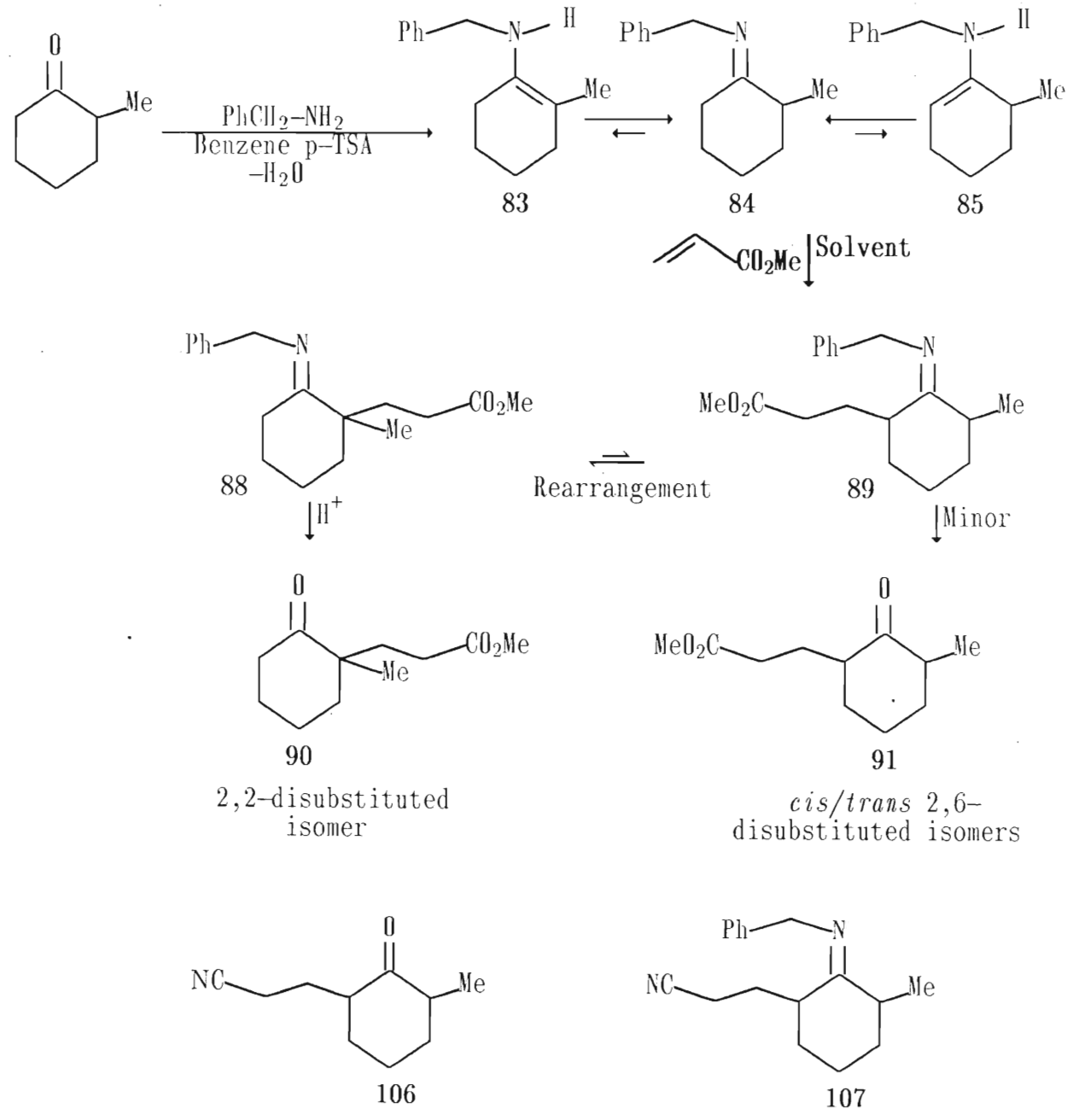
(4) methyl acrylate, 4–dimethylaminopyridine (0,1 equivalents) in methanol heated under reflux for 4 hours;

(5) methyl acrylate in methanol heated under reflux for 20 hours.

The purpose of using the methyl acrylate on the nitrile imine **107** was that if it either replaces the propanenitrile moiety or attacks C–2, the ester carbonyl signal in the infra–red would be separated from the ketone absorption and in the proton nmr spectrum, the –OMe singlet would be well downfield ($\approx\delta$ 3,6), away from the methylene/methine envelope. CGC would also show any changes to the starting ketone **106**.

The synthesis of the ketones (**91** and **106**: **Scheme 19**) was effected *via* the pyrrolidine enamine of 2–methylcyclohexanone, methyl acrylate or acrylonitrile, in dry methanol following Stork's method.[3] This gave the desired 2,6– products [methyl 3–(3–methyl–2–oxocyclohexyl)propanoate: 91 and 3–(3–methyl–2–oxocyclohexyl)propanenitrile: **106** respectively] which gave spectra and analytical data consistent with these compounds.

The formation of the imines **89** and **107** (**Scheme 19**) proved more difficult to achieve, since the imine molecules are sterically hindered, and so are difficult to synthesize.



SCHEME 19

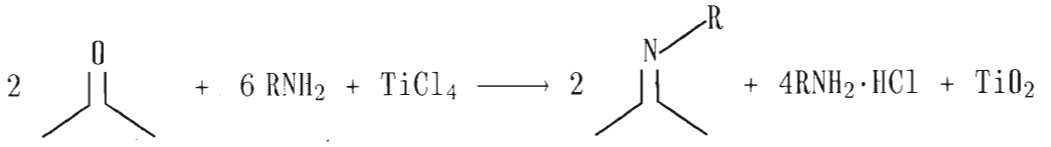
The reaction in toluene, using toluene–4–sulphonic acid as catalyst, of benzylamine and ketone **91** failed to give the desired imine **89** after refluxing the mixture under a Dean and Stark head for 21 hours. Examination of the fractions obtained from the vacuum distillation of the residue using infra–red spectroscopy showed no characteristic C=N absorption at 1660 cm^{-1}.

An attempt to form the benzylamine imine of 3–(3–methyl–2–oxocyclohexyl)propanenitrile using toluene–4–sulphonic acid as catalyst in benzene, using the same technique also failed. Fractional vacuum distillation of the residue, after removal of the solvent on a rotary evaporator, gave several fractions none of which showed the characteristic infra–red C=N absorption.

White and Weingarten *et al.*[115,116] outlined the use of titanium tetrachloride in the synthesis of enamines and ketimines of ketones or amines which were volatile or highly substituted. These papers provide highly important routes to the synthesis of sterically hindered enamines and imines.

The $TiCl_4$ is a very effective water scavenger and it can act catalytically (although not a true catalyst, since it is consumed in the reaction) in the Lewis acid sense, to polarize the carbonyl bond. The titanium atom coordinates the carbonyl oxygen which prepares it for the reaction with the amine and for the transfer of the carbonyl oxygen from carbon to titanium.[116]

The reaction in outline is as follows:



A slight excess over the stoichiometry of both amine and titanium tetrachloride gives best results for the formation of the imine.

Carlson and Nilsson[117] proposed a modified method for the generation of enamines of sterically hindered carbonyl compounds, the reactions being accomplished in very short reaction times.

The reaction involves the initial formation of the amine–$TiCl_4$ complex in dry hexane at 0° C, followed by the addition of the ketone in one portion to the reaction flask. After the addition of the ketone, the solution is allowed to return to ambient temperature and stirred for 2 hours prior to filtration through a sintered glass funnel and removal of the hexane on a rotary evaporator. It was discovered that the filtration may be speeded up considerably by placing dried diatomaceous earth onto the sinter prior to filtration and also not to fill the funnel with sample, but rather to allow a slow steady stream to hit the filter cake.

Firstly, imine **89** was prepared by the addition of ketone **91** to the preformed $TiCl_4$–benzylamine complex in dry hexane. After filtration, the hexane was removed on a rotary evaporator. In an attempt to remove as much of the excess benzylamine as possible, the residue was pumped under reduced pressure and finally fractionally vacuum distilled to give a 69% yield of the desired imine. The infra–red spectrum showed the C=N and ester carbonyl

absorptions at 1663 and 1739 cm^{-1} respectively, whilst the proton nmr spectrum showed the methyl group as a multiplet (δ 0,9 – 1,3); twelve protons in the region δ 1,3 – 2,7; the methoxy methyl as a singlet at δ 3,6; the benzyl methylene group at δ 4,5 and five benzene ring protons as a broad singlet centred on δ 7,2. The carbon spectrum showed that the compound was not very stable and had partially decomposed by the time the spectrum was run, but CGC, executed immediately after distillation indicated that the compound was quite clean and the accurate mass measurement was consistent with the structure proposed.

In a separate reaction an increase in the yield to 80% occurred when the reaction mixture was heated under reflux for 2 hours, prior to the removal of the solvent and fractional vacuum distillation.

The benzylamine imine (**89**) of methyl 3–(3–methyl–2–oxocyclohexyl)-propanoate (**91**) when heated with methyl acrylate (2 equivalents) in "super–dry" methanol heated under reflux gave, after the usual aqueous workup, only 3–(3–methyl–2–oxocyclohexyl)-propanoate (**91**). In the proton nmr of the product, the methyl doublet (δ 1,1; J = 17 Hz) had not collapsed to a singlet, as it would have done had alkylation occurred at the carbon to which the methyl group was attached. Also the methyl integrated for three protons. Further there was no evidence of any 2,2–disubstituted ketone (**90**) when the product was subjected to CGC analysis.

Similarly, when imine **89** was heated under refluxed in dry methanol for 4 hours, the product, upon hydrolysis and the usual aqueous workup gave only unchanged 2,6–disubstituted ketone (**91**).

The preparation of the benzylamine imine (**107**) of 3–(3–methyl–2–oxo-cyclohexyl)propanenitrile (**106**) was also effected *via* the titanium tetrachloride

method, the reaction mixture being heated under reflux for 2 hours prior to filtration, removal of the solvent and fractional vacuum distillation. Although the yield was relatively low (21%) the spectral and analytical data were consistent with the structure proposed for the imine. The infra–red spectrum showed both the C=N and C≡N absorptions at 1661 and 2253 cm^{-1} respectively; the proton nmr spectrum showed the methyl group as a doublet (δ 1,1; J = 7,6 Hz); twelve protons between δ 1,3 and 2,8; the benzyl methylene group as a singlet at δ 4,5 and finally the five benzene ring protons as a broad singlet at δ 7,3. The ^{13}C–nmr spectrum was consistent with the proposed structure, although some of the peaks were 'twinned' most probably due to the presence of the other possible isomers. The nitrile singlet appears at δ 120,9; the imine C=N singlet at δ 176,15; the methyl quartet at δ 16,6 and the two doublets consistent with the 2,6–structure of the starting imine at δ 31.1 and 40,0 respectively. The accurate mass measurement was consistent with the molecular formula for this compound.
A repeat reaction where the reaction mixture was stirred for 19 hours and not heated under reflux after reaching ambient temperature gave a slightly better yield (44%).

The benzylamine imine (**107**) of 3–(3–methyl–2–oxocyclohexyl)propane-nitrile (**106**) was heated under reflux in "super–dry" methanol for 4 hours and gave after the usual workup only the starting ketone (**106**). CGC also only showed 3–(3–methyl–2–oxocyclohexyl)propanenitrile (**106**). No evidence of any 3–(1–methyl–2–oxocyclohexyl)propanenitrile was seen.

Imine **107** was then heated under reflux in the presence of methyl acrylate (1 equivalent) in "super–dry" methanol for 4 hours. Again after the usual workup, no 3–(1–methyl–2–oxocyclohexyl)propanenitrile was present in the

reaction mixture.

The addition of 4–dimethylaminopyridine (0,1 equivalents) to imine **107** in "super–dry" methanol under reflux for 4 hours in an attempt to catalyse rearrangement by initial carbanion formation α– to the methoxycarbonyl group also proved fruitless.

The addition of methyl acrylate (1 equivalent) to a repeat of this reaction also showed only starting ketone **106** and no 3–(1–methyl–2–oxocyclohexyl)-propanenitrile.

This proves beyond doubt that the initial formation of the product does not involve the rearrangement of imine **107** but that the substitution takes place at the more substituted position leading, after hydrolysis, to the α,α–disubstituted ketone.

2.3.2 EXPERIMENTAL:

Synthesis of pyrrolidine enamine of 2–methylcyclohexanone.

Following the method of Stork[3] the pyrrolidine enamine of 2–methylcyclohexanone was prepared as follows:
2–Methylcyclohexanone (80,00 g; 0,71 mol), pyrrolidine (55,80 g; 0,78 mol) and 4–toluenesulphonic acid (0,1 g) in benzene (200 ml) were refluxed using a Dean and Stark water separator until no further water was liberated. The benzene and excess pyrrolidine were removed on a rotary evaporator and the resulting product was vacuum distilled to give starting ketone (16,61 g) and 3–methyl–2–(N–pyrrolidinyl)cyclohexene (84,58 g; 83%; taking into account the recovered starting ketone).

Boiling point: 70 – 77 °C / 2 mmHg (Lit.[3]: 112 – 114° C/15 mmHg).

IR:	ν_{max}	film	cm^{-1}
	1 638	C–C	

Preparation of methyl 3–(3–methyl–2–oxocyclohexyl)propanoate.

Using the method described by Firrell[96], methyl 3–(3–methyl-2–oxocyclohexyl)propanoate was prepared in the following manner: The pyrrolidine enamine of 2–methylcyclohexanone (62,09 g; 0,376 mol), methyl acrylate (32,36 g; 0,376 mol), and methanol (50 ml) were refluxed for 3 hours. Water (5 ml) was added and the mixture refluxed for a further hour. The solvent and excess methyl acrylate were removed on a rotary evaporator and the

residue extracted with ether (100 ml). The ethereal layer was washed with dil. aq. hydrochloric acid (2M; 4 x 25 ml), satd. aq. sodium hydrogen carbonate (25 ml), water (3 x 25 ml) and satd. aq. sodium chloride (25 ml). The ether solution was dried over anhydrous magnesium sulphate and after removal of the ether on a rotary evaporator, the residue was distilled under vacuum to give methyl 3–(3–methyl–2–oxocyclohexyl)propanoate (40,84 g; 54%).

In a repeat reaction, the yield was increased to 68% apparently because the reaction mixture was inadvertently refluxed for a further 2 hours after having stood at room temperature for 24 hours.

Boiling point: 102 °C / 1 mmHg (Lit.[96]: 88 –90° C/53 Pa))

IR:	ν_{max}	film	cm^{-1}
	1 669	C=O	

^{1}H NMR	δ	($CDCl_3$) ppm.
	0,9	d, J = 6 Hz, CH_3
	1,2 – 2,6	Methylene envelope; 12 H
	3,6	s, OMe

<u>Preparation of 3–(3–methyl–2–oxocyclohexyl)propanenitrile.</u>

In a similar manner the 3–(3–methyl–2–oxocyclohexyl)propanenitrile was prepared:[3]

The pyrrolidine enamine of 2–methylcyclohexanone (25,19 g; 0,139 mol), acrylonitrile (14,74 g; 0,278 mol), and methanol (50 ml) were refluxed for 3

hours. Water (5 ml) was added and the mixture refluxed for a further hour. The solvents and excess acrylonitrile were removed on a rotary evaporator and water (250 ml) was added and the mixture extracted with ether (3 x 250 ml). The ethereal layer was washed with dil. aq. hydrochloric acid (2M; 4 X 50 ml), satd. aq. sodium hydrogen carbonate (50 ml), water (50 ml) and satd. aq. sodium chloride (50 ml), and dried over anhydrous magnesium sulphate. Removal of the ether gave an oil (24,31 g) which was distilled under vacuum to give 3-(3-methyl-2–oxocyclohexyl)propanenitrile (18,04 g; 79%).

Boiling point: 130 °C / 3,3 mmHg (Lit.[3]: 132 – 133/ 2 mmHg).

IR:	ν_{max}	film	cm^{-1}
	1 713	C=O	
	2 220	C≡N	

^1H NMR	δ (CDCl$_3$) ppm.	
	0,96	d; J = 6,4 Hz; CH_3–CH
	1,1 – 2,8	Methylene envelope; 12 H

<u>Attempted preparation of the benzylamine imine of methyl 3–(3–methyl-2-oxocyclohexyl)propanoate using the azeotropic method</u>.

Methyl 3–(3–methyl–2–oxocyclohexyl)propanoate (40,84 g; 0,206 mol), benzylamine (44,15 g; 0,412 mol), 4–toluenesulphonic acid (0,12 g) in toluene (70 ml) were refluxed using a Dean and Stark water separator for 21 h. The toluene was removed on a rotary evaporator and the residue

distilled under vacuum to give four fractions. None of the fractions gave the imine, as evidenced by the absence of an imine absorption in the infra–red spectra run on each of the fractions.

Attempted preparation of the benzylamine imine of 3–(3–methyl–2–oxocyclohexyl)propanenitrile.

3–(3–methyl–2–oxocyclohexyl)propanenitrile (18,00 g; 0,109 mol), benzylamine (11,79 g; 0,110 mol), 4–toluene–sulphonic acid (0,1 g) in benzene (100 ml) were refluxed using a Dean and Stark water separator for 21,5 h. The benzene was removed on a rotary evaporator and the residue distilled under vacuum. None of the fractions showed the C=N absorption in the infra–red and hence none contained the imine.

Preparation of the benzylamine imine of methyl 3–(3–methyl–2–oxocyclohexyl)propanoate using the titanium tetrachloride method.

Following the method used by Carlson and Nilsson[99] for the preparation of enamines, a three necked, round bottomed flask (250 ml) was fitted with a pressure equalising dropping funnel, a reflux condenser fitted with a guard tube containing anhydrous calcium chloride, and a mechanical stirrer. The whole apparatus was flushed with dry nitrogen. Benzylamine (6,43 g; 60 mmol) in dry hexane (80 ml) was introduced into the flask and cooled in ice/water to 0 °C. Titanium tetrachloride (1 ml; 9 mmol) in dry hexane (10 ml) was added dropwise to the benzylamine solution with stirring and under a positive pressure of dry nitrogen. After the addition had been

completed, the methyl 3–(3–methyl–2-oxocyclohexyl)propanoate (1,98 g; 10 mmol) was added in one portion to the flask. The solution was stirred for two hours at room temperature and then filtered through oven dried diatomaceous earth contained in a sintered glass funnel (porosity 3). After filtration, the hexane was removed on a rotary evaporator and the residue pumped under reduced pressure (0,1 mmHg) in an attempt to remove as much of the benzylamine as possible to give an oil (3,98 g). A portion (3,41 g) was vacuum distilled to give a mixture of starting ketone and benzylamine (0,50 g) and the imine: *N–[2–(2–methoxycarbonylethyl)–2-methylcyclohexylidene]benzylamine* (1,98 g; 69%).

Boiling point: 148 – 150 °C/ 0,27 mm Hg

IR:	ν_{max}	film	cm^{-1}
	1 663	C=N	
	1 739	CO_2Me	

^1H NMR δ ($CDCl_3$) ppm.

0,9 – 1,3	m; 3H; CH_3
1,3 – 2,7	methylene/methine envelope; 12 H
3,6	s; 3H; OMe
4,5	s; 2H; N–CH_2
7,2	br.s; 5H; Ph–

Accurate mass:	Found:	287,1885
	Calc. for $C_{18}H_{25}O_2N$:	287,1885

In a repeat preparation, titanium tetrachloride (3 ml; 27 mmol) in dry hexane (30 ml) was added dropwise to benzylamine (19,29 g; 180 mmol) in dry hexane (240 ml) at 0 °C. To this complex, was added methyl 3–(3–methyl–2–oxocyclohexyl)propanoate (5,94 g; 30 mmol). After the

temperature had risen to room temperature, the mixture was raised to the boil and was heated under reflux for 2 hours, prior to removal of the hexane and vacuum distillation to give a mixture of benzylamine and starting ketone (2,04 g) and the desired imine in greatly improved yield (6,88 g; 80%).

Preparation of the benzylamine imine of 3–(3–methyl–2–oxocyclohexyl)propanenitrile using the titanium tetrachloride method.

Using the same general method used above, a three necked, round bottomed flask (250 ml) was fitted with a pressure equalising dropping funnel, a reflux condenser fitted with a guard tube filled with anhydrous calcium chloride, and a mechanical stirrer. The whole apparatus was flushed with dry nitrogen. Benzylamine (6,43 g; 60 mmol) in dry hexane (80 ml) was introduced into the flask and cooled in ice/water to 0 °C. Titanium tetrachloride (1 ml; 9 mmol) in dry hexane (10 ml) was added dropwise to the benzylamine solution with stirring and under a positive pressure of dry nitrogen. After the addition had been completed, the ketone (1,65 g; 10 mmol) was added in one portion to the flask Once the temperature reached room temperature, the mixture was raised to the boil for 2 hours, before being filtered through oven dried diatomaceous earth in a sintered glass funnel (porosity 3). After filtration, the hexane was removed on a rotary evaporator. The residue was pumped under reduced pressure (0,1 0mmHg) in an attempt to remove the benzylamine and gave an oil (2,51 g), which was vacuum distilled and gave the imine: *N–[2–(2–cyanoethyl)–6–methylcyclohexylidene]benzylamine* (0,53 g; 21%).

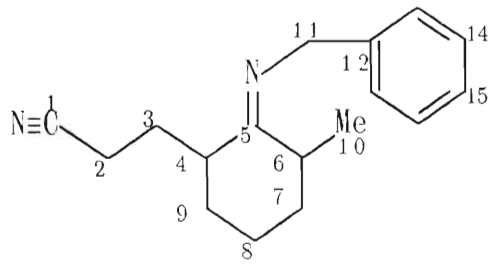
Boiling point: 70–72 °C / 0,15 mmHg

IR: ν_{max} film cm^{-1}

1 661	C=N
2 253	C≡N

^1H NMR δ ($CDCl_3$) ppm.

1,1	d; J = 7,6 Hz, CH_3–CH
1,3 – 2,8	methylene/methine envelope; 12 H
4,5	s; 2H; N–CH_2–Ph
7,3	br.s; 5H; Ph



^{13}C NMR: δ ($CDCl_3$)

176,4	s	C–5	34,7	t	C–3
140,9	s	C–12	33,0	t	C–7
128,3	d	C–15	31,4	d	C–6
127,3	d	C–14	27,3	t	C–9
126,4	d	C–13	20,4	t	C–8
120,4	s	C–1	16,9	q	C–10
53,1	t	C–11	15,2	t	C–2
40,3	d	C–4			

Accurate mass:	Found:	254,1771
	Calc. for $C_{17}H_{22}N_2$	254,1783

This reaction was repeated using titanium tetrachloride (6,06 ml; 54,5 mmol) in hexane (60 ml), benzylamine (38,97 g; 363,6 mmol) in hexane (485 ml) and 3–(3–methyl–2–oxocyclohexyl)propanenitrile (10 g; 60,6 mmol) using the same technique, except that the reaction mixture was allowed to return to room temperature, with stirring, for a total of 24 hours.

This gave an oil (10,66 g) which on fractional vacuum distillation gave three fractions. The first fraction (1,95 g) was benzylamine, the second fraction (0,5 g) was a mixture of benzylamine and starting ketone and the final fraction was the desired imine (6,76 g; 44%).

Boiling Point: 181,5° C/1,2 mmHg.

Attempted reaction of the benzylamine imine of methyl 3–(3–methyl–2-oxo-cyclohexyl)propanoate with methyl acrylate in methanol.

The imine (2,58 g; 9 mmol), methyl acrylate (1,55 g; 18 mmol) were refluxed in methanol (20 ml), the reflux condenser being fitted with a guard tube, for 4 h. Water (10 ml) was added and the mixture refluxed for a further hour. The methanol and excess methyl acrylate were removed on a rotary evaporator and the product extracted with ether (3 x 50 ml). The ethereal extract was washed dil. aq. hydrochloric acid (4 x 25 ml ; 2 M), satd. aq. sodium hydrogen carbonate (25 ml), water (3 x 25 ml) and satd. aq. sodium chloride (25 ml). The ethereal solution was dried over anhydrous magnesium sulphate after which the solvent was removed on a rotary evaporator to give an oil (2,02 g). GLC showed that this was methyl 3–(3–methyl–2–oxocyclohexyl)propanoate.

Attempted rearrangement of the benzylamine imine of 3–(3–methyl–2–oxo-cyclohexyl)propanenitrile with methyl acrylate (1 equivalent) in methanol.

The imine (0,30 g; 1,2 mmol), methyl acrylate (0,10 g; 1,2 mmol) in "super–dry" methanol (5 ml) were heated under reflux for 4 hours. After the usual hydrolysis and aqueous workup, only unchanged starting

3–(3–methyl-2–oxocyclohexyl)propanenitrile (0,16 g) was recovered. This was verified using CGC and the known standards.

Attempted rearrangement of the benzylamine imine of 3–(3–methyl–2–oxo-cyclohexyl)propanenitrile in refluxing methanol.

The imine (1,00 g; 3,93 mmol) was heated under reflux in "super–dry" methanol (10 ml) for 4 hours. After the usual hydrolysis and aqueous workup, only unchanged starting 3–(3–methyl-2–oxocyclohexyl)propane-nitrile (0,64 g) was recovered. This was verified using CGC and the known standards.

Attempted rearrangement of the benzylamine imine of 3–(3–methyl–2–oxo-cyclohexyl)propanenitrile in refluxing methanol with the base: 4–dimethylaminopyridine:

The imine (1,00 g; 3,93 mmol), 4–dimethylaminopyridine (0,05 g; 0,393 mmol) were heated under reflux in "super–dry" methanol (10 ml) for 4 hours. After the usual hydrolysis and aqueous workup, only unchanged starting 3–(3–methyl-2–oxocyclohexyl)propanenitrile (0,62 g) was recovered. This was verified using CGC and the known standards.

Attempted rearrangement of the benzylamine imine of 3–(3–methyl–2–oxo-cyclohexyl)propanenitrile in refluxing methanol with the base: 4–dimethylaminopyridine and methyl acrylate (1 equivalent):

The imine (1,50 g; 5,90 mmol), methyl acrylate (0,50 g; 5,90 mmol), 4–dimethylaminopyridine (0,07g; 0,59 mmol) were heated under reflux in "super–dry" methanol (14 ml) for 4 hours. After the usual hydrolysis and aqueous workup, only unchanged starting 3–(3–methyl-2–oxocyclohexyl)-propanenitrile (0,97 g) was recovered. This was verified using CGC and the known standards.

Attempted rearrangement of the benzylamine imine of 3–(3–methyl–2–oxo-cyclohexyl)propanenitrile in refluxing methanol with methyl acrylate (2 equivalents) using an extended reaction time (20 hours):

The imine (1,50 g; 5,90 mmol), methyl acrylate (1,02 g; 11,81 mmol) in "super–dry" methanol (14 ml) were heated under reflux for 4 hours. After the usual hydrolysis and aqueous workup, only unchanged starting 3–(3–methyl-2–oxocyclohexyl)propanenitrile (0,88 g) was recovered. This was verified using CGC and the known standards.

Gas Chromatography:

Column: Carbowax 20M capillary column (25 m)

Instrumental parameters:

Detector temperature: (FID)	280° C
Injector temperature:	280° C
Chart speed:	0,5 cm/min
Attenuation:	2 x 10
Oven temperature:	150° C

Firstly, the 3–(3–methyl–2–oxocyclohexyl)propanoate was injected onto the column in order to ascertain the positions of the *cis*– and *trans*– isomers. Secondly the 3–(1–methyl–2–oxocyclohexyl)propanoate was injected onto the column under the same conditions. This showed that this mixture contained mainly the 3–(1–methyl–2–oxocyclohexyl)propanoate but also present were the *cis*– and *trans*– isomers of 3–(3–methyl–2–oxocyclohexyl)-propanoate. These peaks appeared at 13,29; 12,83 and 12,64 minutes respectively. (These are uncorrected retention times).

After the attempted reaction of the benzylamine imine of 3–(3–methyl–2-oxocyclohexyl)propanoate with methyl acrylate in "super-dry" methanol for 4 hours, the product obtained from the hydrolysis was injected onto the same column under the same instrumental conditions.

The chromatogram clearly shows that no 3–(1–methyl–2–oxocyclohexyl)-propanoate was formed in the reaction, and that the main product are the isomers of 3–(3–methyl–2–oxocyclohexyl)propanoate. There were other peaks at much longer retention times and these were probably due to polymerisation products resulting from the methyl acrylate.

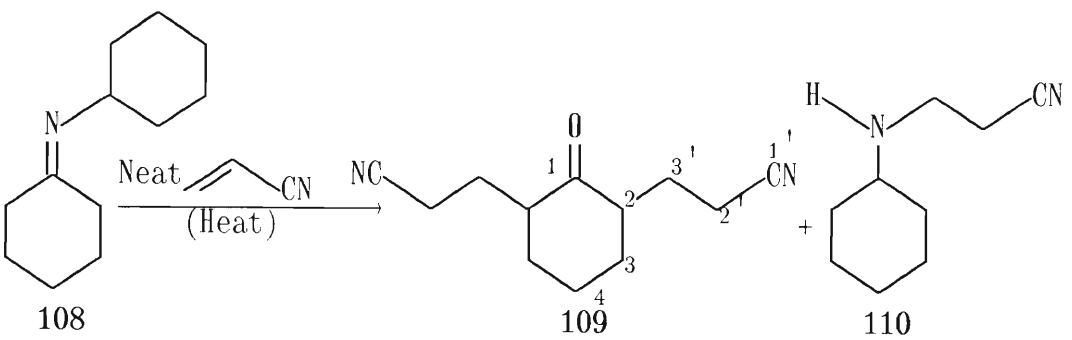
All the other hydrolysed reaction mixtures described above were subjected to a similar analysis using authentic 3–(3–methyl–2–oxocyclohexyl)-propanenitrile, methyl 3–(3–methyl–2–oxocyclohexyl)propanoate and methyl 3–(1–methyl–2–oxocyclohexyl)propanoate under the same instrumental conditions and using the same column and in every case **only** 3–(3–methyl–2–oxocyclohexyl)propanenitrile was recovered from the hydrolysed reaction mixture.

2.3 ALKYLATION OF CYCLOHEXANONE IMINES WITH ELECTROPHILIC ALKENES:

2.3.1 DISCUSSION

Having carried out the work discussed in Section 2.2, we became aware of conflicting reports in the patent literature[77] which claimed that the alkylation of N–cyclohexylidenecyclohexylamine (**108**) with neat acrylonitrile gave 2,6–bis(2–cyanoethyl)cyclohexanone (**109**) after hydrolysis.

This was clearly in conflict with the work carried out by the author[89] and by Pfau.[91] The implication was that either the patent literature was incorrect or that the reaction of N–cyclohexylidenecyclohexylamine (**108**) with neat acrylonitrile did not follow the same reaction pathway as the alkylation of the imines of 2–methylcyclohexanone with electrophilic alkenes in boiling methanol.

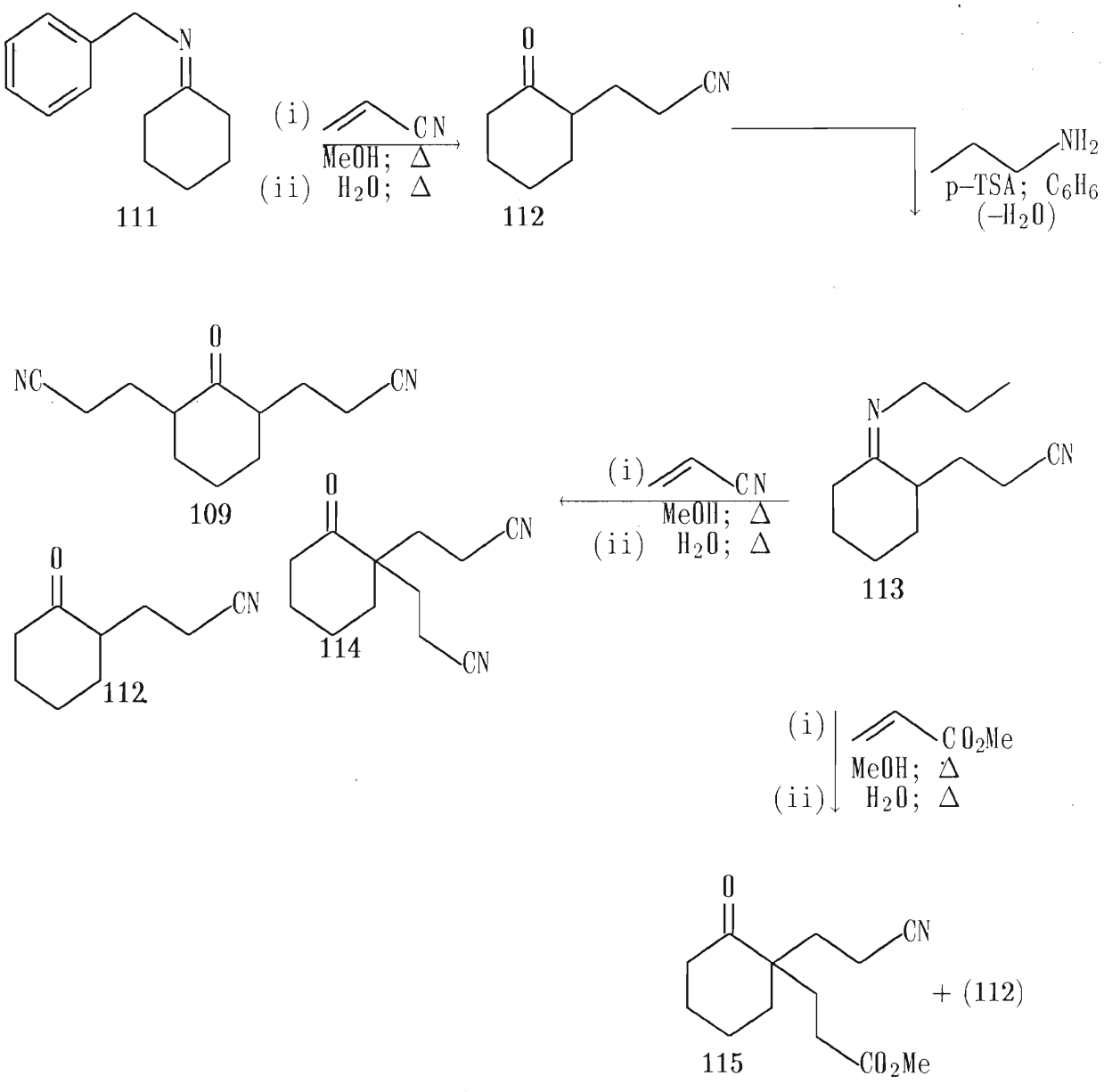


108 **109** **110**

SCHEME 20

It was therefore necessary to re–investigate this reaction and in the course

of this work we have found that the course of the imine–alkylation reaction is surprisingly sensitive to both steric effects and to the relative reactivity of the electrophilic reagents. Repetition of the reaction between N–cyclohexylidenecyclohexylamine (**108**) and neat acrylonitrile was carried out at 100° C, using an oil bath to maintain a constant temperature, and an efficient condenser to prevent any possible loss of acrylonitrile. The infra–red spectrum of the crude product prior to hydrolysis showed an imine absorption at 1649 cm^{-1}, a weak carbonyl absorption at 1709 cm^{-1} and a relatively strong nitrile absorption at 2260 cm^{-1}. However, when the reaction mixture was fractionally distilled in *vacuo* three fractions were obtained, none of which showed an imine absorption. The carbon spectrum clearly showed the C–2 and C–6 signals as doublets (δ_C 48,5), the C≡N (C–3') peaks as a singlet (δ_C 119,0) and the carbonyl (C–1) as a singlet (δ_C 210,8). Because of the symmetry of the molecule there were three triplets of unusually high intensities indicating the presence of two carbons at each chemical shift. The triplets C–1', C–2' and C–3 appeared at δ_C 14,2; 24,6 and 34,2 ppm respectively. A triplet with a much lower intensity (C_4) appeared at δ_C 24,2 ppm. The IR spectrum showed the nitrile and carbonyl absorbances at 2 227 and 1 708 cm^{-1} respectively, which is consistent with the spectrum obtained for 2,6–bis(cyanoethyl)cyclohexanone (**109A**) prepared by authentic methods.[3] This reaction also yielded the N–alkylated amine, N–(2–cyanoethyl)cyclohexylamine (**110**) as the only other product. There appeared to be no 2,2–bis(cyanoethyl)cyclohexanone present in the reaction mixture as none was isolated in any of the fractions.


111
(i)
MeOH; Δ
(ii) H2O; Δ
112
NH2
p-TSA; C6H6
(-H2O)
109
114
112
113
115
+ (112)
CO2Me

SCHEME 21

It would therefore appear that the patent report [77] is correct and 2,6–di–alkylation does indeed occur under these conditions to give 2,6–bis(cyanoethyl)cyclohexanone. The observation that the 2,6–bis compound is formed preferentially in the absence of solvent is important, for whilst attempting to optimise the conditions for the alkylation of various imines of 2–methylcyclohexanone, the author had noticed in his preliminary work [94] that the more concentrated the imine solution became the more 2,6–product was obtained.

It was decided that the alkylation of unsubstituted cyclohexanone should be investigated under similar reaction conditions to those which produced the 2,2–disubstituted 2–methylcyclohexanones.

If an electrophilic alkene were to react once with the cyclohexanone imine in either of the positions adjacent to the carbonyl group to produce the mono-alkylated imine, the latter should react with a further equivalent of the electrophilic alkene to give the bis-2,2-disubstituted cyclohexanone, provided that steric constraints and the relative reactivities of the alkenes were such that further alkylation could proceed. This forms the basis of this section of the project.

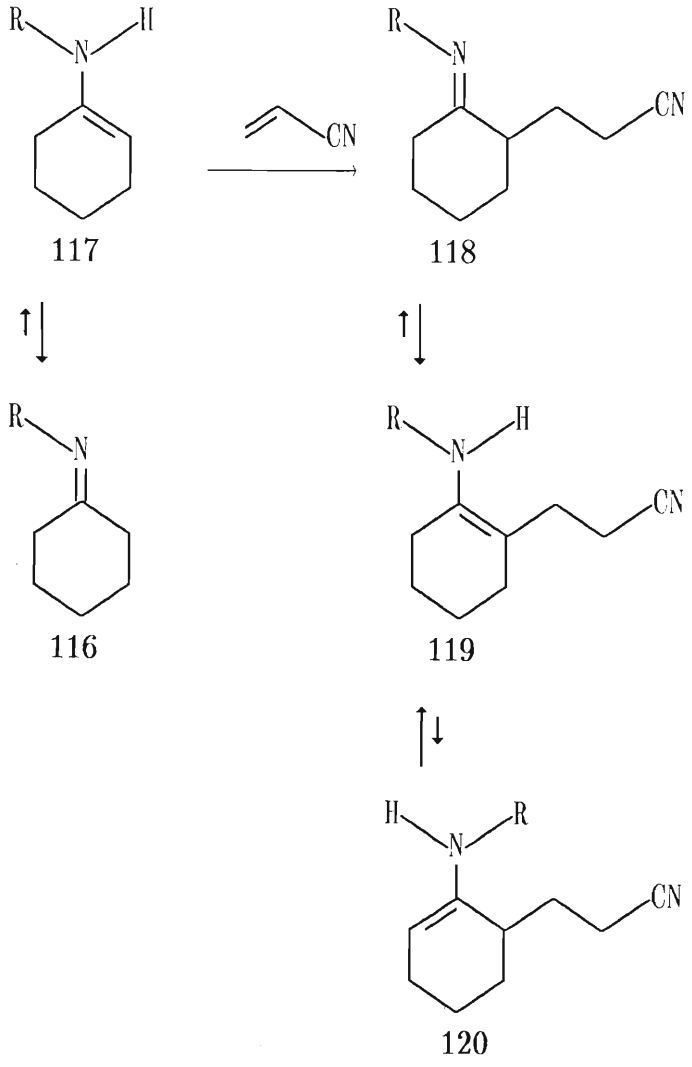
The benzylamine imine of cyclohexanone (**111**) and dry acrylonitrile (6 equivalents) were heated under reflux for 21 hours in "super dry" methanol, and hydrolysed by boiling with water (10 ml) for an hour, giving only the mono–alkylated product, 2–(2–cyanoethyl)cyclohexanone (**112**). This product was identical with authentic 2–(2–cyanoethyl)cyclohexanone [3]

showing the C–2 signal in the ^{13}C–nmr spectrum as a doublet (δ_C 48,2). The 2–(2–cyanoethyl)cyclohexanone was then converted to the propylamine imine (**113**), *via* the standard azeotropic method,[95] in order to reduce the steric hindrance by replacing the benzyl group by the less bulky n–propyl group. This imine was then treated with acrylonitrile in boiling methanol. After aqueous hydrolysis and purification using flash chromatography,[117] mainly unchanged 2–(2–cyanoethyl)cyclohexanone (**112**) was recovered, together with small amounts of approximately equal proportions of 2,6–bis(2–cyanoethyl)cyclohexanone (**109**) (5%) and 2,2–bis(2-cyanoethyl)-cyclohexanone (**114**) (6%). The former was identical with that previously prepared. The latter compound was identified from both analytical and spectral data. It was clear from the ^{13}C–nmr spectrum that the C–2 signal was now a singlet (δ_C 49,8), and no trace of the C–2 doublet of the 2,6–disubstituted compound (**109**) could be detected.

However, when the propylamine imine of 2–(2–cyanoethyl)cyclohexanone (**113**) was treated with methyl acrylate under reflux, after hydrolysis and the usual hydrolytic work–up and flash chromatography, the product was 2–(2–cyanoethyl)-2–[2–(methoxycarbonyl)ethyl]cyclohexanone (**115**), obtained as an oil in a 43% yield, together with some unchanged 2–(2–cyanoethyl)cyclohexanone (**112**).

This showed that the more substituted enamine tautomer of imine (**113**) is the favoured enamine tautomer, since no 2,6–disubstituted analogue of (**115**) was isolated. The differences in yields and product/s obtained for the alkylations set out in **Scheme 21** may be ascribed to the greater polarity of methyl acrylate over acrylonitrile. Methyl acrylate was thus able to overcome the steric impediment of the cyanoethyl group at C–2 of the more substituted enamine tautomer of imine (**113**) to give only (**115**). This molecule (**115**) showed absorptions in the infra–red at 2230 and 1744 cm^{-1}

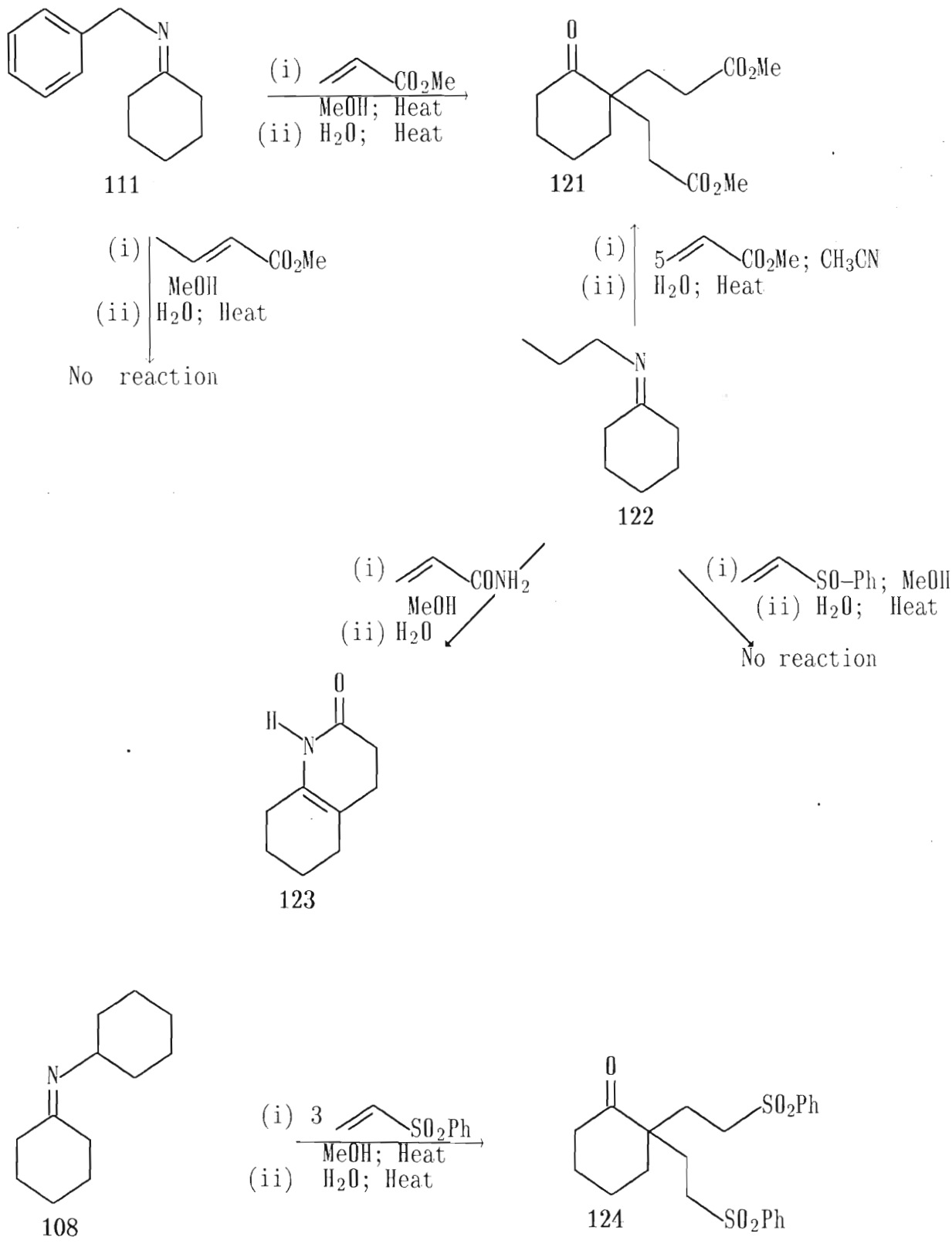
which correspond to the nitrile and ester side–chains and the cyclohexanone carbonyl (1710 cm^{-1}). The proton nmr spectrum showed a methylene envelope between δ 1,6 and 2,6 (16 H) and the singlet methoxy methyl at δ 3,66. The ^{13}C–nmr spectrum showed: the methoxy quartet at δ_c 51,3; the nitrile carbon as a singlet at δ_c 119,4.; the cyclohexanone ring and ester side–chain carbonyls at δ_c 212,6 and 172,8 respectively, and a singlet due to C–2 at δ_c 49,9. The analytical and accurate mass measurements were consistent for the proposed structure.



SCHEME 22

The explanation which we offer for these results is summarised in **Scheme 22**. Initial reaction at C–2 of the secondary enamine tautomer (**117**) occurs in each case to give the mono–alkylated imine (**118**) in equilibrium with the secondary enamine tautomer (**119**).

Now however further reaction at C–2 is impeded by the cyanoethyl group, which can plausibly be expected to exert a greater steric impediment to reaction than the methyl group in the corresponding reaction of 2–methylcyclohexanone imines.[89] Using more forcing conditions (i.e. neat acrylonitrile at 100 – 130 °C),[77] reaction is likely to occur at the less sterically hindered C–6 position to give **109** after hydrolysis. The change to the propylamine imine from the benzylamine imine, may have reduced the steric interactions with the approaching electrophile sufficiently to allow some bonding to occur at the 2–position as well.


111
(i) CO2Me
MeOH; Heat
(ii) H2O; Heat
121
CO2Me
CO2Me
(i) CO2Me
MeOH
(ii) H2O; Heat
No reaction
(i) 5 CO2Me; CH3CN
(ii) H2O; Heat
122
(i) CONH2
MeOH
(ii) H2O
(i) SO-Ph; MeOH
(ii) H2O; Heat
No reaction
123
108
(i) 3 SO2Ph
MeOH; Heat
(ii) H2O; Heat
124
SO2Ph
SO2Ph

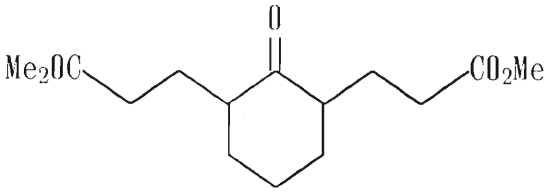
SCHEME 23

For the reaction between N–(cyclohexylidene)benzylamine and methyl acrylate, it was hoped that, since methyl acrylate could substitute the 2–(2–cyanoethyl)cyclohexanone at C–2, it might be able to di–alkylate this cyclohexanone imine at the 2–position. The reaction was carried out several times using different numbers of equivalents of methyl acrylate in methanol at reaction times of 3 and 21 hours and also in acetonitrile using 5 equivalents of methyl acrylate. In every case, the only product obtained was 2,2–bis–[2–methoxycarbonylethyl]cyclohexanone (**121**). In the first reaction 2 equivalents of methyl acrylate with N–cyclohexylidene-benzylamine (2 M) in "super–dry" methanol were heated under reflux for 3 hours. After hydrolysis under reflux with water and the usual hydrolytic work–up, the residue was subjected to flash chromatography which gave an oil (30 %) which was shown to be 2,2–bis–[2–methoxycarbonylethyl]cyclohexanone (**121**). When the reaction was repeated using 4 equivalents of methyl acrylate in methanol at the same imine concentration, after the usual hydrolysis, extraction, hydrolytic work–up, fractional vacuum distillation and column chromatography, the yield was marginally increased to 35%.

The reaction was repeated twice using 6 equivalents of methyl acrylate in both instances, again at the same imine concentration in methanol under reflux for 21 hours, but the yields remained low (40 and 36% respectively) at these concentrations and reaction times.

In view of the previous finding that propylamine is less of a steric impediment to the alkylation of the propylamine imine of 2–(2-cyano-ethyl)cyclohexanone with acrylonitrile, it was decided to attempt the alkylation of N–cyclohexylidenepropylamine with methyl acrylate

(5 equivalents). The solvent was changed to dry acetonitrile and 4–dimethylaminopyridine (1 equivalent) was added in an attempt to improve the yield of the reaction by catalyzing the imine–enamine interconversion . A dramatic increase in the yield of 2,2–bis–[2-methoxycarbonylethyl]cyclohexanone (**121**) resulted. After the usual work–up, described in the experimental section of this chapter, the crude product was fractionally vacuum distilled to give 15,03 g (77%). The infra–red spectrum showed the side–chain ester carbonyls and the cyclohexanone carbonyl absorptions at 1744 and 1709 cm^{-1} respectively. The proton nmr spectrum showed 16 hydrogens in the methylene envelope between δ 1,6 and 2,5; and the singlet methoxy methyl groups (6H; δ 3,52). The ^{13}C nmr spectrum showed the methoxy methyl quartet at δ 50,7; the ester carbonyls (δ_c 172,8); the ring carbonyl (δ_c 212,6) and the singlet (δ_c 49,2) for C–2 of the cyclohexanone ring, showing categorically that 2,2–bis-disubstitution had taken place. The analysis was consistent with the proposed structure. Further, the 2,6–bis–[2-methoxycarbonylethyl]-cyclohexanone (**121(b)**) was prepared as described by Stork [3] for the



121(b)

diethyl ester. This was a crystalline compound with a melting point of 82,5 – 83,0° C. The ^{13}C nmr spectrum showed the doublets at the 2– and 6–positions of the cyclohexanone ring (δ_c 49,9) which clearly differentiates the 2,6–bis–compound from the 2,2–bis–compound described. Other spectral data are provided in the experimental section for the 2,6–bis–[2-methoxycarbonylethyl]cyclohexanone [**(121(b)**].

The reaction of methyl crotonate with imine **111** proved fruitless and no alkylated product was recovered after hydrolysis of the reaction mixture and

hydrolytic work–up. This result is not surprising because of the reduced reactivity arising from the hyperconjugative effect and steric impediment of the methyl group. The electron donating ability of a methyl group under these conditions will have reduced the positive charge on the carbon of the double bond furthest from the ester moiety to the extent that it was no longer able to undergo a bonding interaction from sufficient distance to minimize developing steric interactions. It has already been shown that acrylonitrile is not as effective at 2,2–bis–alkylating as is methyl acrylate, and this is no doubt due to the increased electron withdrawing effect of the methyl ester compared to the nitrile group. The greater electrophilicity of methyl acrylate over acrylonitrile follows from the fact that reaction with a nucleophile (Nu) produces an anionic centre (Nu–$CH_2\bar{C}H$–Z) adjacent to the electron withdrawing group (Z), and it has been shown that the anion stabilising ability of such groups decreases in the order: SO_2 > CO_2R > CN > $CONH_2$.[119] The greater reactivity means that the transition state for the alkylation will be more reactant–like in nature, and the bonding interaction will commence at greater interatomic distances. This decreases the influence of steric effects and, despite the greater steric impediment of the β–methoxycarbonylethyl group attached at C–2 initially, a second molecule is able also to attack at C–2.

Pearson's [118] anion stabilising sequence suggests that vinyl sulphones should be even more reactive than vinyl esters and so phenyl vinyl sulphone should also give the 2,2–bis–dialkylated cyclohexanone. This was confirmed in the reaction between N–cyclohexylidenecyclohexylamine and phenyl vinyl sulphone in methanol at the boil (4 hours). Subsequent aqueous hydrolysis and the usual hydrolytic work–up gave, in fairly good yield (48%), 2,2–bis[(2–phenylsulphonyl)ethyl]cyclohexanone **124**. The proton nmr

spectrum shows 16 protons within the methylene envelope (δ 1,2 – 3,1); and the benzene ring protons (10 H) appear between δ 7,4 and 7,9. Again the most important information gleaned from the ^{13}C nmr is the C–2 singlet (δ 49,4) which shows that 2,2–bis–dialkylation has occurred. The analysis was consistent with the molecular formula for this compound.

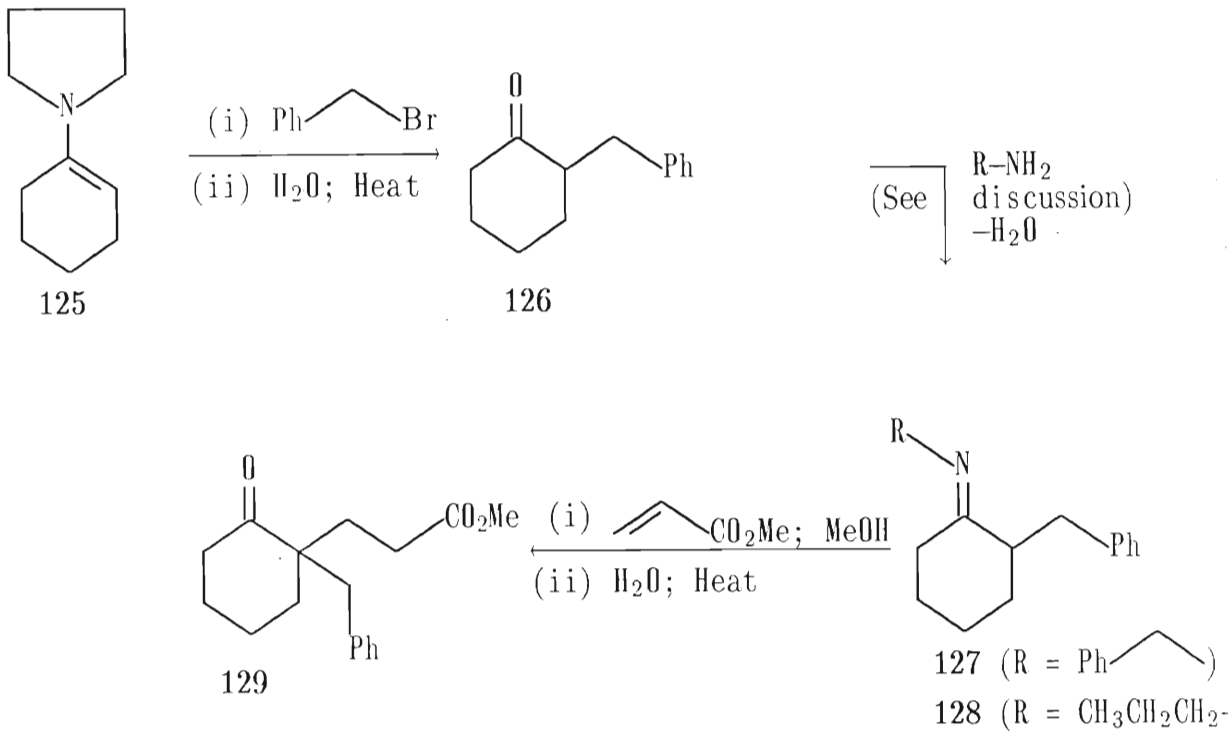
It has already been shown that methyl acrylate can alkylate the imine of 2–(2–cyanoethyl)cyclohexanone at C–2, whereas acrylonitrile could do so only if the amine moiety was not very bulky, and even then the yields were low and the regioselectivity poor.

Following this line of reasoning, it was expected that acrylamide would only react once at C–2 of the cyclohexanone imine. This was confirmed, but the initial alkylation product could not be isolated since it cyclised to give 2–oxo–$\Delta^{4a,8a}$–octahydroquinoline (**123**). The infra–red spectrum showed the amide carbonyl absorption at 1670 cm^{-1} and the expected NH absorptions in the region 3100 – 3200 cm^{-1}. Further, there was no cyclohexanone carbonyl absorption around 1710 cm^{-1}. The proton nmr spectrum proved that it was the $\Delta^{4a(8a)}$–isomer because it showed no olefinic signals, however, the ^{13}C nmr spectrum showed the olefinic signals at δ 109,3 and 128,2 respectively; and the amide carbonyl singlet appeared at δ 171,6. Both accurate mass measurement and analysis were unequivocal for the proposed molecular formula for the compound.

Two further aspects of the 2,2–alkylation of cyclohexanone still needed to be examined, *viz.*:

(1) whether a larger substituent, such as a benzyl group at the 2–position of the cyclohexanone imine would provide a sufficient steric impediment to prevent alkylation with methyl acrylate taking place at the mono–substituted 2–position; and

(2) if the benzyl group failed to prevent alkylation at the 2–position of 2–benzylcyclohexanone imine, this may have been due to the fact that the cyclohexanone ring was able to adopt a number of different conformations. If this were the case, then the ring could be fixed into a chair conformation with a tertiary–butyl group at the 4–position of the 2–benzylcyclohexanone imine (**132**; **133**: **Scheme 25**). The combined effect of these two bulky substituents could have the effect of maintaining the ring rigid in the chair conformation since the t–butyl group would adopt an equatorial orientation because of its bulk and it was also likely that the 2–benzyl group would also be preferentially equatorial if the 2–benzyl–4–t-butylcyclohexanone (**131**) were prepared from 4–t–butylcyclohexanone.



SCHEME 24

Following Stork's method,[3] the pyrrolidine enamine of cyclohexanone was alkylated using benzyl bromide in dry dioxane under reflux for 12 hours, prior to the hydrolysis with water under reflux for a further 3 hours. After the usual hydrolytic work–up, the crude product was fractionally vacuum distilled to give a good yield (76 %; 21,43 g). (A repeat preparation gave a yield of 70 %).

The proton nmr spectrum showed a complex methylene envelope (δ 1,2 – 2,7; 10H), a multiplet at δ 3,22 (1H) and the aromatic protons (δ 7,12; s; 5 H).

The infra–red spectrum showed the ring carbonyl absorption at 1708 cm^{-1} and the aromatic absorptions above 3000 cm^{-1}.

All the spectral data were consistent with the structure for 2–benzylcyclo-hexanone.

The benzylamine imine of 2–benzylcyclohexanone, N–(2–benzylcyclohexylidene)benzylamine (**127**) was prepared using the $TiCl_4$ method of Carlson and Nilsson [117] giving a yield of 72% by CGC.

The infra–red spectrum showed the C=N absorption at 1652 cm^{-1}

The proton nmr spectrum showed two benzene rings at δ 7,19 and 7,09 respectively. The former signal corresponds to **Ph**–CH_2–N and the latter to the 2–benzyl phenyl group by comparison to the propylamine imine (**128**) which shows the benzyl phenyl at δ 7,10.

The benzylamine CH_2 signal appears as a 2 proton singlet at δ 4,57 and the remaining 11 protons between δ 1,2 and 4,3 as a complex methylene/methine envelope.

Finally, the accurate mass measurement for imine **127** was consistent with the proposed formula.

Imine **127** was treated with methyl acrylate in "super–dry" methanol for 4 hours and after aqueous hydrolysis and the usual hydrolytic work–up gave an oil which was subjected to flash chromatography on a glass column containing silica gel (Merck Art.: 9385) using 10% ethyl acetate in hexane as eluant.

Combination of the fractions on the basis of TLC yielded two main components, the first having an R_f of 0,36 (0,53 g) which proved to be starting ketone (**126**) and the second with R_f 0,18 (1,33 g; 54%) which was shown to be the desired 2–benzyl–2-[(2–methoxycarbonyl)ethyl]cyclohexanone (**129**).

The accurate mass measurement is consistent with the proposed structure and the proton nmr spectrum clearly shows the benzyl phenyl group (δ 7,07 – 7,32; c.m.; 5 H), the singlet methoxy methyl (δ 3,66; 3H), the benzyl

methylene protons as a singlet at δ 2,88 (2 H). The infra–red spectrum shows the cyclohexanone carbonyl at 1710 cm^{-1} and the ester carbonyl at 1745 cm^{-1}.

In an attempt to improve the yield, it was decided to try to prepare the propylamine imine (**128**) of 2–benzylcyclohexanone (**126**). To our surprise, the preparation *via* the usual azeotropic method failed.

At the time the author thought that the benzyl group at the 2–position of the cyclohexanone was providing too great a steric impediment for the formation of the imine. Changing the solvent from benzene to toluene (to increase the temperature) also met with no success.

It was only very much later that this problem was solved. The boiling point of the propylamine is so low that if the volume of benzene or toluene is too small, only the propylamine will reflux and not the solvent being used to azeotropically remove the water. The author found that if no water was liberated azeotropically into the Dean and Stark apparatus, the addition of an increased volume, of whatever solvent was being used, often solved the problem, especially when no real reasons could be found for the non–formation of the imine.

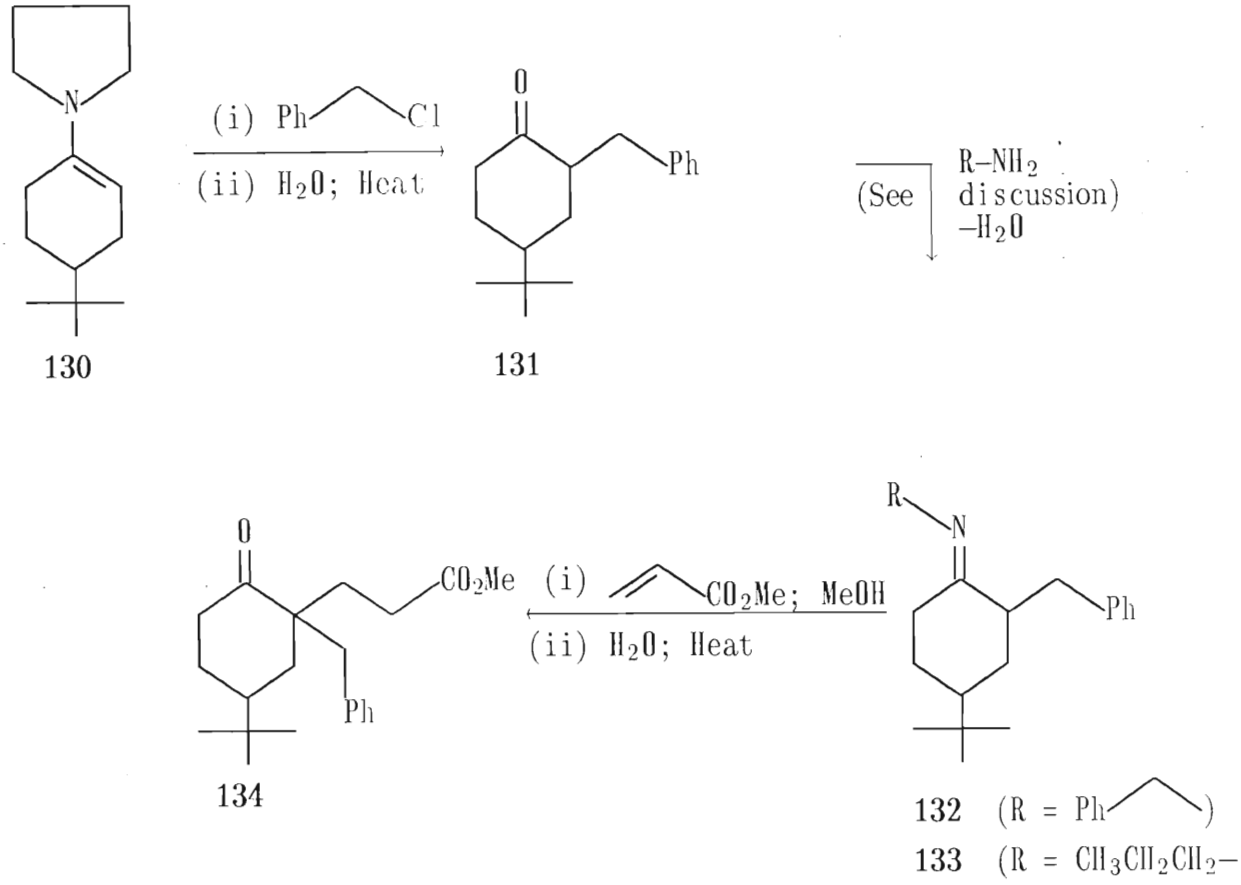
In this case, the imine was prepared very easily *via* the $TiCl_4$ method of Carlson and Nilsson, [117] as with the previous imine (**127**). After filtration through dried kieselguhr and evaporation of the solvents, the N–(2–benzyl-cyclohexylidene)propylamine (**128**) was considered sufficiently pure to be used without distillation.

(Another advantage of the use of propylamine, besides its smaller steric bulk, is that, compared to benzylamine, it is very easy to remove under vacuum).

The infra–red spectrum of imine (**128**) showed the C=N absorption at 1652 cm^{-1} and the proton spectrum showed the terminal methyl of the N–propyl group as a triplet (δ 0,90; 3 H; J = 9 Hz). The methylene closest to the imine nitrogen appeared as a quartet (δ 3,17; 2H; J = 9 Hz); and the phenyl group (δ 7,1; 5 H) which was used to estimate the number of protons under the methylene / methine envelope (13H; δ 1,1 – 2,9).

Finally, the accurate mass measurement was consistent with the structure proposed for the imine (**128**).

Imine (**128**) was treated with methyl acrylate (5 equivalents) in "super–dry" methanol under reflux for 4 hours. After the usual hydrolysis and hydrolytic work–up an oil (7,57 g) was obtained. This oil was shown to be identical with that obtained from the benzylamine imine of 2–benzylcyclohexanone (**127**) by TLC. When chromatographed in 10% ethyl acetate in hexane, two spots were obtained, one (R_f 0,15) being starting ketone and the other (R_f 0,33) being 2–benzyl–2–[2–methoxycarbonylethyl]cyclohexanone (5,84 g; 61 %).



SCHEME 25

In an attempt to determine whether the flexibility of the ring was related to the formation of the alkylated product, the pyrrolidine enamine of 4–t–butylcyclohexanone (**130**) was prepared by a literature method,[3] and this was alkylated as described by Stork[3] using benzyl chloride in "super–dry" methanol. After aqueous hydrolysis of the product, the usual hydrolytic work–up, and fractional vacuum distillation, the yield of 2–benzyl–4–t-butylcyclohexanone (**131**) was 99% (29,4 g), if the recovered starting ketone was taken into account. The proton nmr spectrum was consistent with 2–benzyl–4–t-butyl-cyclohexanone (**131**) with five benzene protons (δ 7,15); the three methyl groups of the t–butyl group (δ 0,84) and

10 protons in the methylene/methine envelope (δ 1,1 – 3,4).
This structure is a ring which has two equatorial groups, effectively holding the ring in the chair conformation.

The benzylamine imine, N–(–2–benzyl–4–t–butylcyclohexylidene)-benzylamine (**132**) was prepared *via* both the azeotropic and $TiCl_4$ methods, the structure being confirmed by both spectroscopic and accurate mass measurement. Imine (**132**) was then treated with methyl acrylate in "super–dry" methanol, under reflux for 4 hours. After aqueous hydrolysis and the usual hydrolytic work–up, an oil (6,01 g) was obtained. A portion (2,40 g) was purified on thin layer TLC plates (Merck Art.: 5745) using 10 % ethyl acetate in hexane as eluant. The bands were visualised under ultra–violet light and on this basis the plates were separated into nine bands. After extraction, the fractions were combined on the basis of TLC. The major fraction (1,13 g; 39%) was shown to be 2–benzyl–4–t–butyl–2-[2–methoxycarbonylethyl]cyclohexanone (**134**) using both accurate mass measurement and spectral data, obtained as a mixture of geometric isomers. The proton nmr spectrum showed three of the sets of peaks to be "twinned": the phenyl group (δ 7,16 and 7,12), the methoxy methyl (δ 3,64 and 3,58) and the t–butyl group methyls (δ 0,91 and 0,84). The ratio of the peak heights is of the order of 4:1. The phenyl group appeared as a broad singlet at δ 7,18 (5 H), the methoxy singlet at δ 3,64 (3H; s), a broad methylene/methine envelope (δ 1,1 – 3,1; 13 H) and the t–butyl methyl groups at δ 0,82 (9 H; s). [Only the chemical shift of the major isomeric form is given for these assignments.]

The ^{13}C nmr spectrum showed the keto–carbonyl at δ_c 213,9 and the ester carbonyl at δ_c 173,3; and the important C–2 singlet appears at δ_c 27,1. The remainder of the assignment is given in the experimental section.

Thus it has been shown that despite the rigidity of the ring owing to the 4–t–butyl group, alkylation at the singly substituted 2–position of the cyclohexanone ring still occurs with methyl acrylate.

CONCLUSION:

It has been shown that the ease of 2,2–bis–alkylation of cyclohexanone imine depends upon the anion stabilising power of the electrophilic group in the electrophilic alkene, and that methyl acrylate and phenyl vinyl sulphone are capable of forming the 2,2–bis cyclohexanones, whereas acrylonitrile and acrylamide have only the potential for mono–alkylation under the conditions described. Further it was shown that phenyl vinyl sulphoxide and methyl crotonate were unable to alkylate the imines of cyclohexanone under the conditions used for the other alkylations.

In an attempt to evaluate the effect of other substituents present at C–2 of cyclohexanone on the alkylation of imines formed from them it has been shown that the imines of 2–benzylcyclohexanone may be alkylated using methyl acrylate, and presumably phenyl vinyl sulphone, at C–2 despite the bulk of the benzyl group. The same alkylation was observed when the rigidity of the ring was fixed by placing a t–butyl group at C–4 of 2–benzylcyclohexanone, which shows that the rigidity of the ring does not affect the alkylation.

Further investigations in this area should include the following:

(1) An attempt should be made to alkylate N–(2–benzyl–4–t–butyl-cyclohexylidene) propylamine with acrylonitrile in order to determine whether the analogous compound to **134** is formed.

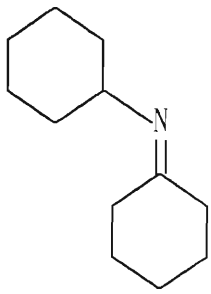
(2) The steric impediment of the substituent at C–2 of cyclohexanone should be increased in order to determine the nature of the impediment required to prevent alkylation at C–2 of cyclohexanone.

4.2.2 EXPERIMENTAL

4.2.2.1 Preparation of imines

Preparation of N–(cyclohexylidene)cyclohexylamine (108)

Cyclohexanone (60,00 g; 0,61 mol), cyclohexylamine (69,72 g; 0,70 mol), toluene–4–sulphonic acid (p–TSA) (0,1 g) and dry benzene were heated under reflux using a Dean and Stark water separator until the calculated quantity of water had been liberated, whereupon the benzene was removed on a rotary evaporator. The residue was fractionally distilled under vacuum to give one fraction (102,66 g; 94 %).



108

Boiling point: 74–78 °C/0,07 mmHg

(Lit.:[77] 88° C/0,9 mmHg)

IR:

ν_{max} (film) cm^{-1}	
1 659	C=N

^{1}H NMR: δ ($CDCl_3$) ppm

4,26	1H, br.s., CH–N
2,6 – 3,3	4H, m., CH_2–C(=N)–CH_2
1,3 – 2,5	16H, methine/methylene envelope

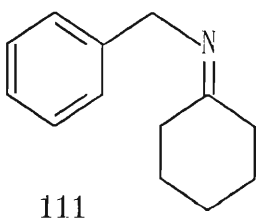
Preparation of N–(cyclohexylidene)benzylamine (111)[120]

The usual method[95] of preparation of imines using benzene failed to give the desired imine, and it was decided to attempt the method of Beydatsch *et al.*[120]

Cyclohexanone (49,05 g; 0,500 mol), benzylamine (53,58 g; 0,500 mol), 4–toluenesulphonic acid (0,20 g) and dry pentane (500 ml) were heated under reflux under a Dean and Stark water separator. Only 3 of the required 9 ml of water separated after 2,5 h, whereupon the pentane was removed on a rotary evaporator and the residue fractionally distilled under vacuum. The first three fractions showed no imine absorption in the infra–red, but the fourth fraction proved to be N–(cyclohexylidene)benzylamine (111) (18,91 g; 20%).

Boiling point: 100 °C/ 0,23 mmHg

Lit.: [122] 130 °C/ 5 mmHg



111

IR: ν_{max} (film) cm^{-1}

1 660 C=N

^{1}H NMR: δ ($CDCl_3$) ppm

1,3 – 2,0	6H, m, 3 x CH_2
2,1 – 2,5	4H, m, 2 x CH_2
4,33	2H, s, CH_2–N
7,20	5H, s, Ph–

In papers by Ninoniya *et al.*[121,122] it was noted that they had not employed toluene–4–sulphonic acid. In the former paper, benzene was the solvent and the the latter, toluene and the yield in both cases was 84 %, so it was decided to repeat the reaction without using the toluene–4–sulphonic acid. Cyclohexanone (24,00 g; 0,245 mol), benzylamine (27,50 g; 0,257 mol) in dry benzene (200 ml) were heated under reflux under a Dean and Stark head for 24 hours. (It was noted that an exothermic reaction occurred when the benzylamine was added to the cyclohexanone and when the benzene was added the reaction mixture went cloudy, something not observed when the ketone was 2–methylcyclohexanone). The benzene was removed on a rotary evaporator and the residue fractionally distilled under vacuum to give an oil (33,5 g; 73%) which was shown to be N–(cyclohexylidene)benzylamine.
A small quantity of benzylamine (1,00 g) was recovered in the first fraction.

Boiling point: 96,8 – 98 °C/ 0,12 mmHg

Lit.: [121] 124 – 132 °C/ 4 mmHg

The imine was identical with the one first prepared. It would seem that the toluene–4–sulphonic acid is not required for the reaction in this case and may catalyse some form of cyclisation as previously hypothesized when considering the low yields experienced with the alkylation of the imines of 2–methylcyclohexanone. This could have accounted for the low yield in the first preparation.

Preparation of N–[2–(2–cyanoethyl)cyclohexylidene]propylamine (113)

A solution of 2–(2–cyanoethyl)cyclohexanone (10,0 g; 66 mmol), propylamine (4,31 g; 73 mmol), and toluene–4–sulphonic acid (0,1 g) in benzene (50 ml) was heated under reflux under a Dean and Stark head for 8 h. Removal of the solvent under vacuum and distillation of the residue gave *N–[2–(2–cyanoethyl)cyclohexylidene]propylamine* (10,3 g; 81%).

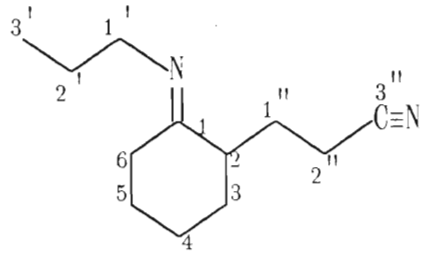
Boiling point: 101 – 102 °C/0,07 mmHg

IR: ν_{max} (film) cm^{-1}

2 250	C≡N
1 663	C=N

^{1}H NMR: δ ($CDCl_3$) ppm

1,0	3H, t, J = 6,2 Hz; CH_3
1,3 – 3,0	15H, methylene envelope
3,3	2H, t, J = 6,2 Hz; CH_2CN



113

^{13}C NMR: δ ($CDCl_3$) ppm

C–1	171,4	s	C–1'	51,7	t
C–2	48,5	d	C–2'	27,4*	t
C–3	34,7	t	C–3'	11,9	q
C–4	24,2	t	C–1''	25,2	t
C–5	28,2*	t	C–2''	15,1	t
C–6	28,5*	t	C–3''	120,3	s

* = *interchangeable*

Analysis and Accurate Mass Measurement:

Found:	N, 9,16% M^+, 192,1625
Calc. for $C_{12}H_{20}N_2$:	N, 9,26%; M^+, 192,1626

Preparation of N–cyclohexylidenepropylamine (122)

A solution of cyclohexanone (63,33 g; 680 mmol), propylamine (43,94 g; 740 mmol, and toluene–4–sulphonic acid (0,25 g) in benzene (100 ml) was heated under reflux under a Dean and Stark head for 8 h. The solvent was removed under vacuum and the residual oil distilled to give N–(cyclohexylidene)propylamine (29,8 g; 31%).

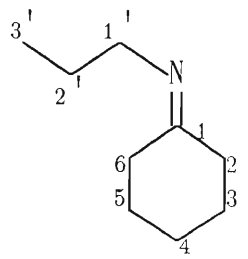
Boiling point: 34 – 36 °C/0,17 mmHg

IR: ν_{max} (film) cm^{-1}

1 660	C=N

^{1}H NMR: δ ($CDCl_3$) ppm

0,9	3H, t, J 7,2 Hz, CH_3
1,3 – 1,9	8H, m, 4 x CH_2
2,0 – 2,5	4H, m, 2 x CH_2
3,2	2H, t, J 6,9 Hz, CH_2CN



122

^{13}C NMR: δ ($CDCl_3$) ppm

C–1	170,7	s	C–1'	51,1	t
C–2	25,2	t	C–2'	25,2	t
C–3/5	27,0	t	C–3'	11,1	q
C–4	26,2	t			
C–6	27,2	t			

Preparation of N–(2–benzylcyclohexylidene)benzylamine (127)

Titanium tetrachloride (5 ml; 45 mmol) in cold dry hexane (50 ml) was added dropwise over a period of 1 hour into a solution of benzylamine (32,15 g; 300 mmol) in hexane (400 ml; 0° C) contained in a three–necked flask fitted with a stirrer and under a positive pressure of dry nitrogen. 2–Benzylcyclohexanone (9,40 g; 50 mmol) was added in a single aliquot to the $TiCl_4$–benzylamine complex and the mixture stirred for 4 hours at room temperature and then filtered through dry kieselguhr on a sintered glass funnel (porosity 4A) to remove the precipitated TiO_2. The hexane was then removed on a rotary evaporator and the residue pumped under vacuum for 6 hours in an attempt to remove as much of the benzylamine as possible. The residue was not distilled for fear of decomposition but was assumed to be 100 % pure, CGC revealing that only trace impurities were present and that the major component (98 % using the total integral) was *N–(2–benzylcyclohexylidene)benzylamine* (13,02 g; 94%). This was used without further purification.

IR: ν_{max} (film) cm^{-1}

1 652	C=N

^{1}H NMR: δ ($CDCl_3$) ppm

1,2 – 4,3	11H, c, methylene/methine envelope
4,57	2H, s, Ph–CH_2–N
7,09	5H, s, **Ph**–CH_2–CH
7,19	5H, s, **Ph**–CH_2–N

Accurate Mass Measurement:

Found:	M^+, 277.1837
Calc. for $C_{20}H_{23}N$:	M^+; 277,1830

Preparation of N–(2–benzylcyclohexylidene)propylamine (128)

Propylamine (9,43 g; 0,160 mol), 2–benzylcyclohexanone (20,00 g; 0,106 mol), toluene–4–sulphonic acid (0,1 g) in dry benzene (50 ml) were heated under reflux under a Dean and Stark head, but no water was azeotroped off. The reaction was repeated using the same quantities except that the benzene was replaced by toluene, but again no water was liberated into the Dean and Stark trap. It was decided to use the $TiCl_4$ method to prepare this imine.

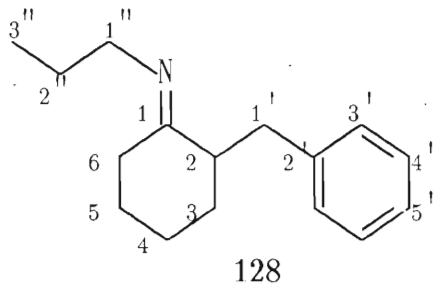
Titanium tetrachloride (5 ml; 45 mmol) in cold dry hexane (50 ml) was added dropwise to a solution of propylamine (19,18 g; 300 mmol) in dry hexane (400 ml) at 0° C with stirring and under a positive pressure of dry nitrogen. 2–Benzylcyclohexanone (9,40 g; 50 mmol) was added to this reaction mixture in one portion and the solution stirred at room temperature for 2,5 hours prior to filtration through dry kieselguhr on a sintered glass funnel (porosity 4A). The hexane was then removed on a rotary evaporator and the residue pumped under vacuum to remove any residual propylamine. CGC indicated that the imine was of high purity (97% based on the total integral) and so it was decided to use it without distillation. The oil (8,93 g; 78 %) was *N–(2–benzylcyclohexylidene)-propylamine* (**128**).

IR: ν_{max} (film) cm^{-1}

1 649 C=N

^{1}H NMR: δ ($CDCl_3$) ppm

0,90	3H, t, J = 7,6 Hz, Me
1,1 – 2,9	13H, c, methylene/methine envelope
7,08	5H, s, Ph.



128

^{13}C NMR: δ ($CDCl_3$) ppm

C–1	172,6	s	C–4'	127,9	d
C–2	49,1	d	C–5'	129,1	d
C–4	24,3	t	C–3''	11,9	q
C–1'	51,8	t		37,4	t
C–2'	141,5	s		32,8	t
C–3'	125,3	d		27,9	t
				27,5	t
				24,6	t

Accurate Mass Measurement:

Found:	M^+, 229,1831
Calc. for $C_{16}H_{23}N$:	M^+; 229,1830

Preparation of N–(2–benzyl–4–t–butylcyclohexylidene)benzylamine (132)

Titanium tetrachloride (2,7 ml; 0,0245 mol) in cold, dry hexane (25 ml) was added slowly to a solution of benzylamine (17,76 g; 0,1660 mol) in dry hexane (250 ml; 0° C) with stirring and under a positive pressure of dry nitrogen. 2–Benzyl–4–t–butylcyclohexanone (6,75 g; 0,0277 mol) was added in one portion to this reaction mixture which was allowed to stir at room temperature for 3 hours. The mixture was filtered through dry kieselguhr contained in a sintered glass funnel (porosity 4A) prior to the removal of the hexane on a rotary evaporator. The imine was assumed to be 100 % pure and was used without further purification.

IR: ν_{max} (film) cm^{-1}

1 665	C=N

^{1}H NMR: δ ($CDCl_3$) ppm

0,80	9H, s, –C(**Me**)$_3$
1,1 – 4,4	10H, c, methylene/methine envelope
4,60	2H, s, Ph–C**H$_2$**–N
7,20	5H, s, **Ph**–CH$_2$–CH
7,26	5H, s, **Ph**–CH$_2$–N

Preparation of N–(2–benzyl–4–t–butylcyclohexylidene)propylamine (133)

Titanium tetrachloride (3 ml; 26 mmol) in cold hexane (28 ml) was added dropwise to a solution of propylamine (10,17 g; 0,172 mol) in cold hexane (250 ml; 0 °C) and then 2–benzyl–4–t–butylcyclohexanone (7,00 g; 29 mmol) was added in one portion to the reaction vessel with stirring and under a positive pressure of dry nitrogen. After stirring for 3 hours the reaction mixture was filtered through dry kieselguhr contained on a sintered glass funnel (4A). The hexane and propylamine were removed on a rotary evaporator to give an oil (7,28 g) which was shown by CGC to be 98 % pure. The oil was shown to be *N–(2–benzyl–4–t–butylcyclohexylidene)-propylamine* (**133**) (7,13 g; 85 %)

IR: ν_{max} (film) cm^{-1}

1 650	C=N

^{1}H NMR: δ ($CDCl_3$) ppm

0,82	9H, s, $-C(Me)_3$
1,1 – 3,7	17H, c, methylene, methine, methyl envelope
7,14	5H, s, $Ph-CH_2-CH$

Accurate Mass Measurement:

Found:	M^+, 285,2452
Calc. for $C_{16}H_{23}N$:	M^+; 285,2456

4.2.2.2 Preparation of enamines

Preparation of the pyrrolidine enamine of cyclohexanone (125)

This enamine was prepared using the method of Stork.[3]

Cyclohexanone (50,00 g; 0,510 mol), pyrrolidine (54,32 g; 0,765 mol), toluene–4–sulphonic acid (0,13 g) in dry benzene (150 ml) were heated under reflux using a Dean and Stark head until the required amount of was had been liberated. After removal of the benzene, the oil was fractionally vacuum distilled to give three fractions, all of which proved to be the desired enamine (125) (71,71 g;93 %). A repeat preparation using the same quantities gave 69,84 g (91 %).

Boiling point: 58 – 66 °C / 0,03 mmHg

IR:

ν_{max} (film) cm^{-1}	
1 642	C=C

Preparation of the pyrrolidine enamine of 4–t–butylcyclohexanone (130)

This enamine was prepared following the method of Firrell.[96]

4–Tertiary–butylcyclohexanone (49,26 g; 0,3 mol), pyrrolidine (23,43 g; 0,33 mol), and toluene–4–sulphonic acid (0,18 g) in dry benzene (100 ml) were heated under reflux using a Dean and Stark head until the desired quantity of water had been liberated (15,5 hours). Removal of the solvent on a rotary evaporator and fractional vacuum distillation gave the desired product (58,90 g; 94 %). All other spectral data were consistent with those of Firrell.[96]

Boiling point:	121° C/ 1,3 mmHg
Lit.:[96]	90 – 92 ° C / 33 Nm^{-1} (= 0,24 mmHg)

4.2.2.3 Alkylation of imines: General method.

The electrophilic alkene was added to the imine (in the molecular proportions indicated) in super–dry[90] methanol or dry acetonitrile, and the solution heated under reflux for the time indicated.

Hydrolysis of the mixture was effected by the addition of water (10 – 20 ml) and heating under reflux for 1 h.

The solvent was then removed on a rotary evaporator and the residue extracted with ether.

The ethereal layer was washed with hydrochloric acid (2 M), water, satd. aq. sodium hydrogen carbonate, satd. aq. sodium chloride and finally dried over anhydrous magnesium sulphate.

Filtration and evaporation of the ether gave the crude product, which was purified by vacuum distillation and/or flash chromatography.[118]

Reaction between neat acrylonitrile and N–(cyclohexylidene)cyclohexylamine (108) (Scheme 20)

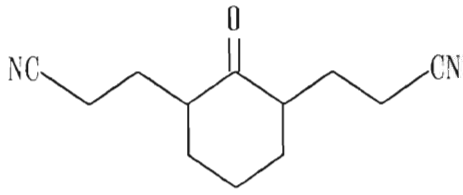
N–(Cyclohexylidene)cyclohexylamine (**108**) (34,94 g; 195 mmol) was placed in a flask, fitted with an efficient condenser and a Teflon–coated magnetic stirrer bar, was positioned in an oil bath (100 °C).

Acrylonitrile (20,69 g; 390 mmol) and hydroquinone (0,25g) were placed in a pressure equalising dropping funnel and the mixture added dropwise to the imine over a period of one hour with vigorous stirring.

The temperature of the oil bath was then raised to 130 °C which was maintained for a further 2 hours. Water (20 ml) was added and the mixture heated under reflux for a further hour. Removal of the solvent on a rotary evaporator gave an oil (55,12 g) a portion (29,98 g) of which was subjected to fractional distillation under vacuum. Three fractions were obtained: the first (0,41 g; BP 86 – 94 °C/0,21 mmHg) was cyclohexylamine; the second fraction (1,09 g; BP 94 – 97 °C) was a mixture of N–(2–cyanoethyl)cyclohexylamine and 2,6–bis-(2–cyanoethyl)cyclohexanone and the third fraction was the 2,6–bis-(2–cyanoethyl)cyclohexanone (3,31 g; BP 89 – 106 °C / 0,17 mmHg).

IR: ν_{max} (film) cm^{-1}

2 255	C≡N
1 706	C=O



109

^{13}C NMR: δ ($CDCl_3$) ppm

C–1	211,2	s	C–1'	14,7	t
C–2	49,0	d	C–2'	25,1	t
C–3	34,6	t	C–3'	119,7	s
C–4	24,7	t			
C–5	34,6	t			
C–6	49,0	d			

Accurate Mass Measurement:

Found:	M^+; 204,1259
$C_{12}H_{16}N_2O$ requires:	M^+; 204,1263

Preparation of authentic 2–(2–cyanoethyl)cyclohexanone (112)[3]

1–Pyrrolidinylcyclohexene (80 g; 0,53 mol), acrylonitrile (35,5 g; 0,67 mol) were heated under reflux in dioxane (200 ml) for 12 hours under a Dean and Stark water separator. Water (10 ml) was added and the mixture heated under reflux for a further hour. After the usual extraction and aqueous work–up an oil (64,03 g) was obtained which was fractionally distilled under vacuum to give two fractions with fairly similar boiling points. Both fractions were combined on the basis of spectral evidence to give 2–(2–cyanoethyl)cyclohexanone (**112 A**) (54,88 g; 69 %).

Boiling point: 112,5 – 116 °C/ 0,59 mmHg

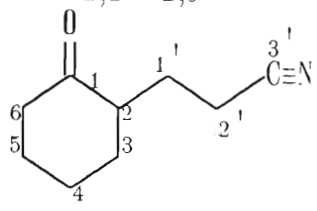
Lit:[3] 141 – 145 °C/ 10 mmHg

IR: ν_{max} (film) cm^{-1}

1 712	C=O
2 256	C≡N

^{1}H NMR: δ ($CDCl_3$) ppm

1,1 – 2,9 methylene/methine envelope



112 A (Authentic)

^{13}C NMR: δ ($CDCl_3$) ppm

C–1	211,3	s	C–1'	25,4	t
C–2	48,7	d	C–2'	14,8	t
C–3	36,0	t	C–3'	119,5	s
C–4	24,8	t			
C–5	33,8	t			
C–6	41,9	t			

Preparation of authentic 2,6–bis–(2–cyanoethyl)cyclohexanone (109 A)[3]

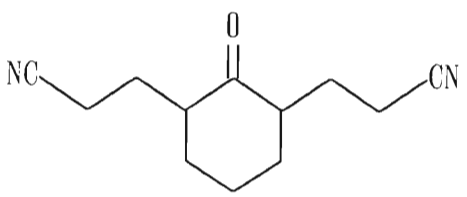
1–Pyrrolidinylcyclohexene (11,03 g; 73 mmol), acrylonitrile (11,61 g; 0,219 mol) in "super–dry" methanol were heated under reflux for 4 hours. After the usual aqueous hydrolysis and hydrolytic work–up, an oil (12,64 g) was obtained. A portion of this (11,99 g) was diluted with diethyl ether (ether) (30 ml) and then subjected to flash chromatography[118] using a mixture of ethyl acetate, pet. ether (40–60), and dichloromethane (6. 50 and 50 ml respectively) as eluant, taking 50 x 30 ml fractions. The component with R_f 0,82 proved to be the 2,6–bis(2–cyanoethyl)cyclohexanone (**109 A**; A = authentic) (7,72 g; 54 %).

IR: ν_{max} (film) cm^{-1}

2 228	C≡N
1 708	C=O

^{1}H NMR: δ ($CDCl_3$) ppm

1,3 – 1,6	Methylene/methine envelope



109 A

Analysis and Accurate Mass Measurement:

Found:	C: 70,26; H: 8,05; N: 13,56 %	M^+; 204,1262
$C_{12}H_{16}N_2O$ requires:	C: 70,56; H: 7,90; N: 13,71 %	M^+; 204,1263

Preparation of authentic 2,6–bis[2–methoxycarbonylethyl]cyclohexanone

Using the method of Stork[3] for the preparation of diethyl cyclohexanone-2,6–dipropionate, the dimethyl analogue was prepared using methyl acrylate.

1–Pyrrolidinylcyclohexene (125) (10,00 g; 66 mmol), methyl acrylate (17,09 g; 199 mmol; 3 eq.) in "super–dry" methanol (50 ml) was heated under reflux for 4 hours. After the usual aqueous hydrolysis, hydrolytic work–up and removal of the solvent on a rotary evaporator, a pale pink crystalline compound (15,91 g) remained. This was recrystallised from diethyl ether/hexane to give colourless crystals (10,54 g; 59 %)

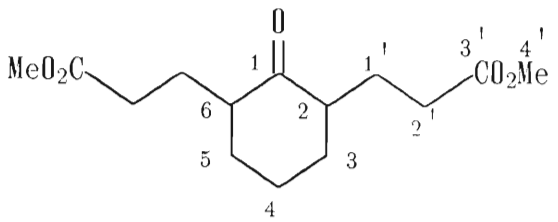
Melting Point: 52,5 – 83,0 °C

IR: ν_{max} (film) cm^{-1}

1 692	C=O
1 738	Me–O–C=O

^{1}H NMR: δ ($CDCl_3$) ppm

1,0 – 2,9	16H, methylene/methine envelope
3,67	6H, 2 x –OMe



^{13}C NMR: δ ($CDCl_3$) ppm

C–1	212,3	s	C–1'	24,4	t
C–2	49,9	d	C–2'	31,4	t
C–3	35,2	t	C–3'	173,8	s
C–4	25,2	t	C–4'	51,2	q

Reaction of acrylonitrile with N–(cyclohexylidene)benzylamine in methanol.

Acrylonitrile (13,6 g; 260 mmol), N–(cyclohexylidene)benzylamine (8,0 g; 43 mmol), and methanol (20 ml) were heated under reflux for 21 h. Distillation gave only the mono–alkylated product, 2–(2–cyanoethyl)-cyclohexanone (**112**) (1,98 g; 31%), which was identical with authentic material obtained by alkylation of 1–pyrrolidinylcyclohexene.

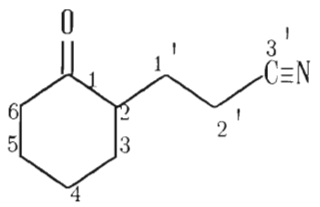
Boiling point: 112 – 115 C/0,6 mmHg

IR: ν_{max} (film) cm^{-1}

2 226	C≡N
1 7141	C=O

^{1}H NMR: δ ($CDCl_3$) ppm

1,4 – 2,6 Methylene/Methine envelope



112

^{13}C NMR: δ ($CDCl_3$) ppm

C–1	210,9	s	C–1'	25,0	t
C–2	48,2	d	C–2'	14,4	t
C–3	33,4	t	C–3'	119,1	s
C–4	24,4	t			
C–5	27,2	t			
C–6	41,5	t			

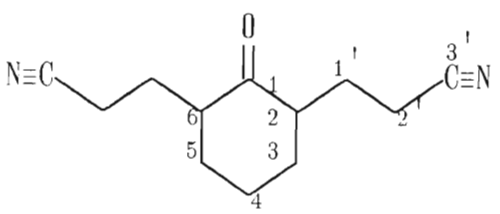
Reaction between acrylonitrile and N–[2–(2–cyanoethyl)cyclohexylidene]-propylamine in methanol.

Acrylonitrile (2,76 g; 52 mmol), N–[2–(2–cyanoethyl)cyclohexylidene]-propylamine (5,0 g; 26 mmol), and methanol (20 ml) were heated under reflux for 4 h. Flash chromatography of the crude product [hexane – dichloromethane – ethyl acetate (50:50:9)] gave unchanged 2–(2–cyano-ethyl)cyclohexanone (**112**) (1,51 g), 2,6–bis(2–cyanoethyl)cyclohexanone (**109**) (0,29 g; 5%) which was identical with authentic material[3] prepared by the alkylation of 1–N–pyrrolidinylcyclohexene, and *2,2–bis(2–cyanoethyl)-cyclohexanone* (**114**) (0,31 g; 6%).

2,6–bis(2–cyanoethyl)cyclohexanone (109)

IR:

ν_{max} (film) cm^{-1}	
2 227	C≡N
1 708	C=O



109

^{1}H NMR: δ ($CDCl_3$) ppm

1,3 – 2,6 Methylene/methine envelope

^{13}C NMR: δ ($CDCl_3$) ppm

C–1	210,8	s	C–1'	14,2	t
C–2	48,5	d	C–2'	24,6	t
C–3	34,2	t	C–3'	119,0	s
C–4	24,2	t			
C–5	34,2	t			
C–6	48,5	d			

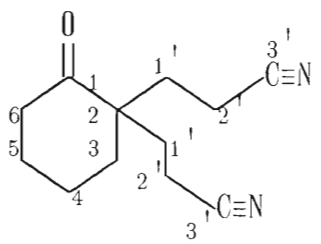
Analysis and Accurate Mass Measurement:

Found:	N	13,6%;	M^+	204,1262
$C_{12}H_{16}N_{20}$ requires:	N	13,7%;	M^+	204,1263

2,2–*bis*(2–cyanoethyl)cyclohexanone (114)

IR:

ν_{max} (film) cm^{-1}	
2 228	C≡N
1 710	C=O



114

^1H NMR: δ ($CDCl_3$) ppm

1,7 – 2,4 Methylene envelope

^{13}C NMR: δ ($CDCl_3$) ppm

C–1	211,9	s	C–1'	11,4	t
C–2	49,8	s	C–2'	29,5	t
C–3	34,5	t	C–3'	119,1	s
C–4	19,8	t			
C–5	26,0	t			
C–6	38,4	t			

Analysis and Accurate Mass Measurement:

Found:	N	13,7%;	M^+	204,1250
Calc. for $C_{12}H_{16}N_{20}$:	N	13,7%;	M^+	204,1263

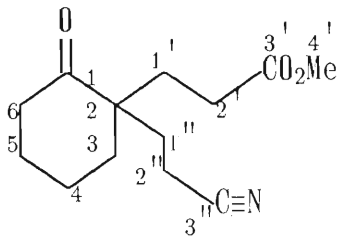
Reaction of methyl acrylate with N–(2–cyanoethylcyclohexylidene)propylamine in methanol

Methyl acrylate (4,44 g; 52 mmol) and N–[2–(2–cyanoethyl)cyclohexylidene]propylamine (4,96 g; 26 mmol) were heated under reflux in "super-dry" methanol (20 ml) for 4 hours. Water (10 ml) was added and the mixture heated under reflux for a further hour. The solvent was removed on a rotary evaporator and the residue taken up in ether (200 ml). The ether layer was washed with dil. aq. hydrochloric acid (4 x 25 ml), satd. aq. sodium hydrogen carbonate (25 ml), water (2 x 25 ml) and satd. aq. sodium chloride (25 ml) and dried over anhydrous magnesium sulphate. Removal of the ether gave an oil (3,63 g). A portion of the crude product (3,20 g) was subjected to flash chromatography using a mixture of ethyl acetate-hexane-dichloromethane (1:5:5) as eluant and taking ≃40 ml fractions. The fractions were combined on the basis of TLC to give unchanged 2–(2–cyanoethyl)-cyclohexanone (**112**) (0,64 g) and *2–(2-cyanoethyl)-2–(2–methoxycarbonylethyl)cyclohexanone* (**115**) (1,96 g; 43%).

Boiling point: 146 °C/ 0,1 mm Hg

IR:

ν_{max} (film) cm^{-1}	
2 230	C≡N
1 744	CO_2Me
1 710	C=O



115

^{1}H NMR: δ ($CDCl_3$) ppm

1,6 – 2,6	methylene envelope
3,66	3 H; OMe.

^{13}C NMR: δ ($CDCl_3$) ppm

C–1	212,6	s	C–1'	27,8	t
C–2	49,9	s	C–2'	28,8	t
C–3	35,0	t	C–3'	172,8	s
C–4	20,0	t	C–4'	51,3	q
C–5	26,3	t	C–1''	29,8	t
C–6	38,4	t	C–2''	11.6	t
			C–3''	119,1	s

Accurate Mass Measurement:

Found:	M^+	237,1370
Calc. for $C_{13}H_{19}NO_3$:	M^+	237,1365

Analysis:

Found:	C:	65,6;	H:	8,3	N:	6,1%.
Calc. for $C_{13}H_{19}NO_3$:	C:	65,8;	H:	8,0	N:	5,9%

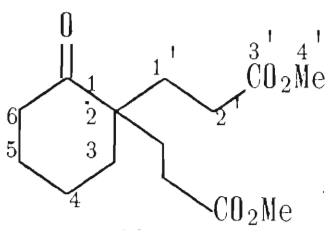
Reaction of methyl acrylate with N–(cyclohexylidene)benzylamine (111) in methanol

Methyl acrylate (7,38 g; 86 mmol), N–cyclohexylidenebenzylamine (8,0 g; 43 mmol), in methanol (20 ml) were heated under reflux for 3 h. After hydrolysis, the usual hydrolytic workup, removal of the solvent, distillation under vacuum gave the 2,2–diester (2,86 g; 25 %), which was further purified by flash chromatography using hexane–dichloromethane–ethyl acetate (12,5:12,5:1) as eluant to give *2,2–bis[2–methoxycarbonylethyl]-cyclohexanone* (121).

Boiling point: 146 °C/ 0,04 mm Hg.

IR:

ν_{max} (film) cm^{-1}	
1 744	CO_2Me
1 709	C=O



121

^{1}H NMR: δ ($CDCl_3$) ppm

1,6 – 2,5	16 H; methylene envelope
3,52	6 H; 2 x OMe.

^{13}C NMR: δ ($CDCl_3$) ppm

C–1	212,6	s	C–1'	27,6	t
C–2	49,4	s	C–2'	28,6	t
C–3	35,2	t	C–3'	172,8	s
C–4	19,9	t	C–4'	50,7	q
C–5	26,1	t			
C–6	38,1	t			

Accurate Mass:

Found:	M^+	270,1461
Calc. for $C_{14}H_{22}O_5$:	M^+	270,1467

Analysis:

Found:	C:	62,1;	H:	8,3%
Calc. for $C_{14}H_{22}O_5$:	C:	62,2;	H:	8,2%

Reaction between methyl acrylate and N–cyclohexylidenepropylamine (122) in dry acetonitrile in the presence of 4–dimethylaminopyridine

Methyl acrylate (30,94 g; 360 mmol), N–cyclohexylidenepropylamine (10,0 g; 72 mmol), quinol (0,09 g), 4–dimethylaminopyridine (8,79 g; 0,072 mol) was heated under reflux in dry acetonitrile for 4 h. Vacuum distillation gave the 2,2–*bis*[2–methoxycarbonyl)ethyl]cyclohexanone (121) in far greater yield (15,03 g; 77%) than the reaction carried out in methanol.

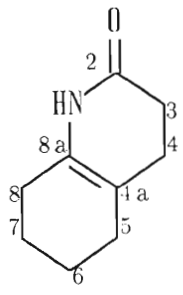
Reaction between acrylamide and N–cyclohexylidenepropylamine in dry methanol

Acrylamide (42,1 g; 590 mmol) and N–cyclohexylidenepropylamine (13,77 g; 99 mmol) were heated under reflux in dry methanol for 4 h. The crude product was subjected to flash chromatography using hexane-dichloro-methane–ethyl acetate (8:4:5) which gave *2–oxo–*$\Delta^{4a(8a)}$*-octahydroquino-line* (2,68 g; 18%).

Melting point: 138,5 – 140,0 °C (Recrystallised from hexane–dichloromethane).

IR: ν_{max} (Nujol) cm^{-1}

3 210	NH
3 180	NH
3 100	NH
1 670	CONH



123

^{1}H NMR: δ ($CDCl_3$) ppm [250 MHz]

1,56 – 1,74	4 H;	m; 2 x CH_2
1,95 – 2,12	4 H;	m; 2 x CH_2
2,18	2 H;	t: J = 10,5 Hz; CH_2
2,47	2 H;	t; J = 8 Hz; CH_2
8,47	1 H;	s; NH

^{13}C NMR: δ ($CDCl_3$) ppm [63 MHz]

C–2	171,6	s	C–6	22,1	t
C–3	30,6	t	C–7	22,6	t
C–4	27,7	t	C–8	26,0	t
C–4a	109,3	s	C–8a	128,2	s
C–5	25,7	t			

Accurate Mass Measurement:

Found:	M^+	151,0998
Calc. for $C_9H_{13}NO$:	M^+	151,0997

Analysis:

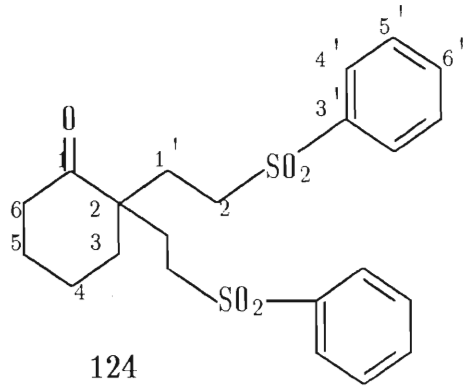
Found:	C:	71,2;	II:	8,8	N:	9,2%.
Calc. for $C_{14}H_{22}O_5$:	C:	71,4;	II:	8,6	N:	9,2%

Attempted reaction between phenyl vinyl sulphoxide and N–(cyclohexylidene)propylamine in dry methanol

N–(cyclohexylidene)propylamine (1,46 g; 11 mmol), phenyl vinyl sulphoxide (4,80 g; 32 mmol) in "super–dry" methanol (25 ml) were heated under reflux for 4 hours prior to the usual aqueous hydrolysis and hydrolytic work–up. The crude product (1,25 g) showed no phenyl group in the proton nmr. The crude material was subjected to flash chromatography and 137 fractions (30 ml each) were taken, but it was not possible to identify a single component.

Reaction between phenyl vinyl sulphone and N–(cyclohexylidene)-cyclohexylamine in dry methanol

Phenyl vinyl sulphone (2,20 g; 13 mmol), and N–(cyclohexylidene)-cyclohexylamine (0,82 g; 4,6 mmol) were heated under reflux in methanol (2 ml) for 4 hours. The hydrolysis was carried out as per the general method given above except that dichloromethane (4 x 25 ml) was used for the extraction instead of diethyl ether. The crude product was purified using flash chromatography with a hexane–dichloromethane–ethyl acetate eluant (2:1:1) which gave recovered phenyl vinyl sulphone (0,28 g) and *2,2–bis[2–phenylsulphonylethyl]cyclohexanone* (0,76 g; 48%).



124

^{1}H NMR: δ ($CDCl_3$) ppm

1,2 – 3,1	16 H; methylene envelope
7,4 – 7,9	10 H; 2 x Ph.

^{13}C NMR: δ ($CDCl_3$) ppm

C–1	212,1	s	C–1'	26,4	t
C–2	49,4	s	C–2'	50,6	t
C–3	35,5	t	C–3'	138,4	s
C–4	20,0	t	C–4'	127,6	d
C–5	26,2	t	C–5'	129,1	d
C–6	38,3	t	C–6'	133,6	d

Accurate Mass Measurement:

Found:	M^+	434,1230
Calc. for $C_{22}H_{26}S_2O_5$:	M^+	434,1222

Analysis:

Found:	C:	60,8;	H:	6,0	S:	14,8%
Calc. for $C_{22}H_{26}S_2O_5$:	C:	60,5;	H:	6,0	S:	15,0%

This reaction was also carried out by heating N–(cyclohexylidene)cyclohexylamine (0,82 g; 4,6 mmol) and phenyl vinyl sulphone (2,20 g; 13 mmol) in dry methanol (2 ml) under reflux for 4 h., but the yield was very low (0,51 g; 25,8%).

Accurate Mass Measurement:

Found:	M^+	434,1228
Calc. for $C_{22}H_{26}S_2O_5$:	M^+	434,1222

Attempted reaction between methyl crotonate and N–(cyclohexylidene) benzylamine in dry methanol

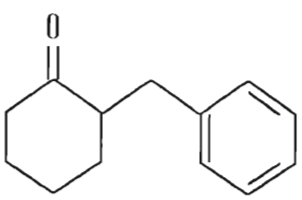
N–(cyclohexylidene)propylamine (5,00 g; 36 mmol), methyl crotonate (21,61 g; 216 mmol) in "super–dry" methanol (17 ml) were heated under reflux for 4 hours prior to aqueous hydrolysis and the usual hydrolytic work–up. The proton nmr spectrum of the crude product (0,77 g) showed that no alkylation had occurred since there was a complete absence of the required methoxy peak. The same was true of the methoxy carbonyl absorption in the infra–red spectrum.

Preparation of 2–benzylcyclohexanone (126)

1–Pyrrolidinylcyclohexene (22,64 g; 150 mmol), benzyl bromide (36,72 g; 215 mmol) in dry dioxane (100 ml) were heated under reflux for 12 hours. Water (20 ml) was added and the mixture heated under reflux for a further 3 hours. The reaction mixture was extracted with diethyl ether (1 x 300 ml; 2 x 100 ml) and the combined extracts reduced to approximately 200 ml on a rotary evaporator. This extract was then subjected to the usual hydrolytic work–up used on all the hydrolysed imine extracts. The oil obtained was then fractionally distilled under vacuum to give three fractions. The first fraction (5,15 g) proved to be unreacted benzyl bromide; the second (1,02 g) was a mixture of benzyl bromide and 2–benzylcyclohexanone; and the final fraction was pure 2–benzylcyclohexanone (**126**) (21,43 g; 76 %)
In a repeat preparation on a similar scale, the yield was 70 %, but the reaction mixture became very dark prior to hydrolysis.

Boiling point: 88 – 94 °C / 0,09 mmHg

Lit:[3] 165 –167 °C / 18 mmHg



126

IR: ν_{max} (film) cm^{-1}

1708 C=O

^{1}H NMR: δ ($CDCl_3$) ppm

1,2 – 2,7	10H, c, 5 x **CH_2**
3,22	1H, m, **H** at C–2
7,12	5H, s, **Ph**

Preparation of 2–[2–methoxycarbonylethyl]–2–benzylcyclohexanone (129)

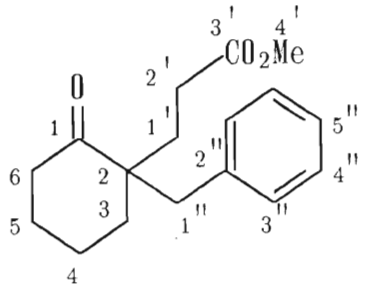
N–(2–benzylcyclohexylidene)benzylamine (2,50 g; 9 mmol), and methyl acrylate (3,88 g; 45 mmol) in "super–dry" methanol (22 ml) were heated under reflux for 4 hours. The usual aqueous hydrolysis, hydrolytic work–up and removal of the solvent gave an oil (2,04 g), which was subjected to flash chromatography on a column of silica gel (Merck Art: 9385) using 10% ethyl acetate in hexane as eluant. Forty fractions (≃ 50 ml) were taken and were combined on the basis of tlc to give two main fractions: the first had an R_f of 0,36 (0,53 g). This proved to be starting ketone; and the second (R_f 0,18) was *2–[2–methoxycarbonylethyl]–2–benzylcyclohexanone* (**129**) (1,33 g; 54 %). The latter was further cleaned up on silica gel plates (Merck Art.: 5745) using the same eluant.

IR: ν_{max} (film) cm^{-1}

1 745	CO_2Me
1 710	C=O

^{1}H NMR: δ ($CDCl_3$) ppm

1,2 – 2,2	6H; c.
2,3 – 2,4	3H; c.
2,88	2H; d.of d; J = 13,8 Hz
3,66	3H; s; –OMe
7,07 – 7,18	2H; m; Ph protons
7,20 – 7,32	3H; m; Ph protons



^{13}C NMR: δ ($CDCl_3$) ppm

C–1	214,9	s	C–3'	174,4	s
C–2	51,9	s	C–4'	52,1	q
C–3	39,6	t	C–1''	29,8	t
C–4	20,8	t	C–2''	137,6	s
C–5	29,0	t	C–3''	126,8	d
C–6	40,6	t	C–4''	128,5	d
C–1'	26,9	t	C–5''	130,9	d
C–2'	35,9	t			

Accurate Mass Measurement:

Found:	M^+; 274,1587
Calc. for $C_{17}H_{22}O_3$:	M^+; 274,1569

Mass Spectrometry:

The mass spectrum showed the following ions:

275 (M+1); 274 (M^+); 257; 256; 243; 242; 225; 224; 188; 187; 91 (base peak).

Preparation of 2–benzyl–4–t–butylcyclohexanone (131)

1–Pyrrolidinyl–4–t–butylcyclohexene (62,10 g; 0,3 mol) and benzyl chloride (75,96 g; 0,6 mol) in "super–dry" methanol were heated under reflux for 4 hours. After the usual aqueous hydrolysis and hydrolytic work–up, the solvent was removed on a rotary evaporator to give which was fractionally distilled under vacuum to give four main fractions: the first (BP 45 – 53 °C / 0,23 mmHg; 24,94 g) proved to be 4–t–butylcyclohexanol; the second (BP 55 – 59 °C / 0,20 mmHg; 1,41 g) was a mixture of starting ketone and benzyl chloride; the third (BP 105 – 108 °C / 0,21 mmHg; 3,54 g) was starting ketone; and the final fraction (BP 128 °C / 0,21 mmHg). This final fraction was re–distilled to give the desired 2–benzyl–4–t–butyl-cyclohexanone (**131**) (29,09 g; 40 %).

Boiling point: 115 – 116 °C/ 0,065 mmHg

IR:

ν_{max} (film) cm^{-1}	
1 708	C=O

^{1}H NMR:

δ ($CDCl_3$) ppm	
0,84	9H; s; –C(**Me**)$_3$
1,1 – 2,44	10H; c; methylene/methine envelope
7,15	5H; s; **Ph**

Preparation of 2–[2–methoxycarbonylethyl]–2–benzyl–4–t–butylcyclohexanone (134)

N–(2–benzyl–4–t–butylcyclohexylidene)propylamine (**132**) (6,78 g; 24 mmol) and methyl acrylate (10,23 g; 119 mmol) in "super–dry" methanol were heated under reflux for 4 hours.

After the usual hydrolysis, hydrolytic work–up and removal of the solvent on a rotary evaporator an oil (6,01 g) was obtained.

A portion (3,00 g) was subjected to flash chromatography [118] using silica gel (Merck Art: 9385) and ethyl acetate (10%) in hexane as eluant taking 50 ml fractions (40 fractions). The fractions were combined on the basis of tlc which gave two major fractions: the first was starting ketone (1,23 g) and the second was *2–[2–methoxycarbonylethyl]–2–benzyl–4–t–butylcyclohexanone* (**134**) (1,56 g; 40 %).

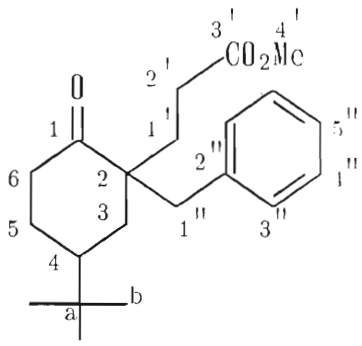
A further portion (2,40 g) of the crude product was chromatographed on eight preparative plates (Merck Art.: 5745) using the same eluant. Nine bands were visualised under an ultra–violet lamp. After extraction of the silica gel with dichloromethane containing methanol (≃10 drops/50 ml), filtrations and evaporation, the fractions were combined on the basis of tlc to give starting ketone (0,34 g) and 2–[2–methoxycarbonylethyl]–2–benzyl–4–t–butylcyclohexanone (**134**) (1,29 g; 41 %).

IR: ν_{max} (film) cm^{-1}

1 715	CO_2Me
1 703	C=O

^{1}H NMR: δ ($CDCl_3$) ppm

0,82	9H; s; $-C(\mathbf{Me})_3$
1,1 – 3,1	13H; c; methylene/methine envelope
3,64	3H; s; **OMe**



^{13}C NMR: δ ($CDCl_3$) ppm

C–1	213,9	s	C–1''	37,3	t
C–2	50,7	s	C–2''	137,6	s
C–3	39,9	t	C–3''	126,1	d
C–4	27,1	d	C–4''	127,8	d
C–5	30,4	t	C–5''	130,6	d
C–6	41,2	t	C–a	32,2	s
C–1'	28,6	t	C–b	27,3	q
C–2'	38,8	t			
C–3'	173,3	s			
C–4'	51,5	q			

Accurate Mass Measurement:

Found:	M^+; 330,2200
Calc. for $C_{21}H_{30}O_3$:	M^+; 330,2195

Mass Spectrometry:

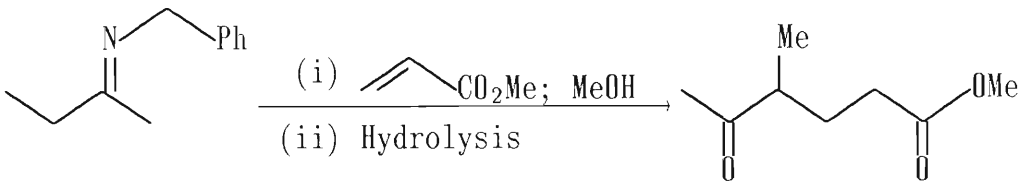
The mass spectrum showed the following ions:

330 (M^+); 312; 299; 298; 183; 273; 270; 255; 244; 243; 91(base peak).

2.5 SYNTHESIS OF THE BICYCLO[2.2.2]OCTANE RING SYSTEM FROM ACYCLIC PRECURSORS

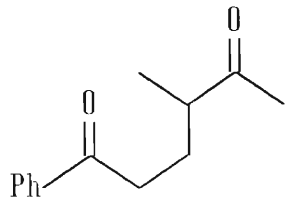
2.5.1 DISCUSSION

Previously,[89] it was shown that methyl acrylate had reacted at the more substituted position of N–(2–butylidene)benzylamine, to give, after hydrolysis, methyl 4–methyl–5–oxohexanoate.

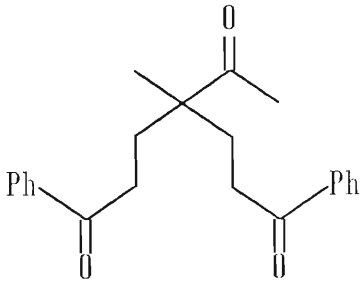


In an extension of this work on the regioselective alkylation of the imines of cyclic [89,93,94,123] and acyclic [92] ketones, the reaction of phenyl vinyl ketone (PVK) with N–(2–butylidene)benzylamine was investigated. The reaction was carried out in "super–dry" methanol under reflux for 4 hours followed by aqueous hydrolysis and the usual hydrolytic workup. The crude reaction mixture was purified using flash chromatography [118] which separated the product into two isomeric forms of **141**. Isomer I was recrystallised from ethyl acetate and crystallised in the I2/a space group.

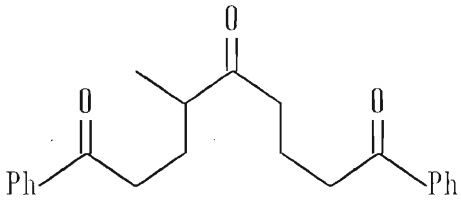
The reaction mixture failed to give any of the expected mono– or di–alkylated products (**135** – **137**) or the plausible cyclisation products (**138** – **140**).



135



136



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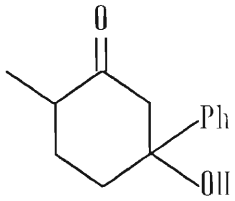

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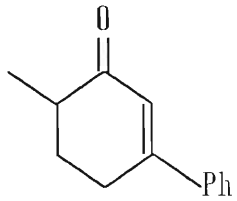

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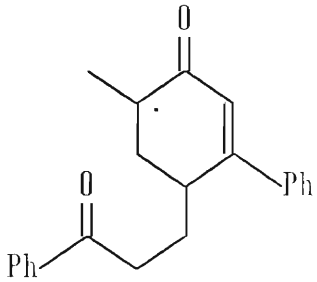

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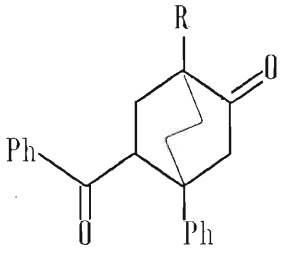
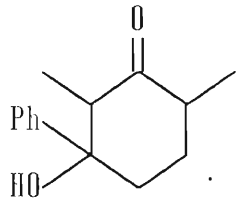


141: R = Me
142: R = Ph



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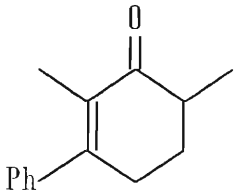

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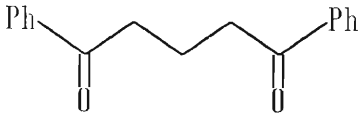
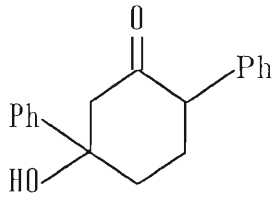
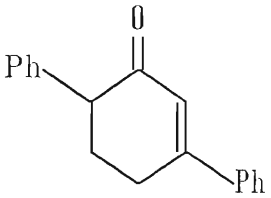


145



146

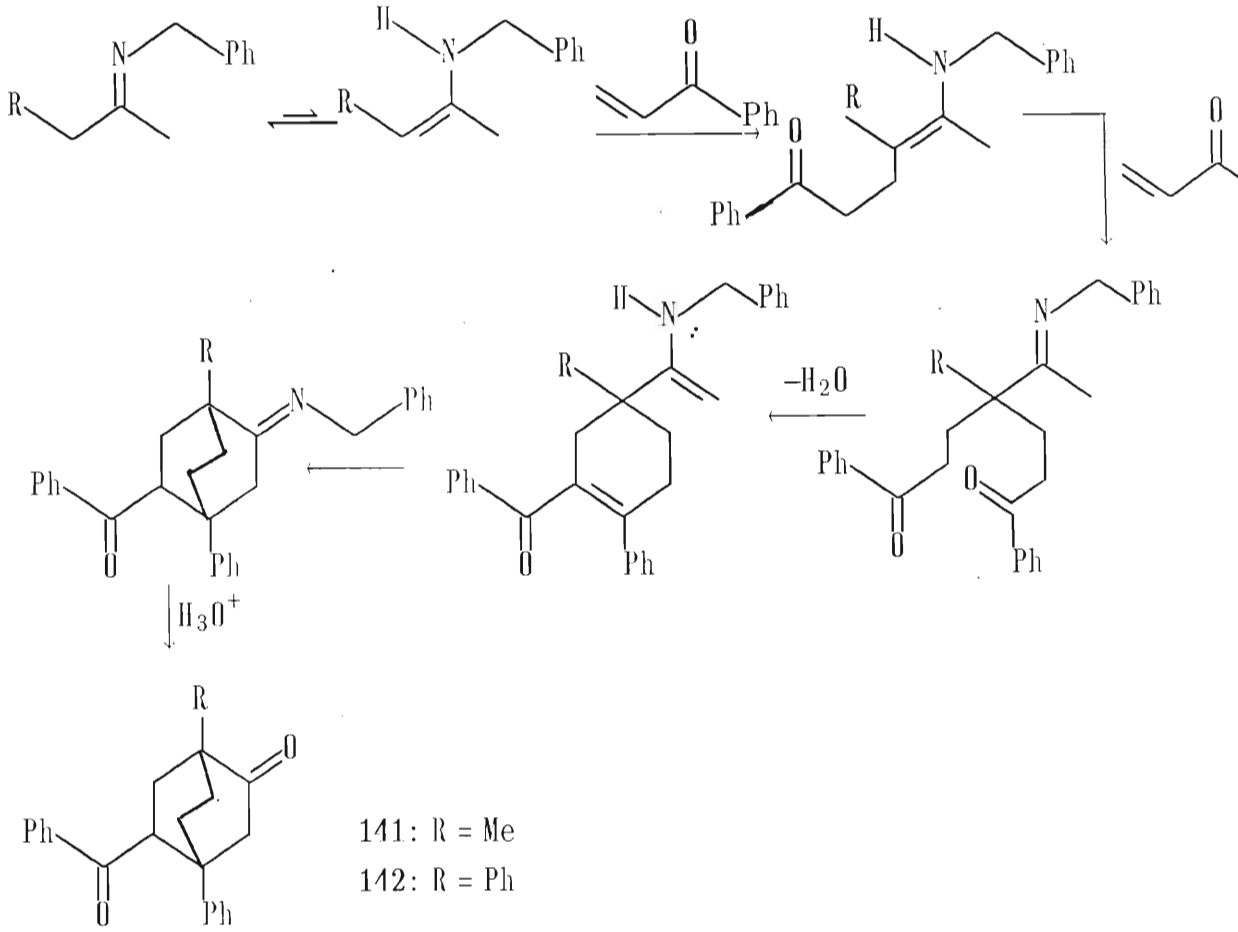


147

The 80 MHz ^{1}H–nmr spectrum of the product failed to show a CH_3CO group, but indicated the presence of two benzene rings and a methyl *singlet* at δ 1,1. The missing CH_3CO group shows that neither the mono– nor the di–alkylated products is possible. The presence of the two benzene rings indicates that possibly two equivalents of PVK per molecule of butanone imine have become attached to the butyl chain.

The only rational explanation for these observations is that two equivalents of PVK have reacted with the N–(2–butylidene)benzylamine, firstly twice at C–3 (of the butyl chain) and then once at C–1.

Consideration of a plausible sequence of events, set out in **Scheme 26** led us to propose the bicyclo[2.2.2]octanone structure (**141**) as the product of this reaction on mechanistic grounds.



141: R = Me
142: R = Ph

SCHEME 26

Further evidence for this structure came from the ^{13}C nmr spectrum (20 MHz) (for both isomers I and II of 141) which indicated the presence of two carbonyls (Ph–CO– and a ring carbonyl), a highfield quartet (Me–C(—)(—)—), a relatively low–field triplet (CH_2–CO), a doublet (CH–CO), two singlets (C–1 and C–4), three triplets for the remaining three $-CH_2-$ groups and two benzene rings.

There were however, significant differences between both the proton and ^{13}C nmr spectra for Isomers I and II of **141**.

The proton nmr spectrum (80 MHz) of Isomer II of 141 indicated that one of

the protons was deshielded to δ 3,67. Comparing the ^{13}C nmr spectra of Isomer I and Isomer II of 141 showed that the triplet at δ_C 51,3 (Isomer I) becomes more shielded in Isomer II (δ_C 43,7) and the triplet at δ_C 25,0 (Isomer I) had shifted to δ_C 34,7 (Isomer II). All the other signals were of comparable chemical shifts. In order to assign the spectra of Isomers I and II (**141**) the samples were submitted for 2D COSY, NOESY and HETCOR plots which were run on a Bruker 500 MHz instrument. The full assignment was accomplished as follows:

Isomer I: 141

Using the COSY plot, the sets of protons with the following chemical shifts (δ ppm) were shown to be coupled:

2,93 (1H) to 2,42 (1H): Geminal coupling; Isolated CH_2;

1,78 (1H) to 2,11 (1H): Geminal coupling; C–CH_2–CH_2–C;

3,04 (1H) to 1,80 (1H): Geminal coupling; C–CH_2–CH_2–C;

1,78 (1H) to 1,80 (1H) and 3,04 (1H): Vicinal coupling;

2,11 (1H) to 1,80 (1H) and 3,04 (1H): Vicinal coupling;

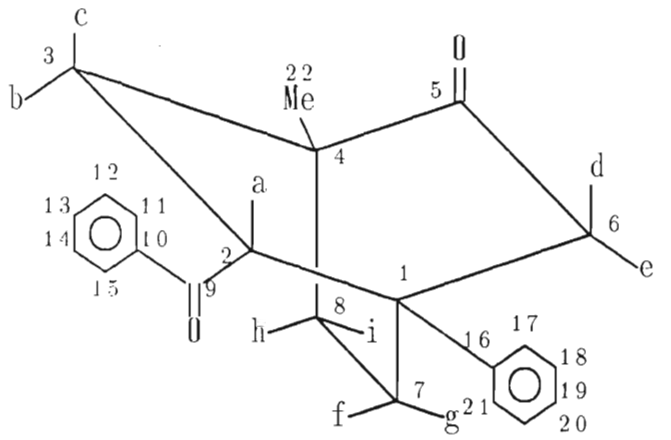
1,95 (1H) to 2,08 (1H): Geminal coupling; C–CH_2–CH–CO;

1,95 and 2,08 to **4,06** (1H): Vicinal coupling; C–CH_2–CH–CO;

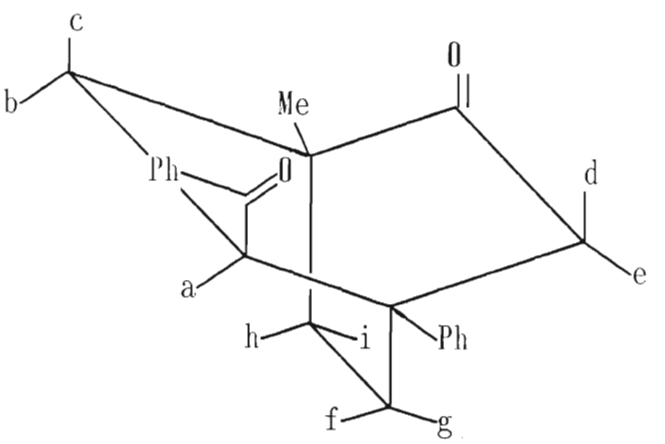
7,51 (2H) to 7,22 (2H) to 7,37 (1H): **Ph**–CO;

7,20 (2H) to 7,09 (2H) to 6,99 (1H): Ph–C(—)(—)—.

On the basis of these couplings, letters were assigned to each proton. These and the carbon numbering used are shown in the diagrams below for Isomers I and II (**141**).



141 : ISOMER I



141 : ISOMER II

From the HETCOR, the protons associated with each carbon could be assigned and hence the remainder of the carbons:

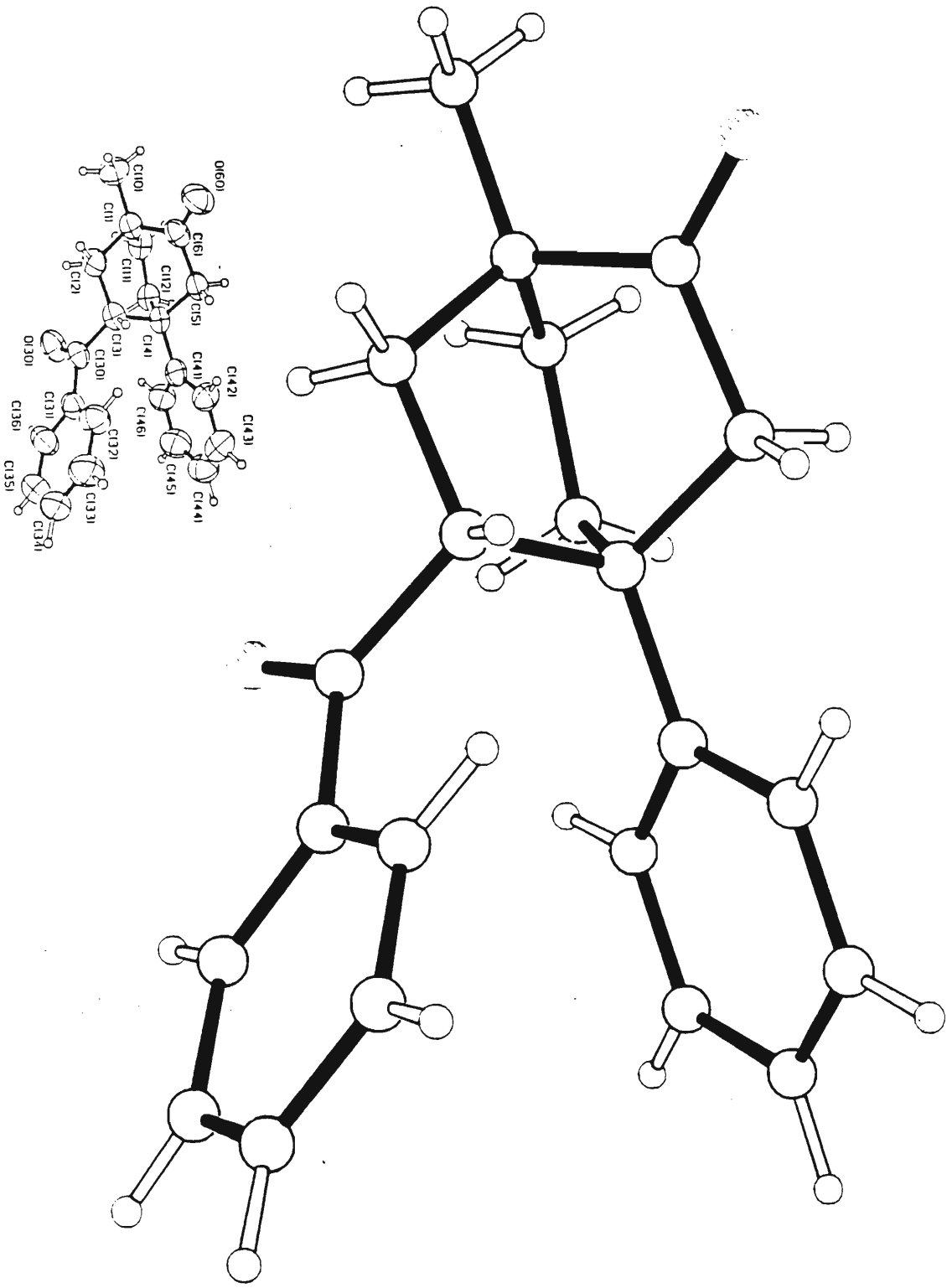
	δ_C	Proton Assignment	δ_H
C–1	43,8		
C–2	48,5	a	4,06
C–3	35,7	b; c	2,08; 1,95
C–4	43,2		
C–5	215,6		
C–6	51,3	d; e	2,93; 2,42
C–7	25,1	f; g	3,04; 1,80
C–8	30,8	h; i	2,11; 1,78
C–9	202,7		
C–10	143,3		
C–11/C–15	127,8		7,51
C–12/C–14	128,1		7,22
C–13	132,5		7,37
C–16	137,9		
C–17/C–21	125,9		7,20
C–18/C–20	128,3		7,09
C–19	126,6		6,99
C–22	19,5		1,09

The NOESY plot showed nuclear Overhauser effects between protons:

a and d; a and b; a and c; f and h; f and i; e and g; as well as the geminal n.O.e's: f and g; d and e; h and i; and b and c.

The single crystal X–ray structure determination also corroborates the above assignment for Isomer I (**141**).

Crystal Structure of 141 (Isomer I)



12-14 (I2/a)

It is interesting to note in the solution that the space group I2/A is non–standard. This space group was chosen in order to obtain β as close to 90° as possible. When viewing the cage structure, the torsion angle C1–C11–C12–C–4 is of the order of 10°, which is normal for this type of structure.[124]

Certain of the bond lengths are foreshortened because of thermal motion. All the C–C bond lengths in the benzene rings should be around 0,140 nm whereas nearly all are shorter than this at around 0,138 nm.
The bond length C1–C6 and C5–C6 (both sp^3–sp^2) are around 0,150 nm which is slightly longer than they would be expected (0,142 nm) to be.
The sp^3–sp^3 bond length between C1 and the methyl carbon, C10 is also foreshortened from 0,154 nm to 0,152 nm.
The two benzene rings are pseudo–parallel due to the interactions of the benzene hydrogens and the delocalised π–electrons above and below the plane of the rings.

The assignment of **141**: Isomer II was executed in a similar manner and the only significant differences in chemical shifts between the two isomers occur at positions 6 and 7. In **141**: Isomer I, C–7 experiences a steric compression shift [125] to high field relative to C–7 in **141**: Isomer II (δ_c 25,1 and 34,8, respectively), whereas proton f (attached to C–7) is deshielded in Isomer I by the close proximity of the benzoyl carbonyl group and appears at lower field relative to proton f in Isomer II (δ 3,67 and 2,93, respectively).
Furthermore, a strong n.O.e. was observed between protons a and d in Isomer I, which was not present in Isomer II which confirms the orientation of the benzoyl group as being *exo* to the cyclohexanone ring in Isomer I and

endo in Isomer II. Long range W coupling was observed between protons a and e in Isomer II (1,6 Hz) whereas in Isomer I the W coupling occurred between a and g (0,9 Hz). In both isomers W coupling was also observed between protons c and i (2,8 Hz), and between protons d and f (3,5 Hz).

This discovery is most significant, for as far as is known, the formation of four different carbon–carbon bonds sequentially (**Scheme 26**) constitutes the first one–step synthesis of a bridged bicyclic system from acyclic precursors.

The reaction was repeated using two equivalents of PVK but this only increased the yield of Isomer II from 5,6 to 35 %, none of Isomer I being isolated under these conditions. As it was possible that the water eliminated in the first cyclisation step (**Scheme 26**) could result in partial hydrolysis of the imine–enamine mixture, the reaction was repeated by Jutle[126]in the presence of molecular sieves which resulted in a further increase in yield to 54 %.[126]

The reaction followed a different course when applied to N–(3–pentylidene)-benzylamine. In this case, only one equivalent of PVK reacted with one equivalent of the imine at C–2 of the imine. This was followed by cyclisation onto C–4 of the imine to give 3–hydroxy–2,6–dimethyl–3-phenylcyclohexanone (**143**) (0,33 g; 11 %). During the reaction, however, most of **143** underwent a dehydration reaction to give 6–methyl-3–phenylcyclohex–2–enone (**139**) (1,30 g; 45 %).

3–Hydroxy–2,6–dimethyl–3-phenylcyclohexanone (**143**) showed a sharp OH absorbance (3580 cm^{-1}) in the infra–red spectrum as well as carbonyl absorbance at 1710 cm^{-1}.

The proton nmr spectra showed that the chemical shift of the OH proton was concentration dependent. All the protons and carbons were assigned from the ^{1}H (500 MHz) and ^{13}C nmr (125 MHz) spectra using HETCOR, COSY and NOESY plots (500 MHz).

The carbon at C–3 appeared as a singlet (δ_C 81,5) and the carbons at C–2 and C–6 appeared as doublets, the latter proving that mono–substitution and cyclisation had occurred. Carbon/hydrogen analysis was consistent with the molecular formula for **143**.

From the crystal structure, the cyclohexanone ring presents as an almost perfect chair. Around the ring, the torsion angles average out at about 55° which is absolutely normal as rings are always slightly flattened. In fact this value is approximately 5° smaller than ideality.

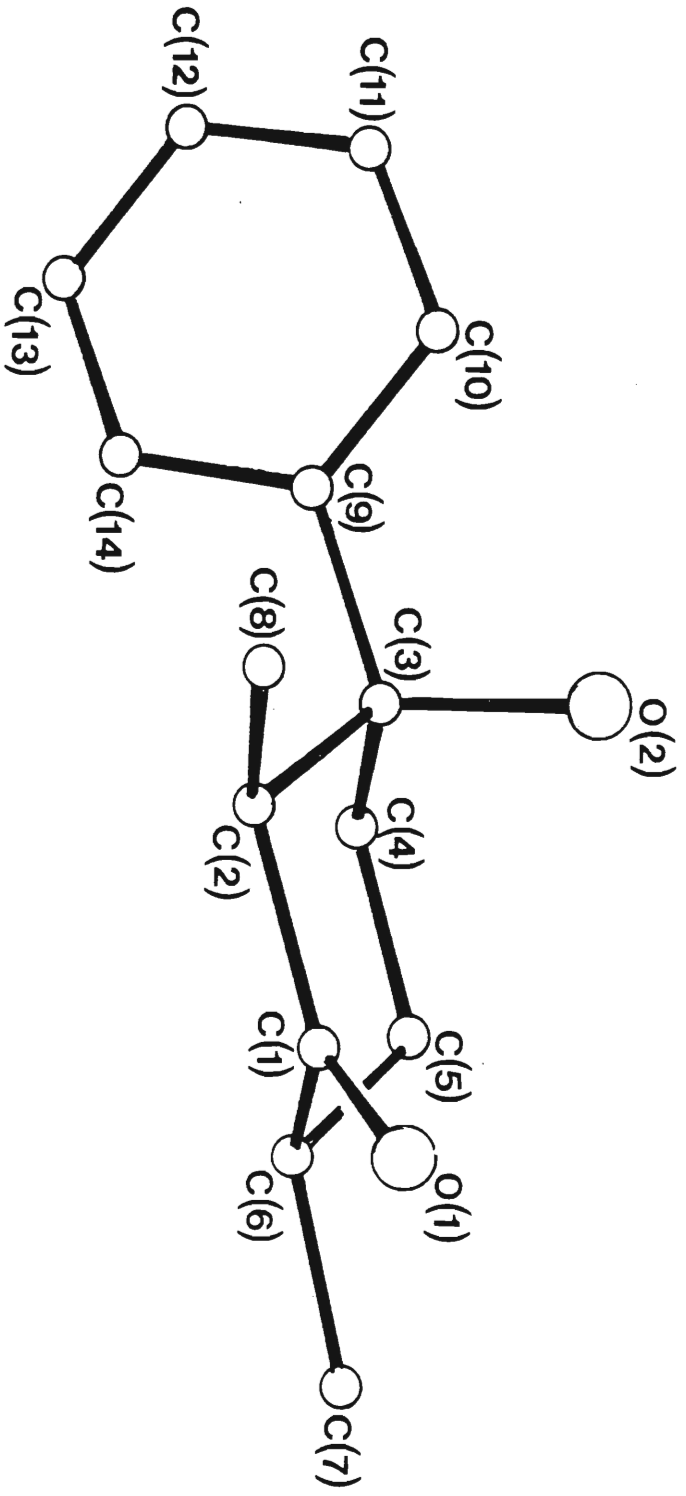
The torsion angle O1–C1–C6–C7 (C7 being the methyl carbon) is 4° showing that the carbonyl is eclipsed with the methyl carbon. Further the carbonyl is eclipsed with C8, the torsion angle C8–C2–C1–O1 being –5°. C7 and C8 are equatorial as is the C9 of the benzene ring. C8 and C9 are staggered with a torsion angle of –59°.

The hydroxy group is perfectly axial to the ring and the torsion angle C8–C2–C3–O2 is 62°.

The bond lengths C1–C1 (0,150 nm) and C1–C6 (0,151 nm) are typical of sp^2–sp^3 carbon–carbon bond lengths.

The apparent bond lengths in the benzene ring are severely foreshortened which is indicative of thermal motion and artifacts within the refinement of the crystal structure.

CRYSTAL STRUCTURE OF 143



In the reaction between phenyl vinyl ketone and N–(1–phenyl–1-ethylidene)benzylamine in methanol, only the mono–substituted product, 1,5–diphenylpentan–1,5–dione (**145**), was isolated. This reaction was carried out in order to attempt to determine whether it was possible to force di–alkylation at the methyl group of the imine. It appears that, from GC–MS work carried out on the crude product, only the mono–alkylated product is formed. Although it was not possible to obtain this compound in a pure enough form for complete analysis, despite repeated flash chromatography, the GC–MS work carried out gave a good molecular ion for **145** (M^+ 252). The proton nmr spectrum fits the proposed compound, and clearly shows the two phenyl groups (δ 7,3 – 8,1), a four proton triplet (δ 3,11) and a two proton multiplet (δ 2,19).

Finally, as it appeared that the bicyclo[2.2.2]octanone synthesis was restricted to methyl ketones, it was decided to attempt to synthesize the bicyclo[2.2.2]octanone (**142**) of benzyl methyl ketone (1–phenyl–2-propanone) *via* the reaction between PVK and N–(1–phenyl–2-propylidene)-propylamine in boiling methanol.

The benzyl methyl ketone was prepared from α–phenylacetoaceto-nitrile.[128,129] The propylamine imine of benzyl methyl ketone was prepared using the azeotropic technique in benzene and gave N–(1–phenyl–2-propylidene)propylamine, which was used without further purification for the reaction with PVK in methanol. The infra–red spectrum showed the C=N absorption at 1 665 cm^{-1} and although a small ketone peak was evident, it was decided to use the imine without further purification as capillary CGC showed that the purity of the imine was of the order of 98 %.

It was decided to carry out the reaction in the presence of freshly activated molecular sieves (3A) in order to prevent any water liberated by the reaction causing hydrolysis of the imine. The reaction was allowed to proceed for 6 hours at the boil in methanol in the presence of molecular sieves (50 g; 3A). After hydrolysis of the reaction mixture and the usual hydrolytic work up, a portion (2,15 g) of the crude material was subjected to flash chromatography. The fractions obtained were analysed using GC–MS. Fractions 10–13 gave several peaks, two of which could be identified using the mass spectra obtained. The two peaks gave molecular ions consistent with 2,5–diphenyl–5–hydroxycyclohexanone (**146**) (M^+ 266) and 3,6–diphenylcyclohex–2–enone (**147**) (M^+ 248).

Fraction 14 gave almost pure 3,6–diphenylcyclohex–2–enone (**147**) (0,48 g; 12%) and although it was not possible to obtain this compound in a pure enough form for complete analysis, GC–MS showed the compound to have a molecular ion of 248 which is consistent with 3,6–diphenylcyclohex-2–enone. (**147**). The proton nmr spectrum showed two phenyl groups, a low field singlet proton (δ 6,58), two CH_2–groups (δ 2,44 and 2,86) and a multiplet (δ 3,66). The low field singlet is consistent with an uncoupled olefinic proton which fits the picture for the proton at C–2. The proton at δ 3,66 is consistent with the proton at C–6. In the ^{13}C nmr spectrum, the conjugated enone–system showed up quite clearly at δ_c 159,7 (s), 130,5 (d) and 200,2 (s) for carbons 3, 2 and 1 respectively. Further, the doublet at C–2 appeared at δ_c 52,6. Although it was not possible to assign all the aromatic signals, they were consistent with there being two phenyl rings, having different chemical environments, in the molecule.

Fractions 33– 51 was shown to be the bicyclic compound 2–benzoyl–1,4-diphenylbicyclo[2.2.2]octan–5–one (**142**) (0,23 g; 4 %). Further column chromatography enabled this compound to be obtained in a pure form for analysis. The iufra–red spectrum showed the ring carbonyl and benzoyl carbonyl at ν 1 718 and 1 674 respectively.

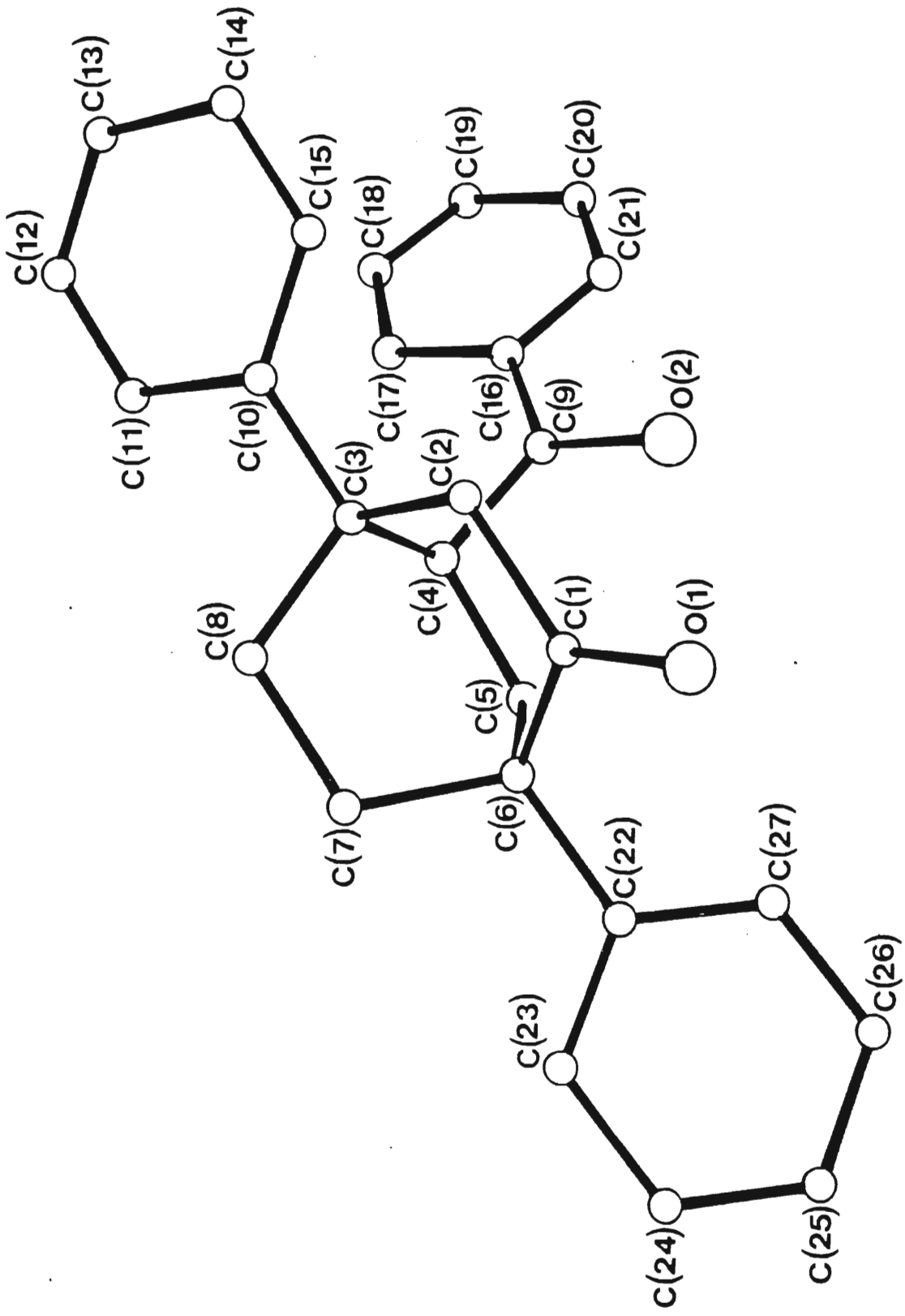
The proton spectrum was completely assigned, except for the aromatic protons, using the 200 MHz proton spectrum and the HETCOR plot. The position of the signals compared to the spectra of **141**, indicate that the compound crystallised as the *endo* isomer showing the same shielding of C–6. This assignment of the structure is based on the HETCOR plot.

The crystal structure was determined and merely serves to confirm the assignments above.

In the cage the torsion angles all have the same handedness:
[C6–C7–C8–C3 (–8°); C6–C5–C4–C3 (–6°) and C6–C1–C2–C3 (–3)°].
This appears to be similar to the previous bicyclic molecule (**141**). This means that the twist within the cage is small and all three twists occur in the same direction, which is what one might expect. The twists are small because the sp^2 hybridized carbon at C1 forces a certain rigidity on the C6–C1–O1–C2 limb of the cage. This is borne out by the small size of this torsion angle which is –3° compared with the other two at –6 and –8° respectively.

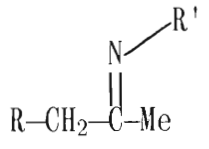
Further it interesting to note that C–22 is eclipsed with O–1, the torsion angle O1–C1–C6–C22 being –2,7°, and C9–C10 are staggered with the torsion angle (C9–C4–C3–C10) being 62° which is to be expected because of the bulk of the two benzene rings.

CRYSTAL STRUCTURE OF 142



As noticed with the previous molecule, the carbon–carbon bonds in the benzene rings are foreshortened for the reasons previously presented.

CONCLUSION:

It would appear that only imines of the type  form the bicyclic structure and this synthesis may be restricted to these molecules only, unless a means can be found to inhibit the final cyclisation step until α,α–dialkylation has taken place.

Further investigations could include:

(1) attempted alkylation using PVK of molecules of the form R–CH_2CH_2–CO–Me where R is aryl or alkyl;

(2) reaction of symmetrical ketones with PVK in the presence of Lewis acids to promote;

(3) the addition of molecular sieves to the reactions between imine and PVK in an attempt to improve the yield of the bicyclic compounds, since in **Section 5**, no attempt was made to optimise the yields.

2.5.2 EXPERIMENTAL:

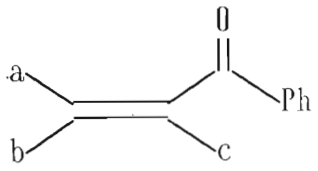
Preparation of phenyl vinyl ketone (PVK) [127]

Acetophenone (22,18 g; 0,19 mol), dimethylamine hydrochloride (20,00 g; 0,25 mol) and paraformaldehyde (7,5 g; 84 mmol) were placed in a round–bottomed flask and then a mixture of conc. HCl (0,38 ml) in ethanol (95 %; 80 ml) was added to the flask. When the addition had been completed, the mixture was raised to the boil and heated under reflux for 2 hours. Acetone (150 ml) was added to the warm reaction mixture. On cooling, crystals separated. These were filtered and dried (40 – 50 °C) for 3 hours to give β–dimethylaminopropiophenone hydrochloride.

The β–dimethylaminopropiophenone hydrochloride (20,00 g) was steam distilled to give phenyl vinyl ketone, which was extracted with dichloromethane (3 x 50 ml). The solution was dried over anhydrous magnesium sulphate to which quinol (0,01 g) had been added and then the solvent was removed on a rotary evaporator to give the desired ketone (10,88 g; 73 %).

IR:

ν(Neat film)	cm^{-1}
1 670	C=O
1 610	C=C



^{1}H nmr $\delta_{(CDCl_3)}$ ppm

b	5,87	d.o.d.; J = 10 Hz; J = 2 Hz
a	6,40	d.o.d.; J = 17 Hz; J = 2 Hz
c	7,30	q (Partially hidden under aromatic protons)
	7,3 – 8,3	

Preparation of 1–phenylpropan–2–one [128]

1. *α*–Phenylacetonitrile

Sodium ethoxide was prepared by adding sodium metal (12,0 g; 0,51 mol) to "super–dry" ethanol [90] (140 ml), which was then heated under reflux for 5 hours. A mixture of benzyl cyanide (47,4 g; 0,41 mol) and dry ethyl acetate (51,39 g; 0,58 mol) was added to the hot sodium ethoxide solution. The thick cream coloured mixture was heated on a steam bath for 2 hours and then stood for 12 hours. The mixture was then cooled to –4° C on an ice–salt bath and then filtered. The precipitate was washed with ether and then dissolved in water (250 ml) and cooled to ice point. Glacial acetic acid (18 ml) was added dropwise, the temperature being maintained below 10 °C. A pale yellow precipitate formed which was filtered off and washed with water to give *α*–phenylacetoacetonitrile. This was used without further purification.

Melting point: 78 °C

Lit:[128] 87 –89 °C

IR:

$\nu_{(KBr)}$	cm^{-1}
2 200	C≡N
1 656	CH–CO–CH_3

^{1}H nmr:

$\delta_{(CDCl_3)}$ ppm			
2,3	3H	s	CH_3–CO
4,7	1H	s	Ph–CH
7,4	5H	s	Ph

2. 1–Phenylpropan–2–one

Concentrated sulphuric acid (70 ml) was cooled to –4° C in ice–salt and the moist α–phenylacetonitrile was added slowly to the acid, the temperature being maintained below 20 °C. When the addition had been completed, the mixture was heated on a steam bath, which gave a clear, coloured liquid. The solution was then cooled to 2° C whereupon water (350 ml) was added rapidly. The mixture was then heated on a steam bath for 2 hours. After cooling, the oil was separated and the aqueous layer extracted with ether (2 x 100 ml). The ethereal extract and the oil were combined, washed with water (2 x 20 ml), dried over anhydrous magnesium sulphate and the solvent removed on a rotary evaporator. Fractional vacuum distillation gave the desired 1–phenylpropan-2-one (13,74 g; 25 %).

Boiling point:	59 – 64 °C/ 5 mmHg
Lit:[129]	109 – 112 °C/ 24 mmHg

IR:

$\nu_{(KBr)}$	cm^{-1}
1 709	C=O

^1H nmr

$\delta_{(CDCl_3)}$	ppm		
2,1	3H	s	CH_3CO
3,6	2H	s	$Ph-CH_2$
7,2	5H	s	Ph

N–(2–butylidene)benzylamine

Butan–2–one (36,0 g; 0,50 mol), benzylamine (54,6 g; 0,51 mol) and toluene–4–sulphonic acid (0,6 g) were heated under reflux in benzene (100 ml), the water being removed azeotropically *via* a Dean and Stark water separator for 49 hours. The solvent was then removed on a rotary evaporator, and the residue distilled under vacuum to give N–(2–butylidene)benzylamine (28,52 g; 34 %).

Boiling point: 66 – 70 °C/0,53 mmHg

IR:

$\nu_{(Neat\ film)}$	cm^{-1}
1 663	C=N

^{1}H nmr $\delta_{(CDCl_3)}$ ppm

1,12	3H	m	CH_3–CH_2
1,6 – 2,6	2H	m	CH_3–CH_2
4,48	1H	s	Ph–CH_2–N
7,33	5H	s	Ph–CH_2–N

Preparation of N–(1–phenyl–2–propylidene)propylamine

1–Phenylpropan–2–one (13,76 g; 0,10 mol), propylamine (6,97 g; 0,12 mol) and toluene–4–sulphonic acid (0,02 g) were heated under reflux in benzene (150 ml), the water being removed azeotropically *via* a Dean and Stark water separator for 5 hours. The solvent was then removed on a rotary evaporator, and the residue distilled under vacuum to give N–(1–phenyl–2-propylidene)propylamine.

IR: $\nu_{(Neat\ film)}$ cm^{-1}

1 665	C=N

The infra–red spectrum showed a small ketone peak and it was decided to use the imine without purification as capillary gas–liquid chromatography showed that it was very pure (98 % using the total area) showing only a trace of the starting ketone.

Preparation of N–(1–phenyl–1–ethylidene)benzylamine

Acetophenone (32,15 g; 0,30 mol), propylamine (18,32 g; 0,31 mol), and toluene–4–sulphonic acid (0,3 g) in benzene (200 ml) were heated under reflux in benzene (100 ml). No water was removed azeotropically *via* the Dean and Stark water separator, and a futher quantity of benzene had to be added (300 ml) and water was then liberated very rapidly. Within 3 hours the theoretical quantity of water had been collected in the Dean and Stark trap. The solvent was then removed on a rotary evaporator, and the residue distilled under vacuum to give N–(1–phenyl–1–ethylidene)propylamine (30,61 g; 63 %).

Boiling point: 70 °C/0,4 mmHg

IR:

ν(Neat film)		cm^{-1}
1 635	C=N	

^{1}H nmr

δ($CDCl_3$)	ppm		
1,0	3H	t	CH_3–CH_2–CH_2–N
1,3 – 2,7	7H	m	CH_3C=N (δ 2,11; s) plus N–$CH_2CH_2CH_3$

Preparation of N–(3–pentylidene)benzylamine

3–Pentanone (51,60 g; 0,60 mol), benzylamine (73,94 g; 0,69 mol) and toluene–4–sulphonic acid (0,1 g) were heated under reflux in benzene (200 ml), the water being removed azeotropically *via* a Dean and Stark water separator for 8 hours. The solvent was then removed on a rotary evaporator, and the residue distilled under vacuum to give three fractions: the first fraction contained benzylamine (5,55 g), the second was a mixture of benzylamine and N–(3–pentylidene)benzylamine (2,78 g) and the third was pure N–(3–pentylidene)benzylamine (64,54 g; 61%).

Boiling point: 66 – 70 °C/0,53 mmHg

IR:

$\nu_{(\text{Neat film})}$	cm^{-1}
1 662	C=N

^{1}H nmr

$\delta_{(CDCl_3)}$	ppm			
1,00	3H	t (J = 7,4 Hz)		CH_3–CH_2
1,10	3H	t (J = 7,4 Hz)		CH_3–CH_2
2,20	4H	2 x q(J = 7,4 Hz)		CH_3–CH_2
7,29	5H	s	Ph–CH_2–N	

Reaction between phenyl vinyl ketone and N–(2–butylidene)benzylamine

(1 equivalent : 1 equivalent)

N–(2–Butylidene)benzylamine (10,00 g; 67 mmol) and phenyl vinyl ketone (8,80 g; 67 mmol) in "super–dry" methanol (160 ml) were heated under reflux for 4 hours. Water (10 ml) was added and the mixture heated under reflux for a further hour. The solvent was removed on a rotary evaporator and the residue extracted with ether (2 x 100 ml) and dichloromethane (4 x 250 ml). The combined extracts were washed with dil. aq. hydrochloric acid (2 M; 4 x 50 ml), satd. sodium hydrogen carbonate (2 x 50 ml), water (2 x 50 ml) and satd. sodium chloride (50 ml) and finally dried over anhydrous magnesium sulphate. Removal of the solvents on a rotary evaporator gave a brown oil (10,64 g). A portion (3,68 g) was subjected to flash chromatography using ethyl acetate–hexane–chloroform (1:12:7) as eluant and taking 50 fractions (≃ 50 ml). Fractions 12–14 and 17–20 were combined on the basis of tlc and then they were taken up separately in dichloromethane and charcoaled several times to remove the colour (pale pink). These fractions proved to be two isomers of *2–benzoyl–4–methyl–1–phenylbicyclo[2.2.2]octan–5–one* (**141**).

Yield:	Isomer I (Fractions 12–14)	0,09 g; 1,3 %
	Isomer II (Fractions 17–20)	0,38 g; 5,6 %

Melting point:	Isomer I:	170,0 – 170,5 °C
	Isomer II:	161,0 – 163,0 °C

IR: ν cm^{-1}

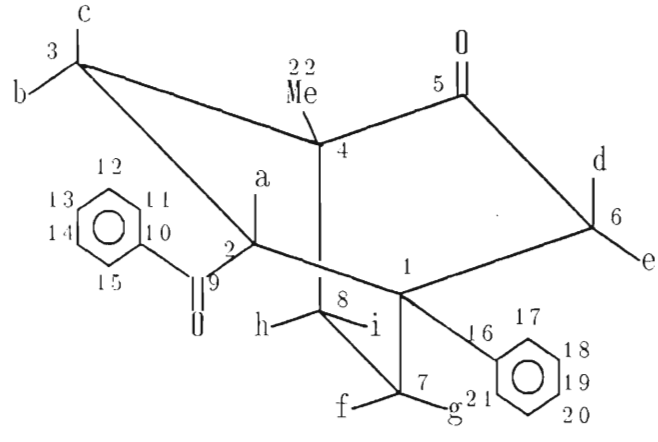
ISOMER I

IR: KBr disk (≃ 1,4 mg/300 mg KBr)
1 659 C=O
1 708 Ph–CO

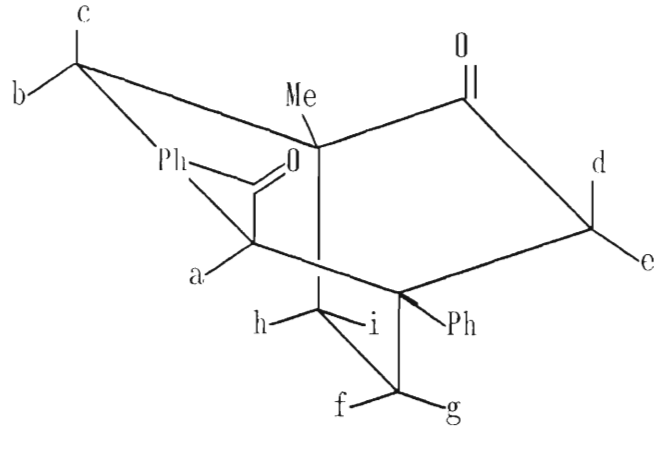
ISOMER II

IR: KBr disk (≃ 1,4 mg/300 mg KBr)
1 660 C=O
1 716 Ph–CO

FTIR ($CDBr_3$; 0,1 mm cell; solvent subtracted)
1 680 C=O (ring)
1 718 Ph–CO



141 : ISOMER I



141 : ISOMER II

^{1}H nmr $\delta_{(CDCl_3)}$ ppm (500 MHz)

	ISOMER I	ISOMER II
a	4,06	4,27
b	2,08	2,10
c	1,95	1,96
d	2,93	3,67
e	2,42	2,51
f	3,04	2,42
g	1,80	1,75
h	2,11	1,81
i	1,78	2,01
H–11/15	7,51	7,59
H–12/14	7,22	7,26
H–13	7,37	7,40
H–17/21	7,20	7,20
H–18/20	7,09	7,11
H–19	6,99	7,00
H–22	1,09	1,10

^{13}C nmr: $\delta_{c(CDCl_3)}$ ppm

	ISOMER I	ISOMER II
C–1*	43,8	43,4
C–2	48,5	47,3
C–3	35,7	36,9
C–1*	43,2	42,9
C–5	215,6	214,5
C–6	51,3	43,7
C–7	25,1	34,8
C–8	30,8	31,1
C–9	202,7	202,7
C–10	143,3	143,4
C–11/15	127,9	127,9
C–12/14	128,1	128,2
C–13	132,4	132,6
C–16	137,9	137,7
C–17/21	125,9	125,8
C–18/20	128,3	128,3
C–19	127,6	126,4
C–22	19,5	19,6

* Interchangeable

Nuclear Overhauser Effect:

Nuclear Overhauser effects were observed between the following protons:

ISOMER I	ISOMER II
a – c	a – b
a – d	d – e
f – g	f – g
d – e	b – c
b – c	c – h
e – g	
f – h	

Analysis:

Found: (Isomer I)	C: 82,9 %	H: 7,0 %
Found: (Isomer II)	C: 82,5 %	H: 6,9 %
Calc. for $C_{22}H_{22}O_2$:	C: 83,0 %;	H: 7,0 %

Reaction between phenyl vinyl ketone and N–(2–butylidene)benzylamine

(2 equivalent : 1 equivalent)

The above reaction was repeated using N–(2–butylidene)benzylamine (4,88 g; 30 mmol) and phenyl vinyl ketone (8,00 g; 61 mmol) in methanol (75 ml) under reflux for 4 hours. Hydrolysis was effected by the addition of dil. acetic acid (10 %; 10 ml) with stirring (12 h). The crystalline material (A) formed was separated from an oil (B) and they were worked up separately. Ether was added to each (100 ml), but dichloromethane (200 ml) had to be added to (A) to effect complete solution of the crystalline material. The usual aqueous workup was then applied to each of (A) and (B). After drying over anhydrous magnesium sulphate and filtration, the solvents were removed on a rotary evaporator and gave oils: (A) 4,61 g; (B) 3,96 g.

(A) was subjected to flash chromatography (Merck: Art. 9385) using ethyl acetate–dichloromethane–hexane (1:10:9). The crystalline fractions were combined and subsequently recrystallised from ethyl acetate to give white crystals (1,74 g).

(B) was similarly chromatographed to give white crystals (1,62 g).

The spectra (^{1}H, ^{13}C, COSY, NOESY, HETCOR and IR) were identical with those obtained for **141**: Isomer II.

CRYSTAL STRUCTURE DETERMINATION:

Crystal size: (mm)	0,05 x 0,13 x 0,25

DATA COLLECTION:

Diffractometer:	Nicolet R3m/V
Radiation:	CuKα (λ = 1,54184 Å)
Temperature:	293 K
Monochromator:	Highly oriented graphite crystal
2θ Range:	0,0 to 115,0 °
Scan type:	2θ – θ
Scan speed:	Variable: 2,93 to 14,65/min.° in ω
Scan range: (ω):	1,10° plus Kα–separation
Background correction:	Stationary crystal and stationary counter at beginning and end of scan, each for 25,0% of total scan time.
Standard reflections:	3 measures every 97 reflections
Index ranges:	$0 \leq h \leq 24$, $0 \leq k \leq 6$, $-25 \leq l \leq 25$

Solution and Refinement:

System used:	Nicolet SHELXTL PLUS (MicroVAX II)
Solution:	Direct Methods
Refinement method:	Full–Matrix Least–Squares
Quantity Minimised:	$\Sigma w(F - F_o)c^2$

FRACTIONAL ATOMIC COORDINATES ($\times 10^4$) WITH ESTIMATED STANDARD DEVIATIONS IN PARENTHESES FOR $C_{22}H_{22}O_2$:

Atom	X/A	Y/B	Z/C
C1	9175(1)	5371(4)	3134(1)
C2	9446(1)	4669(5)	2577(1)
C3	9083(1)	5382(4)	2040(1)
C4	8452(1)	6003(4)	2221(1)
C5	8546(2)	7983(4)	2592(1)
C6	9014(1)	7632(4)	3054(1)
C11	8595(1)	4191(5)	3182(1)
C12	8226(1)	4296(5)	2622(1)
C10	9582(2)	4988(6)	3653(2)
O60	9241(1)	9064(3)	3324(1)
C30	9066(1)	3732(4)	1574(1)
O30	9024(1)	1895(3)	1710(1)
C31	9097(1)	4300(4)	957(1)
C32	9245(2)	6269(6)	768(1)
C33	9289(2)	6673(7)	190(2)
C34	9181(2)	5108(8)	−203(2)
C35	9026(2)	3164(8)	−22(2)
C36	8985(2)	2750(6)	553(2)
C41	8039(1)	6370(4)	1702(1)
C42	8019(2)	8258(5)	1414(1)
C43	7652(2)	8573(7)	937(2)
C44	7292(2)	6995(7)	735(2)
C45	7301(2)	5117(7)	1011(2)
C46	7673(2)	4796(5)	1492(2)
H2A	9466(12)	3080(44)	2562(11)
H2B	9857(14)	5140(43)	2588(12)
H3	9229(11)	6647(39)	1873(10)
H5A	8171(13)	8378(41)	2777(12)
H5B	8660(12)	9142(46)	2357(12)
H11A	8370(13)	4725(45)	3521(13)
H11B	8674(13)	2762(50)	3285(12)
H12A	8231(12)	2882(46)	2408(12)
H12B	7828(14)	4536(42)	2682(11)
H10A	9366(14)	5492(48)	4014(15)
H10B	9676(15)	3410(58)	3669(14)
H10C	9917(18)	5672(57)	3636(16)
H32	9330(15)	7433(55)	1059(16)
H33	9138(19)	8190(68)	43(18)
H34	9225(16)	5381(54)	−606(17)
H35	8922(18)	2042(65)	−274(17)
H36	8864(14)	1345(50)	702(13)
H42	8269(14)	9354(50)	1532(14)
H43	7636(16)	9860(58)	747(15)
H44	7024(15)	7234(49)	397(14)
H45	7081(16)	3845(59)	846(15)
H46	7700(14)	3406(53)	1684(13)

THERMAL PARAMETERS (Å^2) FOR $C_{22}H_{22}O_2$

Atom	U_{11}[a]	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
C1	568(19)	453(16)	472(17)	21(13)	94(14)	−4(14)
C2	459(20)	600(20)	552(19)	−31(15)	85(15)	−27(17)
C3	475(18)	423(16)	519(17)	−19(14)	140(14)	−52(14)
C4	442(16)	404(15)	535(17)	−25(13)	91(13)	12(13)
C5	673(22)	426(17)	523(18)	−20(15)	131(17)	66(16)
C6	712(21)	512(18)	407(16)	−8(14)	139(15)	−26(16)
C11	592(21)	520(19)	650(23)	114(16)	162(18)	−18(16)
C12	463(20)	526(18)	597(20)	17(15)	135(16)	−36(15)
C10	684(26)	682(24)	624(22)	107(18)	−25(19)	−47(21)
O60	1189(21)	564(14)	661(15)	−88(11)	−118(14)	−79(13)
C30	449(17)	495(17)	547(18)	−61(14)	112(14)	−31(14)
O30	874(16)	475(12)	690(14)	−56(10)	221(12)	−72(11)
C31	480(18)	612(18)	498(17)	−62(15)	93(14)	49(15)
C32	668(22)	755(24)	551(21)	56(18)	106(16)	−23(18)
C33	905(28)	1015(29)	613(24)	133(23)	125(20)	54(24)
C34	912(30)	1205(37)	521(24)	62(27)	106(20)	334(26)
C35	1208(36)	991(32)	610(27)	−232(26)	19(22)	280(27)
C36	1032(29)	698(24)	553(22)	−120(19)	116(19)	109(21)
C41	425(17)	519(17)	577(19)	−47(14)	111(14)	15(14)
C42	626(22)	576(20)	633(21)	55(17)	−4(17)	−7(17)
C43	734(26)	804(26)	792(26)	149(22)	−31(21)	76(22)
C44	594(22)	1062(31)	695(25)	−3(24)	−41(19)	4(23)
C45	735(26)	904(29)	747(25)	−83(23)	−31(21)	−159(22)
C46	650(22)	659(22)	656(22)	−30(18)	4(18)	−65(18)

[a]Anisotropic vibrational amplitudes.

Atom	U[b]
H2A	567(78)
H2B	686(92)
H3	467(70)
H5A	617(84)
H5B	662(90)
H11A	733(93)
H11B	680(89)
H12A	629(83)
H12B	620(88)
H10A	878(106)
H10B	925(110)
H10C	983(139)
H32	1016(124)
H33	1354(156)
H34	1058(127)
H35	1177(147)
H36	788(103)
H42	818(111)
H43	973(126)
H44	872(112)
H45	1057(130)
H46	846(106)

[b]Isotropic vibrational amplitudes.

Bond lengths (Å) with estimated standard deviations in parentheses for $C_{22}H_{22}O_2$:

C1–C2	1,533(4)	C1–C6	1,504(4)
C1–C11	1,538(4)	C1–C10	1,521(5)
C2–C3	1,546(4)	C3–C4	1,573(4)
C3–C30	1,518(4)	C4–C5	1,546(4)
C4–C12	1,543(4)	C6–O60	1,219(4)
C4–C41	1,527(4)	C11–C12	1,530(4)
C30–O30	1,224(3)	C30–C31	1,493(4)
C31–C32	1,384(5)	C33–C34	1,375(6)
C34–C35	1,367(7)	C35–C36	1,379(5)
C36–C31	1,387(5)	C41–C42	1,385(4)
C42–C43	1,386(5)	C43–C44	1,377(6)
C45–C46	1,398(5)	C46–C41	1,388(4)
C2–H2A	1,020(29)	C2–H2B	0,989(32)
C3–H3	0,966(25)	C5–H5A	1,010(29)
C5–H5B	0,966(29)	C11–H11A	1,023(30)
C11–H11B	0,963(32)	C12–H12A	1,034(29)
C12–H12B	0,941(33)	C10–H10A	1,047(35)
C10H10B	1,033(37)	C10–H10C	0,866(40)
C32–H32	1,023(35)	C33–H33	1,090(44)
C34–H34	0,967(40)	C35–H35	0,954(42)
C36–H36	1,009(32)	C42–H42	0,940(32)
C43–H43	0,937(37)	C44–H44	0,992(33)
C45–H45	1,026(37)	C46–H46	0,998(33)

Bond Angles (°)

C2–C1–C6	106,4(2)	C2–C1–C10	112,0(3)
C6–C1–C10	113,2(2)	C10–C1–C11	111,5(3)
C1–C2–C3	112,4(2)	C2–C3–C4	109,0(2)
C2–C3–C30	111,9(2)	C4–C3–C30	111,9(2)
C3–C4–C12	108,6(2)	C3–C4–C41	111,9(2)
C5–C4–C12	106,5(2)	C12–C4–C41	112,2(2)
C4–C5–C6	110,9(2)	C1–C6–C5	113,4(2)
C1–C6–O60	124,3(3)	C5–C6–O60	122,3(3)
C1–C11–C12	111,4(3)	C4–C12–C11	111,3(3)
C3–C30–O30	118,9(2)	C3–C30–C31	121,5(2)
C31–C30–O30	119,6(2)	C30–C31–C32	123,6(3)
C30–C31–C36	117,9(3)	C32–C31–C36	118,5(3)
C31–C32–C33	120,8(3)	C32–C33–C34	119,8(4)
C33–C34–C35	120,1(4)	C34–C35–C36	120,4(4)
C31–C36–C35	120,6(4)	C4–C41–C42	121,8(2)
C31–C41–C46	121,1(3)	C42–C41–C46	117,1(3)
C41–C42–C43	121,7(3)	C42–C43–C44	120,4(4)
C43–C44–C45	119,2(4)	C44–C45–C46	120,5(4)
C41–C46–C45	121,1(3)		

Reaction between phenyl vinyl ketone and N–(3–pentylidene)benzylamine

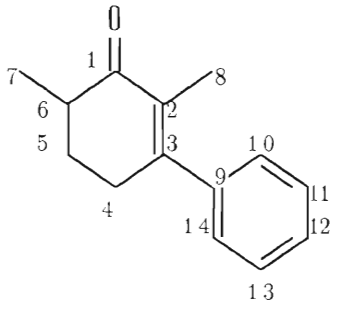
N–(3–Pentylidene)benzylamine (12,60 g; 72 mmol) and phenyl vinyl ketone (9,51 g; 72 mmol) in methanol (180 ml) were heated under reflux for 4 hours. On cooling, a mixture of water–acetic acid–sodium acetate (2:2:1; 10 ml) was added to effect hydrolysis under non–epimerising conditions.[96] Removal of the solvent on a rotary evaporator resulted in the formation of crystals which were taken up in ether and after the usual hydrolytic workup, the solvent was removed to give an oil (11,87 g). A portion (2,33 g) of this was subjected to flash chromatography, using ethyl acetate–hexane–dichloromethane (1:9:10) as eluant, taking 53 fractions (≃ 50 ml). The fractions were combined on the basis of tlc. Two major components were isolated: 2,6–dimethyl–3–phenylcyclohex–2–enone (**144**) (1,30 g; 45 %) and *2,6–dimethyl–3–hydroxy–3–phenylcyclohexanone* (**143**) (0,33 g; 11 %).

2,6–dimethyl–3–phenylcyclohex–2–enone (144)

GC–MS (Gas Chromatography using a mass spectrometer as detector) showed that the molecular ion (M^+ 200) was present although there was an impurity that eluted very close to the 2,6–dimethyl–3–phenylcyclohex–2–enone which was probably why it was not possible to obtain an analysis on this compound. Preliminary indications are, however that this is the compound indicated.

^{1}H nmr $\delta_{(CDCl_3)}$ ppm

1,20	3H; d; (J = 6,8 Hz)	CH_3–CH
1,72	3H; t; (J = 1,8 Hz)	CH_3–C=C(–CH_2)–Ph
1,75 – 1,92	1H; c.m.	
2,03 – 2,18	1H; c.m. (J = 4,4 Hz)	
2,34 – 2,54	1H; c.m.	
2,56 – 2,80	2H; c.m.	
5,15 – 7,43	5H; c. m.	Ph–



^{13}C nmr δ_c(CDCl$_3$) ppm

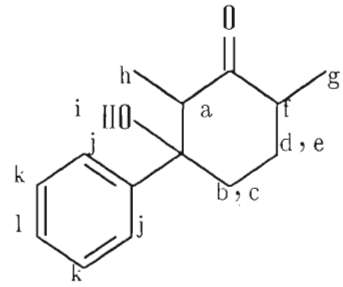
C–1	202,9	C–8	15,6
C–2	155,9	C–9	131,3
C–3	141,8	C–10/14	127,5
C–4	32,2	C–11/13	128,7
C–5	30,9	C–12	128,1
C–6	41,0		
C–7	13,2		

2,6–dimethyl–3–hydroxy–3–phenylcyclohexanone (143)

Melting point: 150 – 151 °C

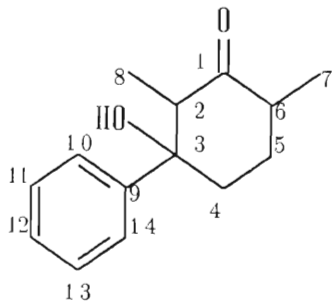
IR $\nu_{(CDBr_3)}$ cm^{-1} (0,1 mm cell; FTIR; solvent subtracted)

1 710	C=O (Ring)
3 580	–OH



^{1}H nmr $\delta_{(CHCl_3)}$ ppm

a	2,58	1H	h	0,79
b	1,89		i	1,92 (concentration dependent)
c	2,04		j	7,44
d	2,32		k	7,27
e	1,96		l	7,38
f	2,58			
g	1,11			



^{13}C nmr δ_c(CDCl$_3$) ppm

C–1	212,2	C–8	14,5
C–2	53,1	C–9	145,9
C–3	81,5	C–10/14	124,4
C–4	31,4	C–11/13	126,9
C–5	40,3	C–12	128,4
C–6	44 ,9		
C–7	9,6		

Analysis:

Found:	C: 76,5 %	H:	8,31%
Calc. for $C_{14}H_{18}O_2$:	C: 77,0 %;	H:	8,31%

X–RAY STRUCTURE DETERMINATION

Formula	$C_{14}H_{18}O_2$
M_r	218.28
Space group	*Pbca*
a/ Å	10.456(2)
b/ Å	11.291(1)
c/ Å	20.306(2)
V/ Å^3	2397(4)
Z	8
d(calc) g.cm^{-3}	1.209
$F(000)$	944
Crystal dimensions	0.77 x 0.27 x 0.28
λ(Mo–$K\alpha$)/ Å	0.71069 (μ = 0.44 cm^{-1})
Scan mode	$\omega - 2\theta$
ω scan angle/°	0.96 + 0.35tanθ
Horizontal aperture width/mm	1.38 + 0.10tanθ
Vertical aperture width/mm	4
Scattering range/°	$2 \leq \theta \leq 30$
Unique intensities	2726
Unique intensities with $I>3\sigma(I)$	1690
Structure solution	Direct methods
Weighting scheme	$2.05/(\sigma^2(F) + 0.001F^2)$
$R = \Sigma(F_o - F_c)\Sigma F_o$	0.051

FRACTIONAL COORDINATES (x 10^4) AND ISOTROPIC THERMAL FACTORS (Å ^{2} X 10^3) FOR $C_{14}H_{18}O_2$

	x/a	y/b	z/c	U
O(1)	−40(2)	1646(2)	2613(1)	56(1)*
O(2)	245(2)	4313(2)	1864(1)	46(1)*
C(1)	931(2)	2173(2)	2490(1)	37(1)*
C(2)	1317(2)	2493(2)	1799(1)	36(1)*
C(3)	1478(2)	3855(2)	1754(1)	34(1)*
C(4)	2393(2)	4288(2)	2295(1)	42(1)*
C(5)	1989(3)	3910(2)	2978(1)	46(1)*
C(6)	1839(2)	2559(2)	3024(1)	42(1)*
C(7)	1460(3)	2146(3)	3706(2)	62(1)*
C(8)	428(3)	2001(3)	1281(2)	56(1)*
C(9)	1995(2)	4217(2)	1084(1)	39(1)*
C(10)	1407(3)	5050(3)	698(2)	59(1)*
C(11)	1916(4)	5392(3)	97(2)	75(1)*
C(12)	3005(4)	4900(3)	−124(2)	70(1)*
C(13)	3604(3)	4072(3)	249(2)	69(1)*
C(14)	3118(3)	3731(3)	846(2)	57(1)*
H(1)	2208(24)	2160(22)	1741(12)	44(7)
H(2)	3204(29)	3975(23)	2189(13)	47(7)
H(3)	2405(22)	5157(23)	2266(12)	42(7)
H(4)	2672(24)	4144(21)	3292(12)	45(7)
H(5)	1104(27)	4283(22)	3105(12)	50(7)
H(6)	2761(23)	2234(22)	2886(13)	46(7)
H(7)	1302(31)	1259(35)	3734(17)	86(10)
H(8)	2159(36)	2377(34)	4005(17)	94(12)
H(9)	630(31)	2429(26)	3847(15)	62(8)
H(10)	−247(32)	2379(30)	1284(17)	76(11)
H(11)	743(28)	2199(25)	808(16)	60(8)
H(12)	461(31)	1134(32)	1311(16)	78(9)
H(13)	668(32)	5350(29)	863(15)	69(10)
H(14)	1573(37)	6058(33)	−156(19)	101(12)
H(15)	3336(29)	5130(26)	−554(18)	75(9)
H(16)	4273(31)	3765(30)	109(17)	72(11)
H(17)	3489(28)	3107(28)	1115(14)	69(9)
H(18)	280(27)	5023(29)	1961(13)	51(8)

* $U_{eq} = \frac{1}{3} \Sigma_i \Sigma_j U_{ij} a^*_i a^*_j (a_i . a_j)$

ANISOTROPIC THERMAL FACTORS ($Å^2 \times 10^3$) FOR $C_{14}H_{18}O_2$

	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
O(1)	46(1)	52(1)	71(1)	18(1)	–1(1)	–15(1)
O(2)	34(1)	37(1)	66(1)	–4(1)	8(1)	7(1)
C(1)	30(1)	26(1)	56(1)	5(1)	1(1)	2(1)
C(2)	31(1)	30(1)	46(1)	6(1)	0(1)	1(1)
C(3)	28(1)	29(1)	44(1)	–3(1)	3(1)	1(1)
C(4)	42(1)	38(1)	46(1)	–4(1)	1(1)	–12(1)
C(5)	48(1)	46(11)	45(1)	–5(1)	–1(1)	–8(1)
C(6)	37(1)	46(1)	45(1)	4(1)	2(1)	2(1)
C(7)	59(2)	71(2)	56(2)	17(2)	1(2)	–2(2)
C(8)	60(2)	48(2)	60(2)	–11(1)	5(1)	–12(1)
C(9)	37(1)	37(1)	42(1)	–1(1)	1(1)	–5(1)
C(10)	58(2)	60(2)	61(2)	11(1)	3(2)	8(1)
C(11)	85(2)	82(2)	59(2)	26(2)	–6(2)	–4(2)
C(12)	80(2)	88(2)	43(2)	3(2)	7(2)	–21(2)
C(13)	61(2)	67(2)	59(2)	7(1)	14(1)	5(1)

INTERATOMIC DISTANCES (Å) FOR $C_{14}H_{18}O_2$

O(1) – C(1)	1,203(3)	O(2) – C(3)	1,406(3)
O(2) – H(18)	0,83(3)	C(1) – C(2)	1,504(3)
C(1) – C(6)	1,506(3)	C(2) – C(3)	1,504(3)
C(2) – C(8)	1,510(4)	C(2) – H(1)	1,01(3)
C(3) – C(4)	1,537(3)	C(3) – C(9)	1,520(3)
C(4) – C(5)	1,512(3)	C(4) – H(2)	0,94(3)
C(4) – H(3)	0,98(3)	C(5) – C(6)	1,537(4)
C(5) – H(4)	0,99(3)	C(5) – H(5)	1,05(3)
C(6) – C(7)	1,514(4)	C(6) – H(6)	1,07(2)
C(7) – H(7)	1,02(4)	C(7) – H(8)	0,99(4)
C(7) – H(9)	0,97(3)	C(8) – H(10)	0,82(3)
C(8) – H(11)	1,04(3)	C(8) – H(12)	0,98(4)
C(9) – C(10)	1,370(4)	C(9) – C(14)	1,383(4)
C(10) – C(11)	1,386(4)	C(10) – H(13)	0,91(3)
C(11) – C(12)	1,344(5)	C(11) – H(14)	0,98(4)
C(12) – C(13)	1,369(4)	C(13) – H(15)	0,97(4)
C(13) – C(14)	1,369(4)	C(13) – H(16)	0,83(3)
C(14) – H(17)	0,97(3)		

INTERATOMIC ANGLES (°) FOR $C_{14}H_{18}O_2$

C(3)–O(2)–H(18)	111(2)	O(1)–C(1)–C(2)	122,5(2)
O(1)–C(1)–C(6)	121,7(2)	C(2)–C(1)–C(6)	115,7(2)
C(1)–C(2)–C(3)	108,8(2)	C(1)–C(2)–C(8)	113,4(2)
C(3)–C(2)–C(8)	113,0(2)	C(1)–C(2)–H(1)	105,5(14
C(3)–C(2)–H(1)	105,2(14)	C(8)–C(2)–H(1)	110,5(13
O(2)–C(3)–C(2)	104,9(2)	O(2)–C(3)–C(4)	109,9(2)
C(2)–C(3)–C(4)	110,0(2)	O(2)–C(3)–C(9)	111,7(2)
C(2)–C(3)–C(9)	111,0(2)	C(4)–C(3)–C(9)	109,4(2)
C(3)–C(4)–C(5)	113,1(2)	C(3)–C(4)–H(2)	106(2)
C(5)–C(4)–H(2)	111(2)	C(3)–C(4)–H(3)	106,5(14
C(5)–C(4)–H(3)	109,8(14)	H(2)–C(4)–H(3)	111(2)
C(4)–C(5)–C(6)	111,4(2)	C(4)–C(5)–H(4)	108,2(14
C(6)–C(5)–H(4)	107,4(14)	C(4)–C(5)–H(5)	111,0(14
C(6)–C(5)–H(5)	107,0(14)	H(4)–C(5)–H(5)	112(2)
C(1)–C(6)–C(5)	107,9(2)	C(1)–C(6)–C(7)	113,9(2)
C(5)–C(6)–C(7)	112,9(2)	C(1)–C(6)–H(6)	106,3(14
C(5)–C(6)–H(6)	103,4(14)	C(7)–C(6)–H(6)	111,8(14
C(6)–C(7)–H(7)	113(2)	C(6)–C(7)–H(8)	107(2)
H(7)–C(7)–H(8)	110(3)	C(6)–C(7)–H(9)	114(2)
H(7)–C(7)–H(9)	99(3)	H(8)–C(7)–H(9)	113(3)
C(2)–C(8)–H(10)	109(2)	C(2)–C(8)–H(11)	112(2)
H(10)–C(8)–H(11)	123(3)	H(11)–C(8)–H(12)	105(2)
C(3)–C(9)–C(10)	117,0(3)	C(9)–C(10)–C(11)	121,5(3)
C(9)–C(10)–H(13)	115(2)	C(11)–C(10)–H(13)	123(2)
C(10)–C(11)–C(12)	120,3(3)	C(10)–C(11)–H(14)	122(2)
C(12)–C(11)–H(14)	117(2)	C(11)–C(12)–C(13)	119,3(3)
C(11)–C(12)–H(15)	119(2)	C(13)–C(12)–H(15)	121(2)
C(12)–C(13)–C(14)	121,1(3)	C(12)–C(13)–H(16)	119(3)
C(14)–C(13)–H(16)	120(3)	C(9)–C(14)–C(13)	120,9(3)
C(9)–C(14)–H(17)	116(2)	C(13)–C(14)–H(17)	124(2)

Table of Torsional Angles (°) for $C_{14}H_{18}O_2$

ATOM: 1	2	3	4	Angle	ATOM 1	2	3	4	Angle
O1	C1	C2	C3	121,71(0,24)	O2	C3	C9	C10	10,39(0,32)
O1	C1	C2	C8	–4,77(0,34)	O2	C3	C9	C14	–171,46(0,24)
C6	C1	C2	C3	–58,09(0,24)	C2	C3	C9	C10	126,80(0,25)
C6	C1	C2	C8	175,43(0,21)	C2	C3	C9	C14	–55,05(0,29)
O1	C1	C6	C5	–121,78(0,25)	C4	C3	C9	C10	–111,83(0,25)
O1	C1	C6	C7	4,17(0,33)	C4	C3	C9	C14	66,32(0,29)
C2	C1	C6	C5	58,02(0,25)	C3	C4	C5	C6	56,17(0,27)
C2	C1	C6	C7	–176,03(0,21)	C4	C5	C6	C1	–54,67(0,26)
C1	C2	C3	O2	–64,88(0,21)	C4	C5	C6	C7	178,85(0,22)
C1	C2	C3	C4	53,39(0,22)	C3	C9	C10	C11	178,07(0,27)
C1	C2	C3	C9	174,38(0,17)	C14	C9	C10	C11	–0,14(0,45)
C8	C2	C3	O2	61,69(0,25)	C3	C9	C14	C13	–178,58(0,28)
C8	C2	C3	C4	179,96(0,24)	C10	C9	C14	C13	–0,33(0,45)
C8	C2	C3	C9	–59,06(0,26)	C9	C10	C11	C12	0,53(0,53)
O2	C3	C4	C5	59,84(0,25)	C10	C11	C12	C13	–0,43(0,56)
C2	C3	C4	C5	–54,95(0,24)	C11	C12	C13	C14	–0,04(0,72)
C9	C3	C4	C5	–176,96(0,19)	C12	C13	C14	C9	0,44(0,53)

Reaction between phenyl vinyl ketone and N–(1–phenyl–1–ethylidene)-benzylamine

N–(1–Phenyl–1–ethylidene)benzylamine (5,80 g; 39 mmol) and phenyl vinyl ketone (5,80 g; 39 mmol) in "super–dry" methanol (100 ml) were heated under reflux for 6 hours and then subjected to the usual hydrolysis and hydrolytic workup. A portion (2,00 g) of the oil obtained (10,09 g), was subjected to flash chromatography using ethyl acetate–hexane–dichloro-methane (15:110:68) on silica gel (Merck Art.: 9385) taking 30 fractions (≃ 50 ml). The fractions were combined on the basis of tlc.

Fractions 11 – 13 gave the mono–substituted product:

1,5–diphenylpentan–1,5–dione (**145**) (0,44 g; 23 %) although not completely pure. The remaining fractions were all intractable mixtures and could not be separated using silica gel, although on GC–MS it was clear that the mono–substituted product was present in almost all the fractions. It was estimated that the mono–substituted product comprised 42 % of the crude material which is an overall yield of 36 %.

^{1}H nmr	$\delta_{(CDCl_3)}$ ppm	
2,19	m (J = 6,7 Hz)	2H; $-CH_2-CH_2-CH_2-$
3,11	t (J = 6,7 Hz)	4H; $-CH_2-CH_2-CH_2-$
7,3 – 8,1	m	10H; 2 x Ph–

Reaction between phenyl vinyl ketone and N–(1–phenyl–2–propylidene)-propylamine

The crude N–(1–phenyl–2–propylidene)propylamine (8,57 g; 49 mmol), phenyl vinyl ketone (12,93 g; 98 mmol) and molecular sieves (3A; 50 g) in "super–dry" methanol (117 ml) were heated under reflux for 4 hours. Water (10 ml) was added and the mixture heated for a further hour under reflux. After removal of the solvent on a rotary evaporator, the residue was extracted with dichloromethane (2 x 100 ml), the extract being subjected to the usual hydrolytic workup. Removal of the solvent gave a dark brown oil (6,32 g).

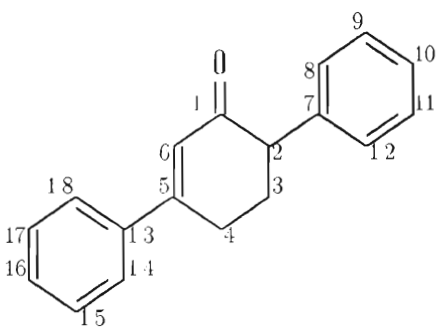
A portion (2,15 g) of this oil was subjected to flash chromatography on a column of silica gel (Merck Art.: 9385) using hexane–dichloromethane–ethyl acetate (14:5:1) as eluant and taking 78 fractions (≃ 50 ml). The fractions were evaporated and combined on the basis of tlc. Although many of the fractions appeared to be pure on tlc, GC–MS showed them to be made up of various components.

In fraction 10 – 13, GC–MS showed the presence of molecular ions good for 2,5–diphenyl–5–hydroxycyclohexanone (**146**) and 3,6–diphenylcyclohex-2-enone (**147**) (M^+ 266 and 248 respectively). Fraction 14 gave almost pure 3,6–diphenylcyclohen–2–enone (0,48 g; 12 %) and although not pure enough for analysis, GC–MS showed the molecular ion (M^+: 248) good for this compound. Fractions 33 – 51 proved, however to be *2–benzoyl–1,4-diphenylbicyclo[2.2.2]octan–5–one* (**142**) (0,23 g; 4 %).

3,6–Diphenylcyclohex–2–enone (147)

^{1}H nmr $\delta_{(CDCl_3)}$ ppm

2,44	t; (J = 6 Hz)	2H; C=C(Ph)–CH_2–CH_2
2,86	m	2H; –CH_2–CH_2–CH
3,66	m	1H; OC–CH-Ph (CH$_2$)
6,58	s	1H; Ph–C=C–CO (H)
7,1 – 7,7	c.m.	10H; 2 x Ph–



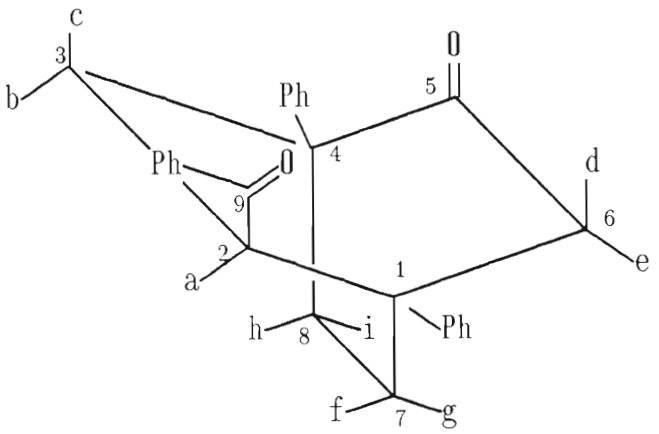
^{13}C nmr $\delta_{c(CDCl_3)}$ ppm

C–1	200,2 (s)	C–7	138,8 (s)
C–2	52,6 (d)	C–13	139,8 (s)
C–3	27,5 (t)	Aromatic carbons:	C–8 – C–11
C–4	30,8 (t)		and C–14 – C–17:
C–5	159,7 (s)	129,2; 128,9; 128,7; 127,3; 126,5; 125,9 (All t.)	
C–6	130,5 (d)		

2–benzoyl–1,4–diphenylbicyclo[2.2.2]octan–5–one (142)

IR $\nu_{(film)}$ cm^{-1}

1 718	Ph–CO
1 674	C=O (ring)



^1H nmr $\delta_{(CDCl_3)}$ ppm

a	4,37	f	
b	2,37	g	
c	2,53	h	
d	3,82	i	
e	2,63		

^{13}C nmr $\delta_c(CDCl_3)$ ppm

C–1	42,9 (s)	C–6	44,5 (t)
C–2	47,2 (d)	C–7	29,0 (t)
C–3	35,8 (t)	C–8	34,6 (t)
C–4	50,7 (s)	C–9	203,4 (s)
C–5	212,5 (s)		

Aromatic carbons:
143,3 (s); 140,2 (s); 137,9 (s); 133,0 (d); 127,3 (d); 126,9 (d); 128,6 (d); 128,5 (d); 128,4 (d); 128,2 (d); 127,6 (d); 126,1 (d).

Analysis:

Found:	C: 85,4	H: 6,4 %
Calc. for $C_{27}H_{24}O_2$:	C: 85,2	H: 6,4 %

X–RAY STRUCTURE DETERMINATION SUMMARY FOR $C_{27}H_{24}O_2$:

Formula	$C_{27}H_{24}O_2$
M_r	380,46
Space group	Pl
a/ Å	6,444(1)
b/ Å	11.764(2)
c/ Å	13,543(2)
V/ Å ^{3}	1009,0(3)
Z	2
d(calc) g.cm^{-3}	1.252
F(000)	202
Crystal dimensions	0.61 x 0.27 x 0.19
λ(Mo–$K\alpha$)/ Å	0.71069 (μ = 0.42 cm^{-1})
Scan mode	$\omega - 2\theta$
ω scan angle/°	0.34 + 0.35tanθ
Horizontal aperture width/mm	1.39 + 0.10tanθ
Vertical aperture width/mm	4
Scattering range/°	$2 \leq \theta \leq 30$
Unique intensities	4834
Unique intensities with I>3σ(I)	3349
Structure solution	Direct methods
Weighting scheme	$4{,}29/(\sigma^2(F) + 0{,}0002F^2)$
$R = \Sigma(F_o - F_c)\Sigma F_o$	0.054

FRACTIONAL COORDINATES (x 10^4) AND ISOTROPIC THERMAL FACTORS ($Å^2$ X 10^3) FOR $C_{27}H_{24}O_2$

	x/a	y/b	z/c	U
O(1)	3779(3)	11523(2)	2038(1)	73(1)*
O(2)	4890(3)	8318(1)	2789(1)	68(1)*
C(1)	2538(3)	10828(2)	2132(2)	46(1)*
C(2)	2563(4)	9976(2)	1367(2)	47(1)*
C(3)	873(3)	9159(2)	1666(2)	43(1)*
C(4)	1214(3)	8576(2)	2726(2)	45(1)*
C(5)	1035(5)	9508(2)	3486(2)	57(1)*
C(6)	803(3)	10744(2)	2995(2)	44(1)*
C(7)	−1222(4)	10885(2)	2486(2)	58(1)*
C(8)	−1259(3)	9930(2)	1797(2)	55(1)*
C(9)	3331(3)	7852(2)	2728(2)	46(1)*
C(10)	886(3)	8257(2)	918(2)	49(1)*
C(11)	−905(4)	7736(2)	848(2)	63(1)*
C(12)	−876(5)	6872(3)	218(3)	79(1)*
C(13)	946(6)	6496(3)	−365(2)	81(1)*
C(14)	2727(6)	6998(3)	−305(2)	77(1)*
C(15)	2711(4)	7864(2)	324(2)	62(1)*
C(16)	3570(3)	6579(2)	2674(2)	46(1)*
C(17)	1972(4)	5959(2)	2528(2)	59(1)*
C(18)	2362(5)	4778(2)	2495(2)	76(1)*
C(19)	4290(6)	4209(3)	2619(2)	80(1)*
C(20)	5883(5)	4823(3)	2756(3)	90(1)*
C(21)	5530(4)	5985(2)	2781(2)	71(1)*
C(22)	877(3)	11614(2)	3763(2)	50(1)*
C(23)	−825(4)	12421(2)	4025(2)	62(1)*
C(24)	−683(6)	13215(2)	4723(2)	78(1)*
C(25)	1129(6)	13213(3)	5150(2)	80(1)*
C(26)	2791(5)	12405(3)	4913(2)	79(1)*
C(27)	2676(4)	11616(2)	4227(2)	64(1)*
H(1)	2211(44)	10339(25)	855(25)	80(2)
H(2)	4046(43)	9501(23)	1247(23)	80(2)
H(3)	54(41)	8082(22)	2941(22)	80(2)
H(4)	2228(41)	9422(22)	3924(22)	80(2)
H(5)	−155(43)	9490(23)	3938(22)	80(2)
H(6)	−2186(45)	10890(25)	2894(25)	80(2)
H(7)	−1370(40)	11564(25)	2052(21)	80(2)
H(8)	−1467(40)	10225(23)	1084(23)	80(2)
H(9)	−2289(44)	9439(23)	1990(21)	80(2)
H(10)	−2087(42)	8005(24)	1231(21)	80(2)
H(11)	−2073(44)	6607(24)	199(21)	80(2)
H(12)	958(39)	5965(23)	−943(21)	80(2)
H(13)	3927(43)	6639(24)	−629(22)	80(2)
H(14)	4045(43)	8094(23)	388(21)	80(2)
H(15)	601(43)	6351(24)	2396(21)	80(2)
H(16)	1266(43)	4472(23)	2277(21)	80(2)

H(17)	4531(39)	3338(25)	2535(20)	80(2)
H(18)	7386(43)	4407(24)	2754(20)	80(2)
H(19)	6781(41)	6424(23)	2837(20)	80(2)
H(20)	−2066(43)	12379(23)	3562(21)	80(2)
H(21)	−1968(42)	13798(23)	4902(20)	80(2)
H(22)	1132(40)	13619(24)	5720(22)	80(2)
H(23)	4004(44)	12369(25)	5066(22)	80(2)
H(24)	3751(42)	11153(24)	4039(22)	80(2)

* $U_{eq} = \frac{1}{3} \Sigma_i \Sigma_j U_{ij} a^*_i a^*_j (a_i . a_j)$

ANISOTROPIC THERMAL FACTORS ($Å^2 \times 10^3$)
FOR $C_{27}H_{24}O_2$

	U(11)	U(22)	U(33)	U(23)	U(13)	U(12)
O(1)	77(1)	77(1)	73(1)	−17(1)	9(1)	−44(1)
O(2)	56(1)	55(1)	99(1)	0(1)	−24(1)	−16(1)
C(1)	43(1)	46(1)	50(1)	2(1)	−6(1)	−11(1)
C(2)	51(1)	48(1)	44(1)	3(1)	−3(1)	−15(1)
C(3)	41(1)	39(1)	51(1)	−2(1)	−6(1)	−7(1)
C(4)	45(1)	39(1)	50(1)	−1(1)	−1(1)	−7(1)
C(5)	79(2)	41(1)	48(1)	−0(1)	1(1)	−4(1)
C(6)	43(1)	38(1)	49(1)	−2(1)	−3(1)	−5(1)
C(7)	43(1)	54(1)	79(2)	−11(1)	−11(1)	−1(2)
C(8)	42(1)	51(1)	74(2)	−5(1)	−13(1)	−8(1)
C(9)	48(1)	43(1)	47(1)	−1(1)	−8(1)	−9(1)
C(10)	57(1)	43(1)	50(1)	1(1)	−13(1)	−9(1)
C(11)	63(2)	59(1)	71(2)	−8(1)	−13(1)	−15(1)
C(12)	88(2)	71(2)	89(2)	−16(2)	−23(2)	−29(2)
C(13)	111(3)	68(2)	70(2)	−20(2)	−20(2)	−20(2)
C(14)	98(2)	70(2)	63(2)	−19(1)	4(2)	−10(2)
C(15)	68(2)	63(1)	55(1)	−9(1)	−1(1)	−14(1)
C(16)	48(1)	44(1)	45(1)	−1(1)	−3(1)	−3(1)
C(17)	63(1)	47(1)	71(2)	−4(1)	−10(1)	−13(1)
C(18)	102(2)	53(1)	80(2)	−6(1)	−15(2)	−24(2)
C(19)	107(2)	47(1)	79(2)	−7(1)	−2(2)	10(2)
C(20)	83(2)	58(2)	121(3)	6(2)	−6(2)	16(2)
C(21)	59(2)	57(1)	95(2)	3(1)	−15(1)	3(1)
C(22)	58(1)	44(1)	47(1)	0(1)	0(1)	−12(1)
C(23)	78(2)	47(1)	59(2)	−6(1)	−4(1)	−2(1)
C(24)	107(2)	55(2)	68(2)	−14(1)	0(2)	0(2)
C(25)	120(3)	68(2)	56(2)	−14(1)	−1(2)	−22(2)
C(26)	88(2)	97(2)	61(2)	−13(2)	−14(2)	−32(2)
C(27)	64(2)	72(2)	58(2)	−12(1)	−6(1)	−13(1)

INTERATOMIC DISTANCES (Å) FOR $C_{27}H_{24}O_2$

O(1) – C(1)	1,204(2)	O(2) – C(9)	1,218(2)
C(1) – C(2)	1,496(3)	C(1) – C(6)	1,525(3)
C(2) – C(3)	1,540(3)	C(2) – H(1)	0,82(3)
C(2) – H(2)	1,05(3)	C(3) – C(4)	1,567(3)
C(3) – C(8)	1,547(3)	C(3) – C(10)	1,523(3)
C(4) – C(5)	1,549(3)	C(4) – C(9)	1,514(3)
C(4) – H(3)	1,01(3)	C(5) – C(6)	1,546(3)
C(5) – H(4)	1,02(3)	C(5) – H(5)	0,92(3)
C(6) – C(7)	1,531(3)	C(6) – C(22)	1,526(3)
C(7) – C(8)	1,521(4)	C(7) – H(6)	0,78(3)
C(7) – H(7)	0,95(3)	C(8) – H(8)	1,02(3)
C(8) – H(9)	0,94(3)	C(9) – C(16)	1,493(3)
C(10) – C(11)	1,390(3)	C(10) – C(15)	1,394(3)
C(11) – C(12)	1,375(4)	C(11) – H(10)	0,91(3)
C(12) – C(13)	1,380(4)	C(12) – H(11)	0,87(3)
C(13) – C(14)	1,369(4)	C(13) – H(12)	1,04(3)
C(14) – C(15)	1,378(4)	C(14) – H(13)	0,91(3)
C(15) – H(14)	0,95(3)	C(16) – C(17)	1,376(3)
C(16) – C(21)	1,381(3)	C(17) – C(18)	1,384(3)
C(17) – H(15)	0,97(3)	C(18) – C(19)	1,357(4)
C(18) – H(16)	0,92(3)	C(19) – C(20)	1,366(5)
C(19) – H(17)	1,03(3)	C(20) – C(21)	1,359(4)
C(20) – H(18)	1,03(3)	C(21) – H(19)	1,02(3)
C(22) – C(23)	1,388(3)	C(22) – C(27)	1,383(3)
C(23) – C(24)	1,400(4)	C(23) – H(20)	1,00(3)
C(24) – C(25)	1,362(5)	C(24) – H(21)	1,02(3)
C(25) – C(26)	1,365(5)	C(25) – H(22)	0,94(3)
C(26) – C(27)	1,379(4)	C(26) – H(23)	0,83(3)
C(27) – C(24)	0,85(3)		

INTERATOMIC ANGLES (°) FOR $C_{27}H_{24}O_2$

O(1)–C(1)–C(2)	121,2(2)	O(1)–C(1)–C(6)	124,6(2)
C(2)–C(1)–C(6)	114,2(2)	C(1)–C(2)–C(3)	111,5(2)
C(1)–C(2)–H(1)	107(2)	C(3)–C(2)–H(1)	105(2)
C(1)–C(2)–H(2)	111(2)	C(3)–C(2)–H(2)	109,9(14
H(1)–C(2)–H(2)	112(2)	C(2)–C(3)–C(4)	108,4(2)
C(2)–C(3)–C(8)	106,2(2)	C(4)–C(3)–C(8)	105,8(2)
C(2)–C(3)–C(10)	113,1(2)	C(4)–C(3)–C(10)	110,7(2)
C(8)–C(3)–C(10)	112,2(2)	C(4)–C(4)–C(5)	109,7(2)
C(3)–C(4)–C(9)	111,8(2)	C(5)–C(4)–C(2)	109,7(2)
C(3)–C(4)–H(3)	109(2)	C(5)–C(4)–H(3)	107(2)
C(9)–C(4)–H(3)	110(2)	C(4)–C(5)–C(6)	113,0(2)
C(4)–C(5)–H(4)	114(2)	C(6)–C(5)–H(4)	109(2)
C(4)–C(5)–H(5)	112(2)	C(6)–C(5)–H(5)	104(2)
H(4)–C(5)–H(5)	104(2)	C(1)–C(6)–C(5)	108,6(2)
C(1)–C(6)–C(7)	103,9(2)	C(5)–C(6)–C(7)	106.6(2)
C(1)–C(6)–C(22)	112,0(2)	C(5)–C(6)–C(22)	110,4(2)
C(7)–C(6)–C(22)	114,9(2)	C(6)–C(7)–C(8)	111,9(2)
C(6)–C(7)–H(6)	109(2)	C(8)–C(7)–H(6)	110(2)
C(6)–C(7)–H(7)	113(2)	C(8)–C(7)–H(7)	103(2)
H(6)–C(7)–H(7)	110(3)	C(3)–C(8)–C(7)	112,2(2)
C(3)–C(8)–H(8)	103(2)	C(7)–C(8)–H(8)	113(2)
C(3)–C(8)–H(9)	107(2)	C(7)–C(8)–H(9)	115(2)
H(8)–C(8)–H(9)	106(2)	O(2)–C(9)–C(4)	119,2(2)
O(2)–C(9)–C(16)	118,7(2)	C(4)–C(9)–C(16)	122,1(2)
C(3)–C(10)–C(11)	121,0(2)	C(3)–C(10)–C(15)	121,9(2)
C(11)–C(10)–C(15)	117,0(2)	C(10)–C(11)–C(12)	121,5(3)
C(10)–C(11)–H(10)	116(2)	C(12)–C(11)–H(10)	122(2)
C(11)–C(12)–C(13)	120,7(3)	C(11)–C(12)–H(11)	116(2)
C(13)–C(12)–H(11)	123(3)	C(12)–C(13)–C(14)	118,7(3)
C(12)–C(13)–H(12)	122,5(14)	C(14)–C(13)–H(12)	117,7(14
C(13)–C(14)–C(15)	120,9(3)	C(13)–C(14)–H(13)	115(2)
C(15)–C(14)–H(13)	124(2)	C(10)–C(15)–C(14)	121,2(3)
C(10)–C(15)–H(14)	123(2)	C(14)–C(15)–H(14)	116(2)
C(9)–C(16)–C(17)	124,5(2)	C(9)–C(16)–C(21)	117,5(2)
C(17)–C(16)–C(21)	117,9(2)	C(16)–C(17)–C(18)	119,8(3)
C(16)–C(17)–H(15)	120(2)	C(18)–C(17)–H(15)	120(2)
C(17)–C(18)–C(19)	121,4(3)	C(17)–C(18)–H(16)	112(2)
C(19)–C(18)–H(16)	126(2)	C(18)–C(19)–C(20)	118,9(3)
C(18)–C(19)–H(17)	118(2)	C(20)–C(19)–H(17)	122(2)
C(19)–C(20)–C(21)	120,4(3)	C(19)–C(20)–H(18)	119(2)
C(21)–C(20)–H(18)	120(2)	C(16)–C(21)–H(20)	121,5(3)
C(16)–C(21)–H(19)	120(2)	C(20)–C(21)–H(19)	118(2)
C(6)–C(22)–C(23)	122,1(2)	C(6)–C(22)–C(27)	120,2(2)
C(23)–C(22)–C(27)	117,7(2)	C(22)–C(23)–C(24)	120,4(3)
C(22)–C(23)–H(20)	113(2)	C(24)–C(23)–H(20)	126(2)
C(23)–C(24)–C(25)	120,6(3)	C(23)–C(24)–H(21)	119(2)
C(25)–C(24)–H(21)	121(2)	C(24)–C(25)–C(26)	119,3(3)
C(24)–C(25)–H(22)	120(2)	C(26)–C(25)–H(22)	118(2)
C(25)–C(26)–C(27)	120,8(3)	C(25)–C(26)–H(23)	126(2)
C(27)–C(26)–H(23)	112(2)	C(22)–C(27)–C(26)	121,2(3)
C(22)–C(27)–H(24)	118(2)	C(26)–C(27)–H(24)	121(2)

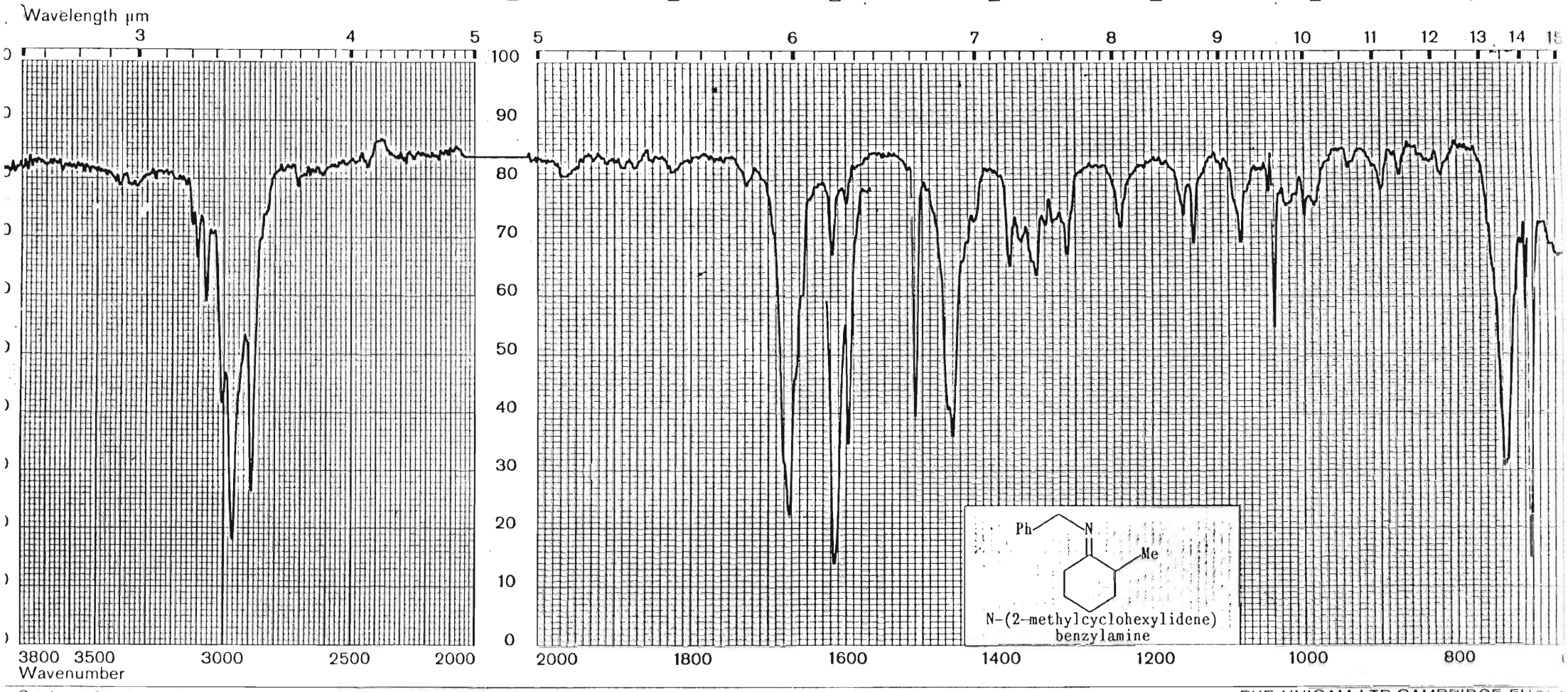
Table of Torsional Angels (°) for $C_{27}O_{24}O_2$

ATOM: 1	2	3	4	ANGLE
O1	C1	C2	C3	176,40(0,22)
C6	C1	C2	C3	–3,07(0,28)
O1	C1	C6	C5	–124,88(0,26)
O1	C1	C6	C7	121,98(0,25)
O1	C1	C6	C22	–2,71(0,33)
C2	C1	C6	C5	56,64(0,26)
C2	C1	C6	C7	–56,49(0,25)
C2	C1	C6	C22	178,82(0,19)
C1	C2	C3	C4	–55,26(0,25)
C1	C2	C3	C8	57,97(0,26)
C1	C2	C3	C10	–178,49(0,19)
C2	C3	C4	C5	59,39(0,24)
C2	C3	C4	C9	–62,49(0,24)
C8	C3	C4	C5	–54,15(0,23)
C8	C3	C4	C9	–176,03(0,18)
C10	C3	C4	C5	–175,97(0,19)
C10	C3	C4	C9	62,15(0,22)
C2	C3	C8	C7	–51,75(0,27)
C4	C3	C8	C7	63,27(0,24)
C10	C3	C8	C7	–175,85(0,21)
C2	C3	C10	C11	–156,22(0,23)
C2	C3	C10	C15	28,07(0,32)
C4	C3	C10	C11	81,89(0,26)
C4	C3	C10	C15	–93,82(0,27)
C8	C3	C10	C11	–36,05(0,32)
C8	C3	C10	C15	148,24(0,23)
C3	C4	C5	C6	–5,84(0,28)
C9	C4	C5	C6	117,25(0,24)
C3	C4	C9	O2	81,79(0,28)
C3	C4	C9	C16	–99,21(0,27)
C5	C4	C9	O2	–40,09(0,32)
C5	C4	C9	C16	138,90(0,24)
C4	C5	C6	C1	–50,66(0,28)
C4	C5	C6	C7	60,69(0,28)
C4	C5	C6	C22	–173,80(0,19)
C1	C6	C7	C8	62,04(0,24)
C5	C6	C7	C8	–52,47(0,27)

ATOM: 1	2	3	4	ANGLE
C22	C6	C7	C8	–175,19(0,21)
C1	C6	C22	C23	122,44(0,24)
C1	C6	C22	C27	–57,76(0,30)
C5	C6	C22	C23	–116,49(0,27)
C5	C6	C22	C27	63,31(0,29)
C7	C6	C22	C23	4,13(0,34)
C7	C6	C22	C27	–176,07(0,23)
C6	C7	C8	C3	–8,18(0,29)
O2	C9	C16	C17	–174,85(0,25)
O2	C9	C16	C21	5,34(0,37)
C4	C9	C16	C17	6,15(0,41)
C4	C9	C16	C21	–173,66(0,25)
C3	C10	C11	C12	–176,00(0,25)
C15	C10	C11	C12	–0,09(0,40)
C3	C10	C15	C14	176,00(0,25)
C11	C10	C15	C14	0,13(0,40)
C10	C11	C12	C13	–0,04(0,42)
C11	C12	C13	C14	0,13(0,48)
C12	C13	C14	C15	–0,09(0,45)
C13	C14	C15	C10	–0,04(0,44)
C9	C16	C17	C18	–179,67(0,26)
C21	C16	C17	C18	0,14(0,40)
C9	C16	C21	C20	179,06(0,29)
C17	C16	C21	C20	–0,76(0,43)
C16	C17	C18	C19	1,01(0,42)
C17	C18	C19	C20	–1,52(0,44)
C18	C19	C20	C21	0,89(0,50)
C19	C20	C21	C16	0,25(0,52)
C6	C22	C23	C24	–179,10(0,23)
C27	C22	C23	C24	1,09(0,38)
C6	C22	C27	C26	179,04(0,25)
C23	C22	C27	C26	–1,14(0,39)
C22	C23	C24	C25	0,45(0,41)
C23	C24	C25	C26	–1,96(0,44)
C24	C25	C26	C27	1,91(0,47)
C25	C26	C27	C22	–0,35(0,45)

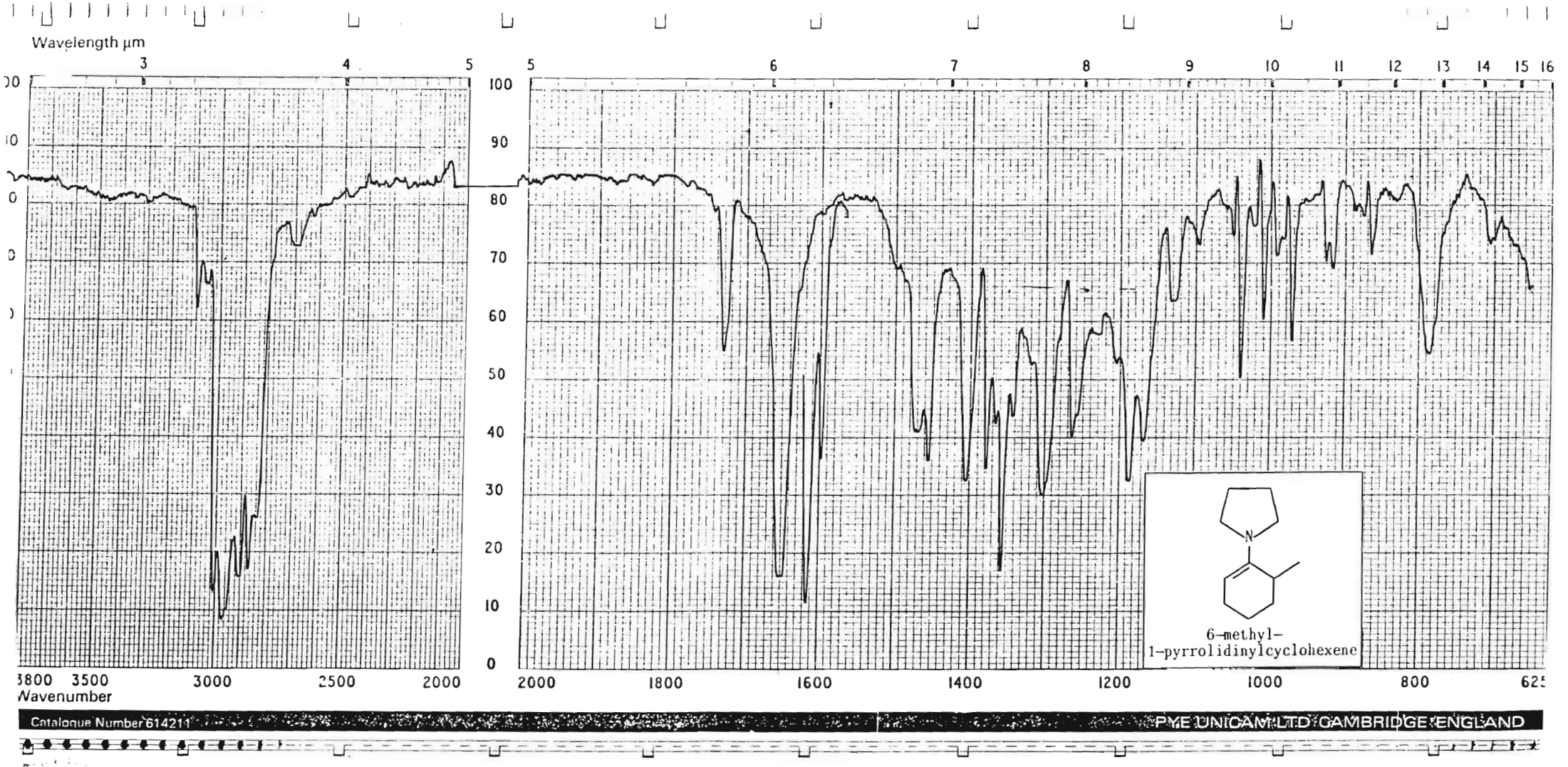
3. SPECTRA

3.1 INFRA–RED SPECTRA



Catalogue Number 614 211

PYE UNICAM LTD CAMBRIDGE ENGL


Wavelength μm
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4
5
5
6
7
8
9
10
11
12
13
14
15
16
100
90
80
70
60
50
40
30
20
10
0
3800
3500
3000
2500
2000
2000
1800
1600
1400
1200
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Wavenumber
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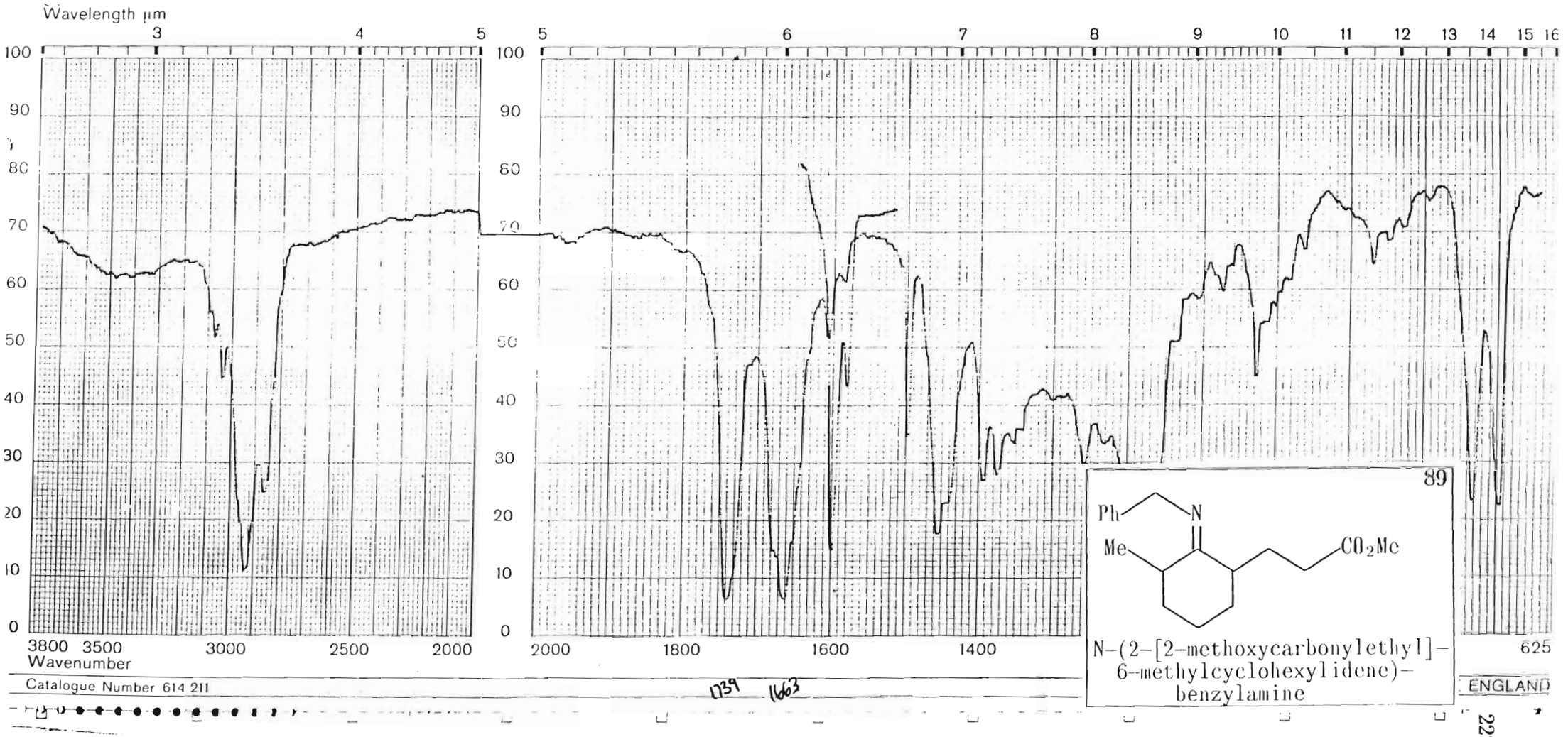
6-methyl-
1-pyrrolidinylcyclohexene
Catalogue Number 614211
PYE UNICAM LTD CAMBRIDGE ENGLAND


Wavelength µm
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4
5
6
7
8
9
10
11
12
13
14
15
16
100
90
80
70
60
50
40
30
20
10
0
3800 3500
3000
2500
2000
1800
1600
1400
625
Wavenumber
1739
1663
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Ph
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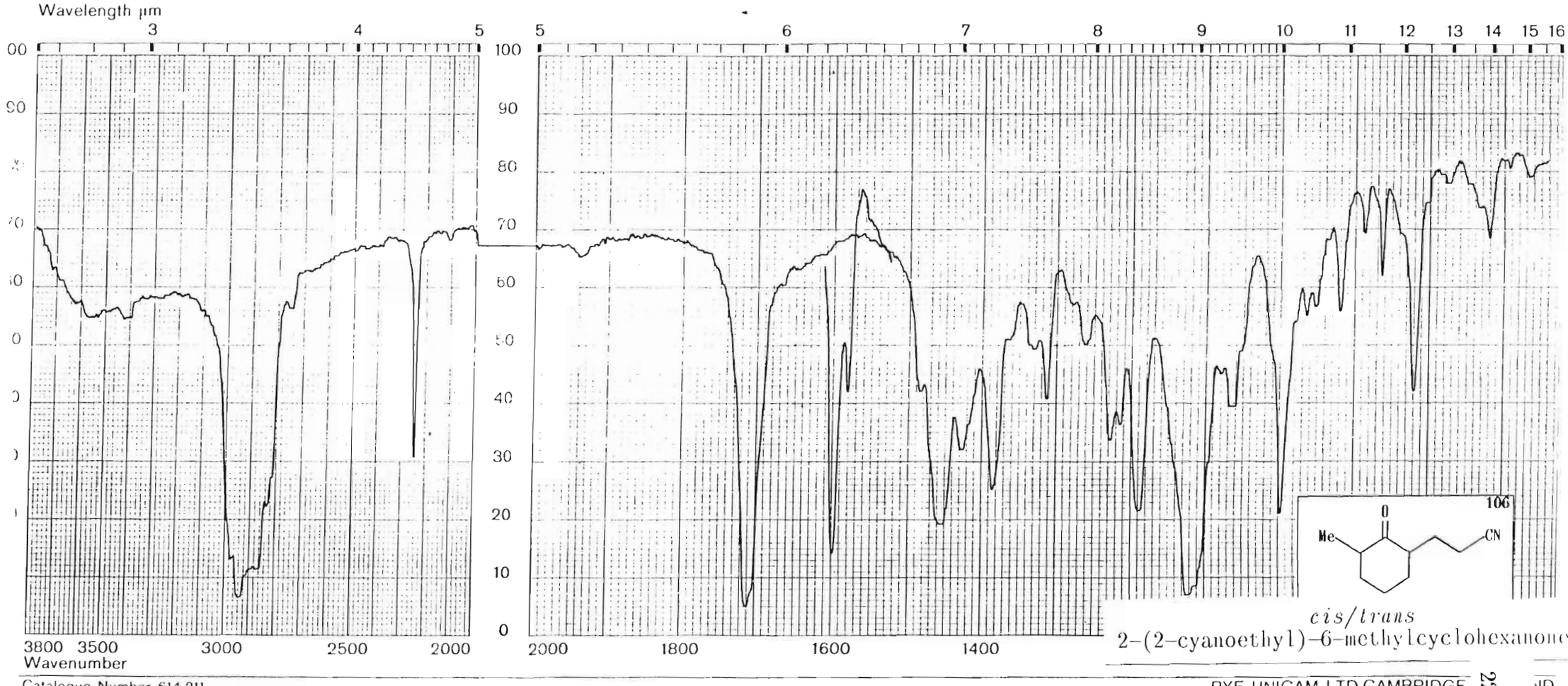
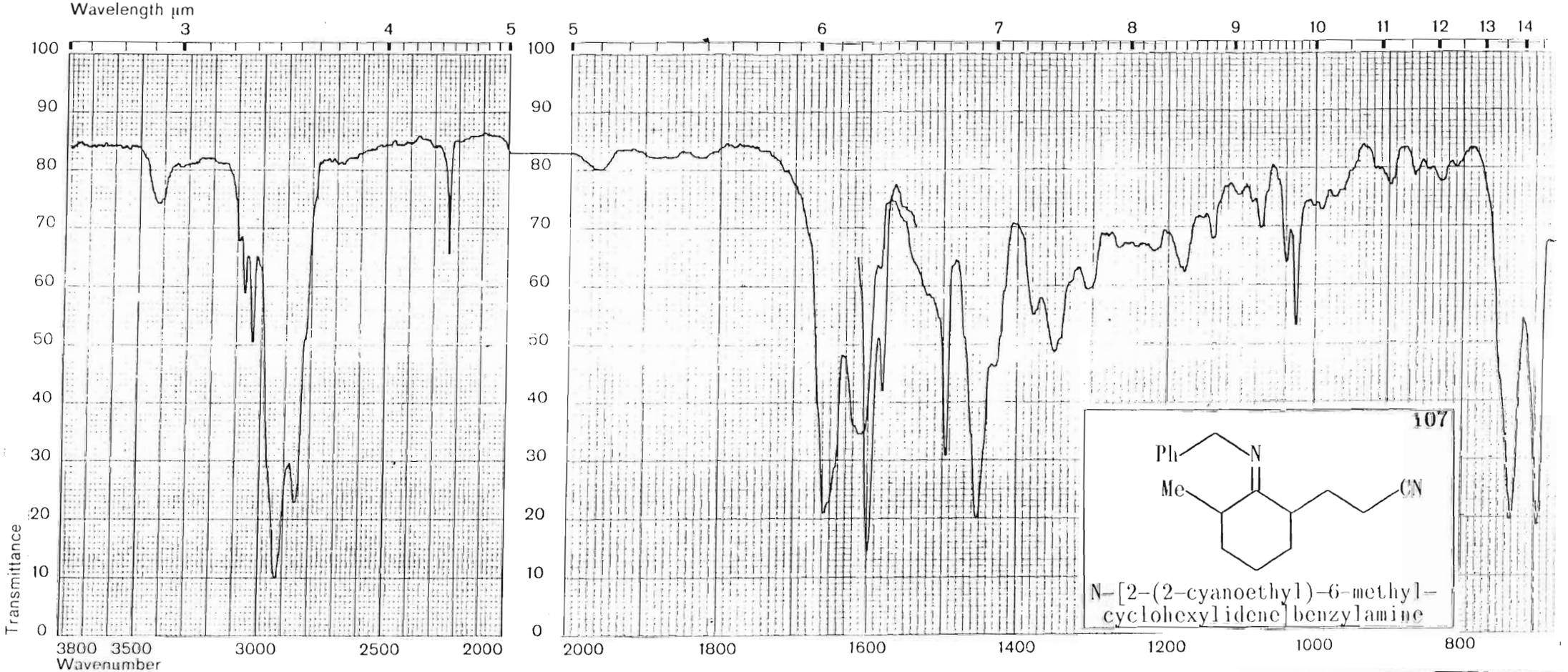
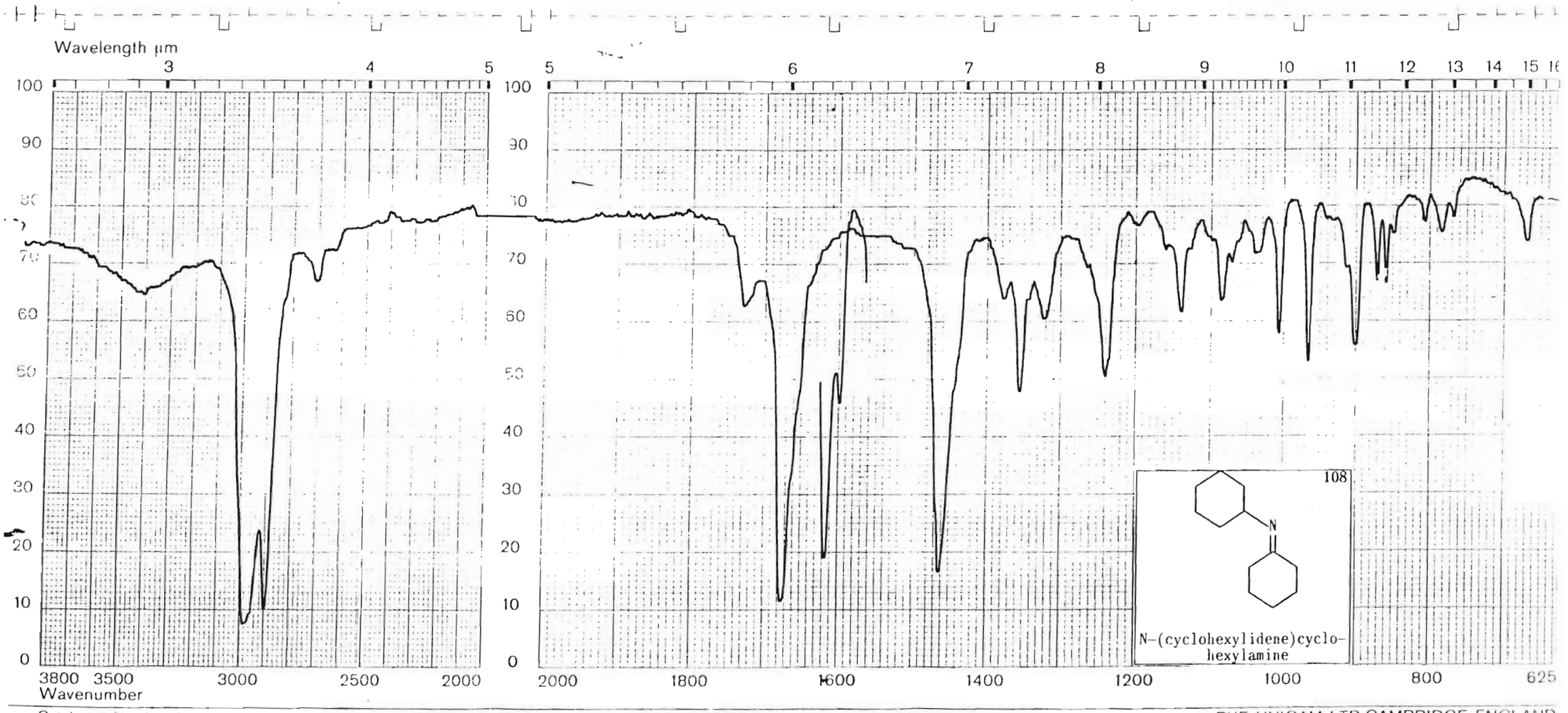
Me
CO2Me
N-(2-[2-methoxycarbonylethyl]-6-methylcyclohexylidene)-benzylamine
Catalogue Number 614 211
ENGLAND
222



cis/trans
2-(2-cyanoethyl)-6-methylcyclohexanone


Wavelength μm
3
4
5
6
7
8
9
10
11
12
13
14
100
90
80
70
60
50
40
30
20
10
0
Transmittance
3800
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
Wavenumber
107
Ph
N
Me
CN
N-[2-(2-cyanoethyl)-6-methyl-cyclohexylidene]benzylamine


Wavelength μm
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4
5
6
7
8
9
10
11
12
13
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100
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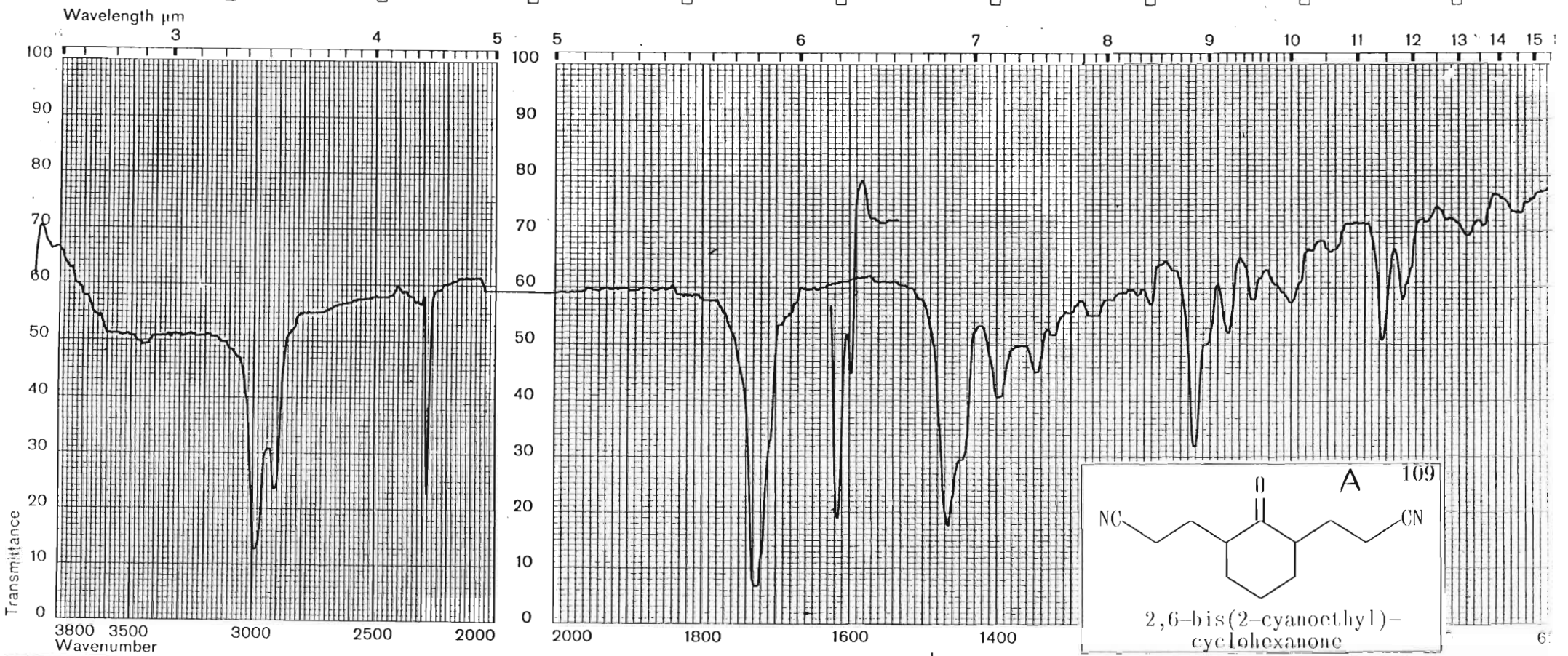
80
70
60
50
40
30
20
10
0
3800
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
625
Wavenumber
108
N
N–(cyclohexylidene)cyclo-hexylamine
Catalogue Number 614 211
PYE UNICAM LTD CAMBRIDGE ENGLAND


Wavelength µm
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4
5
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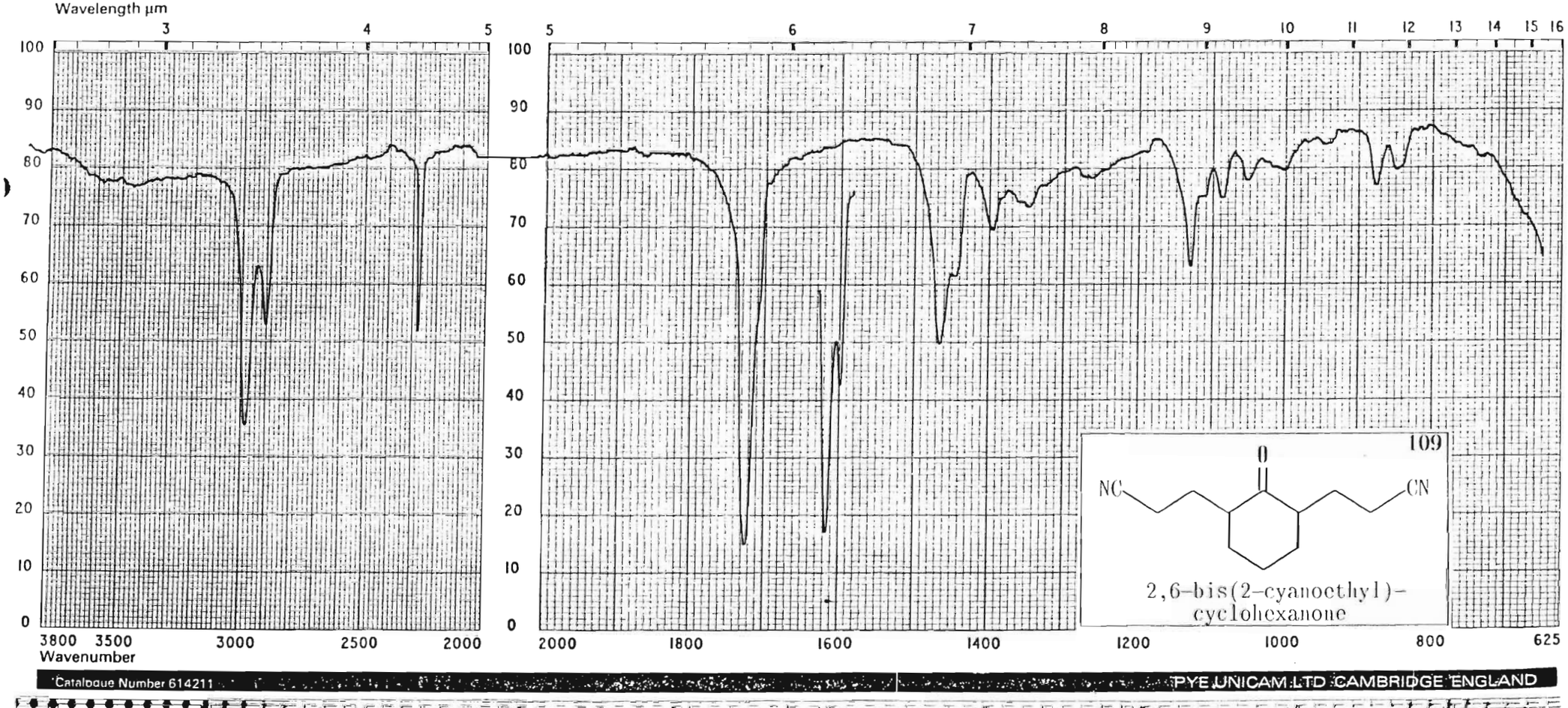
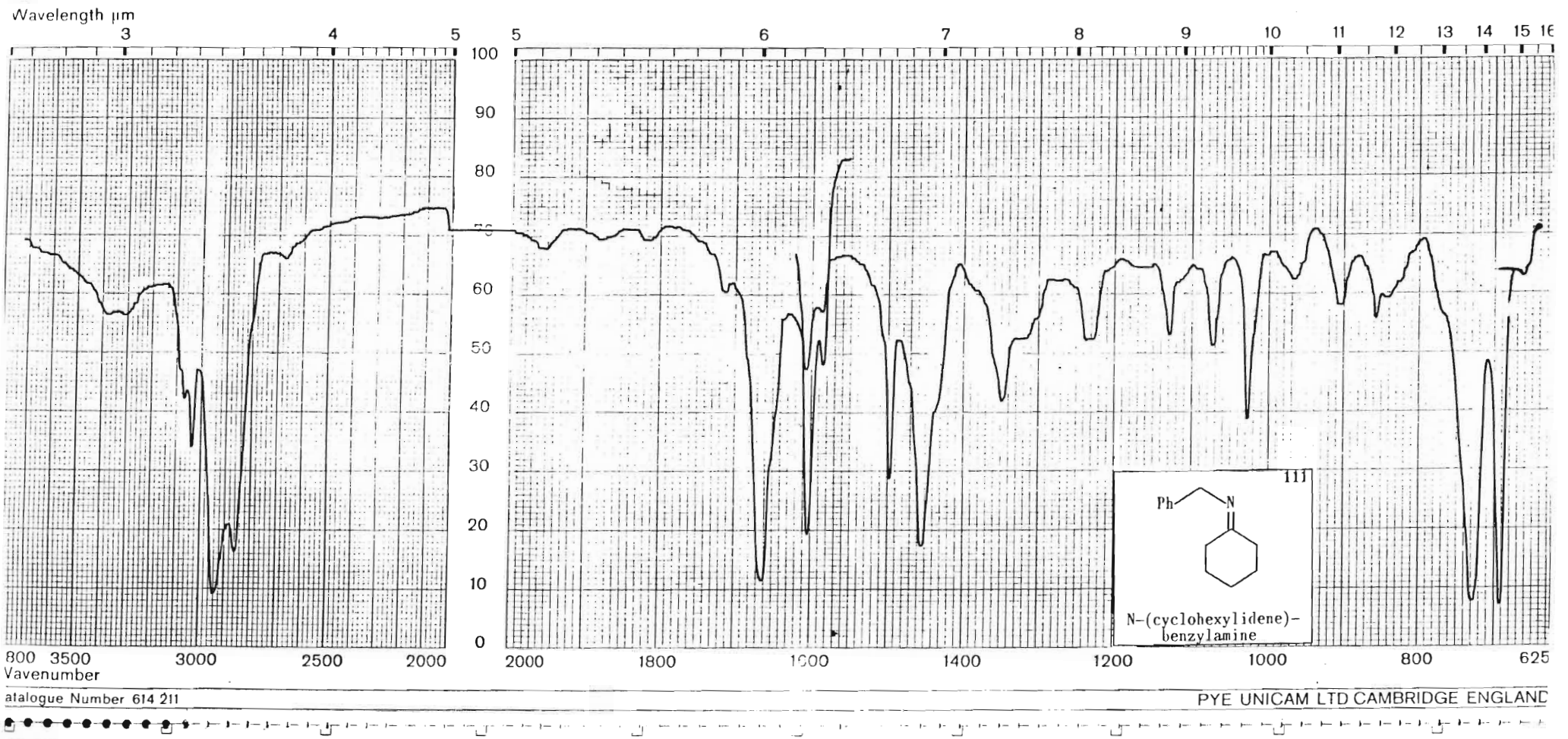
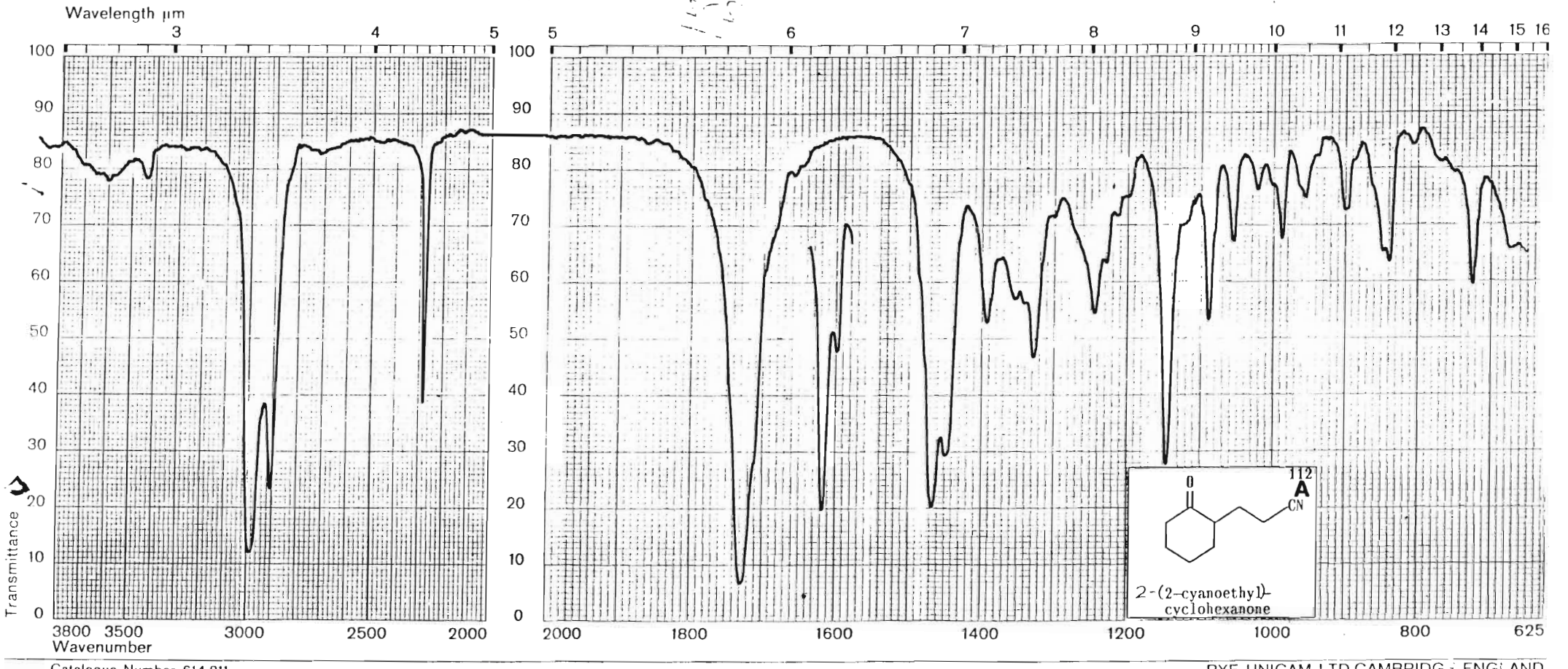
7
8
9
10
11
12
13
14
15
100
90
80
70
60
50
40
30
20
10
0
Transmittance
3800 3500
Wavenumber
3000
2500
2000
2000
1800
1600
1400
A
109
O
NC
CN
2,6-bis(2-cyanoethyl)-
cyclohexanone
Catalogue Number 614 211
PYE UNICAM LTD CAMBRIDGE ENGLA

123

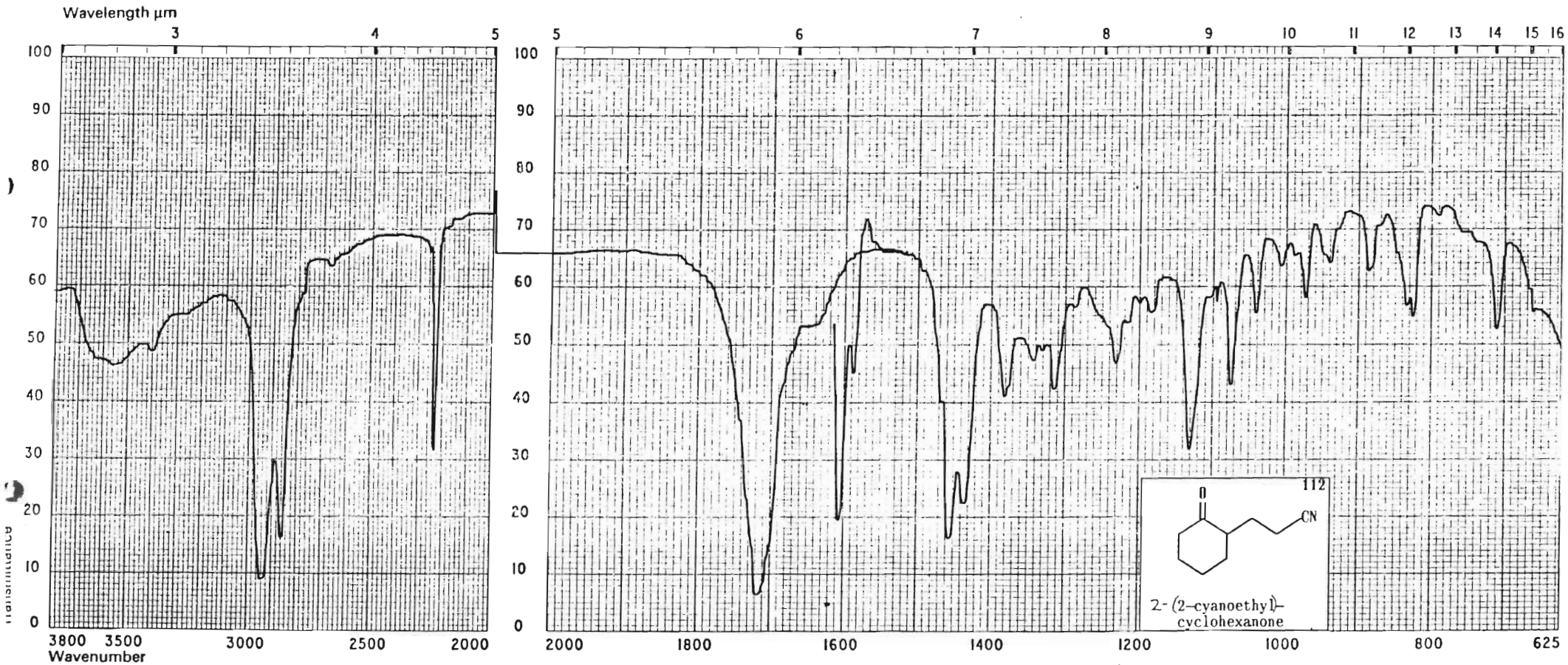

Wavelength µm
3
4
5
6
7
8
9
10
11
12
13
14
15
16
100
90
80
70
60
50
40
30
20
10
0
3800
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
625
Wavenumber
109
O
NC
CN
2,6-bis(2-cyanoethyl)-
cyclohexanone
Catalogue Number 614211
PYE UNICAM LTD CAMBRIDGE ENGLAND


Wavelength µm
3
4
5
5
6
7
8
9
10
11
12
13
14
15
16
100
90
80
60
50
40
30
20
10
0
800 3500
3000
2500
2000
2000
1800
1600
1400
1200
1000
800
625
Wavenumber
111
Ph
N
N-(cyclohexylidene)-
benzylamine
atalogue Number 614 211
PYE UNICAM LTD CAMBRIDGE ENGLAND



Catalogue Number 614 211

PYE UNICAM LTD CAMBRIDGE ENGLAND


Wavelength μm
3
4
5
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7
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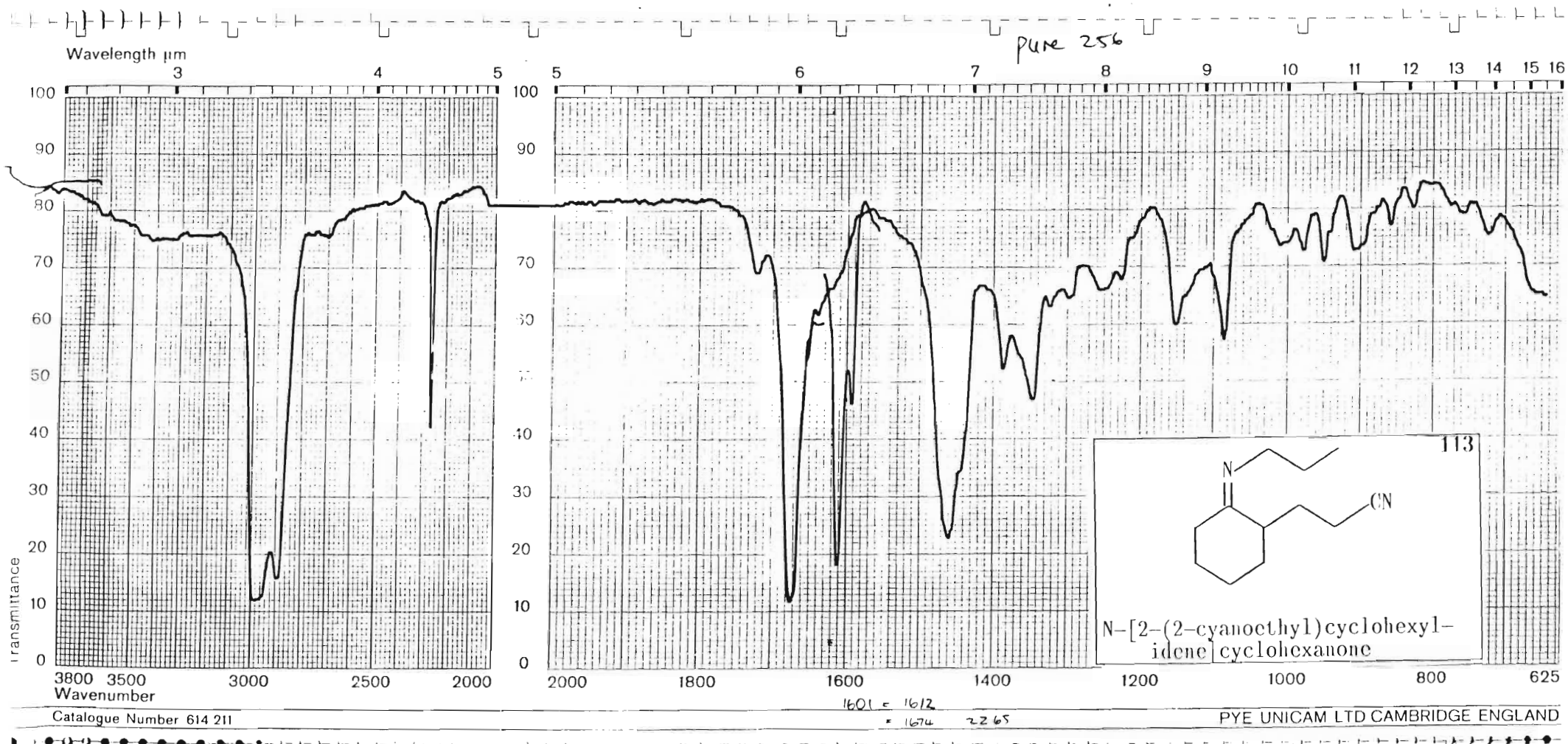
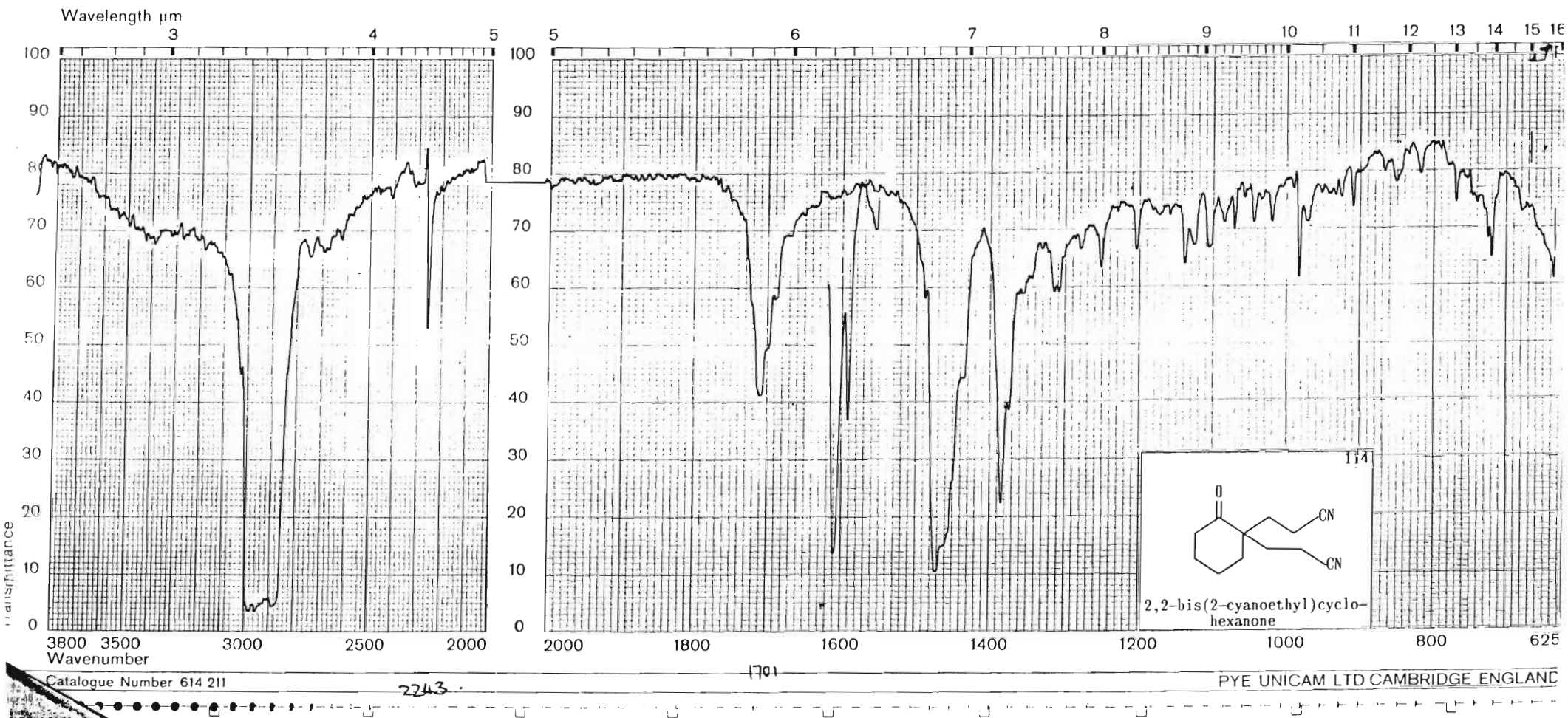
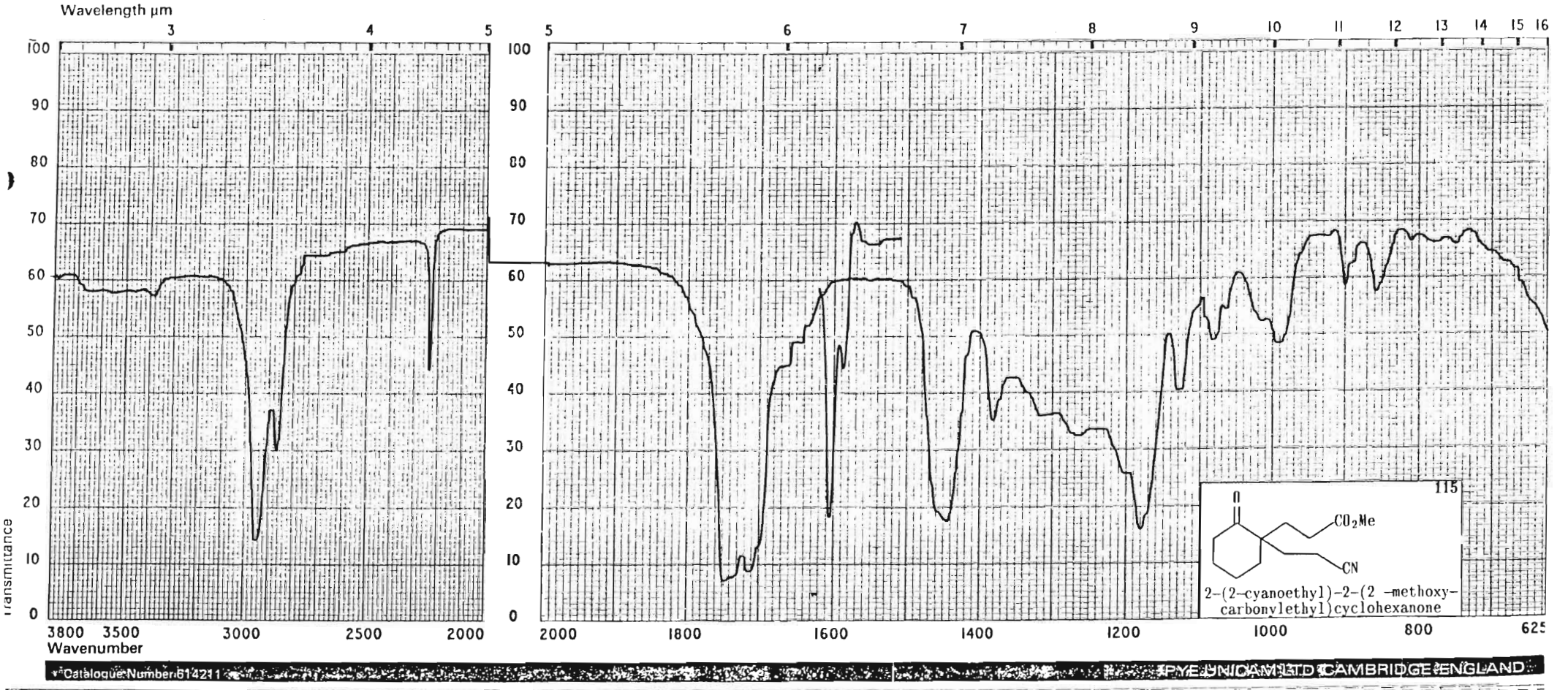
9
10
11
12
13
14
15
16
100
90
80
70
60
50
40
30
20
10
0
3800
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
625
Wavenumber
Transmittance
112
O
CN
2-(2-cyanoethyl)-
cyclohexanone
Catalogue Number 614211
PYE UNICAM LTD. CAMBRIDGE ENGLAND

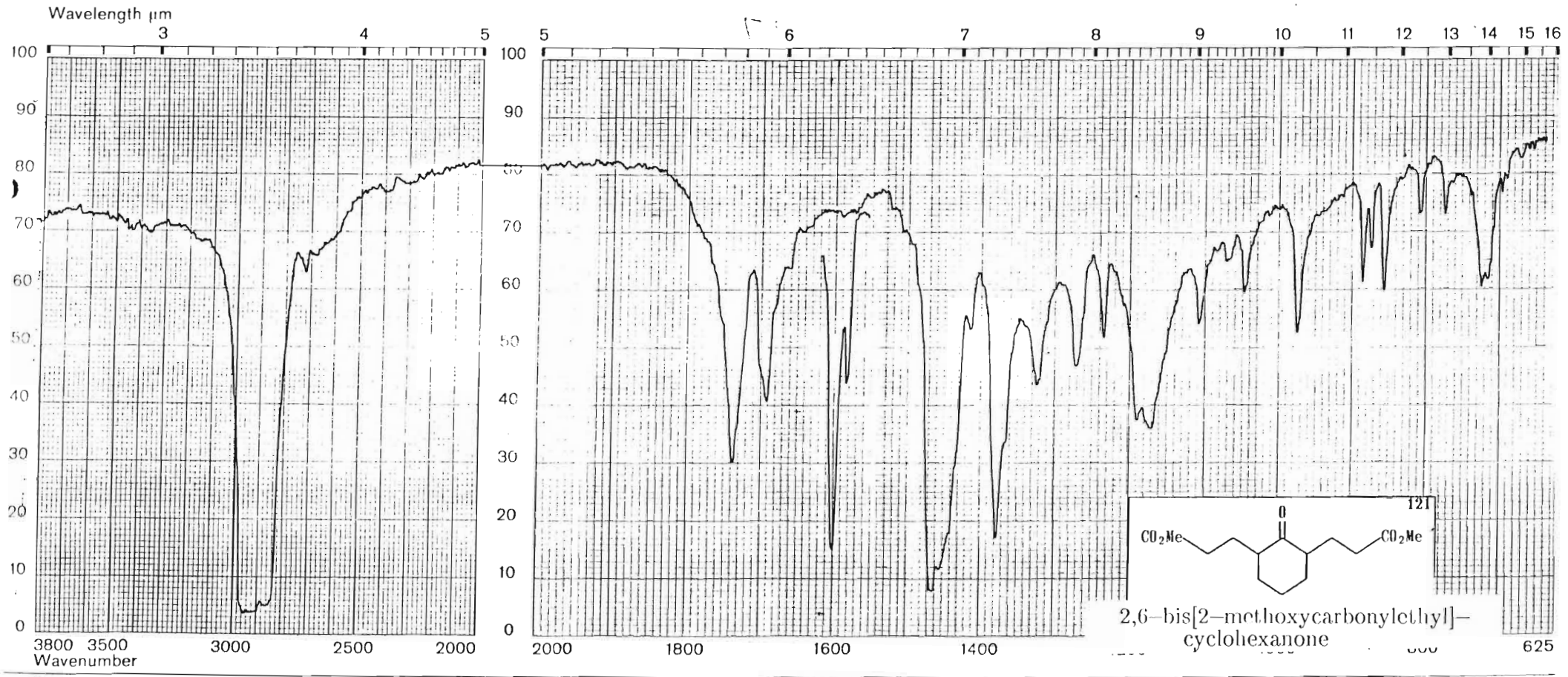


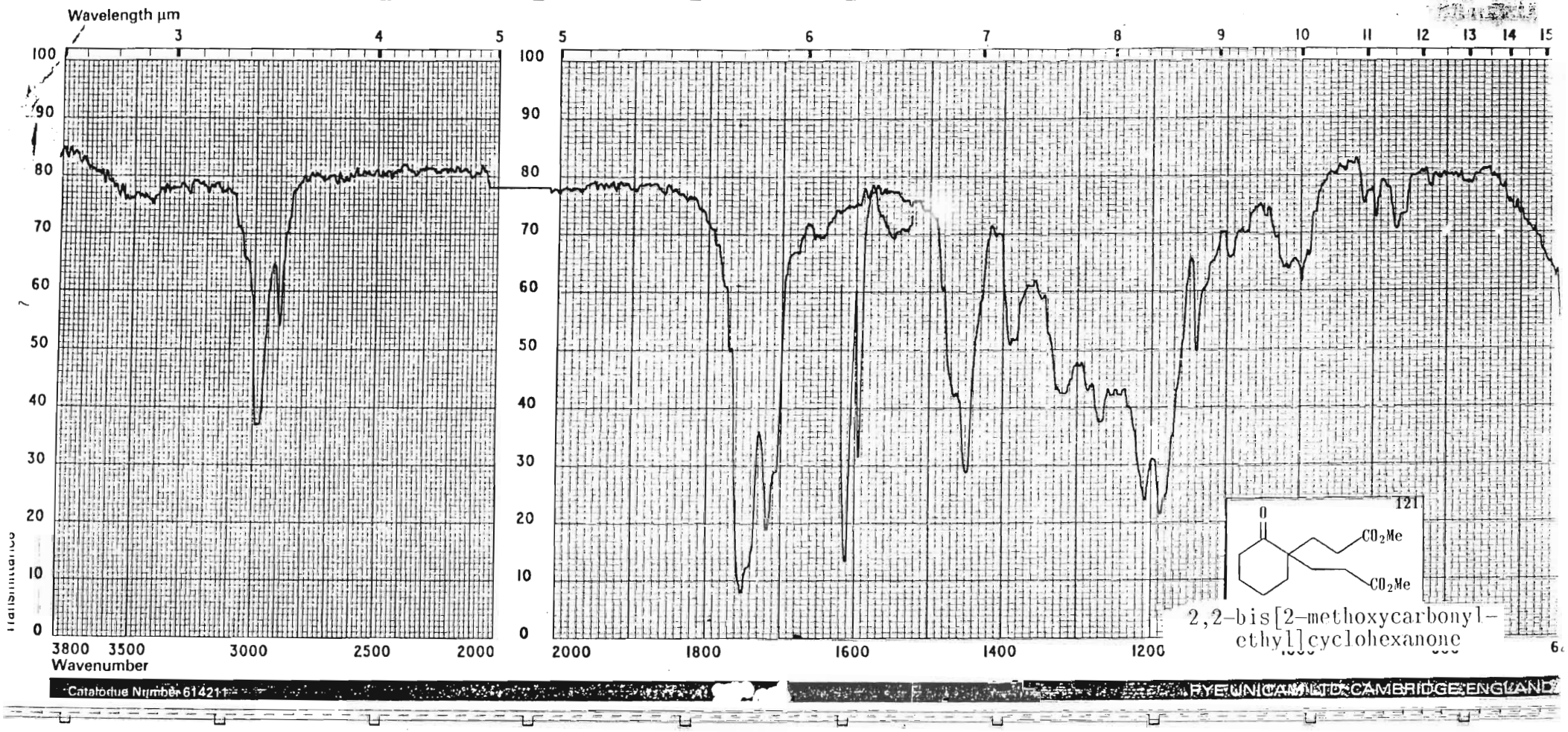
pure 256

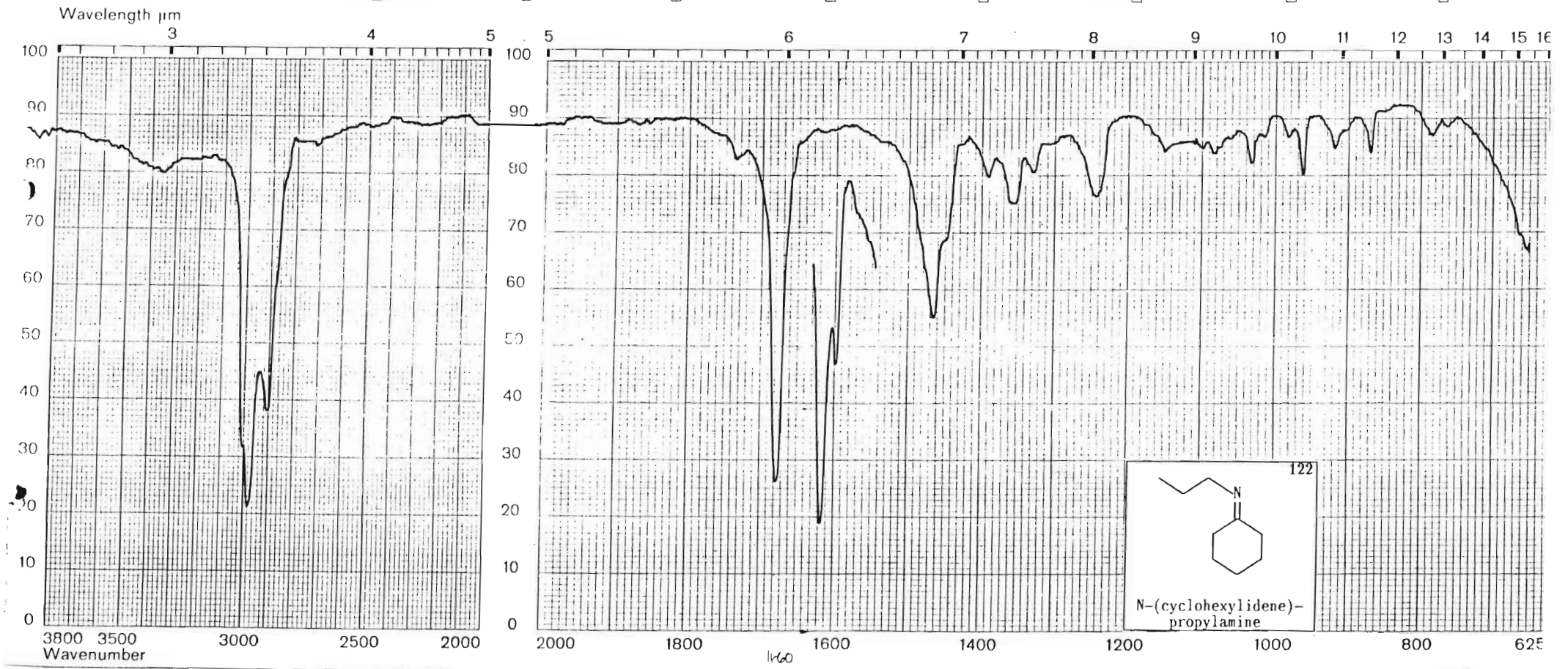
1601 = 1612
= 1674 2265


Wavelength µm
3
4
5
6
7
8
9
10
11
12
13
14
15
16
100
90
80
70
60
50
40
30
20
10
0
Transmittance
3800
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
625
Wavenumber
O
CN
CN
2,2-bis(2-cyanoethyl)cyclo-
hexanone
Catalogue Number 614 211
PYE UNICAM LTD CAMBRIDGE ENGLAND


Wavelength µm
3
4
5
6
7
8
9
10
11
12
13
14
15
16
100
90
80
70
60
50
40
30
20
10
0
Transmittance
3800
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
625
Wavenumber
115
O
CO_2Me
CN
2-(2-cyanoethyl)-2-(2 -methoxy-carbonylethyl)cyclohexanone
Catalogue Number 614211
PYE UNICAM LTD CAMBRIDGE ENGLAND


Wavelength μm
3
4
5
6
7
8
9
10
11
12
13
14
15
16
100
90
80
70
60
50
40
30
20
10
0
3800 3500
3000
2500
2000
Wavenumber
2000
1800
1600
1400
625
121
O
CO2Me
CO2Me
2,6–bis[2–methoxycarbonylethyl]–
cyclohexanone
Catalogue Number 614 211
1738 1692
PYE UNICAM LTD CAMBRIDGE ENGLAND

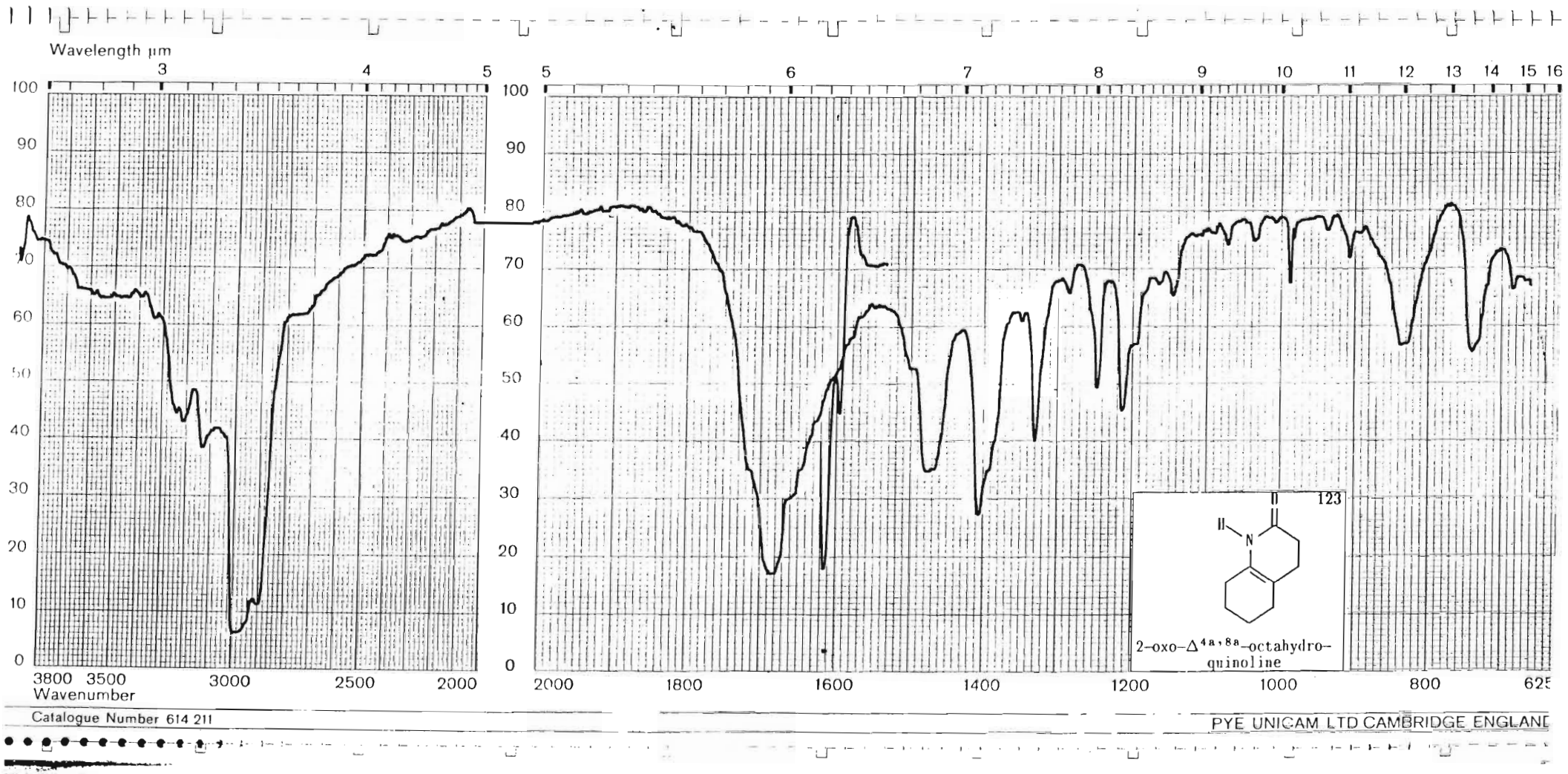

Wavelength μm
3
4
5
6
7
8
9
10
11
12
13
14
15
100
90
80
70
60
50
40
30
20
10
0
3800
3500
3000
2500
2000
1800
1600
1400
1200
Wavenumber
121
O
CO_2Me
CO_2Me
2,2-bis[2-methoxycarbonyl-ethyl]cyclohexanone
Catalogue Number 61421
RYE UNICAM LTD. CAMBRIDGE ENGLAND

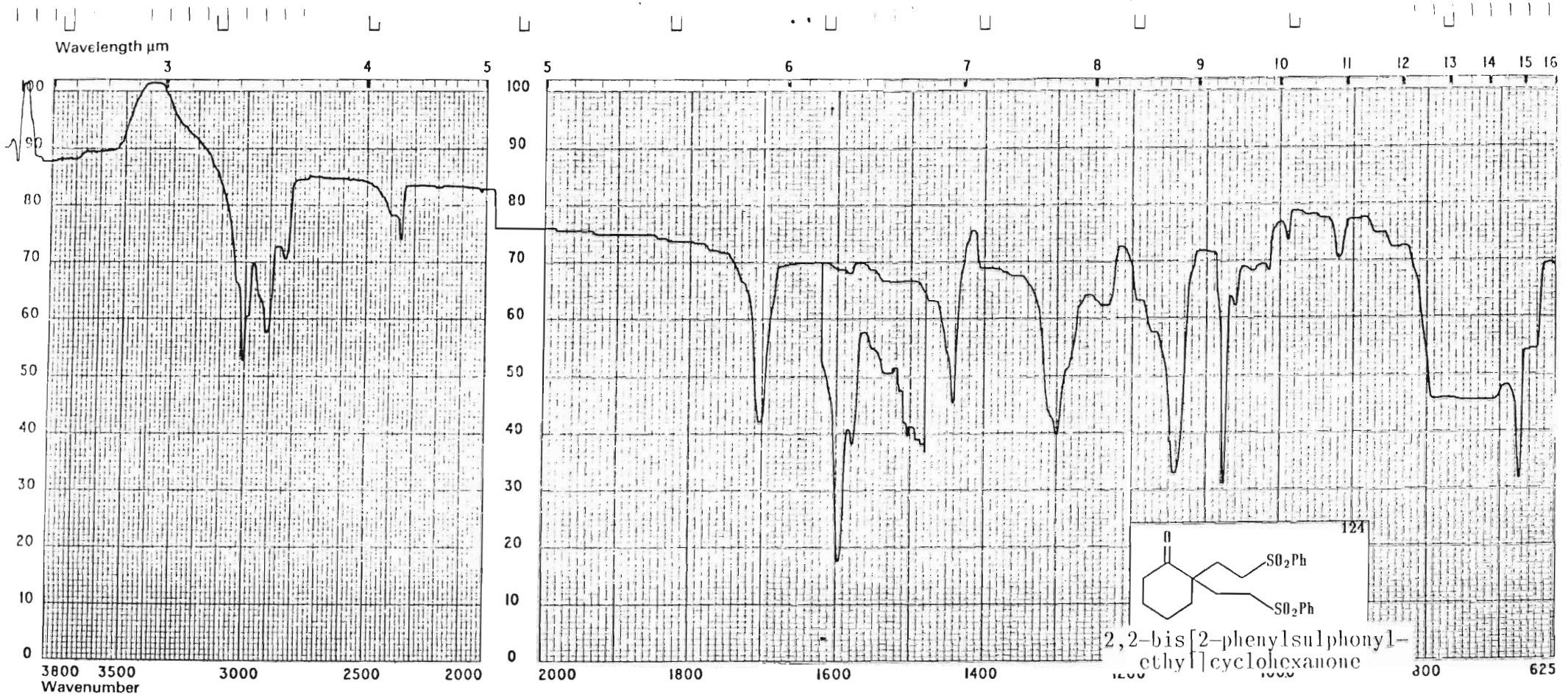


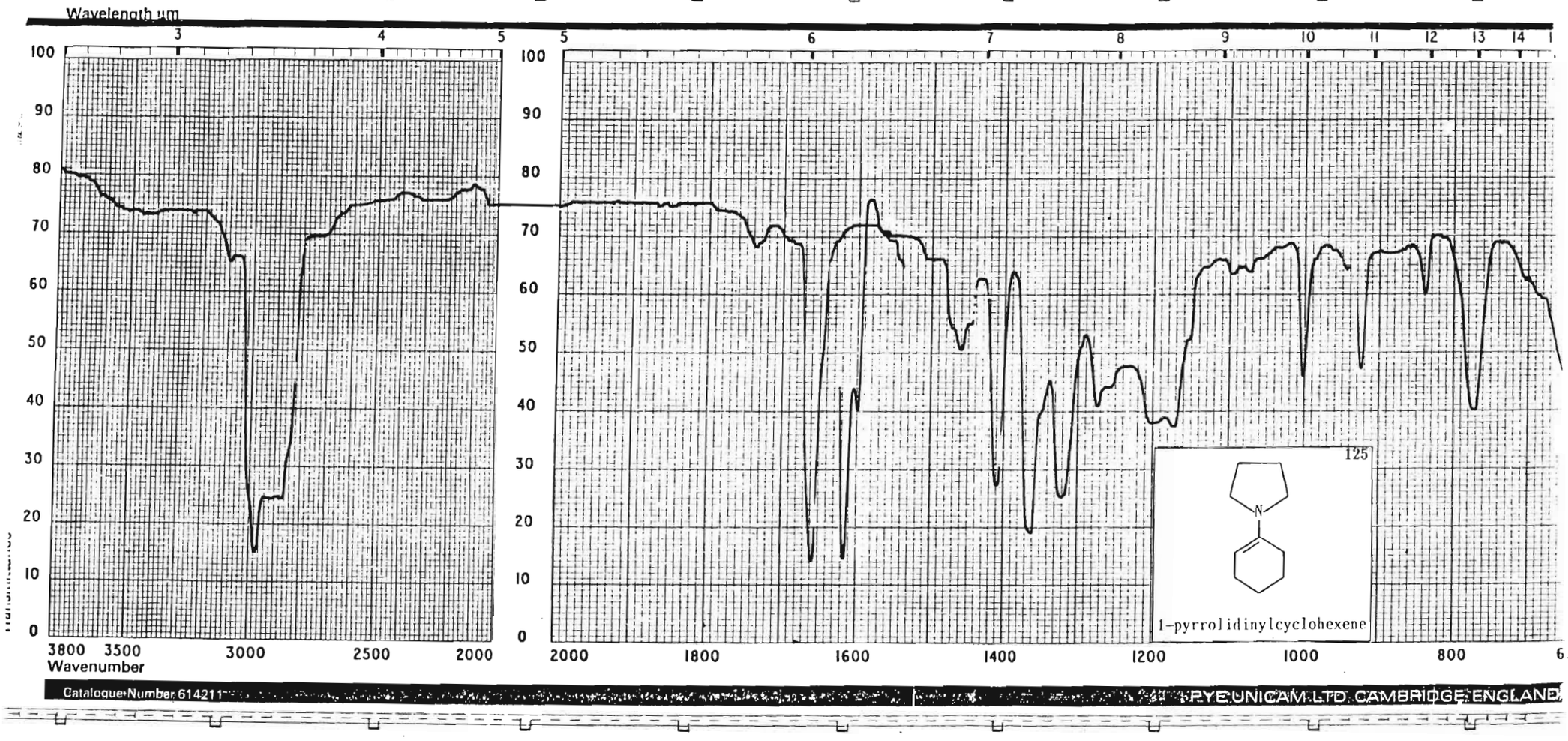
Catalogue Number 614 211

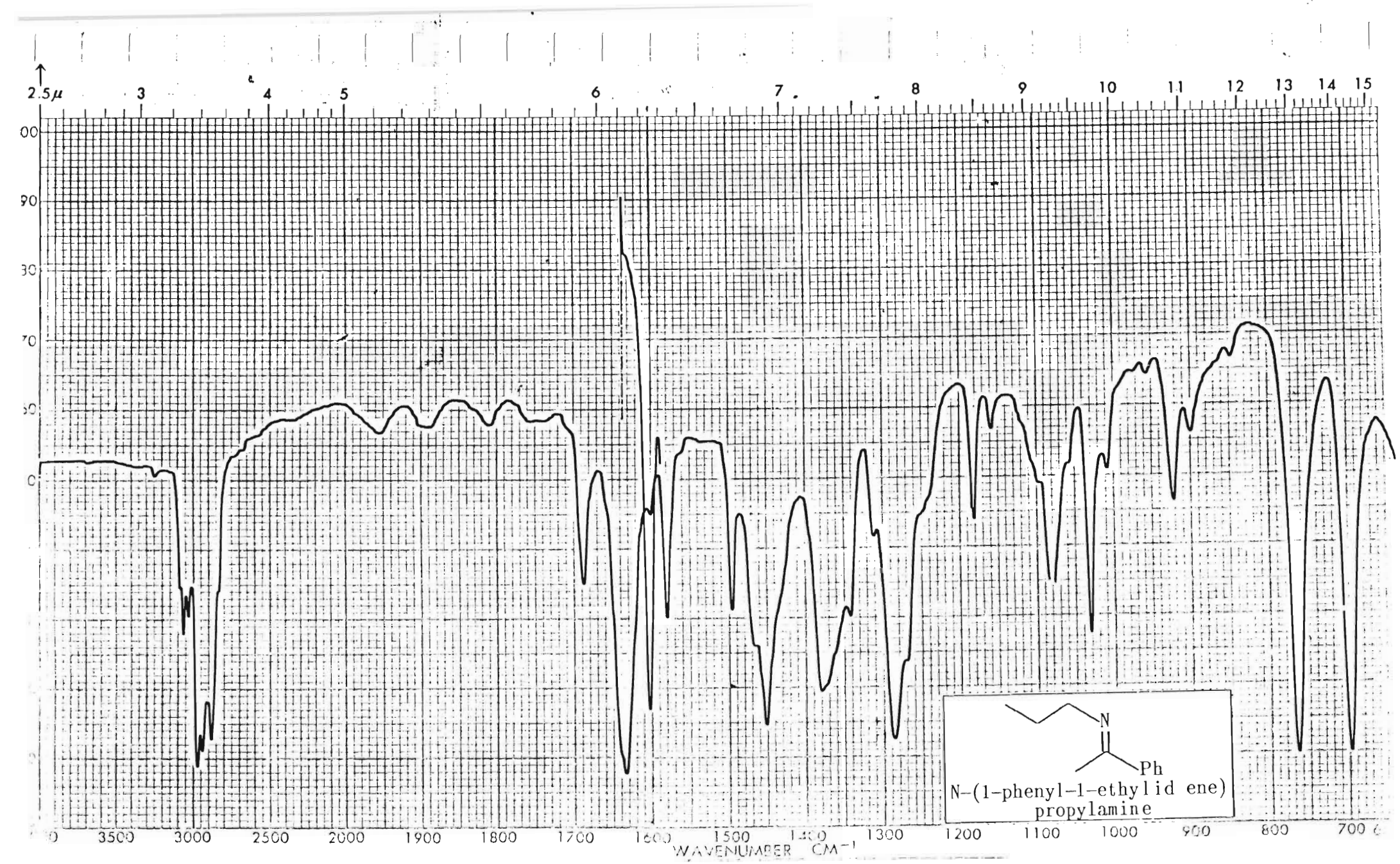
1601 = 1618

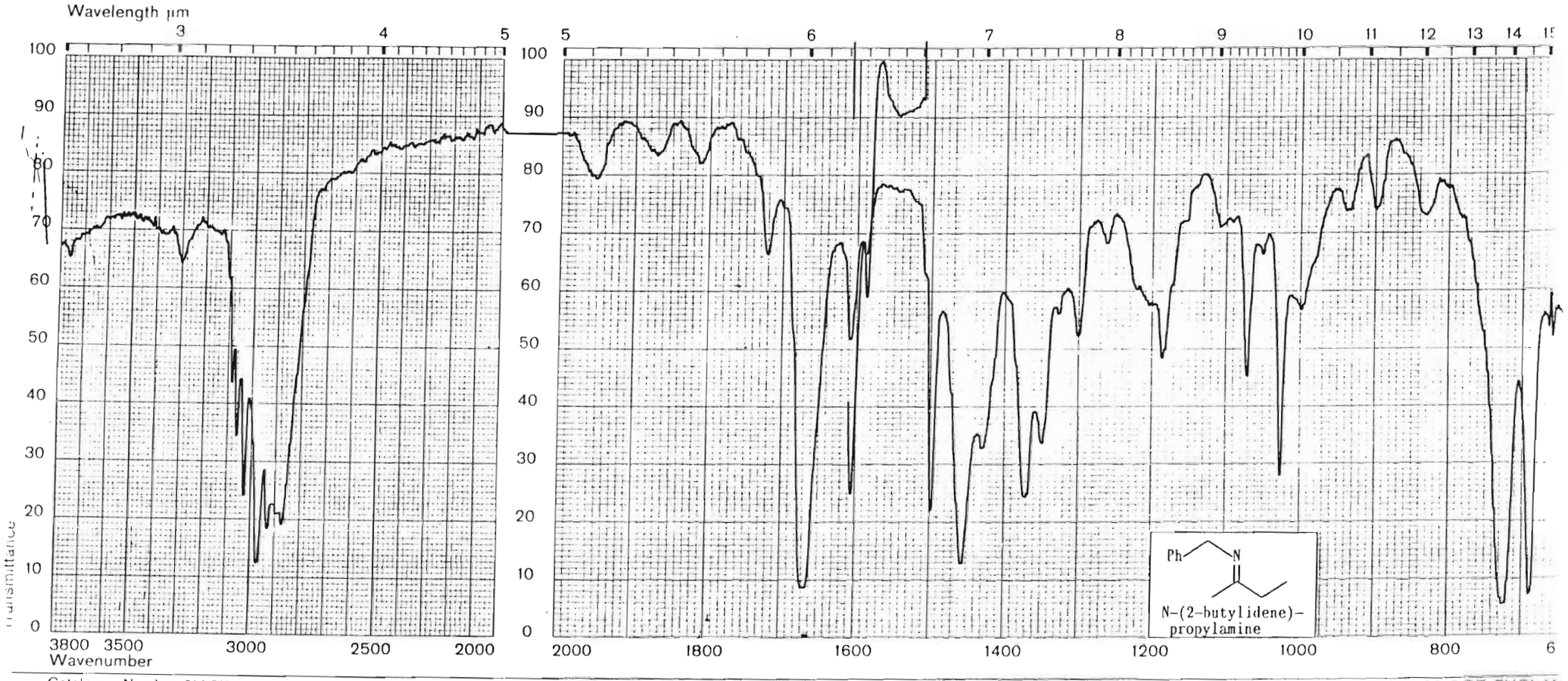
PYE UNICAM LTD CAMBRIDGE ENGLAND

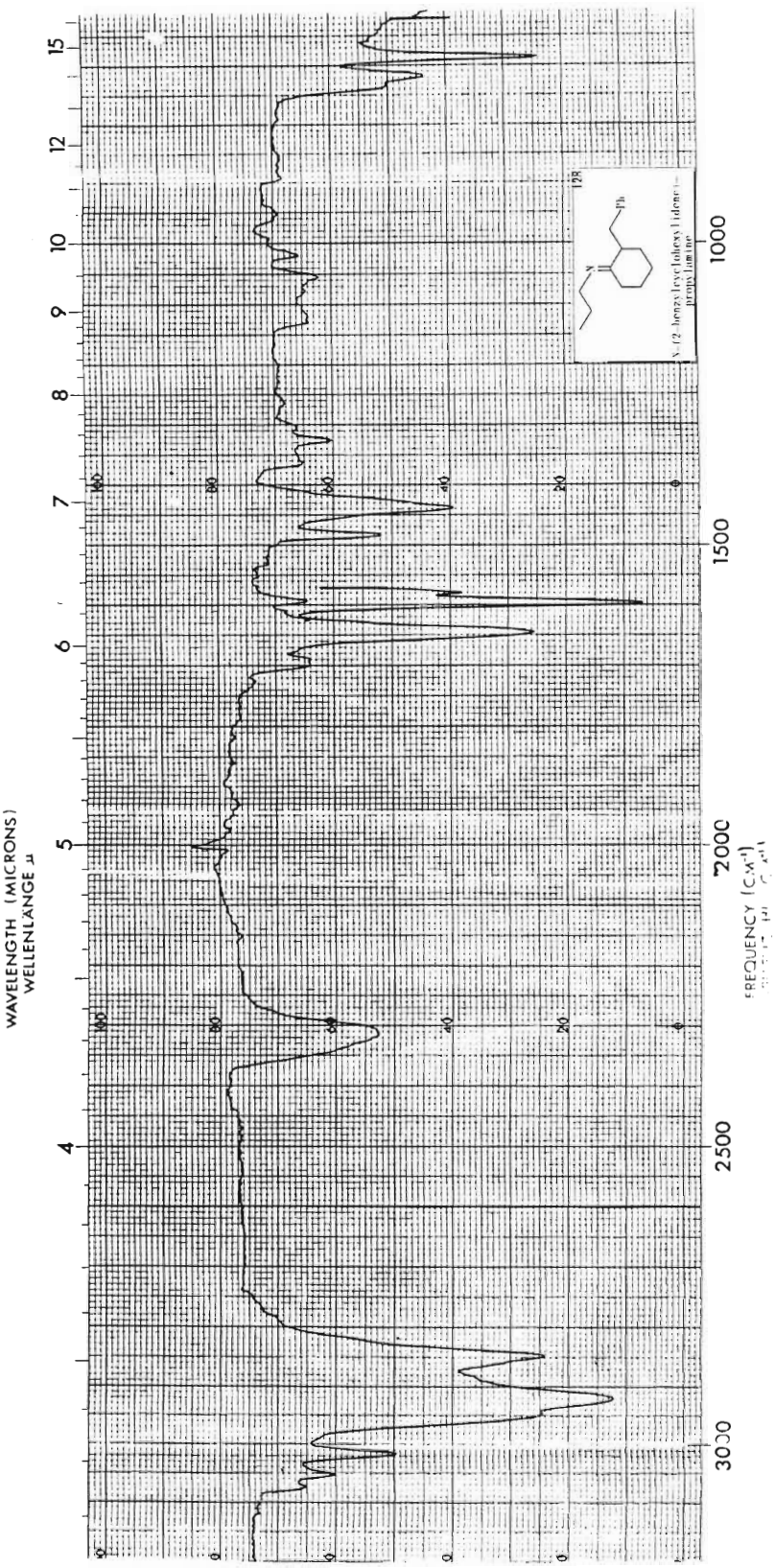

Wavelength μm
3
4
5
6
7
8
9
10
11
12
13
14
15
16
100
90
80
70
60
50
40
30
20
10
0
3800
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
625
Wavenumber
123
2-oxo-Δ4a,8a-octahydro-quinoline
Catalogue Number 614 211
PYE UNICAM LTD CAMBRIDGE ENGLAND

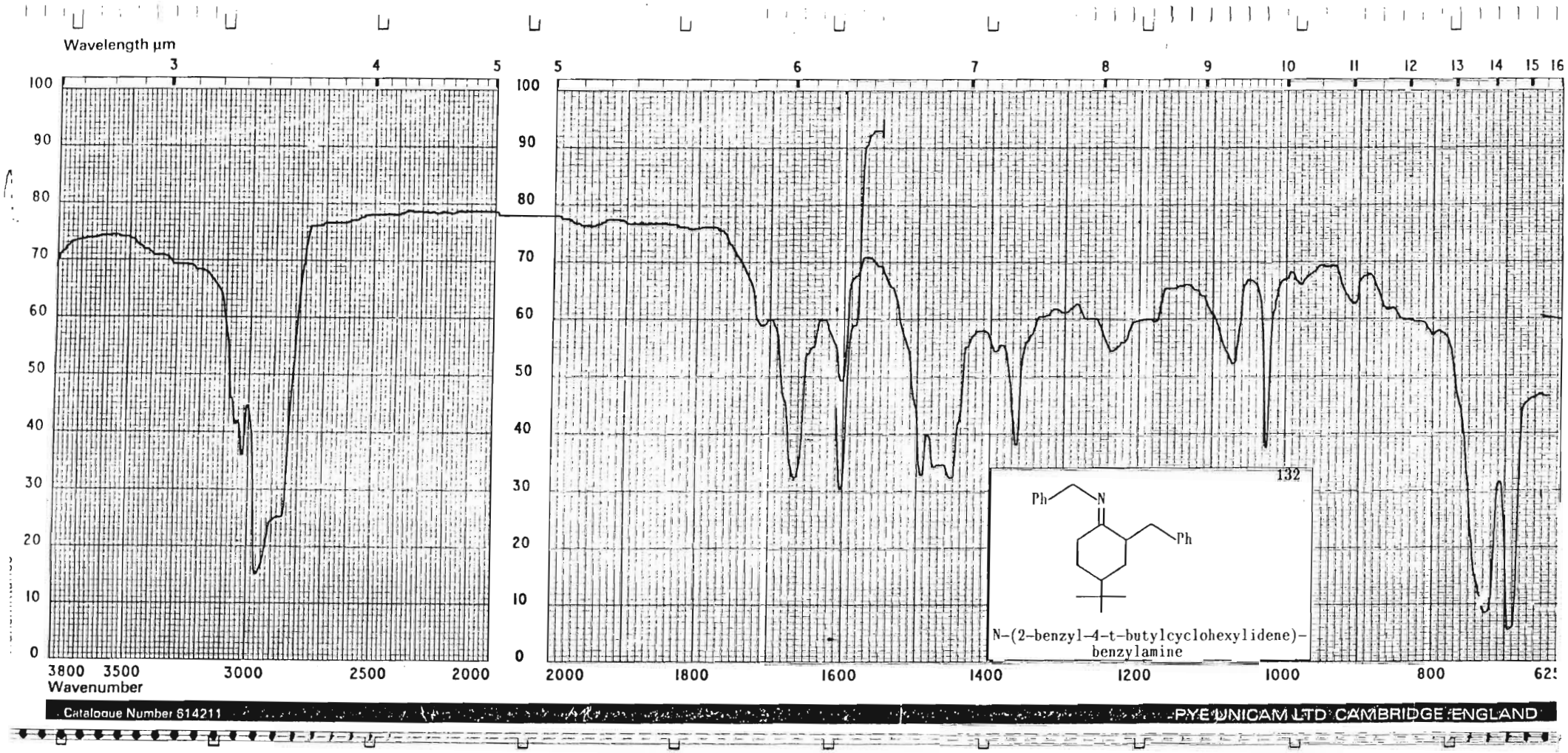

Wavelength μm
3
4
5
6
7
8
9
10
11
12
13
14
15
16
100
90
80
70
60
50
40
30
20
10
0
3800
3500
3000
2500
2000
1800
1600
1400
1200
800
625
Wavenumber
124
O
SO2Ph
SO2Ph
2,2-bis[2-phenylsulphonyl-
ethyl]cyclohexanone
Catalogue Number 614211
PYE UNICAM LTD. CAMBRIDGE ENGLAND

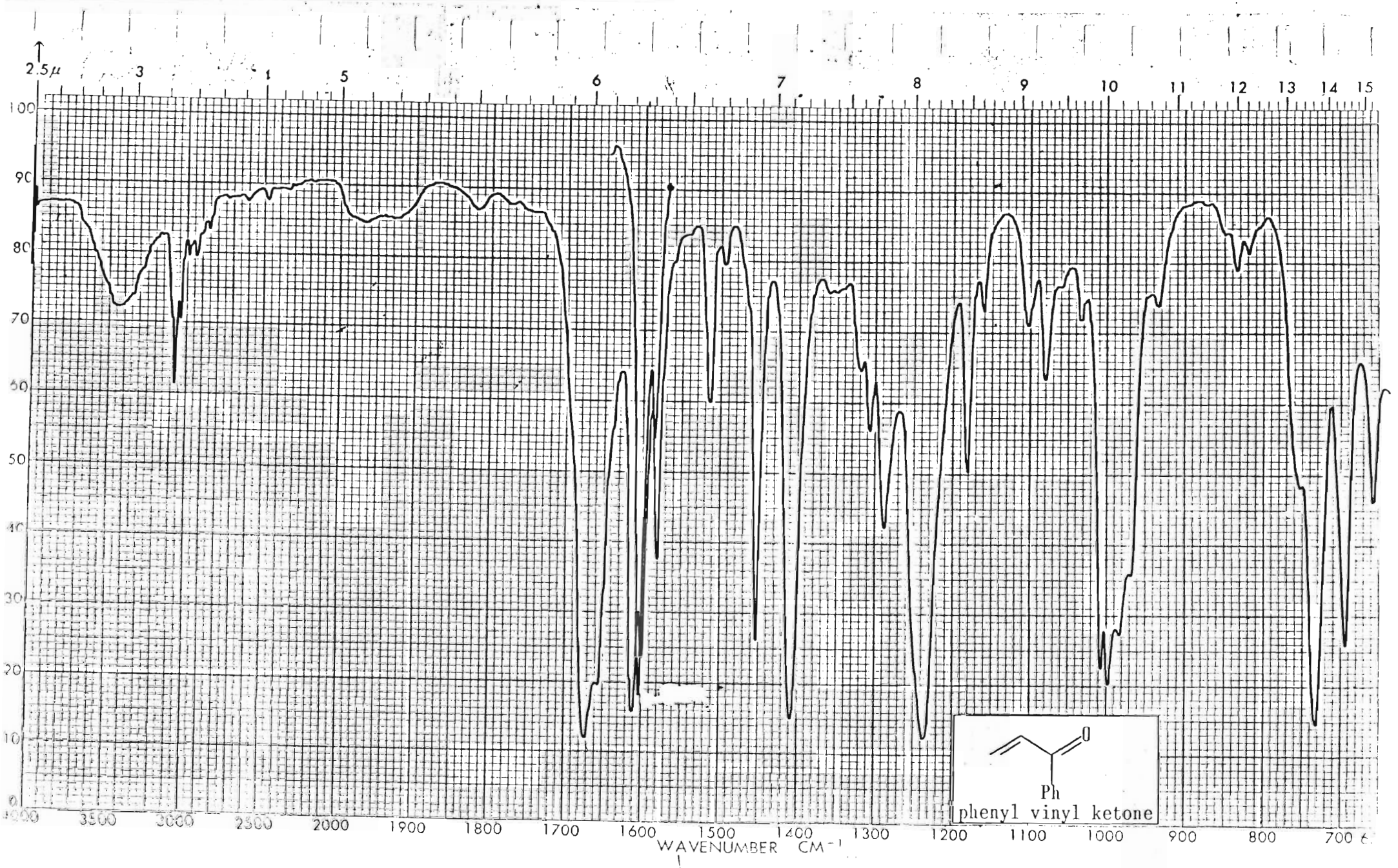

Wavelength µm
3
4
5
5
6
7
8
9
10
11
12
13
14
100
90
80
70
60
50
40
30
20
10
0
3800
3500
3000
2500
2000
Wavenumber
2000
1800
1600
1400
1200
1000
800
125
N
1-pyrrolidinylcyclohexene
Catalogue Number 614211
PYE UNICAM LTD. CAMBRIDGE, ENGLAND

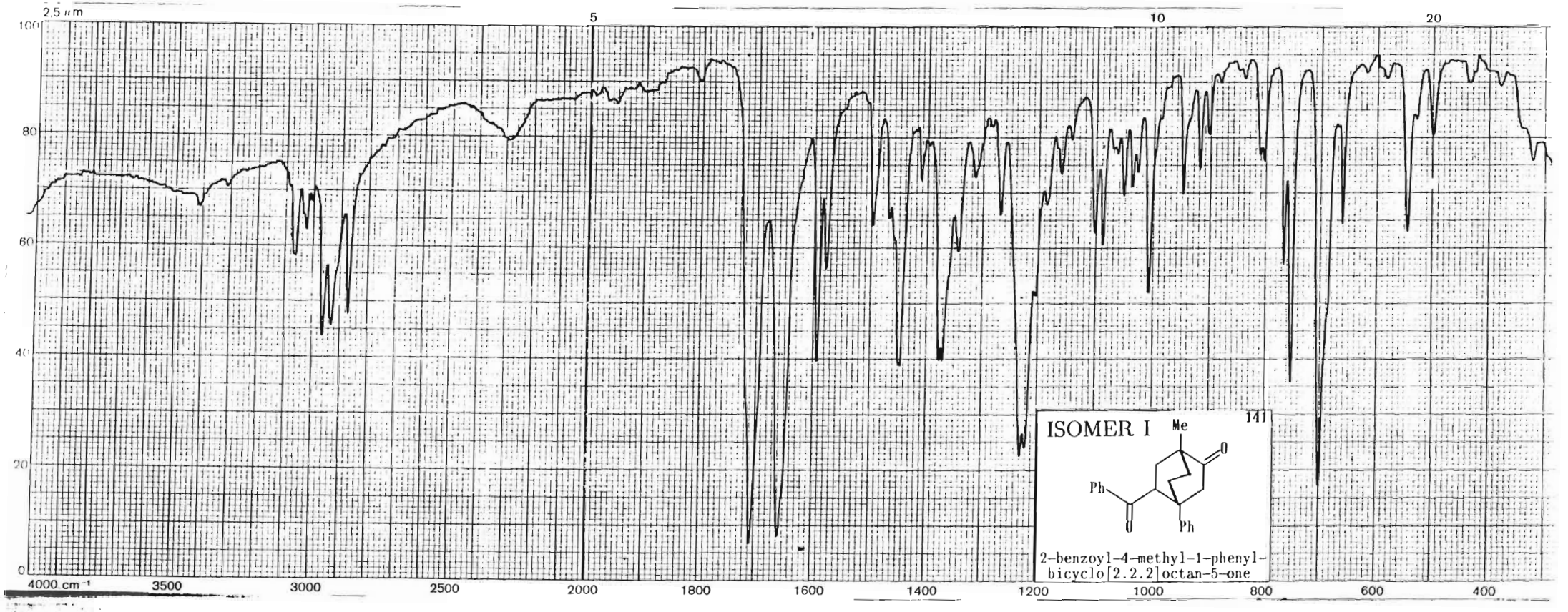

2.5μ
3
4
5
6
7
8
9
10
11
12
13
14
15
3500
3000
2500
2000
1900
1800
1700
1500
1300
1200
1100
1000
900
800
700
WAVENUMBER CM⁻¹
N
Ph
N-(1-phenyl-1-ethylid ene)
propylamine

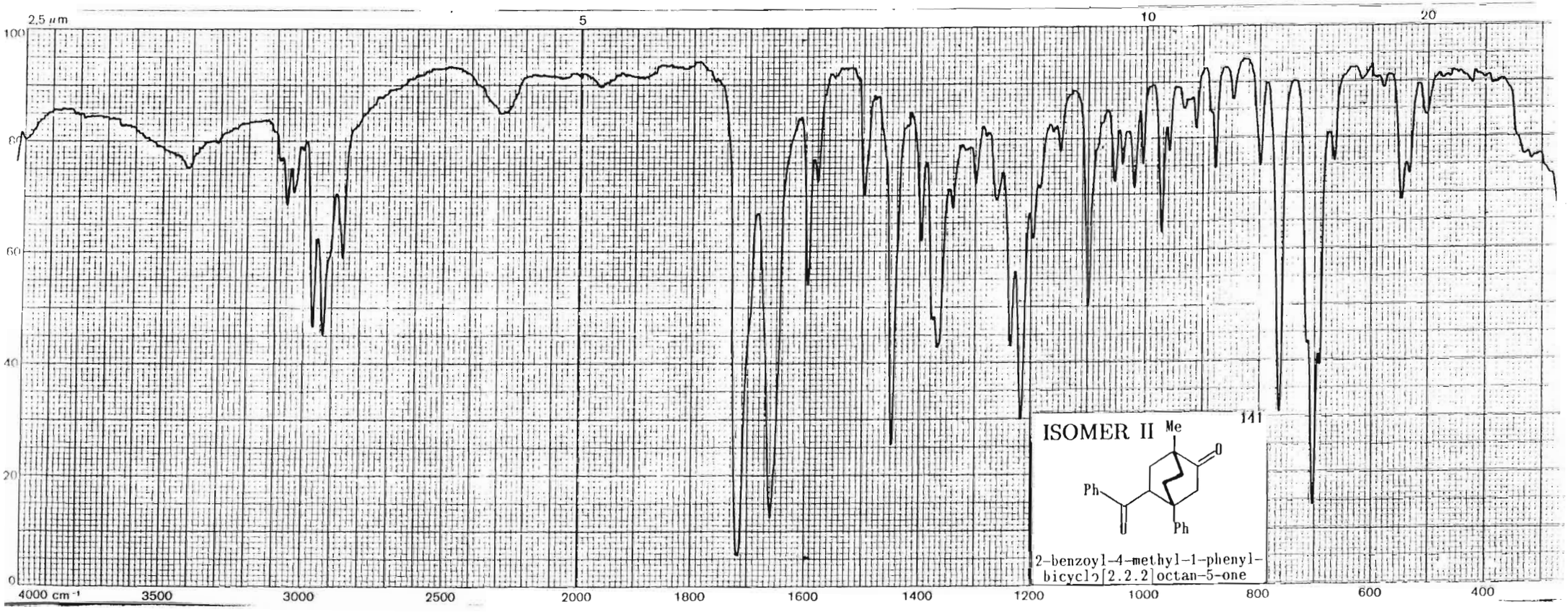

Wavelength μm
3
4
5
6
7
8
9
10
11
12
13
14
100
90
80
70
60
50
40
30
20
10
0
Transmittance
3800
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
Wavenumber
Ph
N
N-(2-butylidene)-
propylamine
Catalogue Number 614 211
PYE UNICAM LTD CAMBRIDGE ENGLAN


WAVELENGTH (MICRONS)
WELLENLÄNGE μ
FREQUENCY (CM⁻¹)
3000
2500
2000
1500
1000
15
12
10
9
8
7
6
5
4
100
80
60
40
20
0

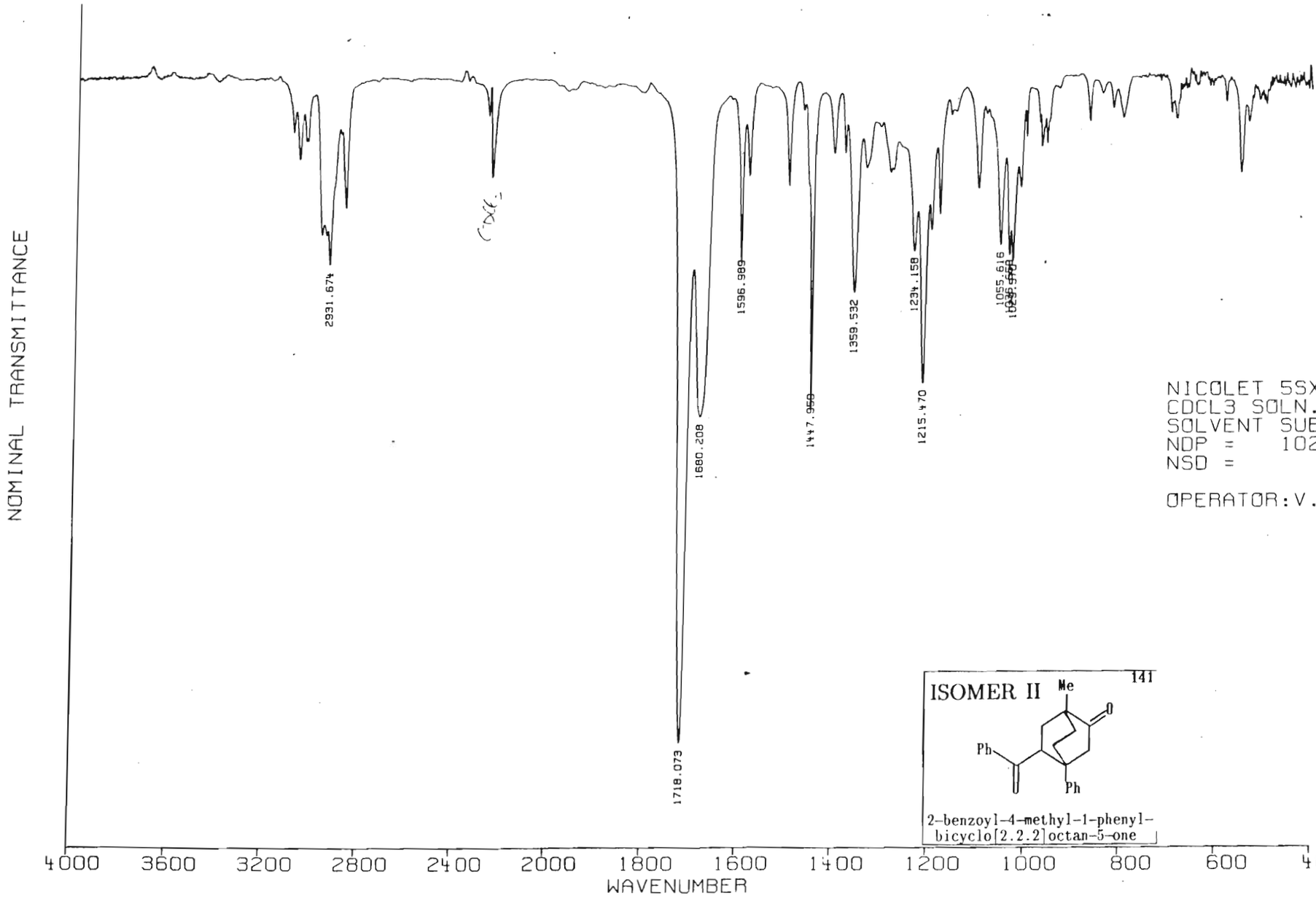

Wavelength µm
3
4
5
6
7
8
9
10
11
12
13
14
15
16
100
90
80
70
60
50
40
30
20
10
0
3800
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
Wavenumber
132
Ph
N
Ph
N-(2-benzyl-4-t-butylcyclohexylidene)-benzylamine
Catalogue Number 614211
PYE UNICAM LTD CAMBRIDGE ENGLAND


2.5μ
3
4
5
6
7
8
9
10
11
12
13
14
15
100
90
80
70
60
50
40
30
20
10
0
4000
3500
3000
2500
2000
1900
1800
1700
1600
1500
1400
1300
1200
1100
1000
900
800
700
WAVENUMBER CM⁻¹
O
Ph
phenyl vinyl ketone


2.5 μm
5
10
20
100
80
60
40
20
0
4000 cm⁻¹
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
ISOMER I
141
Me
O
Ph
O
Ph
2-benzoyl-4-methyl-1-phenyl-
bicyclo[2.2.2]octan-5-one


2,5 µm
5
10
20
100
80
60
40
20
0
4000 cm⁻¹
3500
3000
2500
2000
1800
1600
1400
1200
1000
800
600
400
141
ISOMER II
Me
O
Ph
Ph
2-benzoyl-4-methyl-1-phenyl-
bicyclo[2.2.2]octan-5-one

CSN = 0
418/17/20
11/25/88 11:20:43

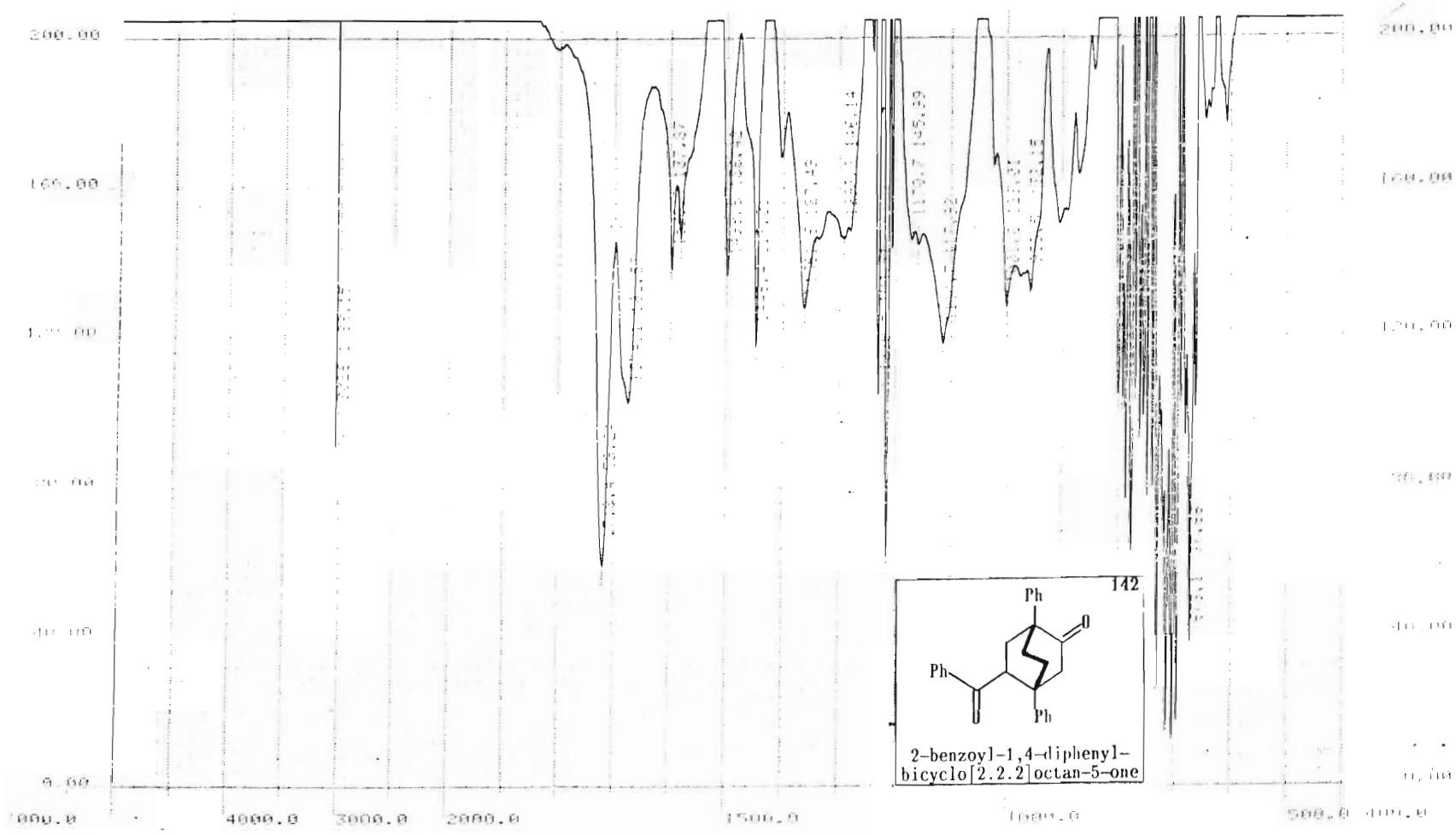


NICOLET 5SXC FTIR
CDCL3 SOLN. 0.1MM CELL
SOLVENT SUBTRACTED
NDP = 10240
NSD = 16

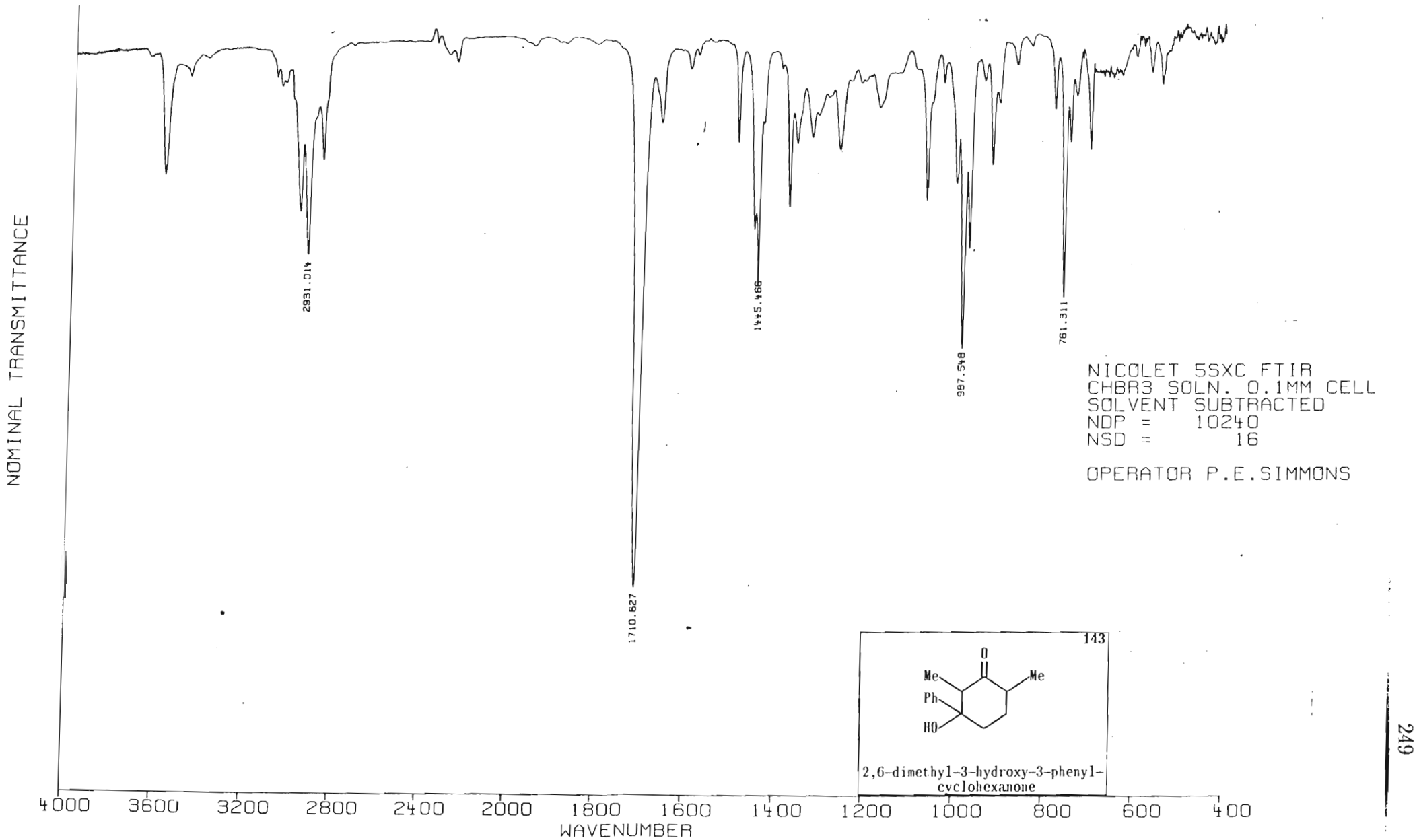
OPERATOR:V.E.WILSON

2-benzoyl-4-methyl-1-phenyl-bicyclo[2.2.2]octan-5-one

1. BR 428



CSN = 135582
423B
11/09/89 15:16:10



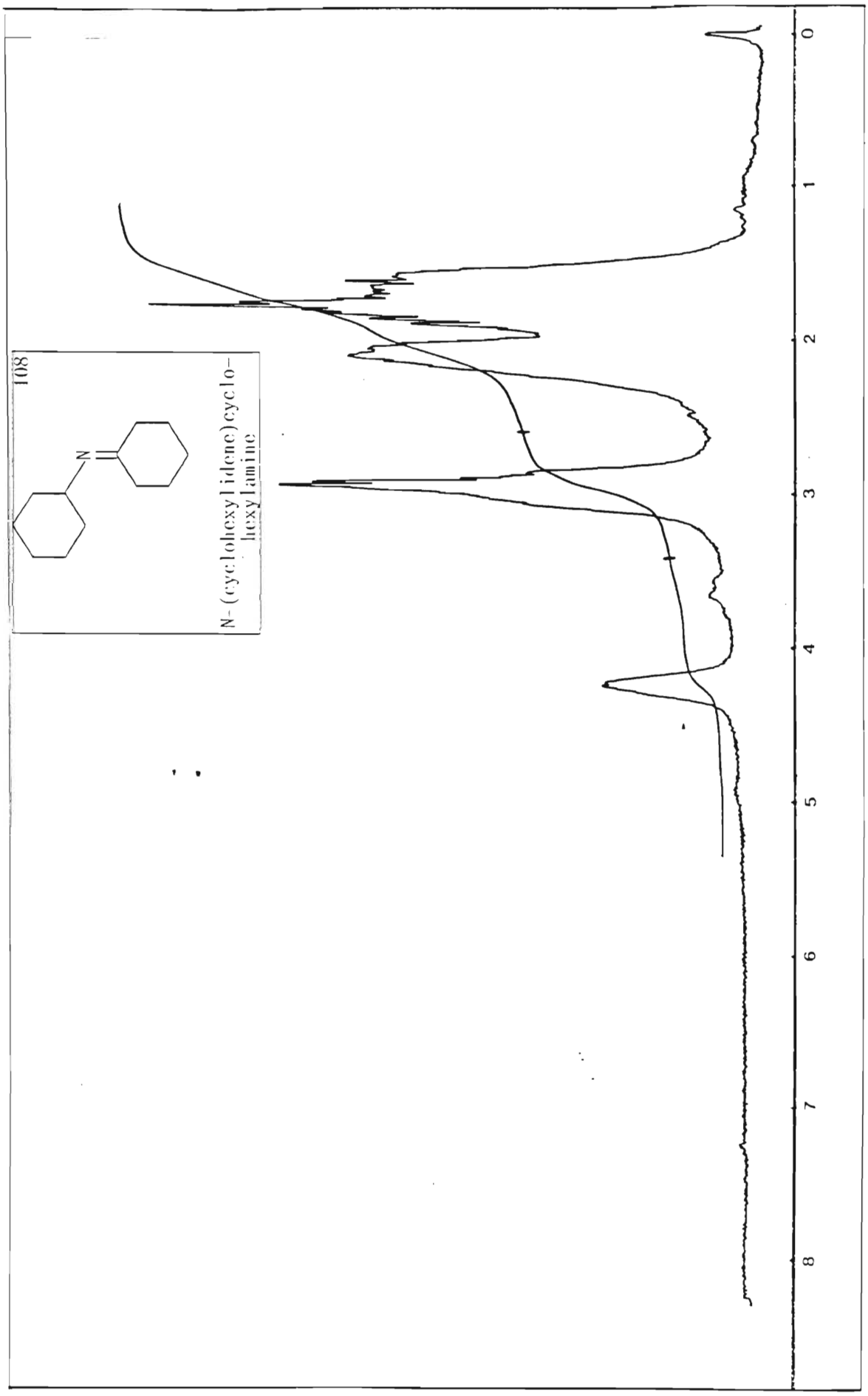
NICOLET 5SXC FTIR
CHBR3 SOLN. 0.1MM CELL
SOLVENT SUBTRACTED
NDP = 10240
NSD = 16

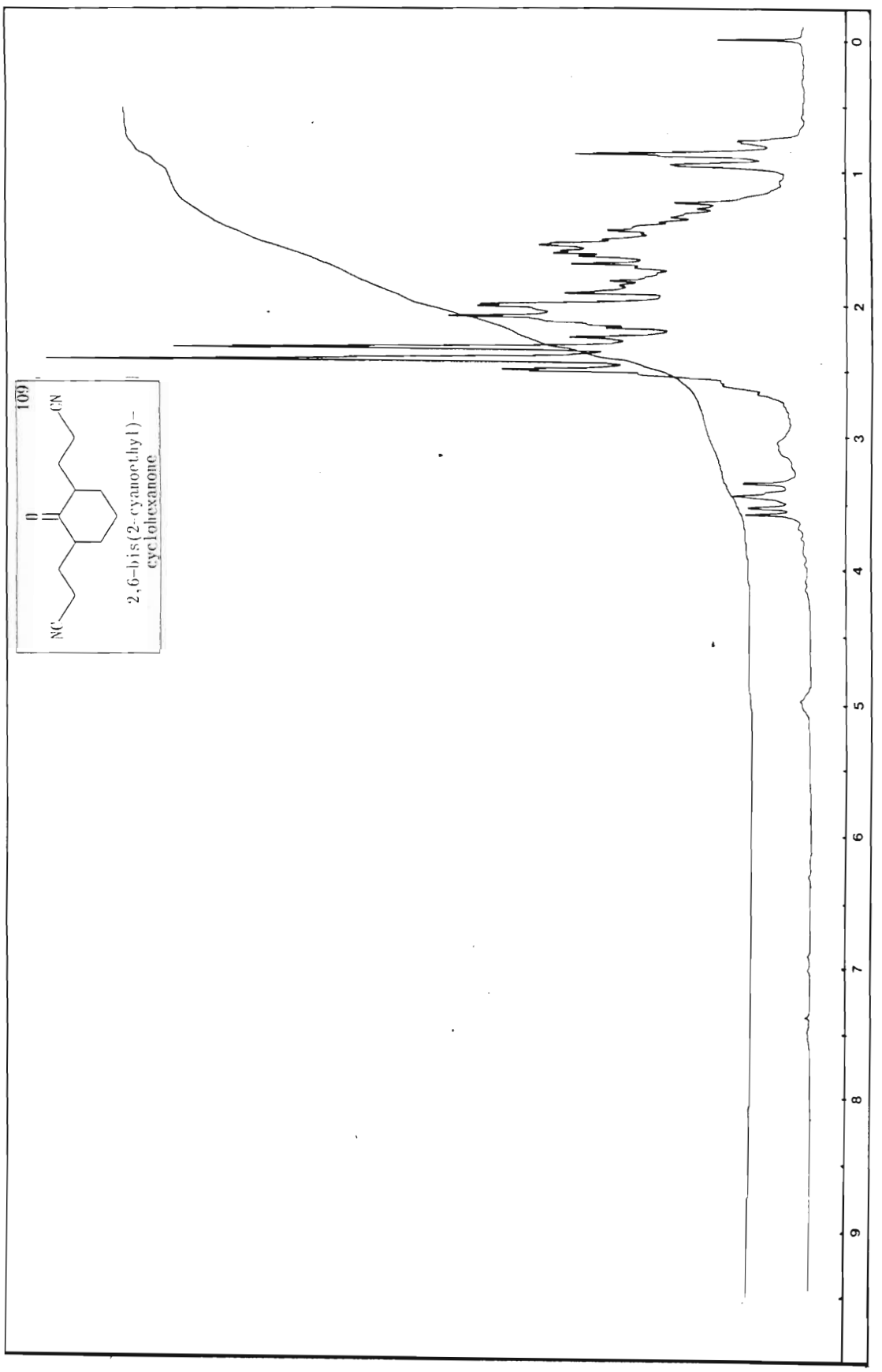
OPERATOR P.E.SIMMONS

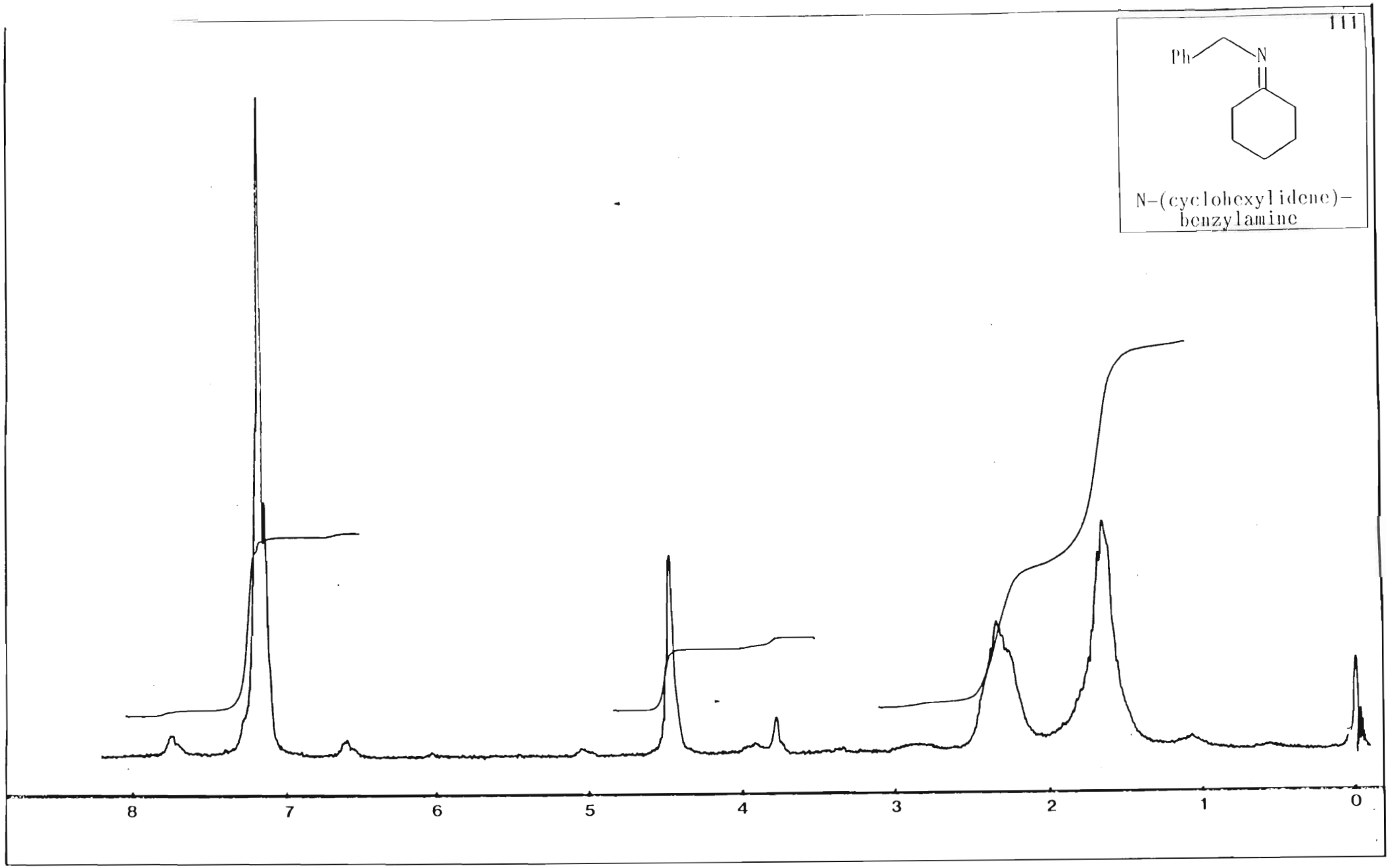
143

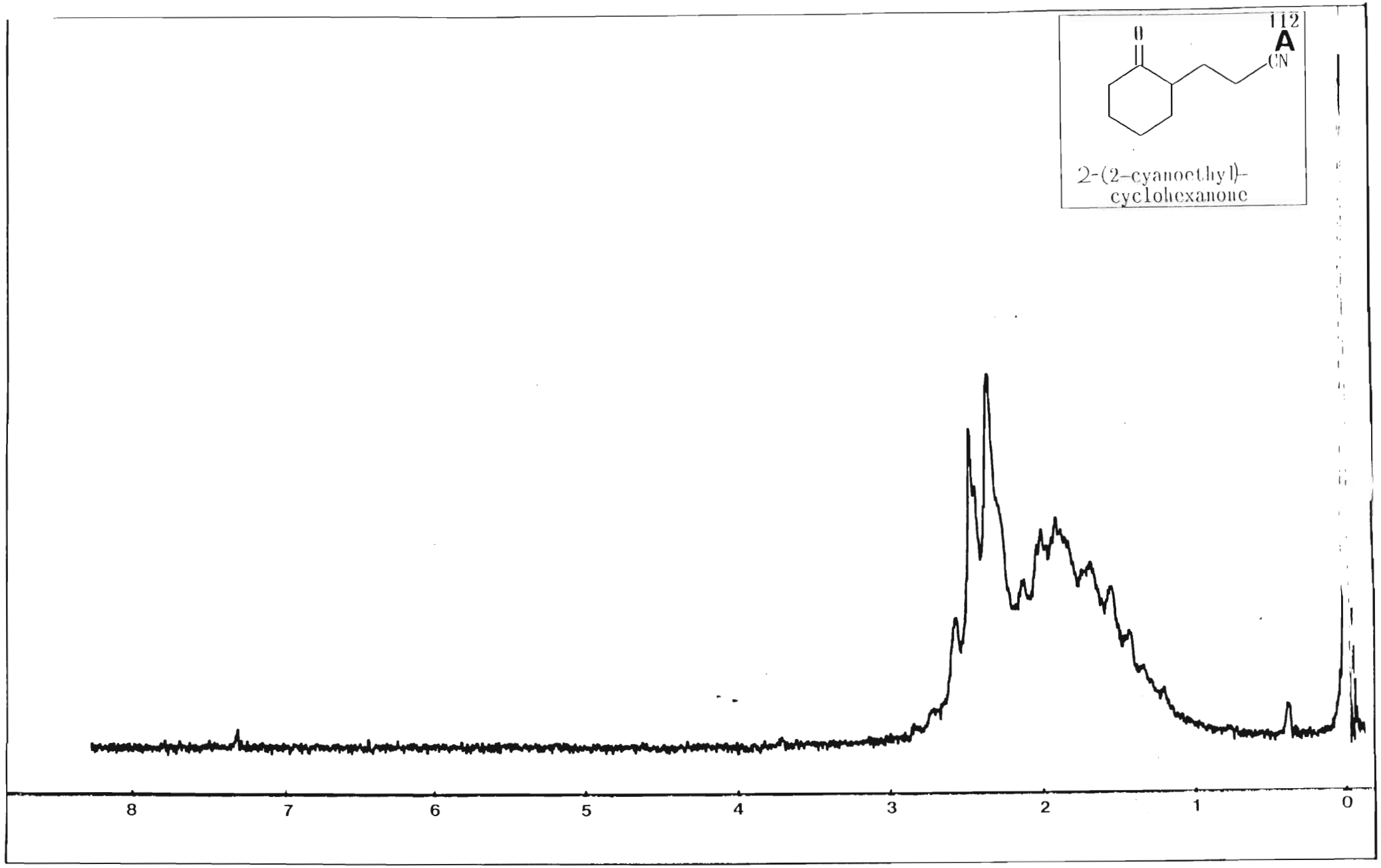
2,6-dimethyl-3-hydroxy-3-phenyl-cyclohexanone

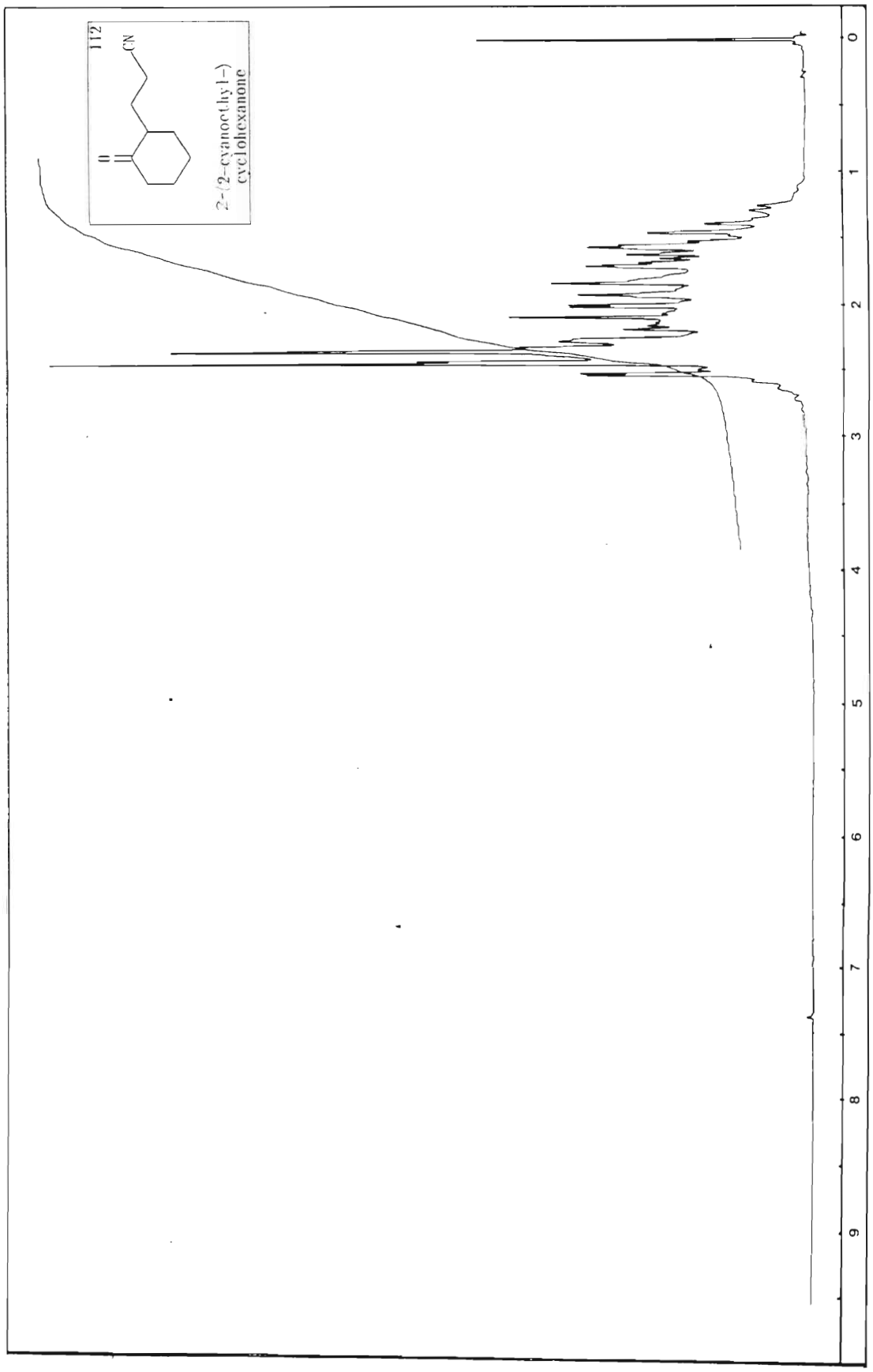
3.2 ^{1}H–NMR SPECTRA

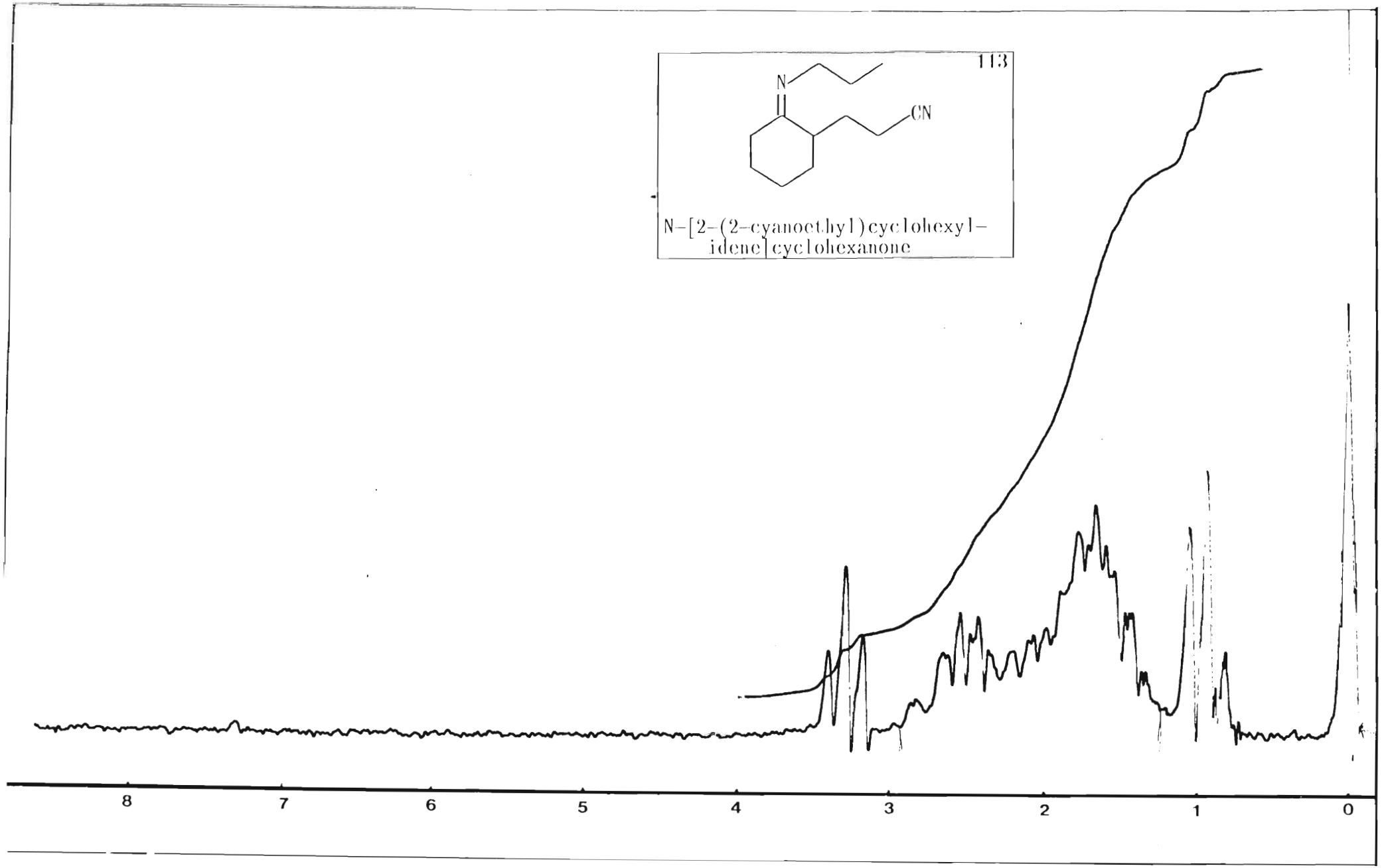

108
N-(cyclohexylidene)cyclo-
hexylamine
0
1
2
3
4
5
6
7
8

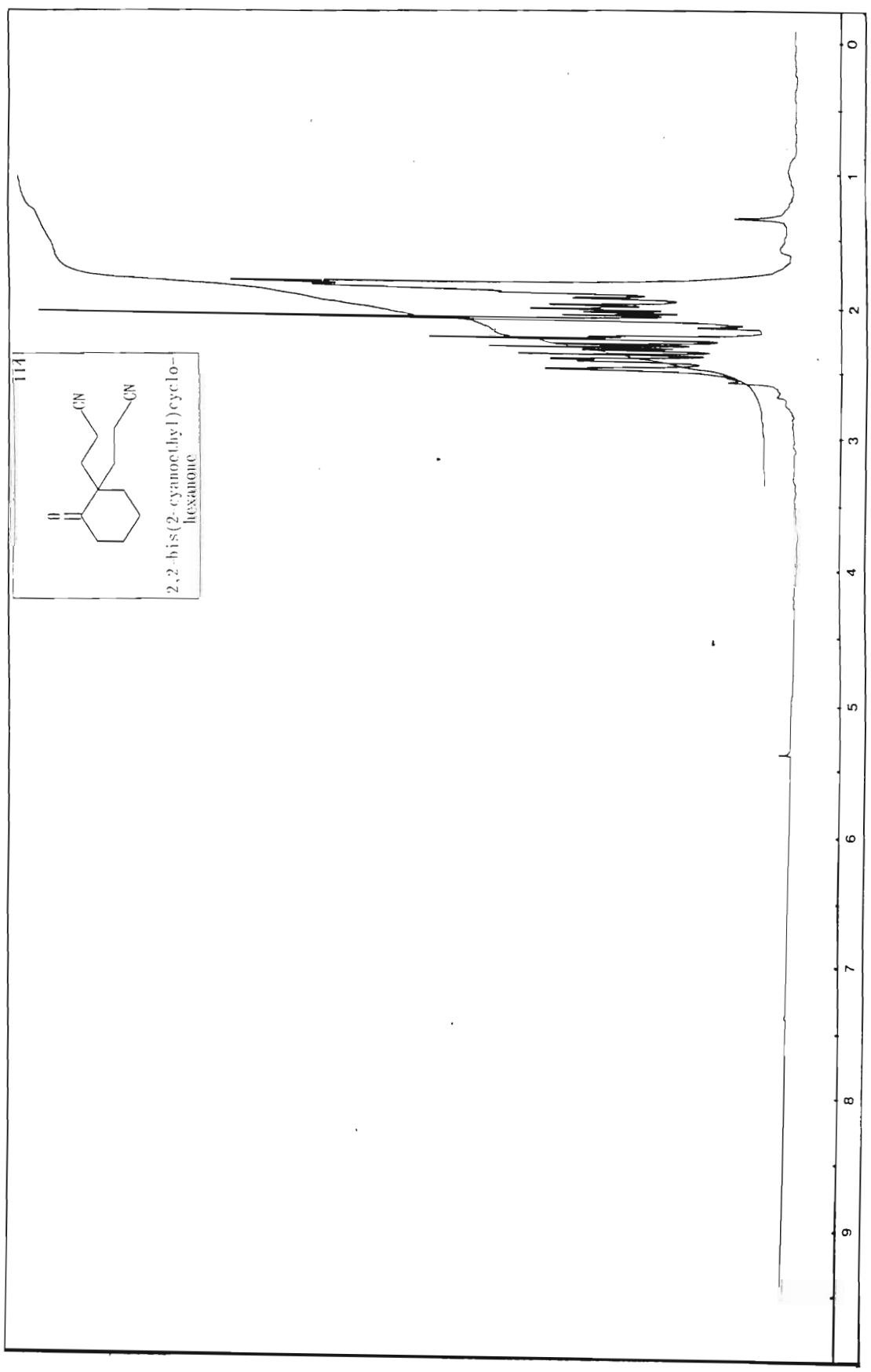

109
NC
CN
O
2,6-bis(2-cyanoethyl)-
cyclohexanone
9
8
7
6
5
4
3
2
1
0

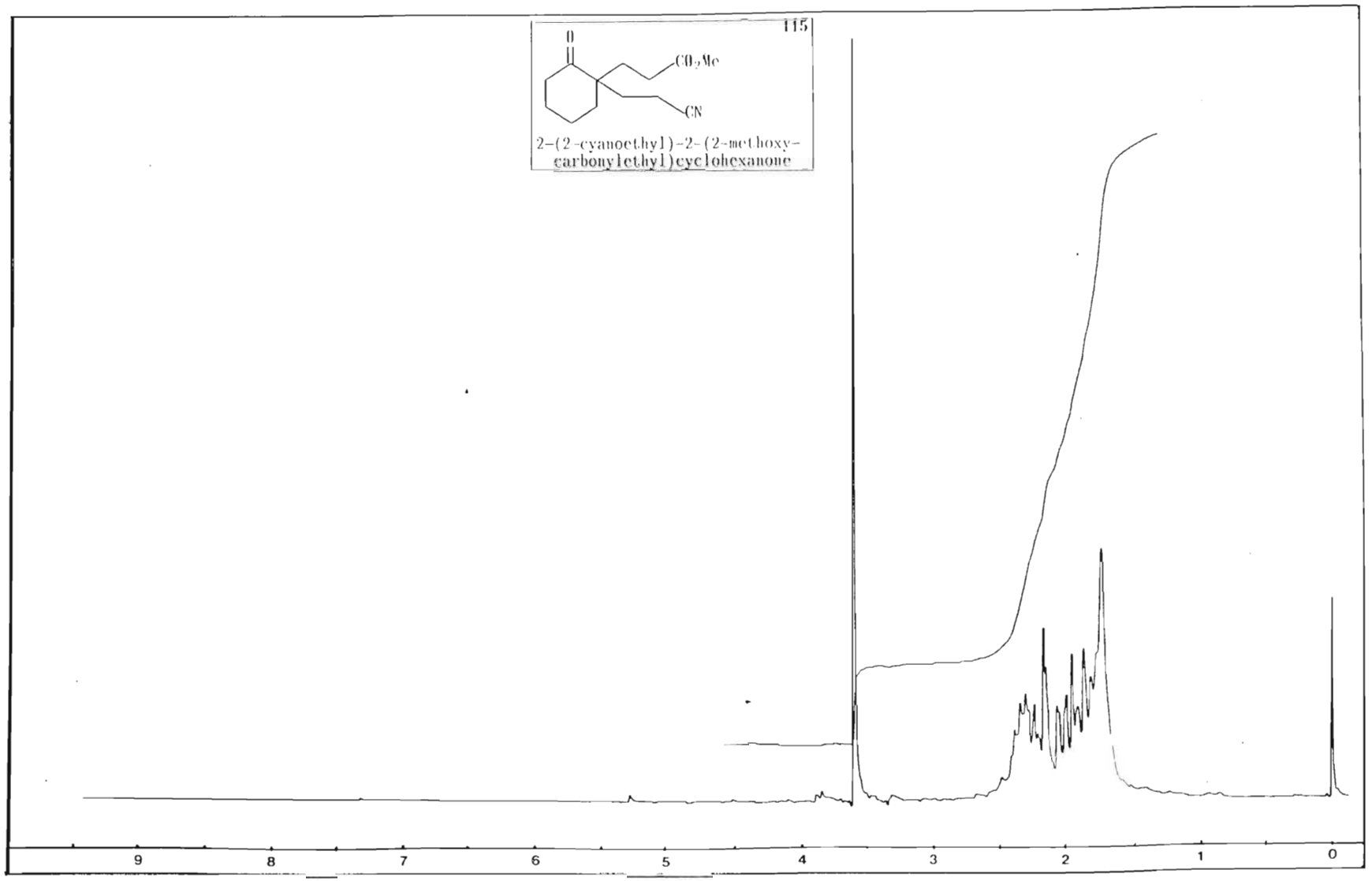

111
Ph
N
N-(cyclohexylidene)-
benzylamine
8
7
6
5
4
3
2
1
0

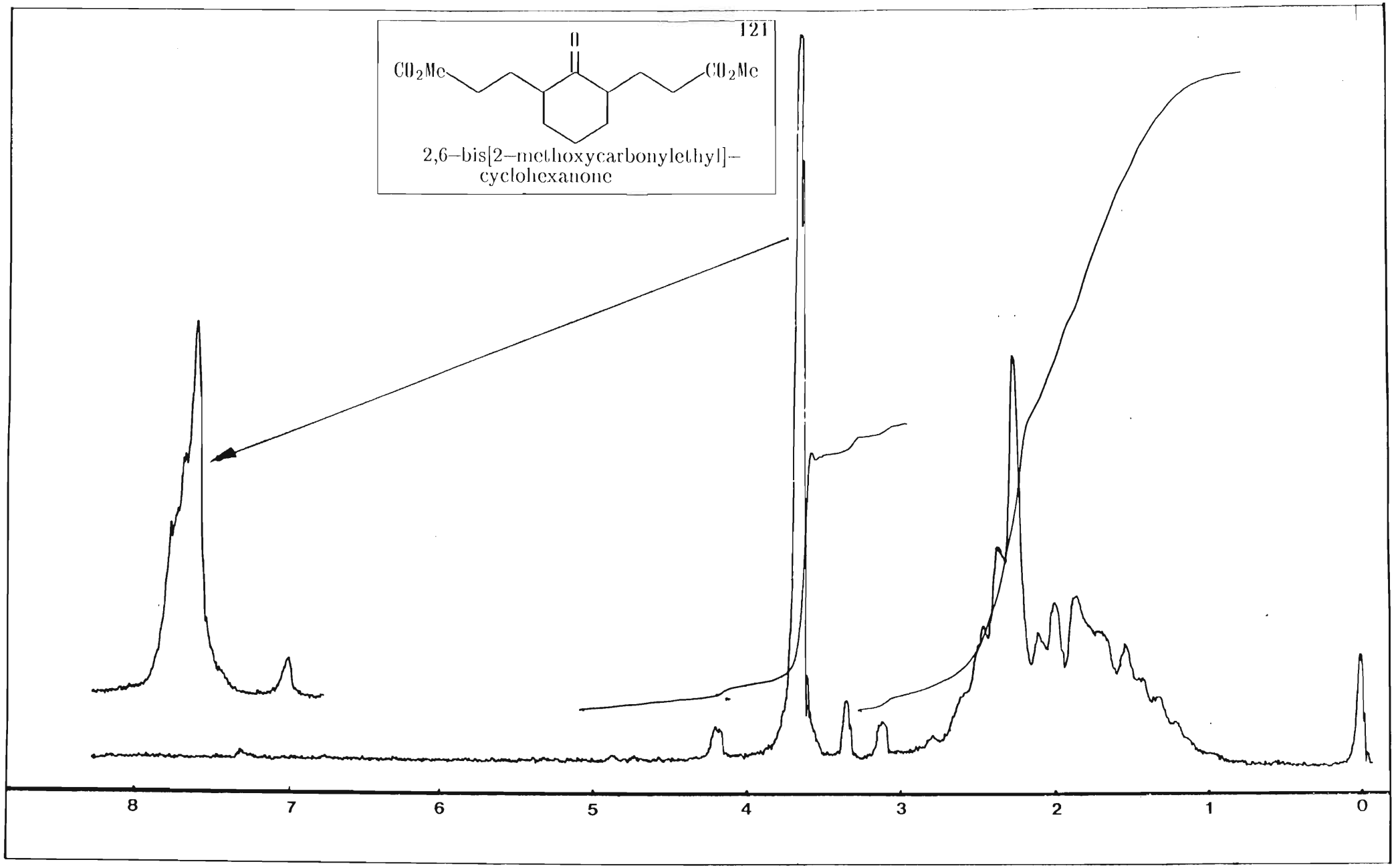

112
A
CN
2-(2-cyanoethyl)-
cyclohexanone
8
7
6
5
4
3
2
1
0

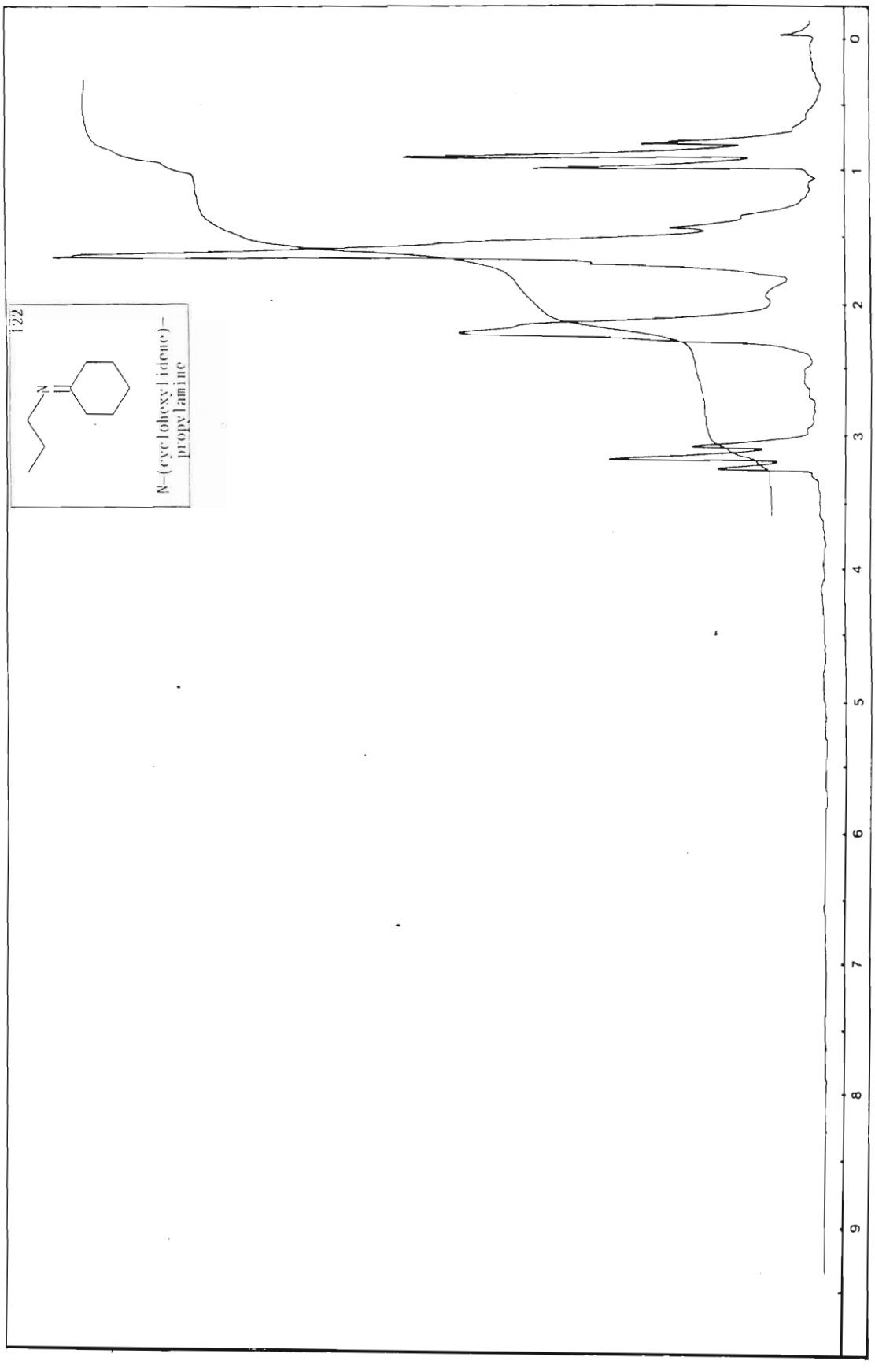

112
CN
2-(2-cyanoethyl-)
cyclohexanone
0
1
2
3
4
5
6
7
8
9

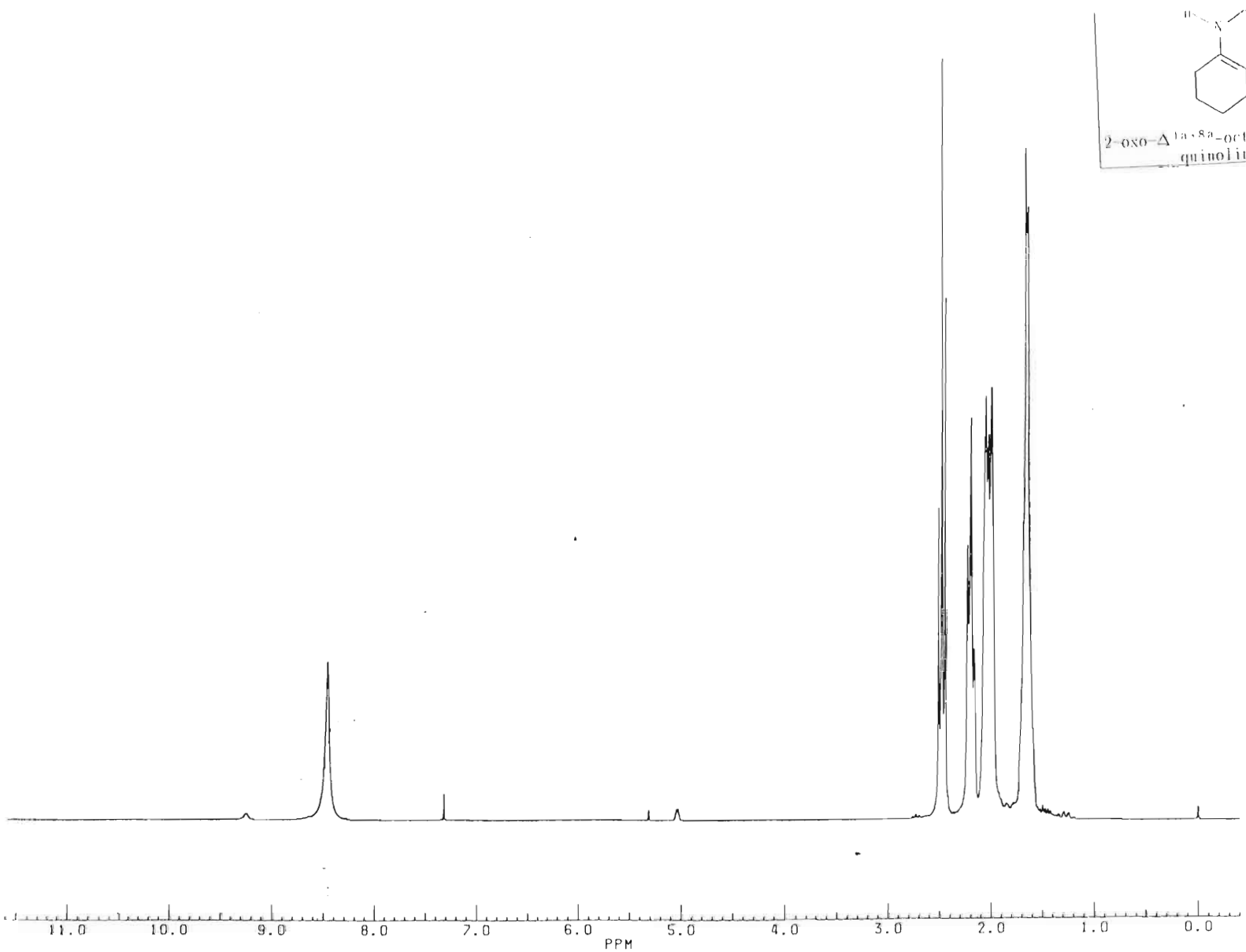

113
N
CN
N-[2-(2-cyanoethyl)cyclohexyl-idene]cyclohexanone
8
7
6
5
4
3
2
1
0

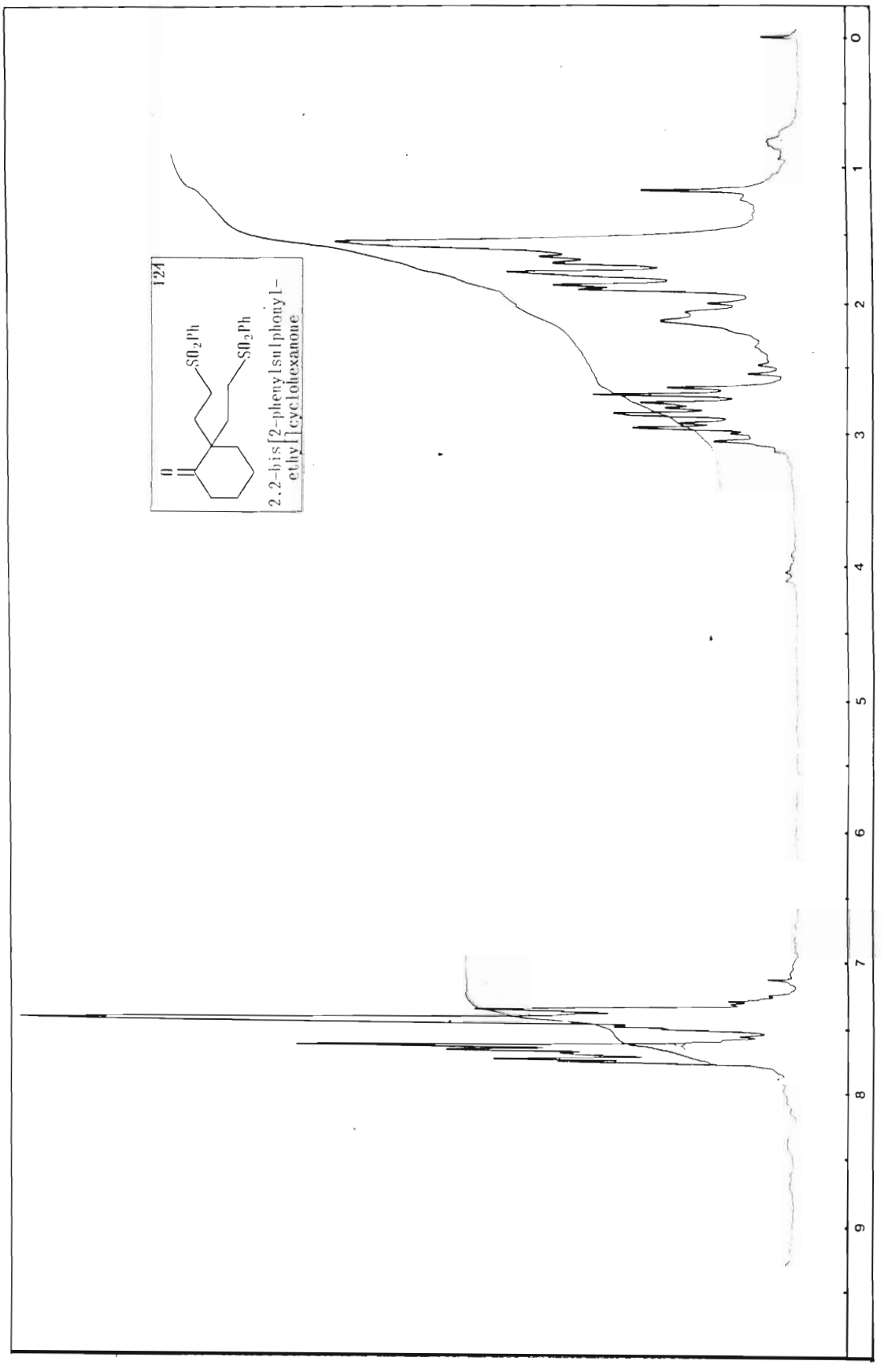

111
CN
CN
O
2,2 bis(2-cyanoethyl)cyclo-
hexanone
0
1
2
3
4
5
6
7
8
9

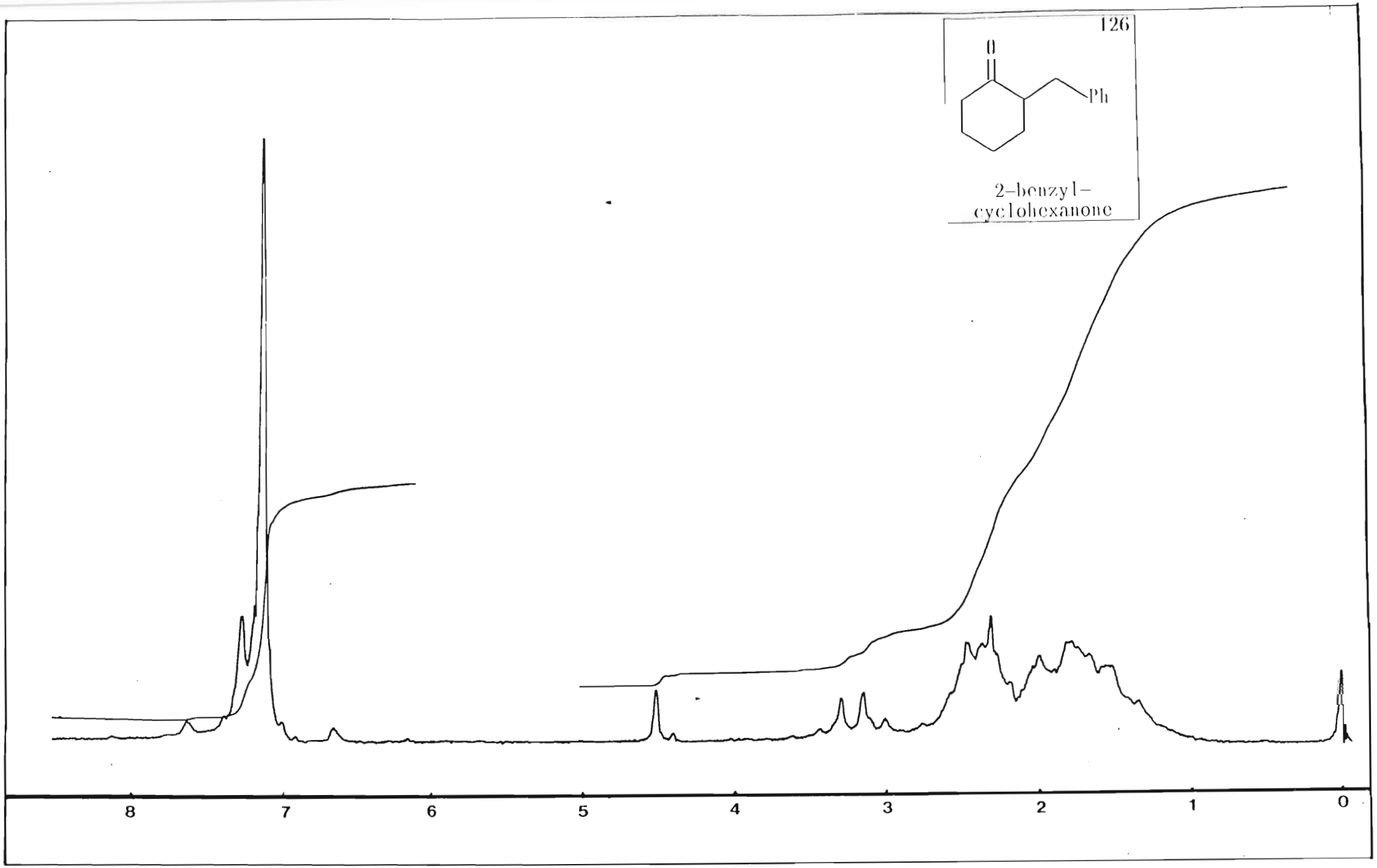

115
O
CO2Me
CN
2-(2-cyanoethyl)-2-(2-methoxy-carbonylethyl)cyclohexanone
9
8
7
6
5
4
3
2
1
0

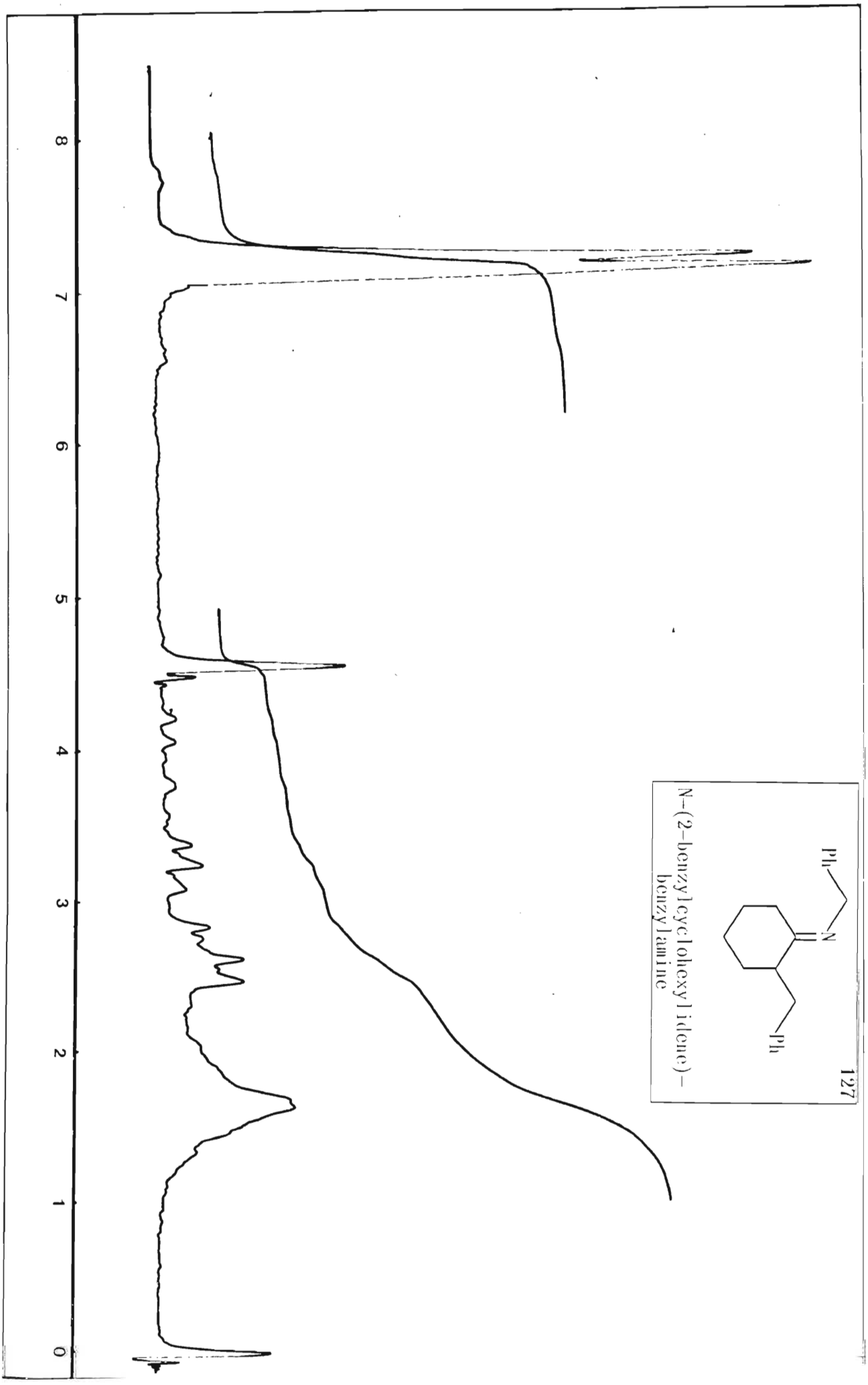

121
CO_2Me
CO_2Me
2,6–bis[2–methoxycarbonylethyl]–
cyclohexanone
8
7
6
5
4
3
2
1
0

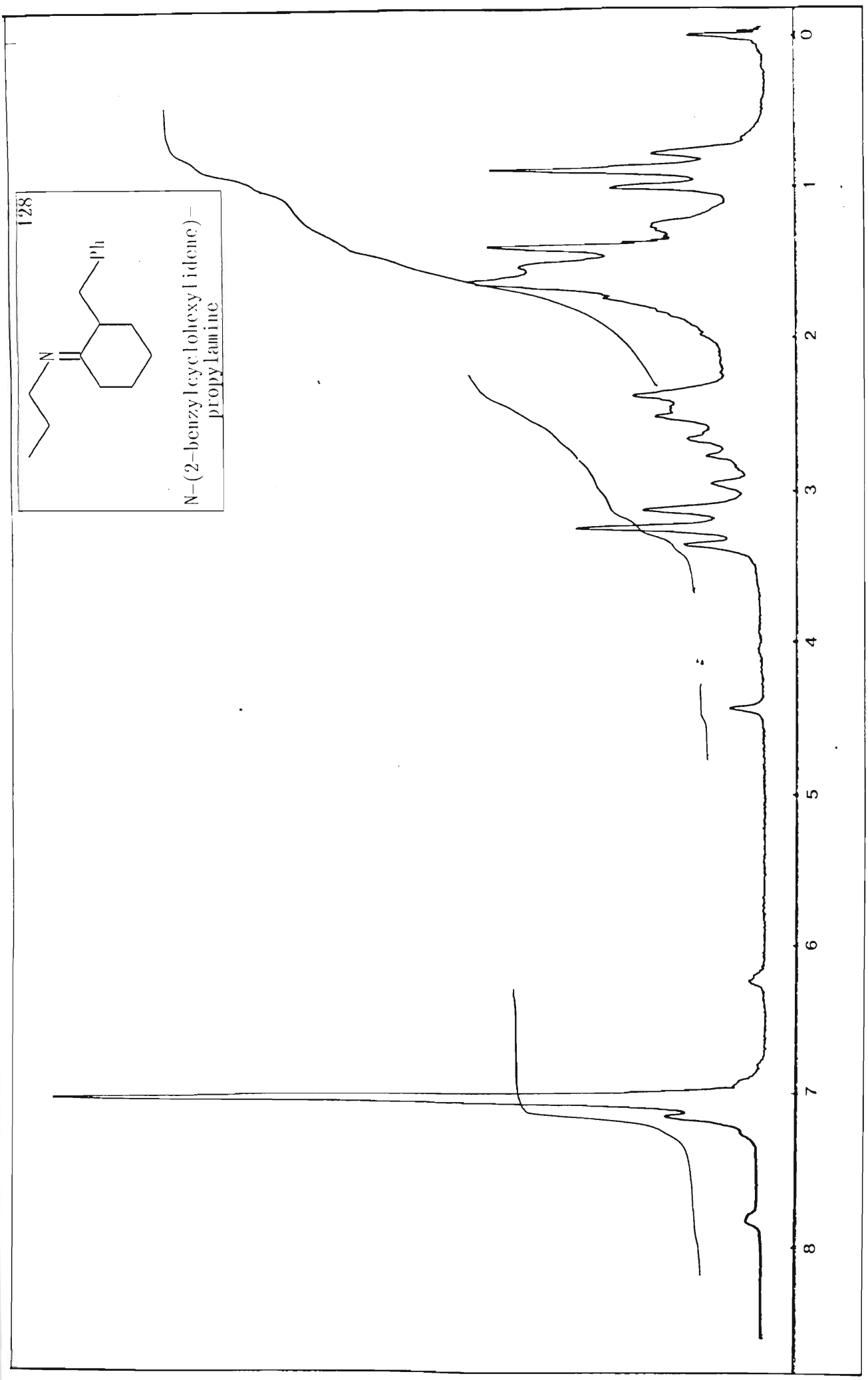

122
N-(cyclohexylidene)-propylamine
9
8
7
6
5
4
3
2
1
0

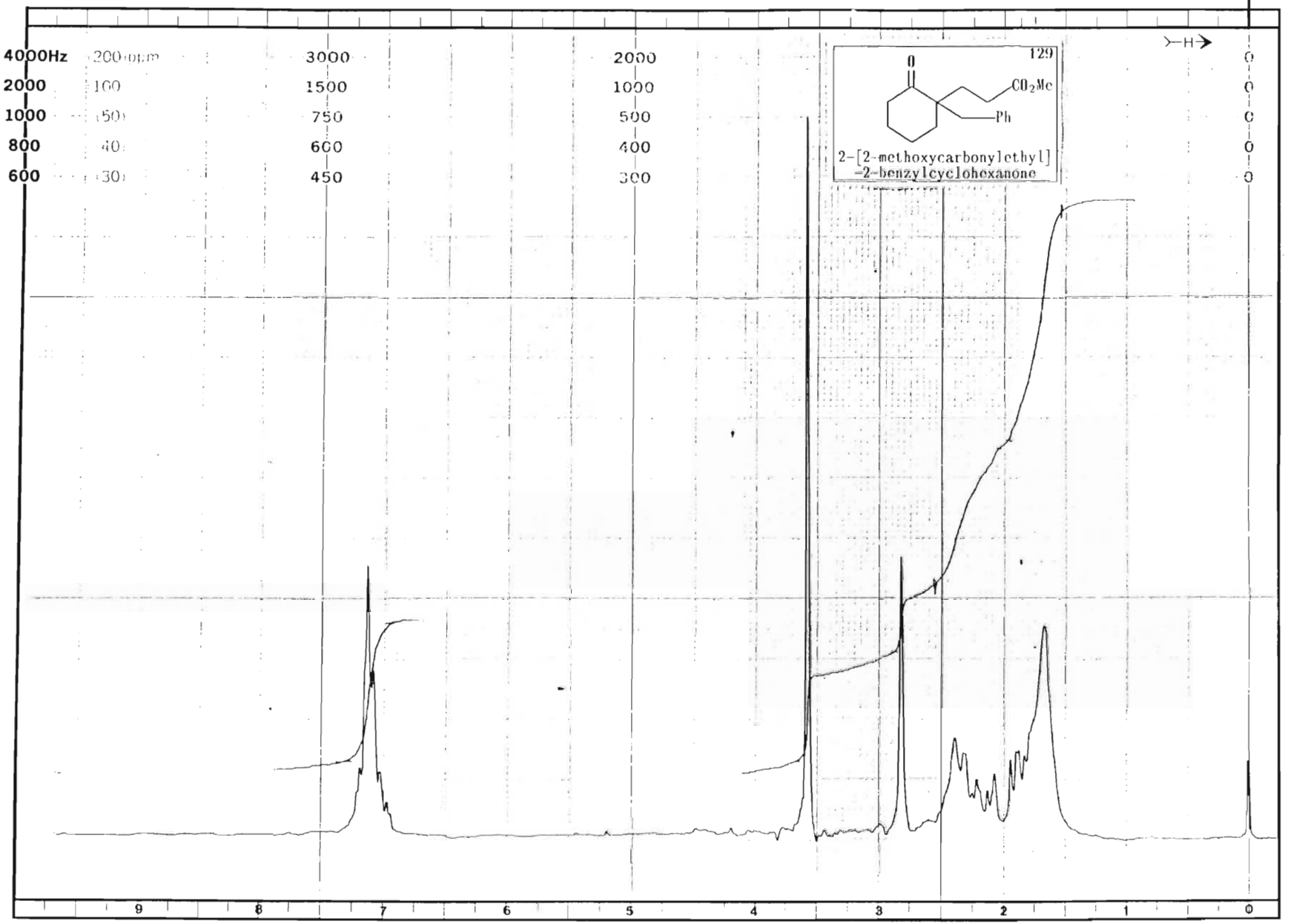

2-oxo-Δ1a,8a-octahydro-quinoline
BRUKER
BR1.001
DATE 27-10-86
TIME 14:09
SOLVENT CDCl3
SF 250.133
O1 4500.000
SI 16384
SW 5000.000
HZ/PT .610
PW 2.0
RD 2.000
RG 8
NS 49
LB .500
CX 30.00
CY 0.0
PPM/CM .400
SR 2840.45
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

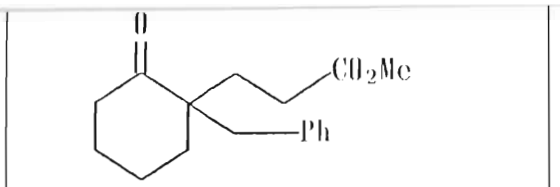

124
SO_2Ph
SO_2Ph
O
2,2-bis[2-phenylsulphonyl-ethyl]cyclohexanone
0
1
2
3
4
5
6
7
8
9


126
O
Ph
2-benzyl-
cyclohexanone
8
7
6
5
4
3
2
1
0


Ph
N
Ph
127
N-(2-benzylcyclohexylidene)-benzylamine
8
7
6
5
4
3
2
1
0

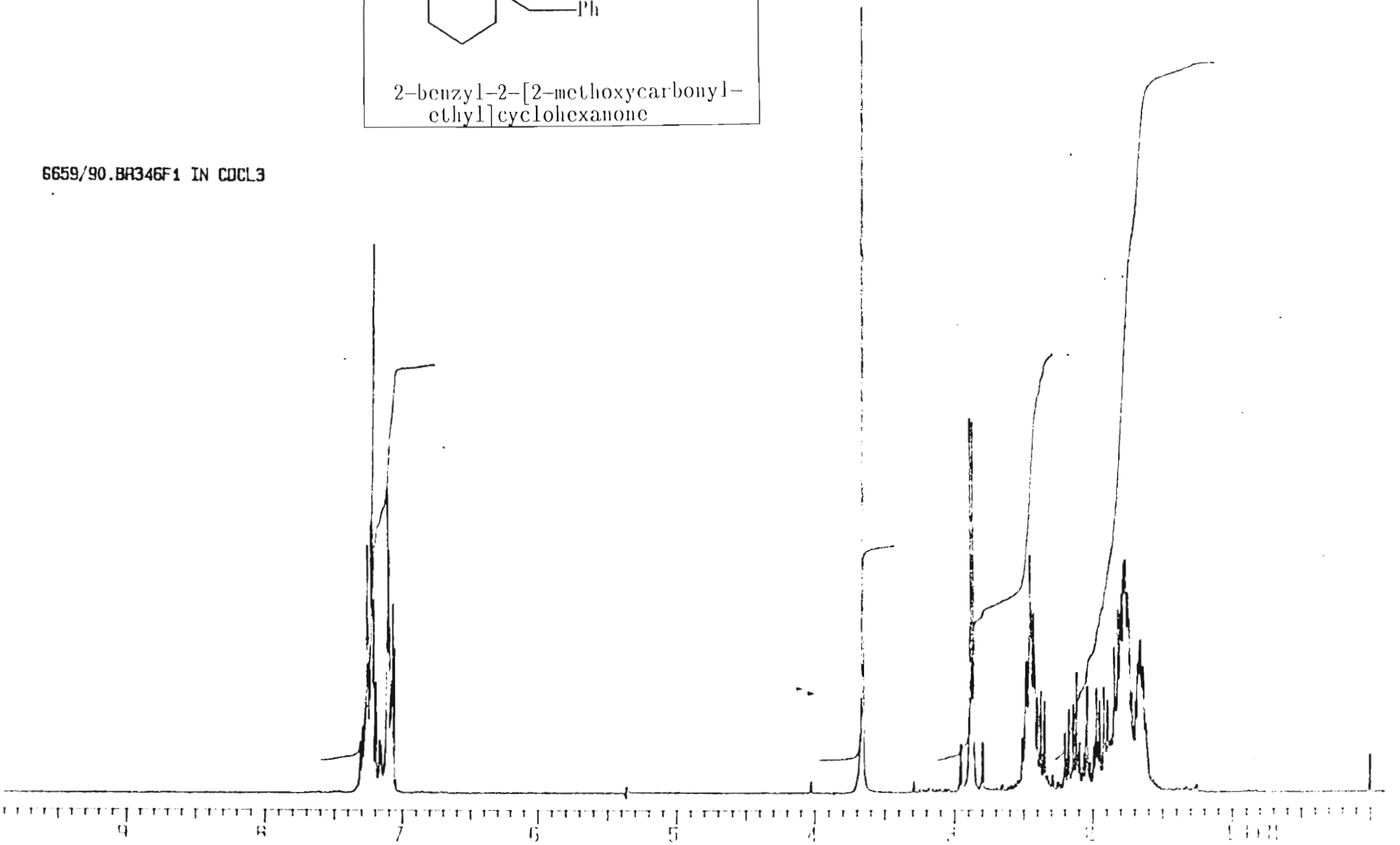

128
N
Ph
N-(2-benzylcyclohexylidene)-
propylamine
0
1
2
3
4
5
6
7
8


4000Hz
2000
1000
800
600
200 ppm
100
50
40
30
3000
1500
750
600
450
2000
1000
500
400
300
129
O
CO_2Me
Ph
2-[2-methoxycarbonylethyl]
-2-benzylcyclohexanone
H
9
8
7
6
5
4
3
2
1
0

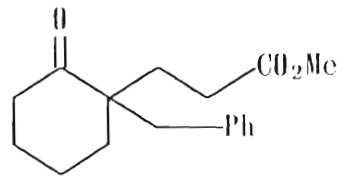


2-benzyl-2-[2-methoxycarbonyl-ethyl]cyclohexanone

6659/90.BR346F1 IN CDCL3

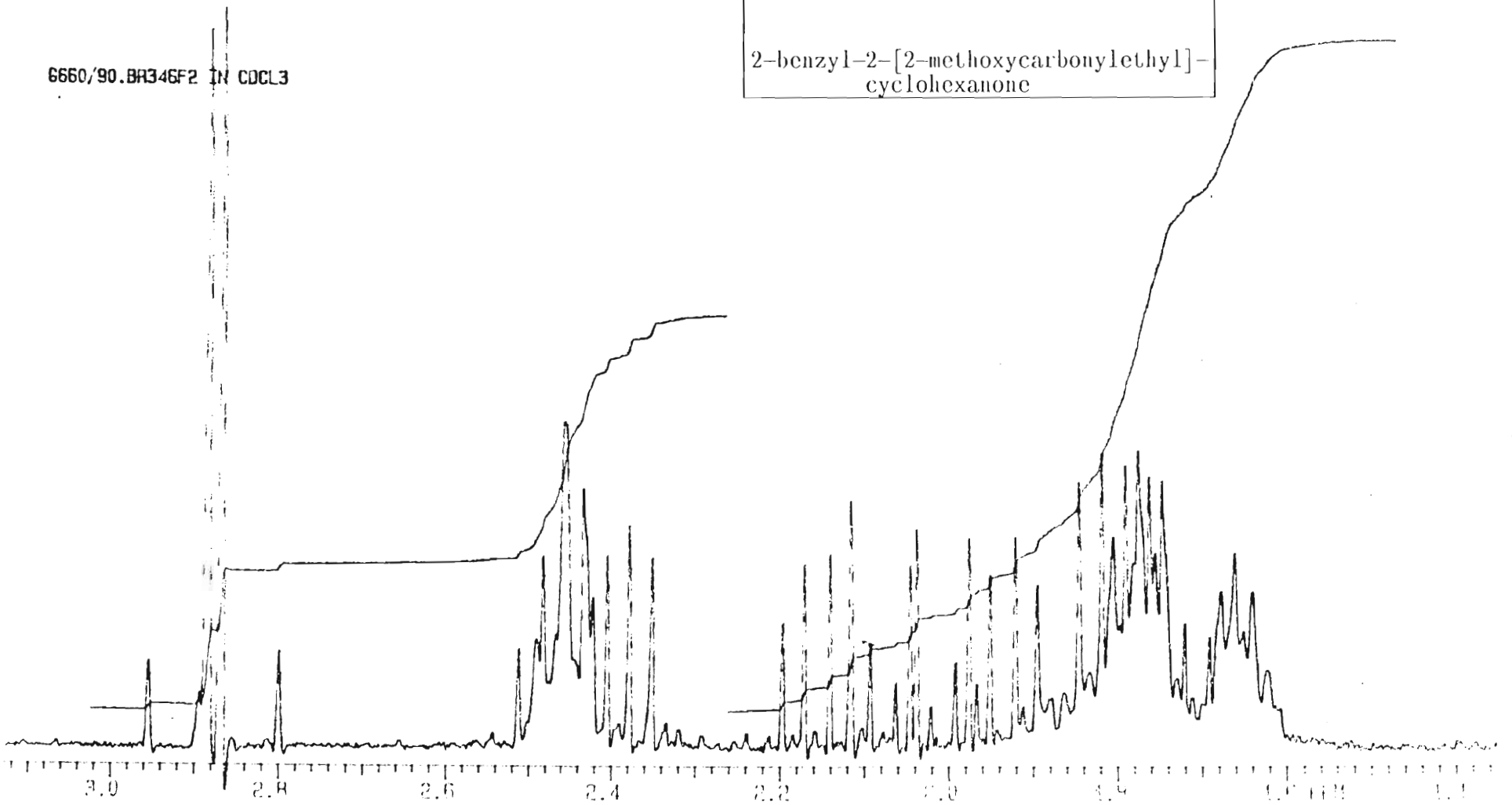


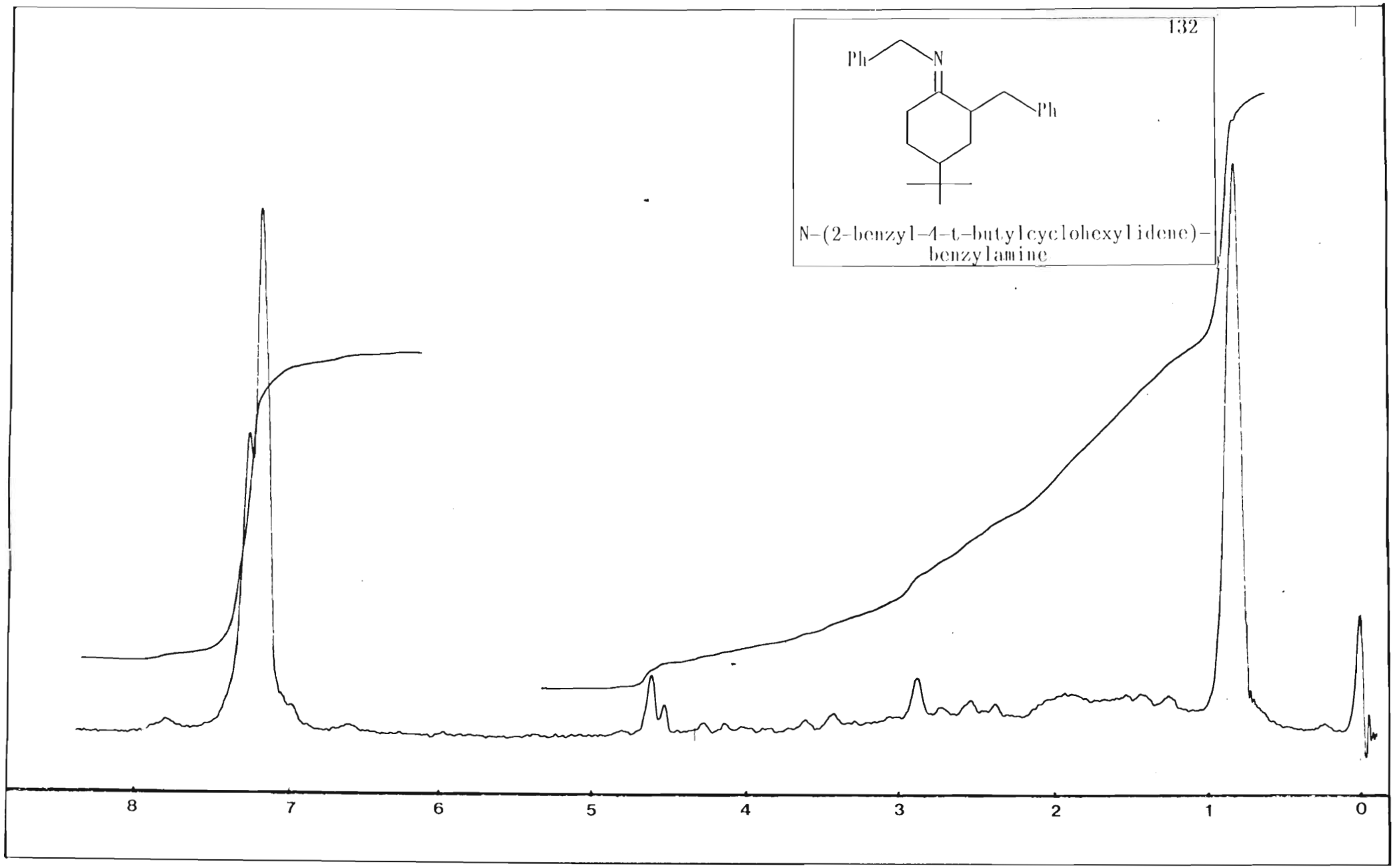
129

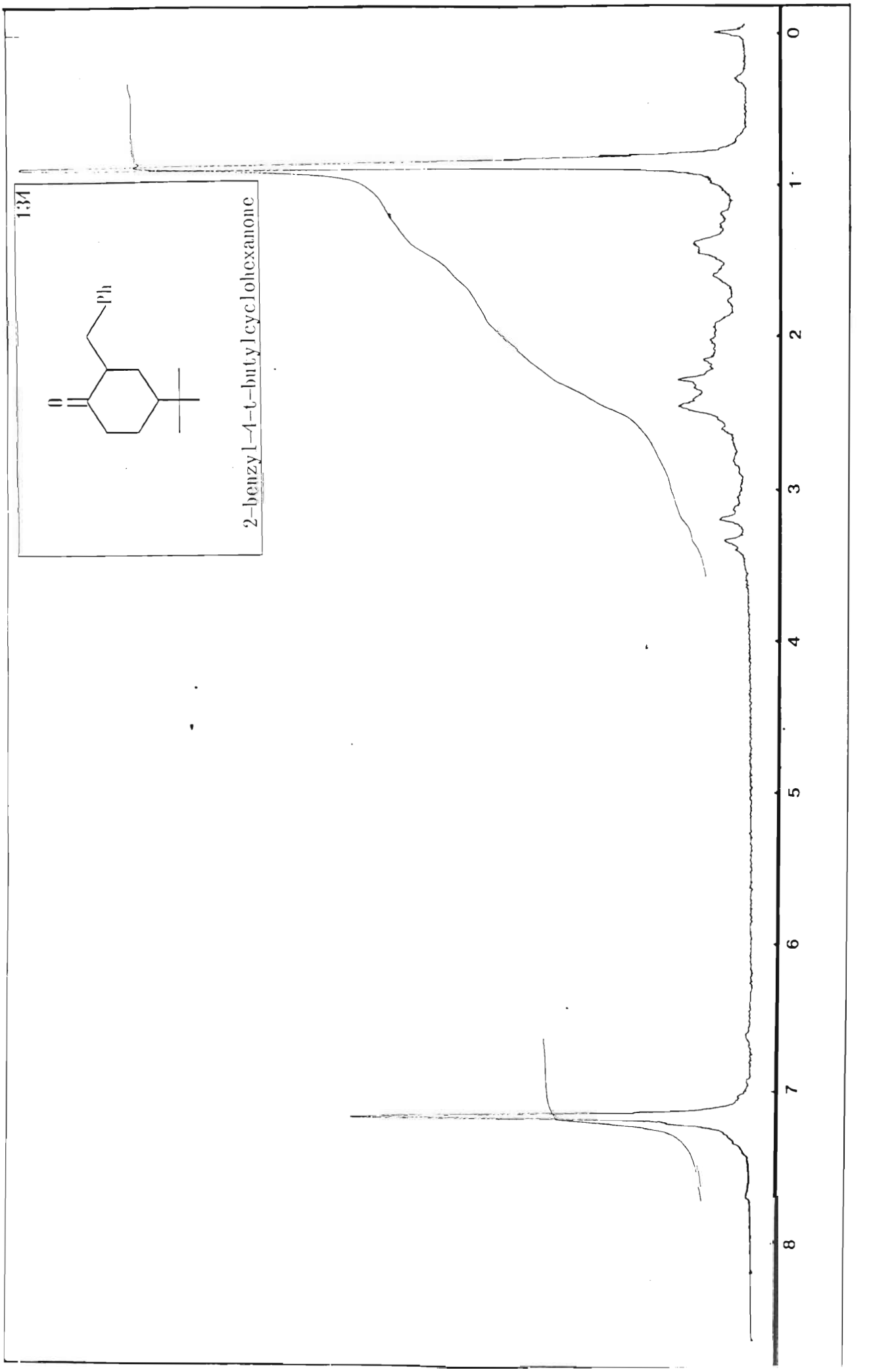


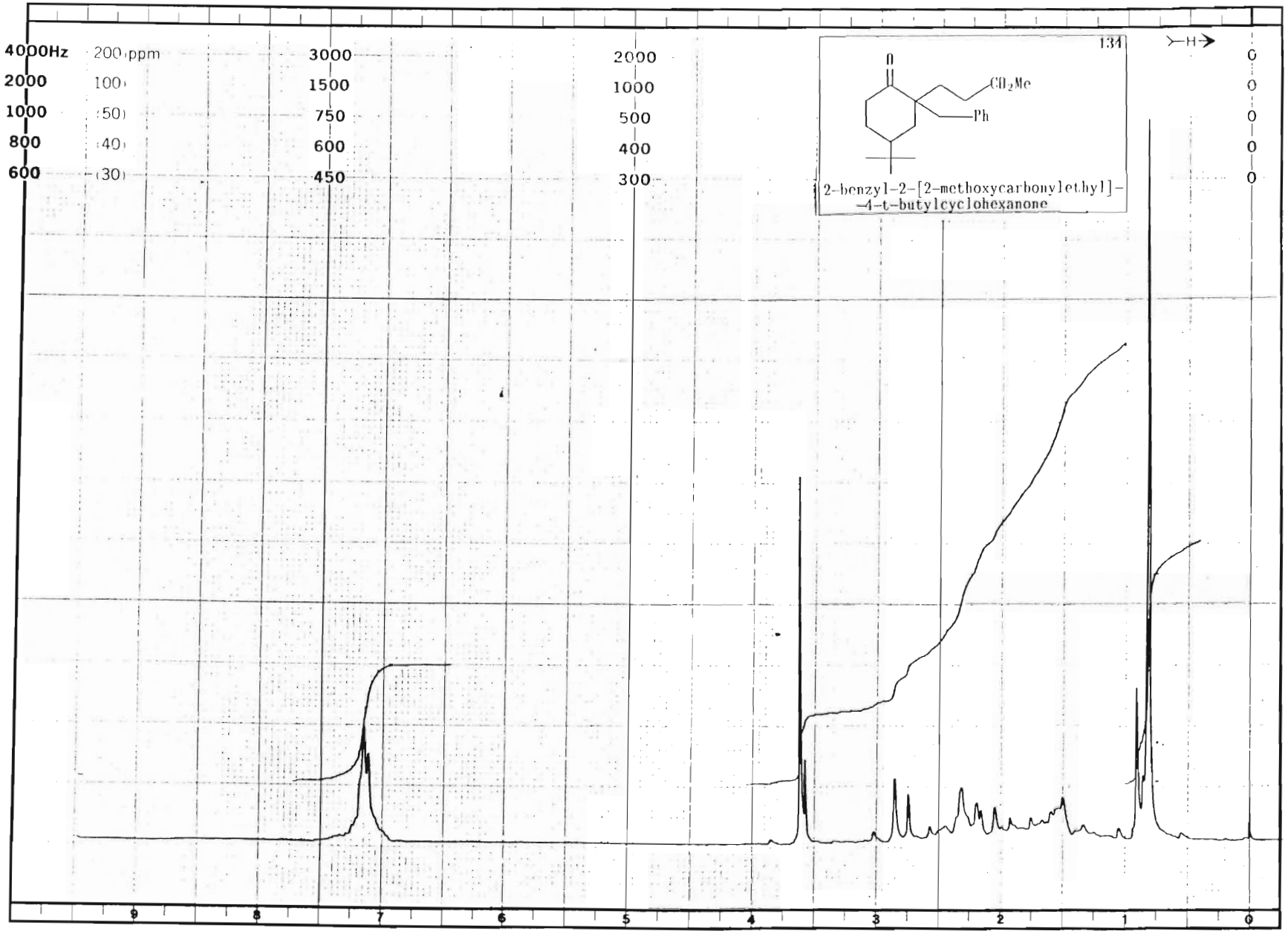
2-benzyl-2-[2-methoxycarbonylethyl]-cyclohexanone

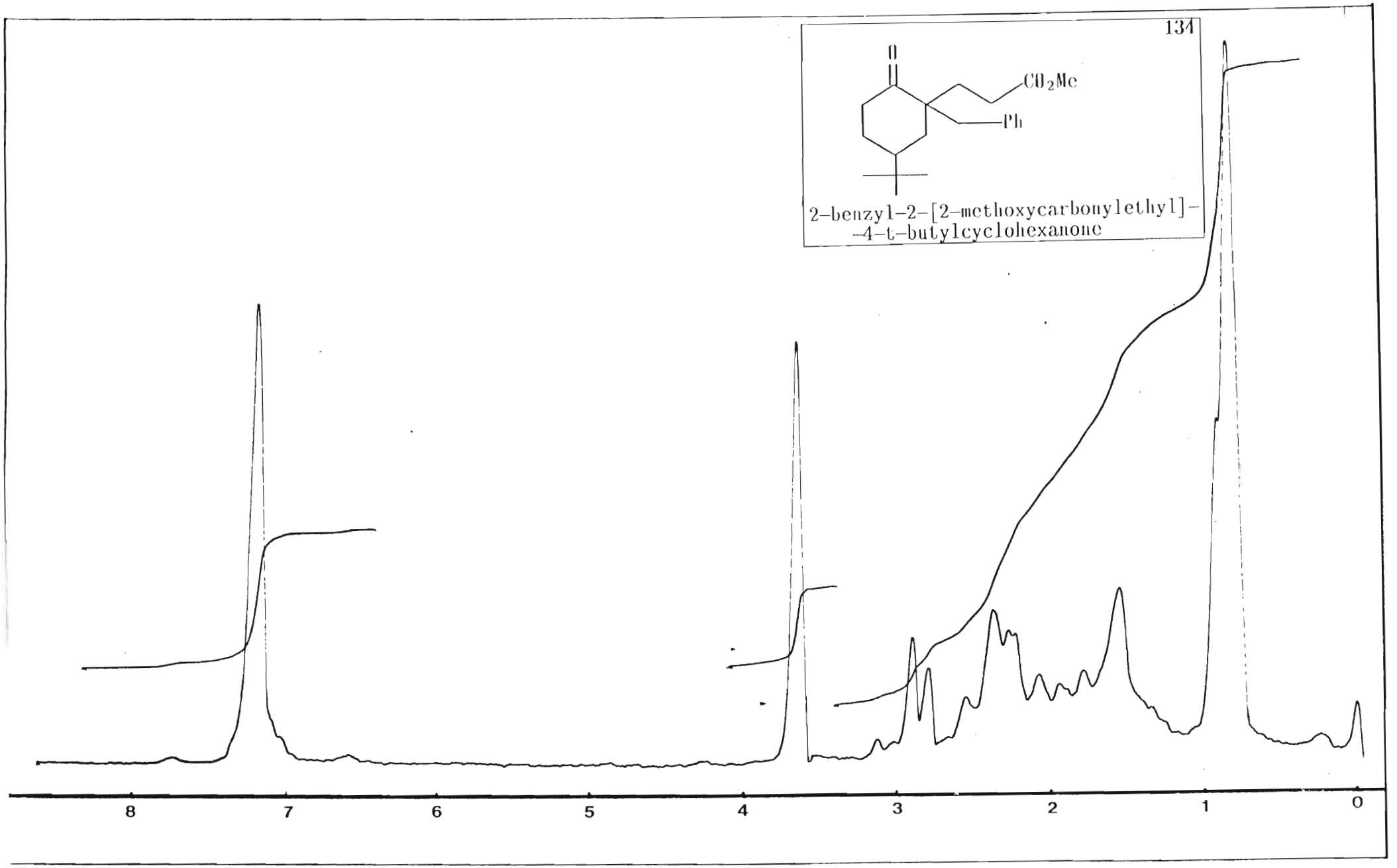
6660/90.BR346F2 IN CDCL3

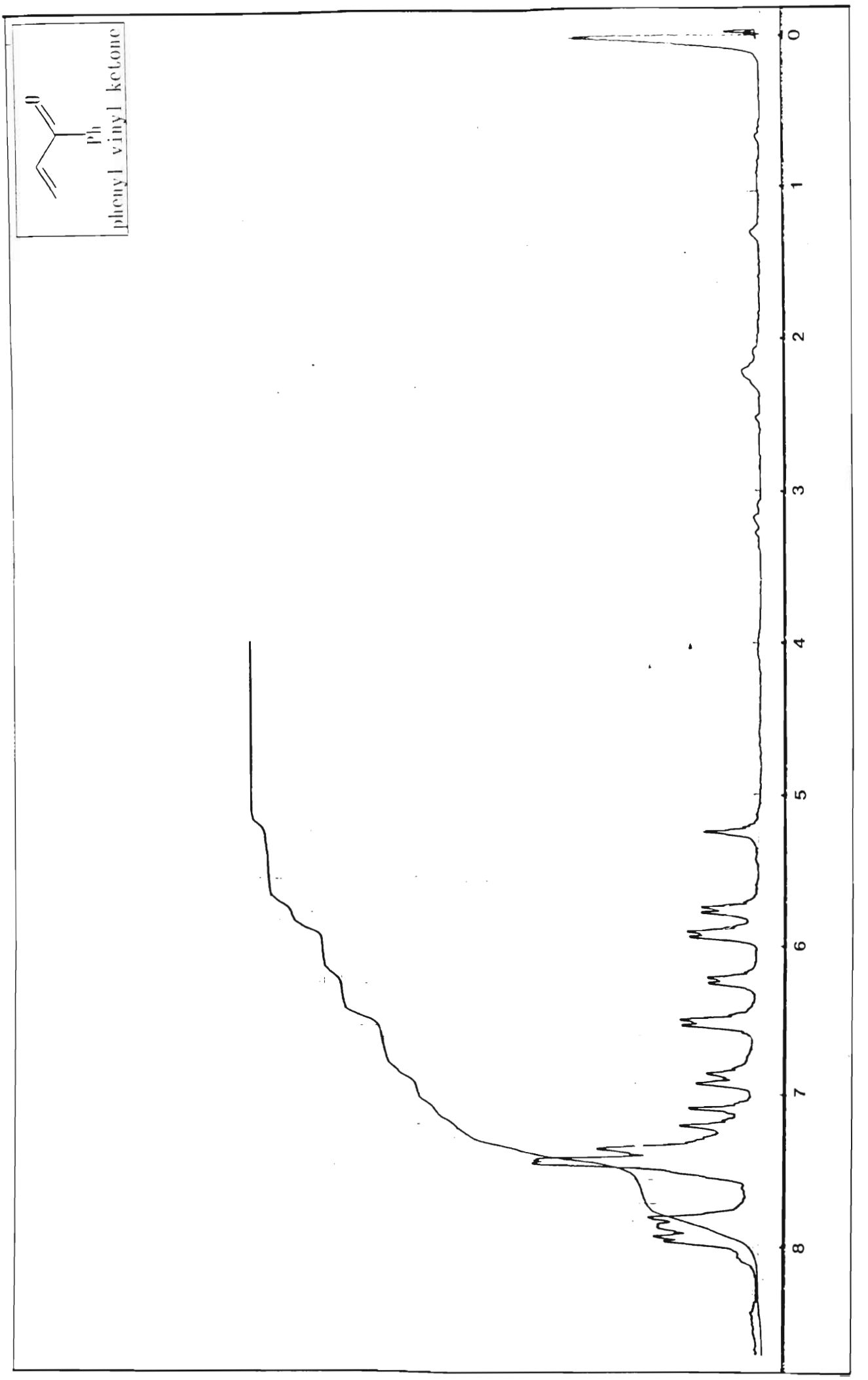


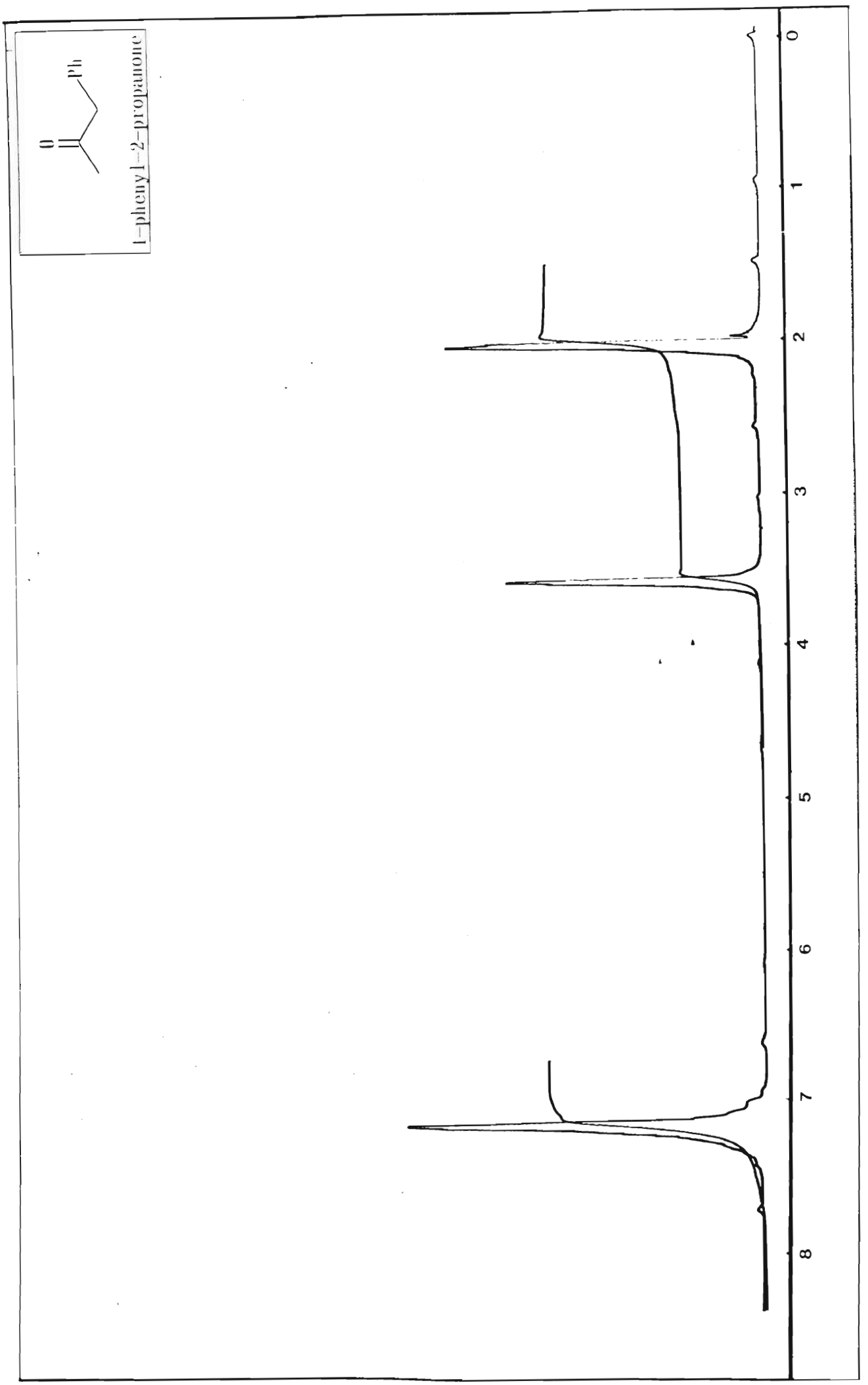

132
Ph
N
Ph
N-(2-benzyl-4-t-butylcyclohexylidene)-
benzylamine
8
7
6
5
4
3
2
1
0

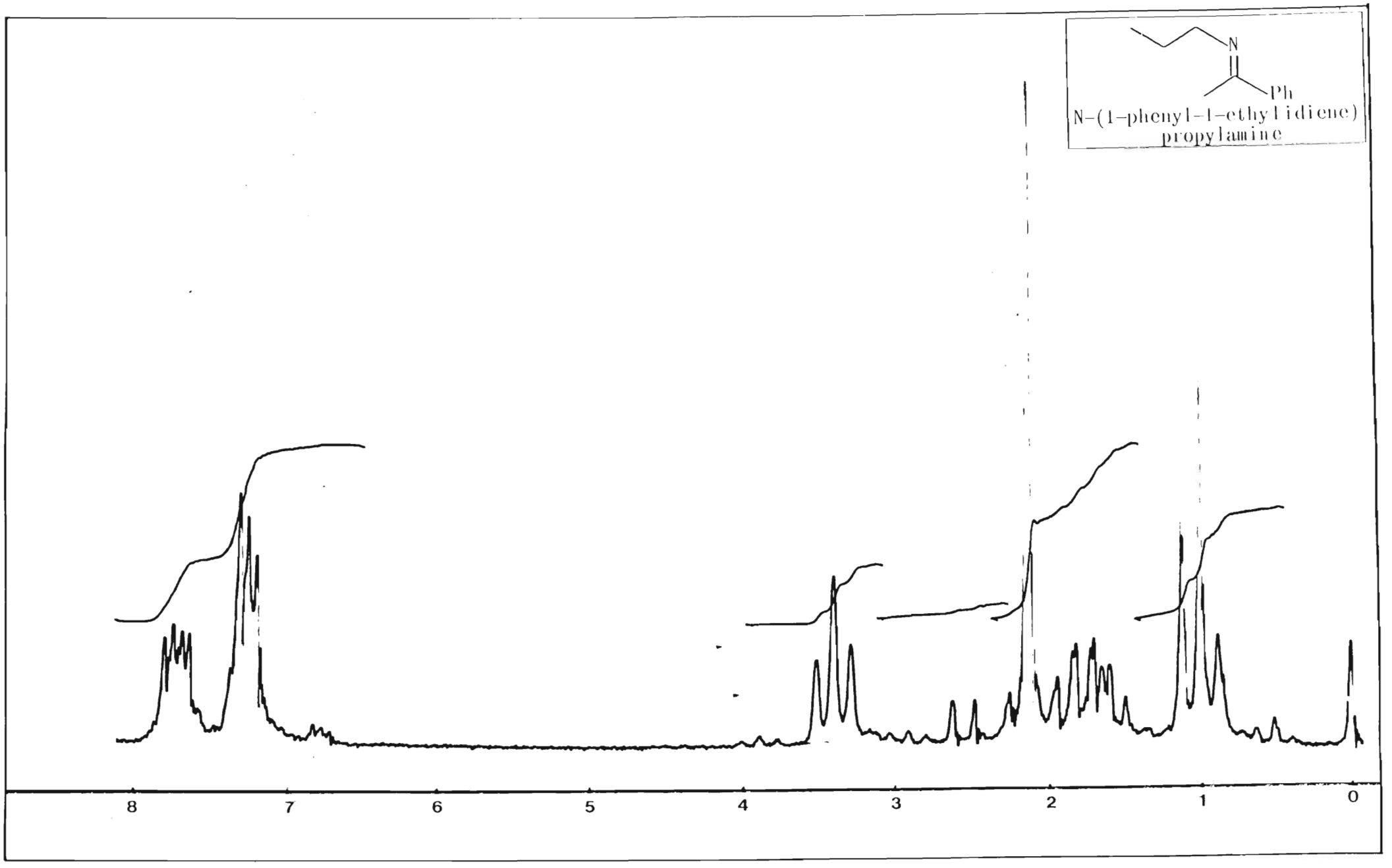

1:3M
2-benzyl-4-t-butylcyclohexanone
Ph
O
0
1
2
3
4
5
6
7
8

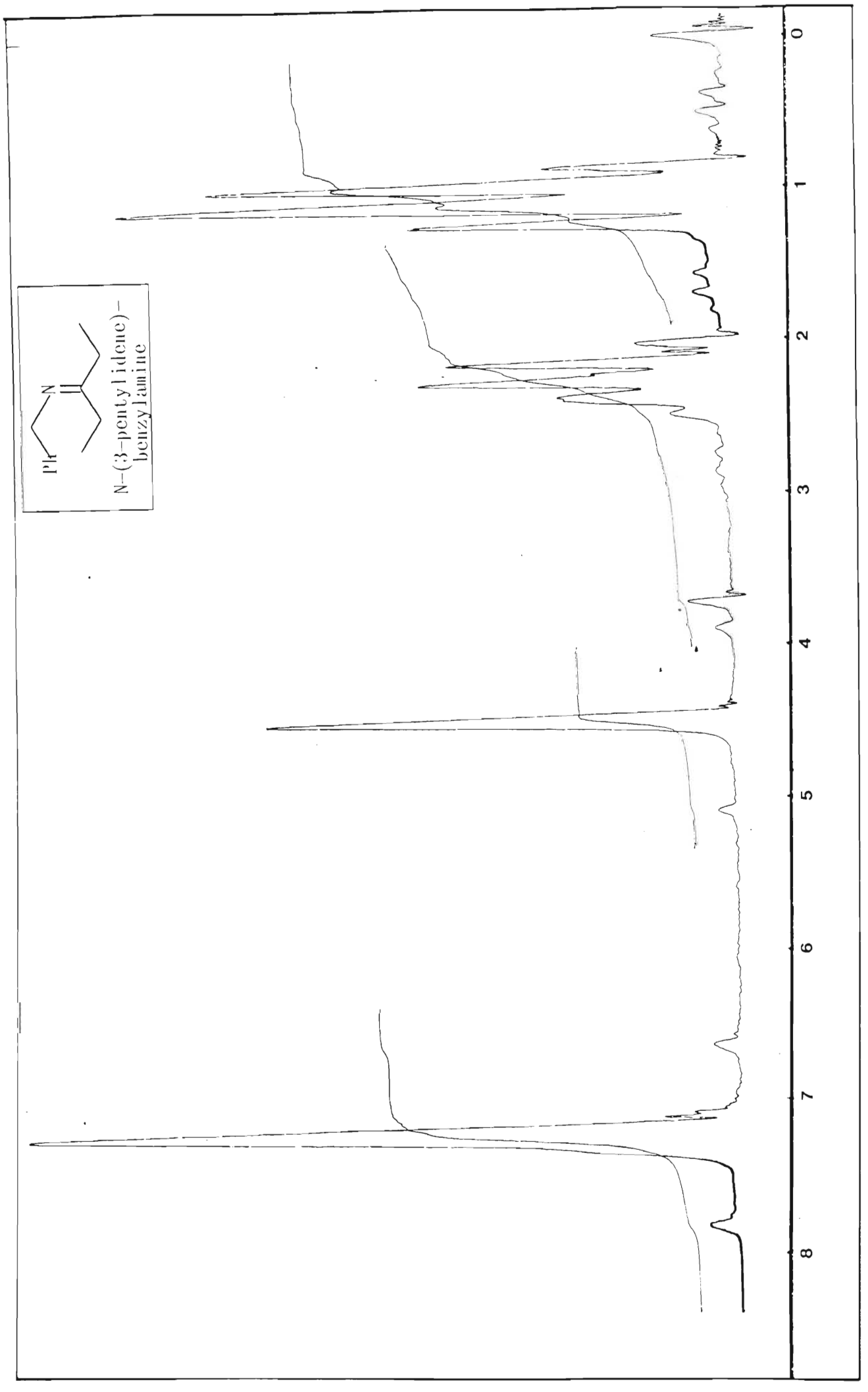

4000Hz
2000
1000
800
600
200 ppm
100
50
40
30
3000
1500
750
600
450
2000
1000
500
400
300
134
H
0
0
0
0
0
CH_2Me
Ph
2-benzyl-2-[2-methoxycarbonylethyl]-
-4-t-butylcyclohexanone
9
8
7
6
5
4
3
2
1
0

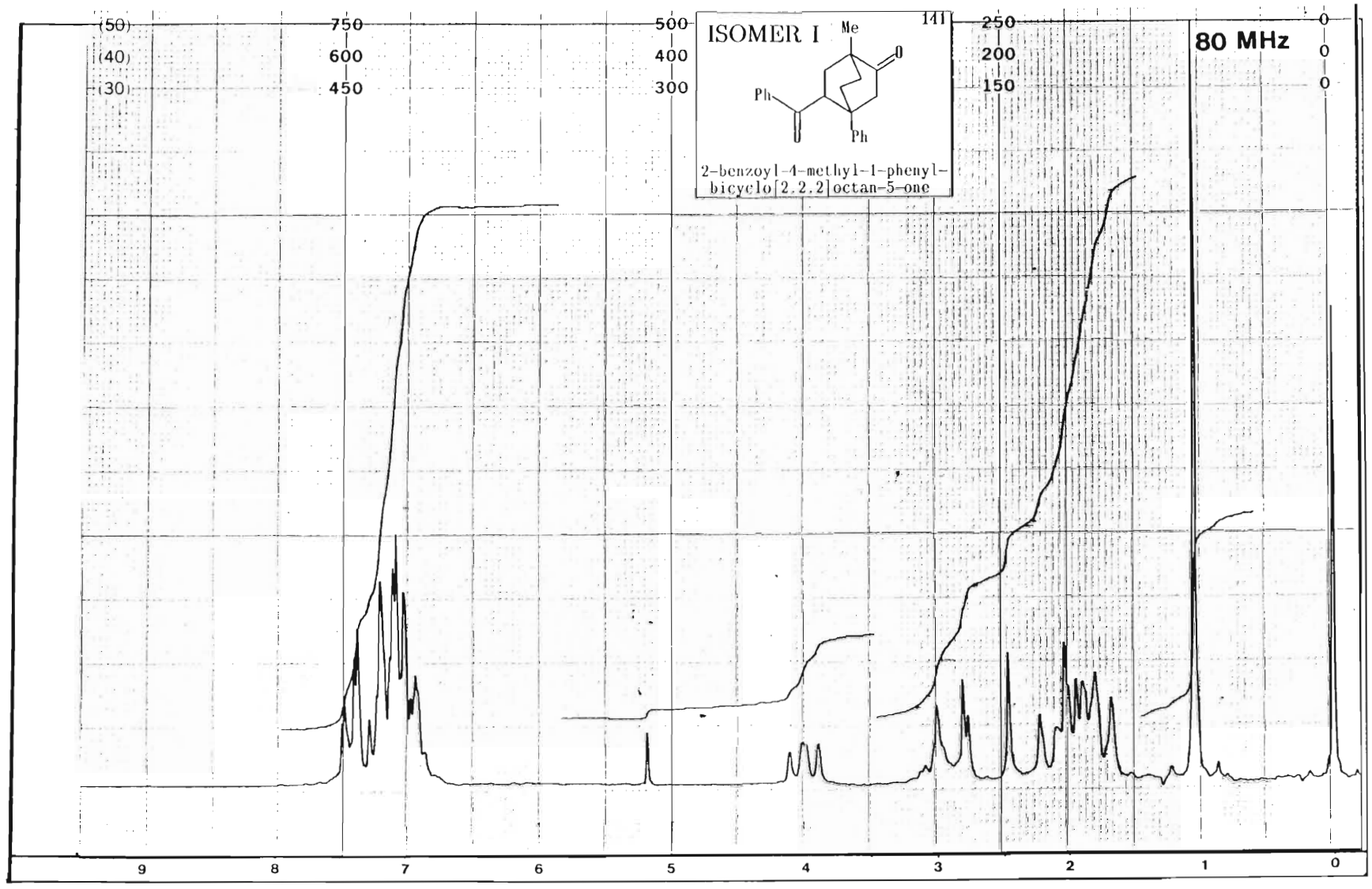

134
O
CO_2Me
Ph
2-benzyl-2-[2-methoxycarbonylethyl]-
-4-t-butylcyclohexanone
8
7
6
5
4
3
2
1
0


Ph
phenyl vinyl ketone
8
7
6
5
4
3
2
1
0

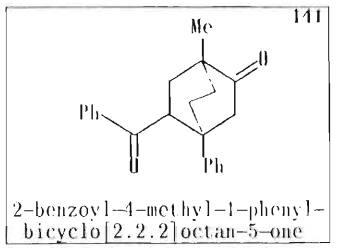

1–phenyl–2–propanone
O
Ph
8
7
6
5
4
3
2
1
0


N
Ph
N-(1-phenyl-1-ethylidiene)
propylamine
8
7
6
5
4
3
2
1
0


N
Ph
N-(3-pentylidene)-
benzylamine
0
1
2
3
4
5
6
7
8


ISOMER I
141
Me
O
Ph
Ph
2-benzoyl-4-methyl-1-phenyl-
bicyclo[2.2.2]octan-5-one
80 MHz
(50)
(40)
(30)
750
600
450
500
400
300
250
200
150
0
0
0
9
8
7
6
5
4
3
2
1
0

ISOMER I



2-benzoyl-4-methyl-1-phenyl-bicyclo[2.2.2]octan-5-one

BRUKER

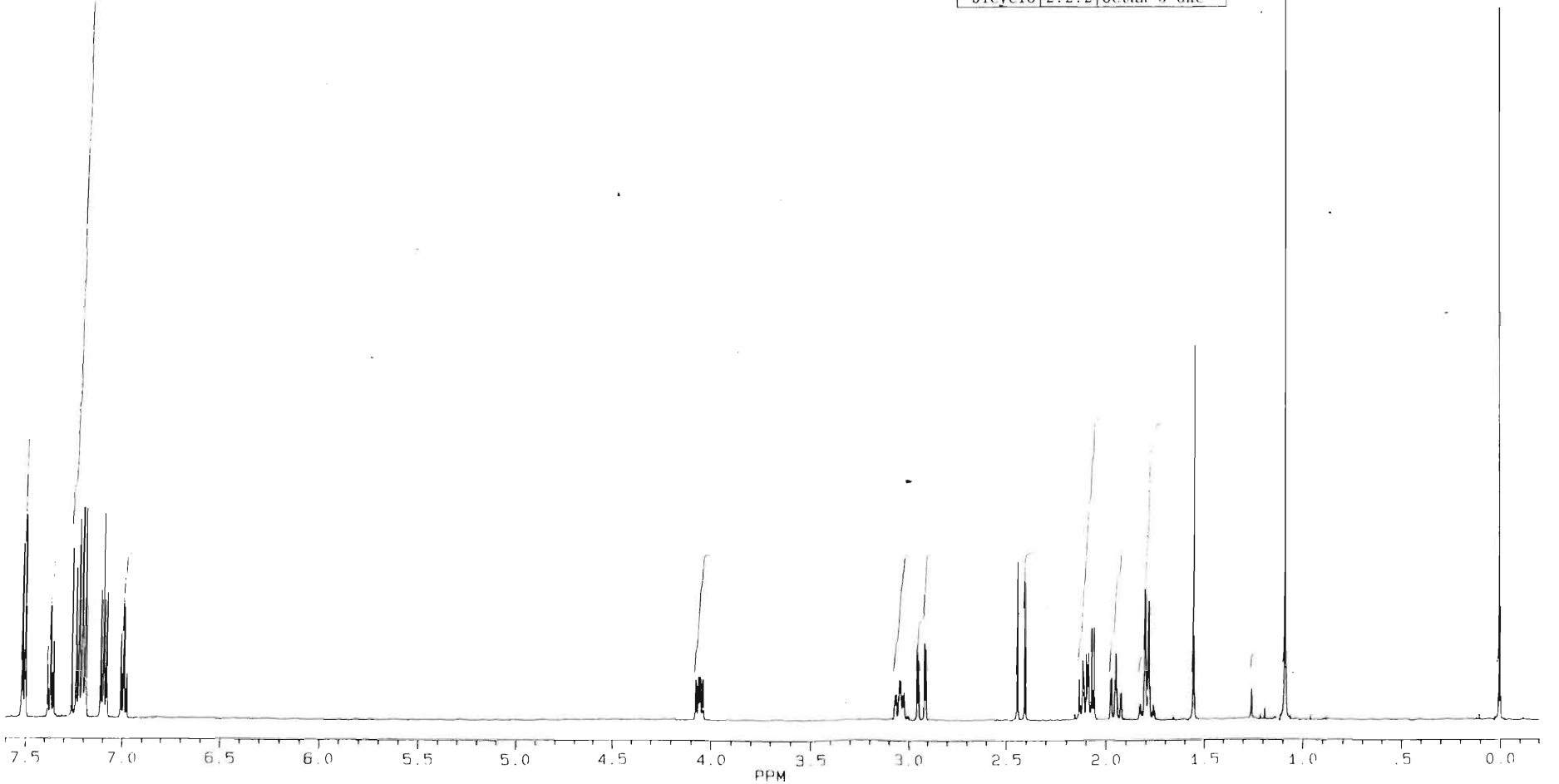
BC1214.001
DATE 11-11-88
TIME 10.23

SF 500.135
O1 8470.020
SI 65536
TD 65536
SW 10000.000
HZ/PT .305

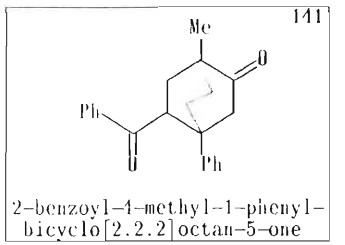
PW 3.0
RD 6.0
AQ 3.277
RG 200
NS 64

O2 0.0
DP 63L PO

LB .300
GB 0.0
F1 7.600P
F2 -.200P
HZ/CM 111.459
PPM/CM .223
SR 5422.23



ISOMER I



BRUKER

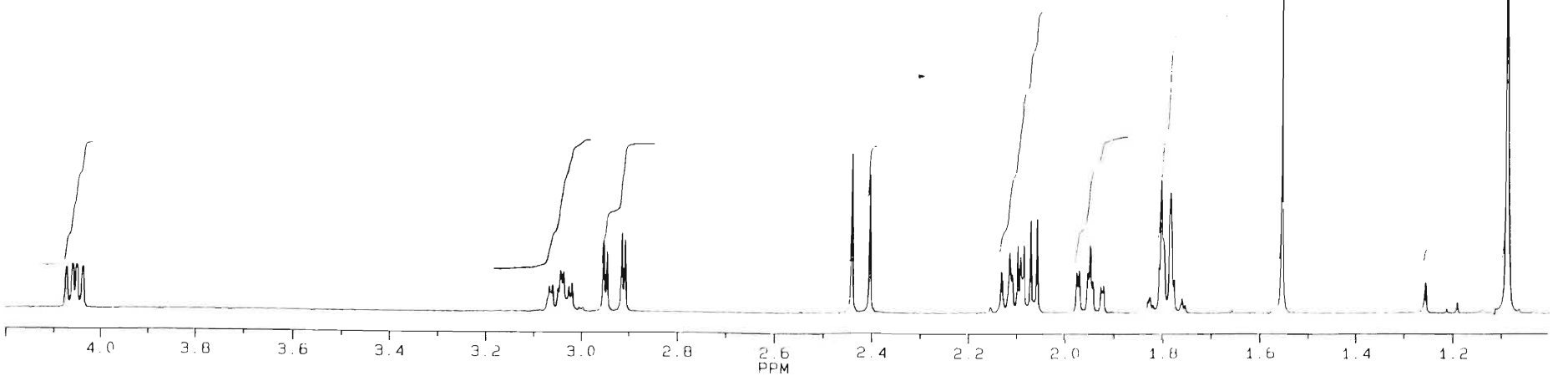
BC1214.001
DATE 11-11-88
TIME 10.23

SF 500.135
O1 8470.020
SI 65536
TD 65536
SW 10000.000
HZ/PT .305

PW 3.0
RD 0.0
AQ 3.277
RG 200
NS 64

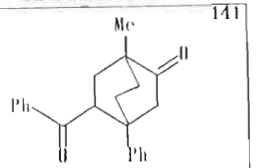
O2 0.0
DP 63L PO

LB .300
GB 0.0
F1 4.200P
F2 1.000P
HZ/CM 45.724
PPM/CM .091
SR 5422.23



ISOMER I

141



2-benzoyl-4-methyl-1-phenyl-bicyclo[2.2.2]octan-5-one

BRUKER

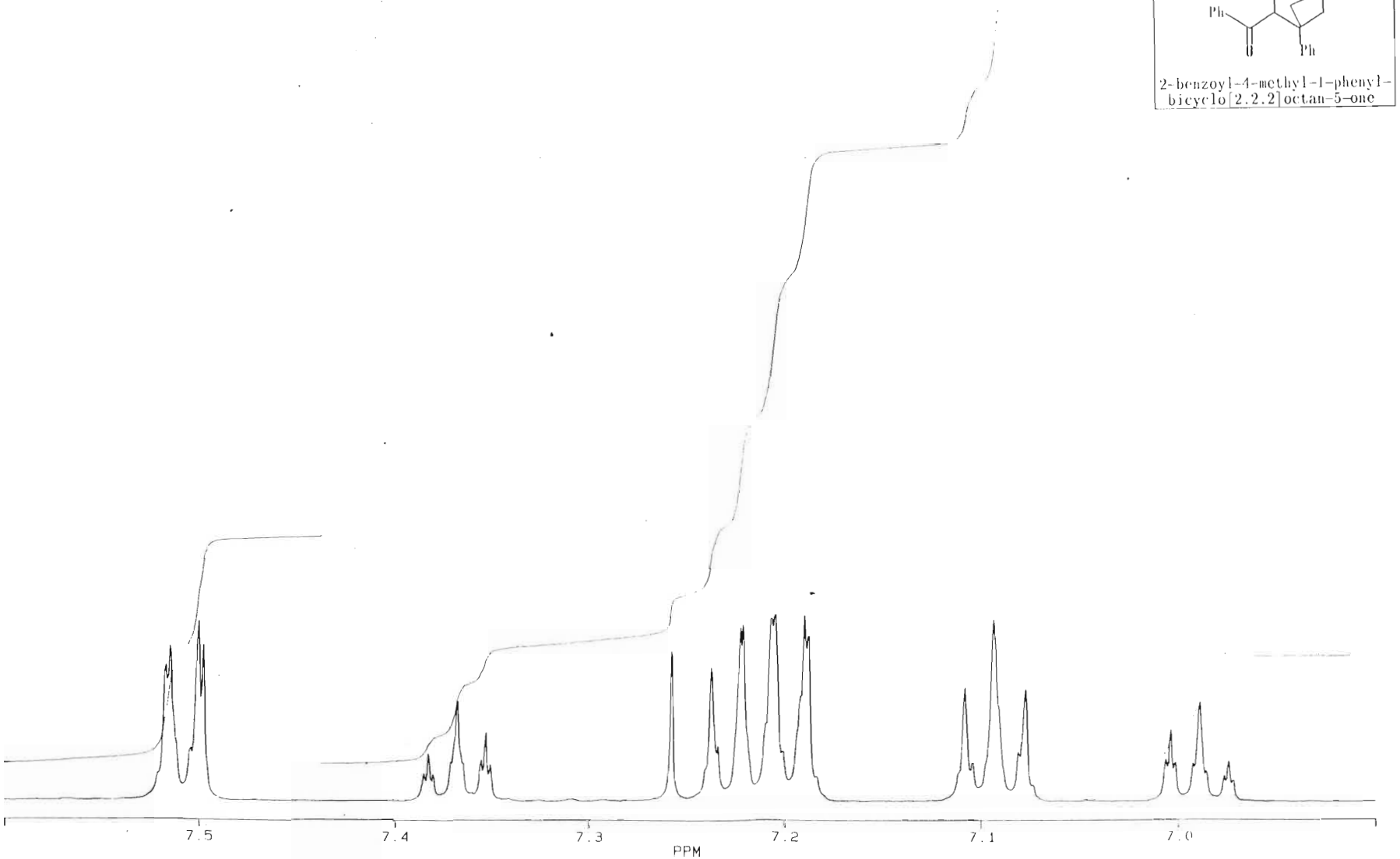
BC1214.001
DATE 11-11-88
TIME 10.23

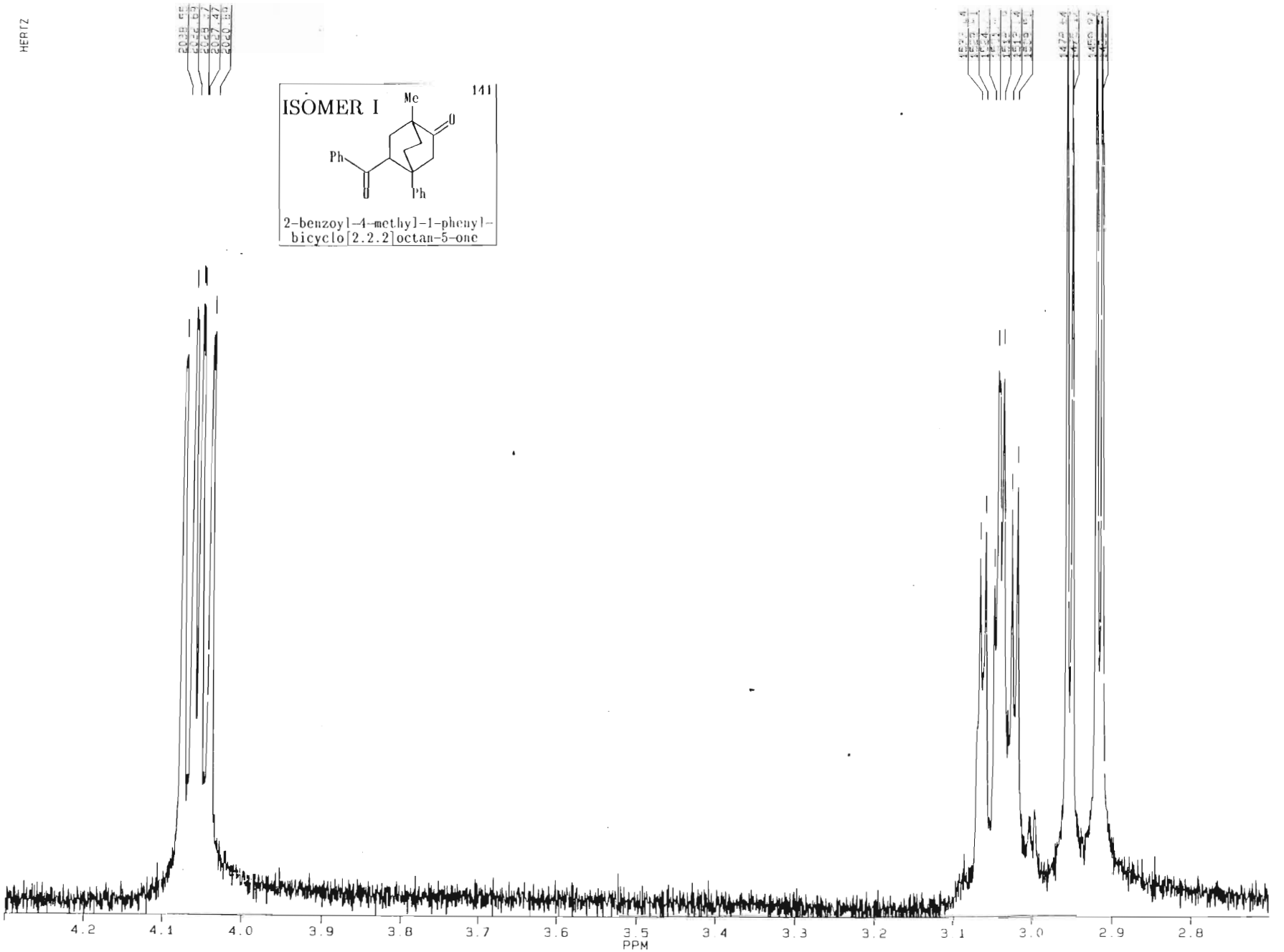
SF 500.135
O1 8470.020
SI 65536
TD 65536
SW 10000.000
HZ/PT .305

PW 3.0
RD 0.0
AQ 3.277
RG 200
NS 64

O2 0.0
DP 63L PO

LB .300
GB 0.0
F1 7.600P
F2 6.900P
HZ/CM 10.001
PPM/CM .020
SR 5422.23

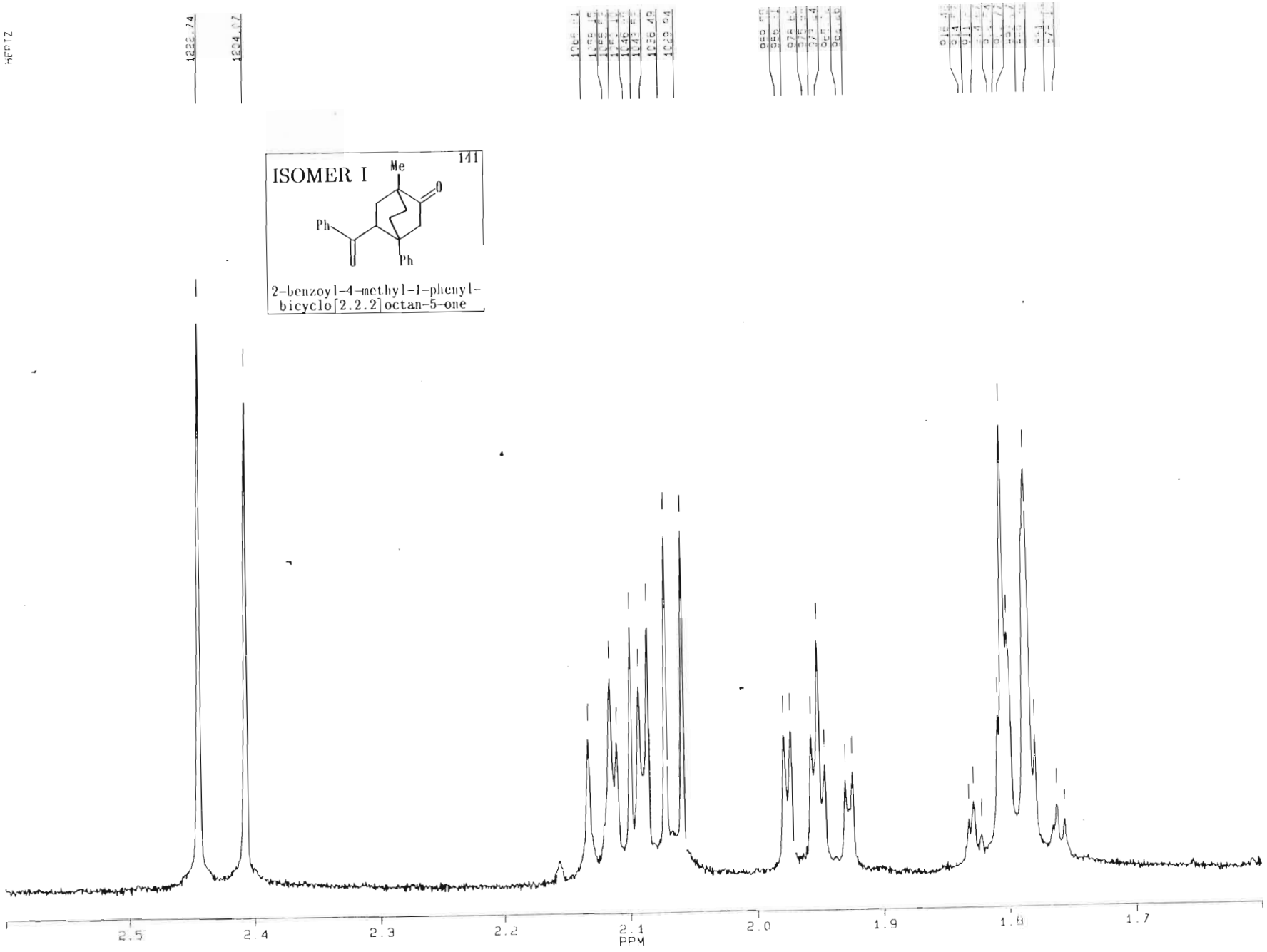


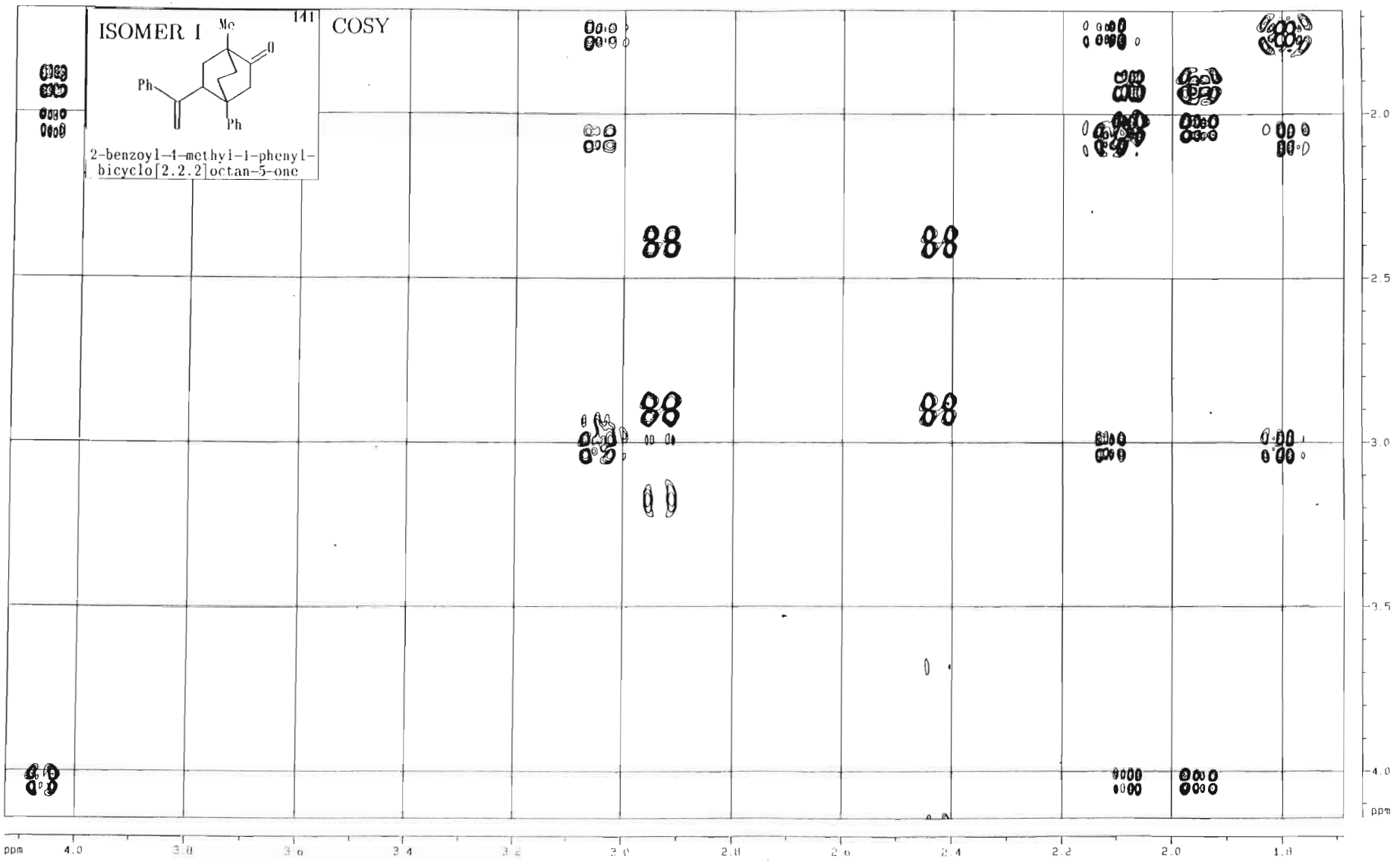


BRUKER

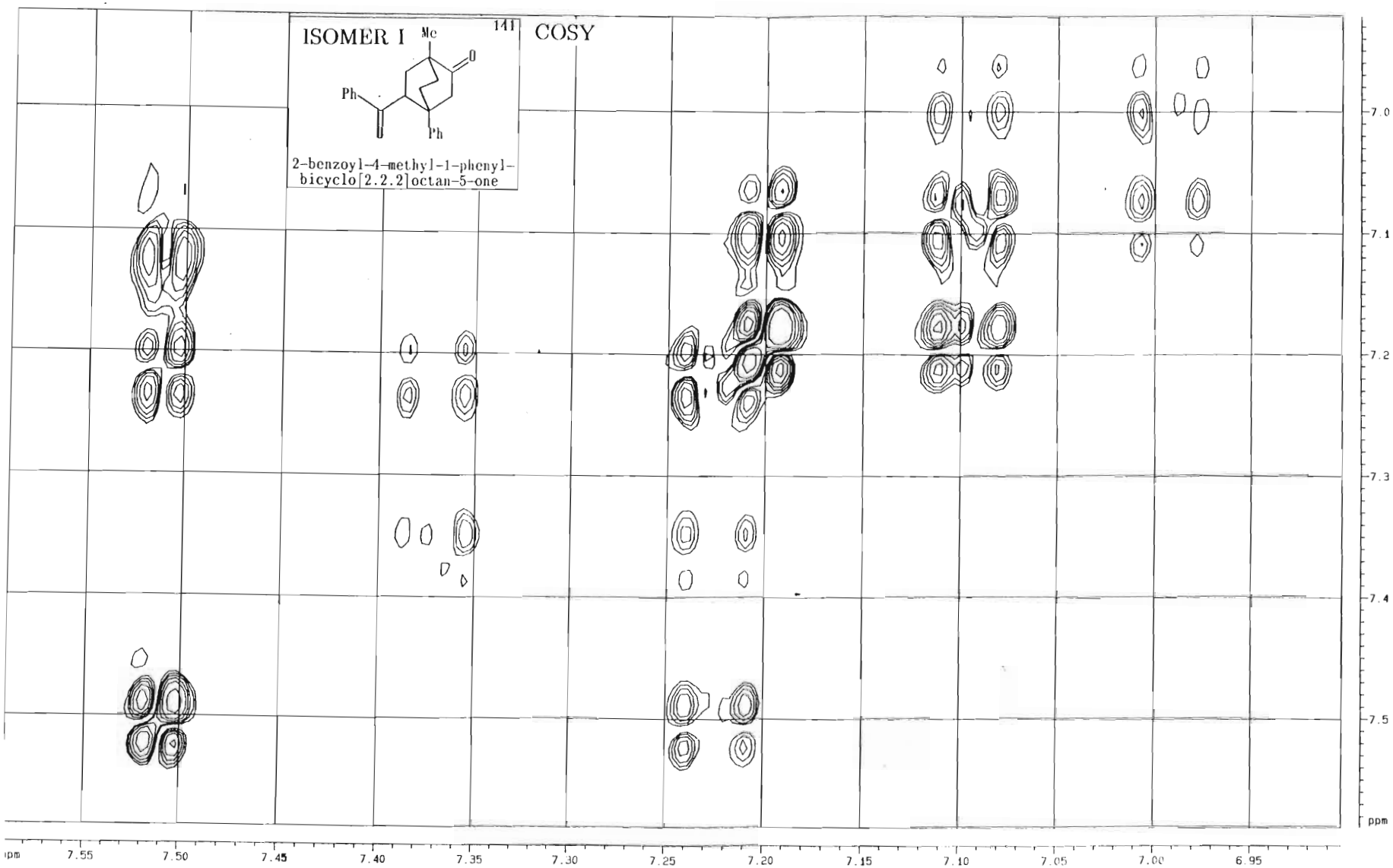
TEMP.003
DATE 29-11-89
TIME 11:07

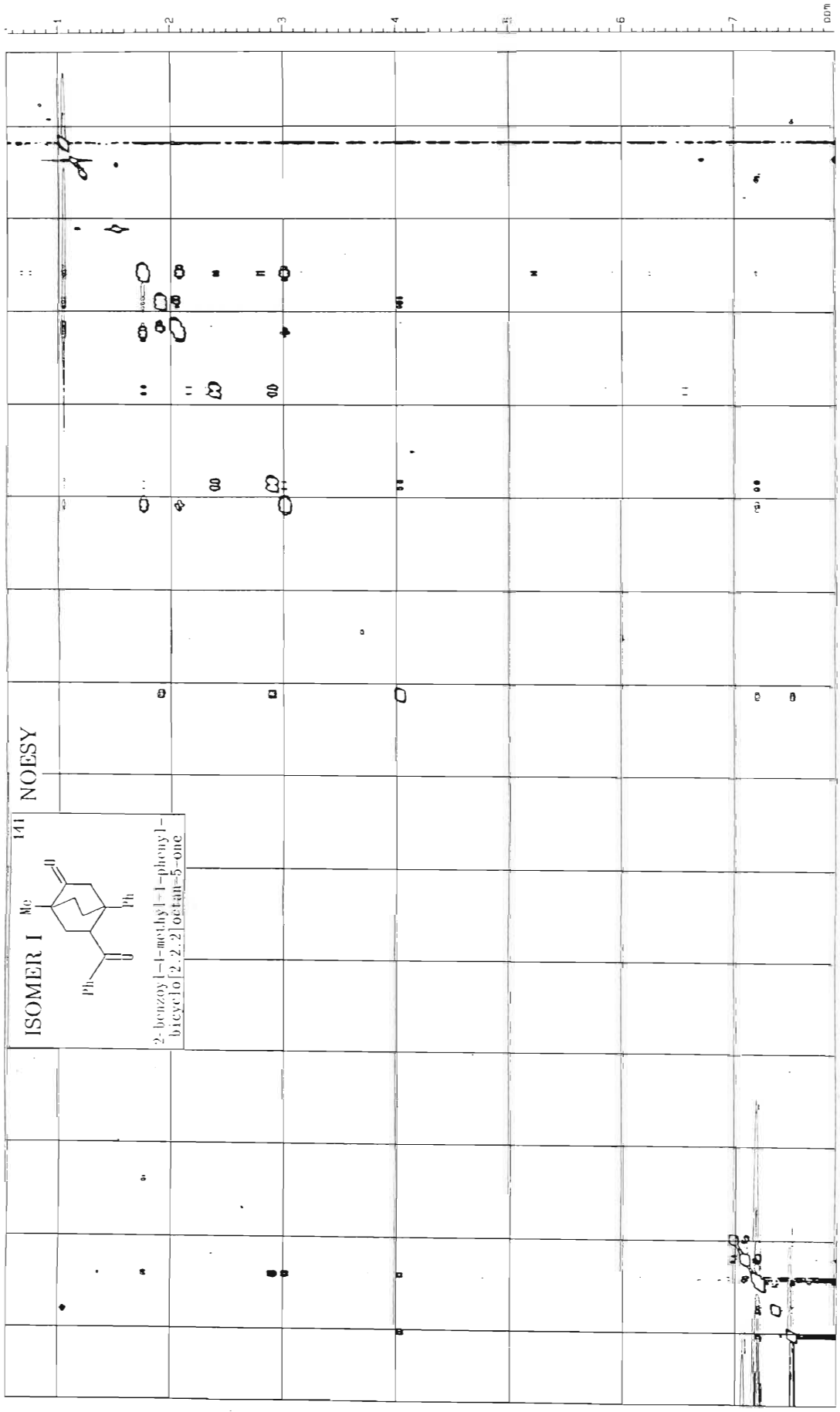
SF	500.135
O1	8470.020
SI	65536
TD	65536
SW	10000.000
HZ/PT	.305
PW	3.0
RD	0.0
AQ	3.277
RG	200
NS	64
O2	0.0
DP	63L P0
LB	0.0
GB	.300
F1	4.300P
F2	2.700P
HZ/CM	22.862
PPM/CM	.046
SR	5420.40

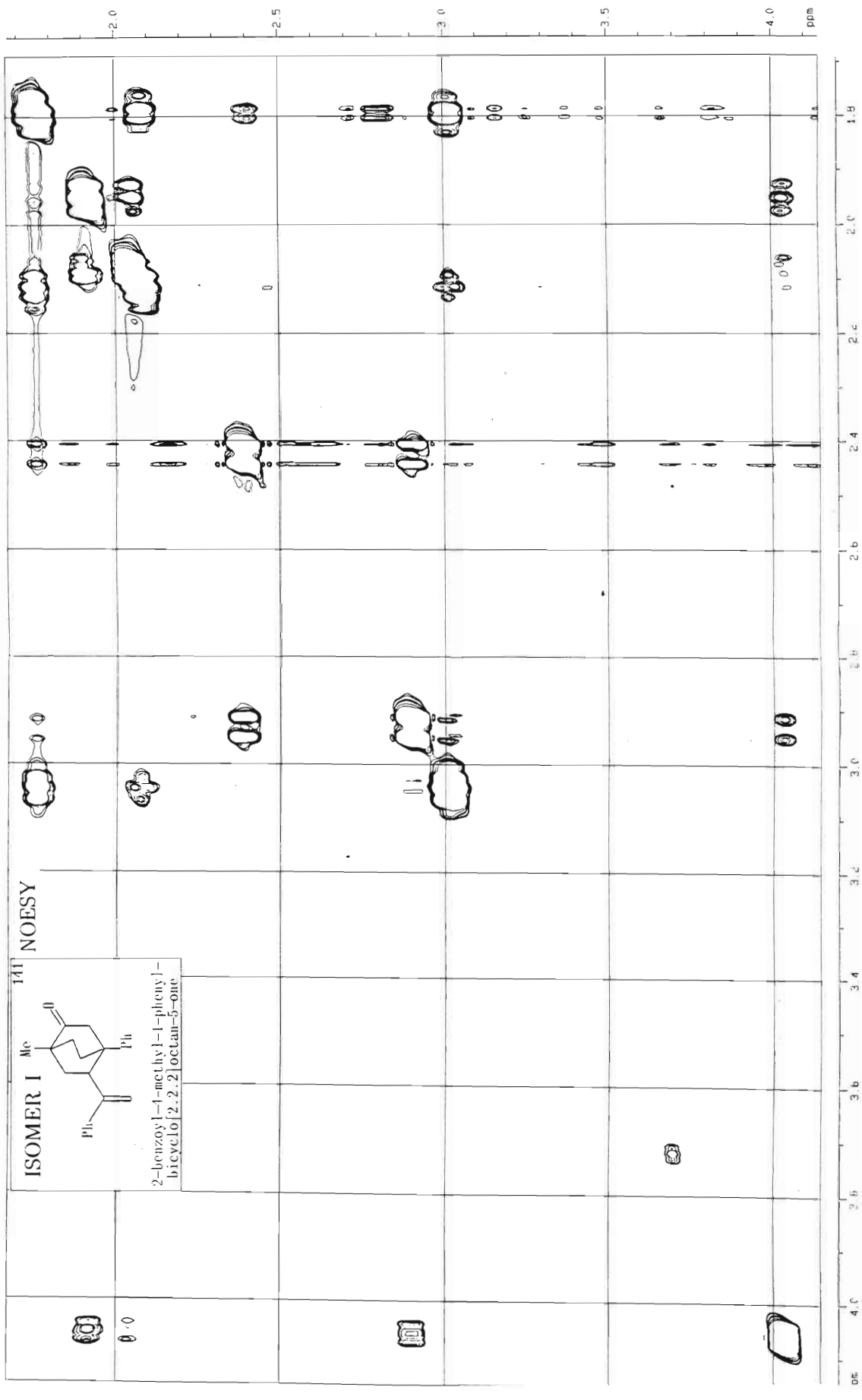

HERTZ
1222.74
1204.02
ISOMER I
141
Me
O
Ph
Ph
2-benzoyl-4-methyl-1-phenyl-
bicyclo[2.2.2]octan-5-one
BRUKER
TEMP.003
DATE 29-11-89
TIME 11.07
SF 500.135
01 8470.020
SI 65536
TD 65536
SW 10000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 200
NS 64
02 0.0
DP 63L PO
LB 0.0
GB .300
F1 2.600P
F2 1.600P
HZ/CM 14.291
PPM/CM .029
SR 5420.40
2.5
2.4
2.3
2.2
2.1
PPM
2.0
1.9
1.8
1.7


ISOMER I
141
COSY
Me
O
Ph
Ph
2-benzoyl-4-methyl-1-phenyl-
bicyclo[2.2.2]octan-5-one
2.0
2.5
3.0
3.5
4.0
ppm
ppm
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
2.0
1.8

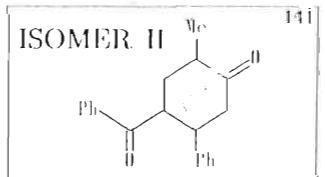
Sample 12/14


ISOMER I
141
COSY
Me
O
Ph
Ph
2-benzoyl-4-methyl-1-phenyl-
bicyclo[2.2.2]octan-5-one
7.0
7.1
7.2
7.3
7.4
7.5
ppm
ppm
7.55
7.50
7.45
7.40
7.35
7.30
7.25
7.20
7.15
7.10
7.05
7.00
6.95


ISOMER I
141
NOESY
2-benzoyl-4-methyl-1-phenyl-bicyclo[2.2.2]octan-5-one
Me
Ph
Ph
O
O
ppm


ISOMER 1
NOESY
Me
Ph
Ph
2-benzoyl-4-methyl-1-phenyl-bicyclo[2.2.2]octan-5-one
ppm

ISOMER II

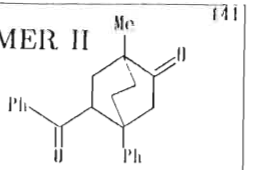


141

2-benzoyl-4-methyl-1-phenyl-bicyclo[2.2.2]octan-5-one

B.RAE SAMPLE 417/17/20

ISOMER II



141

2-benzoyl-1-methyl-4-phenyl-bicyclo[2.2.2]octan-5-one

BRUKER

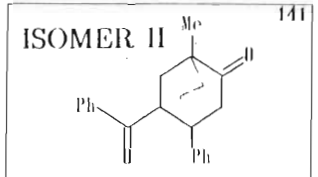
BC1720.001
DATE 12-11-88
TIME 15.47

SF	500.135
O1	8470.020
SI	65536
TD	65536
SW	10000.000
HZ/PT	.305
PW	8.0
RD	0.0
AQ	3.277
RG	20
NS	38
O2	0.0
DP	63L PO
LB	.300
GB	0.0
F1	4.400P
F2	-.200P
HZ/CM	65.735
PPM/CM	.131
SA	5420.70

B.RAE SAMPLE 417/17/20

ISOMER II

141



2-benzoyl-4-methyl-1-phenyl-bicyclo[2.2.2]octan-5-one

BRUKER

BC1720.001
DATE 12-11-90
TIME 15.47

SF 500.135
O1 8470.020
SI 65536
TD 65536
SW 10000.000
HZ/PT .305

PW 3.0
RD 0.0
AQ 3.277
RG 20
NS 30

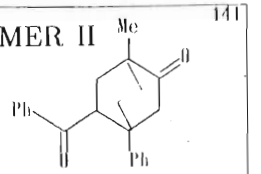
O2 0.0
DP 63L PG

LB .300
GB 0.0
F1 7.700P
F2 -.260P
HZ/CM 112.889
PPM/CM .226
SR 5420.70

B.RAE SAMPLE 417/17/20

141

ISOMER II



2-benzoyl-4-methyl-1-phenyl-bicyclo[2.2.2]octan-5-one

BRUKER

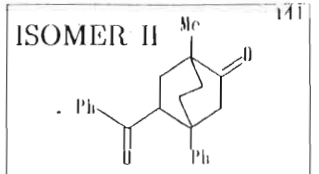
BC1720.001
DATE 12-11-88
TIME 15:47

SF	500.135
O1	8470.020
SI	65536
TD	65536
SW	10000.000
HZ/PT	.305
PW	3.0
RD	0.0
AQ	3.277
RG	20
NS	38
D2	0.0
DP	63L PO
LB	.300
GB	0.0
F1	7.70[illegible]
F2	6.90[illegible]
HZ/CM	11.431
PPM/CM	.022
SR	5420.70

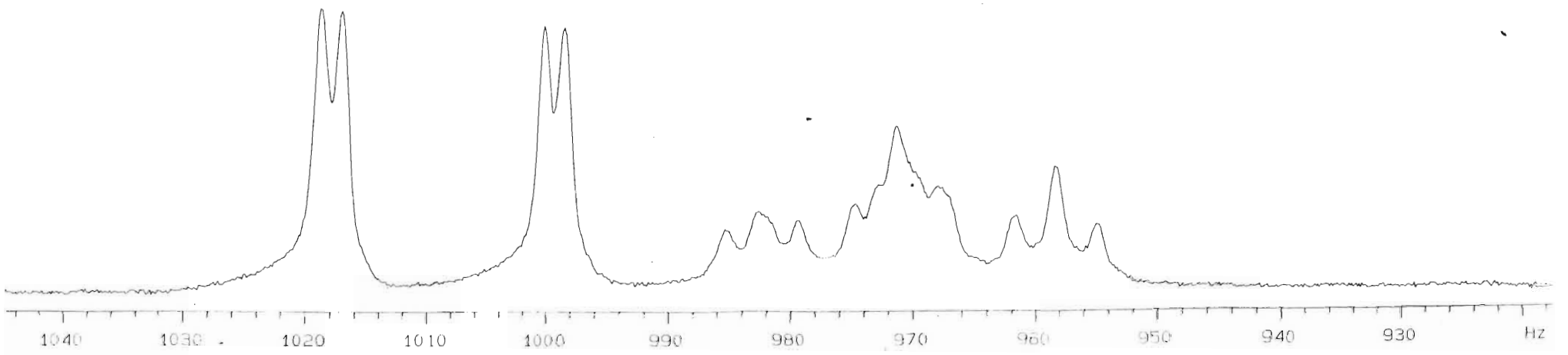
INDEX	FREQUENCY (Hz)	HEIGHT
1	1025.660	15.9
2	1018.891	68.1
3	1017.182	67.5
4	1009.814	64.9
5	998.505	63.5
6	995.443	15.3
7	995.199	15.1
8	994.636	19.4
9	993.269	18.7
10	990.805	12.0
11	990.560	11.8
12	979.462	17.4
13	974.701	21.2
14	973.969	18.1
15	972.670	25.7
16	972.636	25.5
17	971.405	39.7
18	970.306	31.0
19	969.618	28.8
20	969.452	27.2
21	967.997	25.3
22	967.621	25.0
23	961.639	18.3
24	958.465	29.9
25	954.925	16.1

141

ISOMER II

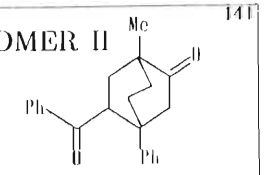


2 benzoyl-4-methyl-1-phenyl-bicyclo[2.2.2]octan-5-one

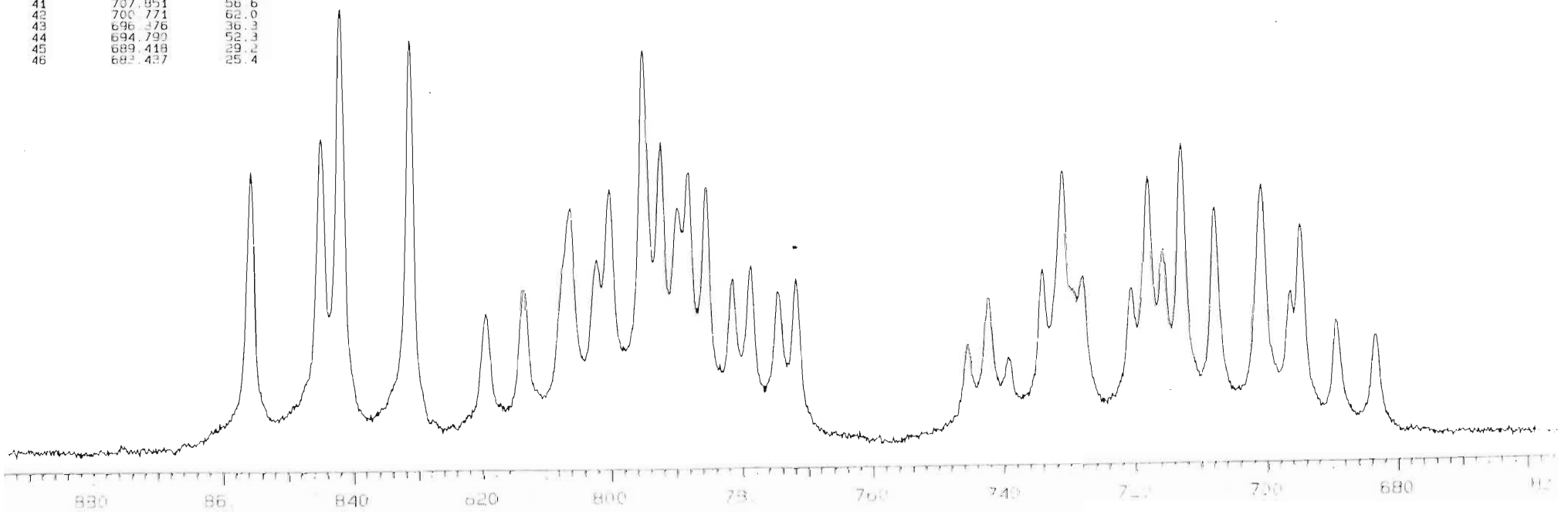


INDEX	FREQUENCY (Hz)	HEIGHT
1	856.164	67.5
2	845.205	75.5
3	841.775	100.0
4	831.634	98.7
5	819.791	32.2
6	813.931	28.9
7	808.486	98.6
8	804.654	22.9
9	804.410	22.1
10	802.457	46.1
11	800.504	62.9
12	798.429	25.3
13	798.185	24.8
14	797.696	25.3
15	797.086	29.6
16	795.277	96.0
17	792.691	73.9
18	791.749	38.0
19	790.128	58.2
20	789.518	53.1
21	788.419	66.6
22	787.076	34.3
23	785.733	63.1
24	781.705	41.2
25	778.997	44.3
26	774.869	38.0
27	772.961	41.1
28	745.572	24.8
29	742.520	35.8
30	734.219	42.6
31	733.120	28.7
32	731.167	65.9
33	729.580	38.0
34	728.848	35.7
35	728.115	40.8
36	720.791	37.9
37	720.181	30.4
38	718.227	64.3
39	715.908	47.0
40	712.978	72.0
41	707.851	56.6
42	700.771	62.0
43	696.376	36.3
44	694.790	52.3
45	689.418	29.2
46	682.437	25.4

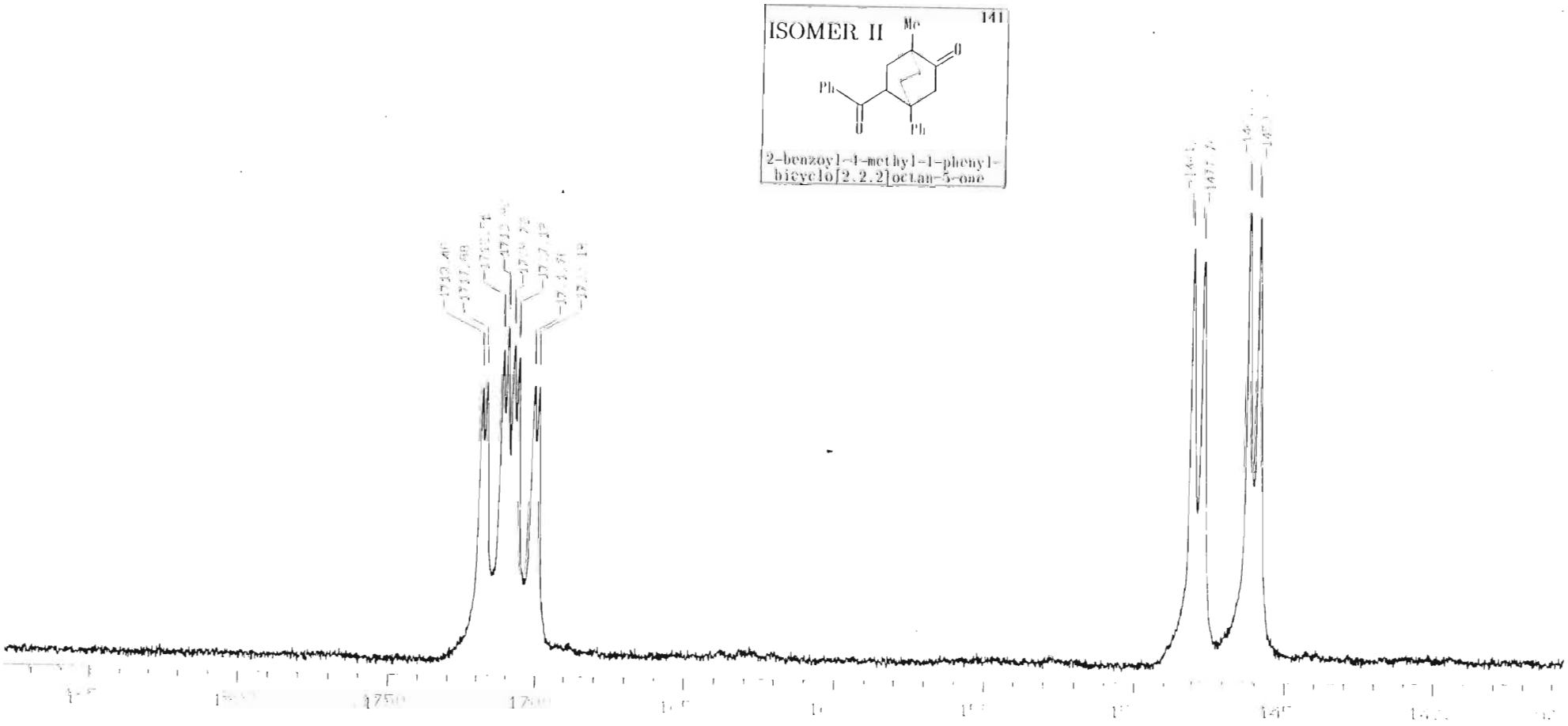
ISOMER II

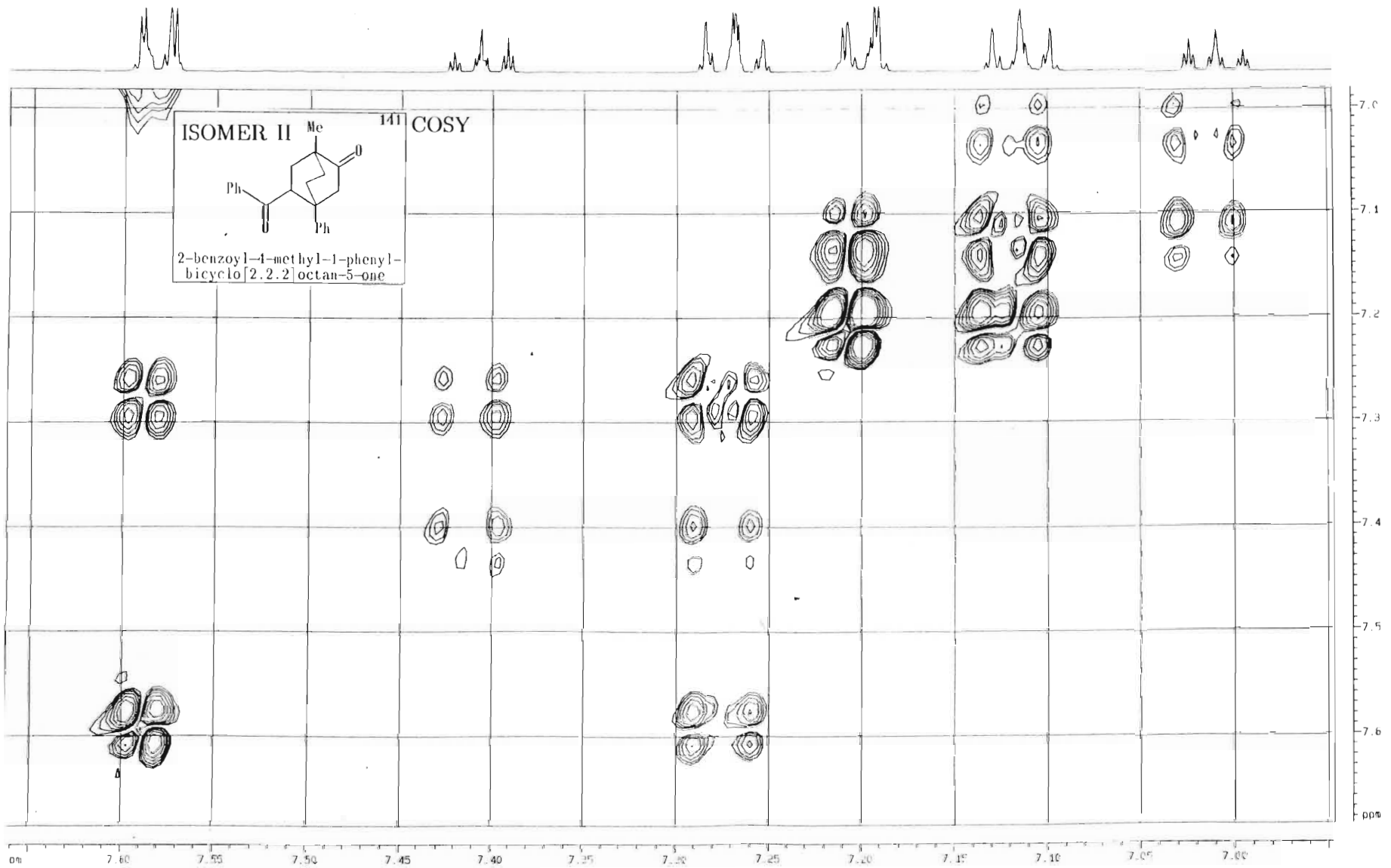


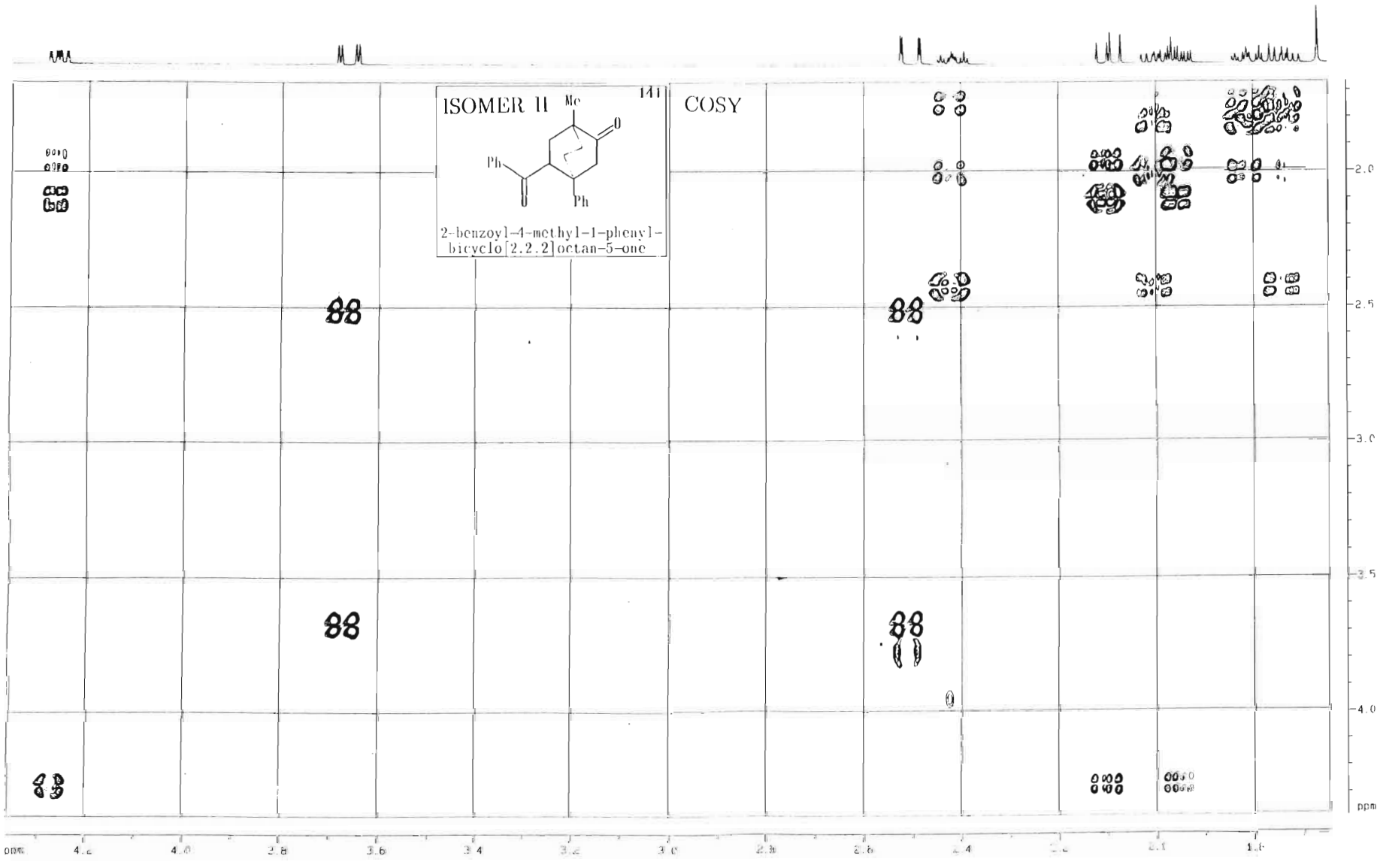
2-benzoyl-4-methyl-1-phenyl-bicyclo[2.2.2]octan-5-one

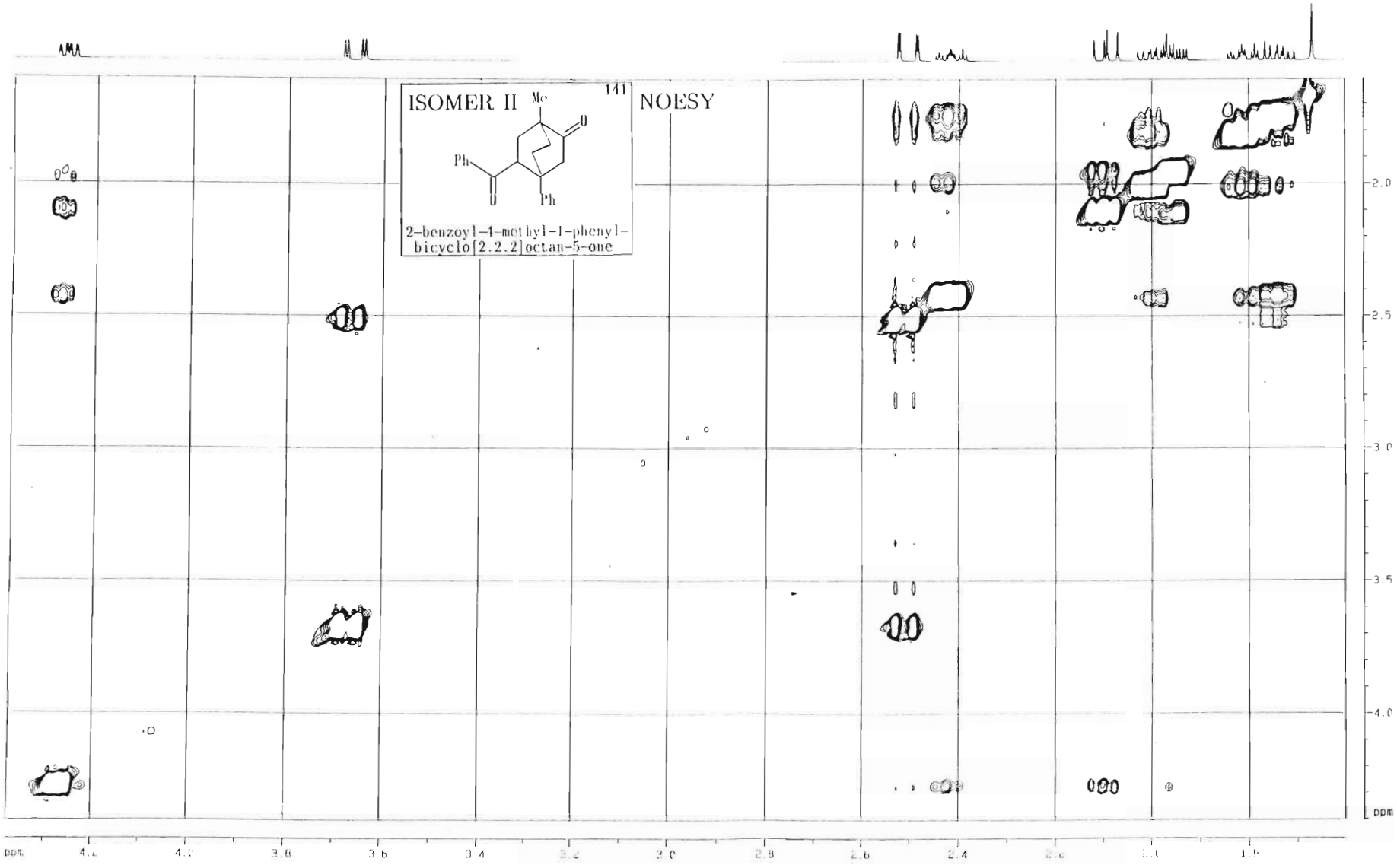


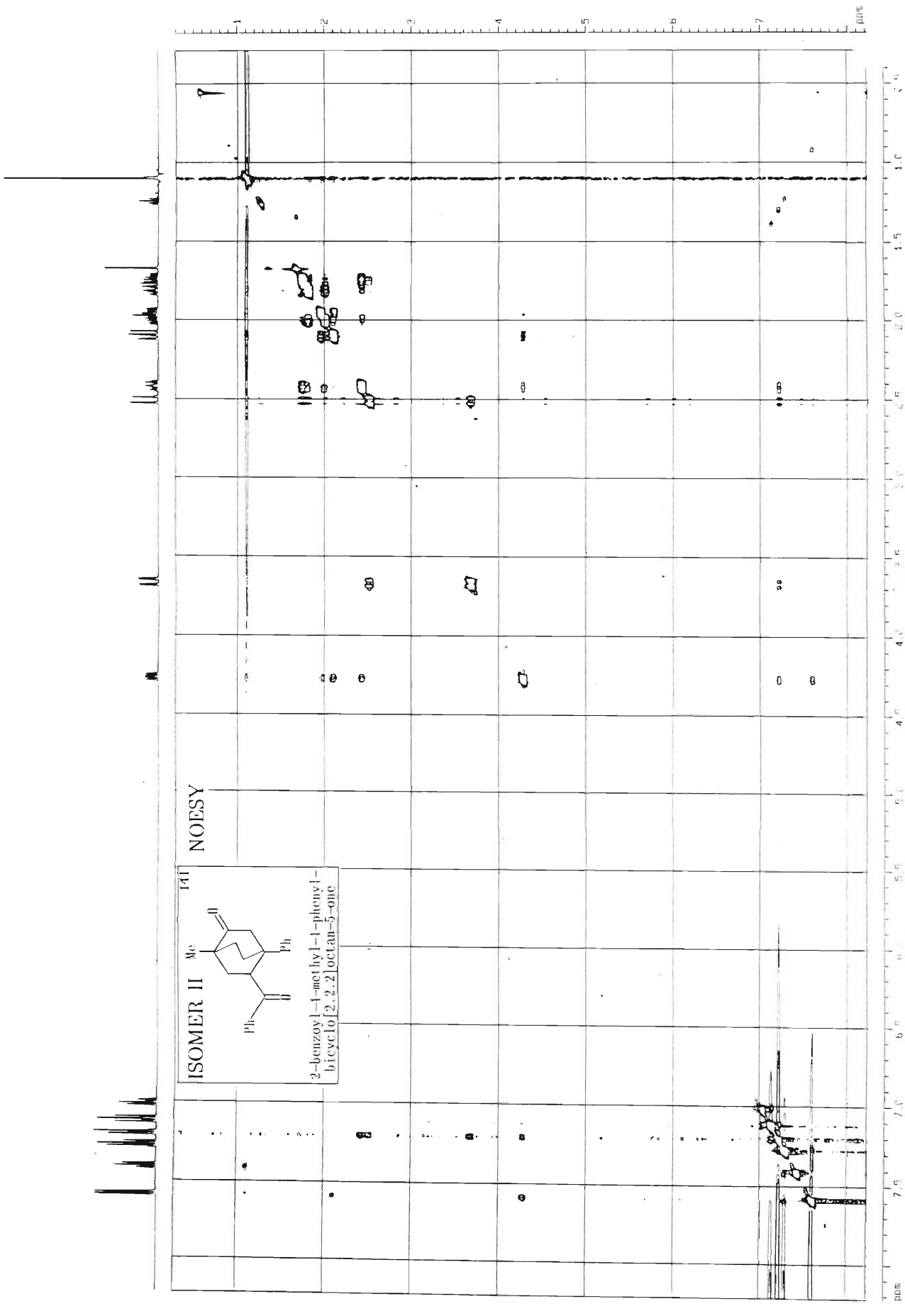
141
ISOMER II
Me
Ph
Ph
O
O
2-benzoyl-4-methyl-1-phenyl-bicyclo[2.2.2]octan-5-one


ISOMER II
141
Me
O
Ph
O
Ph
2-benzoyl-4-methyl-1-phenyl-bicyclo[2.2.2]octan-5-one


ISOMER II
Me
O
Ph
O
Ph
141
COSY
2-benzoyl-4-methyl-1-phenyl-
bicyclo[2.2.2]octan-5-one
7.0
7.1
7.2
7.3
7.4
7.5
7.6
ppm
7.60
7.55
7.50
7.45
7.40
7.25
7.20
7.10

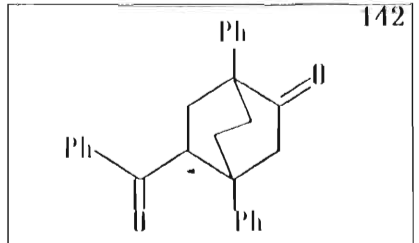

ISOMER II
141
COSY
Me
O
Ph
Ph
O
2-benzoyl-4-methyl-1-phenyl-
bicyclo[2.2.2]octan-5-one
2.0
2.5
3.0
3.5
4.0
ppm
ppm
4.2
4.0
3.8
3.6
3.4
3.2
3.0
2.8
2.6
2.4
2.2
1.8


ISOMER II
141
NOESY
Me
O
Ph
Ph
2-benzoyl-4-methyl-1-phenyl-
bicyclo[2.2.2]octan-5-one
2.0
2.5
3.0
3.5
4.0
ppm
ppm
4.4
4.0
3.6
3.4
3.2
2.8
2.6
2.4
1.6


NOESY
ISOMER II
2-benzoyl-4-methyl-1-phenyl-bicyclo[2.2.2]octan-5-one
Me
Ph
Ph
O
O
ppm

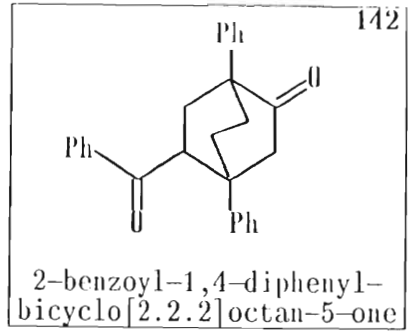
H90301.BR428 IN CDCL3.

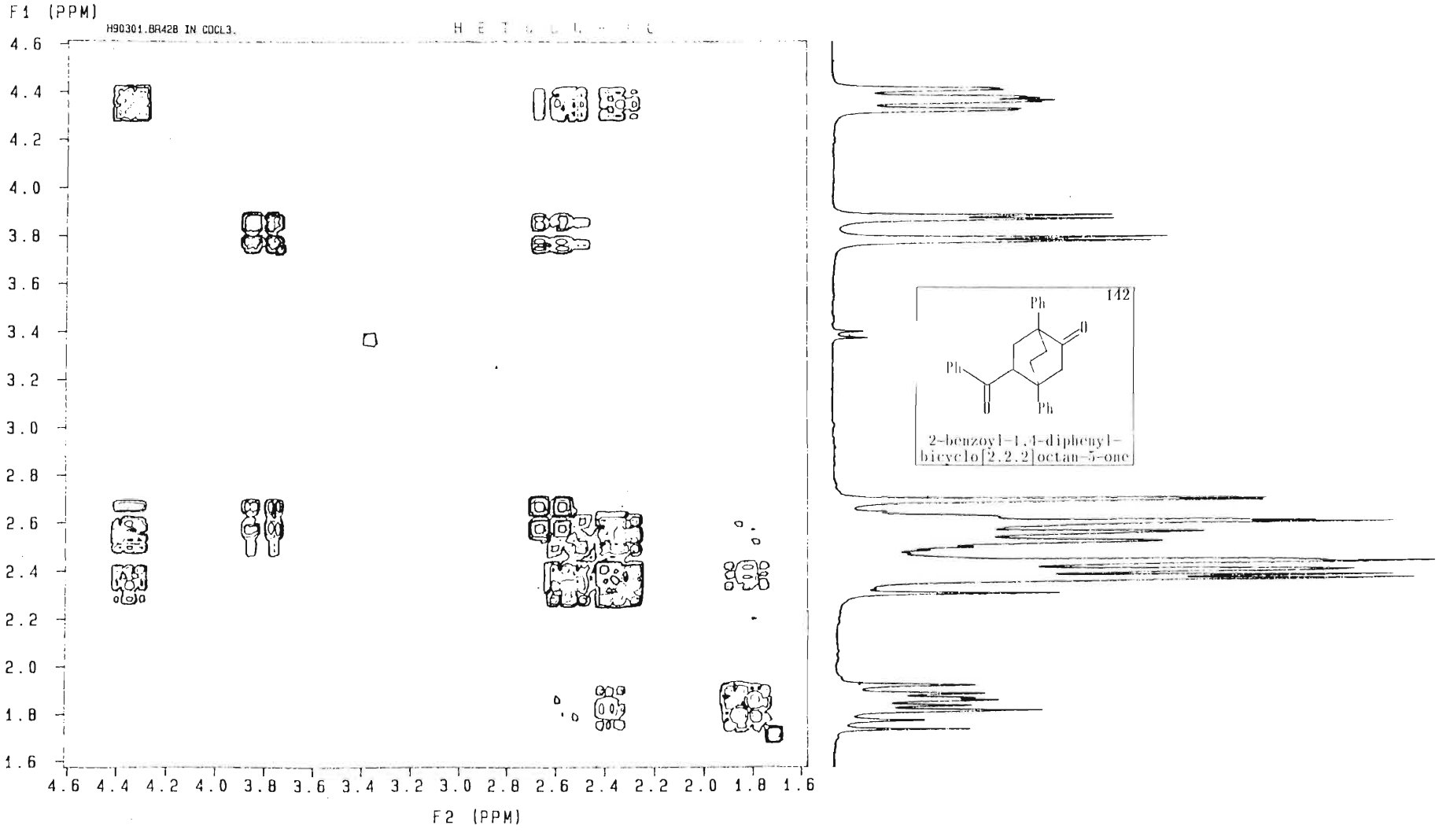
142



2-benzoyl-1,4-diphenyl-bicyclo[2.2.2]octan-5-one

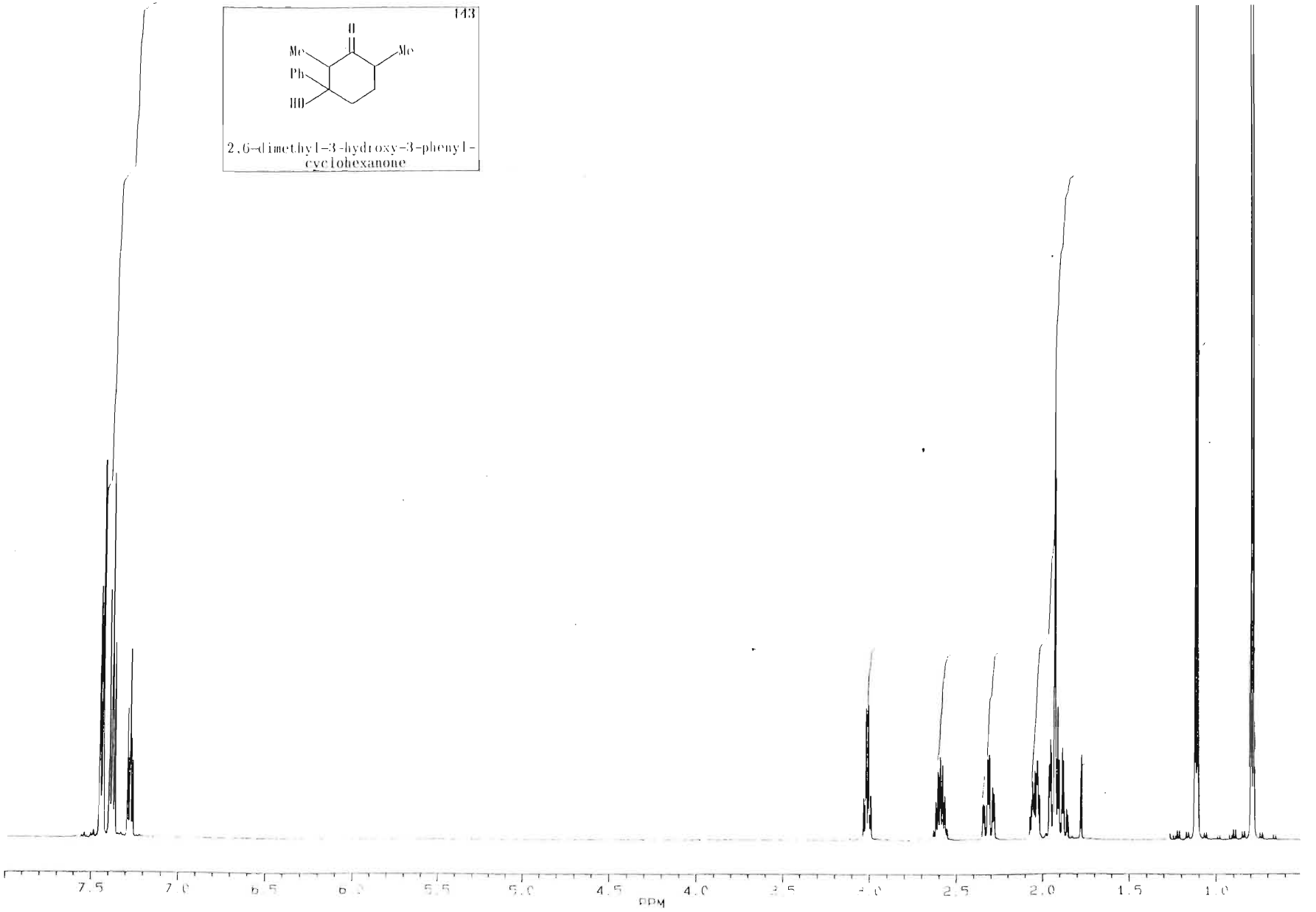
H90301.BR428 IN CDCL3.

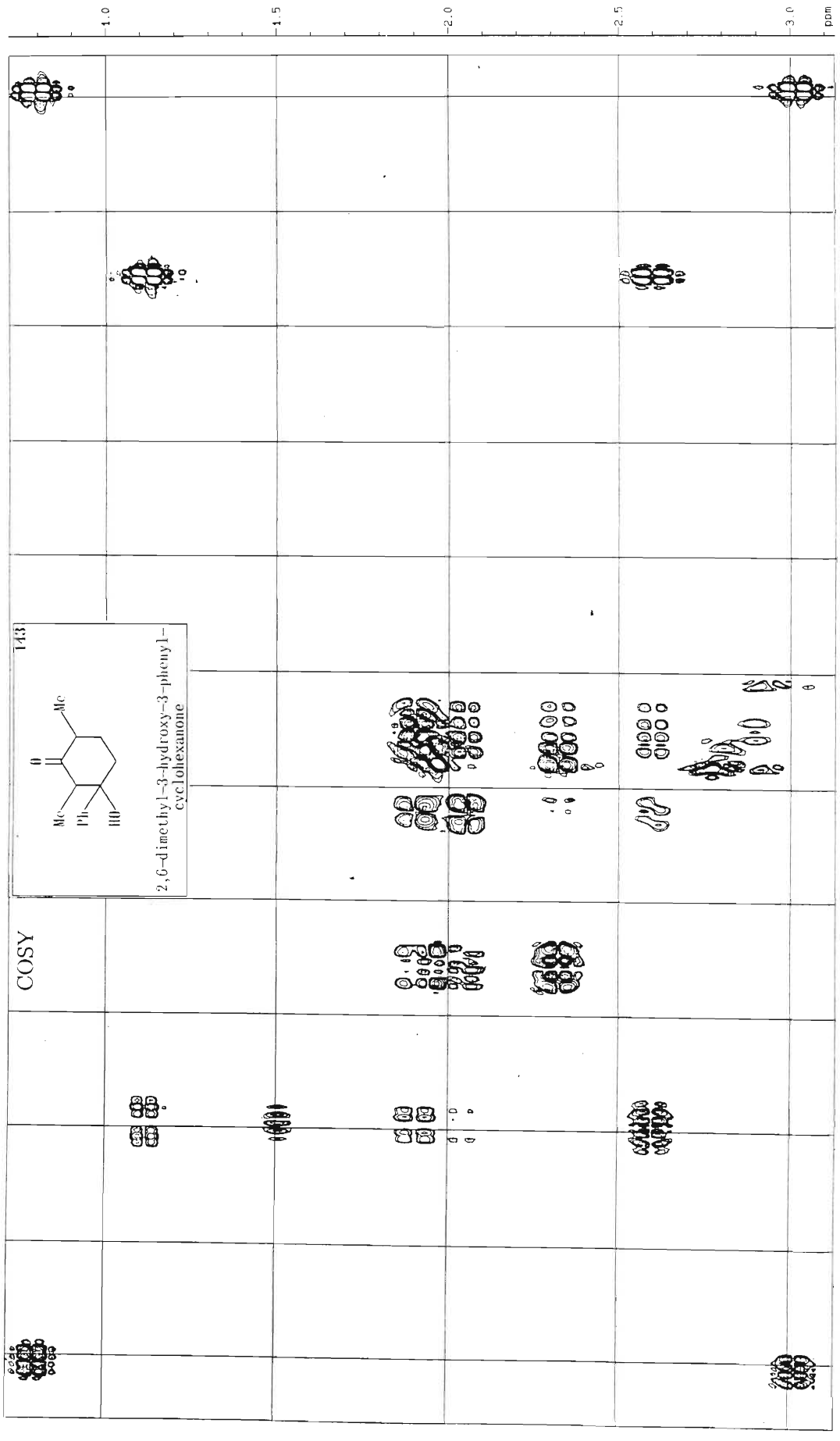


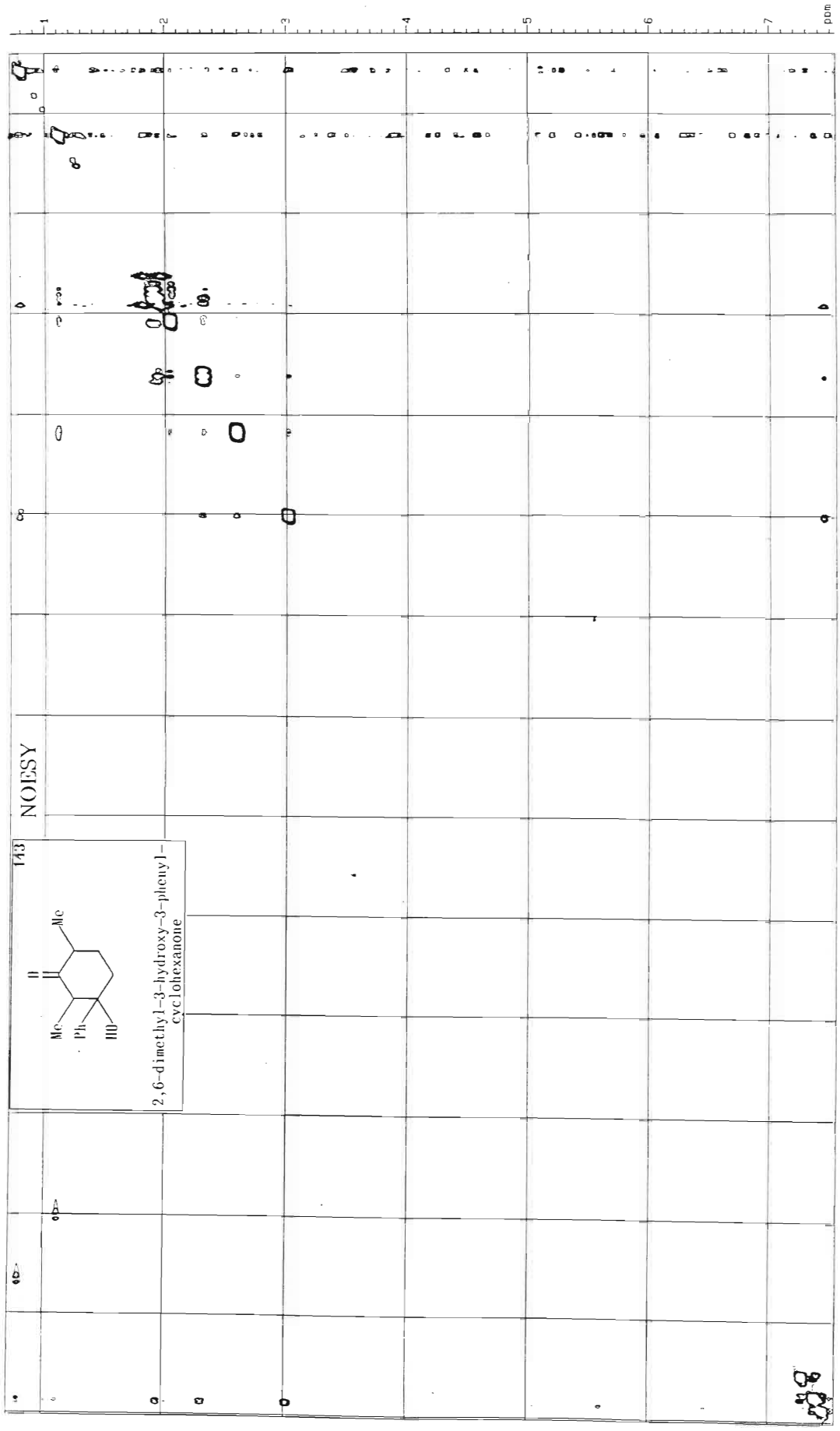


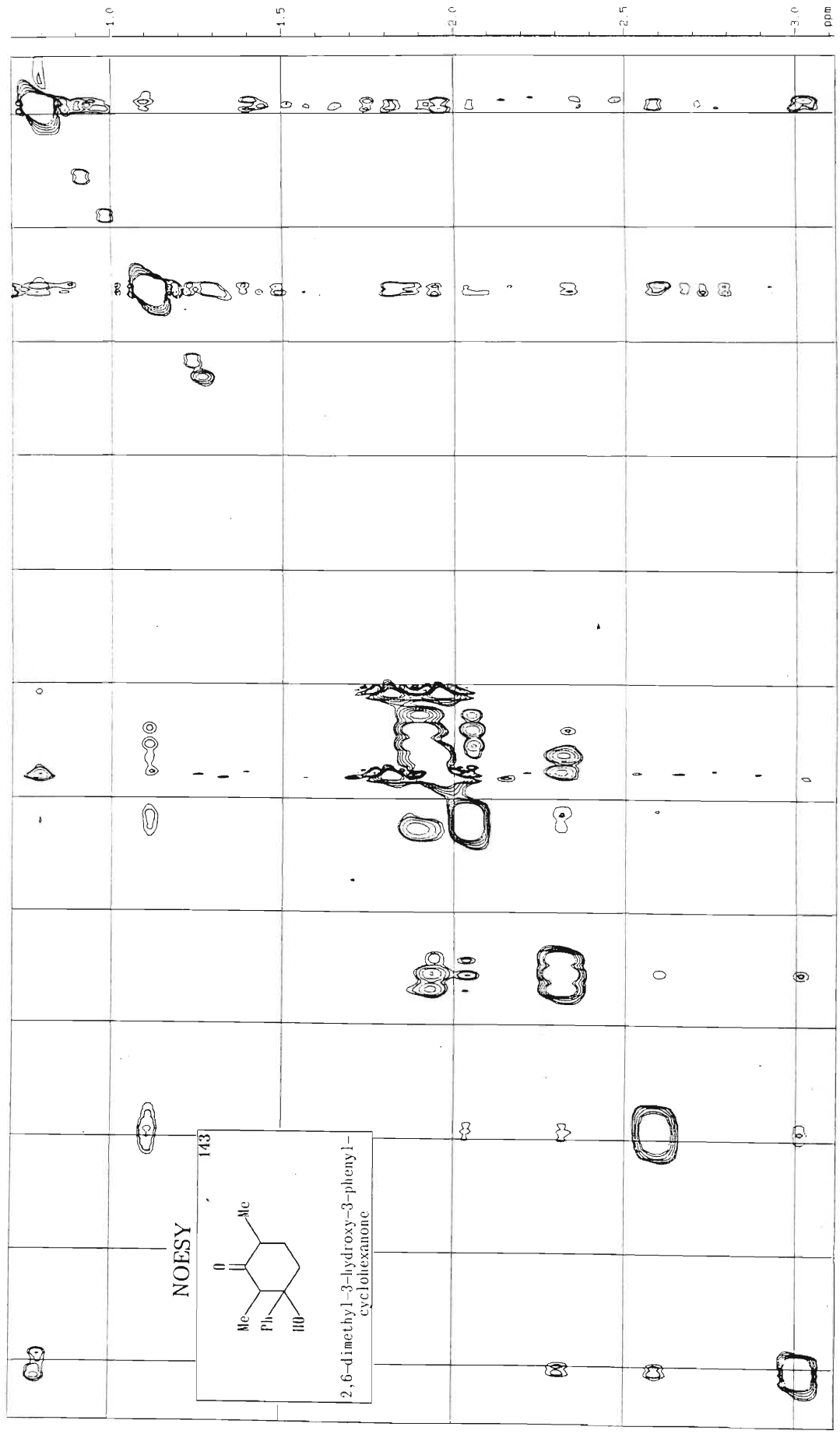
142

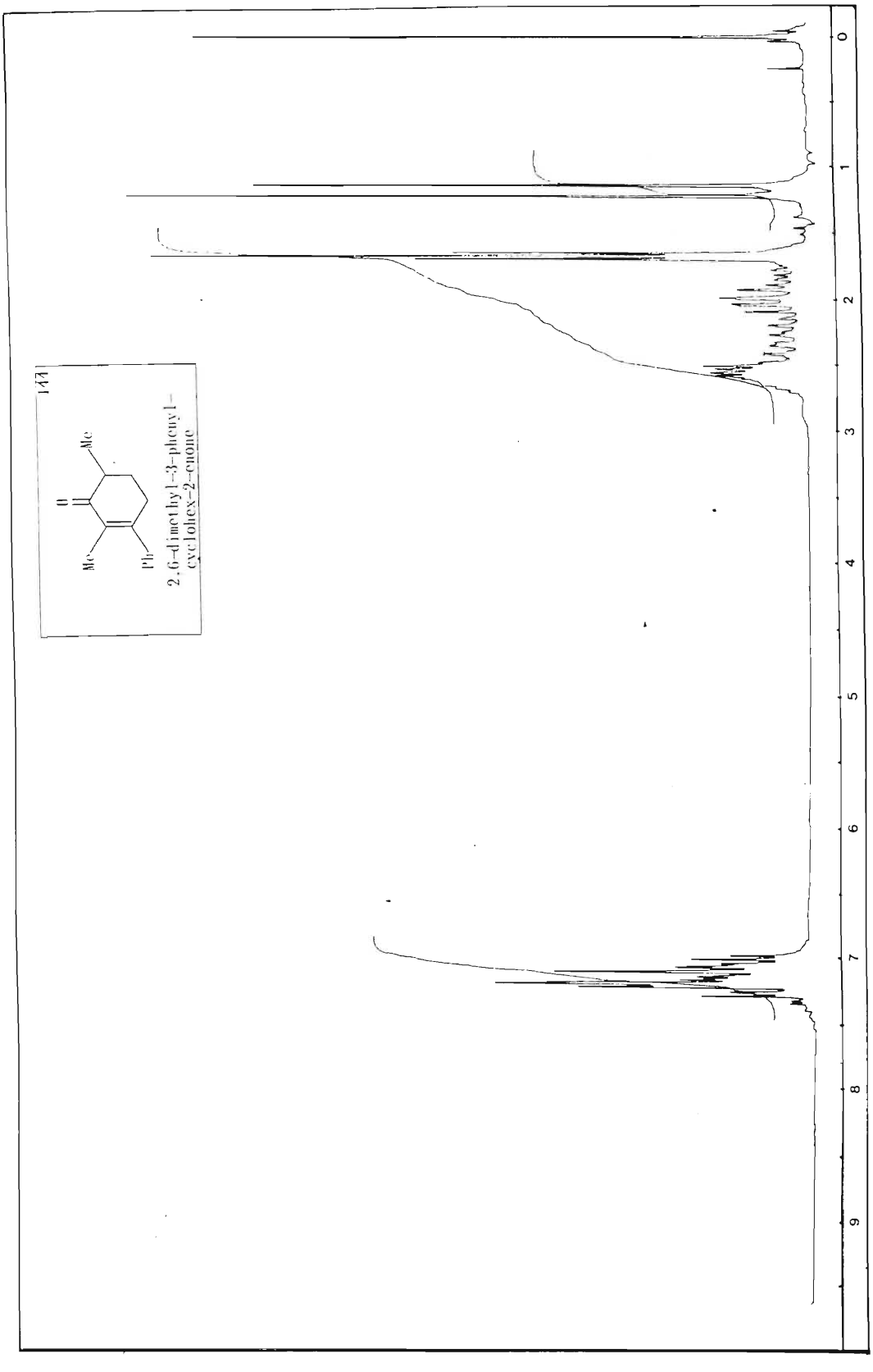
2-benzoyl-1,4-diphenyl-bicyclo[2.2.2]octan-5-one


143
Me
Ph
HO
Me
2,6-dimethyl-3-hydroxy-3-phenyl-cyclohexanone
BRUKER
DATE 5-6-89
TIME 7:40
SF 500.135
O1 8470.020
SI 65536
TD 65536
SW 10000.000
HZ/PT .305
PW 3.0
RD 0.0
AQ 3.277
RG 40
NS 57
O2 0.0
DP 63L PO
LB .300
GB 0.0
F1 8.000P
F2 .501P
HZ/CM 107.169
PPM/CM .214
SR 5416.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
PPM


COSY
143
2,6-dimethyl-3-hydroxy-3-phenyl-cyclohexanone
Me
Ph
HO
ppm

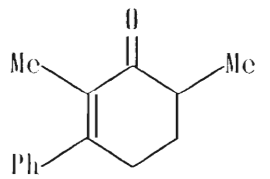

NOESY
143
2,6-dimethyl-3-hydroxy-3-phenyl-cyclohexanone
Me
Me
Ph
HO
ppm


NOESY
143
2,6-dimethyl-3-hydroxy-3-phenyl-cyclohexanone
Me
O
Me
Ph
HO
ppm


143
Me
O
Me
Ph
2,6-dimethyl-3-phenyl-
cyclohex-2-enone
0
1
2
3
4
5
6
7
8
9

H89169.BH423-10 IN CDCL3/TMS.

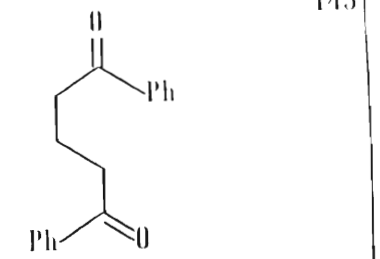
144



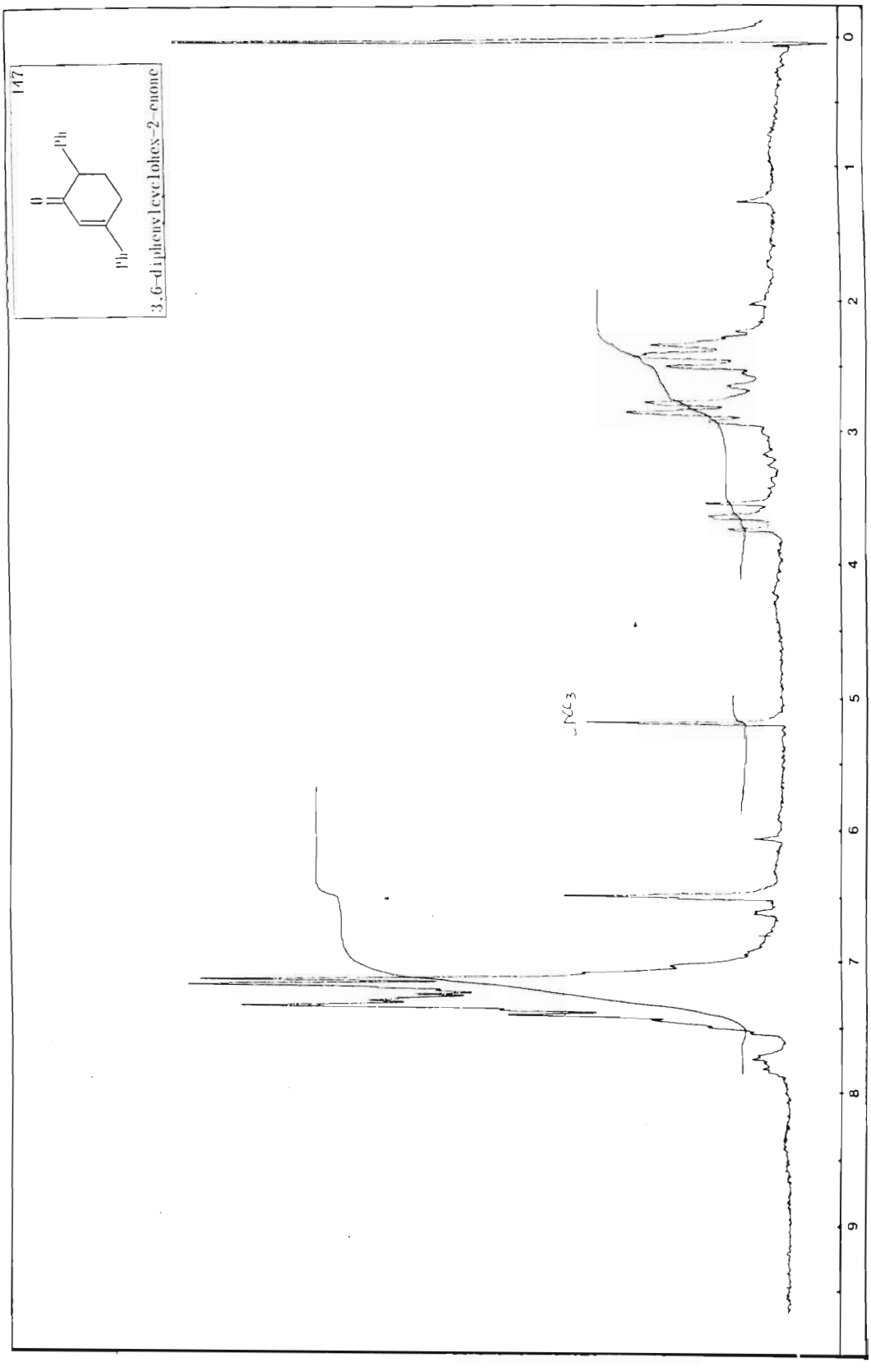
2,6-dimethyl-3-phenyl-cyclohex-2-enone

H89108.BH425-11 IN CDCL3/TMS.

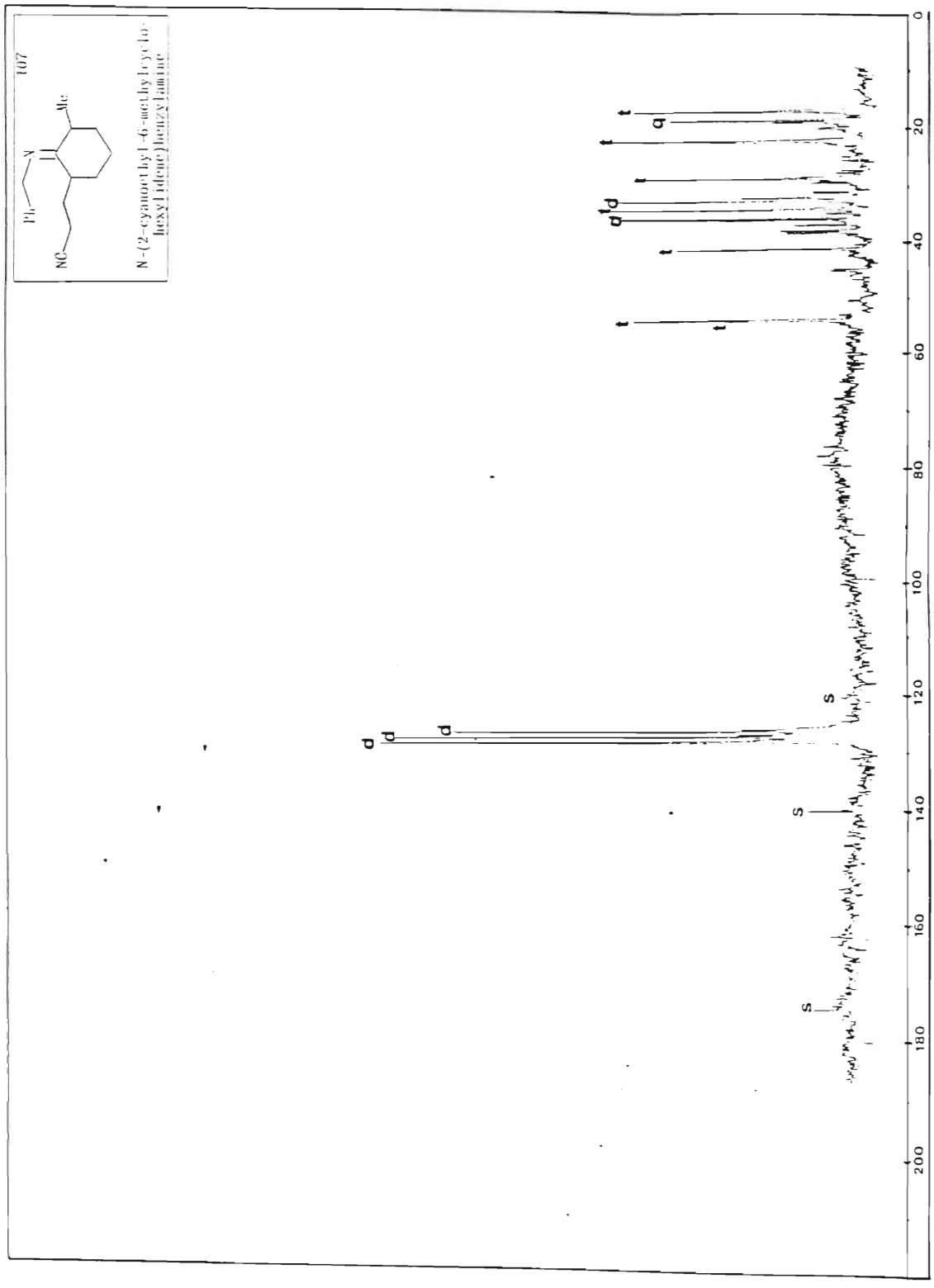
145

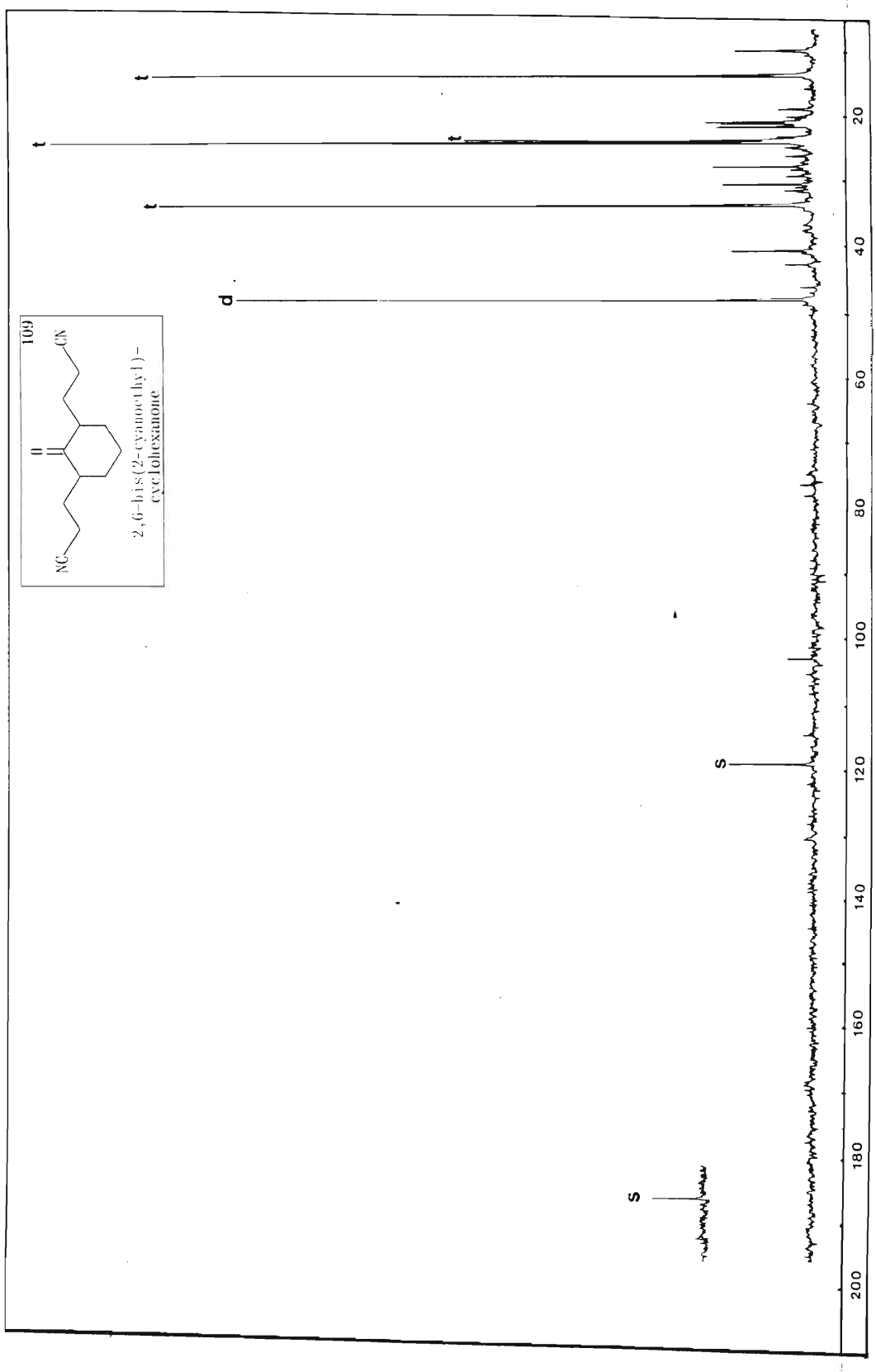


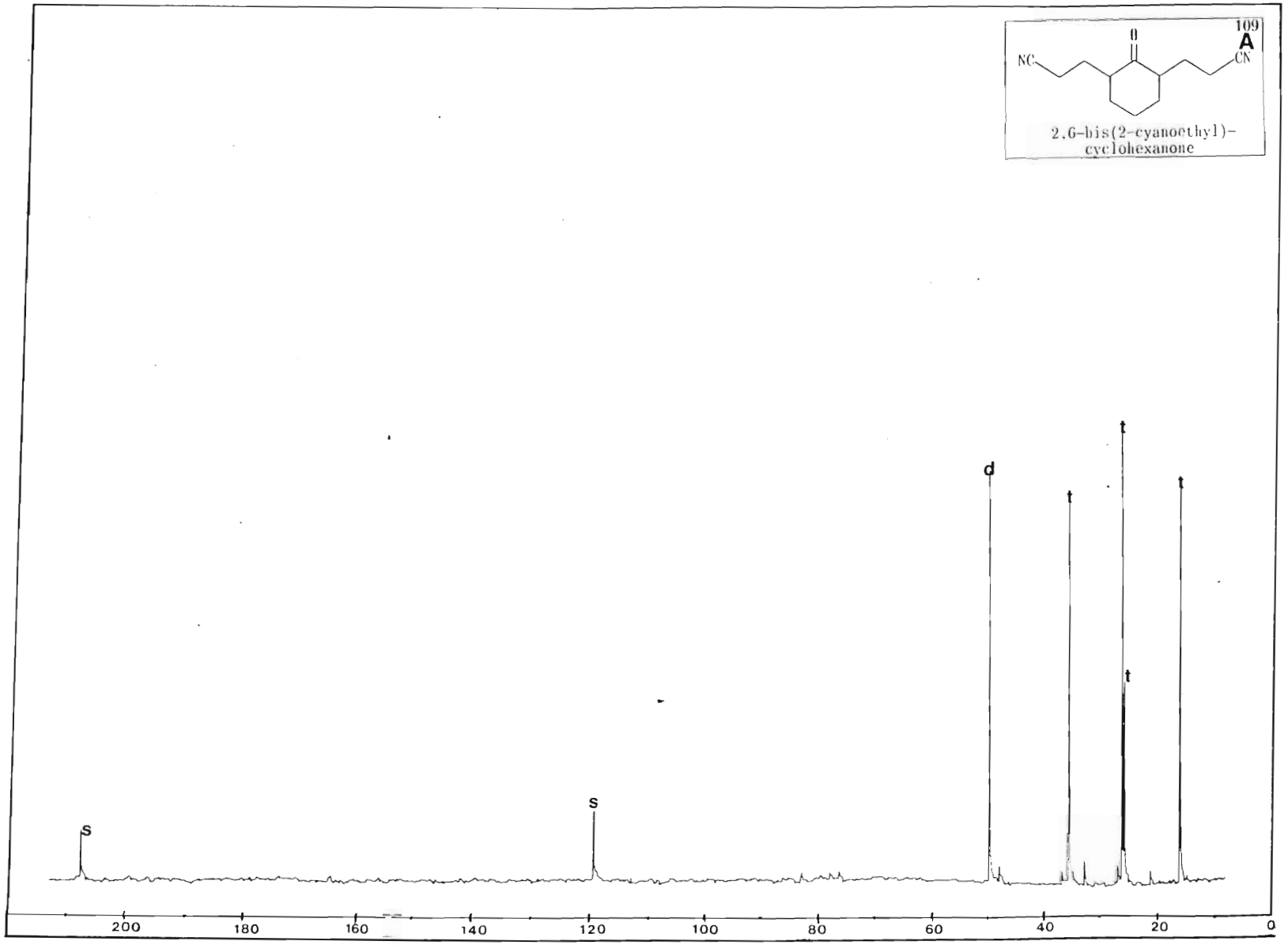
1,5-diphenylpentan-1,5-dione

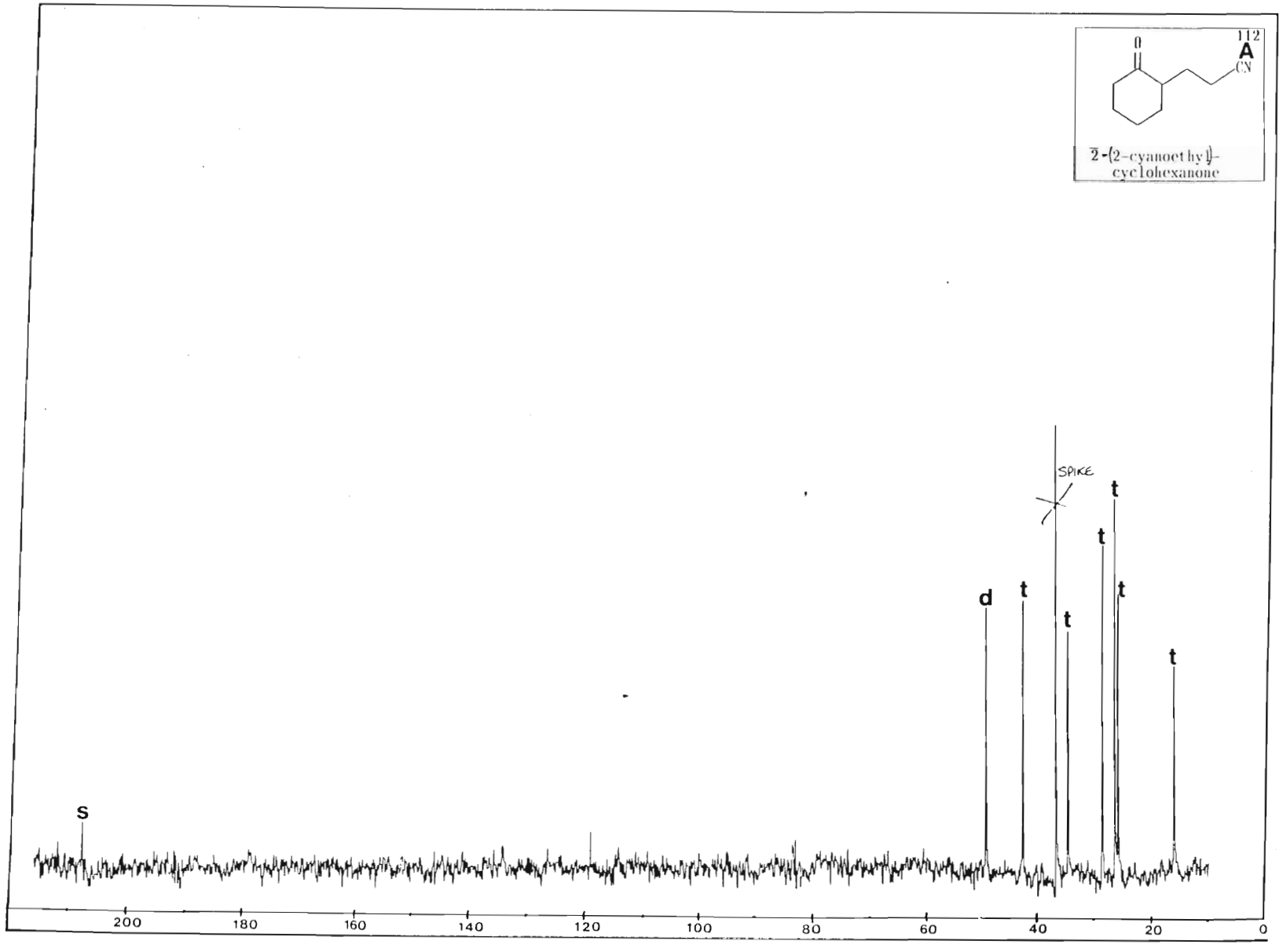

147
3,6-diphenylcyclohex-2-enone
Ph
O
Ph
0
1
2
3
4
5
6
7
8
9

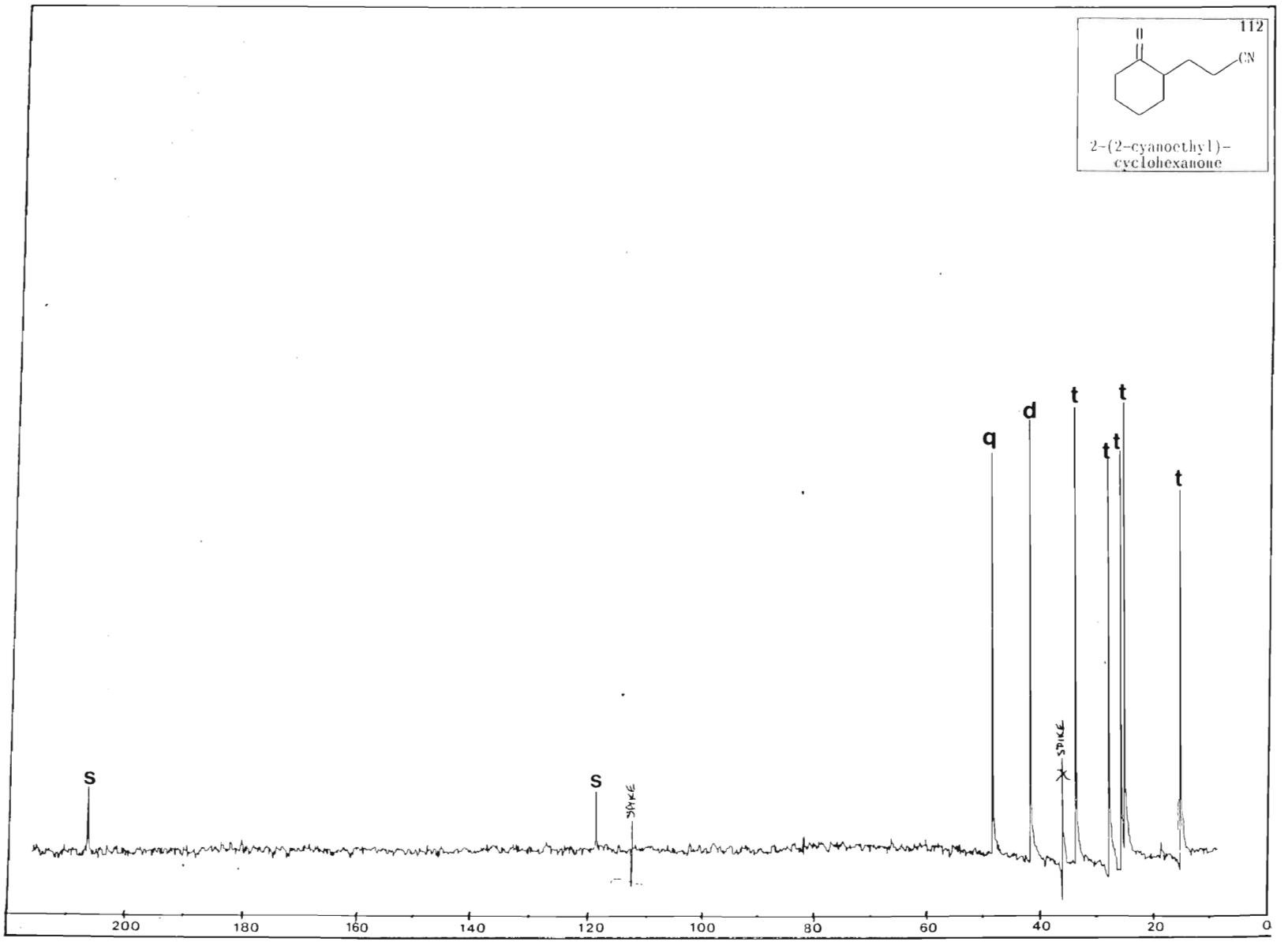
3.3 ^{13}C–NMR SPECTRA

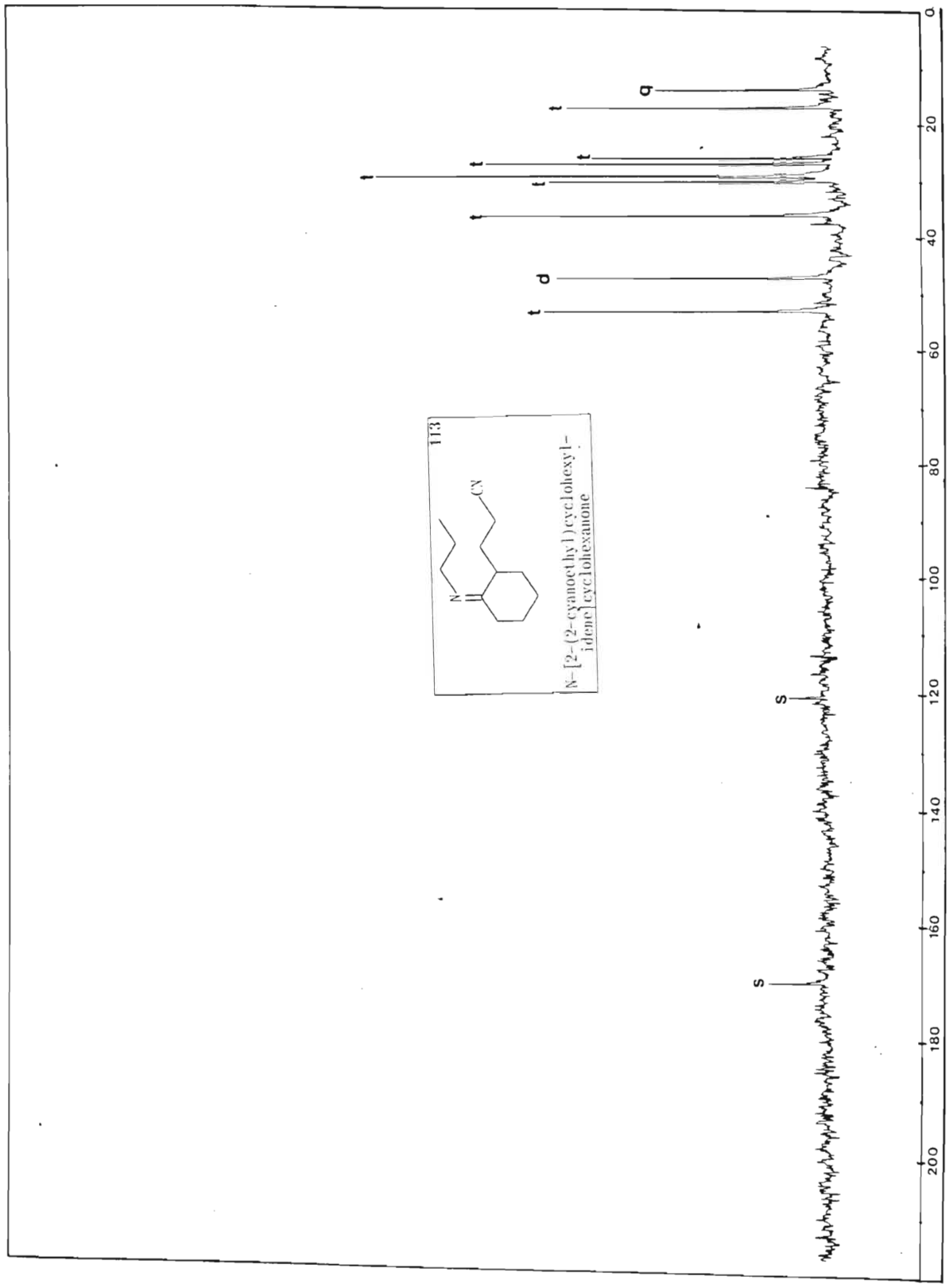

107
Me
N
Ph
NC
N-(2-cyanoethyl-6-methylcyclohexylidene)benzylamine
d
d
d
s
s
s
t
t
t
t
d
d
t
q
t
0
20
40
60
80
100
120
140
160
180
200

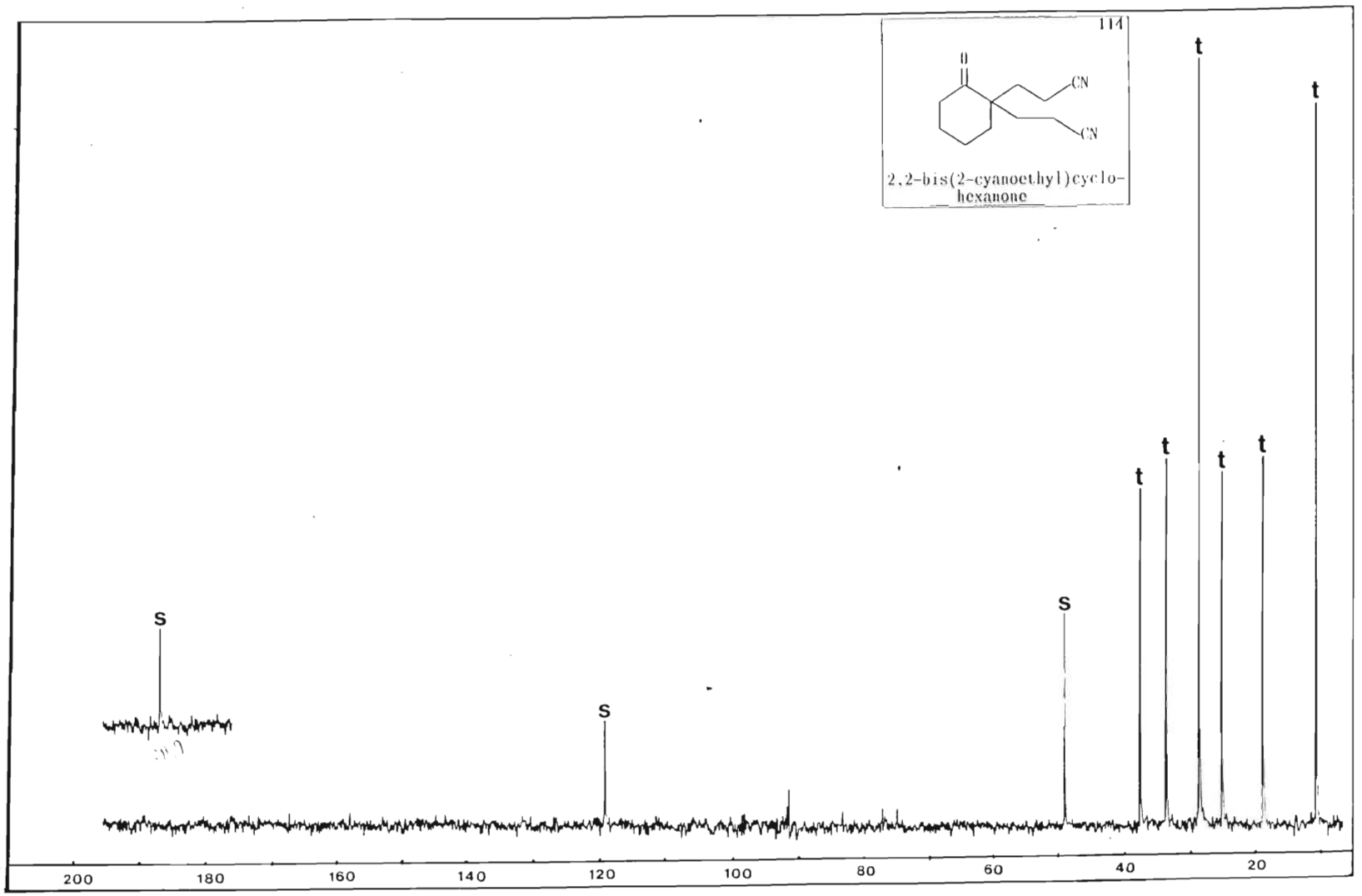

109
NC
CN
O
2,6-bis(2-cyanoethyl)-
cyclohexanone
d
t
t
t
t
t
s
s
20
40
60
80
100
120
140
160
180
200

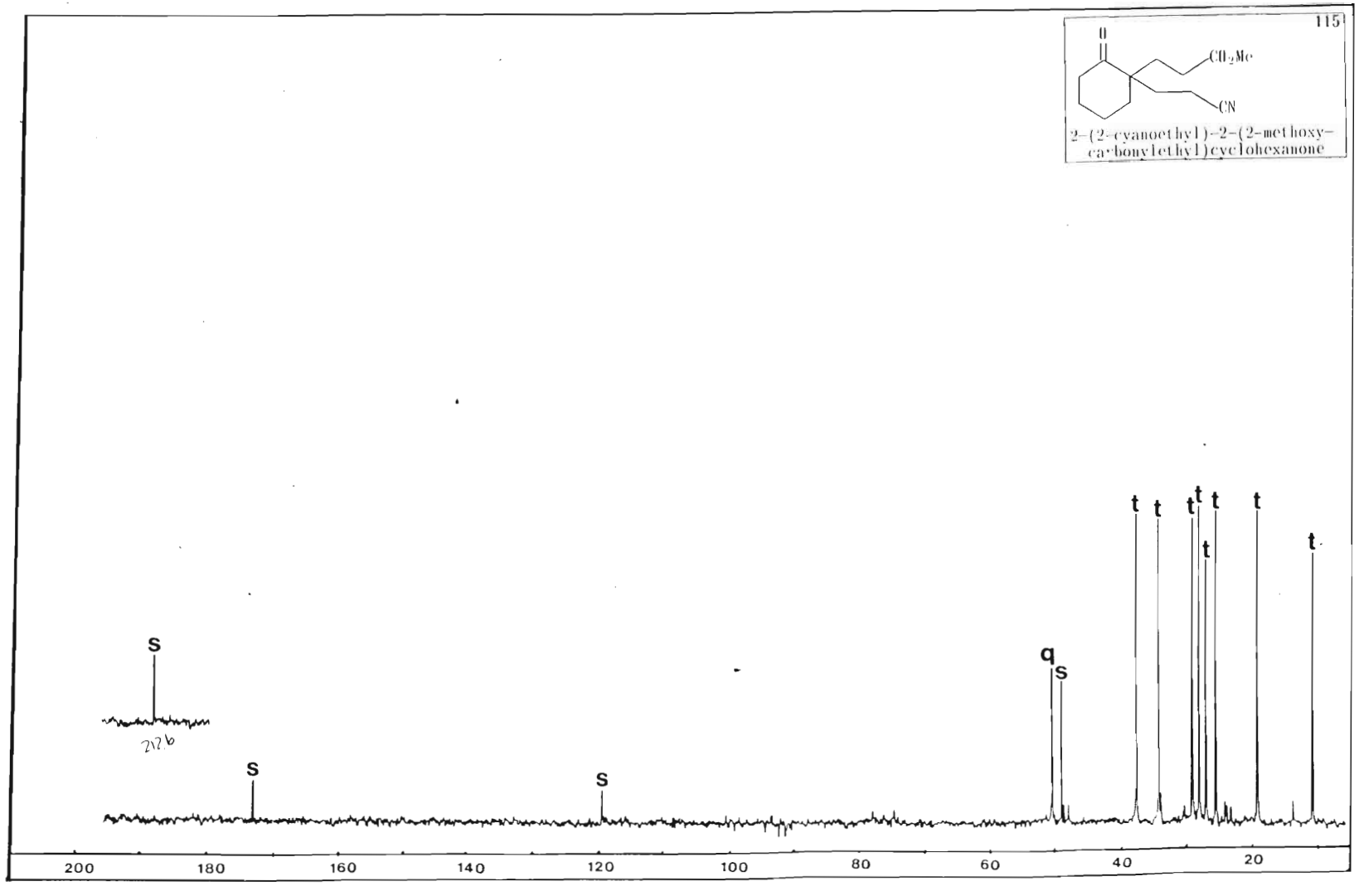

109
A
NC
O
CN
2,6-bis(2-cyanoethyl)-
cyclohexanone
S
S
d
t
t
t
200
180
160
140
120
100
80
60
40
20
0

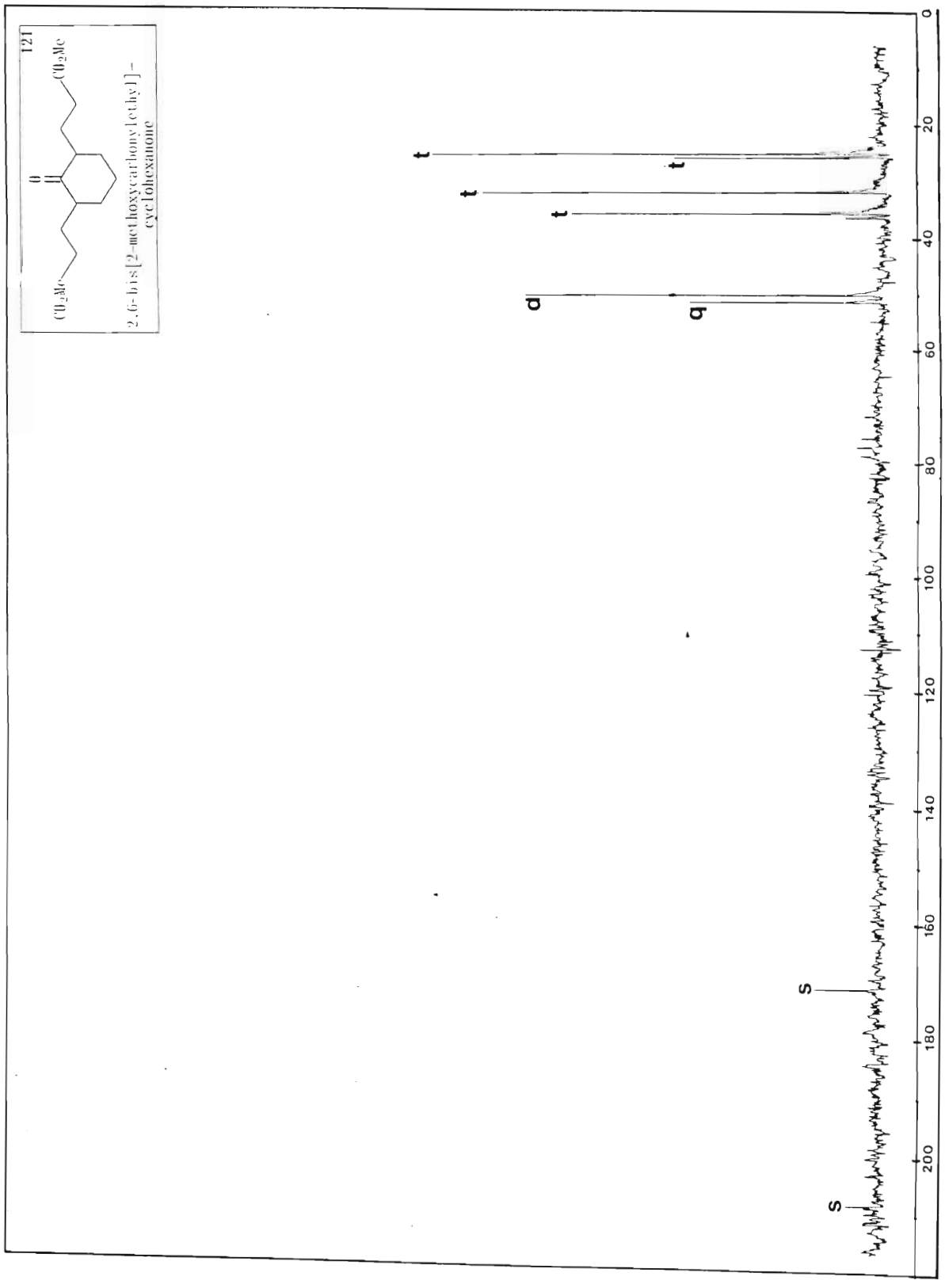

112
A
CN
2-(2-cyanoethyl)-cyclohexanone
SPIKE
s
d
t
t
t
t
t
t
200
180
160
140
120
100
80
60
40
20
0

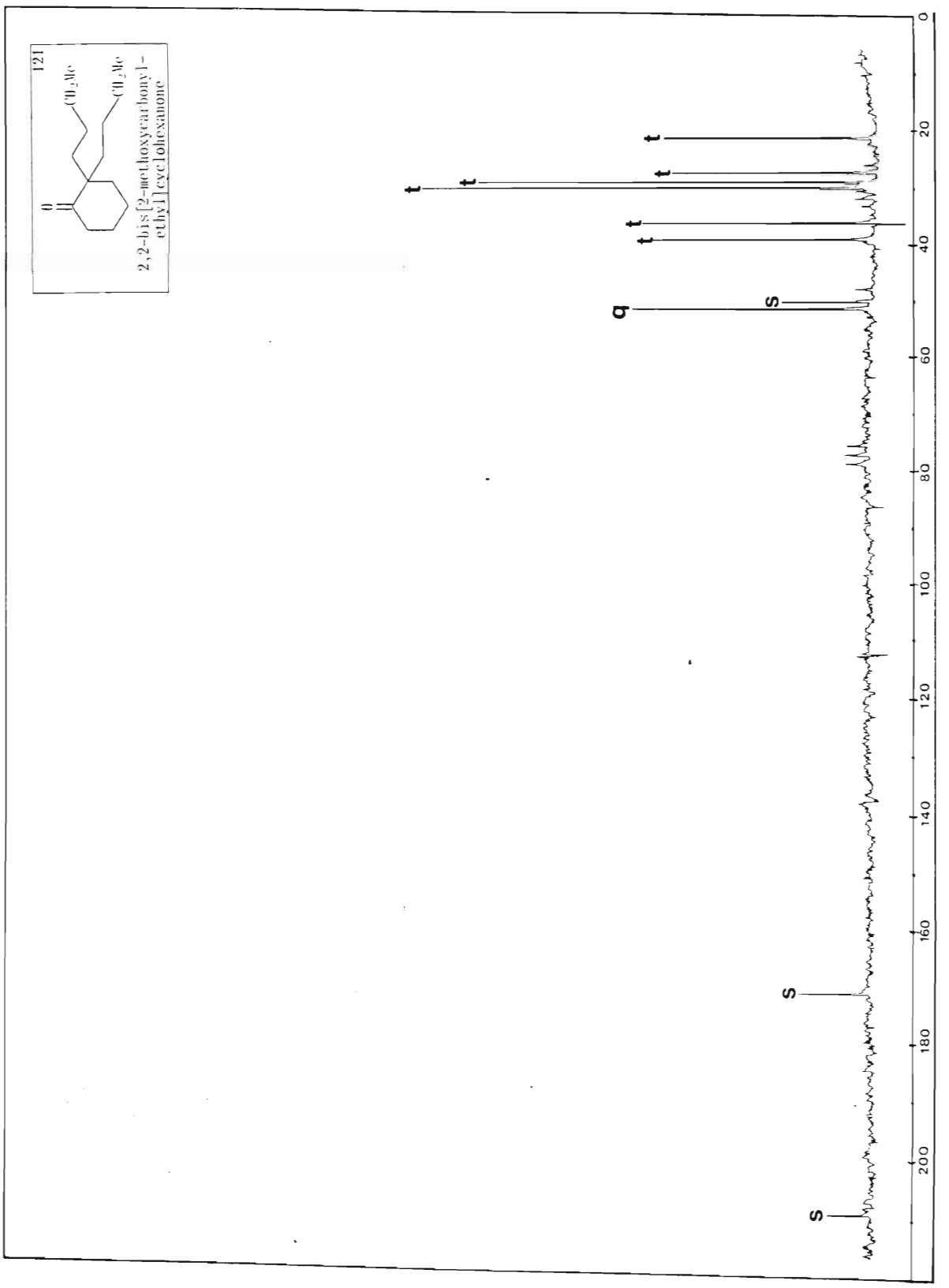

112
O
CN
2-(2-cyanoethyl)-
cyclohexanone
s
s
SPIKE
q
d
t
t
t
t
t
SPIKE
200
180
160
140
120
100
80
60
40
20
0

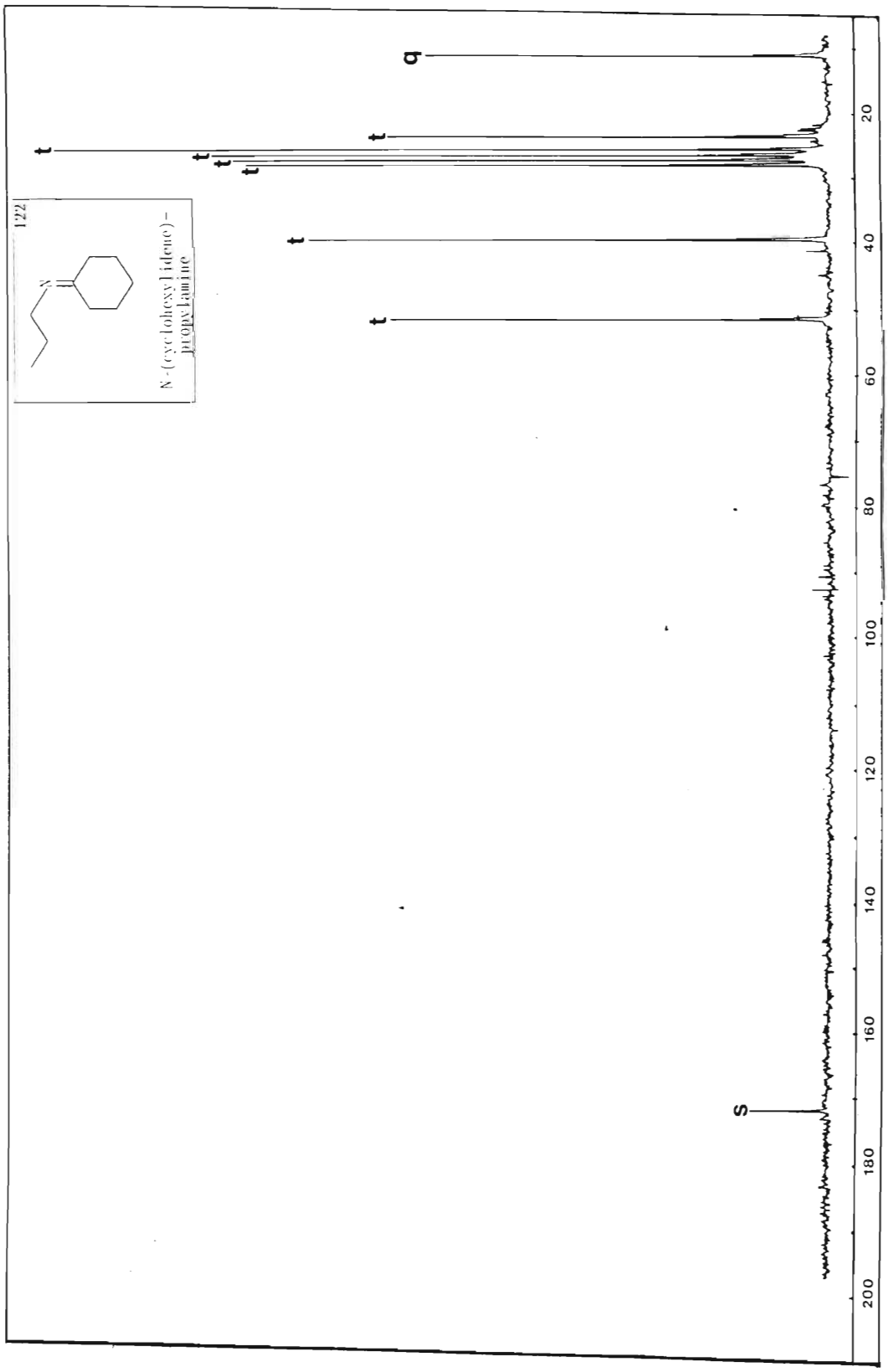

113
N-[2-(2-cyanoethyl)cyclohexyl-idene]cyclohexanone
CN
N
t
t
t
t
t
t
d
t
q
t
s
s
0
20
40
60
80
100
120
140
160
180
200

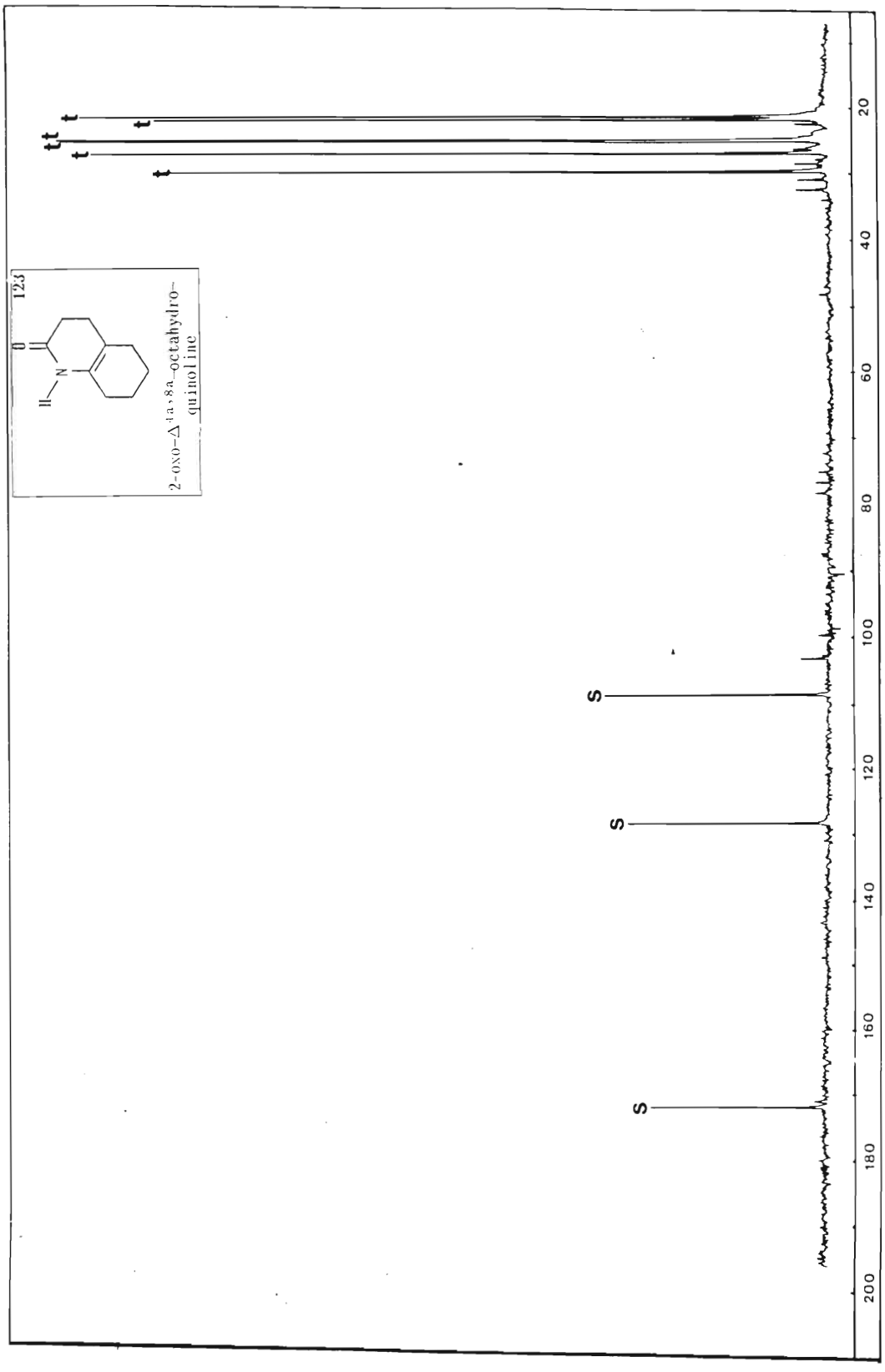

114
O
CN
CN
2,2-bis(2-cyanoethyl)cyclo-
hexanone
t
t
t
t
t
t
S
S
S
200
180
160
140
120
100
80
60
40
20

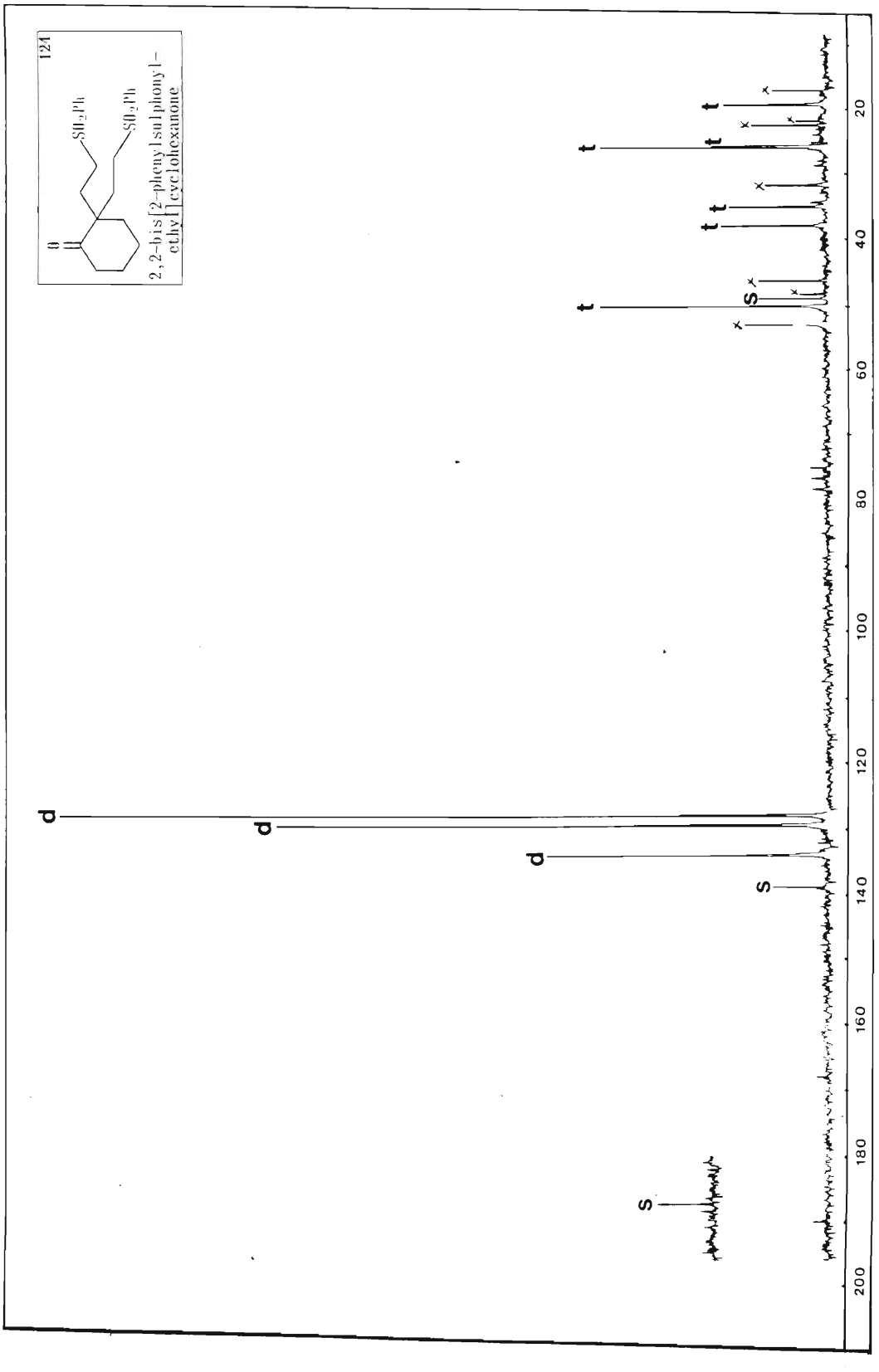

115
O
CH2Me
CN
2-(2-cyanoethyl)-2-(2-methoxy-carbonylethyl)cyclohexanone
s
s
s
q
s
t
t
t
t
t
t
t
t
200
180
160
140
120
100
80
60
40
20

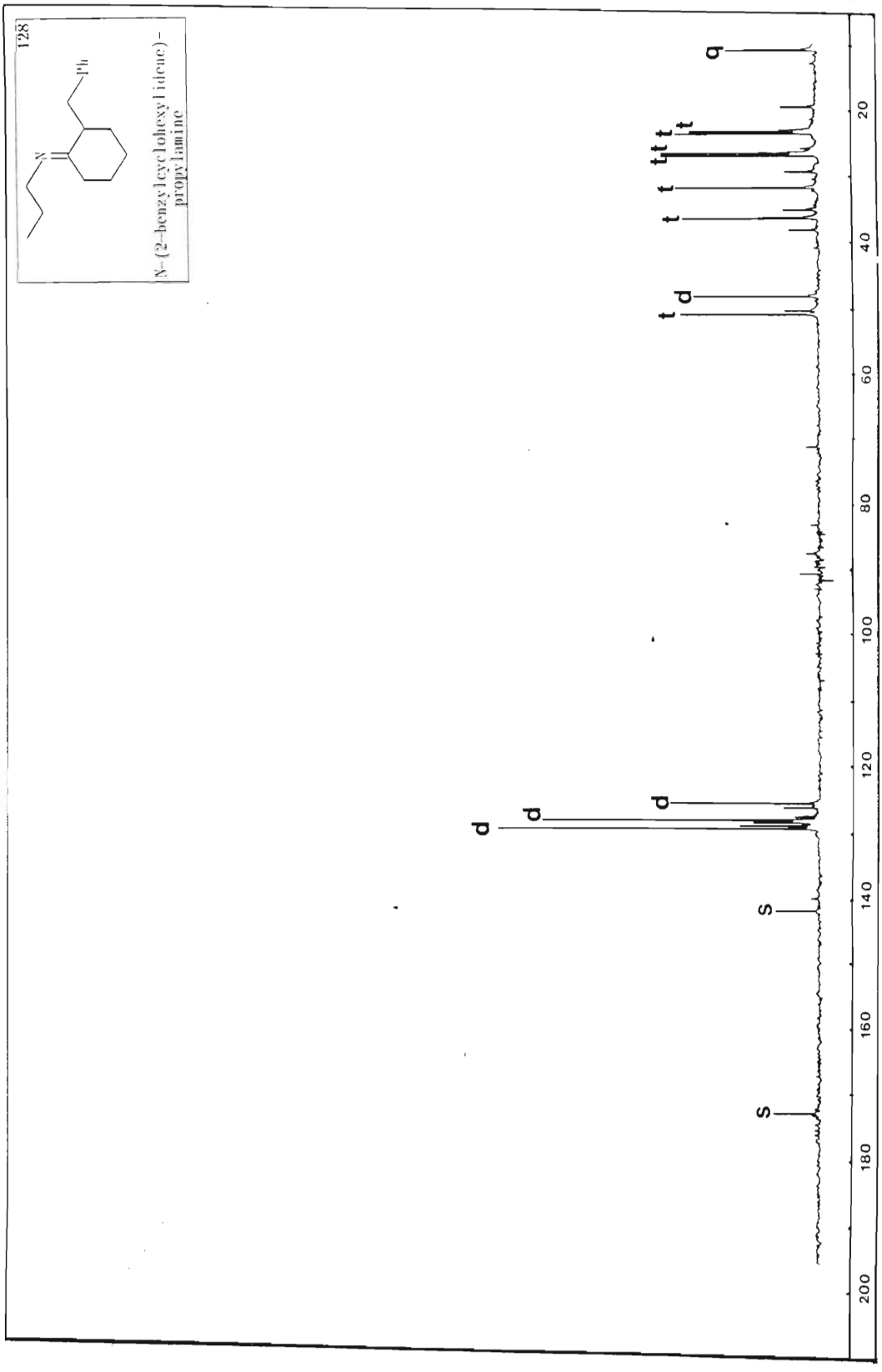

121
O
(O2Me
(O2Me
2,6-bis[2-methoxycarbonylethyl]-
cyclohexanone
t
t
t
t
d
q
s
s
200
180
160
140
120
100
80
60
40
20
0

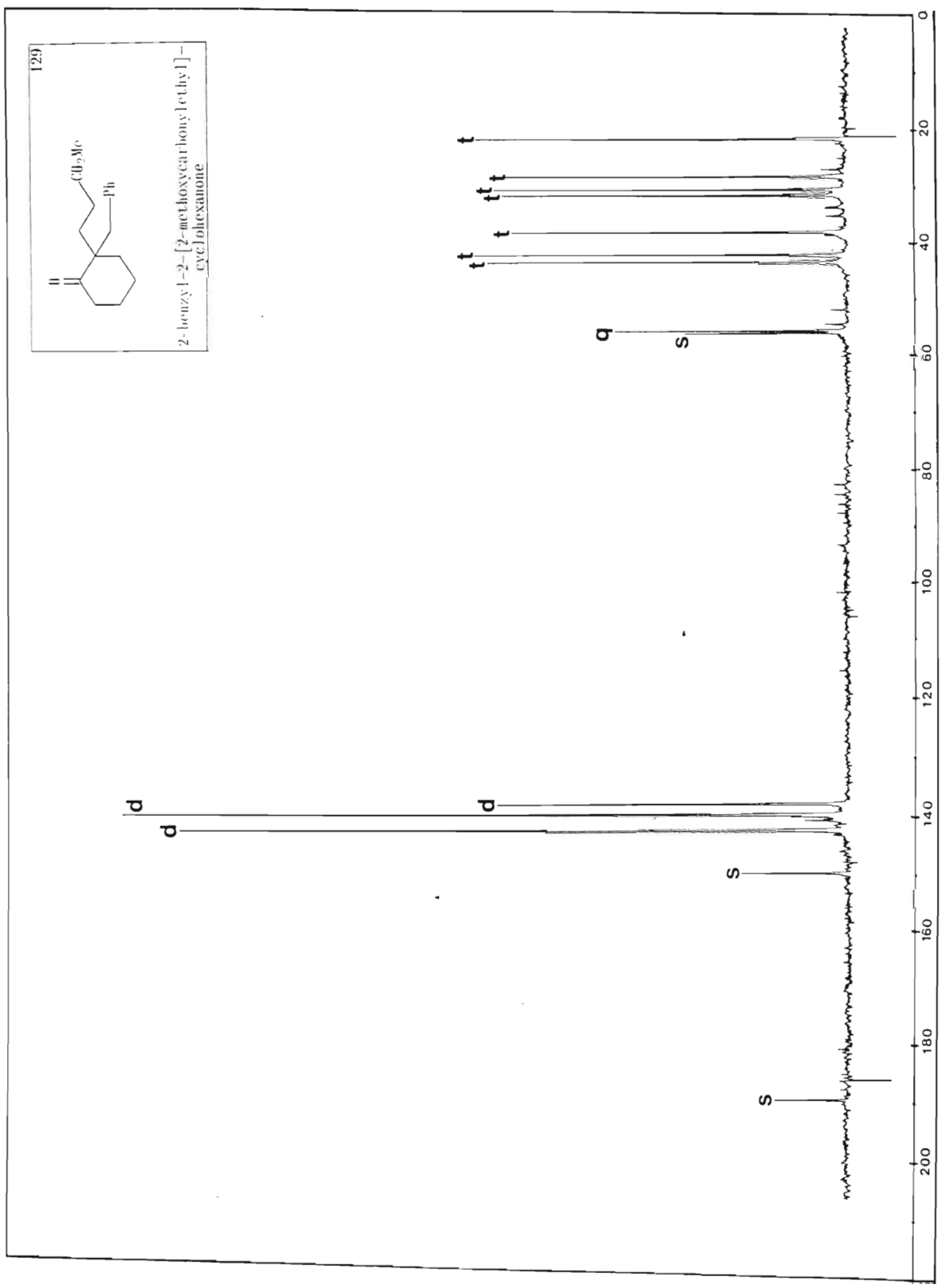

121
CO_2Me
CO_2Me
O
2,2-bis[2-methoxycarbonyl-ethyl]cyclohexanone
t
t
t
t
t
t
q
s
s
s
0
20
40
60
80
100
120
140
160
180
200


122
N-(cyclohexylidene)-propylamine
s
q
t
t
t
t
t
t
20
40
60
80
100
120
140
160
180
200


12.3
2-oxo-Δ4a,8a-octahydro-quinoline
t
t
tt
t
t
s
s
s
20
40
60
80
100
120
140
160
180
200

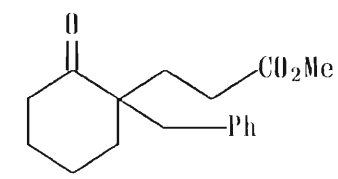

124
O
SO2Ph
SO2Ph
2,2-bis[2-phenylsulphonyl-ethyl]cyclohexanone
d
d
d
s
t
t
t
t
t
s
x
x
x
x
x
x
x
x
s
200
180
160
140
120
100
80
60
40
20


128
N
Ph
N-(2-benzylcyclohexylidene)-propylamine
d
d
d
s
s
t
d
t
t
t
t
t
q
200
180
160
140
120
100
80
60
40
20


129
CO2Me
Ph
2-benzyl-2-[2-methoxycarbonylethyl]-cyclohexanone
d
d
d
s
s
q
s
t
t
t
t
t
t
0
20
40
60
80
100
120
140
160
180
200

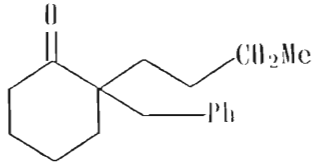
6659/90.BR346F1 IN CDCL3

129



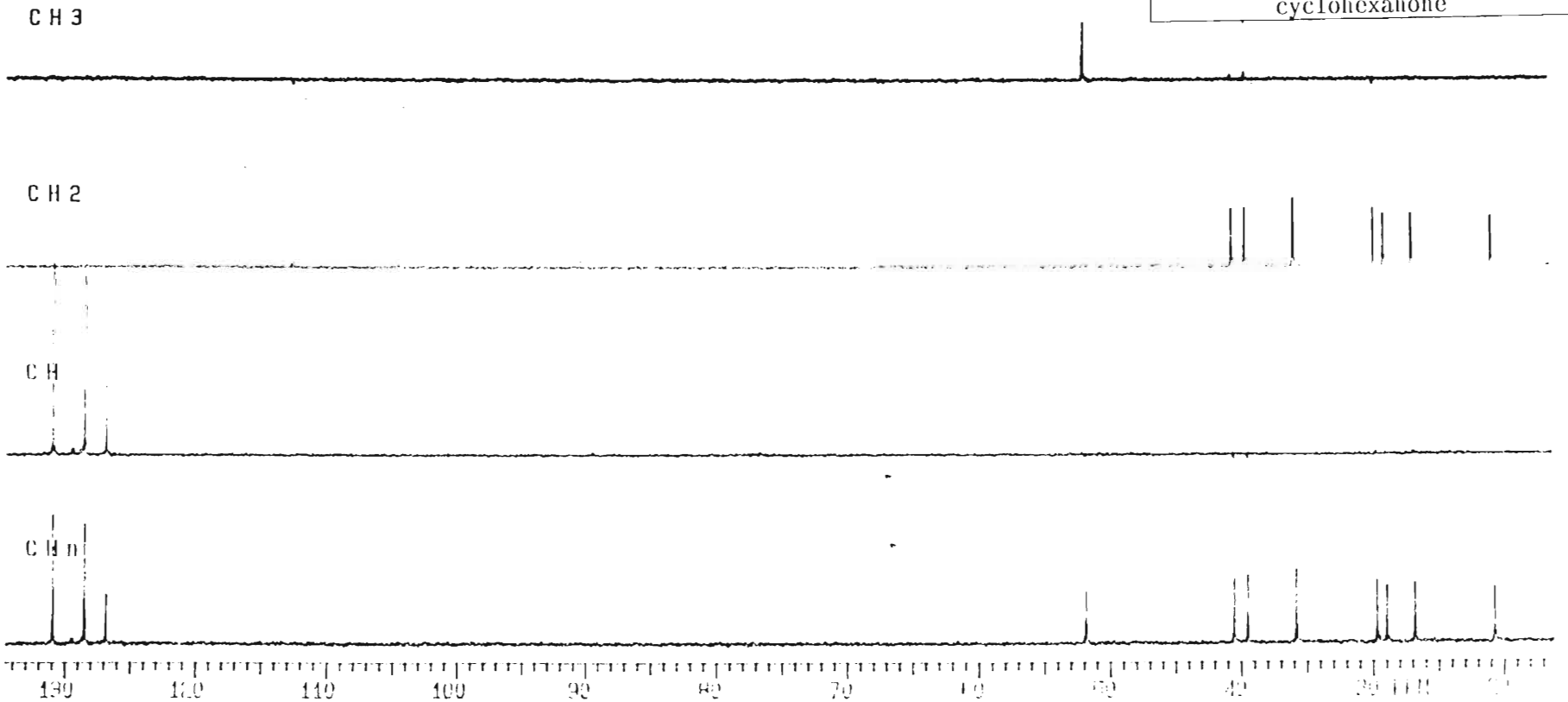
2-benzyl-2-[2-methoxycarbonylethyl]-cyclohexanone

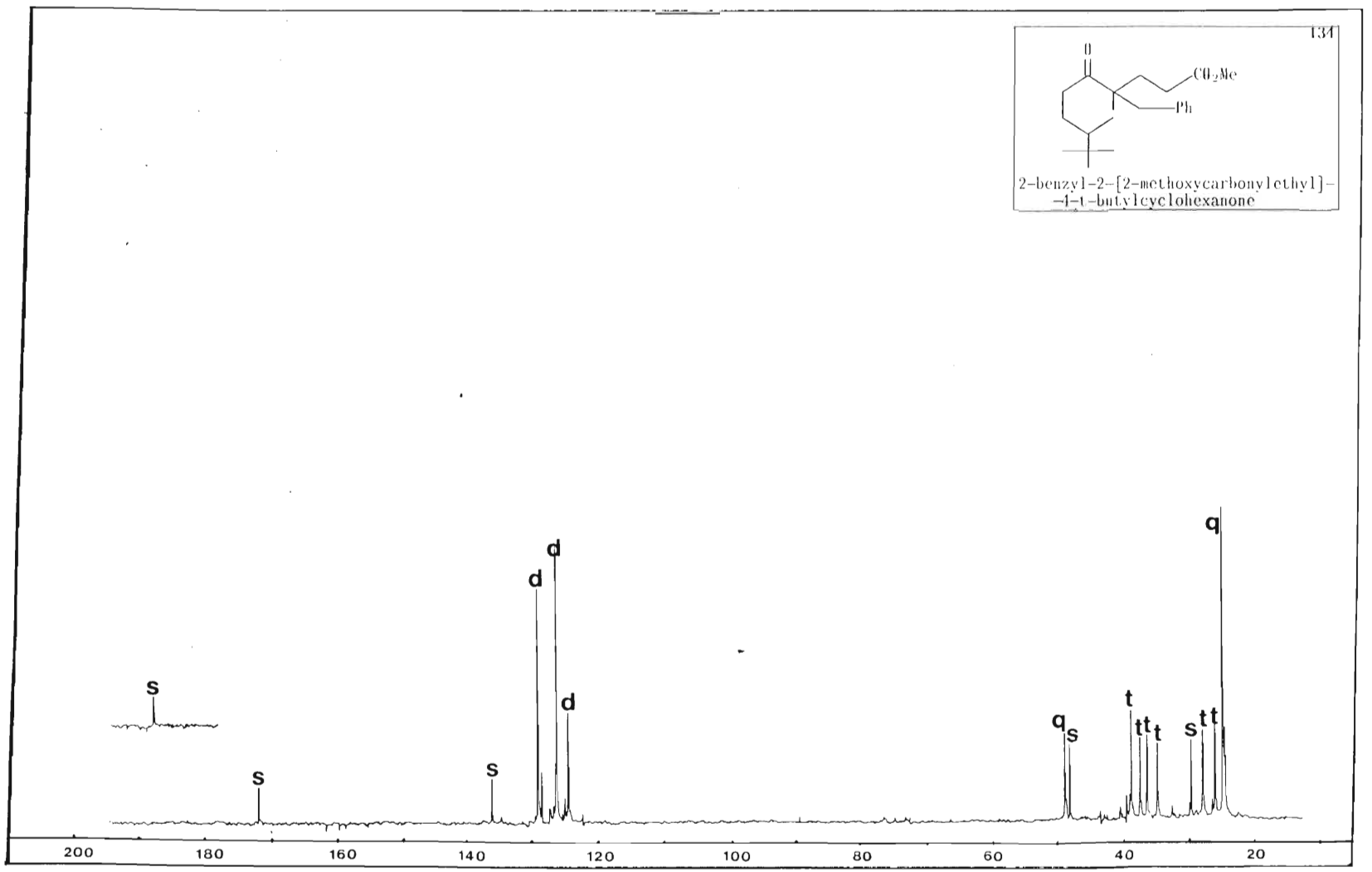
129

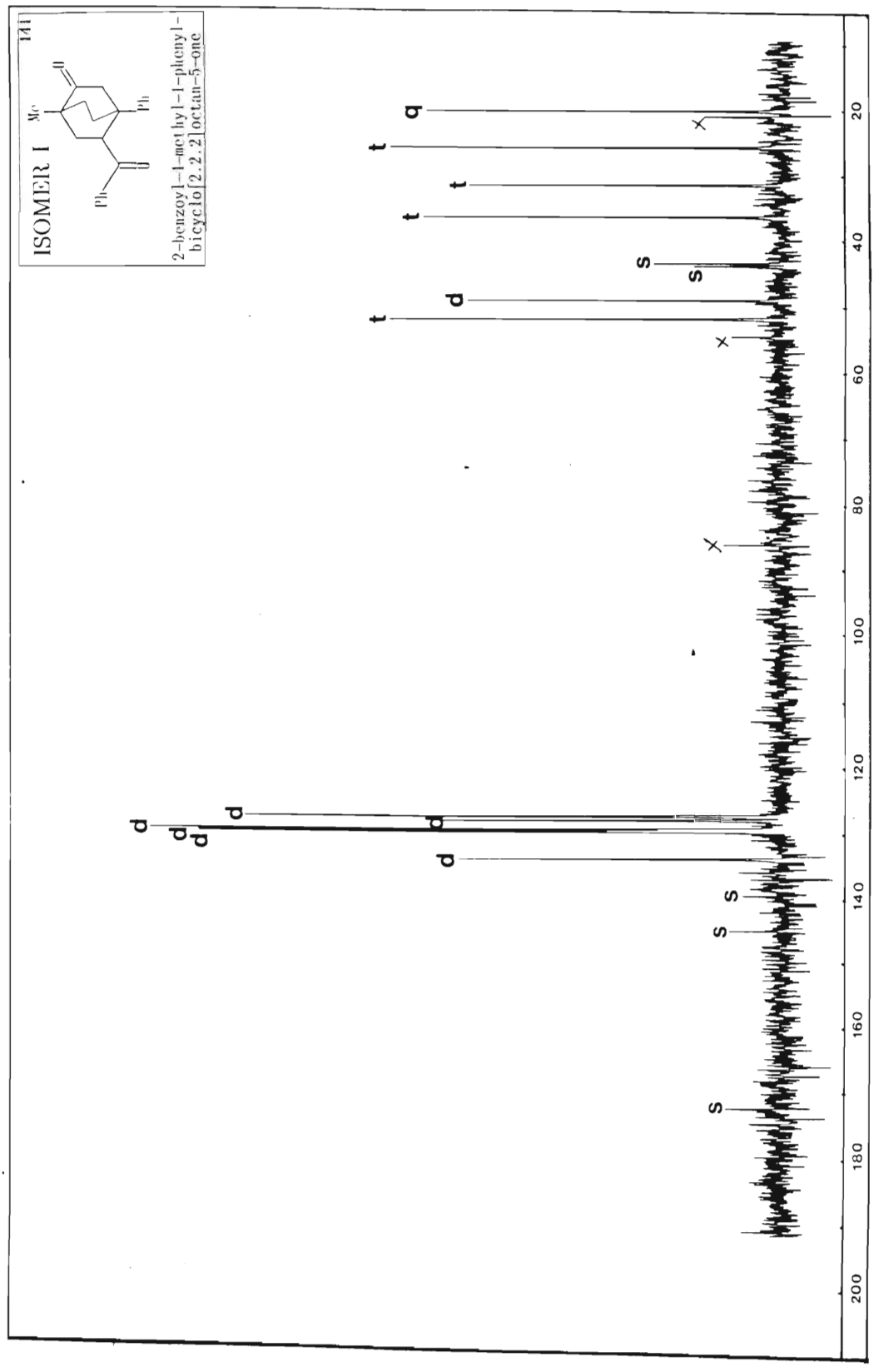


2–benzyl–2–[2–methoxycarbonylethyl]–cyclohexanone

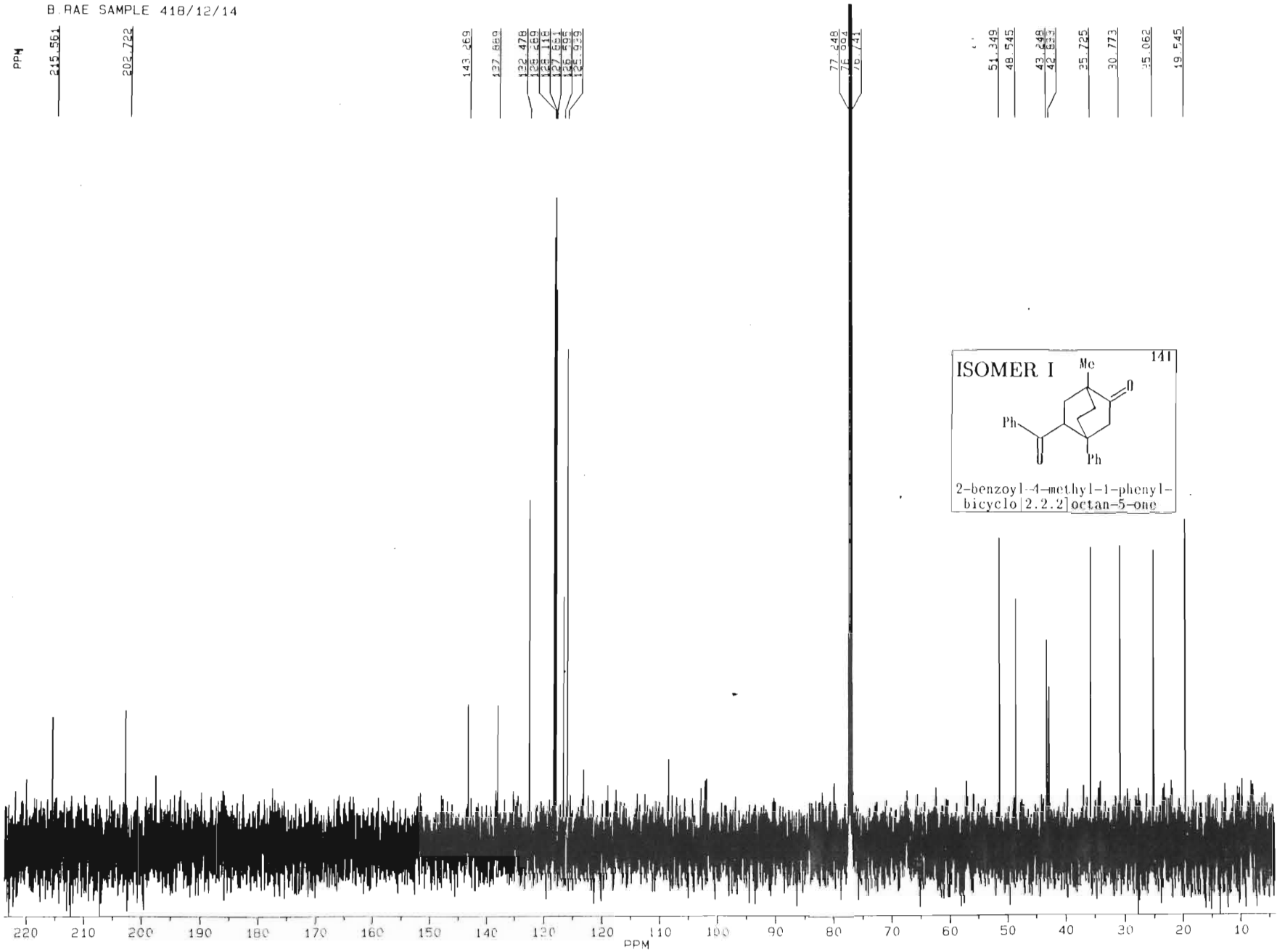
6659/90.BR346F1 IN CDCL3




134
O
CO2Me
Ph
2-benzyl-2-[2-methoxycarbonylethyl]-
-4-t-butylcyclohexanone
s
s
s
d
d
d
q
s
t
t
t
s
t
t
q
200
180
160
140
120
100
80
60
40
20


ISOMER I
141
2-benzoyl-4-methyl-1-phenyl-bicyclo[2.2.2]octan-5-one
Me
Ph
Ph
d
d
d
d
d
t
t
t
t
q
s
s
s
s
x
x
x
200
180
160
140
120
100
80
60
40
20

B.RAE SAMPLE 418/12/14



141

ISOMER I

2-benzoyl-4-methyl-1-phenyl-bicyclo[2.2.2]octan-5-one

BRUKER

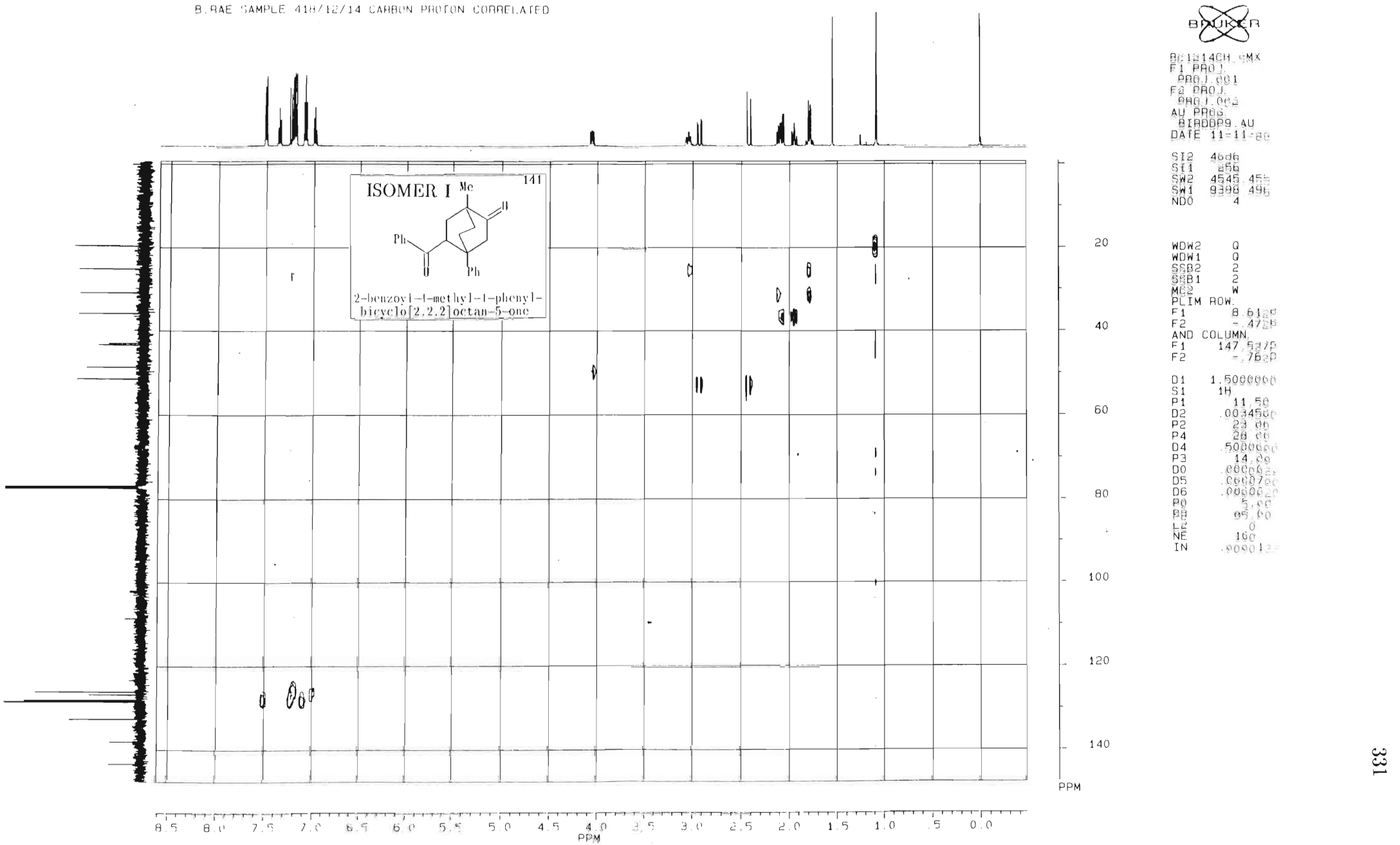
BC1214.001
DATE 18-5-88
TIME 13.12

SF 125.759
O1 23200.000
SI 65536
TD 65536
SW 29411.765
HZ/PT .898

PW 6.0
RD .800
AQ 1.114
RG 400
NS 305

O2 7990.000
DP 20L CPD

LB 1.000
GB 0.0
F1 223.885P
F2 3.950P
HZ/CM 790.251
PPM/CM 6.284
SR 9150.74



BRUKER

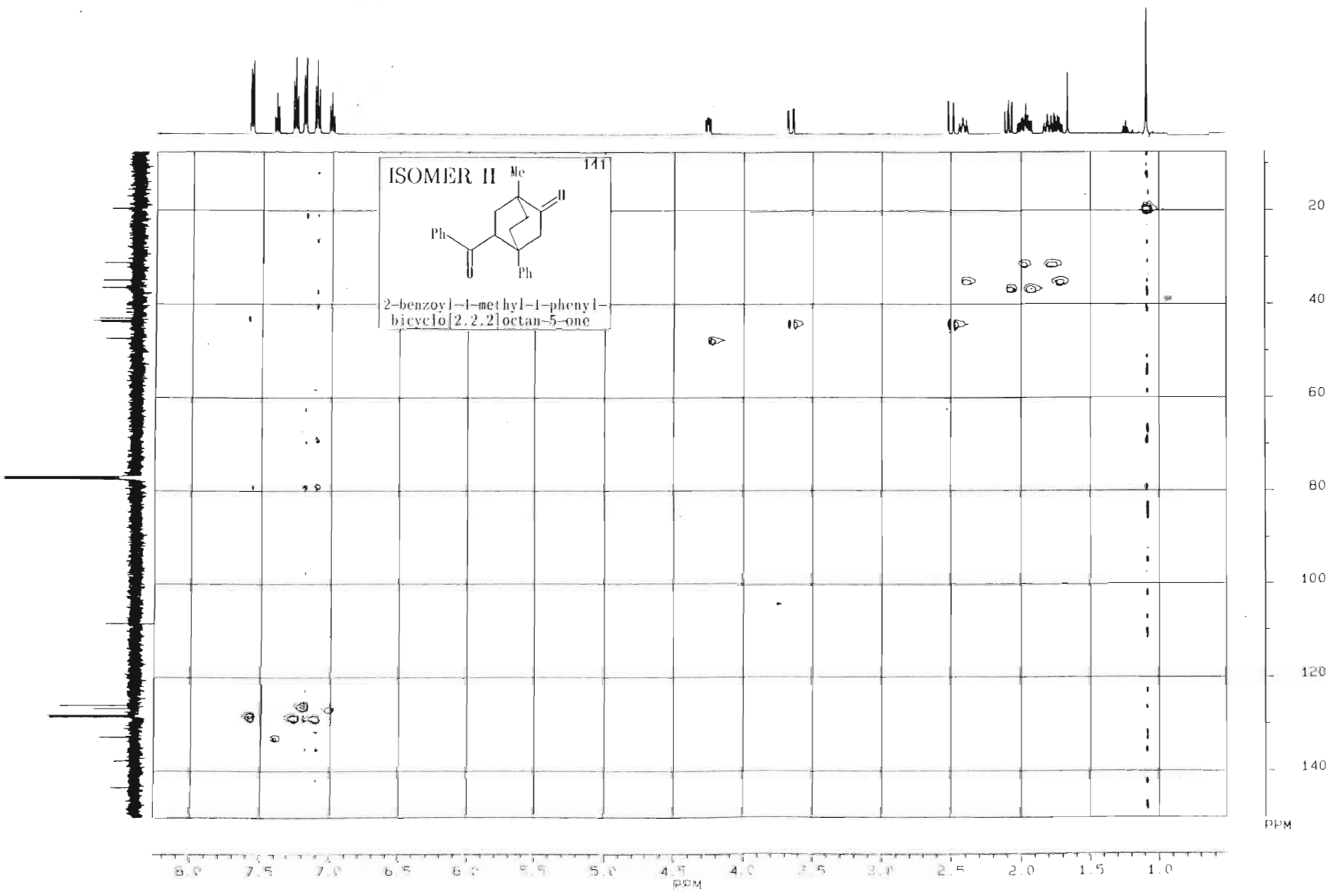
AU PR86
BIRDDP9.AU
DATE 11-11-86

SI2 4kd8
SI1 256
SW2 4545.45
SW1 9398.496
ND0 4

WDW2 Q
WDW1 Q
SSB2 2
SSB1 2
MC2 W
PLIM ROW.
F1 8.61
F2 -.47
AND COLUMN.
F1 147.5
F2 -.7

D1 1.5000000
S1 1H
P1 11.50
D2 .0034500
P2 23.00
P4 23.00
D4 .5000000
P3 14.00
D0 .0000023
D5 .0000700
D6 .0000020
P0 5.00
P8 85.60
LS 0
NE 100
IN .0000125

B.RAE SAMPLE 17/20 CARBON PROTON CORRELATED



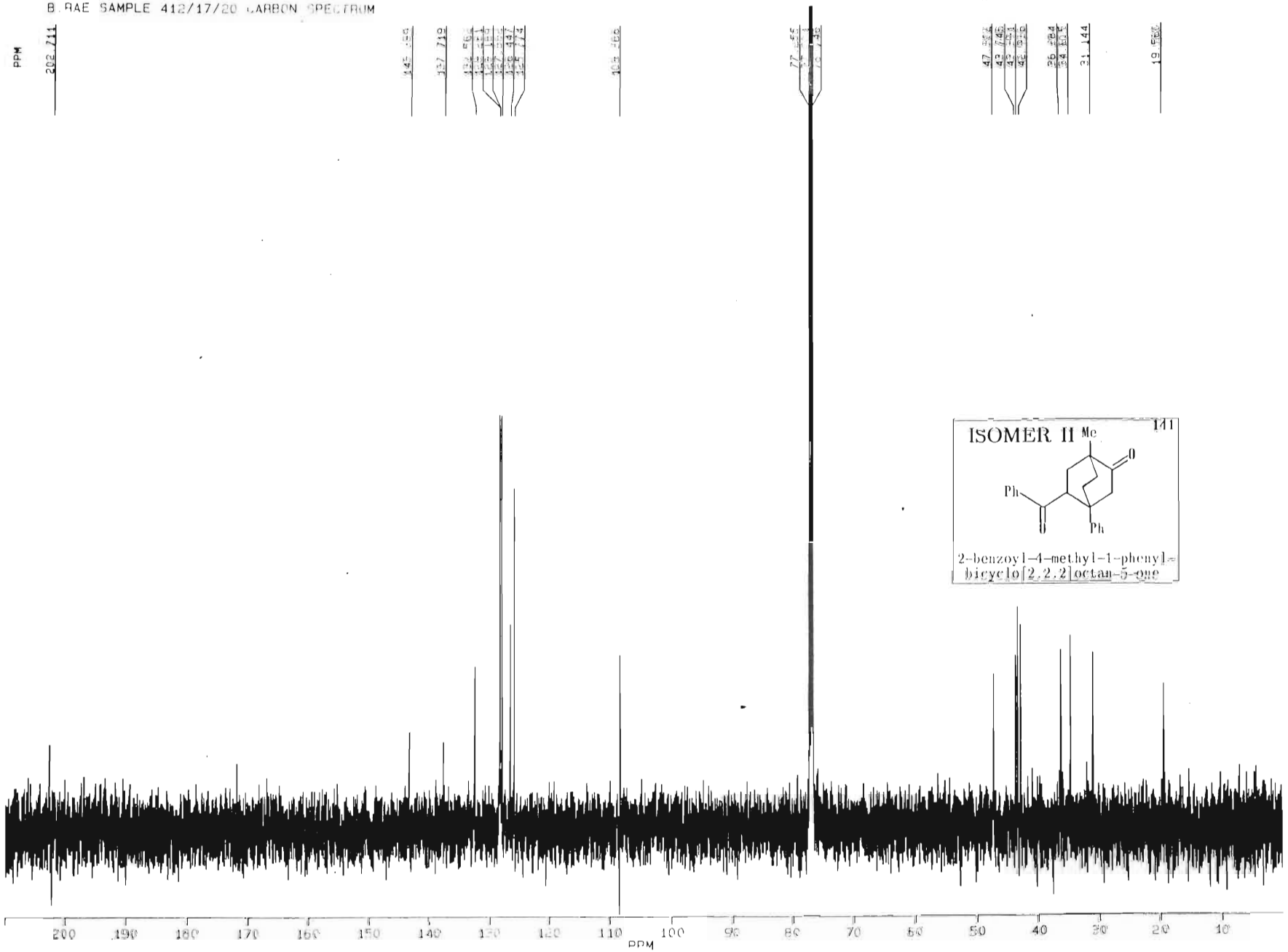
BRUKER

SC17/20CH CMX
F1 PROJ
PROJ 001
F2 PROJ
PROJ.002
AU PROG
BIRDDB9 AU
DATE 14-11-98

SI2 4096
SI1 512
SW2 3675.969
SW1 899.806
NDO 4

WDW2 Q
WDW1 Q
SSB2 2
SSB1 2
MC2 W
PLIM ROW
F1 8.285
F2 .510
AND COLUMN
F1 149.811
F2 7.361

D1 1.500000
S1 1H
P1 11.5
D2 .003450
P2 22.00
P4 28.00
D4 .500000
P3 14.00
D0 .000003
D5 .000050
D6 .000002
P0 5.00
P8 85.00
L2 0
NE 225
IN .00001

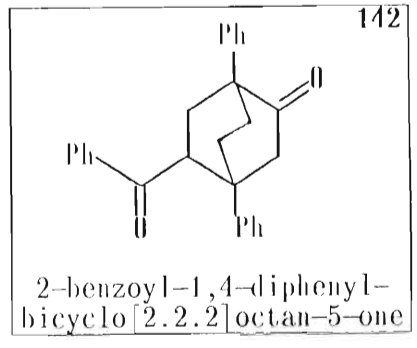


BRUKER

BC1720C.001
DATE 14-11-88
TIME 9.16

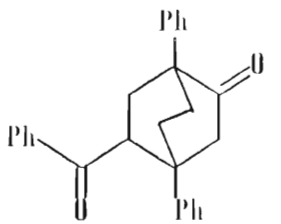
SF	125.759
O1	7200.000
SI	65536
TD	65536
SW	29411.765
HZ/PT	.898
PW	1.7
RD	.800
AQ	1.114
RG	400
NS	959
O2	7990.500
DP	15H CPD
LB	1.000
GB	0.0
F1	210 [illegible]
F2	.00 [illegible]
HZ/CM	754.554
PPM/CM	6.000
SR	9151.53

C301/90PND.BR428 IN CDCL3.



2-benzoyl-1,4-diphenyl-bicyclo[2.2.2]octan-5-one

142



2-benzoyl-1,4-diphenyl-bicyclo[2.2.2]octan-5-one

C301/90DEPT.BR428 IN CDCL3.

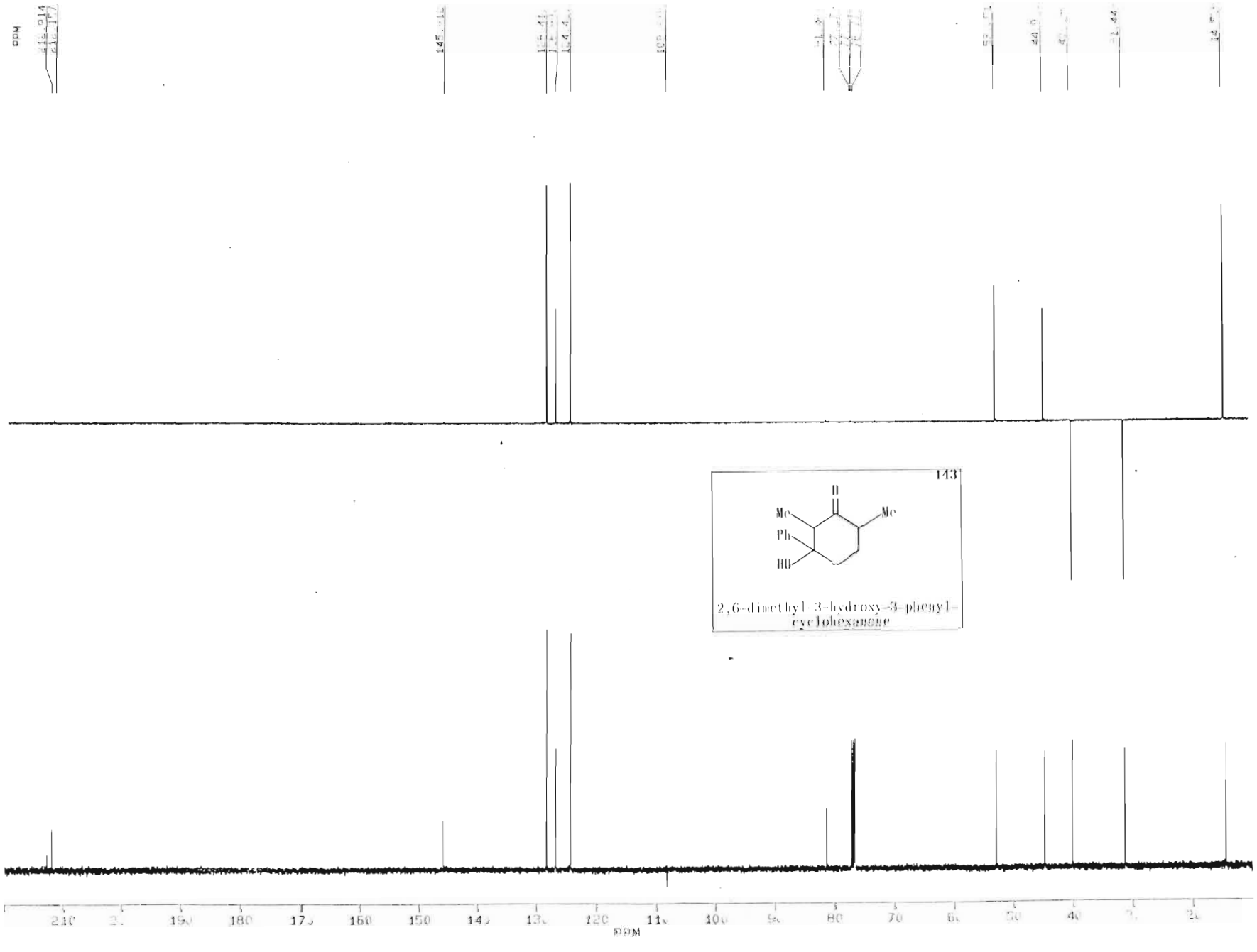
CH3

CH2

CH

CHn

140 120 100 80 60 40



BRUKER

TEMP .001
DATE 18-5-88
TIME 13 12

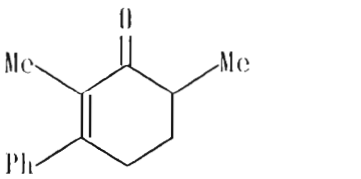
SF 125.759
01 23200.000
SI 65536
TD 65536
SW 29411.765
HZ/PT .898

PW 1.7
RD .800
AQ 1.114
RG 400
NS 61

02 7980.000
DP 15H CPD

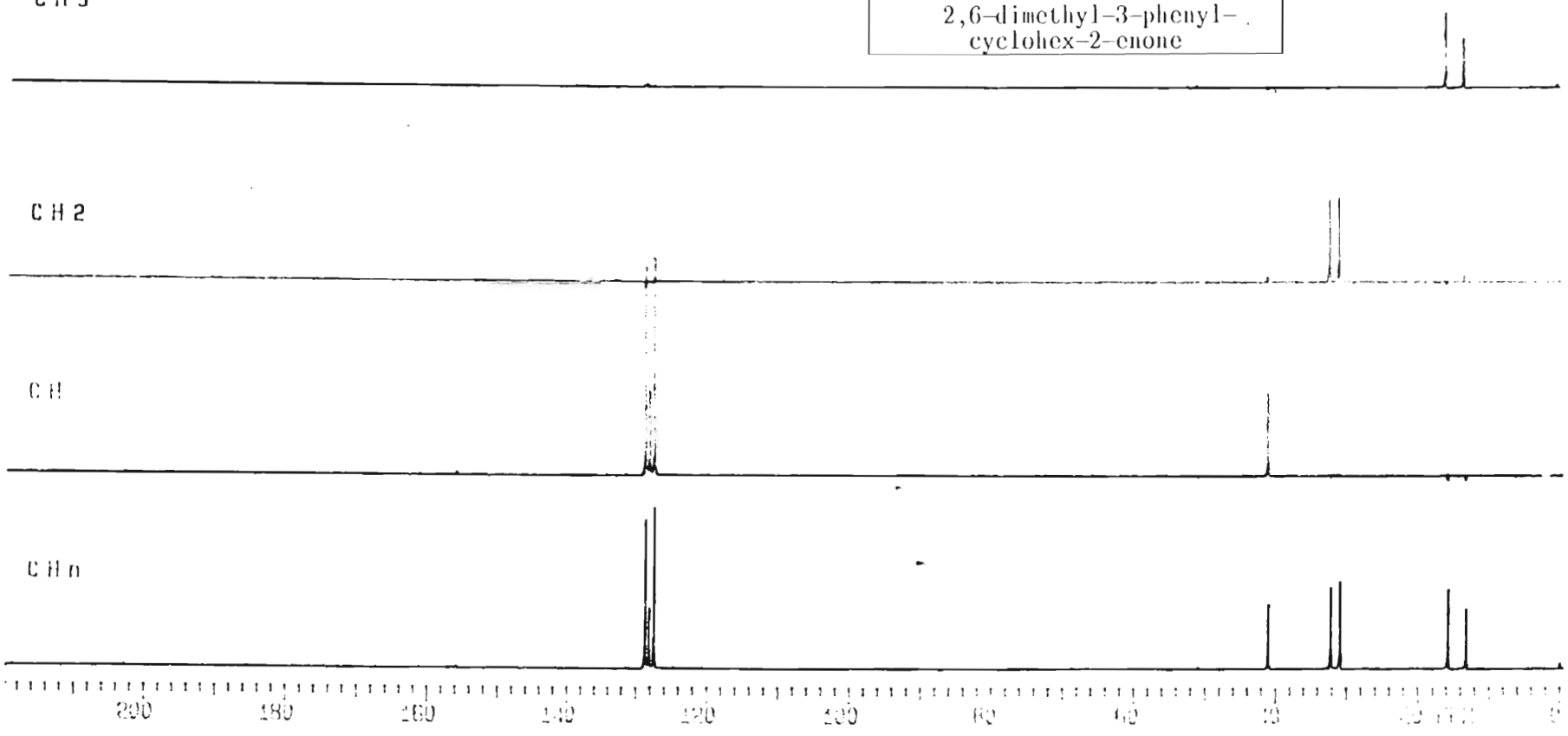
LB 1.000
GB 0.0
F1 220.002P
F2 10.003P
HZ/CM 754.554
PPM/CM 6.00
SR 9155.22

144



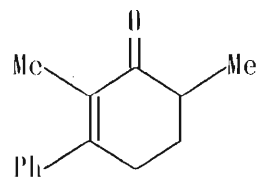
2,6-dimethyl-3-phenyl-cyclohex-2-enone

C169/89DEPT.BH423-10 IN CDCL3/TMS.



C169/83PND.BR423-10 IN CDCL3/TMS.

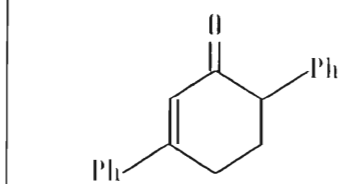
144



2,6-dimethyl-3-phenyl-cyclohex-2-enone

C176/89PND.BR428-14 IN CDCL3/TMS.

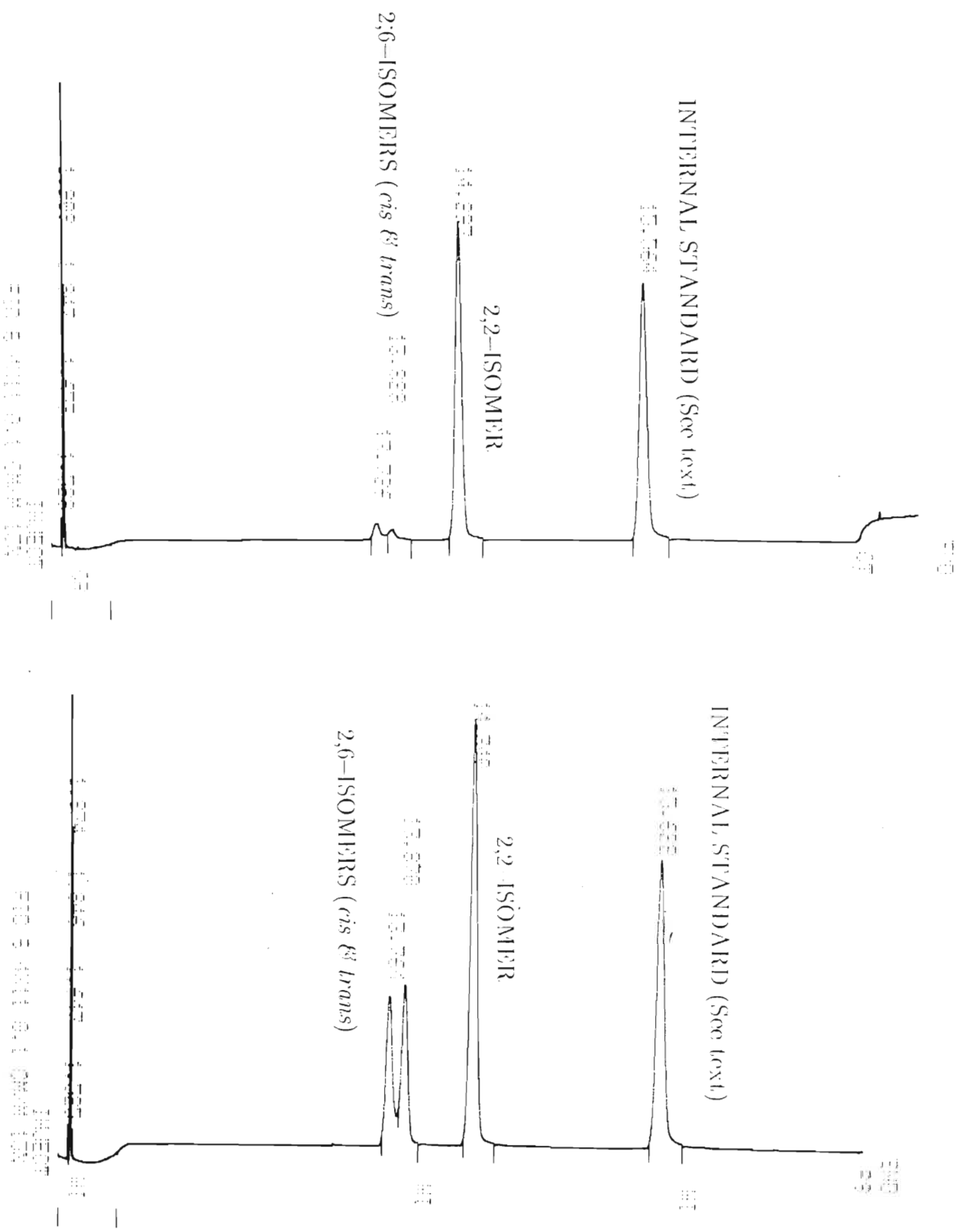
147



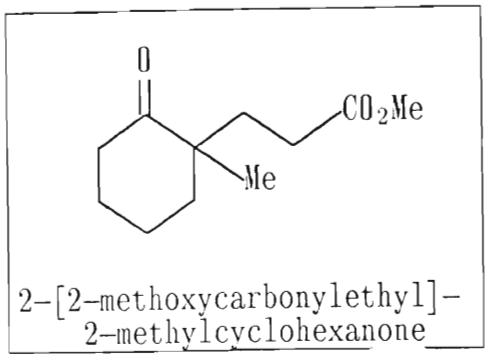
3,6-diphenylcyclohex-2-enone

4. CHROMATOGRAMS / MASS SPECTRA

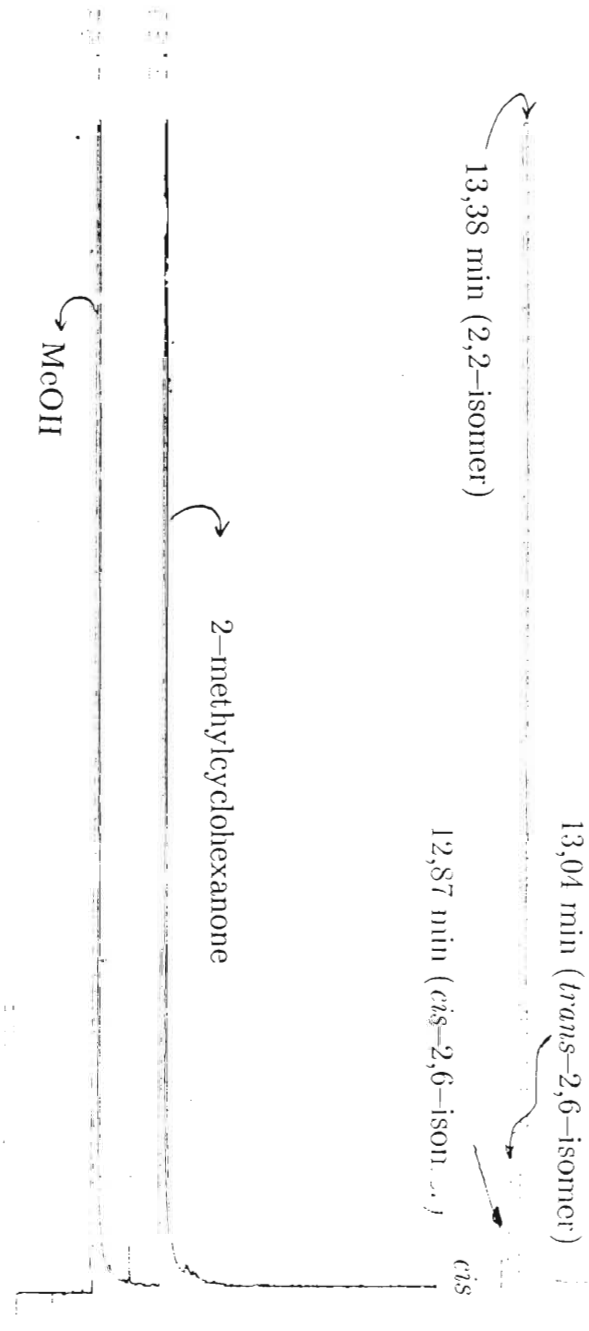
Chromatograms showing two of the many preparations of 2–methyl–2–[(methoxycarbonyl)ethyl]cyclohexanone showing the trace *cis*– and *trans*–2,6–isomers and the internal standard used (t_R = 15,6 minutes)



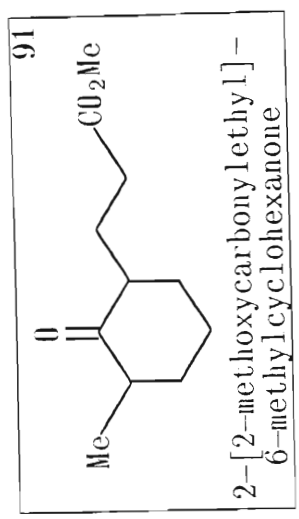
CGC–analysis of 2–methyl–2–[(methoxycarbonyl)ethyl]cyclohexanone showing the trace *cis*– and *trans*–2,6–isomers, spiked with 2–methyl–cyclohexanone.

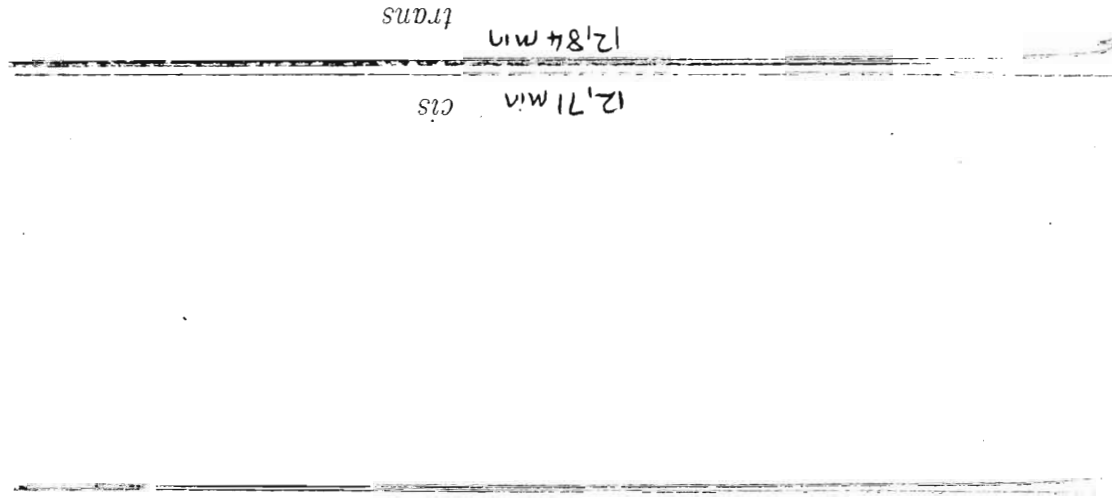


2–[2–methoxycarbonylethyl]–
2–methylcyclohexanone



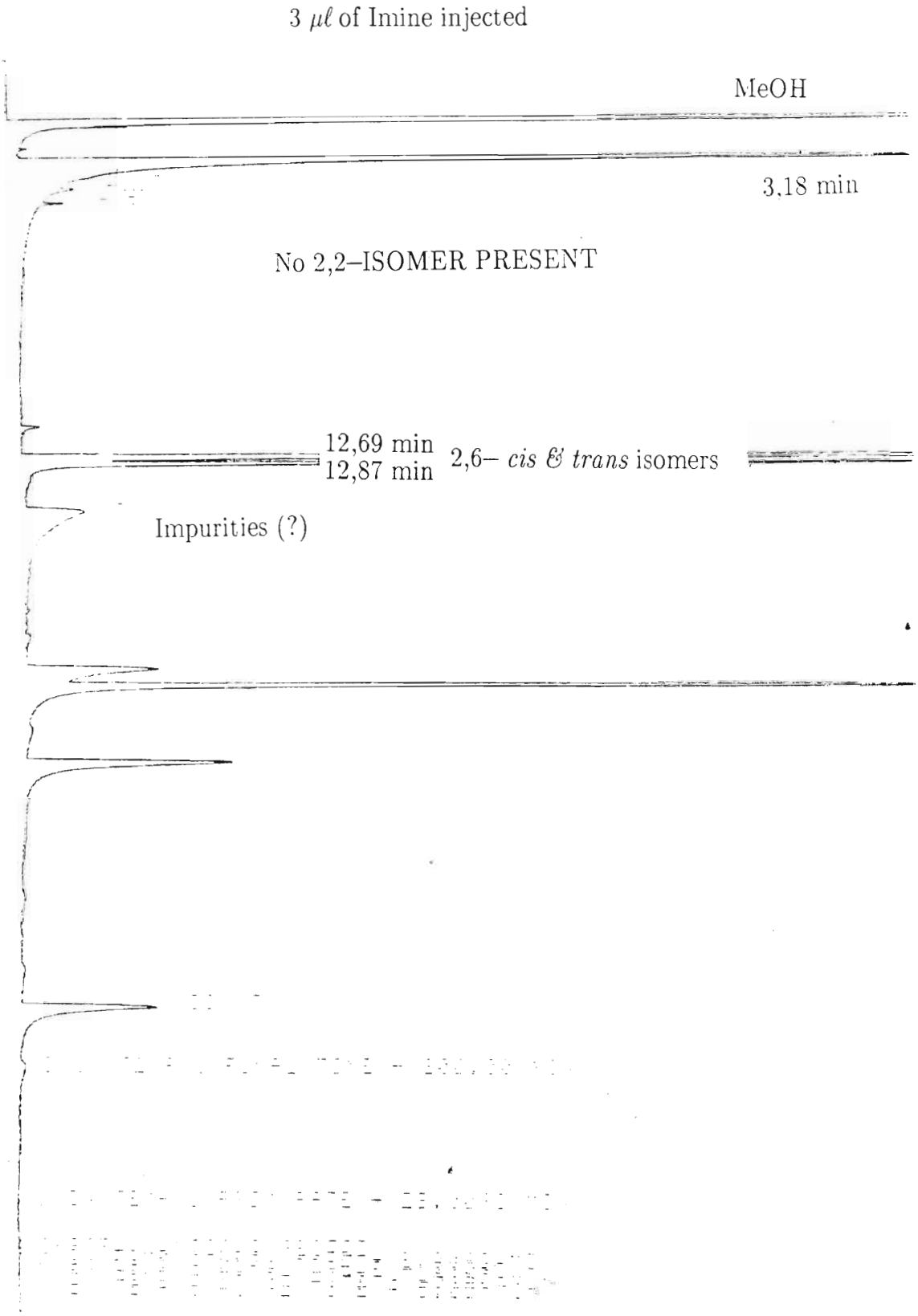
CGC–analysis of 6–methyl–2–[(methoxycarbonyl)ethyl]cyclohexanone used as starting material for the preparation of the benzylamine imine (using the $TiCl_4$ method).





CGC–analysis of hydrolysed benzylamine imine of
6–methyl–2–[(methoxycarbonyl)ethyl]cyclohexanone
without any attempted reaction having been carried out.

GGC–analysis of the attempted rearrangement of the benzylamine imine of 6–methyl–2–[(methoxycarbonyl)ethyl]-cyclohexanone in methanol (4 h.) after hydrolysis.

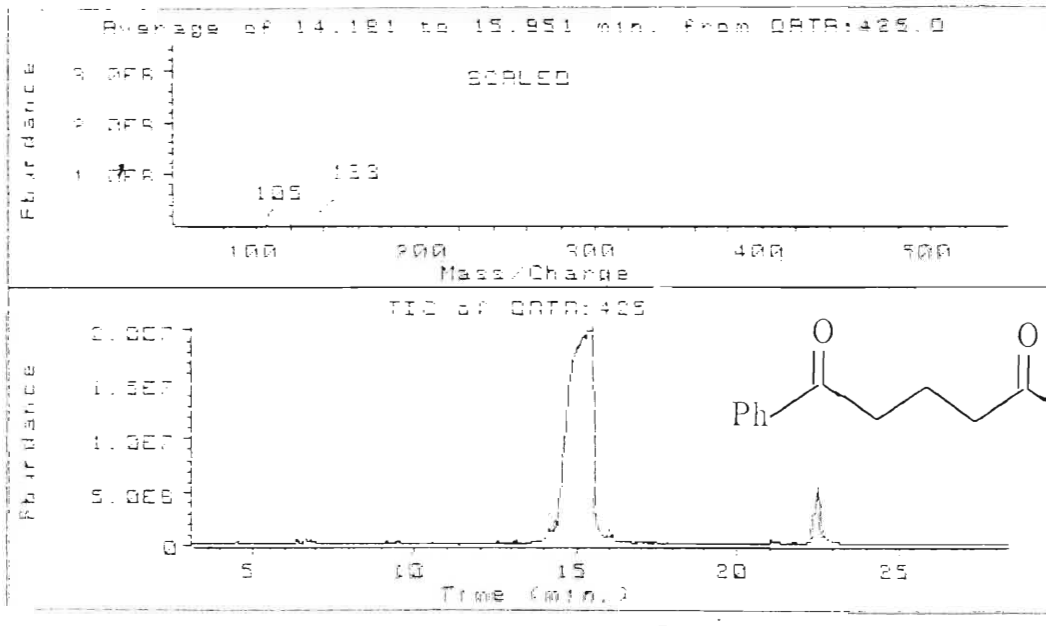


CGC–analysis of the attempted reaction between methyl acrylate and the benzylamine imine of 6–methyl–2–[(methoxycarbonyl)ethyl]–cyclohexanone showing the *cis*– and *trans*–2,6–isomers, other impurities, but NO 2,2–product.

Total ion chromatogram and GC–MS mass spectrum for 1,5–diphenyl–1,5–pentandione (**145**)

Average of 14.181 to 15.951 min. from DATA:425.D
fr.11-13

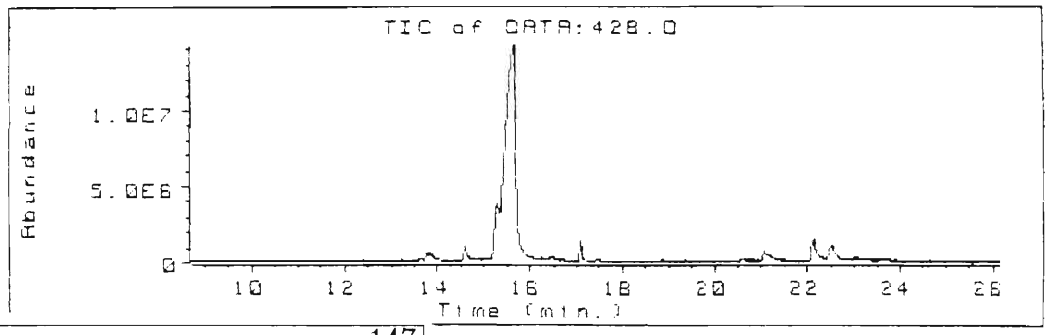
m/z	abund.	m/z	abund.	m/z	abund.	m/z	abund.
51.00	28	78.00	7	115.00	1	134.00	1
52.00	2	79.00	1	120.00	17	145.00	1
53.00	1	89.00	1	121.00	2	146.00	2
55.00	6	91.00	3	129.00	1	147.00	4
63.00	1	103.00	1	130.00	4	223.00	1
65.00	2	105.00	100	131.00	1	234.00	1
74.00	1	106.00	8	132.00	1	252.00	2
75.00	1	107.00	1	133.00	10	253.00	1
77.00	68						



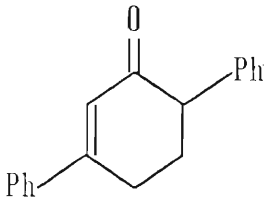
T: null.
Z: TIC of DATA:425.D
Y: null.
X: Average of 14.181 to 15.95

EMS11

Total ion chromatogram for 3,6–diphenylcyclohex–2–enone (147).



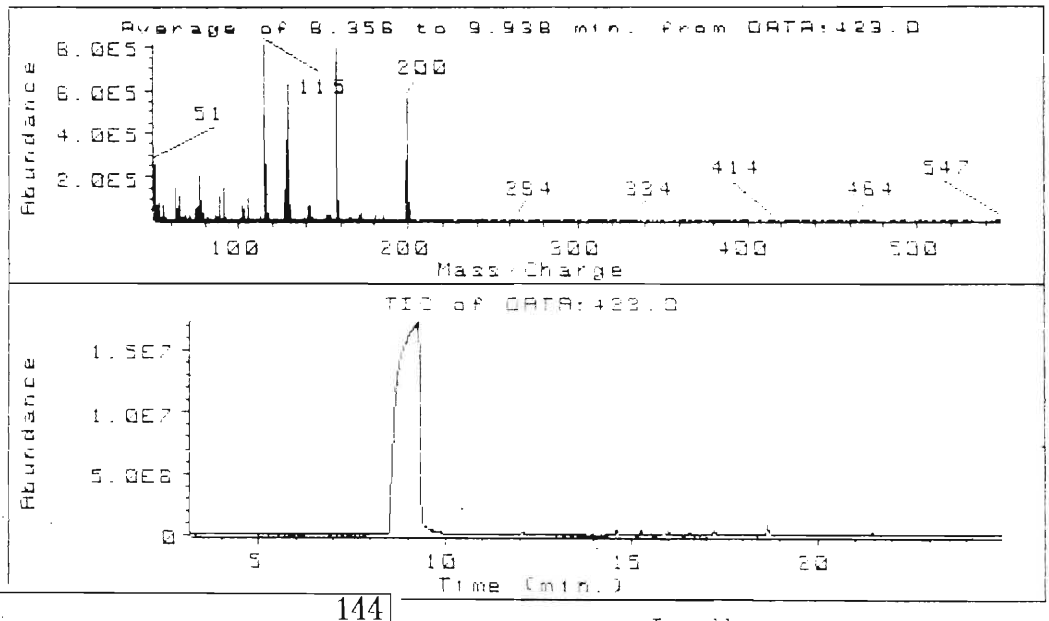
147



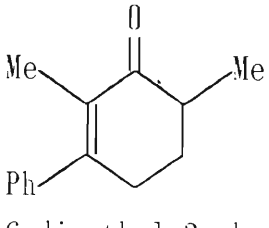
3,6–diphenylcyclohex–2–enone

T: null.
Z: TIC of DATA:428.0
Y: null.
X: null.

Total ion chromatogram and GC–MS mass spectrum for 2,6–dimethyl–3–phenylcyclohex–2–enone (144)



144



2,6–dimethyl–3–phenyl–cyclohex–2–enone

T: null.
Z: TIC of DATA:423.0
Y: null.
X: Average of 8.356 to 9.938

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6. PUBLICATIONS

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REGIOSELECTIVITY OF ENAMINE REACTIONS. PREFERENTIAL 2,2-DISUBSTITUTION OF 2-METHYLCYCLOHEXANONE IMINES

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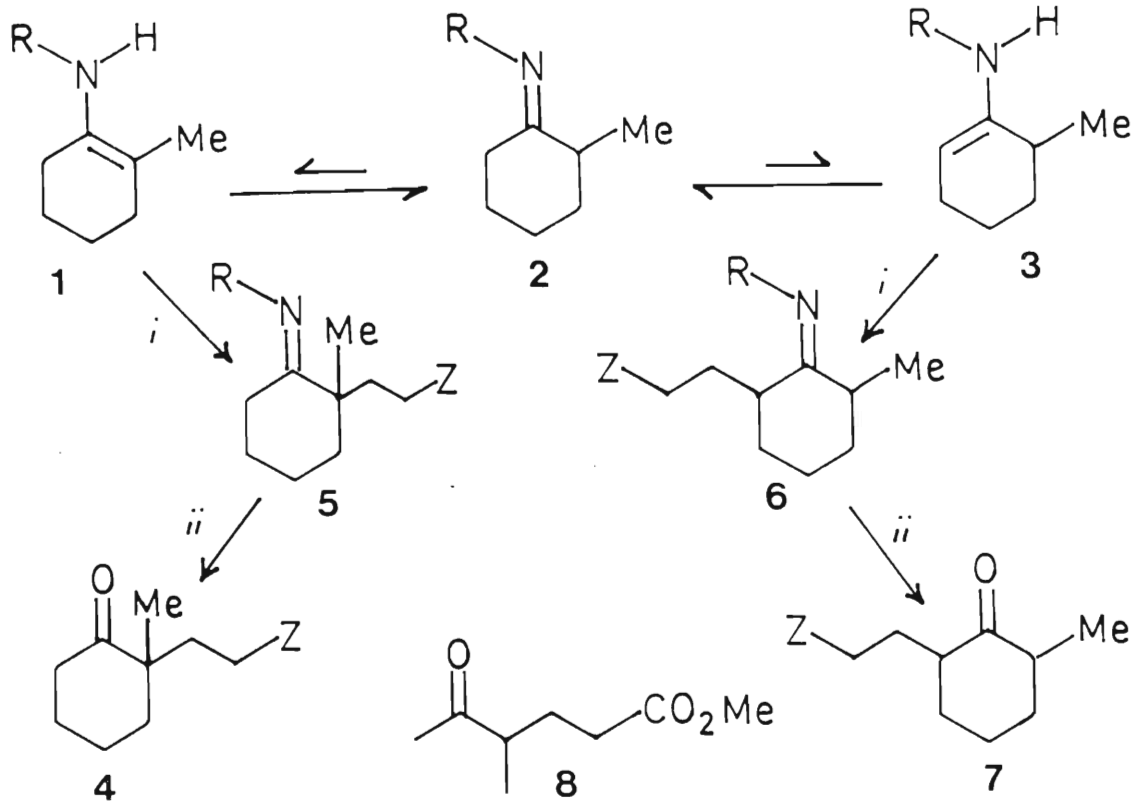
Summary: *Secondary enamines, derived from imines of unsymmetrical α-substituted ketones, react with electrophilic alkenes at the more substituted position to give α,α-disubstituted ketones on hydrolysis.*

Spectroscopic studies[1,2] of imine-enamine tautomerism have shown that, unless the secondary enamine is stabilised by further conjugation with an unsaturated system[1,3,4,5], the equilibrium is usually almost completely in favour of the imine form. With a few exceptions, such as the t-butylamine imine of cyclohexanone ($\delta_{=CH}$ 4.6),[6] signals due to the enamine tautomer cannot be observed in the ^{1}H n.m.r. spectra of imines. Nevertheless imine-enamine tautomerism has been clearly demonstrated in reactions which involve the enamine form reacting with a variety of electrophilic reagents at the α-position to the original carbonyl function (C-3 of the enamine)[2,7,8,9,10] and, despite their thermodynamic instability, methods have been developed for the isolation of secondary enamines[11].

The object of the present study was to investigate the regioselectivity of the reaction between electrophilic alkenes and imines of unsymmetrical ketones. The underlying hypothesis was that the imine of 2-methylcyclohexanone **2** would be in equilibrium mainly with the more substituted secondary enamine **1** rather than the less substituted double bond isomer **3**. The reason for this is that enamine **1** is stabilised over enamine **3** by the hyperconjugative interaction of the methyl group without incurring the allylic destabilization [i.e. $A^{(1,2)}$ strain[12]] normally associated with a tertiary enamine,[13,14] since a bulky N-alkyl substituent or ring residue in the latter has been replaced by a hydrogen atom (in **1** and **3**). Furthermore since there is no $A^{(1,3)}$ strain present in the imine (**5**) produced by alkylation of enamine **1**, and minimal $A^{(1,3)}$ strain in the transition state leading to it, we predicted that alkylation would give mainly the 2,2-disubstituted cyclohexanone **4** on hydrolysis, rather than the 2,6-



Reagents: (i) CH_2=CH-Z ($-H^+$); (ii) H_2O, Δ; Z = CO_2Me, CN, SO_2Ph

disubstituted cyclohexanone 7[15,16]. We now report that these predictions have been fully verified.

The reaction of methyl acrylate with imines of 2-methylcyclohexanone, under various conditions, is summarised in the Table. Under all conditions the 2,2-disubstituted ketone 4 (Z = CO_2Me) was the main product. The benzylamine and cyclohexylamine imines gave comparable yields of 2,2-disubstituted product, but the amount of 2,6-disubstitution appeared to be greater for the latter (Table 1; Nos. 2 and 5). The aniline imine gave very little product (Table 1; No. 6), presumably due to stabilisation of the imine tautomer and/or low reactivity of the enamine tautomer. The benzylamine imine has therefore been used in our preliminary investigations into the optimisation of the experimental conditions. Best yields have so far been obtained in methanol as solvent using a large excess of alkylating agent (Table 1; No. 4) for reasons which have not yet been ascertained. The use of aprotic solvents of low dielectric constant (benzene, toluene) gave very low yields even on prolonged reaction (Nos. 7 and 8). However these yields were significantly improved by the use of a solvent of high dielectric constant (acetonitrile; No. 9) or by the addition of weakly acid (No. 10) or base (Nos. 11-14) catalysts, presumably due to catalysis of the imine-enamine equilibrium.

Table: Reaction of imines of 2-methylcyclohexanone with methyl acrylate[a]

No.	Imine	Equivalents of methyl acrylate	Solvent	Reaction time (h)	Other additives	% Yield[b] 2,2-	% Yield[b] 2,6-[c]
1	Benzylamine	1	MeOH	4	-	13	2
2	Benzylamine	2	MeOH	4	-	46	4
3	Benzylamine	2	MeOH	24[d]	-	45	3
4	Benzylamine	5	MeOH	4	-	64	4
5	Cyclohexylamine	2	MeOH	4	-	42	9
6	Aniline[e]	2	MeOH	4	-	3	Trace
7	Benzylamine	2	Benzene	68	-	3	0
8	Benzylamine	2	Toluene	68	-	33	0
9	Benzylamine	2	CH_3CN	95	-	50	2
10	Benzylamine	2	Benzene	68	Me_2NH, HCl[f]	32	0
11	Benzylamine	2	Benzene	68	Et_3N[f]	32	0
12	Benzylamine	2	Benzene	24	4-DAP[f,g]	40	1
13	Benzylamine	2	Benzene	24	4-DAP[g,h]	49	1
14	Benzylamine	2	MeOH	4	4-DAP[f,g]	59	5

[a] At boiling point of dry solvent unless stated otherwise. [b] Analysed by GLC. [c] Mixture of stereoisomers. [d] At room temperature. [e] Mostly unreacted 2-methylcyclohexanone recovered. [f] One equivalent. [g] 4-Dimethylaminopyridine. [h] 0.1 Equivalents.

In preliminary investigations into the reaction of N-(2-methylcyclohexylidene) benzylamine (**2**, R = $PhCH_2$) with acrylonitrile and phenyl vinyl sulphone in methanol, the spectroscopic evidence again shows quite definitely that reaction has occurred at the more substituted position to give the 2,2-disubstituted ketone **4** (Z = CN or SO_2Ph, respectively) on hydrolysis. The reaction of methyl acrylate with N-(2-butylidene)benzylamine, in methanol, gave methyl 4-methyl-5-oxohexanoate (**8**) on hydrolysis, and indicates that this methodology can be used to direct reaction to the more substituted position of acyclic as well as cyclic ketones.

Acknowledgements

Financial assistance from the Council for Scientific and Industrial Research and the University Research Fund is gratefully acknowledged. We also thank Mrs. C.M.J. Day-Lewis (Sugar Milling Research Institute) for some of the GLC determinations, Mr. G.J. Davison for participating in the early stages of this work, and Mangosuthu Technikon for leave of absence (for B.R.).

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15. The step **3** → **6** has been shown to be irreversible by exposure of **6** (prepared from **7**) to the same reaction conditions [i.e. methanol (4 h, Δ) or benzene (68 h, Δ) with or without alkylating agent]. No 2,2-product (**4**) was formed (GLC). Consequently there is no question of **6** being formed preferentially and then rearranging into **5**.

16. It is difficult to envisage **1** reacting appreciably more rapidly than **3**, whether by reactant-like or product-like transition state. The preference for the formation of **5** over **6** can therefore most probably be attributed to the extremely small amount of **3** present at equilibrium.

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Enamine chemistry. Part 33.[1] Alkylation of cyclohexanone imines with electrophilic alkenes

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The alkylation of cyclohexanone imines with electrophilic alkenes in methanol or acetonitrile has been investigated. The course of this reaction is surprisingly sensitive to both steric effects and the relative reactivity of the electrophilic alkene. The more reactive (*i.e.* methyl acrylate, phenyl vinyl sulphone) react twice with benzylamine or cyclohexylamine imines of cyclohexanone to give the 2,2-disubstituted cyclohexanones on hydrolysis. Under identical conditions, the less reactive acrylonitrile results only in mono-alkylation; 2,2- and 2,6-dialkylation does occur to a small extent on changing to the less sterically impeded propylamine imine. The propylamine imine of 2-(2-cyanoethyl)cyclohexanone can also be further alkylated by methyl acrylate to give 2-(2-cyanoethyl)-2-(2-methoxycarbonylethyl)cyclohexanone on hydrolysis. In the case of acrylamide, only mono-alkylation occurs, followed by cyclization to 2-oxo-$\triangle^{4a(8a)}$-octahydroquinoline.

Die alkilering van sikloheksanoonimiene met elektrofiliese alkene in metanol of asetonitriel is ondersoek. Die reaksieroete is verbasend gevoelig teenoor steriese effekte sowel as die relatiewe reaktiwiteit van die elektrofiliese alkeen. Die meer reaktiewe (d.w.s. metielakrilaat, fenielvinielsulfoon) reageer twee keer met bensielamien- of sikloheksielamienimiene van sikloheksanoon, om die 2,2-digesubstitueerde sikloheksanone na hidrolise te lewer. Onder identiese omstandighede, vind slegs monoalkilering by die minder reaktiewe akrilonitriel plaas; 2,2- en 2,6-dialkilering kom tot 'n mindere mate voor na oorskakeling na die minder steries-verhinderde propielamienimien. Die propielamienimien van 2-(2-sianoetiel)sikloheksanoon kan ook verder met metielakrilaat geälkileer word, om die 2-(2-sianoetiel)-2-(2-metoksiekarbonieletiel)sikloheksanoon na hidrolise te verskaf. In die geval van akrielamied vind slegs monoalkilering plaas, gevolg deur siklisering na 2-okso-$\triangle^{4a(8a)}$-oktahidrokinolien.

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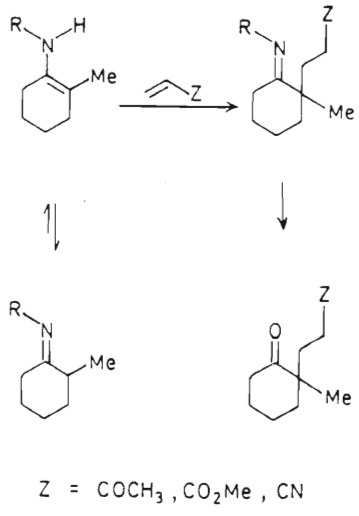
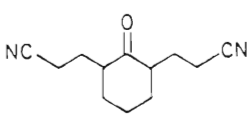
Both we[2] and Pfau *et al.*[3] have recently shown that alkylation of imines of 2-methylcyclohexanone with electrophilic alkenes occurs at the more substituted position, C(2), of the derived secondary enamine tautomer (Scheme 1). This reaction therefore provides a mild and highly regioselective route to 2,2-disubstituted cyclohexanones, complementary to the 2,6-disubstituted cyclohexanones obtained by alkylation of the corresponding tertiary enamine of 2-methylcyclohexanone.[4]

Scheme 1



However, after reporting these observations, we became aware of conflicting reports in the patent literature,[5] claiming that alkylation of the cyclohexylamine imine of cyclohexanone with neat acrylonitrile gave 2,6-bis(2-cyanoethyl)cyclohexanone (**1**) on hydrolysis. Since this clearly conflicts with our own observations, we have investigated the reaction of unsubstituted cyclohexanone imines with various electrophilic alkenes. We find that the course of the imine-alkylation reaction is surprisingly sensitive to both steric effects and to the relative reactivity of the electrophilic alkene. Repetition of the reaction between *N*-cyclohexylidenecyclohexylamine (**2**; R = C_6H_{11}) with neat acrylonitrile at 100°C, confirmed the accuracy of the patent report: 2,6-bis(2-cyanoethyl)cyclohexanone was obtained, identical with authentic material obtained by alkylation of 1-*N*-pyrrolidinylcyclohexene according to the method of Stork *et al.*[6] In particular, the ^{13}C n.m.r. spectrum clearly showed the C(2) and C(6) signals as a doublet (δ_C 48.5).



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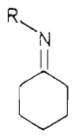

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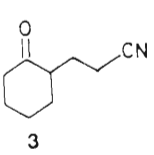

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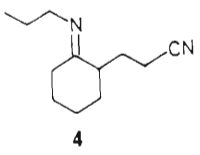

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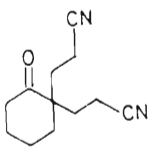

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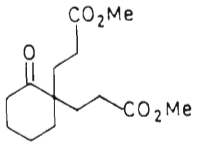

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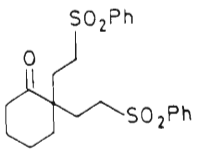

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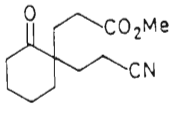

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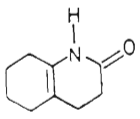
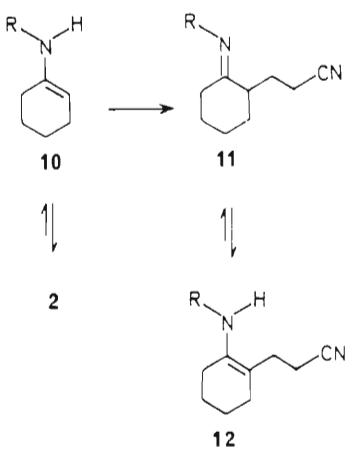


9

The only other compound isolated from this reaction was *N*-(2-cyanoethyl)cyclohexylamine. We then carried out the reaction under our preferred conditions[2] in boiling methanol, using the benzylamine imine of cyclohexanone (**2**; R = $PhCH_2$). This resulted only in the isolation of the mono-alkylated cyclohexanone (**3**) after hydrolysis, again shown to be identical with authentic 2-(2-cyanoethyl)cyclohexanone[6] and again showing the C(2) signal as a doublet (δ_C 48.2). This product was converted into the propylamine imine (**4**) by the standard azeotropic procedure,[8] and subjected to further treatment with acrylonitrile in boiling methanol. This resulted in the formation of a mixture consisting of mainly unchanged 2-(2-cyanoethyl)cyclohexanone together with roughly equal amounts of 2,6-bis(2-cyanoethyl)cyclohexanone and a compound identified by the analytical and spectral data as the expected 2,2-bis(2-cyanoethyl)cyclohexanone (**5**). The ^{13}C n.m.r. spectrum clearly showed the C(2) signal as a singlet (δ_C 49.8).

The explanation which we offer for these results is summarized in Scheme 2. Initial reaction at C(2) of the secondary enamine tautomer (**10**) occurs in each case to give the mono-alkylated imine (**11**) in equilibrium with the secondary enamine tautomer (**12**). Now however, further reaction at C(2) is impeded by the β-cyanoethyl substituent, which can plausibly be expected to exert a greater steric impediment to reaction than the methyl group in the corresponding reaction of 2-methylcyclohexanone imines.[2] Under more forcing conditions (neat acrylonitrile at 100—130°C),[5] reaction therefore occurs at the less sterically hindered 6-position to give **1** on hydrolysis. Presumably, changing to the propylamine imine reduces the steric interactions with the approaching electrophile sufficiently to allow some bonding to occur at the 2-position as well.

Scheme 2



10 11 2 12

We next turned our attention to the reaction of the benzylamine imine of cyclohexanone with methyl acrylate, in boiling methanol. Surprisingly, now only the 2,2-disubstituted cyclohexanone (**6**) was obtained, in reasonable yield. The yield was increased (25% → 77%) by carrying the reaction out in acetonitrile containing 4-dimethylaminopyridine as a base catalyst for the imine–enamine interconversion. The structure of the 2,2-product followed from the analytical and spectral data. In particular, the proton n.m.r. spectrum showed the presence of two methoxyl carbonyl groups (δ_H 3.52) and the ^{13}C n.m.r. spectrum clearly showed the C(2) signal as a singlet (δ_C 49.4). Furthermore, the ^{13}C n.m.r. spectrum was quite different from that of authentic 2,6-bis(2-methoxycarbonylethyl)cyclohexanone.

The reason for this marked change in the ease and regioselectivity of the reaction is attributed to the greater electrophilicity of methyl acrylate relative to acrylonitrile. This follows from the fact that reaction with a nucleophile (Nu) produces an anionic centre (Nu-$CH_2\bar{C}H$-Z) adjacent to the electron withdrawing group (Z), and the anion stabilizing power of such groups has been shown to decrease in the order: SO_2 > CO_2R > CN > $CONH_2$.[7] This greater reactivity means in turn that the transition state for the alkylation will be more reactant-like in nature or, in other words, that the bonding interaction will begin at greater interatomic distances and the influence of steric effects will be decreased. Thus, despite the greater steric impediment of a β-methoxycarbonylethyl group relative to a methyl group, further reaction at C(2) occurs.

This explanation has been confirmed in three ways. First, the anion stabilizing sequence proposed by Pearson[7] suggests that vinyl sulphones should be even more reactive than vinyl esters and should also therefore give the 2,2-dialkylated cyclohexanone. This has been confirmed by reaction of the cyclohexylamine imine of

cyclohexanone with phenyl vinyl sulphone, in methanol. The only product obtained, in good yield, was the 2,2-disubstituted cyclohexanone (**7**). The structure is confirmed by the analytical data, and the ^{13}C n.m.r. spectrum, which clearly shows the C(2) signal as a singlet at δ49.4. Secondly, we have subjected the propylamine imine (**4**) of 2-(2-cyanoethyl)cyclohexanone to further treatment with methyl acrylate. If methyl acrylate is reacting more easily than acrylonitrile because of the aforementioned steric and reactivity effects, then methyl acrylate should react with **4**. This has been confirmed. Reaction of **4** with methyl acrylate in boiling methanol gave the 2,2-disubstituted cyclohexanone (**8**) in reasonable yield (43%). Again, the structure assignment is unequivocal. The proton n.m.r. spectrum shows the presence of the methoxycarbonyl group and the ^{13}C n.m.r. spectrum clearly shows the C(2) signal as a singlet (δ49.9).

Finally, acrylamide could be expected to react only once because of its even lower reactivity. This too has been confirmed. In this case, however, the initial alkylation product was not isolated owing to its cyclization to the 2-oxo-octahydroquinoline (**9**). The i.r. spectrum showed the presence of an amide carbonyl group (ν_{CO} 1670 cm^{-1}), NH absorptions in the 3100—3200 cm^{-1} region, and the absence of the cyclohexanone carbonyl absorption at 1710 cm^{-1}. That the $\Delta^{4a(8a)}$-isomer had been produced followed from the proton n.m.r. spectrum, which showed no olefinic signals, and the ^{13}C n.m.r. spectrum which showed both olefinic signals as singlets (δ109.3 and 128.2).

Experimental

^1H N.m.r. spectra were obtained in deuteriochloroform on Varian T-60 or CFT-20 spectrometers, operating at 60 MHz and 80 MHz respectively. ^{13}C N.m.r. spectra were obtained on a Varian FT80A spectrometer from $CDCl_3$ solutions. I.r. spectra were recorded with Perkin–Elmer SP-1000 or Pye–Unicam SP3-200 spectrometers and calibrated against the 1601 cm^{-1} peak of polystyrene film, using liquid films on KBr discs. Mass spectra were determined with a Varian MAT-212 spectrometer at 70 eV. Microanalyses were carried out by the Chemistry Department of the University of Natal, Pietermaritzburg. Solvents and electrophilic alkenes were dried and distilled before use. Authentic samples of 2-(2-cyanoethyl)cyclohexanone,[6] 2,6-bis(2-cyanoethyl)cyclohexanone,[5,6] and the benzylamine and cyclohexylamine imines of cyclohexanone[8] were prepared by the literature methods, and 2,6-bis(2-methoxycarbonylethyl)cyclohexanone, m.p. 82.5—83.0°C, was prepared as described for the diethyl ester.[6]

N-*Cyclohexylidenepropylamine* (**2**; $R = C_3H_7$)

A solution of cyclohexanone (63.33 g; 680 mmol), propylamine (43.94 g; 740 mmol), and toluene-*p*-sulphonic acid (0.25 g) in benzene (100 ml) was heated under reflux under a Dean and Stark head for 8 h. The solvent was removed under vacuum and the residual oil distilled to give N-*cyclohexylidenepropylamine* (29.8 g; 31%), b.p. 34—36°C/0.17mm Hg; ν_{max} (film) 1660 cm^{-1} (C=N); δ_H 0.9 (3H, t, *J* 7.2 Hz, CH_3), 1.3—1.9 (8H, m, 4 × CH_2), 2.0—2.5 (4H, m, 2 × α-CH_2), and 3.2 (2H, t, *J* 6.9 Hz, CH_2CN); δ_C 11.1 (q, CH_3), 23.4, 25.2, 26.2, 27.0, 27.7, 39.1 (each t, 6 × CH_2), 51.1 (t, CH_2CN), and 170.7 (s, C=N).

N-[2-(2-*Cyanoethyl)cyclohexylidene] propylamine* (**4**)

A solution of 2-(2-cyanoethyl)cyclohexanone (**3**) (10.0 g; 66 mmol), propylamine (4.31 g; 73 mmol), and toluene-*p*-sulphonic acid (0.1 g) in benzene (50 ml) was heated under reflux under a Dean and Stark head for 8 h. Removal of the solvent under vacuum and distillation of the residue gave N-[2-(2-*cyanoethyl)cyclohexylidene] propylamine* (**4**) (10.3 g; 81%), b.p. 101—102°C/0.07 mm Hg; ν_{max} (film) 2250 (C≡N) and 1663 (C=N) cm^{-1}; δ_H 1.0 (3H, t, CH_3), 1.3—3.0 (15H, methylene envelope), and 3.3 (2H, t, CH_2CN); δ_C 11.9 (q, CH_3), 15.1 (t, CH_2CN), 24.2, 25.2, 27.4, 28.2, 28.5 (each t, 5 × CH_2), 34.7 (t, C-3), 48.5 (d, C-2), 51.7 (t, CH_2N), 120.3 (s, C≡N), and 171.4 (s, C=N) (Found: N, 9.16%; M^+, 192.1625). Calc. for $C_{12}H_{20}N_2$: N, 9.26%; *M*, 192.1626).

Alkylation of imines. General method

The electrophilic alkene was added to the imine (in the molecular proportions indicated below) in dry methanol or acetonitrile, and the solution was heated under reflux for the time stated. The mixture was hydrolysed by addition of water (10—20 ml) and heated under reflux for 1 h. The solvent was then removed *in vacuo* and the residue was extracted with ether. The ether layer was washed with 2M-hydrochloric acid until the washings were colourless, and then with water until acid-free, and dried ($MgSO_4$). Filtration and evaporation of the ether gave the crude product, which was purified by vacuum distillation and / or flash chromatography. In this way the following compounds were prepared.

2,2-*Bis(2-cyanoethyl)cyclohexanone* (**5**)

(a) Acrylonitrile (13.6 g; 260 mmol), *N*-cyclohexylidenebenzylamine (**2**; R = $PhCH_2$) (8.0 g; 43 mmol), methanol (20 ml), 21 h reflux. Distillation gave only the mono-alkylation product, 2-(2-cyanoethyl)cyclohexanone (**3**) (1.98 g; 31%), b.p. 112—115°C / 0.6 mm Hg, identical with authentic material obtained by alkylation of 1-pyrrolidinylcyclohexene[6] [ν_{max} (film) 2223 (C≡N) and 1711 (C=O); δ_H 1.4—2.6 (methylene envelope); δ_C 14.4 (t, C-2'), 24.4, 25.0, 27.2 (each t, 3 × CH_2), 33.4 (t, C-3), 41.5 (t, C-6), 48.2 (d, C-2), 119.1 (s, CN), and 210.9 (s, C-1)].

(b) Acrylonitrile (2.76 g; 52 mmol), *N*-[2-(2-cyanoethyl)cyclohexylidene] propylamine (**4**) (5.0 g; 26 mmol), methanol (20 ml), 4 h reflux. Flash chromatography of the crude product [hexane–dichloromethane–ethyl acetate (50 : 50 : 9)] gave unchanged 2-(2-cyanoethyl)cyclohexanone (1.51 g); 2,6-bis(2-cyanoethyl)cyclohexanone (0.29 g; 5%), identical with authentic material[6] prepared by

alkylation of 1-*N*-pyrrolidinylcyclohexene [ν_{max} (film) 2227 (C≡N) and 1708 (C=O) cm^{-1}; δ_H 1.3—2.6 (methylene envelope); δ_C 14.2 (s, C-2'), 24.2 (t, C-4), 24.6 (t, C-1'), 34.2 (t, C-3), 48.5 (d, C-2), 119.0 (s, CN), and 210.8 (s, C-7) (Found: N, 13.5%; M^+, 204.1262. Calc. for $C_{12}H_{16}N_2O$: N, 13.4%; *M*, 204.1263)], and 2,2-*bis*(*2-cyanoethyl)cyclohexanone* (**5**) (0.31 g; 6%); ν_{max} (film) 2228 (C≡N) and 1710 (C=O) cm^{-1}; δ_H 1.7—2.4 (methylene envelope); δ_C 11.4 (t, C-2'), 19.8 (t, C-4), 26.0 (t, C-5), 29.5 (t, C-1'), 34.5 (t, C-3), 38.4 (t, C-6), 49.8 (s, C-2), 119.1 (s, CN), and 211.8 (s, C-1) (Found: N, 13.7%; M^+, 204.1250. Calc. for $C_{12}H_{16}N_2O$: N, 13.7%; *M*, 204.1263).

2,2-*Bis*[(*2-methoxycarbonyl)ethyl]cyclohexanone* (**6**)

(a) Methyl acrylate (7.38 g; 86 mmol); *N*-cyclohexylidenebenzylamine (**2**; R=$PhCH_2$) (8.0 g; 43 mmol), methanol (20 ml), 3 h reflux. Distillation gave the 2,2-diester (**6**) (2.86 g; 25%), b.p. 140—146°C / 0.04 mm Hg, which was further purified by flash chromatography [hexane–dichloromethane–ethyl acetate (12.5 : 12.5 : 1)] to give 2,2-*bis*-[(*2-methoxycarbonyl)ethyl*]*cyclohexanone* (**6**), ν_{max} (film) 1744 (CO_2Me) and 1709 (C=O) cm^{-1}; δ_H 1.6—2.5 (16H, methylene envelope) and 3.52 (6H, 2 × OCH_3); δ_C 19.9 (t, C-4), 26.1 (t, C-5), 27.6 (t, C-1'), 28.6 (t, C-2'), 35.2 (t, C-3), 38.1 (t, C-6), 49.4 (s, C-2), 50.7 (q, OCH_3), 172.8 (s, CO_2Me), and 212.6 (s, C-1) (Found: C, 62.1, H, 8.3%. Calc. for $C_{14}H_{22}O_5$: C, 62.2; H, 8.15%).

(b) Methyl acrylate (30.94 g; 360 mmol), *N*-cyclohexylidenepropylamine (**2**; R=C_3H_7) (10.0 g; 72 mmol), quinol (0.09 g), 4-dimethylaminopyridine (8.79 g; 0.072 mol), dry acetonitrile (30 ml), 4 h reflux. Distillation gave the 2,2-diester (**6**) in considerably increased yield (15.03 g; 77%).

2,2-*Bis*[(*2-phenylsulphonyl)ethyl*]*cyclohexanone* (**7**)

Phenyl vinyl sulphone (2.20 g; 13 mmol), *N*-cyclohexylidenecyclohexylamine (**2**; R=C_6H_{11}) (0.82 g; 4.6 mmol), methanol (2 ml), 4 h reflux, hydrolysed and worked-up as in the *General method*, except that dichloromethane (4 × 25 ml) was used instead of ether. Purification by flash chromatography [hexane–dichloromethane–ethyl acetate (2 : 1 : 1)] gave recovered phenyl vinyl sulphone (0.28 g) and 2,2-*bis*[(*2-phenylsulphonyl)ethyl*]*cyclohexanone* (0.76 g; 48%); δ_H 1.2—3.1 (16H, methylene envelope) and 7.4—7.9 (10H, 2 × C_6H_5); δ_C 20.0 (t, C-4), 26.2 (t, C-5), 26.4 (t, C-1'), 35.5 (t, C-3), 38.3 (t, C-6), 49.4 (s, C-2), 50.6 (t, C-2'), 127.6d, 129.1d, 133.6d, 138.4s, (Ph), and 212.1 (s, C-1) (Found: C, 60.5; H, 6.0; S, 15.0%; M^+, 434.1230. Calc. for $C_{22}H_{26}O_5S_2$: C, 60.8; H, 6.0; S, 14.8%; *M*, 434.1222).

2-(*2-Cyanoethyl*)-2-(*2'-methoxycarbonylethyl)cyclohexanone* (**8**)

Methyl acrylate (4.44 g; 52 mmol), *N*-[2-(2-cyanoethyl)-cyclohexylidene] propylamine (**4**) (4.96 g; 26 mmol), methanol (20 ml); 4 h reflux. Flash chromatography of a portion of the crude product gave unchanged 2-(2-cyanoethyl)cyclohexanone and 2-(*2-cyanoethyl*)-2-(*2'-methoxycarbonylethyl)cyclohexanone* (43%), b.p. 146 °C / 0.1mm Hg; ν_{max} (film) 2230 (C≡N), 1744 (CO_2Me), and 1710 (C=O) cm^{-1}; δ_H 1.6—2.6 (methylene envelope) and 3.66 (3H, s, OMe); δ_C 11.6 (t, C-2'), 20.0 (t, C-4), 26.3 (t, C-5), 27.8 (t, C-1''), 28.8 (t, C-2''), 29.8 (t, C-1'), 35.0 (t, C-3), 38.4 (t, C-6), 49.9 (s, C-2), 51.3 (q, OCH_3), 119.4 (s, CN), 172.8 (s, CO_2Me), and 212.6 (s, C-1) (Found: C, 65.65; H, 8.3; N, 6.1%; M^+, 237.1370). Calc. for $C_{13}H_{19}NO_3$: C, 65.8; H, 8.0; N, 5.9%; *M*, 237.1365).

2-*Oxo*-$\Delta^{4a(8a)}$-*octahydroquinoline* (**9**)

Acrylamide (42.1 g; 590 mmol), *N*-cyclohexylidenepropylamine (**2**; R=C_3H_7) (13.77 g; 99 mol), methanol (50 ml), 4 h reflux. Flash chromatography [hexane–dichloromethane–ethyl acetate (8 : 4 : 5)] gave 2-oxo-$\Delta^{4a(8a)}$-octahydroquinoline (2.68 g; 18%), m.p. 138.5—140.0°C (hexane–dichloromethane); ν_{max} (Nujol) 3210, 3180, 3100 (NH), and 1670 (CONH) cm^{-1}; δ_H (250 MHz) 1.56—1.74 (4H, m, 2 × CH_2), 1.95—2.12 (4H, m, 2 × CH_2), 2.18 (2H, t, *J* 10.5 Hz, CH_2), 2.47 (2H, t, *J* 8.0 Hz, CH_2), and 8.47 (1H, s, NH); δ_C 22.1, 22.6, 25.7, 26.0 (each 4 × CH_2), 27.7 (t, C-4), 30.6 (t, C-3), 109.3 (s, C-4a), 128.2 (s, C-8a), and 171.6 (s, C-2) (Found: C, 71.2; H, 8.8; N, 9.2%; M^+, 151.0998. Calc. for $C_9H_{13}NO$: C, 71.4; H, 8.6; N, 9.25%; *M*, 151.0997).

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One-step synthesis of the bicyclo[2.2.2]-octane ring system from acyclic precursors. Preparation of 2-benzoyl-4-methyl-1-phenylbicyclo[2.2.2]octan-5-one from phenyl vinyl ketone and *N*-2-butylidene-benzylamine. Crystal structure.

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Reaction of the benzylamine imine of butanone with phenyl vinyl ketone gives 2-benzoyl-4-methyl-1-phenylbicyclo[2.2.2]-octan-5-one in a new one-step synthesis of a bicyclic ring system from acyclic precursors, in which four carbon–carbon bonds are formed sequentially.

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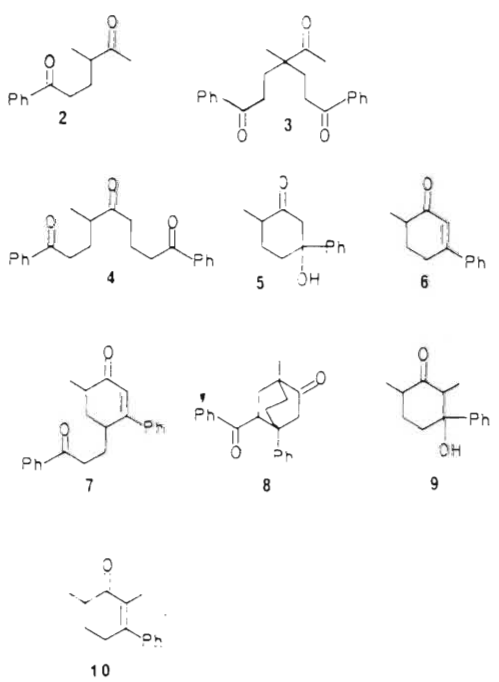
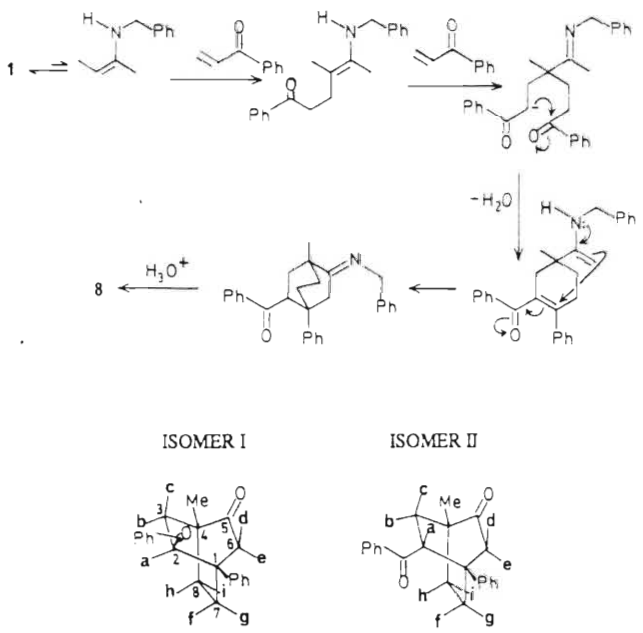
Reaksie van die bensielamienimien van butanoon met feniel-vinielketoon lewer 2-bensoïel-4-metiel-1-fenielbisiklo[2.2.2]-oktan-5-oon in 'n nuwe eenstap-sintese van 'n bisikliese ring-sisteem van asikliese voorgangers, waarin vier koolstof–koolstofbindings opeenvolgend gevorm word.

In an extension of our work on the regioselective alkylation of imines of cyclic[1–3] and acyclic[4] ketones, we now report our preliminary investigations into the unusual course of the reaction with phenyl vinyl ketone (PVK). Reaction of the benzylamine imine (**1**) of butanone with one equivalent of PVK in boiling dry methanol (4 h reflux) followed by hydrolytic work-up, failed to give any of the expected mono- or di-alkylation products (**2**) — (**4**) or the plausible cyclization products (**5**) — (**7**). The 80 MHz ^{1}H n.m.r. spectrum of the product showed the presence of two benzene rings, the absence of the CH_3CO group, and a methyl *singlet* at δ 1,1.



These observations indicated that only two equivalents of PVK had, in some way, reacted three times with the butanone imine, once at C(1) and twice at C(3). Consideration of the probable sequence of events (Scheme 1) led us to propose the bicyclo[2.2.2]octanone structure (**8**) as the product of this reaction on mechanistic grounds. This has now been confirmed by 500 MHz n.m.r. and a single crystal *X*-ray structure determination. Flash chromatography (ethyl acetate–hexane–chloroform; 1:12:7) separated the product into two isomeric forms of (**8**), isomer I (1,3% yield; m.p. 170—170,5°C) and isomer II (5,6% yield; m.p. 161—163°C). Isomer I ($C_{22}H_{22}O_2$) crystallized from ethyl acetate in the space group *I*2/*a*, a = 22,922(3), b = 6,408(1), c = 23,381(3) Å, β = 92,37(1)°, U = 3431,3 Å^3, z = 8, D_c = 1,239 g cm^{-3}, λ = 1,5418 Å, $F(000)$ = 1360, and μ (Cu–K_α) = 5,7 cm^{-1}. Data were collected from a crystal of dimensions 0,05 × 0,13 × 0,25 mm on a Nicolet R3 m/v diffractometer using the θ–2θ scan method (θ < 57,5°). From 2321

Scheme 1



unique measured reflections corrected for Lorentz and polarization effects but not for absorption, 1394 with $I > 3\,\sigma\,(I)$ were used in the structure solution (direct methods) and refinement which converged at R and R_w values 0,071 and 0,058 respectively. Atomic coordinates are given in Table 1 and the atomic numbering and molecular structure is given in Figure 1.[5]

Table 1 Fractional coordinates (× 10^4) for structure (**8**) (Isomer I)

Atom	*x* / *a*	*y* / *b*	*z* / *c*
C(1)	9175 (1)	5371 (4)	3134 (1)
C(2)	9446 (1)	4669 (5)	2577 (1)
C(3)	9083 (1)	5382 (4)	2040 (1)
C(4)	8452 (1)	6003 (4)	2221 (1)
C(5)	8546 (2)	7983 (4)	2592 (1)
C(6)	9014 (1)	7632 (4)	3054 (1)
C(11)	8595 (1)	4191 (5)	3182 (1)
C(12)	8226 (1)	4296 (5)	2621 (1)
C(10)	9582 (2)	4988 (6)	3653 (2)
O(60)	9241 (1)	9064 (3)	3324 (1)
C(30)	9066 (1)	3732 (4)	1574 (1)
O(30)	9024 (1)	1895 (3)	1710 (1)
C(31)	9097 (1)	4300 (4)	957 (1)
C(32)	9245 (2)	6269 (6)	768 (1)
C(33)	9289 (2)	6737 (7)	190 (2)
C(34)	9181 (2)	5108 (8)	–203 (2)
C(35)	9026 (2)	3164 (8)	–22 (2)
C(36)	8985 (2)	2750 (6)	553 (2)
C(41)	8039 (1)	6370 (4)	1702 (1)
C(42)	8019 (2)	8258 (5)	1414 (1)
C(43)	7652 (2)	8573 (7)	937 (2)
C(44)	7292 (2)	6995 (7)	735 (2)
C(45)	7301 (2)	5117 (7)	1011 (2)
C(46)	7673 (2)	4796 (5)	1492 (2)

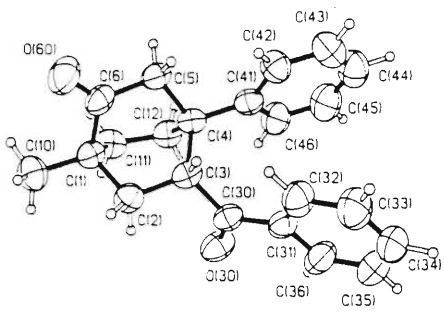


Figure 1 Crystal structure of **8** (isomer I).

Four different carbon–carbon bonds are formed sequentially in this reaction (Scheme 1) which, as far as we are aware, constitutes the first one-step synthesis of a bridged bicyclic system from acyclic precursors. Repeating the reaction with two equivalents of PVK increased the yield of isomer II[6] from 5,6 to 35%, none of isomer I being isolated under these conditions. Since the water eliminated in the first cyclization step (Scheme 1) could result in partial hydrolysis of imine-enamine mixture, the reaction was repeated in the presence of a molecular sieve. This resulted in a further increase in yield to 50%.[7] The 500 MHz proton and ^{13}C n.m.r. assignments are summarized in Table 2.

Table 2 Chemical shift assignments for structure (**8**)[a]

	Proton			Carbon	
H	Isomer I	Isomer II	C	Isomer I	Isomer II
a	4,06	4,27	1[b]	43,8	43,4
b	2,08	2,10	2	48,5	47,3
c	1,95	1,96	3	35,7	36,9
d	2,93	3,67	4[b]	43,2	42,9
e	2,42	2,51	5	215,6	214,5
f	3,04	2,42	6	51,3	43,7
g	1,80	1,75	7	25,1	34,8
h	2,11	1,81	8	30,8	31,1
i	1,78	2,01	PhCO	202,7	202,7
Me	1,09	1,10	Me	19,5	19,6

[a] Based on 2D COSY, NOESY, and HETCOR plots, and the observed splitting and coupling constants.
[b] Interchangeable.

As can be seen, the only significant differences in chemical shifts between the two isomers occur at positions 6 and 7. In isomer I, C(7) experiences a steric compression shift[8] to high field relative to C(7) in II (δ25,1 and 34,8, respectively), whereas the attached proton f is deshielded by the close proximity of the benzoyl carbonyl group and appears at lower field relative to proton f in II (δ3,04 and 2,42, respectively). Conversely, C(6) is shielded in isomer II relative to I (δ43,7 and 51,3, respectively), whereas the attached proton d is deshielded in II relative to I (δ3,67 and 2,93, respectively). Furthermore, a strong n.O.e. was observed between protons a and d in I, which was absent in II and thus confirms the orientation of the benzoyl group as being *exo* to the cyclohexanone ring in I and *endo* in II. There was also strong **W** coupling between protons a and e in II, whereas in I the **W** coupling occurred between a and g, thus confirming the stereochemical assignments.

The reaction followed a different course when applied to the benzylamine imine of pentan-3-one. In this case, only one equivalent of PVK reacted with one equivalent of the imine, but this was followed by cyclization onto C(2) to produce 3-hydroxy-2,6-dimethyl-3-phenylcyclohexanone (**9**) (m.p. 150—151°C; 11%) and 2,6-dimethyl-3-phenylcyclohex-2-enone (**10**; 45%), on hydrolysis.

It therefore appears that the bicyclo[2.2.2]octanone synthesis may be restricted to methyl ketones unless a means can be found to inhibit the final cyclization step until α,α-dialkylation has taken place. With this end in view, further investigations into the effect of substituents and experimental conditions on the yield and course of the reaction have been initiated.

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