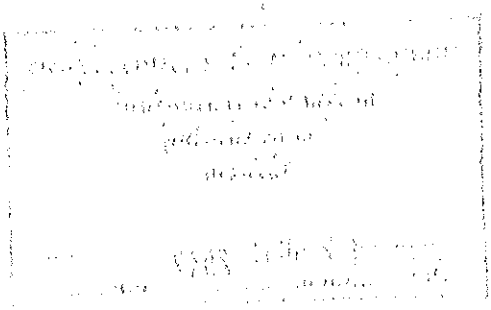
Synthesis of Acarnidine and Polyamine Derivatives

Chonlatid Na Phatthalung



Master of Science Thesis in Organic Chemistry

Prince of Songkla University

1994

Thesis Title	Synthesis of Acarnidine and Polyamine Derivatives
Author	Mr. Chonlatid Na Phatthalung
Major Program	Organic Chemistry

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The Graduate School, Prince of Songkla University, has approved this Thesis as partial fulfillment of the requirement for the Master of Science degree in Organic Chemistry.

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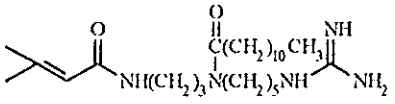
(Dr. Pairat Sanguansai)

Dean, Graduate School

Thesis Title	Synthesis of Acarnidine and Polyamine Derivatives
Author	Mr.Chonlatid Na Phatthalung
Major Program	Organic Chemistry
Academic Year	1994

ABSTRACT

The new synthetic route to acarnidine (73), the biologically active marine natural products and that of acarnidine homologue (188) has been developed using the mono-protected hexahydropyrimidines (175), and (40), respectively as common precursors.



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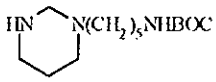

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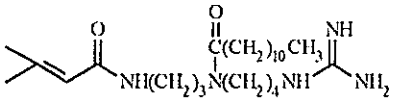

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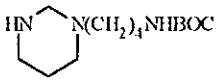
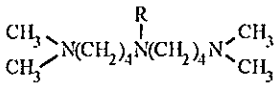
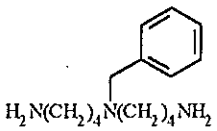


(40)

Also, a convenient and selective synthesis of solamine (68), solapalmitine (69) and solapalmitenine (70) has been achieved via N^5-benzylhomospermidine (157).

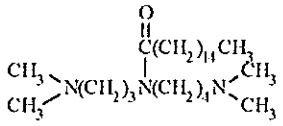


R =	H,	solamine	(68)
R =	$CH_3(CH_2)_{14}CO$	solapalmitine	(69)
R =	$CH_3(CH_2)_{12}CH\overset{E}{=}CHCO$	solapalmitenine	(70)



(157)

Solapalmitine homologue (165) and solapalmitenine homologue (168) have been synthesized by a versatile general method whose key feature is the formation of N^1,N^8-di(*tert*-butyloxycarbonyl)spermidine (124) from spermidine.



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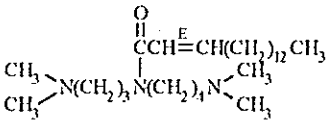

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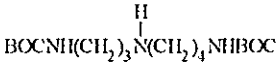


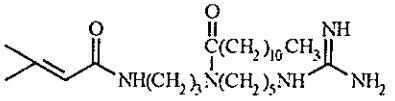
(124)

The present work provided the methods for a large scale preparation of acarnidine (73), acarnidine homologue (188) and polyamine derivatives (68), (69), (70), (165) and (168). This work has made possible an extensive evaluation of structure-activity relationships in polyamine derivatives.

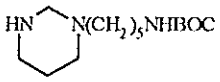
ชื่อวิทยานิพนธ์	การสังเคราะห์สารประกอบอะคาร์นิดีนและอนุพันธ์โพลีเอมีน
ผู้เขียน	นายชลธิศ ณ พัทลุง
สาขาวิชา	เคมีอินทรีย์
ปีการศึกษา	2537

บทคัดย่อ

แนวทางใหม่ในการสังเคราะห์สารประกอบ acarnidine (73) ซึ่งเป็นสารชีวภาพจากผลิตภัณฑ์ธรรมชาติทางทะเล (biologically active marine natural products) และ acarnidine homologue (188) ได้ถูกพัฒนาขึ้นโดยการใช้ mono-protected hexahydropyrimidines (175) และ (40) เป็นตัวนำทาง (precursor)



(73)



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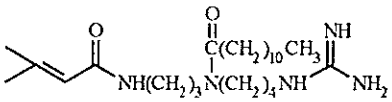

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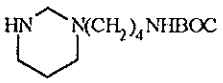
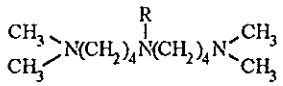
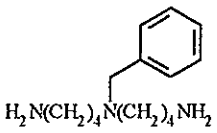


(40)

การสังเคราะห์แบบง่ายและเลือกสรร (Selective) ของสารประกอบ solamine (18), solapalmitine (69) และ solapalmitenine (70) ได้ประสบความสำเร็จโดยการเตรียมผ่านสารประกอบ N^5-benzylhomospermidine (157)

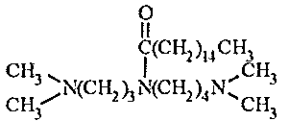


R = H,		solamine	(68)
R = $CH_3(CH_2)_{14}CO$		solapalmitine	(69)
R = $CH_3(CH_2)_{12}CH=^{E}CHCO$		solapalmitenine	(70)



(157)

solapalmitine homologue (165) และ solapalmitenine homologue (168) ได้ถูกสังเคราะห์โดยใช้วิธีที่เป็นที่นิยมโดยทั่วไป ซึ่งอาศัยลักษณะเด่นของการสร้างสารประกอบ N^{1},N^{8}-di(*tert*-butyloxycarbonyl)spermidine (124) จาก spermidine



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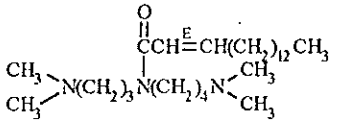

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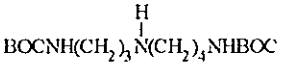

(124)

งานในครั้งนี้เป็นการเสนอวิธีการในการเตรียมสารประกอบ acamidine (73), acarnidine homologue (188) and polyamine derivatives (68), (69), (70), (165) และ (168) ให้ได้ปริมาณมาก และเป็นไปได้ที่จะขยายงานในครั้งนี้เพื่อหาค่าความสัมพันธ์ระหว่างโครงสร้างกับความมีฤทธิ์ (structure-activity relationships) ของสารประกอบอนุพันธ์โพลีเอมีน

ACKNOWLEDGEMENT

I wish to express my gratitude to my supervisor, Associate Professor Dr. Kan Chantrapromma and my co-supervisor, Dr. Chatchanok Karalai for all their advice, encouragement and guidance throughout this work.

I am also very grateful to Assistant Professor Chanita Ponglimanont, Associate Professor Dr. Vichu Lojanapiwatna and Associate Professor Dr. Feeya David for their comments and valuable suggestions. In particular I would like to thank Mr. Bunsit Watanathai for NMR spectroscopy measurements.

I am especially grateful to Professor Dr. W.C Taylor, Assistant Professor Chanita Ponglimanont and Mrs. Panida Sooksimuang for their conscientious proof-reading. I would like to thank Mr. Pongnarin Chanhom for his extremety careful typing of the manuscript. Finally I would like to express my deepest appreciation to my parents for their love and attention throughout my life.

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Chonlatid Na Phatthalung

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Scheme

Table

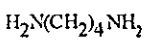
ABBREVIATIONS AND SYMBOLS

DCC	dicyclohexylcarbodiimide
DMAP	4-dimethylamiopyrimidine
$(BOC)_2O$	di-*tert*-butyl-dicarbonate
BOC-ON	2-(BOC-oxyimino)-2-phenylacetonitrile
TFA	trifluoroacetic acid
THF	tetrahydrofuran
Py	pyridine
Pi	piperidine

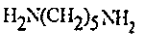
CHAPTER 1

INTRODUCTION

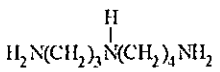
Anton von Leeuwenhock first observed living spermatozoa with the primative microscope in 1677. He also discovered a crystalline substance from human seminal fluid (Leeuwenhock,1678), the spermine phosphate, a salt of the first known naturally occurring polyamines, that had so easily and spontaneously precipitated under Leewenhock's lens. However it took a long succession (> 250 years) of distinguished naturalists and medical investigators to unravel the identity of this substance (William and Ashman, 1965). In a brilliant series of papers after the first world war, Rosenheim (Rosenheim, 1925) and Fanselow (Fanselow, *et al.*, 1927) used the organic synthesis to establish conclusively the correct composition of spermidine and a related base, spermine. Together with the simpler diamine putrescine and cadaverine, which were discovered in decomposing animal carcasses, these four aliphatic bases constitute the principle members of an ubiquitous family of natural products.



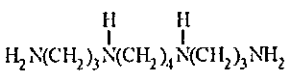
putrescine
(1)



cadaverine
(2)



spermidine
(3)



spermine
(4)

Classification of Polyamines

Polyamines can be classified into three groups on the basis of their nitrogen-containing structural features:

1. putrescine type (1)
2. spermidine type (3)
3. spermine type (4)

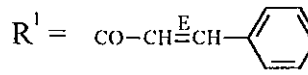
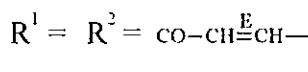
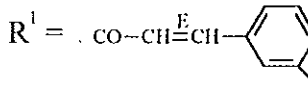
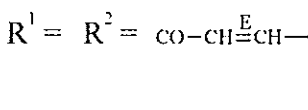
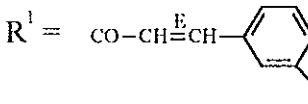
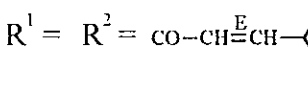
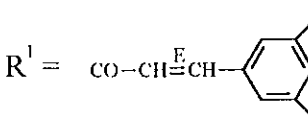
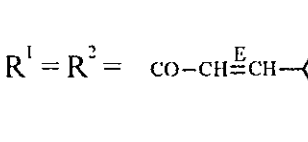
As already mentioned, these three bases belong to the biogenetic amines, but their derivatives (mostly containing fatty acid or cinnamic acid residues) are considered to be polyamines.

1. Putrescine Type

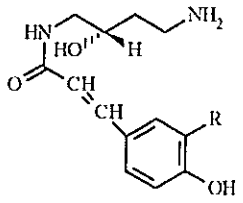
1.1 Simple Derivatives of Putrescine

A number of putrescine derivatives have been detected in nature containing one or two cinnamic acid derivatives attached through amide linkages. Paucine (9) is one of the first diaminoalkane alkaloids, which has been known since 1894 as a component of the seeds of *Pentaclethra macropylla*. Its structure was deduced from spectroscopic data (Hollerbach and Spileller, 1970). Other derivatives of putrescine are shown in **Table 1.** Several compounds were synthesized and compared to those obtained as natural producs. (Stoessl, 1965; Bird and Smith, 1981).

Table 1. Naturally occurring putrescine alkaloids

R^1-NH(CH_2)$_3$NH-R^2	NAME
R^1 =  , R^2 = H	4-coumaroyl putrescine (5)
R^1 = R^2 = 	di-4-coumaroyl putrescine (6)
R^1 =  ,R_2 = H	feruloyl putrescine (7) (Subaphyline)
R^1 = R^2 = 	diferuloyl putrescine (8)
R^1 =  , R_2 = H	caffeoyl putrescine (paucine) (9)
R^1 = R^2 = 	dicaffeoyl putrescine (10)
R^1 =  , R_2 = H	sinapoyl putrescine (11)
R^1 = R^2 = 	disinapoyl putrescine (12)

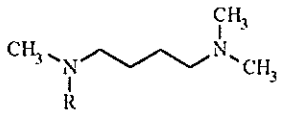
Two natural derivatives of 2-hydroxyputrescine have been found in wheat: N-(4-coumaroyl)- and N-feruloyl-2-hydroxyputrescine (13 and 14, respectively) and the synthesis of N-(4-coumaroyl)-2-hydroxyputrescine (13) has been reported by Mizusaki and co-workers (Mizusaki, *et al.*, 1971).



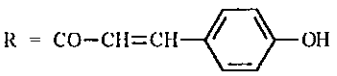
R = H N-(4-coumaroyl)-2-hydroxyputrescine (13)

R = OCH_3 N-(feruloyl)-2-hydroxyputrescine (14)

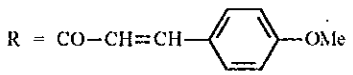
Three methylated derivatives of putrescine are also known. Tetramethyl putrescine (15) was the first methylated derivative to be isolated from *Hyosyamus muticus* in 1907 (Hevbner and Willstatter, 1907). The comparison of the synthetic sample to the quaternized natural products proved the identity of both tetramethylene1,4-ditrimethyl ammonium diiodide (Hevbner and Willstatter, 1907). N,N,N^1-Trimethyl-N^1-(4-hydroxy-2-cinnamoyl)putrescine (16) and N,N,N^1-trimethyl-N^1-(4-methoxy-2-cinnamoyl)putrescine (17) were isolated from three *Kniphofia* species (Budzikiewcz, *et al*,. 1970).



R = CH_3 (15)



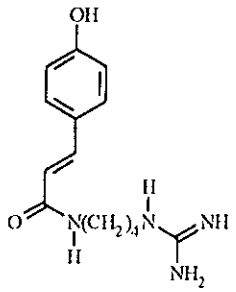
(16)



(17)

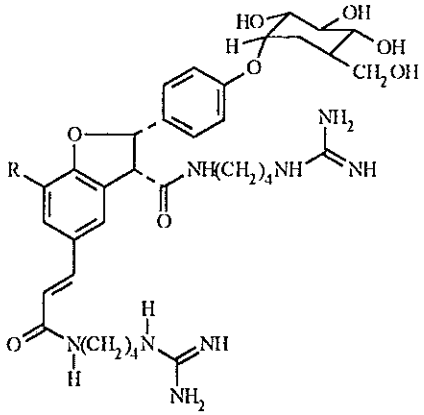
1.2 Agmatine Derivatives

Several agmatine derivatives have been isolated from barley seedings. All are conjugates of coumaric acid, for example 4-coumaroylagmatine (18) and possess antifungal activity (Stoessl, 1966).



(18)

The other compounds are hordatine A (19) and hordatine B (20). The mixture of hordatine A and B glucosides, called hordatine M, has not been separated yet (Stoessl, 1966, 1967).

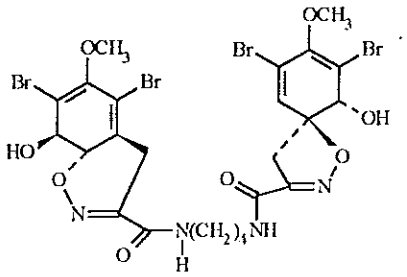


R = H hordatine A (19)

R = OCH_3 hordatine B (20)

1.3 Aerothionine

Aerothionine, a tetrabromo derivative, has been isolated from sponges *Aplysian aerophoba* and *Verongia thiona*. The proposed structure is (21) (Fattōrusso, *et al.*, 1970).



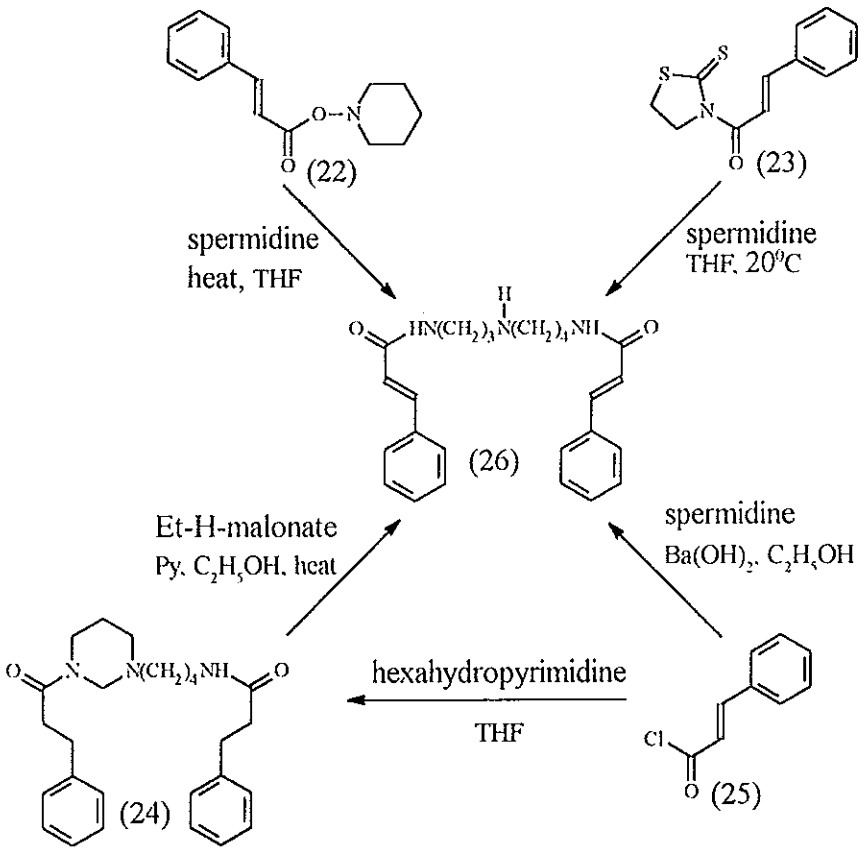
(21)

2. Spermidine Type

2.1 The Simple Open-chain Spermidine Derivative of Natural Origin

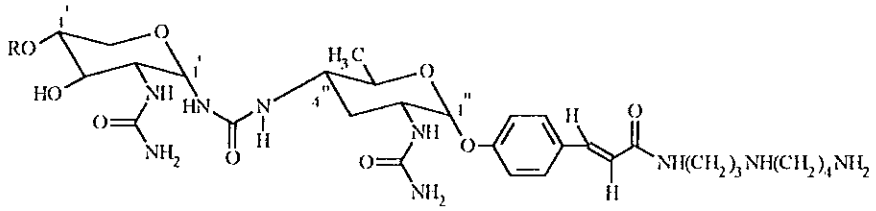
Spermidines substituted with cinnamic acid derivatives seem to be widely distributed in the plant kingdom. Cinnamic acid (alkaloid maytenine), caffeic acid (caffeoylspermidine, dicaffeoylspermidine), coumaric acid (coumaroylspermidine, dicoumaroylspermidine, tricoumaroylspermidine), ferulic acid (feruloylspermidine, diferuloylspermidine) and sinapic acid (sinapoylspermidine, disinapoylspermidine) are known as aromatic amide substituents of spermidine. Several compounds were synthesized in the past (Bergeron, *et al.*, 1980, 1981; Bhargava, *et al.*, 1980; Fujita, *et al.*, 1980).

Maytenine (26) was the first of these so-called simple alkaloids to be isolated and identified structurally by use of MS, NMR and UV spectroscopy (Neilands, *et al.*, 1979). Several syntheses of (26) have been reported as shown in **Scheme 1**.

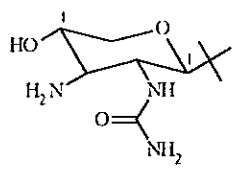


Scheme 1. Syntheses of maytenine (26)

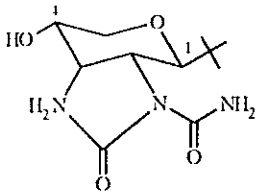
The most fascinating compounds are the glycocinnamoyl spermidines LL-BM123 β, γ_1, and γ_2 (27-29) which were isolated from an unidentified species of *Nocardia* (Broscharaol, *et al.*, 1978). The γ_1 and γ_2 components are of special interest in view of their potent activity against gram-negative organisms and their protective effects against infection.



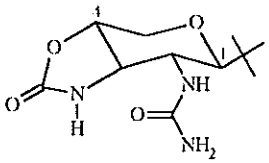
R =



BM 123 β
(27)

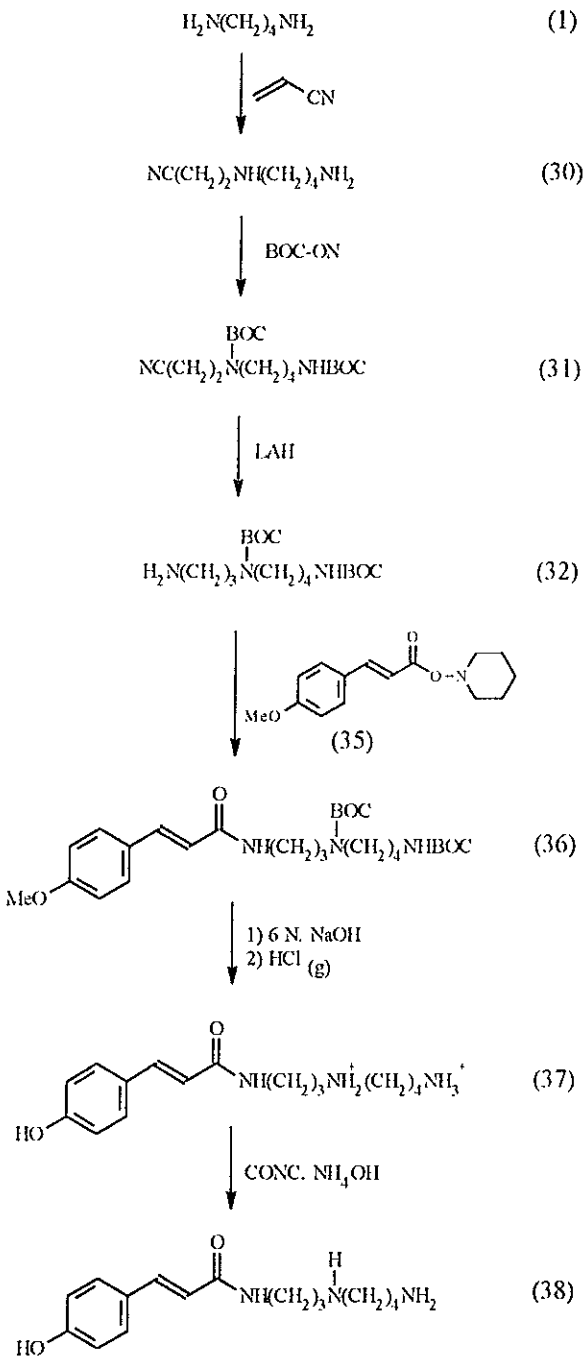


BM 123 γ_1
(28)



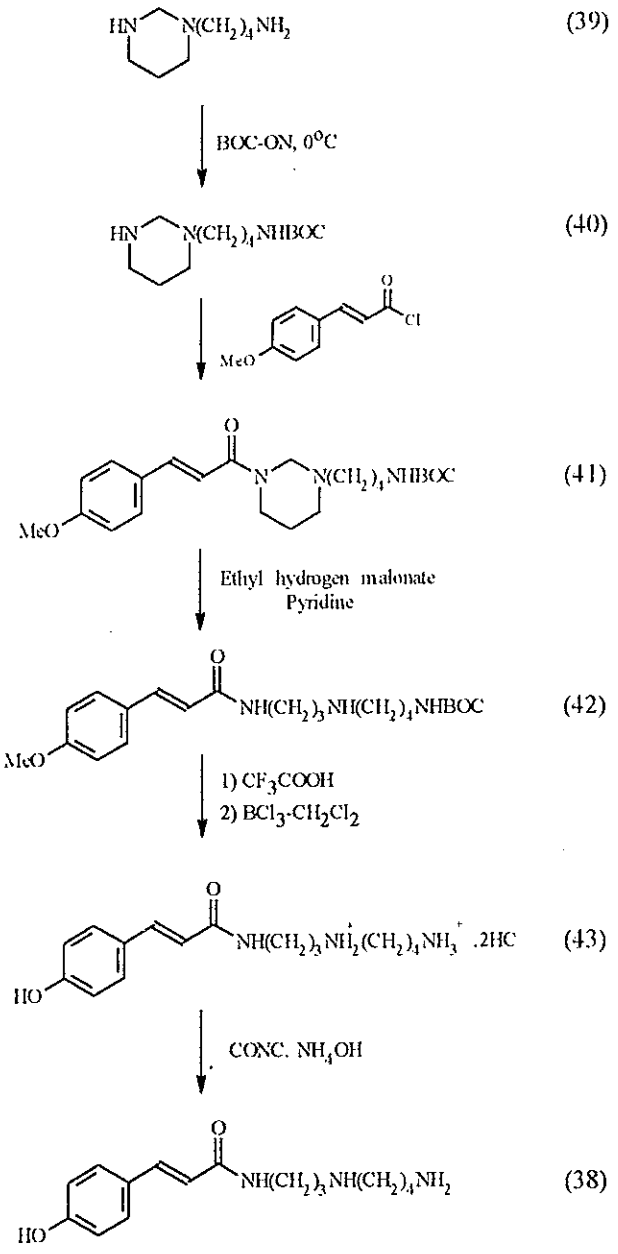
BM 123 γ_2
(29)

The first synthesis of the aglycone LL-BM123 (38) was reported by Michael Humora and James Quick (Humora and Quick, 1979). The synthesis approach is depicted in **Scheme 2.**



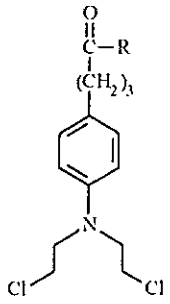
Scheme 2 Synthesis of the aglycone LL-BM123 (38) (Hamura and Quick, 1979)

Chantrapromma and co-workers have prepared the agylcone LL-BM 123 (29) by using hexahydropyrimdine (39) (Chantrapromma, *et al.*, 1990). The synthesis route to the aglycone LL-BM 123 is shown in **Scheme 3**.

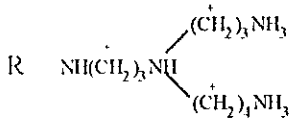


Scheme 3 Synthesis of the aglycone LL-BM123 (29) (Chantrapromma, *et al.*, 1990).

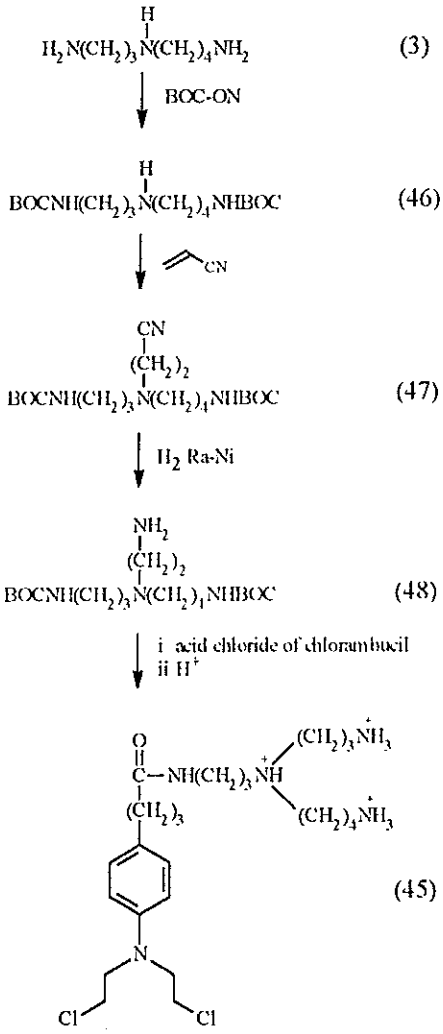
Recently Gerald M. Cohen and co-workers have published the synthesis of chloroambucil spermidine conjugated (45) from spermidine (3) via N^1, N^8-bis-BOC-spermidine (46) as shown in **Scheme 4**. The compound (45) has been shown to crosslink DNA 10^4 times more efficiently than chlorambucil (44), a well known aromatic nitrogen widely used in the treatment of chronic lymphocytic leukaemia, lymphomas and ovarian carcinoma (Cohen, *et al.*, 1992).



R = OH chlorambucil (44)



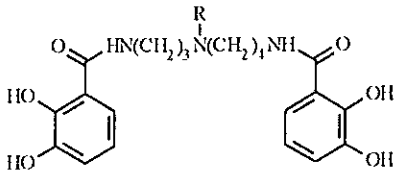
chlorambucil spermidine conjugated (45)

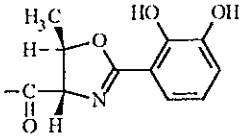


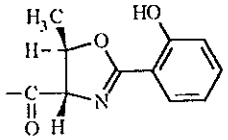
Scheme 4. Synthesis of chlorambucil spermidine conjugated (45).

2.2 Siderophores

Three siderophores (microbia iron-transport agents) belonging to the class of spermidine alkaloides: agrobactine (49) was isolated from *Agrobacterium tumefacien* and both parabactine (50) and 1,8-bis(2,3-dihydroxybenzamido)-4-azaoctane (51) were isolated from *Psaracocus denitrificane* (Neilands, *et al.*, 1979; Tail, 1975). The syntheses of these compounds have been reported. (Bergeron, *et al*,.1980,1981; Bhargava, *et al.*,1980; Fujita, *et al.*,1980).

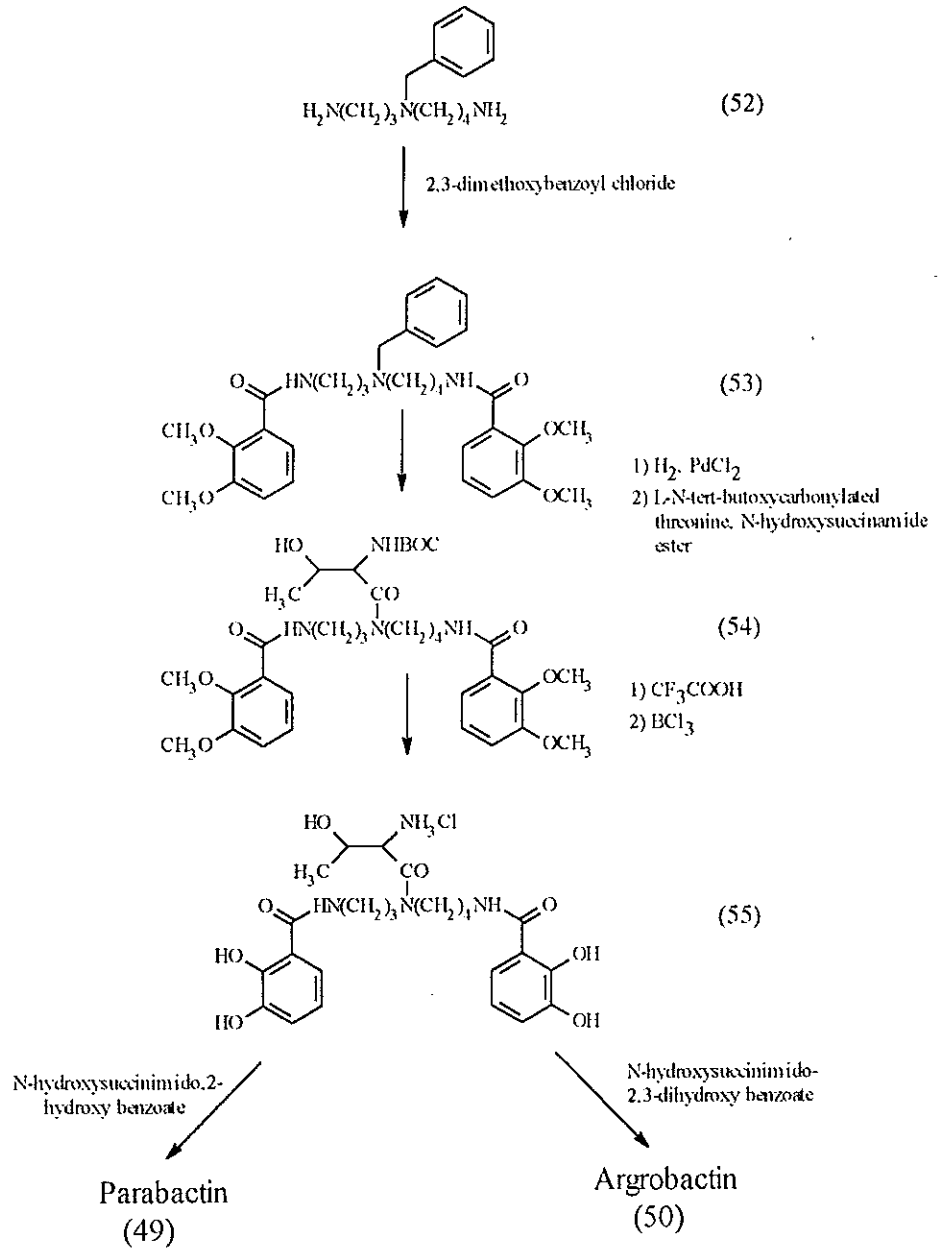


R =  agrobactine (49)

R =  parabactine (50)

R = H 1,8-bis(2,3-dihydroxybenzamido)-4-azaoctane (51)

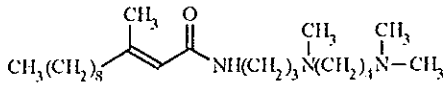
The synthesis of two polyamine catecholamide iron chelators, including parabactine (49) and agrobactine (50) is outlined in **Scheme 5** (Bergeron, *et al.*, 1980, 1981)



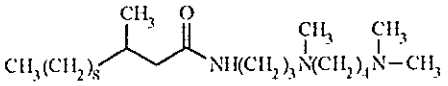
Scheme 5 Synthesis of Parabactine (49) and Agrobactine (50).

2.3 Spermidine of Soft Corals

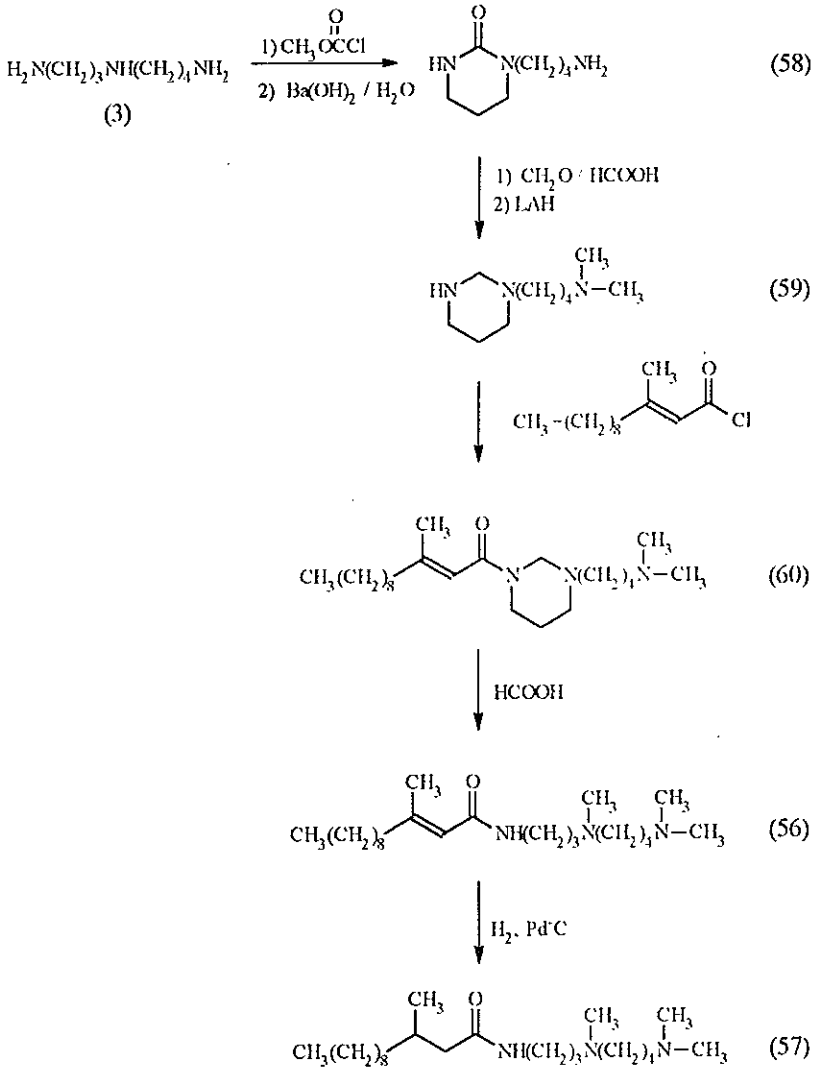
Two cytotoxic spermidine derivatives were isolated as a mixture from the Pacific soft coral *Sinularia brongersmai* : 5,12-dimethyl-1-dimethylamino-5-9-diazaheneicos-11-en-10-one (56) and its 11,12-dihydroderivative (57) (ratio 9:1) (Hollenbeak, *et al.*, 1979). The synthesis of (56) and (57) was accomplished according to **Scheme 6** (Chantrapromma, *et al.*, 1980).



(56)

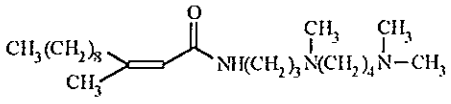


(57)

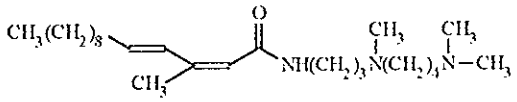


Scheme 6. Synthesis of 5,12-dimethyl-1-dimethylamino-5,9-diazaheneicos-11-en-10-one (56) and its 11,12-dihydroderivative (57)

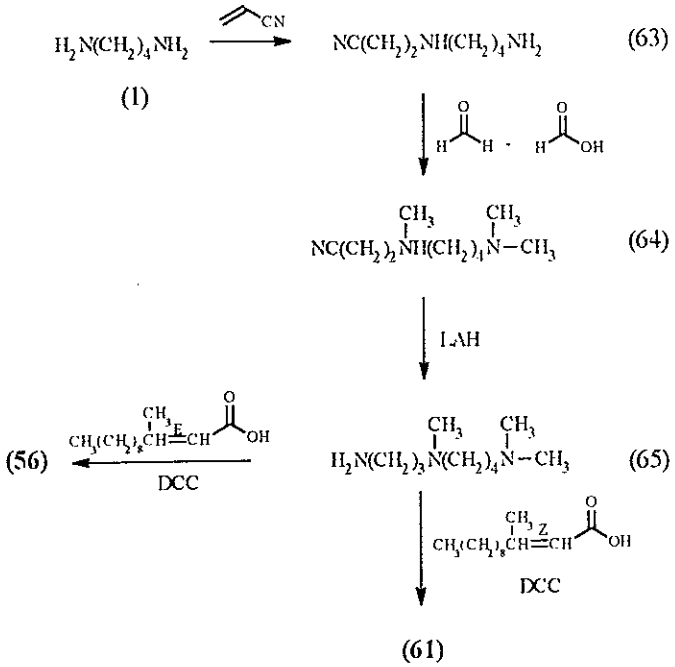
Two N-methylated spermidines (61) and (62) were isolated from a soft coral, *Simularia sp* (Kazlauskas, *et al.*, 1982). These compounds have shown potent *in vitro* and *in vivo* activity against a human pathogenic bacterium *Pseudomonas aeruginosa*. The alternative synthesis of (56) and (61) was reported (Kazlauskas, *et al.*, 1982) as indicated in **Scheme 7**.



(61)



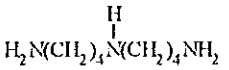
(62)



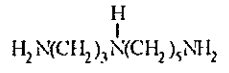
Scheme 7. Synthesis of spermidine derivatives (56) and (61)

2.4 Derivatives of Spermidine Lengthened by one Methylene Group (Homospermidine)

Homospermidine (Bachrach, 1973; Smith, 1977) is a type of polyamines, and the name is commonly used for the symmetric triamine (66) but once was also used for its unsymmetric isomer (67). Both skeletons can be found in derivatives of natural origin.

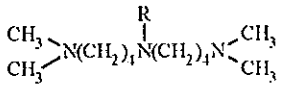


symmetrical homospermidine (66)



unsymmetrical homospermidine (67)

From plants belonging to the family Solanaceae, five alkaloids were isolated containing symmetrical homospermidine as the basic backbone : solamine (68), solapalmitine (69), solapalmitenine (70), solacaproine (71) and solaurethine (72). The common characteristic features of these compounds are the terminal bisdimethylamino groups and the central nitrogen atom in the form of an amide (except for 68).



R = H solamine (68)

R = $CH_3(CH_2)_{14}CO$ solapalmitine (69)

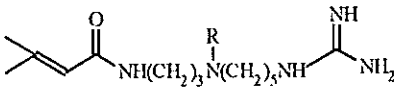
R = $CH_3(CH_2)_{12}CH^{E}{=}CHCO$ solapalmitenine (70)

R = $CH_3(CH_2)_6CO$ solacaproine (71)

R = CH_3CH_2OCO solaurethine (72)

Solamine (68) was found to be the principle component of *Cyphomandra betacea*. The structure of solamine from natural products was confirmed by direct comparison with synthetic material. Treatment of solamine (68) with palmitoyl chloride, *trans*-2-hexadecenoyl chloride, *n*-hexanoyl chloride, and ethyl chloroformate produced solapalmitine (69), solapalmitenine (70), solacaproine (71), and solaurethine (72), respectively (Barboutis, *et al.*, 1967, 1969; Evan, *et al.*, 1972, 1977). Solapalmitine (69) and solapalmitenine (70), two tetramethylated acylderivatives of solamine (68) studied by Barboutis and co-worker, possess significant tumor-inhibitory activity (Barboutis, *et al.*, 1967, 1969).

A trio of marine natural products, a family of trifunctional unsymmetrical homospermidine is known as the acarnidines (73), (74) and (75), was isolated in 1978 by Carter and co-workers from the red-orange encrusting sponge *Acarnus erithacus (de Laubenfels)*. The compouds were reported to have mild activity against *Herpes simplex virus* type I, as well as broad spectrum antimicrobial activities (Carter, *et al.*, 1978).



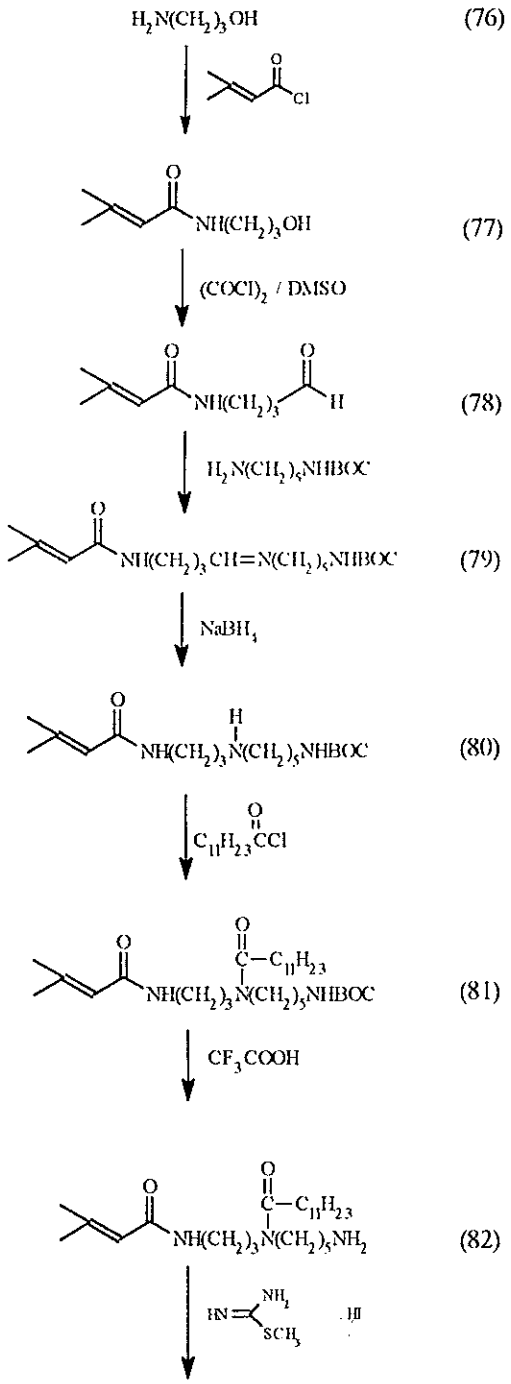
Acarnidines

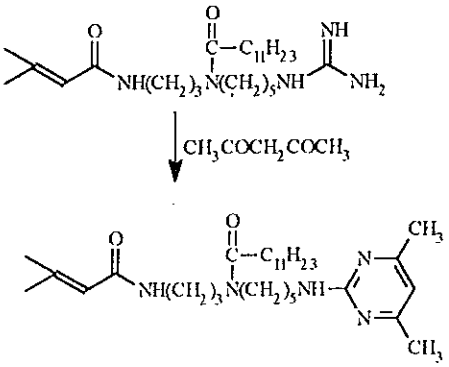
R = $CO(CH_2)_{10}CH_3$ (73)

R = cis $CO(CH_2)_3CH{=}CH(CH_2)_5CH_3$ (74)

R = $COC_{13}H_{21}$ (75)

The first synthesis of acarnidine (73) was reported by Blunt and co-workers (Blunt, *et al*, 1982, 1986) as shown in **Scheme 8**.



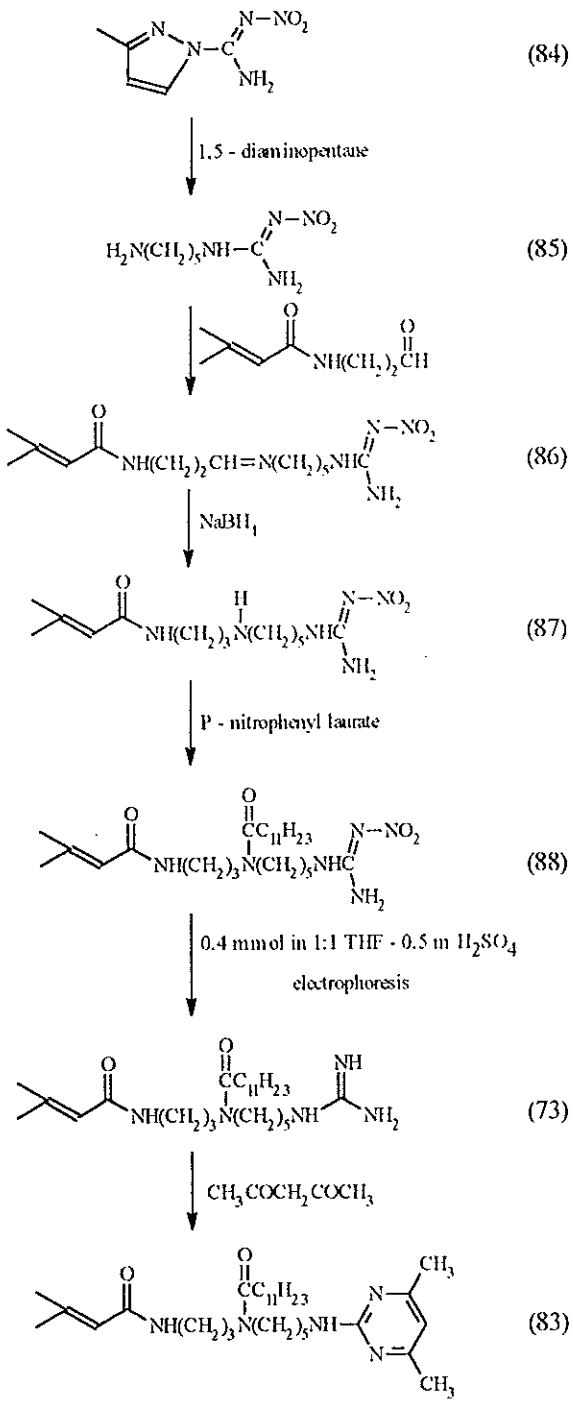


(73)

(83)

Scheme 8. Synthesis of acarnidine (73) and 4,6-dimethylpyrimidine derivative (83) (Blunt, *et al.*, 1986)

The synthesis of acarnidine (73) has also been reported by Boukouvalas and coworkers (Boukouvalas, *et al.*, 1983) as shown in **Scheme 9**.



Scheme 9. Synthesis of acarnidine (73) and 4,6-dimethylpyrimidine derivative (83)(Boukouvalas, *et al.*, 1983)

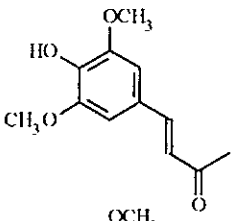
3. Spermine Type

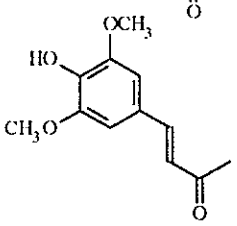
3.1 Simple Spermine Derivatives

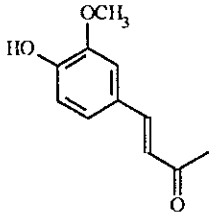
The structure elucidation of three simple spermine compounds sinapoylspermine (90), disinapoylspermine (91), and diferuloylspermine (92) was performed on the basis of chromatographic identification of their hydrolyzed products (Cabanne, *et al.*, 1978).

$R^1NH(CH_2)_3NH(CH_2)_4NH(CH_2)_3NHR^2$

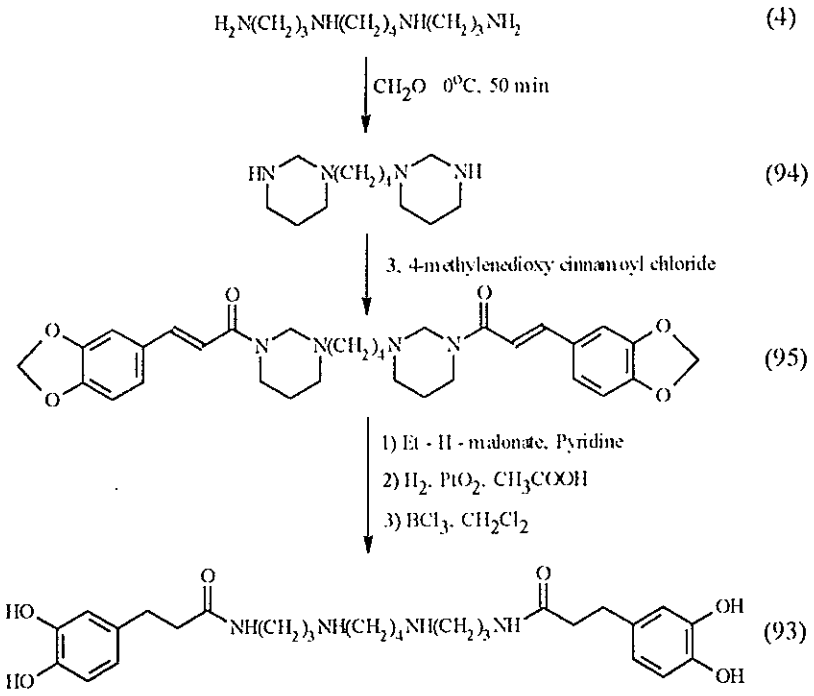
$R^1 = R^2 = H$ spermine (89)

$R^1 =$  $R^2 = H$ sinapoylspermine (90)

$R^1 = R^2 =$  disinapoylspermine (91)

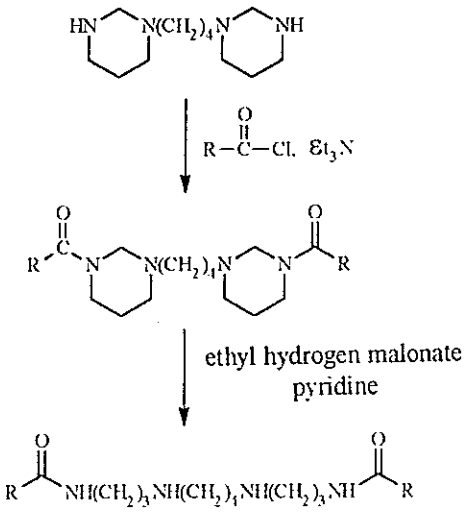
$R^1 = R^2 =$  diferuloylspermine(92)

Kukoamine A (93) was isolated from the crude drug "jikoppi", which is prepared from *Lycium chinense* (Funayama, *et al.*, 1980). In the kukoamine A synthesis, formaldehyde was used to form an aminal with the 1,3-diaminopropane part of spermine. The 1,4-diaminobutane portion of the base does not react under these conditions; the central amino group will, therefore, be protected by formaldehyde. The two other amino groups can now react with 3,4-methylenedioxycinnamoyl chloride. After deprotection and catalytic hydrogenation, kukoamine A (93) was isolated in 62% overall yield (**Scheme 10**) (Ganem, *et al.*, 1982).



Scheme 10. Synthesis of kukoamine A (93)

Some kukoamine A derivatives (97-102) and (106-111) have also been prepared in high yield (Chantrapromma, *et al.*, 1990) as shown in **Schemes** 11 and 12.



R = CH_3 (97)

R = Ph (98)

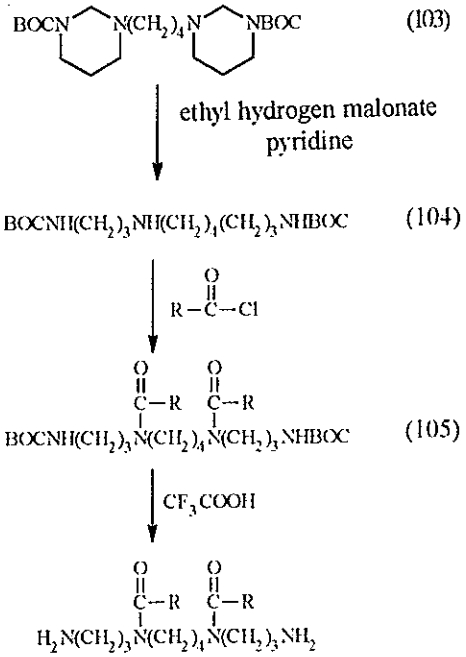
R = CH=CHPh (99)

R = CH_2CH_2Ph (100)

R = $CH{=}CH(C_6H_4)(OH)$ (101)

R = $CH{=}CH(C_6H_3)(OH)_2$ (102)

Scheme 11. Synthesis of kukoamine A derivatives (97-102)



R = CH_3 (106)

R = Ph (107)

R = CH=CHPh (108)

R = CH_2CH_2Ph (109)

R = $CH{=}CH(C_6H_4)OH$ (110)

R = $CH{=}CH(C_6H_3)(OH)_2$ (111)

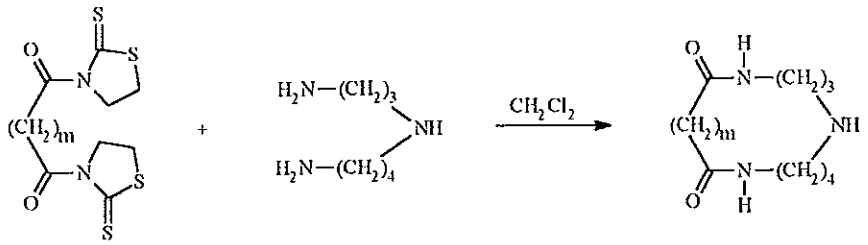
Scheme 12. Synthesis of kukoamine A derivatives (106-111)

Strategy for Polyamine Synthesis

In order to obtain the desired compounds in the synthesis of polyamines, it is very important to protect selectively the various amine functions in the polyamines. From the synthetic point of view, selective protection allows the synthesis of long chain polyamines or branched polyamines. For example, without protecting certain amine groups, acylation reactions of the polyamines with acid chloride and acid anhydride gives mixtures of products (Kawbata, *et al.*, 1980; Schlittler, *et al.*, 1973; Husson, *et al.*, 1973). There are examples of acylation of primary amines in the presence of secondary amines by means of bulky or aromatic acylation agents, but one can not always assure of such selective acylations, thus selective methods to protect only primary or only secondary amine have been developed.

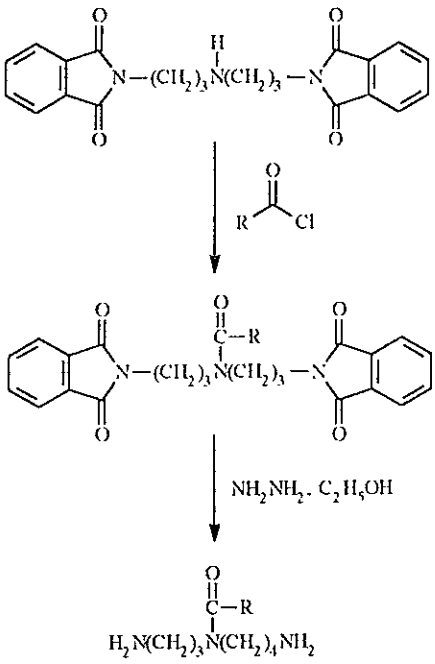
1. Protection of Primary Amines

The protection of primary amines can be achieved by simple selective reagent in one step or by multi-step processes. Certain esters or acid coupling agents can be used to acylate only primary amines. Some of these processes utilize an ester of 1-hydroxypiperidine (Besselievre, 1983; Husson, 1973), various 3-acylthiazolidine-2-thione derivatives (Fujita, *et al*, 1980, 1981, 1982), and esters derivative from a carboxylic acid and N,N^{1}-dicarboxyldimidazole (Joshua and Scott, 1984). The use of the 3-acylthiazolidine-3-thione to react with the terminal primary amine of spermidine, was reported by Kojima and co-workers, is shown below. In these cases, only the primary amines react to form the cyclams (114) (Kojima, *et al.*, 1983).

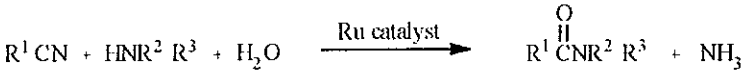


(112) (3) (114)

Many researchers have reported that primary amines react with phthalimide potassium salt in the presence of secondary amines in the polyamine chain to form the phthalimide of the primary amines (115). The secondary amines (116) can then react and the primary amines (117) are recovered by the use of hydrazine as shown below (Gauss, *et al.*, 1952; Lincoln, *et al.*, 1979).

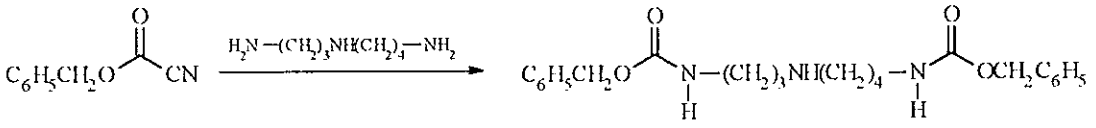


Nitriles react with polyamines in the presence of $RuH_2(PPh_3)_4$ to give the amide (119) in high yield (Murahashi, 1986). Thus, spermidine reacted with acetonitrile to give N^1,N^8-diacetyl spermidine (119) in high yield.



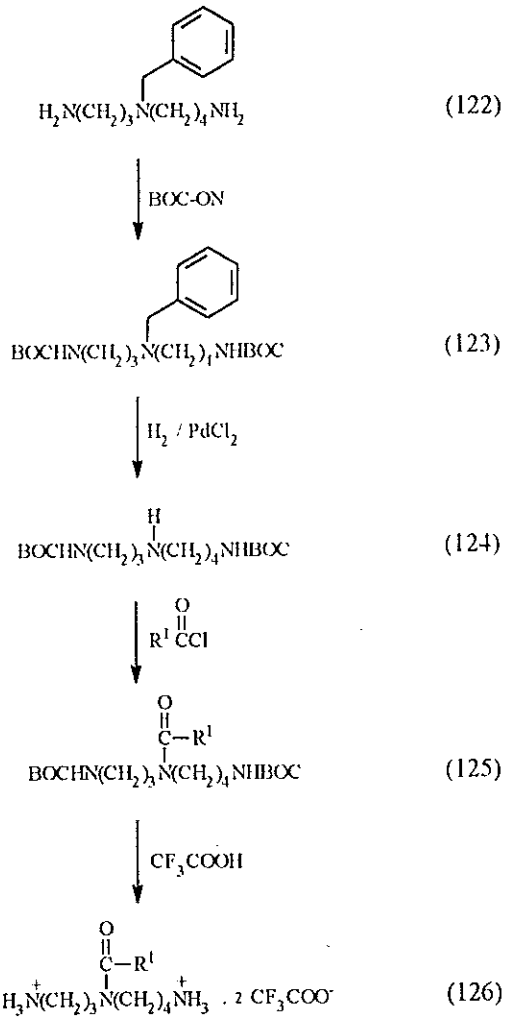
(118) (119)

Acyl cyanides react in the same manner under mild conditions. It is noteworthy that the benzyloxycarbonyl protecting groups can be introduced selectively into spermidine (3) which was reacted with benzylcyanoformate (Murahashi, 1986, 1987) as shown below. The benzyloxycarbonyl group can be removed under mild conditions (Green, 1986).

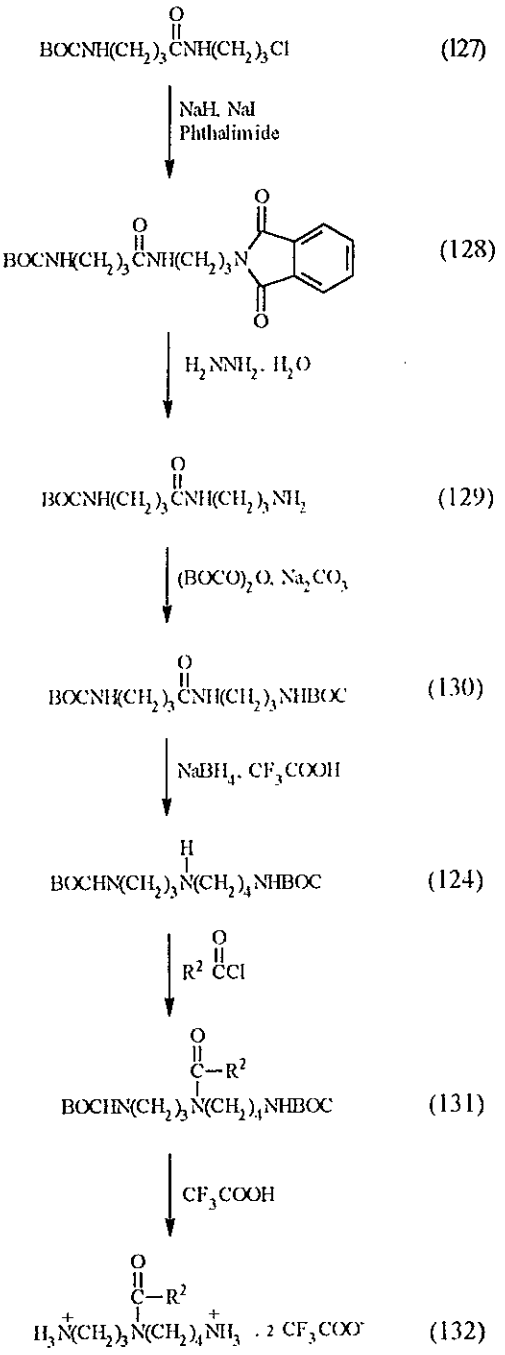


(120) (121)

These procedures are available to protect each type of amine group so that reactions can be conducted on the desired amines group in succession. The protecting groups are then selectively removed (Bergeron, *et al.*, 1982; Das, *et al.*, 1984). It is noteworthly that N^1,N^8-di-(*tert*-butyloxycarbonyl) spermidine (124) is a useful precursor for the synthesis of N^4-acylspermidines (126) and (132). as indicated in **Schemes** 13 and 14.



Scheme 13. The synthesis of N^4-acylspermidine (126) (Bergeron, *et al.*, 1982)

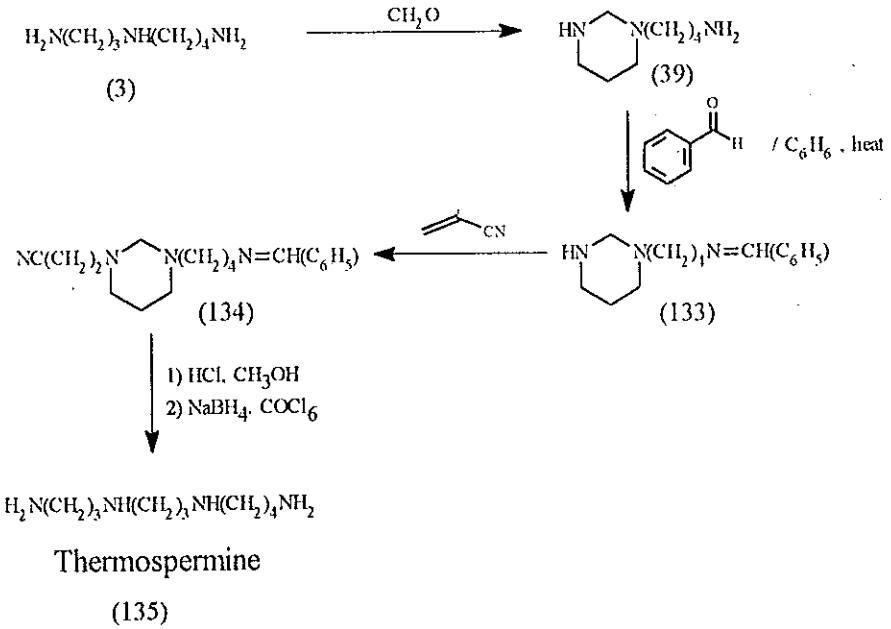


Scheme 14. The synthesis of N^1-acylspermidine (132) (Das, *et al.*, 1980)

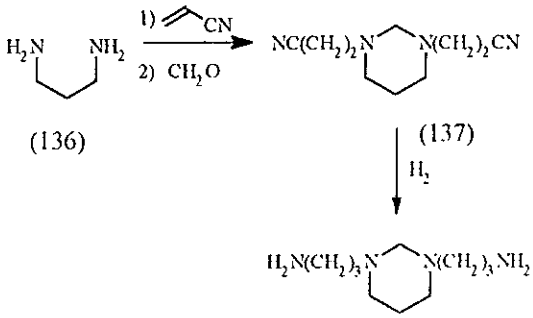
2. Protection of Secondary Amines

It is often important to protect secondary amines in order to carry out reactions on primary amines functions. One important new protection method for the internal secondary amines is to form the hexahydropyrimidine (1,3-diazocyclohexane) by the reaction of a 1,3-diamine with formaldehyde (37% aqueous). The hexahydropyrimidine is easily opened by the Knoevenagel reaction. Even though the first attempt to protect internal amines of spermidine by the reaction with benzaldehyde was not successful, this type of reaction has been used to form macrocyclic polyamines (Ganem, 1982).

The internal secondary amine of spermidine which was successfully protected with formaldehyde (37% aqueous) to give a high yield of the hexahydropyrimidine (39). This compound was acylated or alkylated by variety of reagents and then reduced to form the desired polyamines (Ganem, *et al.*, 1980, 1982, 1985, 1983; Chantrapromma, *et al.*, 1980; Cerami, 1986). An example of this route to thermospermine (135) is shown below.

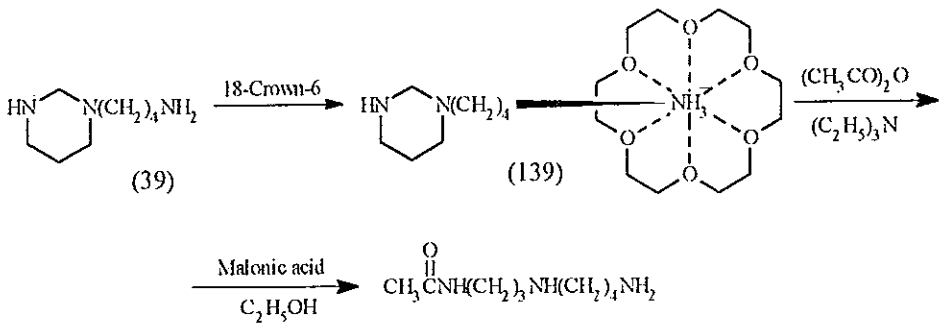


Dutasta and co-workers also prepared 4,8-diaza-1,11-undecanediamine (138) with protected internal amines by reaction of 1,3-propanediamine (136) with 2 moles of acrylonitrile, followed by reaction with formaldehyde (37% aqueous) and reduction as shown below (Dutasta, *et al.*, 1988).



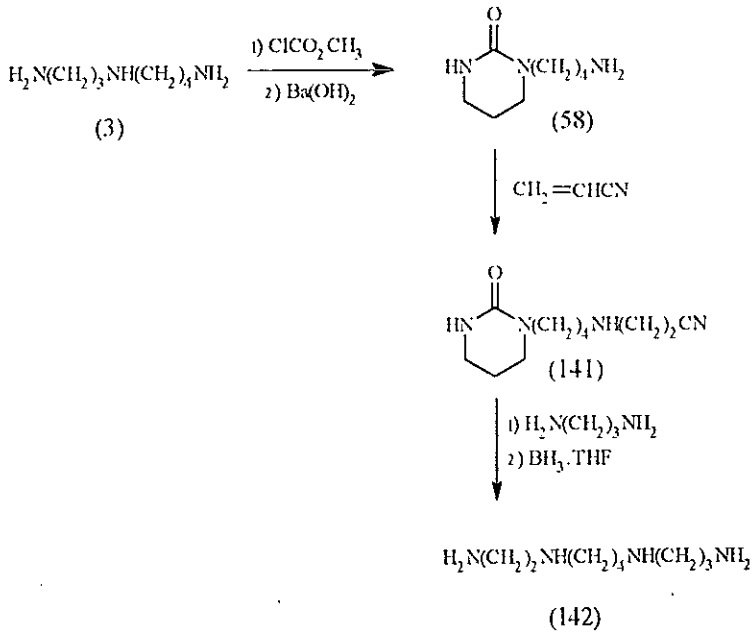
(136) (137) (138)

Tice and Ganem also devised a way to protect both the internal amine and the N^{s}- primary amine of spermidine (Ganem and Tice, 1983). The N^{1} and internal amine were first blocked with formaldehyde and then N^{s}- amine was complexed with 18-crown-6. The N^{1} amine was then acetylated and the methylene bridge was removed to give N^{1}-acetylspermidine (140) as shown below.



(39) (139) (140)

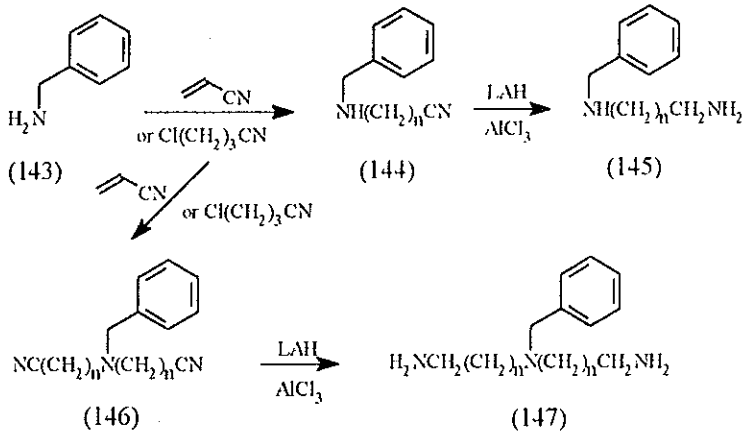
Internal secondary amines have also been protected through the formation of cyclic urea derivatives. The 1,3-diamine portion of spermidine reacted with methyl chloroformate to give the cyclic urea (58). The amide nitrogens of the urea are not reactive so that further reactions take place on the remaining primary amine. Such a process using acrylonitrile is shown below (Ganem, 1982). Cyclic ureas are resistant to hydrolysis so that " urea exchange" with 1,3-propanediamine allowed the isolation of final product (142).



Chantrapromma and co-workers used this method to prepare spermidine derivatives with three different substituents on the three nitrogen atoms as presented in **Scheme 6** (Chantrapromma, *et al.*, 1980).

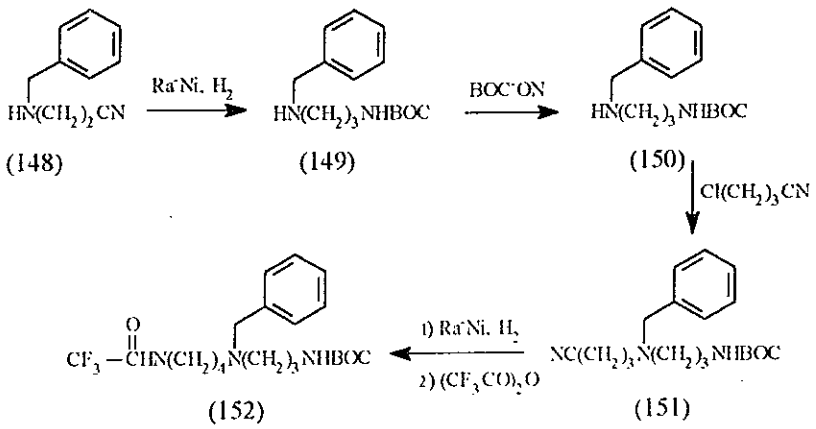
3. Miscellaneous Methods

The preparation of polyamines containing protecting groups on internal secondary nitrogen can be prepared. Bergeron and co-workers reported that benzylamine (155) reacts with one or two molecules of 4-chlorobutanenitrile to form mono or dicyano derivatives. The cyano groups were reduced with lithium aluminium hydride in the presence of aluminium chloride to give the benzyl protected triamine (147). Benzyl groups are reductively cleaved by hydrogenolysis (Bergeron, *et al.*, 1981, 1984, 1986).

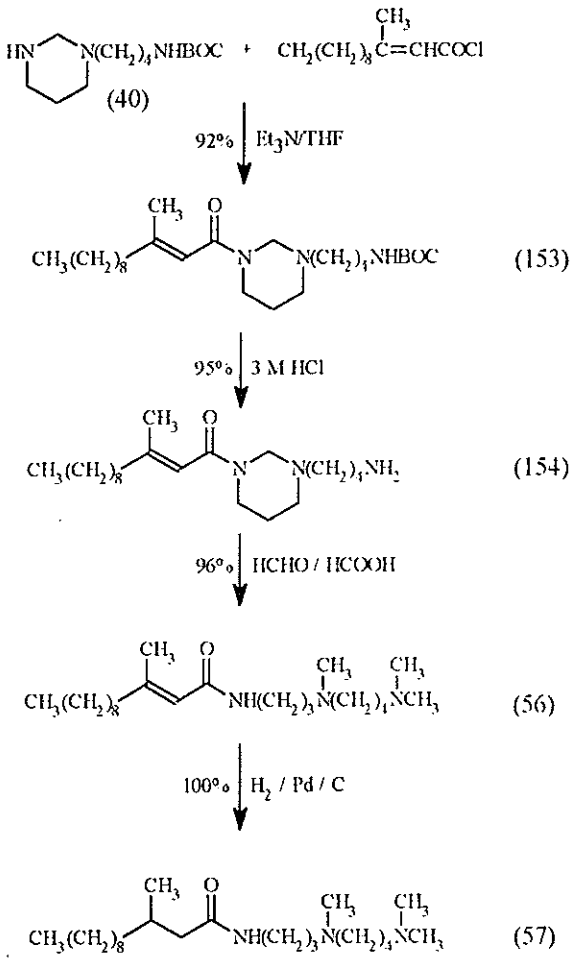


n = 2 or 3

The synthesis of a substrate (152) for the selective mono-, di- or tri-N-functionalization of spermidine is shown below. The protecting groups in the spermidine derivatives (152) are easily removed under different conditions (Bergeron, *et al.*, 1984).



Chantrapromma and co-workers have been reported (Chantrapromma, *et al.*, 1990) that hexahydropyrimidine (39) react with BOC-ON to afford N^{δ}-BOC hexahydropyrimidine (40) in reasonable yield. They also used this compounds (40) to prepare the cytotoxic spermidines (56) and (57) as shown in **Scheme** 15 on a large scale for the biological test.



Scheme 15. Synthesis of cytotoxic spermidines (56) and (57)

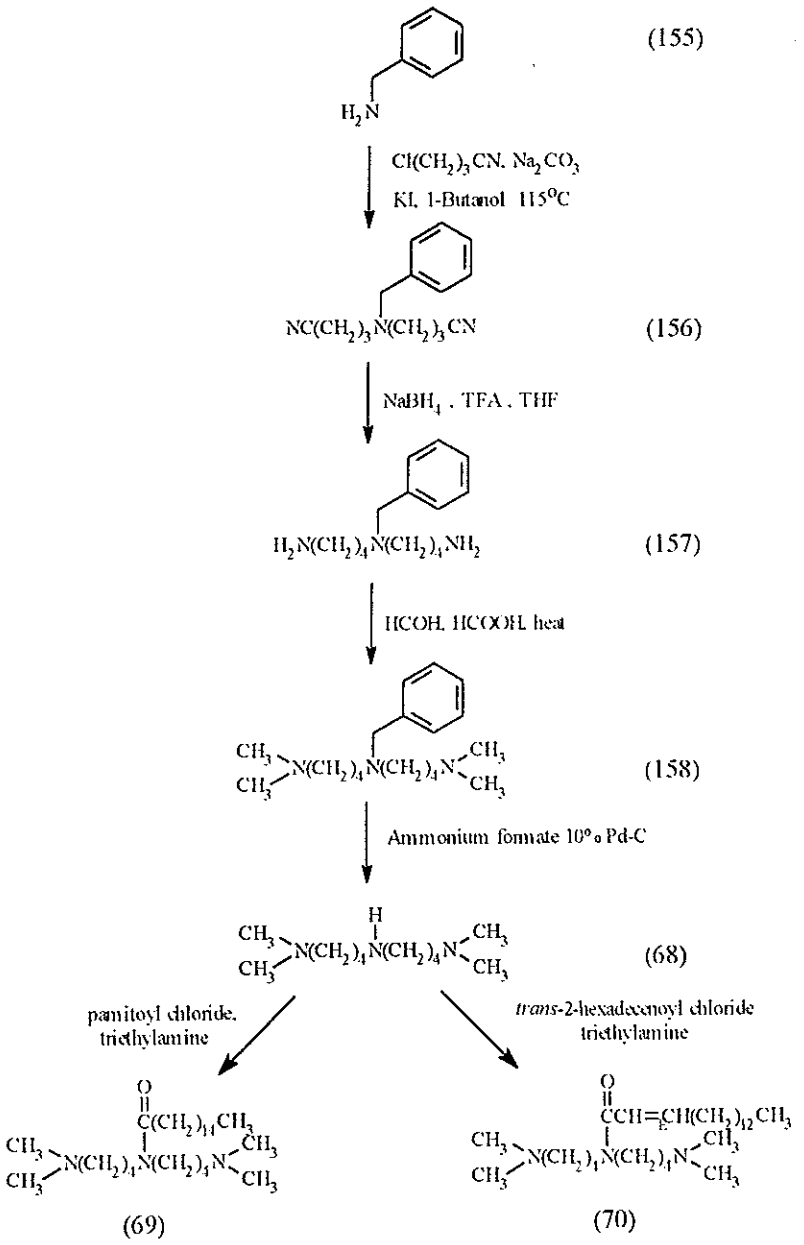
It is likely that certain polyamine homologues may have therapeutic application, particularly, antitumor, antiviral, and the treatment of other proliferative diseases and plant diseases. Clearly, convenient synthetic routes to some polyamine derivatives on a large scale are of value to chemists and biologists. Although interest in the synthesis of selectively functionalized polyamines have quickened in recent years, many of the routes have been unrewarding due to low yields or difficulty in removing the protecting groups. This Thesis covers the synthesis of some important compounds as described in **CHAPTER 2.**

CHAPTER 2

RESULTS AND DISCUSSIONS

2.1 Synthesis of Solamine (68), Solapalmitine (69) and Solapalmitenine (70)

Solamine (68) could be prepared with the use of protected N^5-benzylhomospermidine (157) (Bergeron, *et al.*, 1982). The synthesis involved four steps; alkylation, reduction, reductive methylation and debenzylation, all of which proceeded in high yield. The first step, alkylation of benzylamine (155) with 4-chlorobutanenitrile in 1-butanol and sodium carbonate as the base, proceeded smoothly at 115°C. The resulting N,N-di(3-cyanopropyl)benzylamine (156) was then reduced with sodium borohydride and trifluoroacetic acid in tetrahydrofuran to give N^5-benzylhomospermidine (157) in high yield (81%) (Itoh, *et al.*, 1976). Attempted reduction of the bisnitrile (156) with either sodium borohydride and cobalt (II) chloride ($CoCl_2.8H_2O$) in ethanol or a mixture of lithium aluminium hydride and aluminium chloride in refluxing anhydrous ether (Bergeron, *et al.*, 1981) resulted in low yield, 35% and 68% respectively, of the desired N^5-benzylhomospermidine (157). Methylation of N^5-benzylhomospermidine (157) by using the Eschweiler-Clark method gave N^1,N^9-tetramethyl N^5-benzylhomospermidine (158) in 85% yield. The benzylprotecting goup of the amine (158) was easily removed with ammonium formate and 10% paladium on charcoal in methanol to produce solamine (68) in 92% yield (Green, 1986) as shown in **Scheme 16**.



Scheme 16. Synthesis of solamine (68), solapalmitine (69) and solapalmitenine (70)

The secondary amine nitrogen of solamine (68) was then acylated with palmitoyl chloride (159) and *trans*-2-hexadecenoyl chloride (161) by using the Schotten-Baumann conditions to give solapalmitine (69) (96%) and solapalmitenine (70) (95%) respectively. *trans*-2-Hexadecenoic acid (160) was prepared in the following manner. Condensation of myristaldehyde with triethyl phosphoroacetate by the Horner-Emmons method, the crude was obtained in 96% yield. After saponification (10% NaOH, heat), *trans*-2-hexadecenoic acid (160) (49%) readily crystallized from petroleum ether. However, *trans*-2-hexadecenoic acid (160) was prepared in a better yield by the Knoevenagel-Doebner method (Flowers, *et al.*, 1958) (myristaldehyde, malonic acid, pyridine, piperidine, heat) as indicated in **Table 2**. Therefore, condensation of myristaldehyde with malonic acid gave *trans*-2-hexadecenoic acid (160) (68%) which was also readily crystallized from petroleum ether.

Table 2. Preparation of *trans*-2-hexadecenoic acid (160) from myristaldehyde

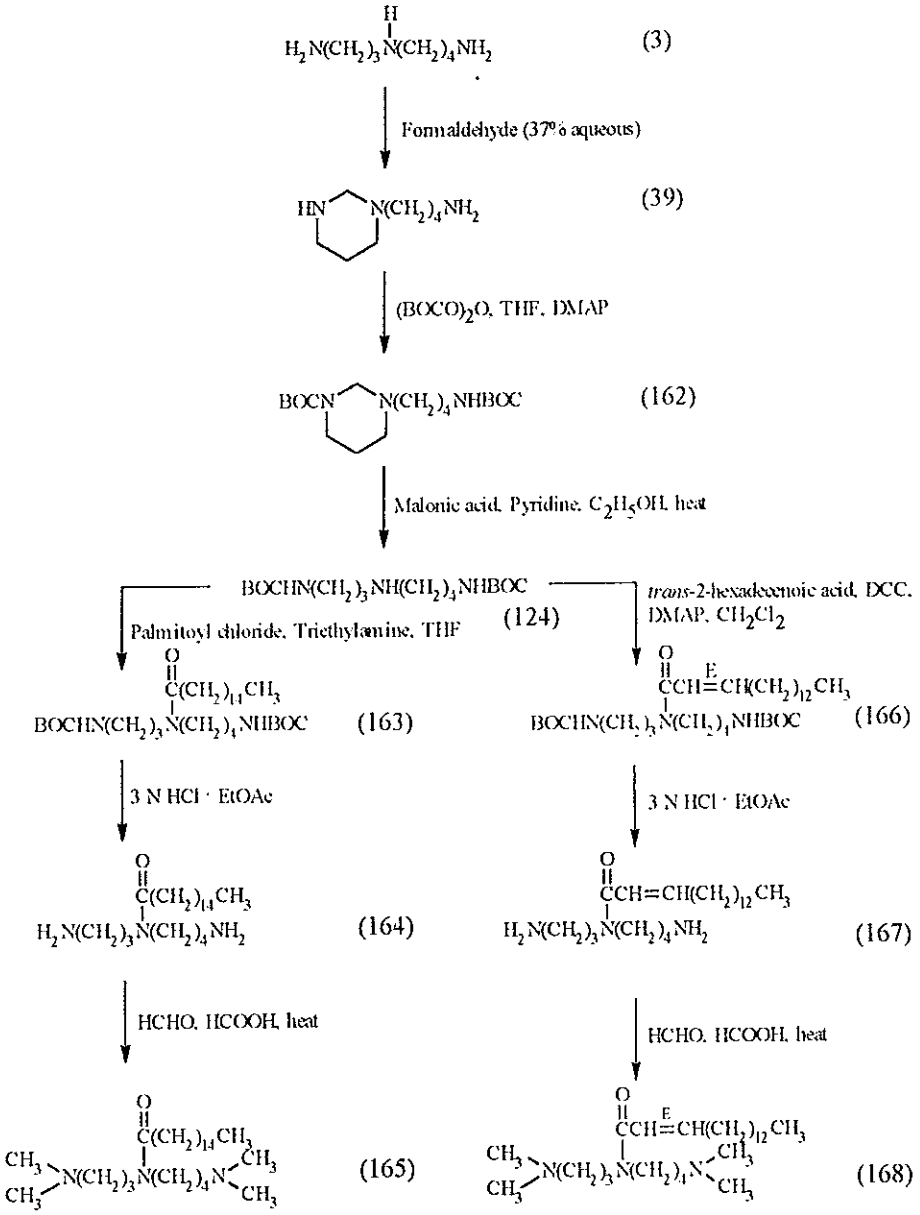
Methods	% yield of *trans* isomer (160)
Horner-Emmons	49
Knoevenagel-Doebner	68

The resulting *trans*-2-hexadecenoic acid (160), a crystalline material, which reacted with thionyl chloride in dry petroleum ether under reflux, formed the corresponding acid chloride (161) in quantitative yield.

2.2 Synthesis of Solapalmitine Homologue (165) and Solapalmitenine Homologue (168)

Solapalmitine homologue (165) and solapalmitenine homologue (168) could be prepared with the use of N^1,N^8-di(*tert*-butyloxycarbonyl)spermidine (124) which was prepared from spermidine as shown in **Scheme 17**. Spermidine (3) reacted with formaldehyde (37% aqueous) at room temperature to produce a 95% yield of the hexahydropyrimidine (39) which was allowed to react with di-*tert*-butyl dicarbonate ($(BOCO)_2O$) in dry tetrahydrofuran with triethylamine as base in the presence of the powerful acylation catalyst 4-dimethylaminopyridine (DMAP), and di-(*tert*-butyloxycarbonyl) hexahydropyrimidine (162) was obtained in 72% yield.

The reaction also proceeded without a base (Greens, 1986) since liberation of carbon dioxide shifted the equilibrium to di(*tert*-butyloxycarbonyl)hexahydropyrimidine (162) (81%). The methylene bridge of the hexahydropyrimidine (162) was selectively removed by the Knoevenagel-like reaction using malonic acid and pyridine in hot ethanol to afford N^1,N^8-di(*tert*-butyloxycarbonyl)spermidine (124) in 81% yield (Ganem, *et al.*, 1985). The secondary amine nitrogen of (124) was easily acylated with palmitoyl chloride in the presence of triethylamine in dry tetrahydrofuran to give the N^4-palmitoyl-N^1,N^8-di(*tert*-butyloxycarbonyl) spermidine (163) in high yield (90%). The *tert*-butyloxycarbonyl groups (BOC) of the protected acylspermidine (163) were then removed by brief exposure to 3 N HCl in ethylacetate to give the corresponding free amine (164) in quantitative yield. The Eschweiler-Clarke methylation (HCHO/HCOOH) of N^5-palmitoylspermidine (164) gave the solapalmitine homologue (165) in 70% yield. Similarly, solapalmitenine homologue (168) was synthesized as indicated in **Scheme 17**.

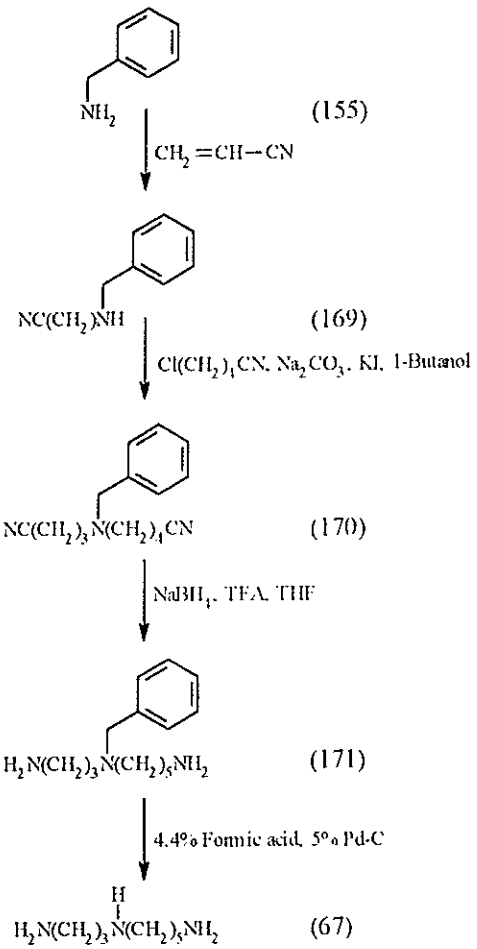


Scheme 17. Synthesis of solapalmitine homologue (165) and solapalmitenine homologue (168)

Condensation of the N^1,N^8-di(*tert*-butyloxycarbonyl)spermidine (124) with *trans*-2-hexadecenoic acid (160) in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine (DMAP) gave N^4-(*trans*-2-hexadecenoyl)-N^1,N^8-di(*tert*-butyloxycarbonyl)spermidine (166) in 72% yield. Upon hydrolysis of the *tert*-butyloxycarbonyl (BOC) groups of the protected acylspermidine (166), the N^4-*trans*-2-hexadecenoylspermidine (167) was obtained in quantitative yield. Fully methylation of the free amine (167) using the Eschweiler-Clarke method (HCHO/HCOOH) gave solapalmitenine homologue (168) in 72% yield.

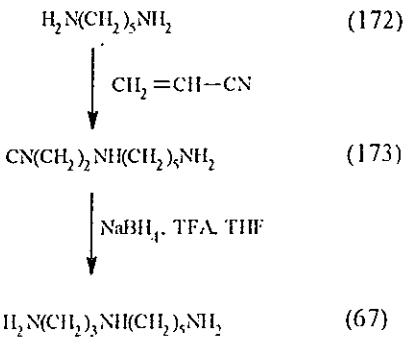
2.3 Synthesis of Unsymmetrical Homospermidine (67)

The unsymmetrical homospermidine (67) could be prepared by different two routes. The first route to unsymmetrical homospermidine (67) was outlined in **Scheme 18a**. Benzylamine (155) was cyanoethylated with acrylonitrile at room temperature to give N-(2-cyanoethyl)benzylamine (169) in excellent yield (97%) (Bergeron, *et al.*, 1980). The resulting compound (169) was alkylated with 5-chloropentanenitrile with sodium carbonate as the base to give N,N-(cyanoethyl)-(cyanobutyl)benzylamine (170) (93%). The bisnitrile (170) was then reduced with sodium borohydride and trifluoroacetic acid in dry tetrahydrofuran to give N^1-benzylhomospermidine (171) (82%) (Itoh, *et al.*, 1976). The debenzylation of N^1-benzylhomospermidine (171) was achieved by catalytic transfer reduction using 4.4% formic acid in methanol and 5% paladium on charcoal to afford unsymmetrical homospermidine (67) in quantitative yield (Greens, 1986).



Scheme 18a. Synthesis of unsymmetrical homospermidine (67)

The second route to unsymmetrical homospermidine (67) was outlined in **Scheme 18b**. Cardaverine (172) reacted with acrylonitrile in dry tetrahydrofuran to give 3[(5-aminobutyl) amino]propanenitrile (173) which was then reduced with sodium borohydride and trifluoroacetic acid in dry tetrahydrofuran to give unsynmmetrical homospermidine (67) (82%). The unsymmetrical homospermidine (67) will be used for the synthesis of acarnidine (73) and discussed later.



Scheme 18b. Synthesis of unsymmetrical homospermidine (67)

2.4 Synthesis of Acarnidine (73) and Acarnidine Homologue (188)

Acarnidine (73) is a triamine with three different substitiuents to the unsymmetrical homospermidine (67) backbone. The N^9-monoBOC hexahydropyrimidine reagent (175) and its homologue (40) were therefore synthesized for the selective functionalization of acarnidine (73) and its homologue (188) with three different groups. These two reagents allow for the selective functionalization of any or all of triamine's three nitrogens in any order with any three different acylating agents. The synthesis of hexahydropyrimidine (39) and its homologue (174) proceeded in one step from available spermidine (3) and unsymmetrical homospermidine (67), respectively with 37% formaldehyde (37% aqueous) (Chantrapromma, *et al*, 1990). The reaction of hexahydropyrimidine (39) with 2[[(*tert*-butyloxycarbonyl) oxy] imino]-2-phenylacetonitrile (BOC-ON) in tetrahydrofuran at various temperature showed that N^8-(*tert*-butyloxycarbonyl)hexahydropyrimidine (40) was formed in low yield when the reaction temperature was below -10°C, while a reasonable yield was obtained when the reaction was carried out at 0°C as shown in **Table 3**.

Table 3. Reaction of hexahydropyrimidine (39) and its homologue (174) with BOC-ON in THF at various temperatures

starting material	temperature	% yield of mono product
(39)	-12°C	33 (40)
(39)	-5°C	53 (40)
(39)	0°C	56 (40)
(174)	0°C,	50 (175)

The monoprotected BOC hexahydropyrimidine (175) and its homologue (40) are now useful precursors for the selective synthesis of acarnidine (73) and acarnidine homologue (188) as described in the following paragraph.

Attempts to prepare 3,3-dimethylacryloyl chloride by treating 3,3-dimethylacrylic acid with thionyl chloride at room temperature resulted in complex mixtures with a deep red color. The correspondingacid chloride could not be detected. However, N^1-(3-methylbut-2-enamido)-N^9-(*tert*-butoxycarbonyl)hexahydropyrimidine (177) and its homologue (184) were acquired in 89%, 86%, respectively by the condensation of 3,3-dimethylacrylic acid with N^9-(*tert*-butyloxycarbonyl)hexahydropyrimidine (175) and its homologue (40) in the presence of dicyclohexylcarbodiimide (DCC) and 4-dimethylaminopyridine in dry chloroform.

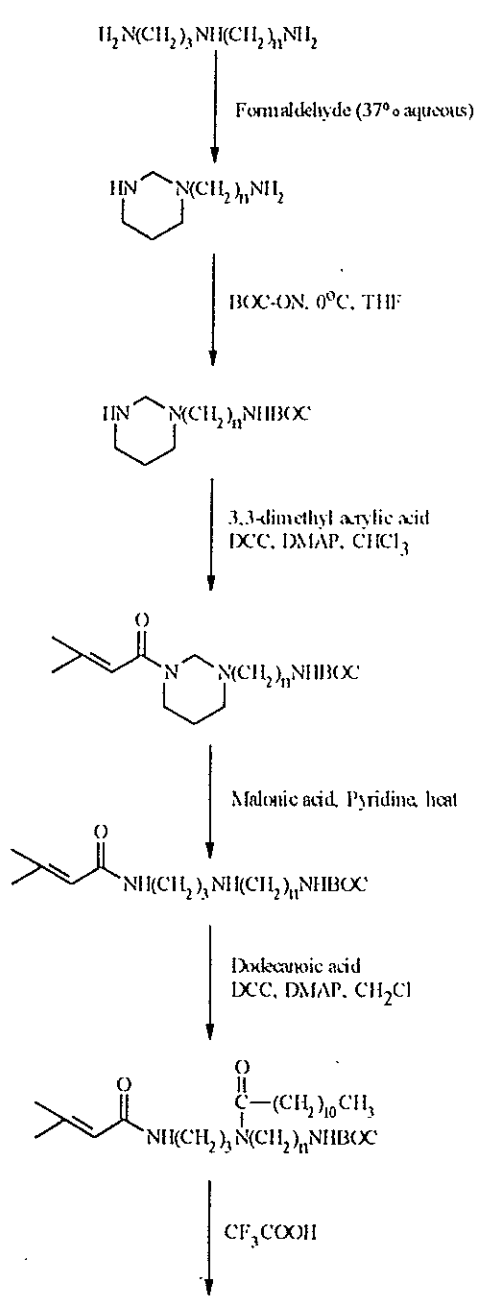
The gemdiamine protecting group of N^1-(3-methybut-2-enamido)-N^8-(*tert*-butyloxycarbonyl) hexahydropyrimidine (177) and its homologue (184) was first removed by using malonic acid and pyridine in hot ethanol to afford N-(*tert*-butyloxycarbonyl) N-[3,(3-methylbut-2-enamido) propyl] 1,5 diaminopentane (179) (89%) (Ganem, *et al.*, 1985) and its homologue (185) (95%), respectively. Similarly, the condensation of dodecanoic acid with (179) and its homologue (185) in the presence of dicyclohexycarbodiimide (DCC) and 4-dimethylaminopyrimidine (DMAP) in dry dichloromethane produced N-[5-(*tert*-butyloxycarbonylamino) pentyl]-N-[3(3-methylbut-2-enamido) propyl]dodecanamind (179) (76%) and its homologue (186) (81%), respectively. Hydrolysis of the *tert*-butyloxycarbonyl (BOC) group with trifluoroacetic acid, the N-(5-aminopentyl)-N-[3,(3-methylbut-2-enamido)propyl] dodecanamide (180) and its homologue (187) were obtained in quantitative yield. The reaction of the primary amine (187) with either S-methyl isothiourea sulfate(190) or S-methyl isothiourea iodide(182) in various conditions (**Table** 4) showed that the yield of acarnidine homologue (188) depended on the choice of reagents. However, when S-methly isothiourea sulfate (190) was used in ethanol at room temperature, the product could not be detected. The insolubility of S-methyl isothiourea sulfate in ethanol may be the cause of the failure. However, acarnidine (73) and acarnidine homologue (188) were obtained in 56% yield and 54% yield when S-methyl isothiourea iodide was used in ethanol at 40°C.

Table 4. Reaction of N-(4-aminobutyl)-N-[3,(3-methylbut-2-enamido) propyl] dodecanamide (187) and its homologue (180) with guanidating agent in various conditions.

starting material	reagent and conditions	% yield of product
(187)	S-methyl isothiourea sulfate, ethanol	undetectable (188)
(187)	S-methyl isothiourea sulfate, ethanol 40°C	8 (188)
(187)	S-methyl isothiourea sulfate, ethanol : water	32 (188)
(187)	S-methyl isothiourea sulfate, ethanol : water, 40°C	41 (188)
(187)	S-methyl isothiourea iodide, ethanol 40°C	54 (188)
(180)	S-methyl isothiourea iodide, ethanol 40°C	56 (73)

The presence of guanidine moeity in structure of acarnidine(183) and acarnidine homologue (189) was confirmed by the Sakaguchi test and the formation of 4,6-dimethylpyrimidine derivatives.

The pyrimidine derivatives of acarnidine(83) and acarnidine homologue (189) were prepared by heating acarnidine (73) and its homologue (188) with an aqueous solution of pentane-2,4-dione (191) and sodium carbonate to give the pyrimidine derivative (83) (58%) and its homologue (189) (56%), respectively. The mass spectra and nmr spectra were identical to those of the pyridityl derivatives reported by Carter and Rinehart in 1986. The acarnidine (73) and its homologue (188) were summarized in **Scheme 19**. Thus, the two polyamine derivatives (73) and (188) are now available in 17-18%overall yield from unsymmetrical homospermidine (67) and spermidine (3), respectively.



n = 4 (3)

n = 5 (67)

n = 4 (39)

n = 5 (174)

n = 4 (40)

n = 5 (175)

n = 4 (184)

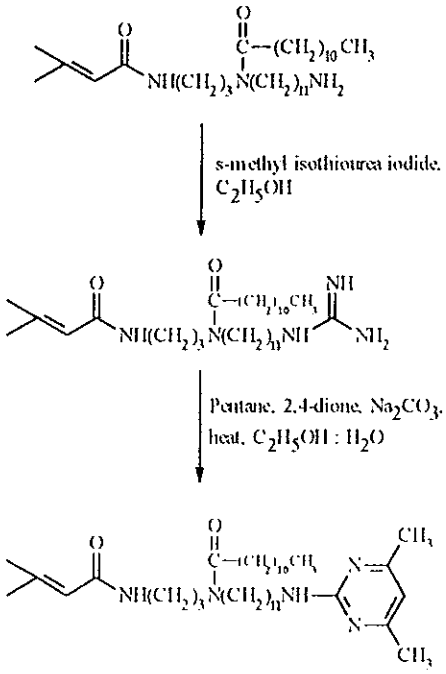
n = 5 (177)

n = 4 (175)

n = 5 (178)

n = 4 (176)

n = 5 (179)



n = 4 (187)
n = 5 (180)

n = 4 (188)
n = 5 (73)

n = 4 (189)
n = 5 (83)

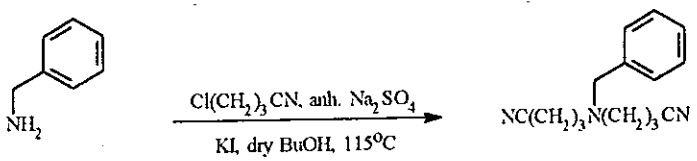
Scheme 19 Synthesis of acarnidine (73) and acarnidine homologue (188)

CHAPTER 3

EXPERIMENTALS

Melting points were determined on ELECTROTHERMAL APPARATUS. Proton nuclear magnetic resonance spectra (^{1}H NMR) were recorded on a JEOL-PMx60 spectrometer and are described as follows:-^{1}H NMR (solvents) δ-values in ppm multiplicity (coupling constants in Hz), number of protons (assignment). The multiplicity of the signal is expressed by the following symbols :- s = singlet, d = doublet, t = triplet, sext = sextet, m = multiplet. All δ-values are related to tetramethylsilane (TMS) (δ = 0) as internal standard in deuterochloroform ($CDCl_3$). Infrared spectra (IR) were recorded on a PERKIN-ELMER IR 783 and are recorded in cm^{-1}. Mass spectra (MS) were recorded on a TRIO-2000. Analytical and Preparative thin layer chromatography (TLC) was carried out on glass plates coated withsilica gel 60 (10-30 μm particle size). Column chromatography was performed with silica gel 60 (63-200 μm particle size). Flash column chromatography refered to the method described by Still *et al* (1978) using silica gel 60 (40-63 μm particle size) and dry column flash chromatography was obtained with silica gel 60 (10-30 μm particle size). All silica gel were purchased form E. MERCK. Spots in TLC plates were located under U.V. light at 254 nm, by exposure to iodide vapour. The polyamine spots were visualized violet-blue by Schlittler reagent.

3.1 N, N-Di(3-cyanopropyl)benzylamine (156)



(155) (156)

A solution of 4-chlorobutanenitrile (810 ml, 8.39 mmol) in dry 1-butanol (10 ml) was added dropwise over 3 h to a stirred mixture of benzylamine (155) (305 ml, 2.79 mmol), anhydrous Na_2CO_3 (890 mg, 8.39 mmol) and KI (150 mg, 1.12 mmol) at 115° C under nitrogen. After refluxing for additional 20 h , the mixture was allowed to cool to room temperature and filtered, the salts were washed with ether (10 ml). The combined filtrate was extracted with 3 N HCl (4 x 10 ml) and water (2 x 10 ml). The acid solution and water extract were combined. The combined solution was washed with ether (3 x 10 ml), made basic with Na_2CO_3 and extracted with ether (4 x 10 ml). The resulting ethereal solution was dried over anhydrous Na_2SO_4 and evaporated to afford an oil. The product was further purified by preparative chromatography on silica gel, eluted with 25% petroleum ether in ether to afford N-N-di(3-cyanopropyl)benzylamine (156) (560 mg, 82%).

IR (neat) cm^{-1} : 2264, 2840, 2962

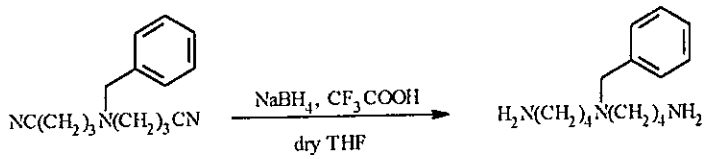
NMR ($CDCl_3$) δ : 1.65-1.98 (4H, m, 2xC-CH_2-C)

: 2.33-2.65 (4H, m, -CH_2-N-CH_2-)

: 3.51 (2H, s, Ph-CH_2-N)

: 7.21 (5H, s, Ar-H)

3.2 N^5-Benzylhomospermidine (157)



(156) **(157)**

To a suspension of $NaBH_4$ (4.9 g, 129.7 mmol) in dry tetrahydrofuran (5 ml) under nitrogen was added slowly CF_3COOH (9.92 ml, 129.7 mol) in dry tetrahydrofuran (5 ml) over a period of 15 minutes at 20°C. To this solution was added N,N-di(3-cyanopropyl)benzylamine (156) (3.13 g, 12.97 mmol) in dry tetrahydrofuran (3 ml), and the reaction mixture was stirred at room temperature for 16 h. The excess reagent was then decomposed with 3 N HCl below 10°C and the reaction mixture was stirred overnight. The resulting mixture was evaporated, made basic with 30% KOH and extracted with chloroform (6 x 20 m).The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford an oil. The crude product was further purified by distillation to afford N^5-benzyl homospermidine (157) (2.63 g, 81%) b.p 210°C / 0.6-0.5 mmHg.

IR (neat) cm^{-1} : 1610, 2950, 3400

NMR ($CDCl_3$) δ : 1.20 (4H, s, 2xC-NH_2)

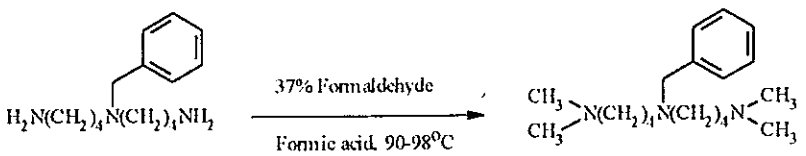
: 1.30-1.66 (8H, m, 4xC-CH_2-C)

: 2.31-1.66 (8H, m, 4x-CH_2-N)

: 3.49 (2H, s, Ph-CH_2-N)

: 7.19 (5H, s, Ar-H)

3.3 N^1, N^9-Tetramethyl-N^5-benzylhomospermidine (158)



(157) (158)

Formic acid (99%) (27.43 ml, 61.85 mmol) was added dropwise to N^5-benzyl homospermidine (157) (5.5 g, 61.85 mmol) at 0° C under nitrogen. Then formaldehyde (11.57 ml, 37% aqueous) was added to the reaction mixture which was stirred and heated under reflux at 98°C for 12 h until the evolution of carbon dioxide ceased. The reaction mixture was cooled and then made basic with 4 N NaOH. The resulting mixture was then extracted with ether (5 x 50 ml). The resulting ethereal solution was dried over anhydrous Na_2SO_4 and evaporated to afford an oil. The product was further purified by distillation to afford N^1, N^9-tetramethyl-N^5-benzylhomospermidine (158) (5.75 g, 85%) b.p. 230 °C / 0.6-0.5 mmHg.

IR (neat) cm^{-1} : 1460, 2780, 2960

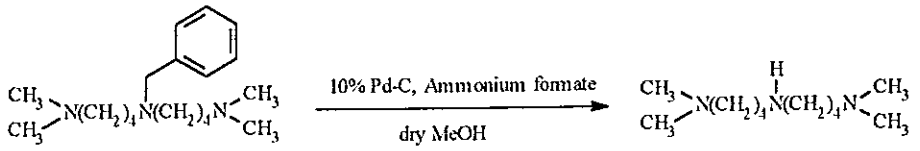
NMR ($CDCl_3$) δ : 1.30-1.55 (4H, s, 2xCH_2C)

: 2.13 (8H, m, 4xC-CH_2-C)

: 2.05-2.55 (8H, m, 2x-CH_2-N,CH_2NCH_2)

: 3.46 (2H, s, Ph-CH_2-N)

3.4 Solamine (68)



(158) (68)

To a solution of N^1, N^9-Tetramethyl-N^5-benzylhomospermidine (158) (4.7 g, 15.39 mmol) in dry methanol (30 ml) were added 10% Pd-C (0.47 g) and anhydrous ammonium formate (3.89 g, 61.58 mmol). The resulting heterogeneous reaction mixture was stirred at room temperature for 12 h under nitrogen and filtered, the catalysts were washed with methanol, and the solution was evaporated. The residue was dissolved in chloroform (40 ml) and the resulting solution was washed with 25% NaOH (2 x 20 ml), water (2 x 20 ml), dried over anhydrous Na_2SO_4 and evaporated to afford an oil. The product was further purified by distillation to afford solamine (68) (3.06 g, 92%) 170°C / 0.4 mmHg.

IR (neat) cm^{-1} : 1472, 2780, 2976, 3280

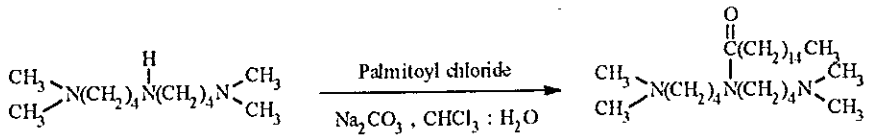
NMR ($CDCl_3$) δ : 1.35-1.58 (8H, m, 4xC-CH_2-C)

: 2.18 (12H, s, 4xCH_3N)

: 2.00-2.35 (4H, m, 2x-CH_2NCH_3)

: 2.46-2.73 (4H, m, -CH_2NCH_2-)

3.5 Solapalmitine (69)



(68) **(69)**

A solution of palmitoyl chloride (1.03 g, 3.78 mmol) in dry chloroform (3 ml) was added slowly to a solution of solamine (68) (800 mg, 3.78 mmol) and Na_2CO_3 (1.90 g, 8.53 mmol) in chloroform (8 ml) and H_2O (4 ml) at 0°C under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred for a further 12 h. Then saturated Na_2CO_3 (40 ml) was added and the mixture was extracted with chloroform (5 x 30 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford an oil. The product was further purified by dry column flash chromatography on silica gel, eluted with 10% ammonium hydroxide in methanol to afford solapalmitine (69) (1.66 g, 98%).

IR (neat) cm^{-1} : 1470, 1655, 2940

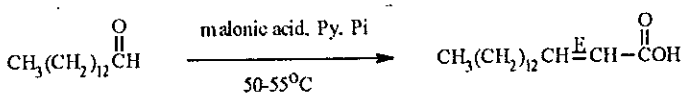
NMR ($CDCl_3$) δ : 0.83 (3H, t, $-CH_3$)

: 1.23-1.83 (34H, m, 13-C-CH_2-C, 2x(C-CH_2-C)

: 2.16-2.50 (18H, s, 4xCH_3N, m, 2xCH_2-N-CH_3, -CH_2-CO-)

: 3.24-3.32 (4H, m, -CH_2-N-CH_2-)

3.6 *trans*-2-Hexadecenoic acid (160)



(160)

Myristaldehyde (3.0 g, 14.12 mmol) was added to a solution of malonic acid (1.76 g, 16.95 mmol) in dry pyridine (3.5 ml) at temperature not exceeding 35°C. After additional of piperidine (120 mg, 1.4125 mmol), the mixture was warmed for 1 h at 50°-55°C and 3 h at 80°-90°C . The reaction mixture was poured into ice-water, concentrated hydrochloric acid (4 ml) was added and the solution mixture was extracted with ether (5x20). The resullting ethereal solution was dried over anhydrous Na_2SO_4 and evaporated to afford an oil. The product was further purified by crystallization from petroleum ether (60-80°C) to afford *trans*-2-hexadecenoic acid (160) (2.50, 69% g) m.p. 48 - 50°C.

IR (CCl_4) cm^{-1} : 1660, 1705, 2850, 2940

NMR ($CDCl_3$) δ : 0.81 (3H, t, CH_3-)

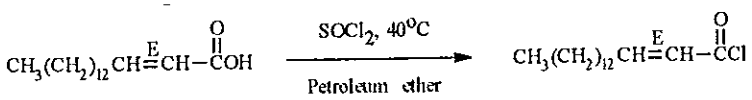
: 1.20 (22H, s, C-CH_2-C)

: 2.03-2.46 (2H, m, CH_2-CH=)

: 5.53-5.80 (1H, d, J =15 Hz, =CH-CO)

: 6.71-7.20 (1H, sext, J = 15 and 7 Hz, CH=C-CO)

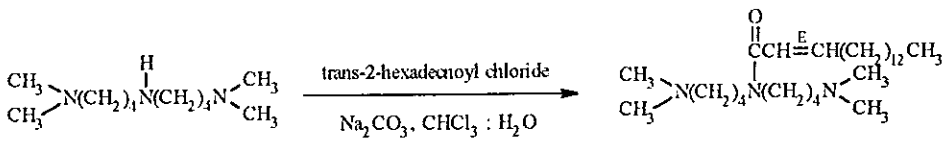
3.7 *trans*-2-Hexadecenoyl chloride (161)



(160) **(161)**

To a warm solution of *trans*-2-hexadecenoic acid (160) (1.0 g, 3.93 mmol) in dry petroleum ether (2 ml) was added thionyl chloride (716 ml, 9.84 mmol). Refluxing was continued for 4 h. After distilling off the solvent and the excess of thionyl chloride *in vacuo*, the latter was removed as completely as possible by distilling the residue twice with petroleum ether (10 ml). The *trans*-2-hexadecaenoyl chloride (161) (1.07 g, 99%) was obtained as a crude yellow liquid, and was used directly in the next step without further purification.

3.8 Solapalmitenine (70)

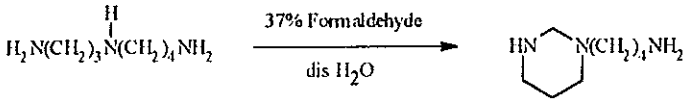


(68) (70)

A solution of *trans*-2-hexadecenoyl chloride (161) (750 mg, 2.75 mmol) in dry chloroform (5 ml) was added slowly to a mixture of solamine (68) (570 mg, 2.29 mmol) and Na_2CO_3 (1.90 mg, 8.53) in chloroform (5 ml) and H_2O (4 ml) at 0° C under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred for a further 12 h. Then saturated Na_2CO_3 (40 ml) was added and the reaction mixture was extracted with chloroform (5 x 20 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford an oil. The product was further purified by dry column flashchromatography on silica gel, eluted with 10%ammonium hydroxide in methanol to afford solapalmitenine (70) (1.14 g, 95%).

IR (neat) cm^{-1}	:	1460, 1620, 1655, 2850, 2920	
NMR ($CDCl_3$) δ	:	0.86	(3H, t, CH_3-)
	:	1.23-1.66	(30H, m, 15xC-CH_2-C)
	:	2.03-2.46	(18H, m, 4xCH_3-N, 2x(-CH_2-N-CH_3, -CH_2-C=)
	:	3.03-3.46	(4H, m, CH_2-N-CH_2)
	:	6.10	(1H, d, J = 15 Hz, =CHCO)
	:	6.75	(1H, sext, J = 15 and 7 Hz, CH=C- CO)

3.9 Hexahydropyrimidine (39)

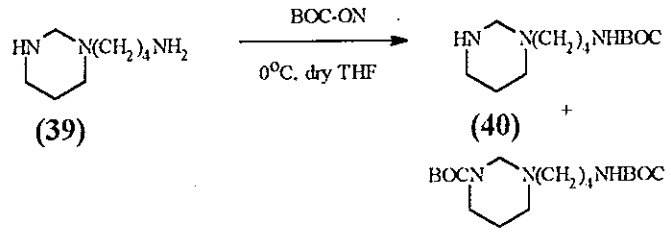


(3) (39)

Spermidine (3) (5.0 g, 34.42 mmol) was dissolved in distilled water (125 ml), and the solution was cooled to 5 °C under nitrogen. Formaldehyde (2.65 ml, 37% aqueous) was slowly added to the cold solution, the reaction mixture was then stirred for 1.5 h at room temperature. The aqueous layer was saturated with solid NaCl and extracted with chloroform (5x50 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford hexahydropyrimidine (39) (5,23 g, 96%) as a nearly pure waxy white solid.

IR (neat) cm^{-1}	:	2850, 3280	
NMR ($CDCl_3$) δ	:	1.46	(9H, m, 3xC-CH_2-C, 3xNH)
	:	2.06-2.85	(8H, m, 4x-CH_2-N)
	:	3.33	(2H, s, N-CH_2-N)

3.10 N^8-(*tert*-Butyloxycarbonyl)hexahydropyrimidine (40)



(39) (40) + (162)

A solution of BOC-ON (814.8 g, 3.30 mmol) in dry tetrahydrofuran (20 ml) was slowly added dropwise to a solution of hexahydropyrimidine (39) (546.7 mg, 3.48 mmol) in dry tetrahydrofuran (30 ml) at 0°C under nitrogen. After the addition was completed, the ice bath was removed and the reaction mixture was stirred for 12 h. The solvent was then evaporated, and the residue was dissolved in chloroform (30 ml), washed with 5% NaOH (4 x 10 ml), dried over anhydrous Na_2SO_4 and evaporated to afford a viscous oil. The oily residue was further purified by column chromatography on silica gel, eluted with chloroform to afford N^1,N^8-di(*tert*-butyloxycarbonyl)hexahydropyrimidine (162) (233.6 mg 19%) and eluted with 5% methanol in chloroform to afford N^8-(*tert*-butyloxycarbonyl)hexahydropyrimidine (40) (497 mg, 56%).

IR (CCl_4) cm^{-1} γ : 1710, 2950, 3300

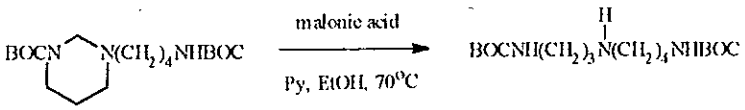
NMR ($CDCl_3$) δ : 1.43-1.76 (15H, m, 3x-C-CH_3, 3xC-CH_2-C)

: 2.06-3.16 (8H, m, 4x-CH_2-N)

: 3.33 (2H, s, N-CH_2-N)

: 5.33-5.83 (1H, br, -NHBOC)

3.11 N^1, N^8-di(*tert*-Butyloxycarbonyl)spermidine (124)



(162) (124)

To a solution of N^1,N^8-di(*tert*-butyloxycarbonyl)hexahydropyrimidine (162) (4.17 g, 11.7 mmol) in dry ethanol (100 ml) under nitrogen were added dry pyridine (3.78 ml, 46.82 mmol) and malonic acid (6.09 g, 58.52 mmol) and the reaction mixture was brought to reflux for 2 h. The solution was concentrated *in vacuo*, water (125 ml) was added and the pH was adjusted to 11 with 10% NaOH and extracted with dichloromethane (5 x 50 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford N^1, N^8-di(*tert*-butyloxycarbonyl)spermidine (124) (3.28, 81%) as a pale yellow solid, m.p. = 85°C.

IR (neat) cm^{-1} : 1510, 1700, 3000, 3380

NMR ($CDCl_3$) δ : 1.36-1.66 (18H, s, 6xCH_3-C-O, 6H, m, 3xC-CH_2-C)

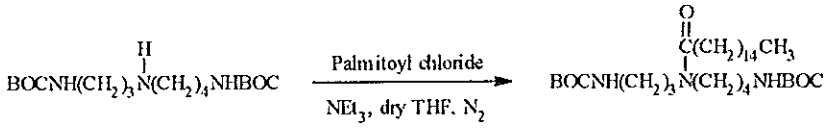
: 2.08 (1H, s, NH)

: 2.43-2.73 (4H, m, -CH_2-N-CH_2-)

: 2.93-3.26 (4H, m, -CH_2-NHBOC)

: 4.50-5.33 (2H, br, -NHBOC)

3.12 N^1, N^8-di(*tert*-Butyloxycarbonyl)-N^4-palmitoylspermidine (163)

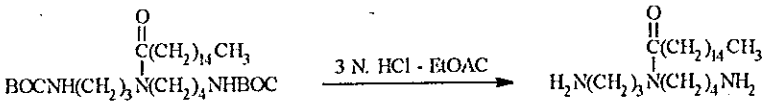


(124) **(163)**

A solution of palmitoyl chloride (1.31, 4.80 mmol) in dry tetrahydrofuran (60 ml) was slowly added to a cooled solution of N^1, N^8-di(*tert*-butyloxycarbonyl)spermidine (124) and triethylamine (809.6 mg, 8.00 mmol) in dry tetrahydrofuran (80 ml) under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred for 18 h. The precipitate was removed by filtration and the solvent was then evaporated. The residue was dissolved in dichloromethane (100 ml), washed with 3% HCl (3x30 ml), water (2x30 ml), 5% $NaHCO_3$ (3x30 ml) and water (2x30 ml), dried over anhydrous Na_2SO_4 and evaporated to afford a crude product. Further purification was effected by dry column flash chromatography on silica gel, eluted with 4% methanol in dichloromethane to afford N^1, N^8-di(*tert*-butyloxycarbonyl)-N^4-palmitoylspermidine (163) (2.16 g, 90%).

IR (CCl_4) cm^{-1}	:	1715, 2850, 2930, 3340	
NMR ($CDCl_3$) δ	:	0.85	(3H, t, CH_3-)
	:	1.23	(26H, s, 13xC-CH_2-C)
	:	1.41	(18H, s, 6xCH_3-C-O)
	:	1.66	(6H, m, 3xC-CH_2-C)
	:	2.29	(2H, t, -CH_2-CO-)
	:	2.76-3.55	(8H, m, 1-CH_2-NHBOC, CH_2NCH_2)
	:	3.83-4.77	(2H, -NHBOC)

3.13 N^4-Palmitoylspermidine (164)



(163) **(164)**

N^1, N^8-di(*tert*-Butyloxycarbonyl)-N^4-palmitoylspermidine (163) (385.7 mg, 0.66 mmol) was dissolved in 3 N HCl-ethylacetate (5 ml). After 30 min the solution was removed *in vacuo* and the oil was then treated with 4 N NaOH (20 ml), extracted with chloroform (5x10 ml). The organic layer was dried over anhydrous Na_2SO_4, and evaporated to afford N^4-palmitoylspermidine (164) (250 mg, 98%).

IR (neat) cm^{-1} : 1469, 1635, 3020, 3370

NMR ($CDCl_3$) δ : 0.83 (3H, t, CH_3-)

: 1.20 (26H, s, 13xC-CH_2-C)

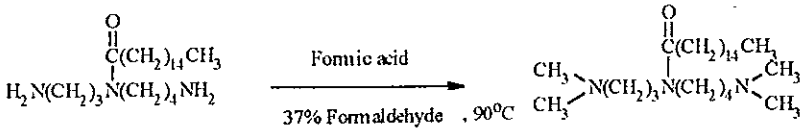
: 1.51 (6H, m, 3xC-CH_2-C)

: 1.83-2.33 (6H, m, -CH_2-$\overset{O}{\overset{\|}{C}}$-, 2xC-$NH_2$)

: 2.43-2.83 (4H, m, 2-CH_2NH_2)

: 3.00-3.52 (4H, m, -CH_2NCH_2-)

3.14 Solapalmitine homologue (165)

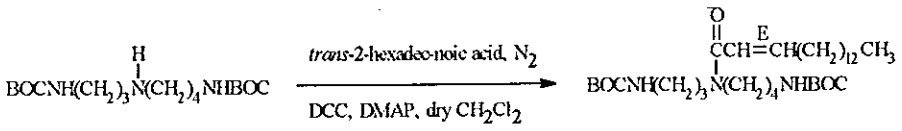


(164) (165)

Formic acid (99 %) (27.4 *ul*, 61.85 mmol) was added dropwise to N^4- palmitoyl spermidine (164) (212.2 mg, 5.54 mmol) at 0°C under nitrogen, then formaladehyde (270 ml, 37% aqueous) was added. The reaction mixture was stirred and heated under reflux for 12 h at 98°C until the evolution of carbon dioxide ceased. The reaction mixture was cooled and then made basic with 4 N NaOH (10 ml). The resulting mixture was extracted with chloroform (5x15 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford an oil. The product was further purified by dry column flash chromatography on silica gel, eluted with 5% ammonium hydroxide in methanol to afford solapalmitine homologue (165) (172.8 mg, 70%).

IR (neat) cm^{-1}	:	1465, 1650, 2930	
NMR ($CDCl_3$) δ	:	0.86	(3H, t, CH_3-)
	:	1.26	(26H, s, 2x13C-CH_2-C)
	:	1.65	(6H, m, 3xC-CH_2-C)
	:	2.00-2.40	(18H,m, 4xCH_3-N, CH_2-NMe_2-CH_2-CO)
	:	3.00-3.43	(4H,m, -CH_2NCH_2-)
MS	:	439	(m/e, M+)

3.15 N^1,N^8-di(*tert*-Butyloxycarbonyl)-N^4-(*trans*-2-hexadecenoyl)spermidine (166)

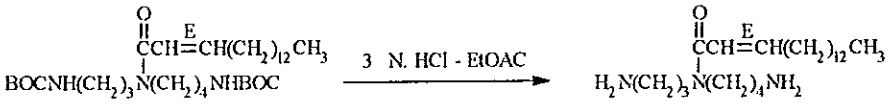


(124) **(166)**

A solution of DCC (232.8 mg, 1.22 mmol) in dry dichloromethane (6 ml) was added to a solution of N^1, N^8-di(*tert*-butyloxycarbonyl)spermidine (124) (349.8 mg, 1.02 mmol), *trans*-2-hexadecenoic acid (284.9 mg, 1.12 mmol) and DMAP (19.9 mg, 0.16 mmol) in dry dichloromethane (18 ml) at 0°C under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred for a further 4 h. The solid was filtered off and washed with dichloromethane. Then dichloromethane was added (50 ml) and the organic layer was washed with 3% HCl (3x15 ml), water (2x15 ml), 5% $NaHCO_3$ (3x15 ml) and water (2x15 ml), dried over anhydrous Na_2SO_4 and evaporated to afford a solid. Further purification was effected by preparative chromatography on silica gel, eluted with 4% methanol in dichloromethane to afford N^1, N^8-di(*tert*-butyloxycarbonyl)-N^4-(*trans*-2-hexadecenoyl)spermidine (166) (374.9 mg, 72%).

IR (CCl_4) cm^{-1}	:	1660, 1725, 2860, 2930, 3350	
NMR ($CDCl_3$) δ	:	0.88	(3H, t, CH_3-)
	:	1.26	(18H, s, 2x$(CH_3)_3$-C-O)
	:	1.43	(26H, m, C-CH_2-C)
	:	1.66	(6H, m, 3xCl-CH_2-C)
	:	2.83-3.66	(10H,m, 4xCH_2-N-, =C-CH_2)
	:	6.13	(1H, d, J = 15 Hz, =CH-CO)
	:	6.76	(1H, sext, J = 15 and 7 Hz, CH-C-CO)

3.16 N^4-*trans*-2-Hexadecenoylspermidine (167)



(166) (167)

N^1, N^8-di(*tert*-butyloxycarbonyl)-N^4-(*trans*-2-hexadecenoyl)spermidine (166) (310.7 mg, 0.52 mmol) was dissolved in 3 N HCl-ethylacetate (5 ml). After 30 min the solution was removed *in vacuo* and the oil was then treated with 4 N NaOH (20 ml), extracted with chloroform (5x10 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford N^4-(*trans*-2-hexadecenoyl)spermidine (167) (196.2 mg, 95%).

IR (neat) cm^{-1} : 1460, 1600, 1655, 2920, 3360

NMR ($CDCl_3$) δ : 0.88 (3H, t, CH_3-)

: 1.26 (26H, s, 13xC-CH_2-C)

: 1.60 (6H, m, 3xC-CH_2-C)

: 1.98-2.40 (6H, br, C-NH_2, =C-CH_2-)

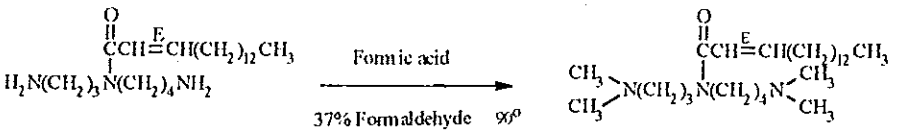
: 2.50-2.83 (2H, m, -CH_2-N-CH_2)

: 3.13-3.60 (4H, m, -CH_2-NH_2)

: 6.10 (1H, d, J = 15 Hz, =CH-CO)

: 6.76 (1H, sext, J = 15 and 7 Hz, CH=C-CO)

3.17 Solapalmitenine homologue (168)

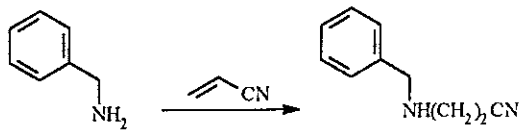


(167) (168)

Formic acid (99%) (344 µl, 9.14 mmol) was added dropwise to N^4-(*trans*-2-hexadecenoyl)spermidine (167) (144.4 mg, 0.36 mmol) at 0°C under nitrogen. Then formaldehyde (185 µl, 37% aqueous) was added to the reaction mixture which was stired and heated under reflux for 12 h at 98°C until the evolution of carbon dioxide ceased. The mixture was cooled and made basic with 4 N NaOH (10 ml). The resulting mixture was extracted with chloroform (5x15 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford an oil. The product was further purified by dry column flash chromatography on silica gel, eluted with 5% ammonium hydroxide in methanol to afford solapalmitenine homologue (168) (119 mg, 72%).

IR (neat) cm^{-1}	:	1455, 1615, 1655, 2920	
NMR ($CDCl_3$) δ	:	0.86	(3H, t, CH_3-)
	:	1.26	(26H, s, C-CH_2-C)
	:	1.63	(6H, m, C-CH_2-C)
	:	2.16	(12H, s, 4xN-CH_3)
	:	2.00-2.46	(6H, m, 4N-CH_3, =C-CH_2)
	:	3.13-3.50	(4H, m, -CH_2-N-CH_3)
	:	6.10	(1H, d, J = 15 Hz, C-CH=CO)
	:	6.80	(1H, sext, J = 15 and 7 Hz, CH=C-CO)
MS	:	437	(m/e, M^+)

3.18 N-(2-Cyanoethyl)benzylamine (169)

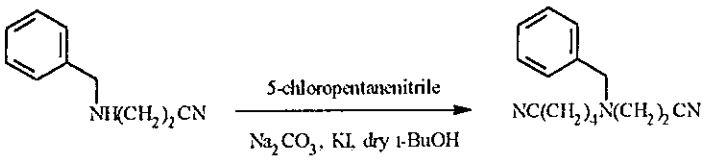


(155) **(169)**

Acrylonitrile (142 µl, 93.32 mmol) was added dropwise to benzylamine (155) (10.18 ml, 93.32 mmol), the mixture was then stirred for 48 h at room temperature under nitrogen. Purification by column chromatography on silica gel with ethylacetate, afforded N-(2-cyanoethyl)benzylamine (169) (14.63 g, 97%).

IR (neat) cm^{-1}	:	1460, 2250, 2860, 3330	
NMR ($CDCl_3$) δ	:	1.70	(1H, s, NH)
	:	2.40	(2H, t, $-CH_2CN$)
	:	2.81	(2H, t, $-CH_2N$)
	:	3.73	(2H, s, Ph-CH_2-N)
	:	7.25	(5H, s, Ar-H)

3.19 N-(2-Cyanoethyl)-N-(4-cyanobutyl)benzylamine (170)



(169) **(170)**

A solution of 5-chloropentanenitrile (15.36 ml, 137.15 mmol) in dry 1- butanol (70 ml) was added over 3 h to a mixture of N-(2- cyanoethyl)benzylamine (169) (14.63 g, 91.43 mmol), anhydrous Na_2CO_3 (14.53 g, 137.15 mmol) and KI (3.74 g, 22.85 mmol) at 115°C under nitrogen. After refluxing for additional 20 h, the reaction mixture was allowed to cool to room temperature and filtered, the salt was washed with ether (50). The combined filtrate was extracted with 3 N HCl (4x25 ml) and water (2x25 ml). The acid solution and water extract were combined and washed with ether (2x25 ml), made basic with K_2CO_3, and extracted with ether (5x50 ml). The resulting ethereal solution was dried over anhydrous Na_2SO_4 and evaporated to afford a crude oil which was purifled by column chromatography, eluted with 3.5% ethylacetate in dichloromethane to afford N-(2 cyanoethyl)-N-(4-cyanobutyl)benzylamine (170) (17.95 g, 93%).

IR (neat) cm^{-1} : 1460, 2260, 2840, 2980, 3040

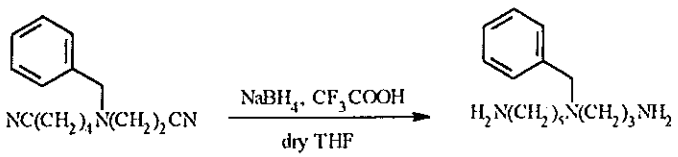
NMR ($CDCl_3$) δ : 1.63 (4H, sext, $-CH_2-CN$, $-CH_2-N$)

: 2.10-2.90 (8H, m, 2x-CH_2CN, 2x-CH_2-N)

: 3.56 (2H, s, Ph-CH_2-N)

: 7.25 (5H, s, Ar-H)

3.20 N^5-Benzylhomospermidine (171)



(170) **(171)**

To a Suspension of $NaBH_4$ (9.93 g, 262.5 mmol) in dry tetrahydrofuran (30 ml) under nitrogen was added slowly CF_3COOH (20.09 ml, 262.58 mmol) in dry tetrahydrofuran (25 ml) at 20°C. To this solution was added N-(3- cyanopropyl)-N^1-(5-cyanopentyl) benzylamine (170) (6.32 g, 26.26 mmol) in dry tetrahydrofuran (30 ml), and the reaction mixture was stirred at room temperature for 16 h. The excess reagent was decomposed with 3 N HCl below 10°C. The resulting mixture was evaporated. made basic with 30% KOH (20 ml) and extracted with dichloromethane (5x50 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford a crude oil which was purified by distillation to afford N^5-benzylhomospermidine (171) (5.38 g, 82%) b.p. 235 °C / mmHg.

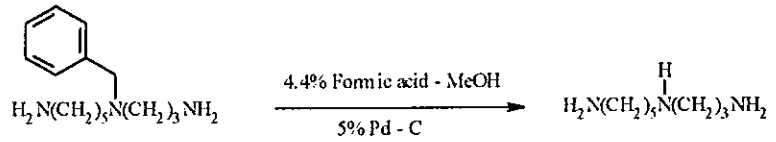
IR (neat) cm^{-1} γ : 1620, 2960, 3450

NMR ($CDCl_3$) δ : 1.16-1.81 (12H, m, 4xC-CH_2C, 2x-NH_2)

: 2.30-2.80 (8H, m, 4xCH_2-N)

: 3.51 (2H, s, Ph-CH_2-N)

3.21 N-(Aminopropyl)-1,5-diaminopentane (67)



(171) (67)

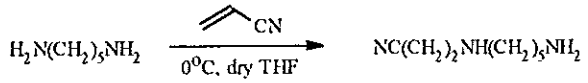
Palladium on charcoal (5%) (3.0 g) was added to the reaction vessel and cooled to 0°C under nitrogen. A 4.4% formic acid in methanol solution (300 ml) was then added slowly followed by a solution of N^5-benzyl homospermidine (171) (3.91 g, 15.73 mmol) in the 4.4% HCO_2H/CH_3OH (100 ml). The reaction mixture was stirred at room temperature for 1 h until vigorous evolution of carbon dioxide ceased, then the reaction was heated at 55°C for 3.5 h and allowed to cool to room temperature and filtered. The filtrate which was concentrated *in vacuo*, produced a pale yellow oil. The oil was taken up in water (50 ml), adjusted to pH 12 with 20% NaOH, and extracted with chloroform (5x50 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford N-(aminopropyl)-1,5-diaminopentane (67) (2.01 g, 99%) as a pale yellow oil.

IR (neat) cm^{-1} : 2990, 3300

NMR ($CDCl_3$) δ : 1.23-1.73 (14H, m, 4xC-CH_2-C, 5xNH)

: 2.46-2.85 (8H,m, 4xCH_2-N)

3.22 3-[(5-Aminobutyl) amino]propanenitrile (173)



(172) **(173)**

Acrylonitrile (1.36 ml, 20.75 mmol) was added dropwise to the solution of cadaverine (172) (2.12 g, 20.75 mmol) in dry tetrahydrofuran (20 ml) at 0°C and the reaction mixture was stirred at room temperature for 12 h under nitrogen. Evaporation of the solvent afforded a residue which was purified by dry column chromatography, eluted with 10% ammonium hydroxide in methanol to afford 3-[(5-aminobutyl) amino]propanenitrile (173) (2.71 g, 84%).

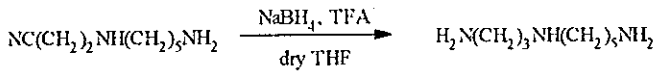
IR (neat) cm^{-1} : 2250, 2970, 3370

NMR ($CDCl_3$) δ : 1.20-1.54 (6H, m, 3x-C-CH_2-C-)

: 1.55-1.90 (3H, s, 3xNH)

: 2.30-3.20 (8H, m, 3x-C-CH_2-N,-CH_2-CN)

3.23 N-(Aminopropyl)-1,5-diaminopentane (67)



(173) **(67)**

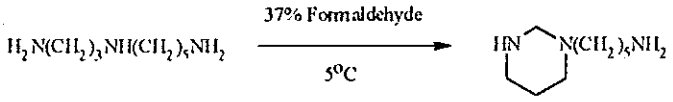
To a suspension of $NaBH_4$ (1.63 g, 43.31 mmol) in dry tetrahydrofuran (16 ml) under nitrogen was added slowly CF_3COOH in dry tetrahydrofuran (10 ml) over a period of 15 minutes at 20°C. To this solution was added 3-[(5-aminobutyl) amino]propanenitrile (173) (1.32 g, 8.66 mmol) in dry tetrahydrofuran (10 ml), and the reaction mixture was stirred at room temperature for 16 h. The excess reagent was decomposed with 3 N HCl below 10°C. The resulting solution was stirred overnight and evaporated, made basic with 30% KOH and extracted with chloroform (5x20 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford an oil. The crude product was taken up with 3 N HCl-methanol and evaporated to afford homospermidine trihydrogen chloride (1.78 g, 72%) (67) as a white solid. The spectrum data of N-(aminopropyl)-1,5-diaminopentane (67) in free base were reported.

IR (neat) cm^{-1} : 2990, 3300

NMR ($CDCl_3$) δ : 1.23-1.73 (14H, m, 4xC-CH_2-C, 5xNH)

: 2.46-2.85 (8H,m, 4xCH_2-N)

3.24 Hexahydropyrimidine (174)



(67) (174)

Homospermidine (67) (1.65 g, 10.39 mmol) was dissolved in distilled water (40 ml), and the solution was cooled to 5°C under nitrogen. Formaldehyde (800 ml, 37% aqueous) was slowly added to the cold solution, the reaction mixture was then stirred for 1.5 h at room temperature. The aqueous layer was saturated with solid NaCl and extracted with chloroform (5x20 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford hexahydropyrimidine (174) (1.74 g, 98%) as a nearly pure waxy white solid.

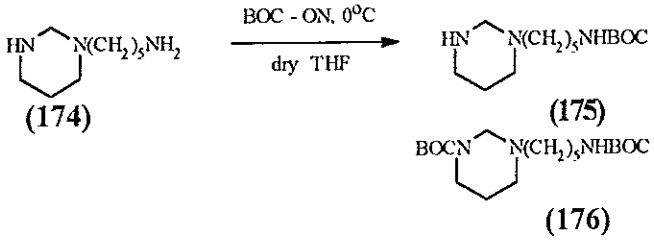
IR (neat) cm^{-1} : 2950, 3300

NMR ($CDCl_3$) δ : 1.60-1.80 (11H,s, 4xC-CH_2-C, 3x-NH)

: 2.13-2.88 (8H, m, 4xCH_2-N)

: 3.5 (2H, s, N-CH_2-N)

3.25 N^9-(*tert*-Butyloxycarbonyl)hexahydropyrimidine (175)



A solution of BOC-ON (1.14 g, 4.64 mmol) in dry tetrahydrofuran (30 ml) was slowly added dropwise to a solution of hexahydropyrimidine (174) (882.8 mg, 5.16 mmol) in dry tetrahydrofuran at 0°C under nitrogen. After the addition was completed and the ice bath was removed and the reaction mixture was stirred for 12 h. The solvent was then evaporated, and the residue was dissolved in chloroform (50 ml), washed with 5% NaOH (4x20 ml), dried over anhydrous Na_2SO_4 and evaporated to afford a viscous oil. The oily residue was further purified by column chromatography on silica gel, eluted with chloroform to afford N^1,N^9-di(*tert*-butyloxycarbonyl)hexahydropyrimidine (176) (326.6 mg, 18%) and eluted with 5% methanol in chloroform to afford N^9-(*tert*-butyloxycarbonyl)hexahydropyrimidine (175) (708.3 mg, 51%).

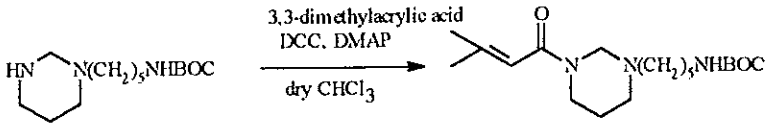
IR (neat) cm^{-1} : 1700, 2940, 3340

NMR ($CDCl_3$) δ : 1.38-1.75 (17H, m, 3xCH_3-C-O, 4xC-CH_2-C)

: 2.13-3.15 (8H, m, 2xCH_2-N)

: 3.33 (2H, m, N-CH_2-N)

3.26 N^1-(3-Methylbut-2-enamido)-N^9-(*tert*-butyloxycarbonyl)hexahydropyrimidine (177)



(175) (177)

A solution of DCC (506 mg, 2.45 mmol) in dry chloroform (10 ml) was added to a solution of N^9-(*tert*-butyloxycarbonyl)hexahydropyrimidine (174) (553.9 mg, 2.05 mmol), 3,3-dimethylacrylic acid (255.1 mg, 2.24 mmol) and DMAP (39.9 mg, 3.2702 mmol) in dry chloroform (15 ml) at 0°C under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred for a further 4 h. The solid was filtered off and washed with chloroform. Then chloroform was added (100 ml) and the organic layer was washed with 5% $NaHCO_3$ (2x20 ml), water (2x20 ml), dried over anhydrous Na_2SO_4 and evaporated to afford an oil. The oily residue was purified by flash column chromatography on silica gel, eluted with 5% ethanol in dichloromethane to afford N^1-(3-methylbut-2-enamido)-N^9-(*tert* butyloxycarbonyl)hexahydropyrimidine (177) (620.2 mg, 89%).

IR (neat) cm^{-1} : 1620, 1710, 2940, 3340

NMR ($CDCl_3$) δ : 1.25-1.61 (17H, m, 3xO-C-CH_3, 4xC-CH_2-C)

: 1.81 (3H, s, CH_3C=C)

: 1.86 (3H, s, CH_3C=C)

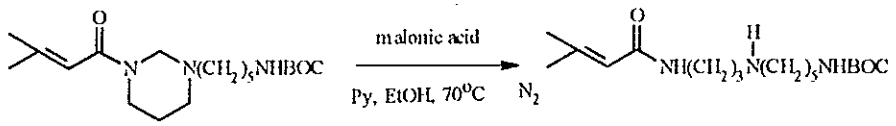
: 2.06-2.76 (8H, m, 4xCH_2-N)

: 4.06 (2H, s, N-CH_2-N)

: 4.33-4.66 (1H, br, -NHBOC)

: 5.66 (1H, s, C=CH)

3.27 N-(*tert*-Butyloxycarbonyl)-N^1-[3-(3-methylbut-2-enamido)propyl] 1, 5-diaminopentane (178)



(177) (178)

To a solution of N^1-(3-methylbut-2-enamido)-N^9-(*tert*-butyloxycarbonyl) hexahydropyrimidine (177) (391.1 mg, 1.10 mmol) in dry ethanol (15 ml) were added dry pyridine (317 µl, 4.01 mmol) and malonic acid (597.3 mg, 5.73 mmol) and the reaction mixture was brougth to reflux for 2 h. The solution was concentrated *in vacuo*, water (20 ml) was added and the pH was adjusted to 11 with 10% NaOH and extracted with dichlomethane (4x25 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford N-(*tert*-butyloxycarbonyl)-N^1-[3-(3-methylbut-2-enamido) propyl] 1,5-diaminopentane (178) (337.4 mg, 89%).

IR (neat) cm^{-1} : 1533, 1700, 2940, 3330

NMR ($CDCl_3$) δ : 1.41-1.63 (17H, m, CH_3-C-O, 4xC-CH_2-C)

: 1.74 (1H, s, NH)

: 1.8 (3H, s, CH_3C=C)

: 2.13 (3H, s, CH_3C=C)

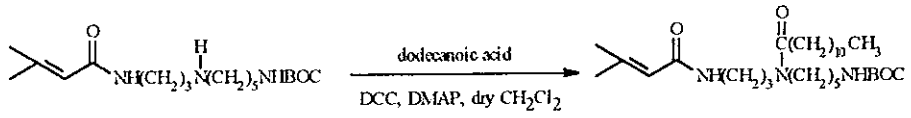
: 2.43-3.45 (8H, m, 4-CH_2-N)

: 4.50 (1H, br, NHBOC)

: 5.41 (1H, s, CH_3C=CH)

: 6.33 (1H, br, -NHCO)

3.28 N-[5-(*tert*-Butyloxycarbonylamino)pentyl]-N-[3-(3-metylbut-2-enamido) propyl] dodecanamide (179)



(178) **(179)**

A solution of DCC (253.9 mg, 1.23 mmol) in dry dichloromethane (8 ml) was added to a solution of N-(tert-butyloxycarbonyl)-N^1-[3-(3-methylbut-2- enamido) propyl] 1,5-diaminopentane (178) (337.4 mg, 0.98 mmol), dodecanoic acid (225.9 mg, 1.12 mmol) and DMAP (20 mg, 0.164 mmol) in dry dichloromethane (10 ml) at 0°C under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred for a further 4 h. The solid was filtered off and washed with dichloromethane. Then dichloromethane was added (50 ml) and the organic layer was washed with 3% HCl (3x15 ml), water (2x15 ml), 5% $NaHCO_3$ (3x15 ml) and water (2x15 ml), dried over anhydrous Na_2SO_4 and evaporated to afford an oil. The oily residue was purified by preperative chromatography on silica gel, eluted with 2% methanol in ether to afford N-[5-(*tert*-butyloxycarbonylamino)pentyl]-N-[3-(3-metylbut-2-enamido)propyl]dodecanamide (179) (402.2 mg, 76%).

IR (neat) cm^{-1} : 1635, 1700, 2940, 3320

NMR ($CDCl_3$) δ : 0.86 (3H, t, CH_3-)

: 1.26 (26H, br, 13xC-CH_2-C)

: 1.43 (9H, s, 3xCH_3-C-O)

: 1.81 (3H, s, CH_3C=C)

: 2.13 (3H, s, CH_3C=C)

: 2.27 (2H, t, -CH_2-CO)

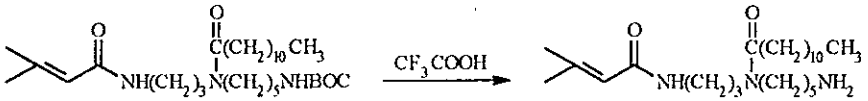
: 2.86-3.46 (8H, m, 4xCH_2-N)

: 4.33-4.66 (1H, br, -NHBOC)

: 5.56 (1H, s, CH_3-C=CH)

: 6.33-6.76 (1H, s, NH-C-)

3.29 N-(5-Aminopentyl)-N-[3-(3-methylbut-2-enamido)propyl]dodecanamide (180)



(179) **(180)**

Trifluoroacetic acid (1 ml) was added to N-[5- (*tert*-butyloxycarbonylamino) pentyl]-N-[3-(3-methylbut-2-enamido)propyl]dodecanamide (179) (335 mg, 0.64 mmol) and the reaction mixture was stirred for 30 min with occasional cooling. The solution was then cooled over ice and made basic with 10% NaOH (3 ml). This solution was extracted with dichloromethane (5x10 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford N-(5-aminopentyl)-N-[3-(3-metylbut-2-enamido)propyl]dodecanamide (180) (260.4 mg, 96%) as an oil.

IR (neat) cm^{-1} : 1645, 2940, 3320

NMR ($CDCl_3$) δ : 0.86 (3H, t, 9xC-CH_2-C)

: 1.26 (18H, br, 3xCH_3-C-O)

: 1.70 (2H, s, -NH_2)

: 1.80 (3H, s, CH_3C=C)

: 2.13 (3H, s, CH_3C=C)

: 2.3 (3H, t, -CH_2-CO)

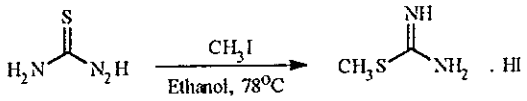
: 2.68 (2H, t, CH_2-N)

: 2.98-3.45 (6H, m, 3xCH_2-N-CO)

: 5.5 (1H, s, C-C=CH-)

: 6.38-6.88 (1H, br, -NH-CO-C)

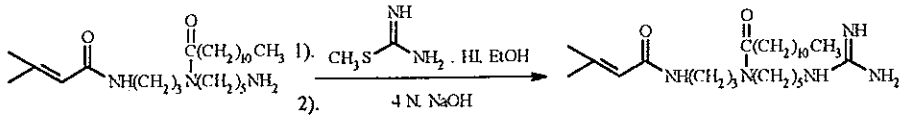
3.30 S-methylisothiourea iodide (182)



(181) **(182)**

Methyl iodide (7.80 ml, 124.3 mmol) was slowly added to the solution of thiourea (181) (6.30 g, 82.89 mmol) in ethanol (15 ml) at 0°C. The reaction mixture was stirred and heated under reflux at for 1.5 h. Upon cooling, the crude product appeared as a solid which was purified by recrystallization in ethanol to afford S-methylisothiourea iodide (182) (17.98 g, 90%).

3.31 N-(5-Guanidinopentyl)-N-[3-(3-methylbut-2-enamido)propyl]dodecanamide (73)



(180) **(73)**

A solution of N-(5-aminopentyl)-N-[3-(3-methylbut-2-enamido)propyl] dodecanamide (250.4 mg, 0.59 mmol) and S-methylisothiourea iodide (182) (171.8 mg, 0.70 mmol) in ethanol (4 ml) was stirred for 36 h at 55°C. The ethanol was removed by evaporation and the residue was basified with 4 N NaOH and extracted with chloroform (5x10 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford a viscous oil which was purified by dry flash column chromatography on alumina, eluted with 10% ammonium hydroxide in methanol to afford acarnidine (73) (154.2 mg, 56%).

IR (neat) cm^{-1} γ : 1630, 1670, 2940, 3100, 3300

NMR ($CDCl_3$) δ : 0.85 (3H, t, CH_3-)

: 1.21-1.65 (24H, br, 12xC-CH_2-C)

: 1.75 (3H, s, CH_3-C=C)

: 2.06 (3H, s, CH_3-C=C)

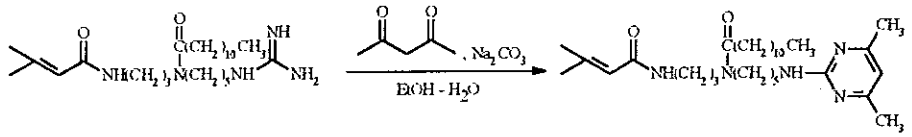
: 2.26 (2H, t, -CH_2-C-)

: 2.83-3.51 (8H, m, 4x-CH_2-N)

: 5.61 (1H, s, C-C=CH)

: 6.33-8.00 (4H, vbr, NH guanidine)

3.31 N-[5-(4, 6-Dimethylpyrimidin)-2-ylamino) pentyl]-N-[3-(3-methylbut-2 enamido) propyl] dodecanamide (83)

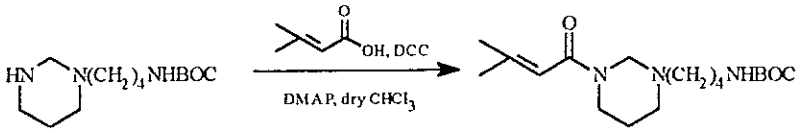


(73) (83)

A solution of acarnidine (73) (67.1 mg, 0.14 mmol), pentane-2, 4-dione (59.5 ml, 0.57 mmol) and Na_2CO_3 (30.58 mg, 0.28 mmol) in water (2 ml) and ethanol (4 ml) was stirred and heated under reflux for 2 h. Then solution was extracted with ether (5x15 ml). The resulting ethereal was dried over anhydrous Na_2SO_4 and evaporated to afford a crude oil which was purified by preparative chromatography on silica gel, eluted with 6% methanol in dichloromethane to afford N-[5-(4, 6-dimethylpyrimidin)-2-ylamino) pentyl]-N[3-(3-methylbut-2-enamido)propyl]dodecanamide (83) (44.27 mg, 58%) as an oil.

IR (neat) cm^{-1} γ	:	1575, 1635, 2940, 3330	
NMR ($CDCl_3$) δ	:	0.85	(3H, t, CH_3-)
	:	1.25	(16H, brs, 8xC-CH_2-C)
	:	1.33-1.73	(8H, br, 4xC-CH_2-C)
	:	1.80	(3H, s, CH_3C=C)
	:	2.11	(3H, s, CH_3C=C)
	:	2.3	(6H, s, 2xPyrCH_3)
	:	2.26-2.33	(2H, t, CH_2-CO)
	:	2.95-3.41	(8H, m, 4x-CH_2-N)
	:	4.91	(1H, br, -NH-Py)
	:	5.55	(1H, s, CH_3-C=CH-)
	:	6.20	(1H, s, Pyr-H)
	:	6.40-6.83	(1H, s, NH-CO)
MS	:	529	(m/e, M^+)

3.32 N^1-(3-Methylbut-2-enamido)-N^8-(*tert*-butyloxycarbonyl)hexahydropyrimidine (184)



(40) **(184)**

A solution of DCC (522.1 mg, 2.53 mmol) in dry chloroform (10 ml) was added to a solution of N^8-(*tert*-butyloxycarbonyl)hexahydropyrimidine (40) (536.8 mg, 2.10 mmol) and DMAP (40.8 mg, 0.33 mmol) in dry chloroform (15 ml) at 0°C under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred for further 4 h. The solid was filtered off and washed with chloroform. Then chloroform was added (100 ml) and the organic layer was washed with 5% $NaHCO_3$ (3x20 ml) and water (2x20 ml), dried over anhydrous Na_2SO_4 and evaporated to afford an oil. The oily residue was purified by column chromatography on silica gel, eluted with 5% ethanol in dichloromethane to afford N^1-(3-methybut-2-enamido)-N^8-(*tert*-butyloxycarbonyl)hexahydropyrimidine (184) (614.2 mg, 86%).

IR (neat) cm^{-1} : 1630, 1715, 2940, 3350

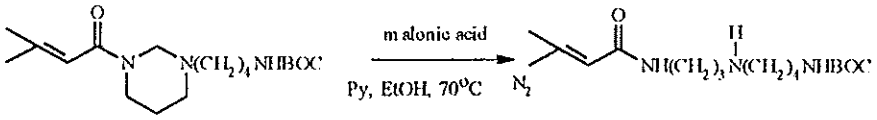
NMR ($CDCl_3$) δ : 1.45-1.66 (15H, s, 3xC-CH_3, 3xC-CH_2-C)

: 1.83-1.90 (6H, s, 2xCH_3-)

: 2.26-2.76 (8H, m, 4xCH_2-N)

: 5.71 (1H, s, C-C=CH)

3.33 N-(*tert*-Butyloxycarbonyl)-N^1[3-(3-methylbut-2-enamido)propyl]-1, 4-diamobutane (185)



(184) **(185)**

To a solution of N^1-(3-methybut-2-enamido)-N^8-(*tert*-butyloxycarbonyl) hexahydropyrimidine (184) (1.72 g, 5.25 mmol) in dry ethanol (50 ml) were added dry pyridine (1.50 ml, 18.4 mmol) and malonic acid (2.73 g, 26.29 mmol) and the reaction mixture was brought to reflux for 2 h. The solution was concentrated *in vacuo*, water (100 ml) was added and the pH was adjusted to 11 with 10% NaOH and extracted with dichloromethane (6x50 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford N-(*tert*-butyloxycarbonyl)-N^1-[3-(3-methylbut-2-enamido) propyl] 1, 4- diaminobutane (185) (1.58 g, 95%).

IR (CCl_4) cm^{-1} : 1540, 1695, 2940, 3330

NMR ($CDCl_3$) δ : 1.43-1.61 (16H, m, 3xCH_3-C-O, 3xC-CH_2-C, N-H)

: 1.80 (3H, s, CH_3-C=)

: 2.11 (3H, s, CH_5C)

: 2.45-2.75 (4H, m, -CH_2NHBOC)

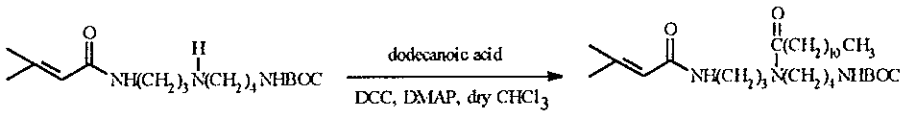
: 2.88-3.45 (4H, m, -CH_2-N-CH_2-)

: 4.78 (1H, br, -NHBOC)

: 5.43 (1H, s, C-C=CH)

: 6.38 (1H, br, -NH-CO)

3.34 N-[4-(*tert*-Butyloxycarbonylamino)butyl]-N-[3-(3-methylbut-2-enamido)propyl] dodecanomide (186)



(185) **(186)**

A solution of DCC (246.0 mg, 1.19 mmol) in dry dichloromethane (10 ml) was added to a solution of N-(*tert*-butyloxycarbonyl)-N^1-[3-(3-methylbut-2-enamido propyl]1,4-diaminobutane (185) (313 mg, 0.97 mmol) and DMAP (17.8 mg, 0.15 mmol) in dry dichloromethane (10 ml) at 0°C under nitrogen. The reaction mixture was allowed to warm to room temperature and stirred for a further 4 h. The solid was filtered off and washed with dichloromethane. Then dichloromethane was added (50 ml) and the organic layer was washed with 3% HCl (3x15 ml), water (2x15 ml), 5% $NaHCO_3$ (3x15 ml) and water (2 x 15 ml), dried over anhydrous Na_2SO_4 and evaporated to afford an oil. The oily residue was purified by preparative chromatography on silica gel, eluted with 2% methanol in ether to afford N-[4-(*tert*-butyloxycarbonylamino) butyl]-N-[3-(3-methylbut-2-enamido) propyl] dodecanamide (186) (480 mg, 95%).

IR (CCl_4) cm^{-1} : 1535, 1640, 1670, 1700, 2930, 3300

NMR ($CDCl_3$) δ : 0.86 (3H, t, CH_3-)

: 1.25-1.40 (24H, m, C-CH_2-C)

: 1.79 (3H, s, CH_3C=C)

: 2.11 (3H, s, CH_3C=C)

: 2.23 (2H, t, -CH_2-CO)

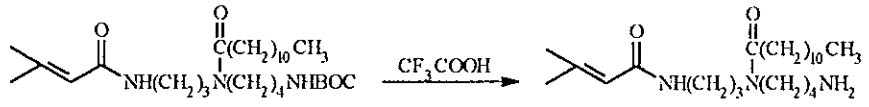
: 2.83-3.42 (8H, m, 4xCH_2-N)

: 4.33-5.00 (1H, br, NHBOC)

: 5.50 (1H, s, C-C=CH)

: 6.33-6.82 (1H, br, NH-CO)

3.35 N-(4-Aminobutyl)-N-[3-(3-methylbut-2-enamido)propyl]dodecanamide (187)



(186) (187)

Trifluoroacetic acid (636 µl) was added to N-[4-(*tert*-butyloxycarbonylamino) butyl]-N-[3-(3-methylbut-2-enamido) propyl]dodecanamide (185) (212.5 mg, 0.41 mmol) and the reaction mixture was stirred for 30 min with occasional cooling. The solution was then cooled over ice and made basic with 10% NaOH. The resulting solution was extracted with dichloromethane (5x10 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford N-(4-aminobutyl)-N-[3-(3-methylbut-2-enamido) propyl]dodecanamide (187) (160.8 mg, 97%) as an oil.

IR (neat) cm^{-1} : 1640, 1670, 2950, 3300

NMR ($CDCl_3$) δ : 0.88 (3H, t, CH_3-)

: 1.26-1.66 (24H, m, C-CH_2-C)

: 1.80 (3H, s, CH_3C=C)

: 2.07 (3H, s, CH_3C=C)

: 2.28 (2H, t, -CH_2-CO)

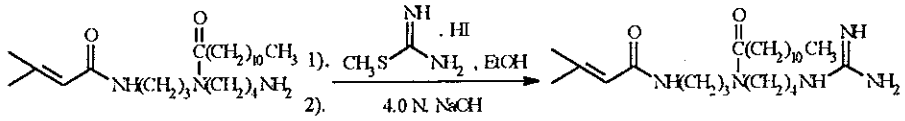
: 2.68 (2H, t, CH_2-NH_2)

: 2.98-3.46 (6H, m, 3x-CH_2NCO)

: 5.51 (1H, s, C-C=CH)

: 6.33-6.73 (1H, br, NH-CO)

3.36 N-(4-Guanidinobutyl)-N-[3-methylbut-2-enamino)propyl]dodecanamide (188)

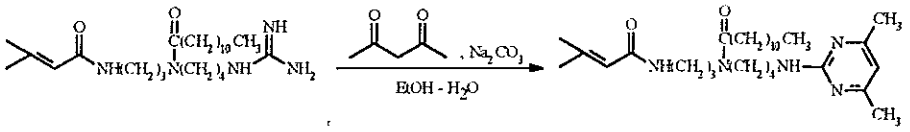


(187) **(188)**

A solution of N-(4-aminobutyl)-N-[3-(3-methylbut-2-enamido) propyl] dodecanamide (187) (200 mg, 0.48 mmol) and S-methylisothiourea iodide (182) (137.2 mg, 0.63 mmol) in ethanol (3 ml) was stirred for 36 h. The ethanol was removed by evaporation and the residue was basified with 4 N NaOH and extracted with chloroform (5x10 ml). The organic layer was dried over anhydrous Na_2SO_4 and evaporated to afford a viscous oil which was purified by dry column flash chromatography on alumina, eluted with 10% ammonium hydroxide in methanol to afford N-(4-guanidinobutyl)-N-[3-methylbut-2-enamino) propyl]dodecanamide (188) (119.8 mg, 54%).

IR (CCl_4) cm^{-1}	:	1630, 1670, 2940, 3100, 3300	
NMR ($CDCl_3$) δ	:	0.86	(3H, t, CH_3-)
	:	1.25	(24H, m, 12xC-CH_2-C)
	:	1.80	(3H, s, CH_3C=C)
	:	2.13	(3H, s, CH_3C=C)
	:	2.30	(2H, t, -CH_2-CO)
	:	3.03-3.66	(8H, m, 4xCH_2N-)
	:	5.66	(1H, s, C-C=CH)
	:	5.33-6.33	(4H, br, guanidine-NH)

3.37 N-[4-(4, 6-Dimethylpyrimidin)-2-ylamino)butyl]-N[3-(3-methylbut-2-enamido) propyl] dodecanamide (189)



(188) (189)

A solution of acarnidine homologue (188) (67.8 mg, 0.15 mmol), pentane-2, 4 dione (59.93 mg, 0.60 mmol), Na_2CO_3 (31.86 mg, 0.30 mmol) in water (2 ml) and ethanol (4 ml) was stirred and heated under reflux for 2 h. The solution was then extracted with ether (5x15 ml). The resulting ethereal solution was dried over anhydrous Na_2SO_4 and evaporated to afford a crude oil which was purified by preparative chromatography on silica gel, eluted with 6% methanol in dichloromethane to afford N-[4-(4, 6-dimethylpyrimidin)-2-ylamino) butyl]-N-[3-(3-methylbut-2-enamido) propyl]dodecanamide (189) (43.70 mg, 56.4%).

IR (neat) cm^{-1}	:	1575, 1635, 2940, 3330	
NMR ($CDCl_3$) δ	:	0.88	(3H, t, CH_3-)
	:	1.20-1.26	(24H, m, 12xC-CH_2-C)
	:	1.81	(3H, s, CH_3C=C)
	:	2.15	(3H, s, CH_3C=C)
	:	2.26	(8H, s, 2xPryCH_3, CH_2-CO)
	:	3.03-3.52	(8H, m, 4x-CH_2-N)
	:	5.10	(1H, br, NH-Pry)
	:	5.6	(1H, s, C-C=CH-)
	:	6.20	(1H, s, Pyr-H)
	:	6.73	(1H, br, NH-CO)
MS	:	515	(m/e, M^+)

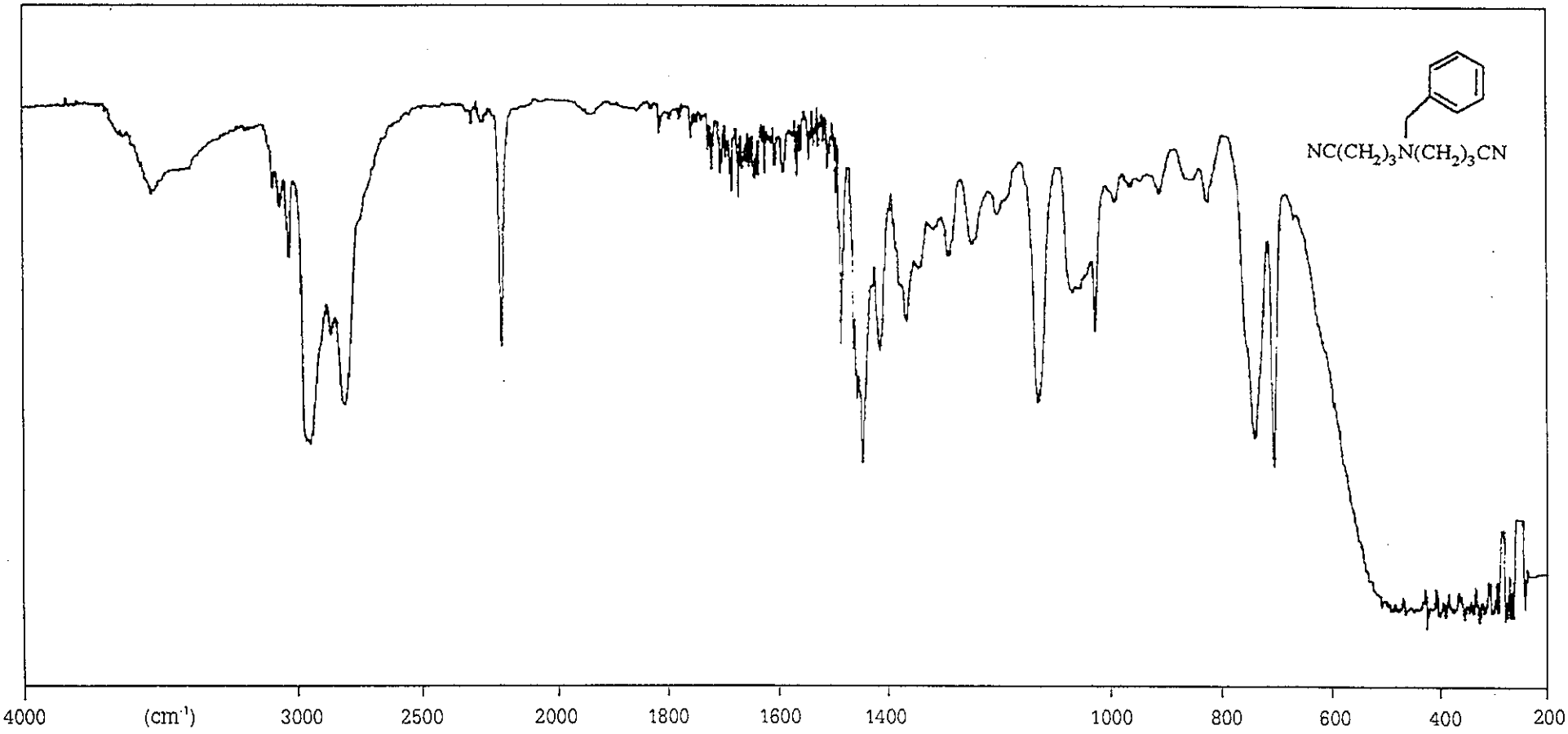


Figure 1 IR spectrum of N, N-di(3-cyanopropyl)benzylamine (156)

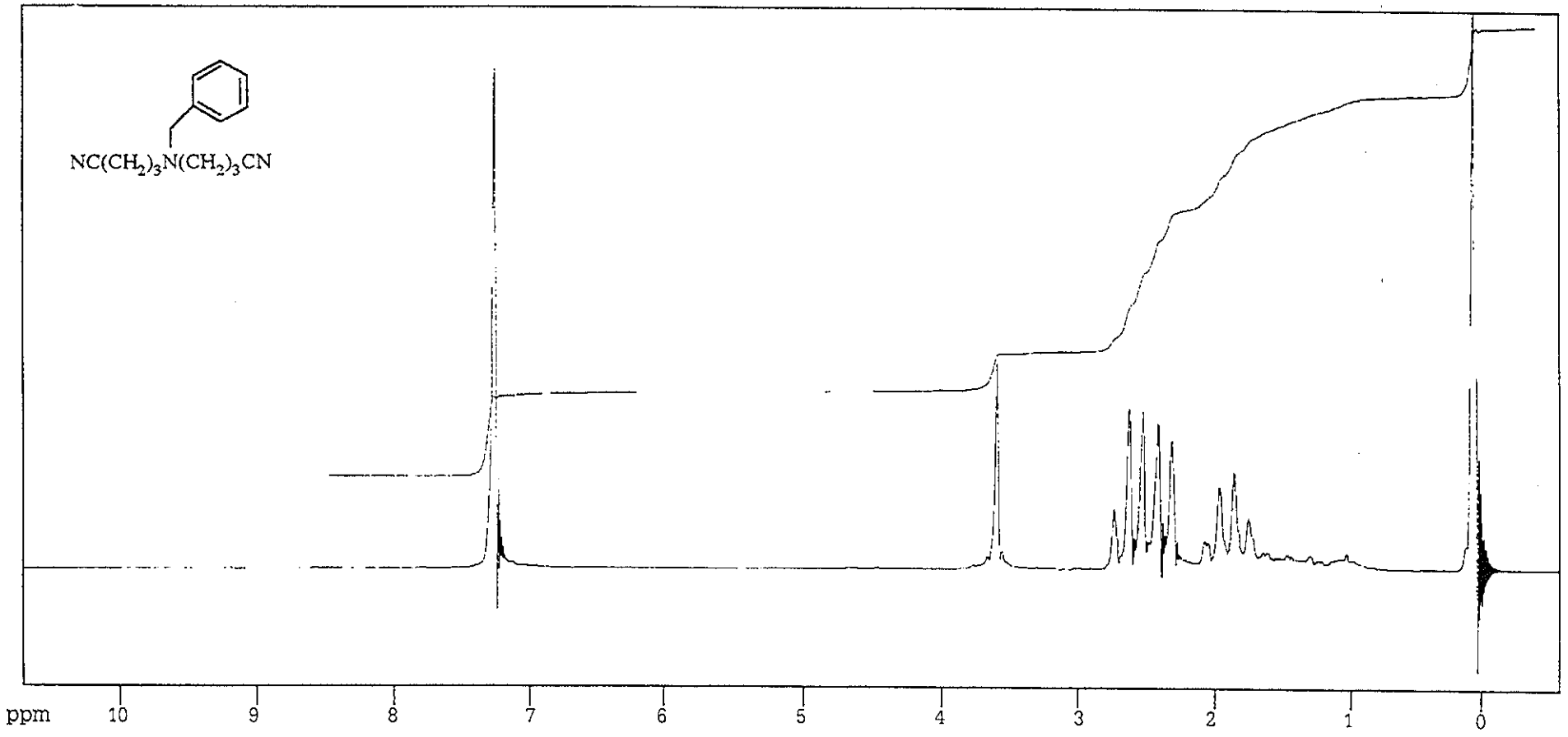


Figure 2 NMR spectrum of N, N-di(3-cyanopropyl)benzylamine (156)

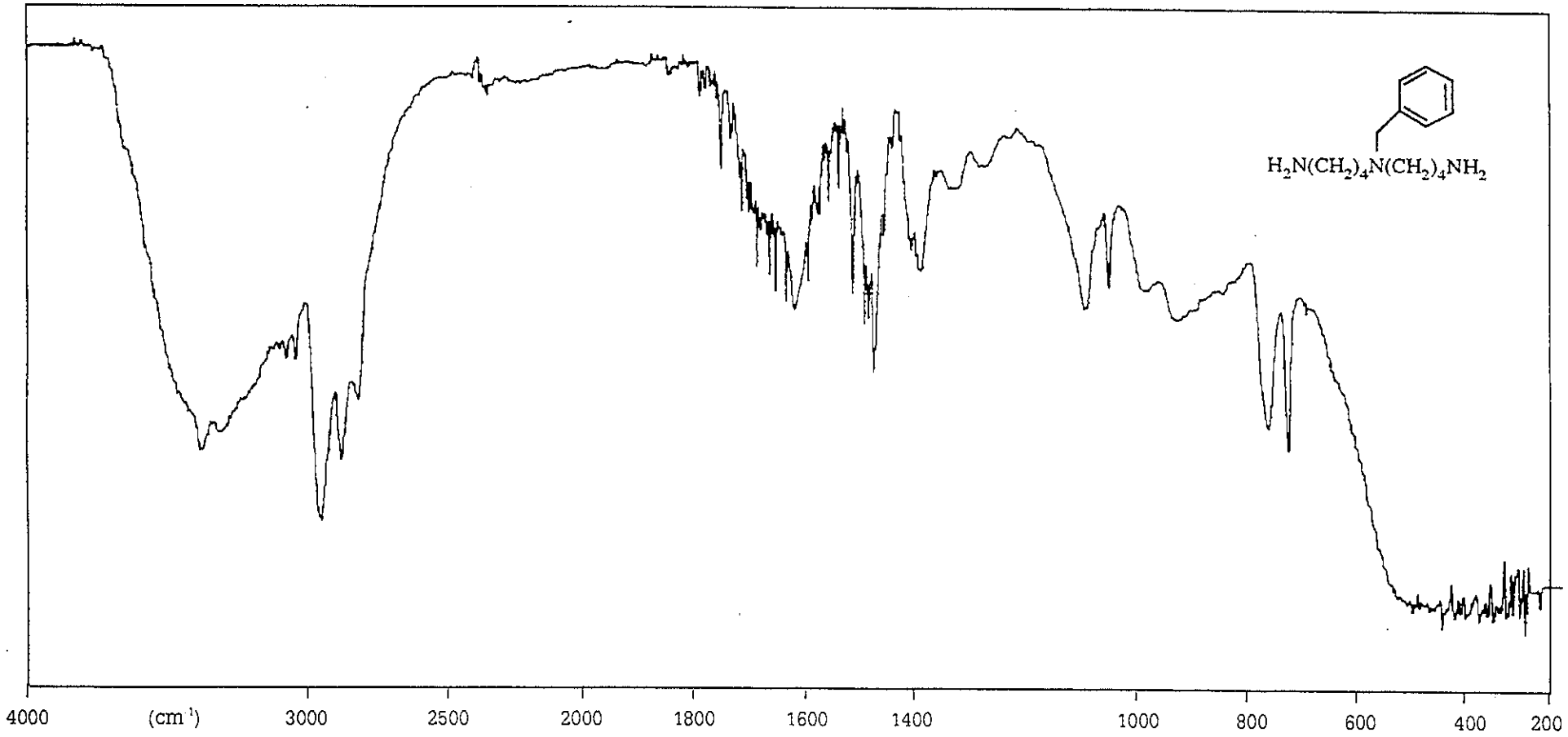


Figure 3 IR spectrum of N^5 - benzylhomospermidine (157)

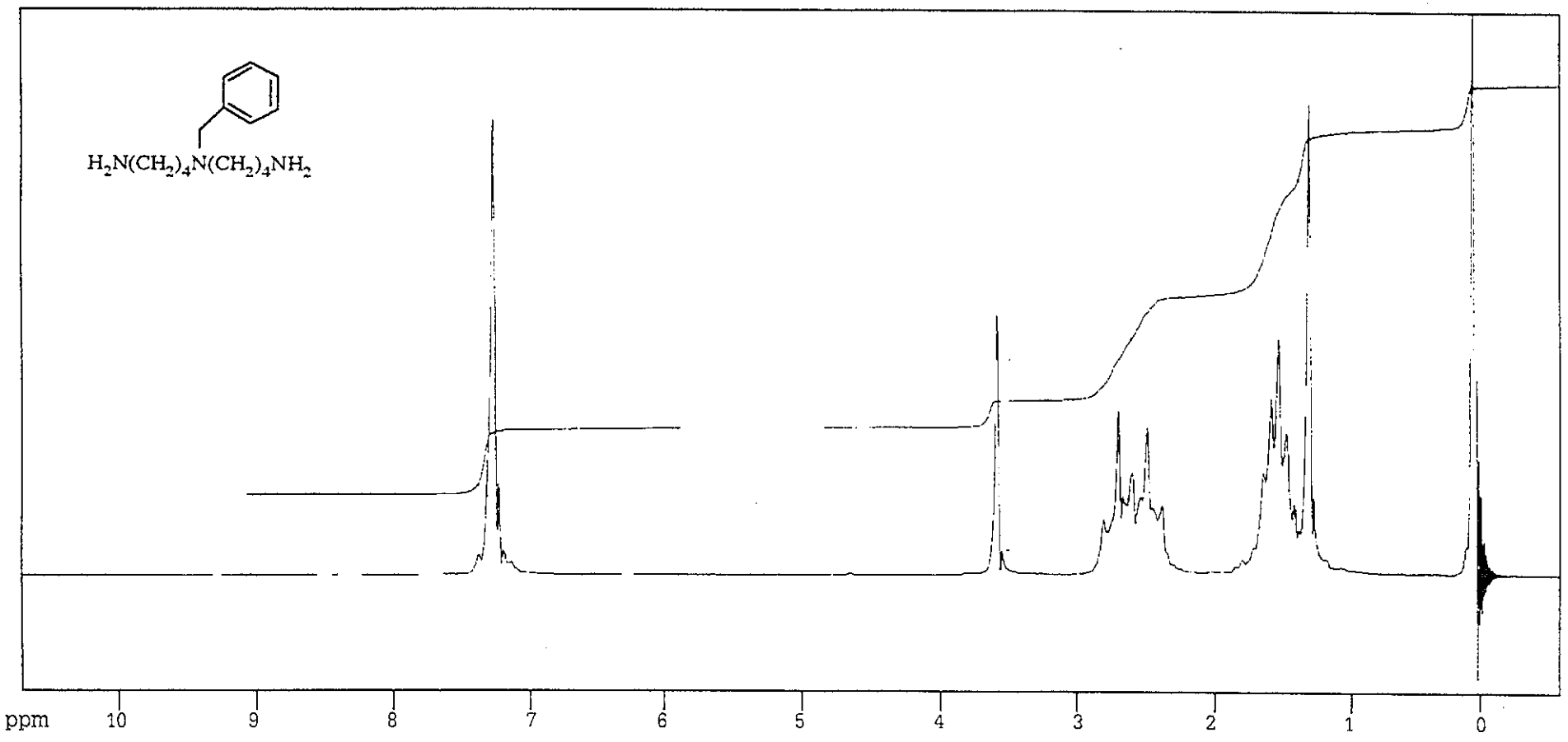


Figure 4 NMR spectrum of N^5- benzylhomospermidine (157)

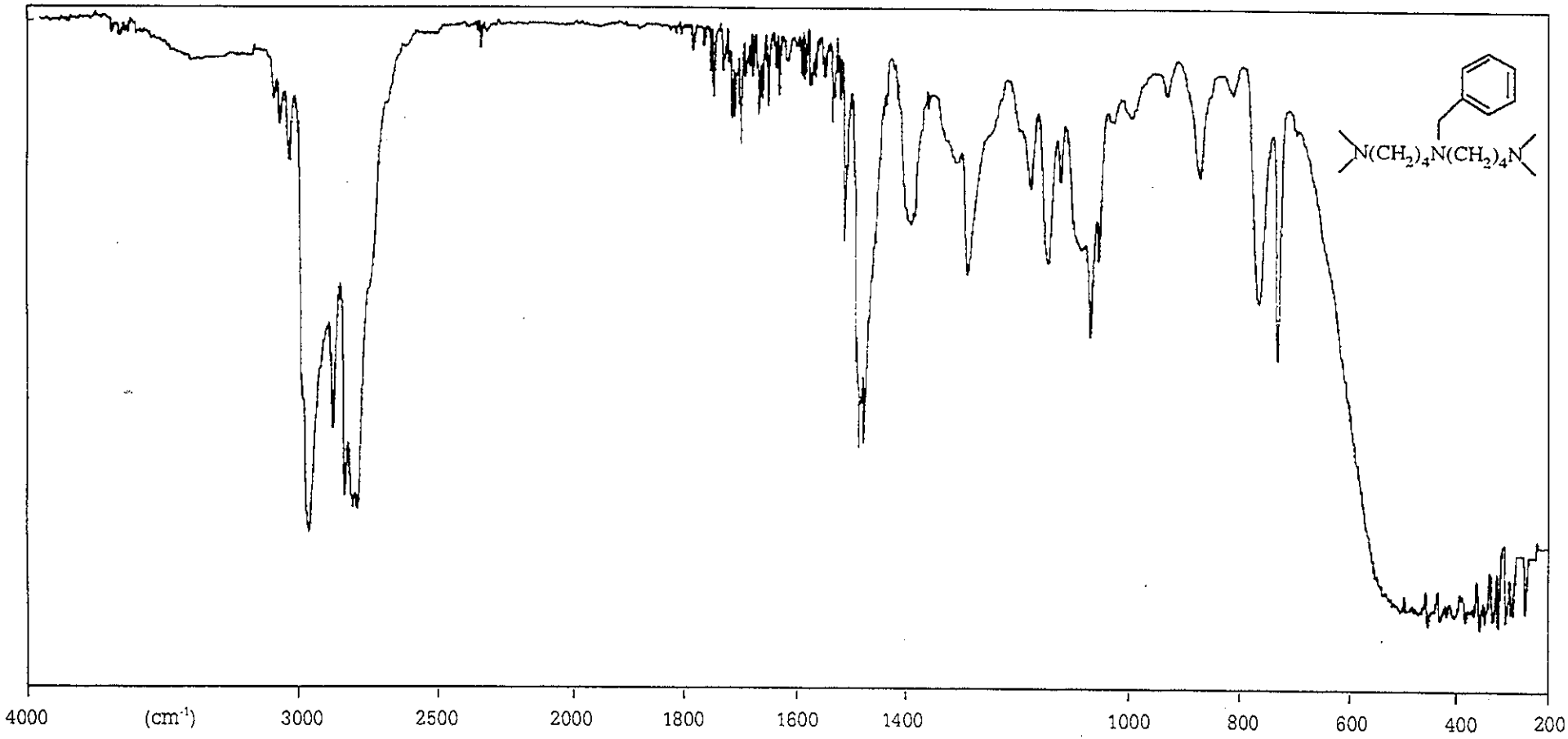


Figure 5 IR spectrum of N^1, N^9-tetramethyl-N^5-benzylhomospermidine (158)

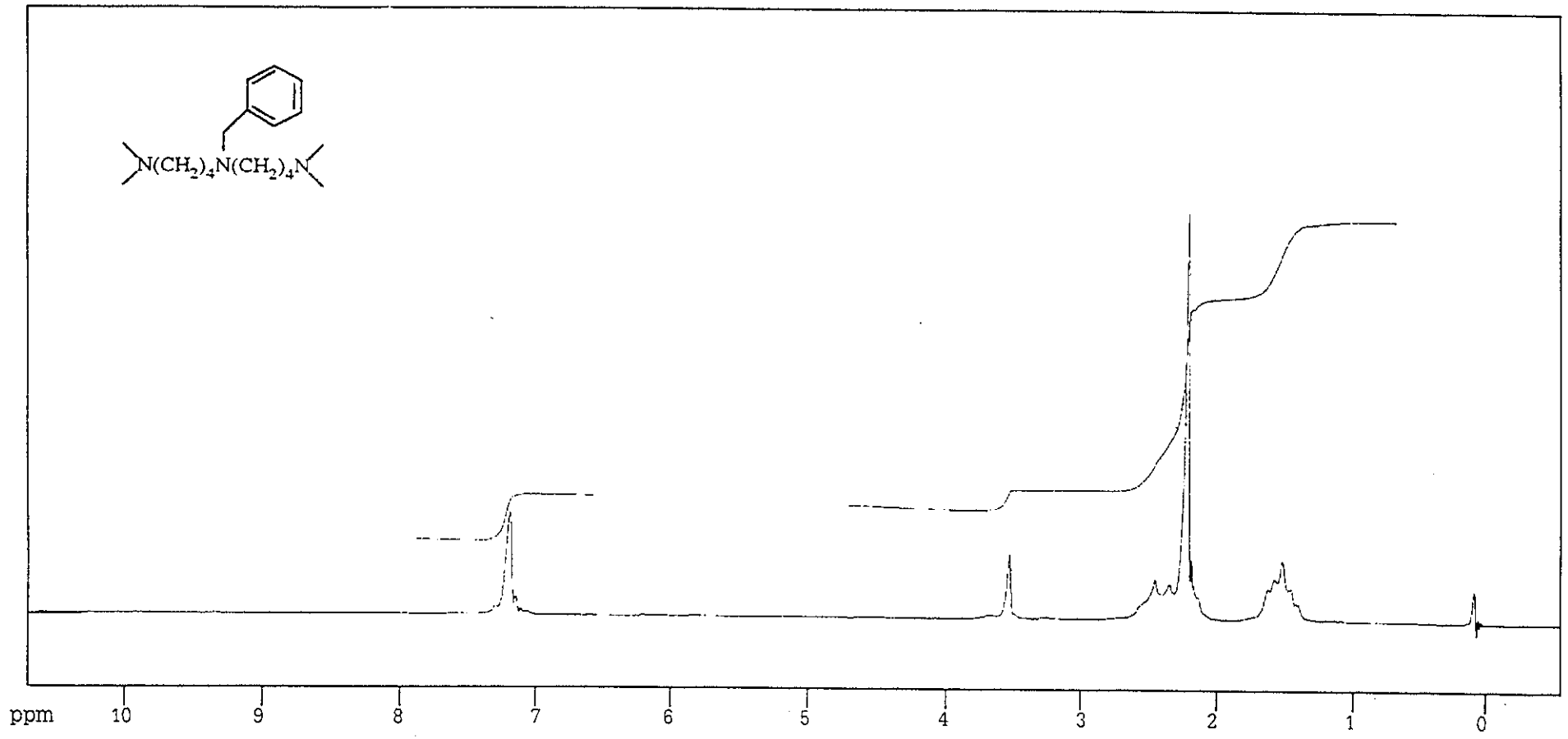


Figure 6 NMR spectrum of N^1, N^9-tetramethyl-N^5-benzylhomospermidine (158)

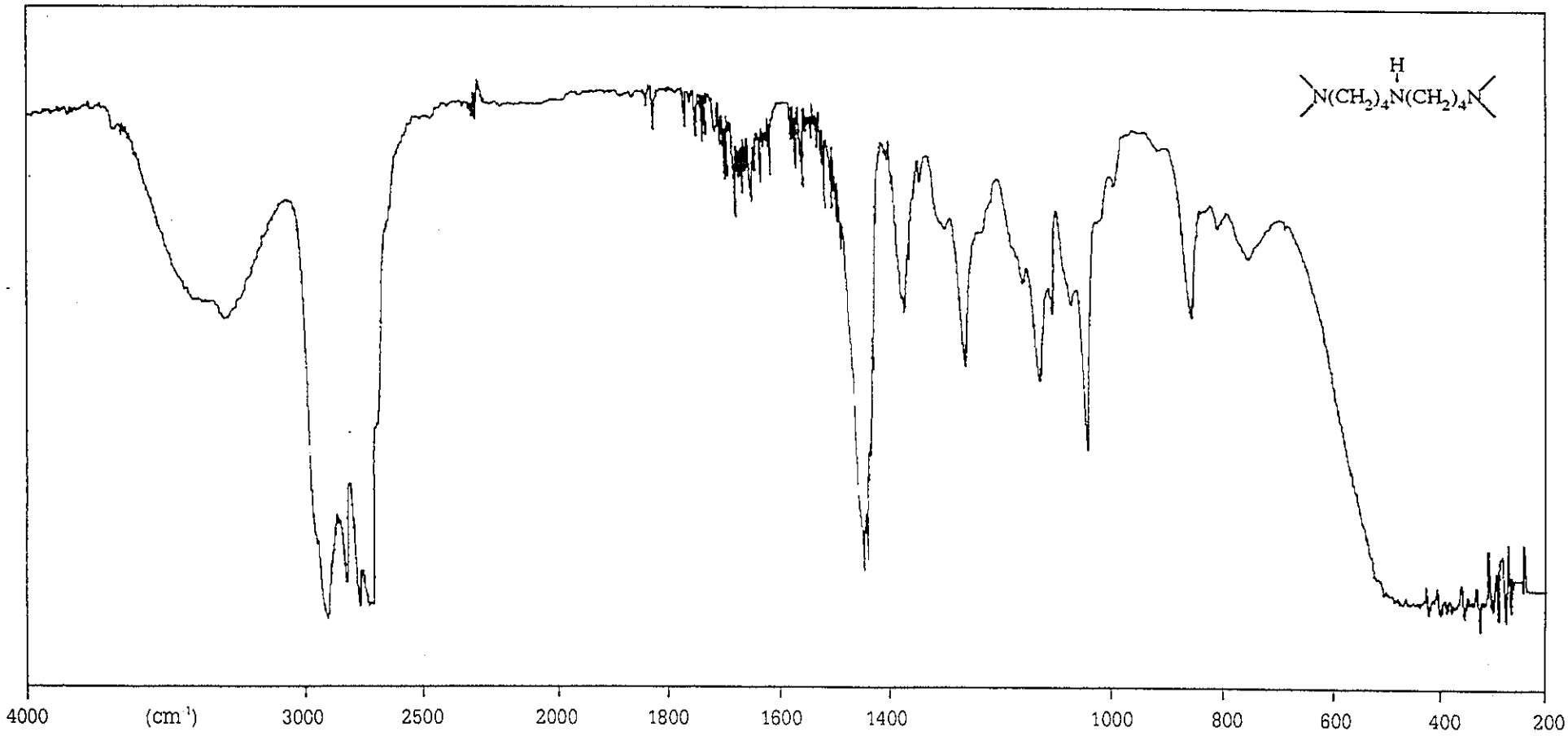


Figure 7 IR spectrum of solamine (68)

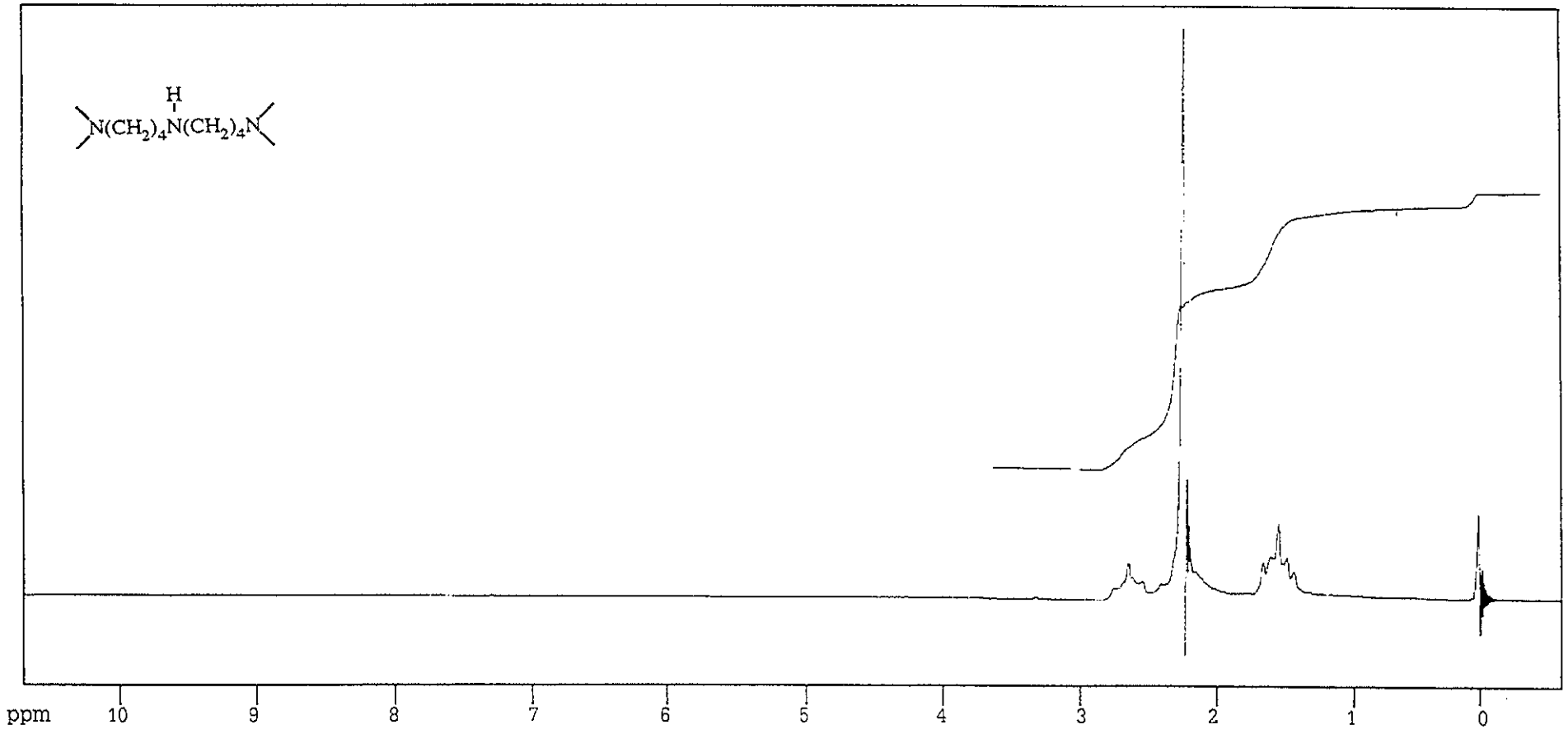


Figure 8 NMR spectrum of solamine (68)

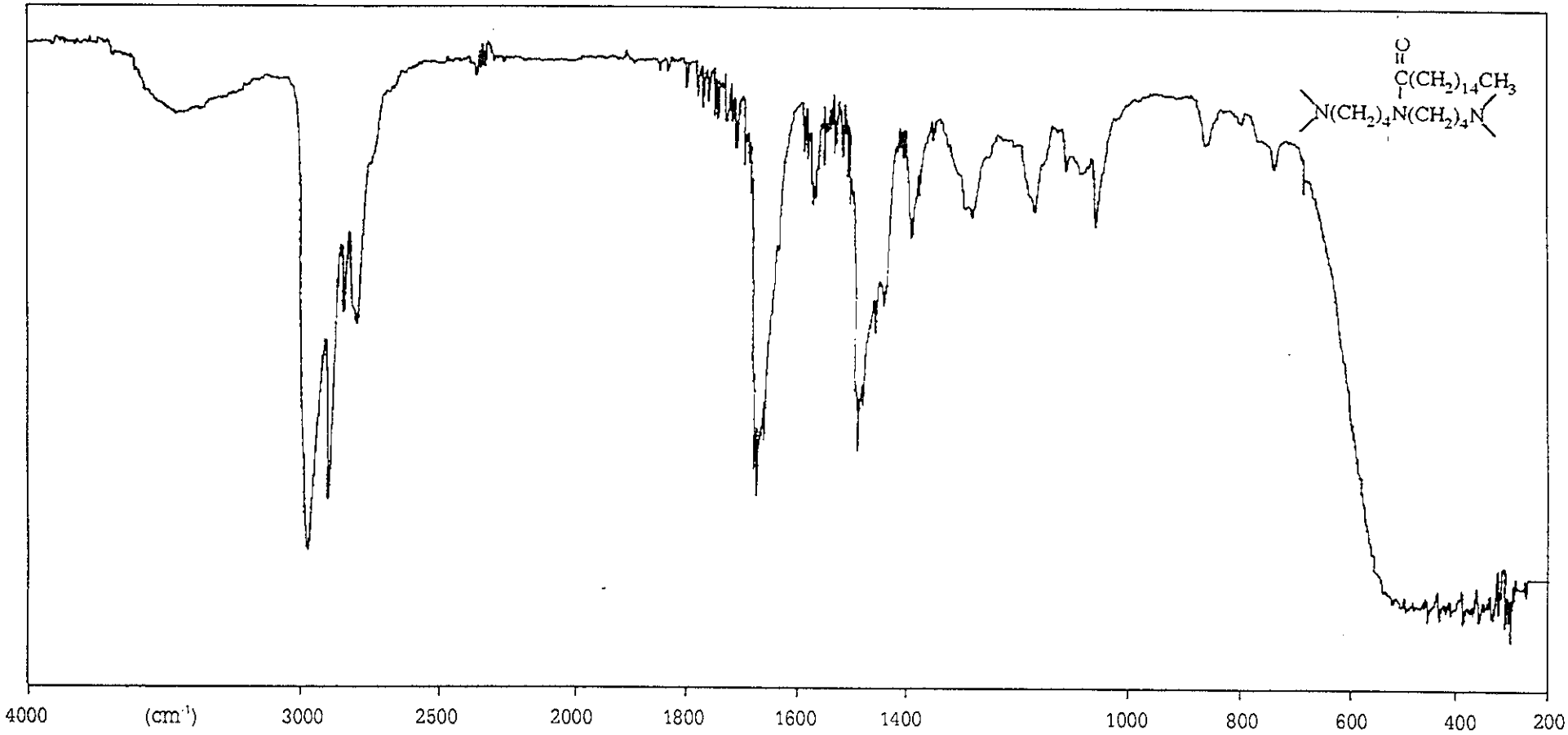


Figure 9 IR spectrum of solapalmitine (69)

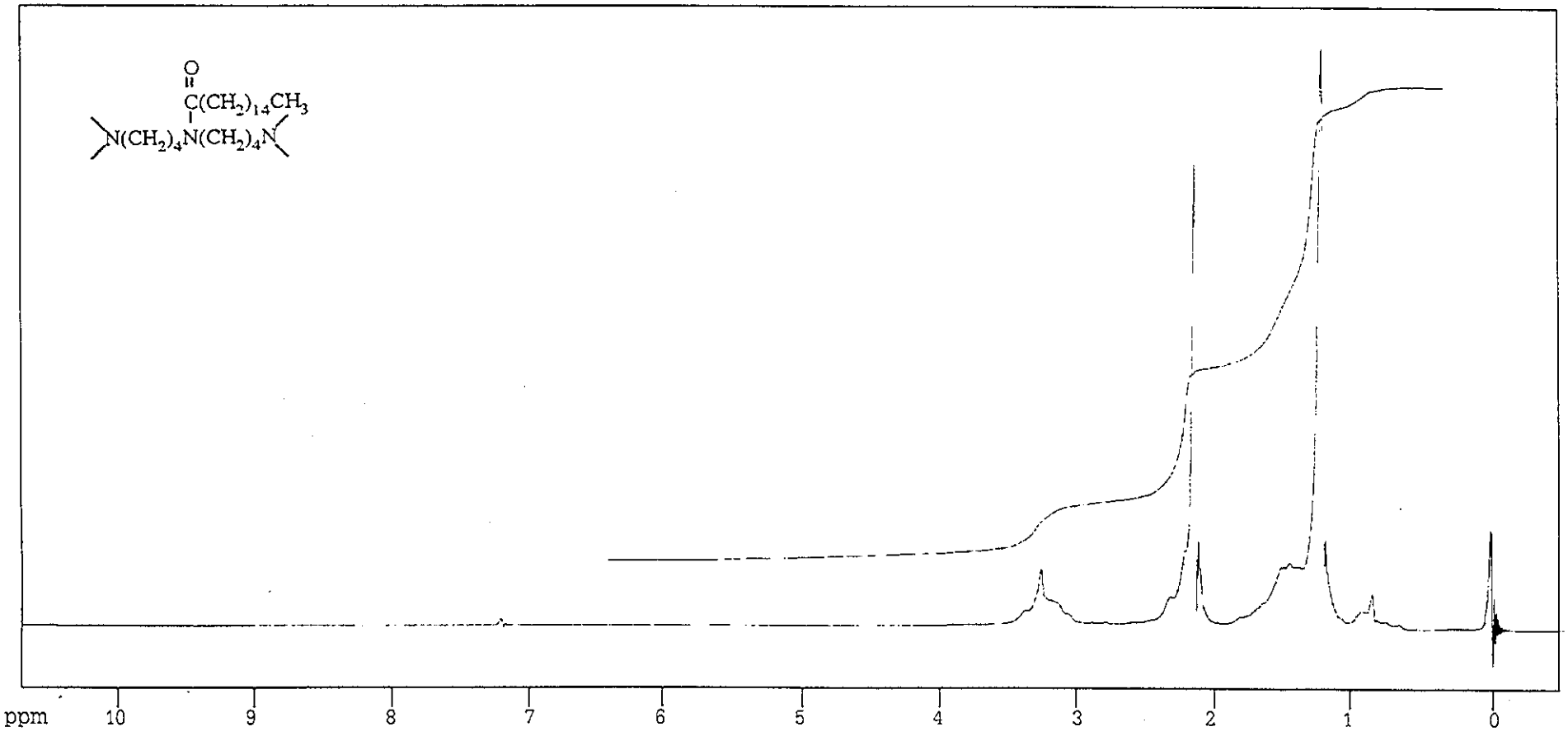


Figure 10 NMR spectrum of solapalmitine (69)

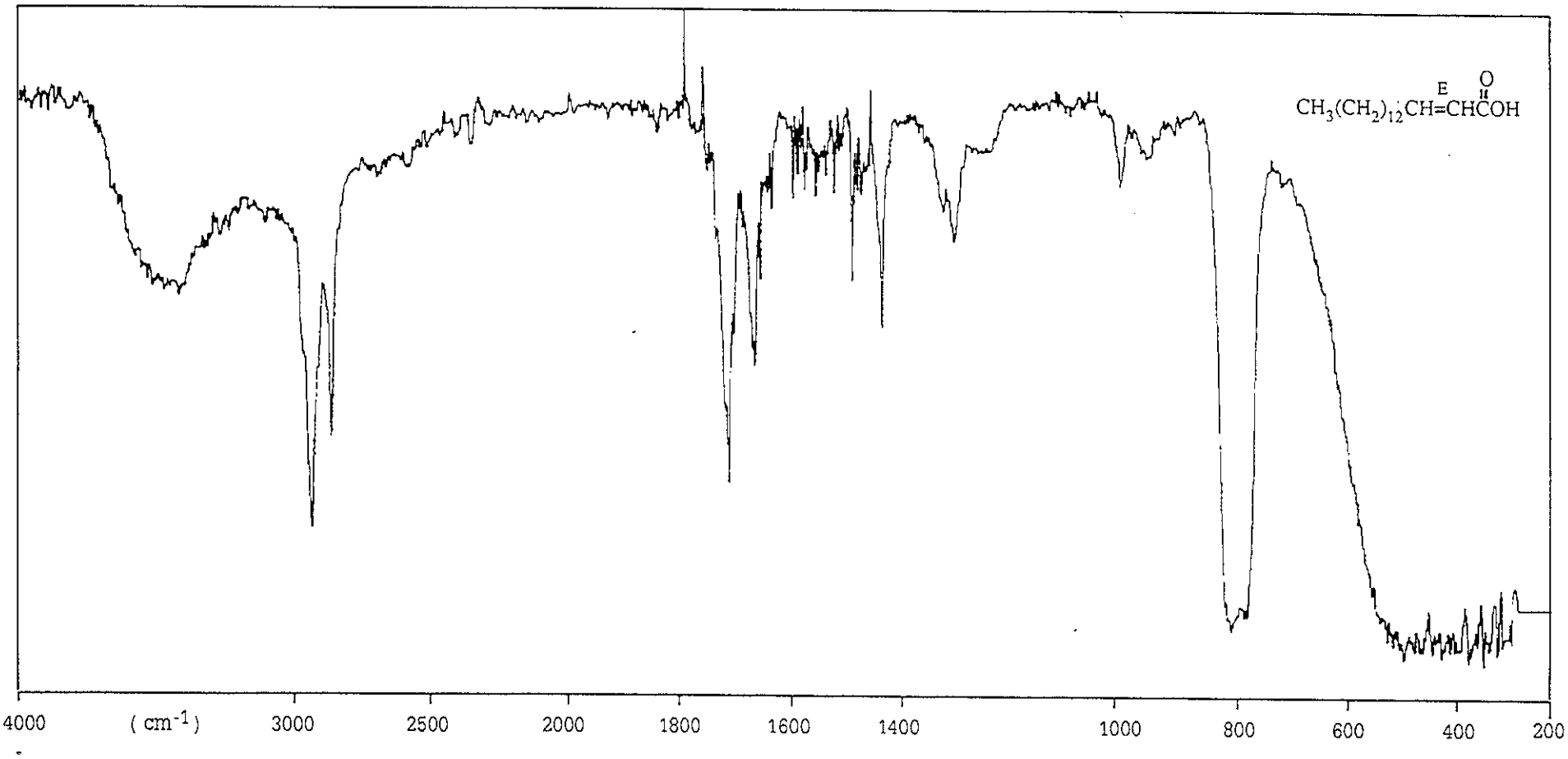


Figure 11 IR spectrum of *trans*-2-hexadecenoic acid (160)

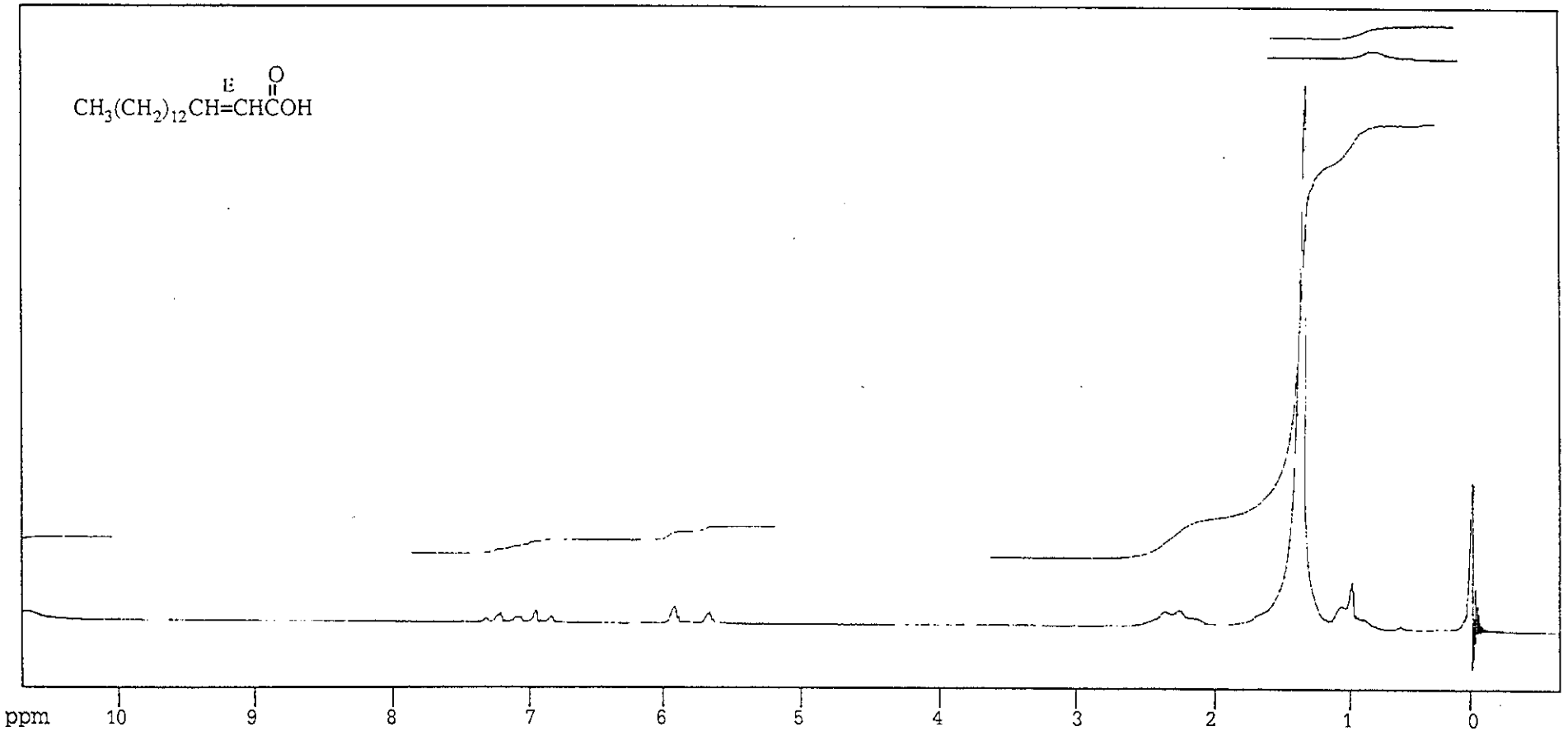


Figure 12 NMR spectrum of *trans*-2-hexadecenoic acid (160)

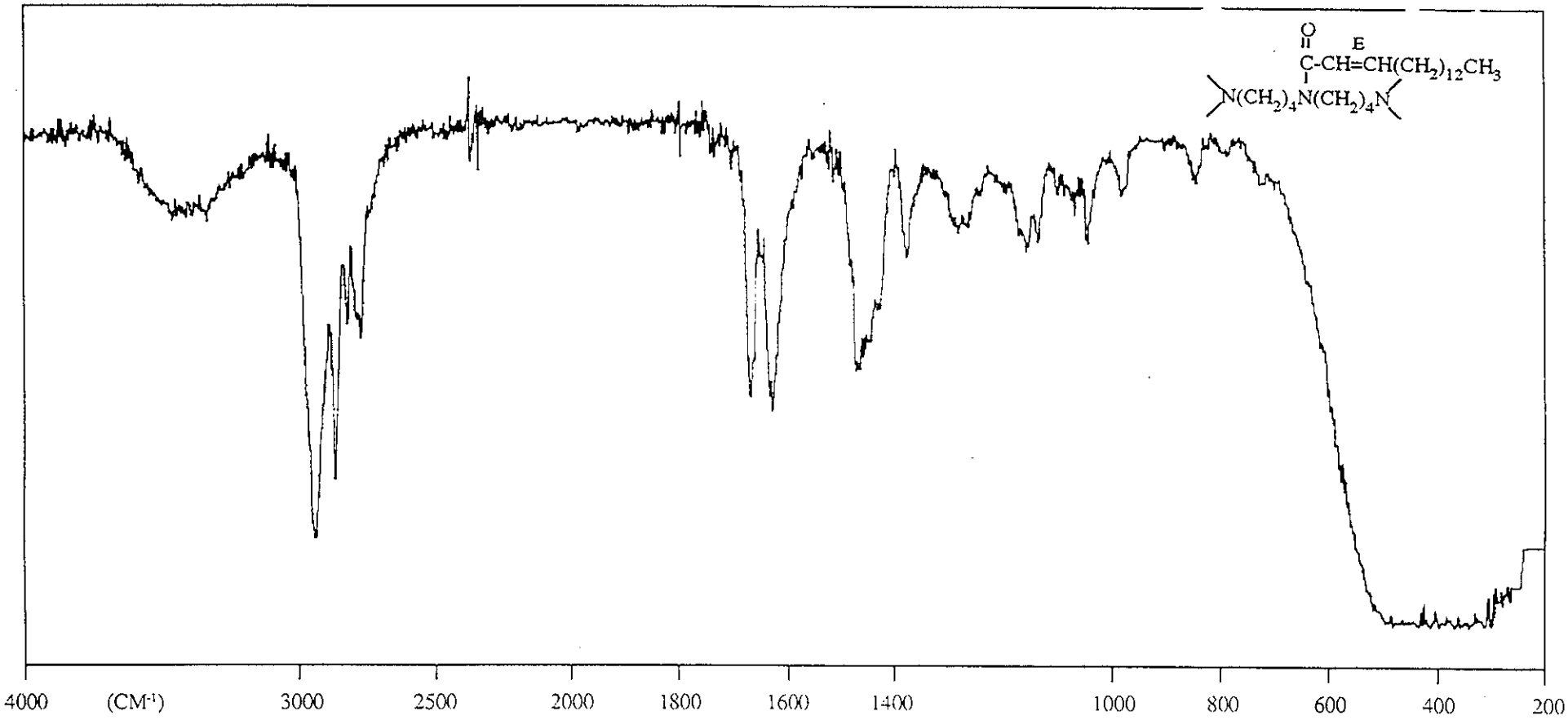


Figure 13 IR spectrum of solapalmitenine (70)

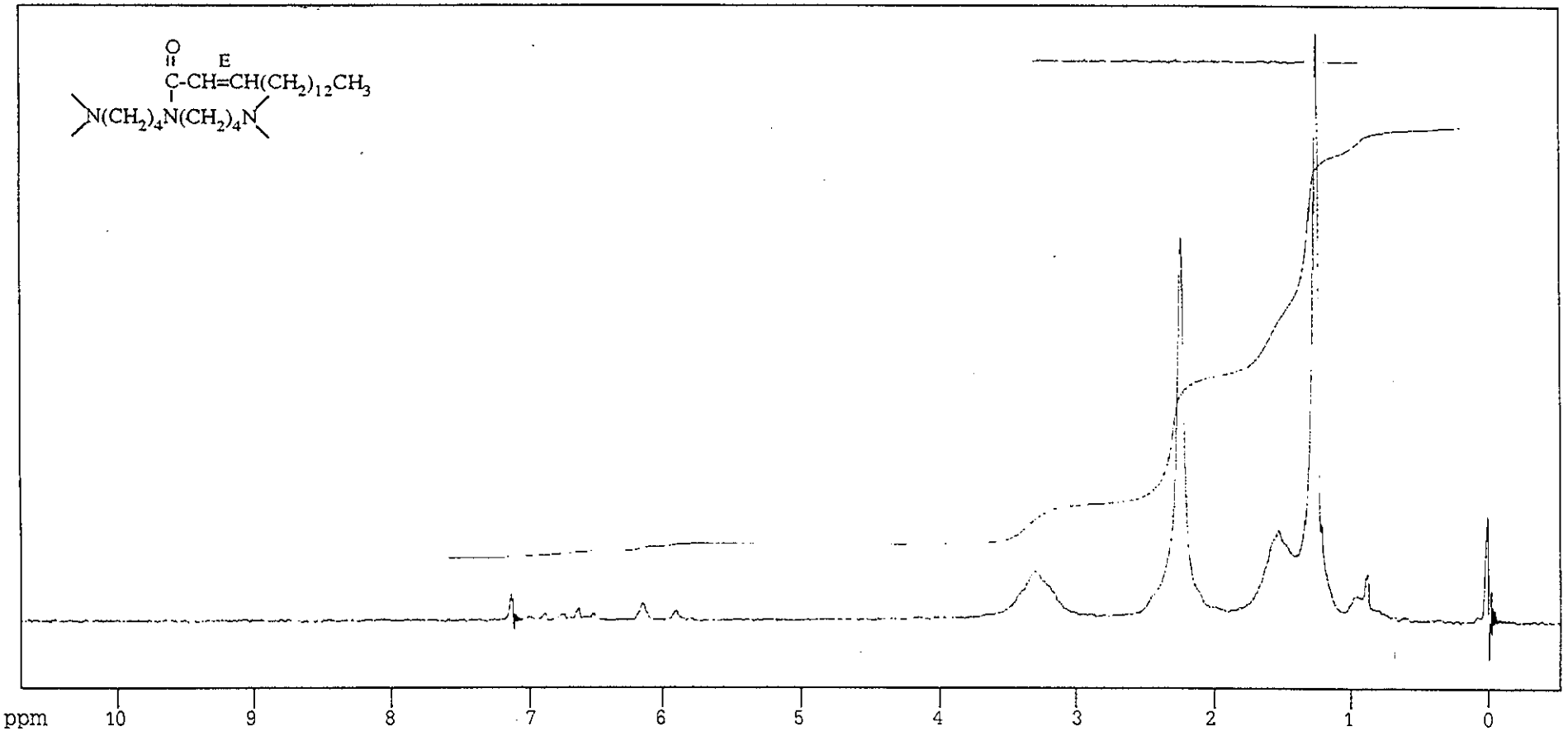


Figure 14 NMR spectrum of solapalmitenine (70)

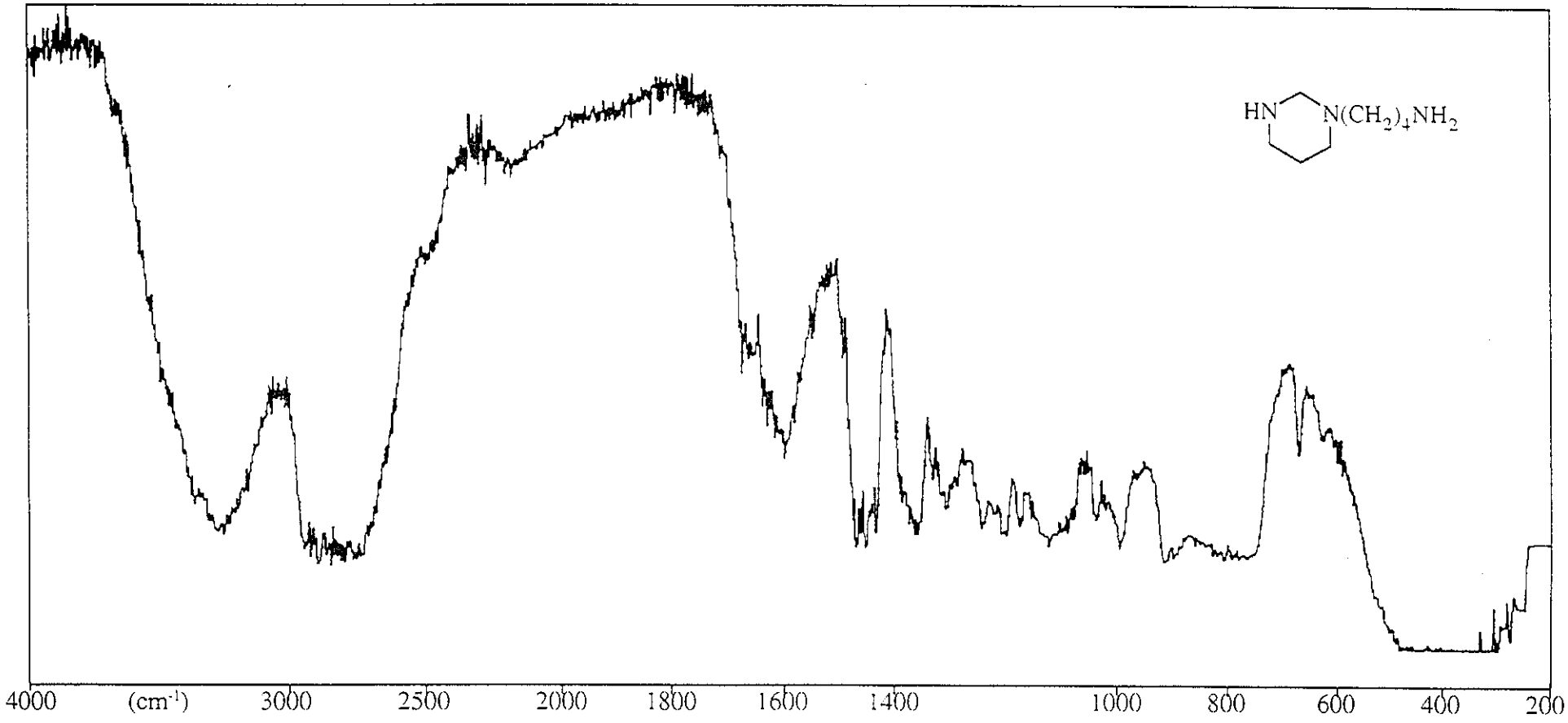


Figure 15 IR spectrum of hexahydropyrimidine (39)

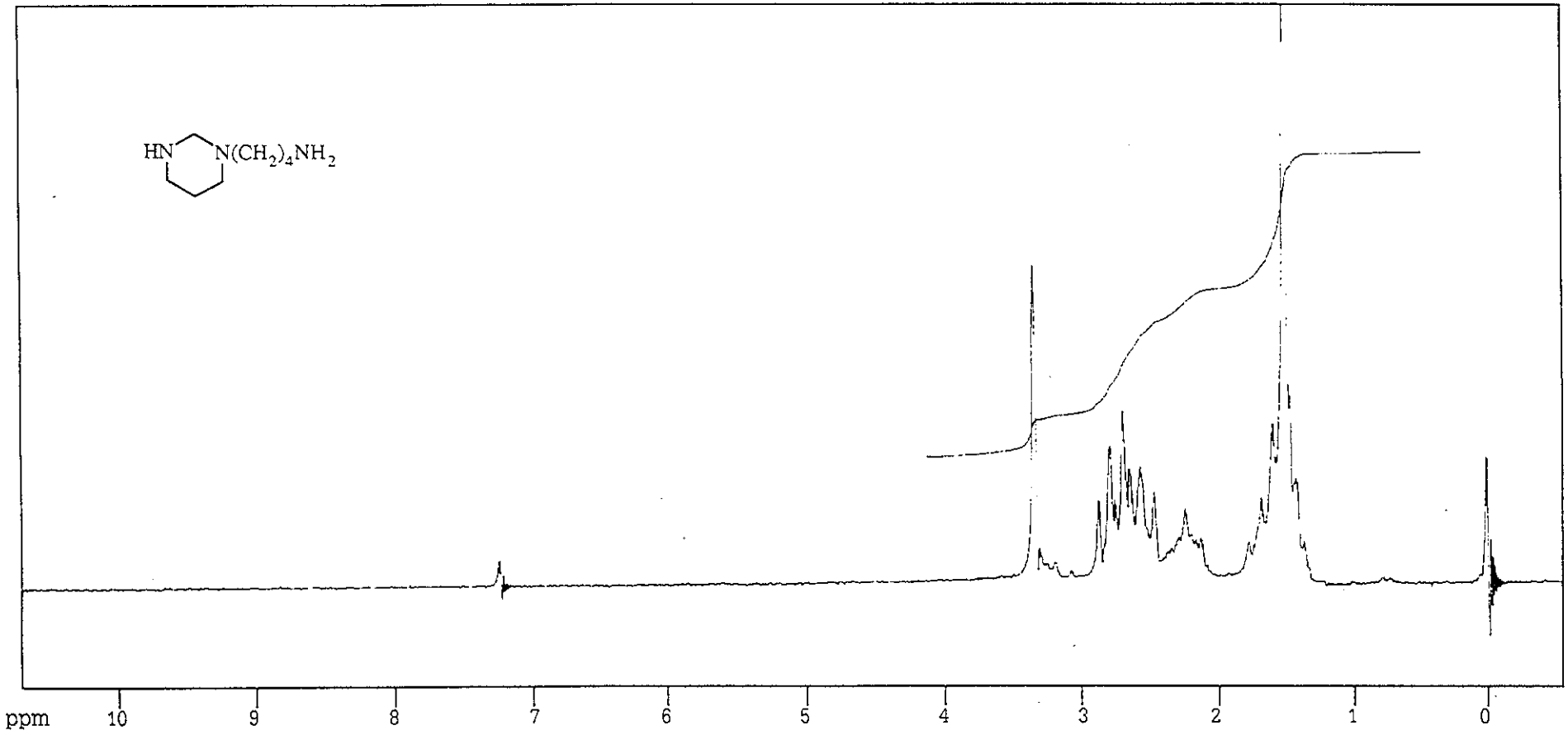


Figure 16 NMR spectrum of hexahydropyrimidine (39)

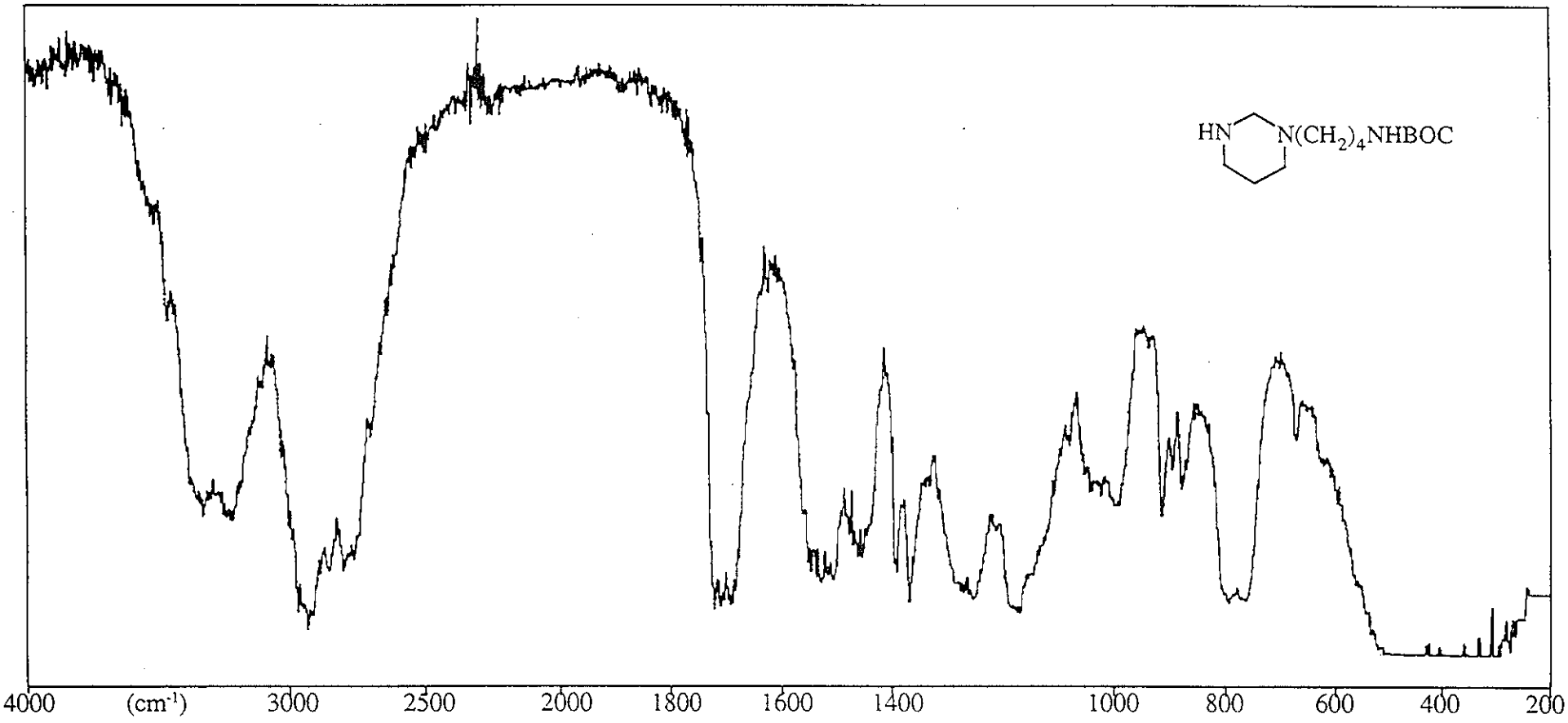


Figure 17 IR spectrum of N^8-(*tert*-butyloxycarbonyl)hexahydropyrimidine (40)

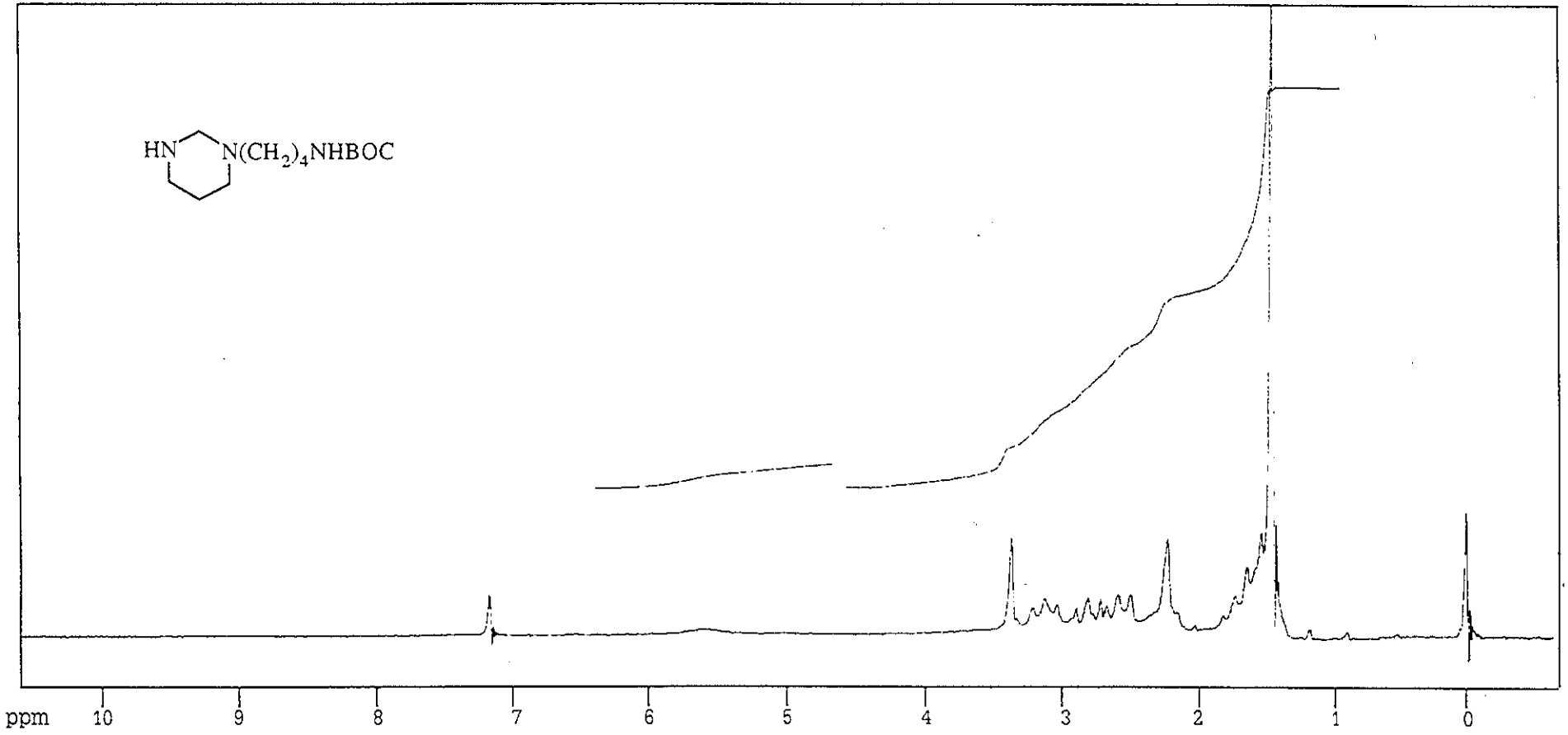


Figure 18 NMR spectrum of N^8-(*tert*-butyloxycarbonyl)hexahydropyrimidine (40)

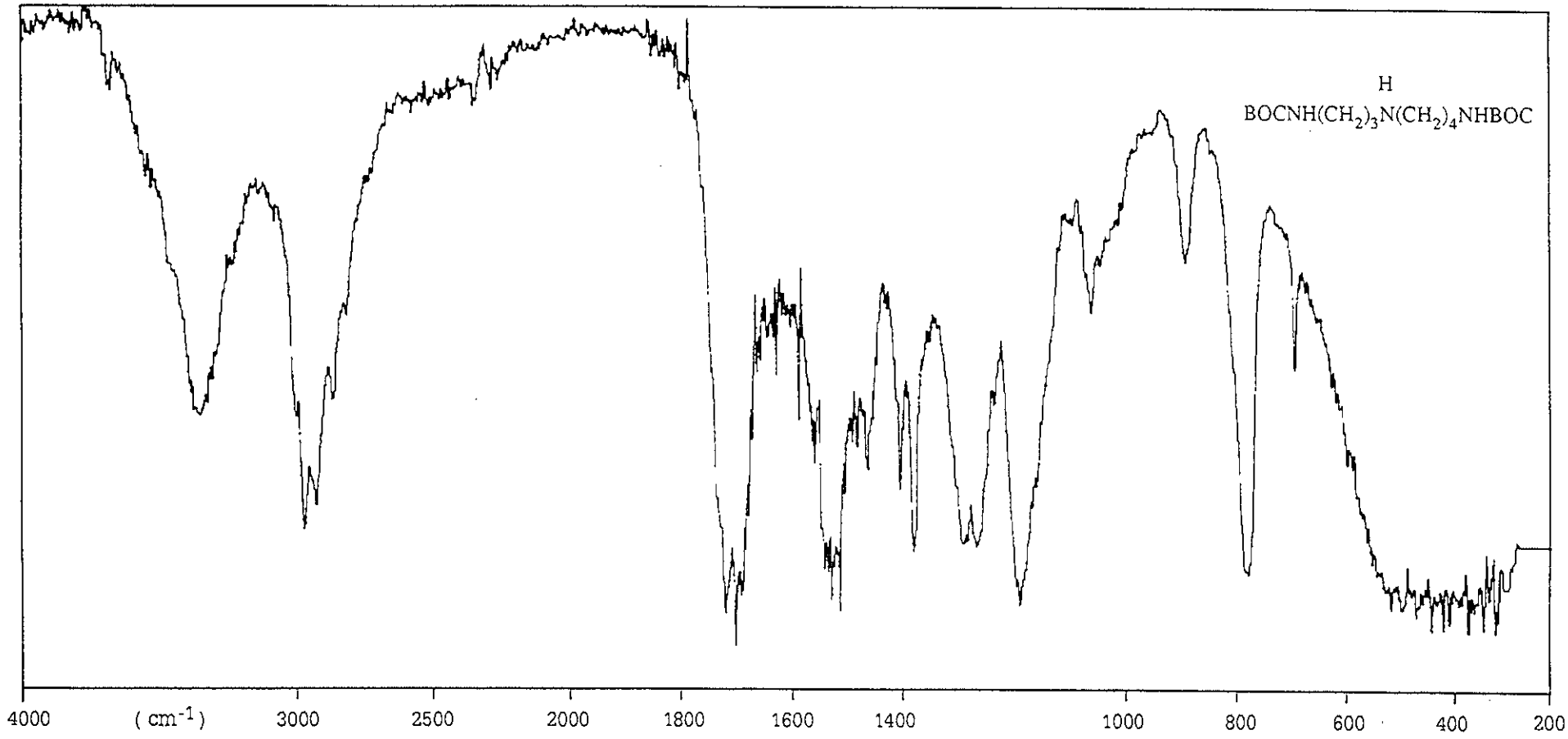


Figure 19 IR spectrum of N^1, N^8-di(*tert*-butyloxycarbonyl)spermidine (124).

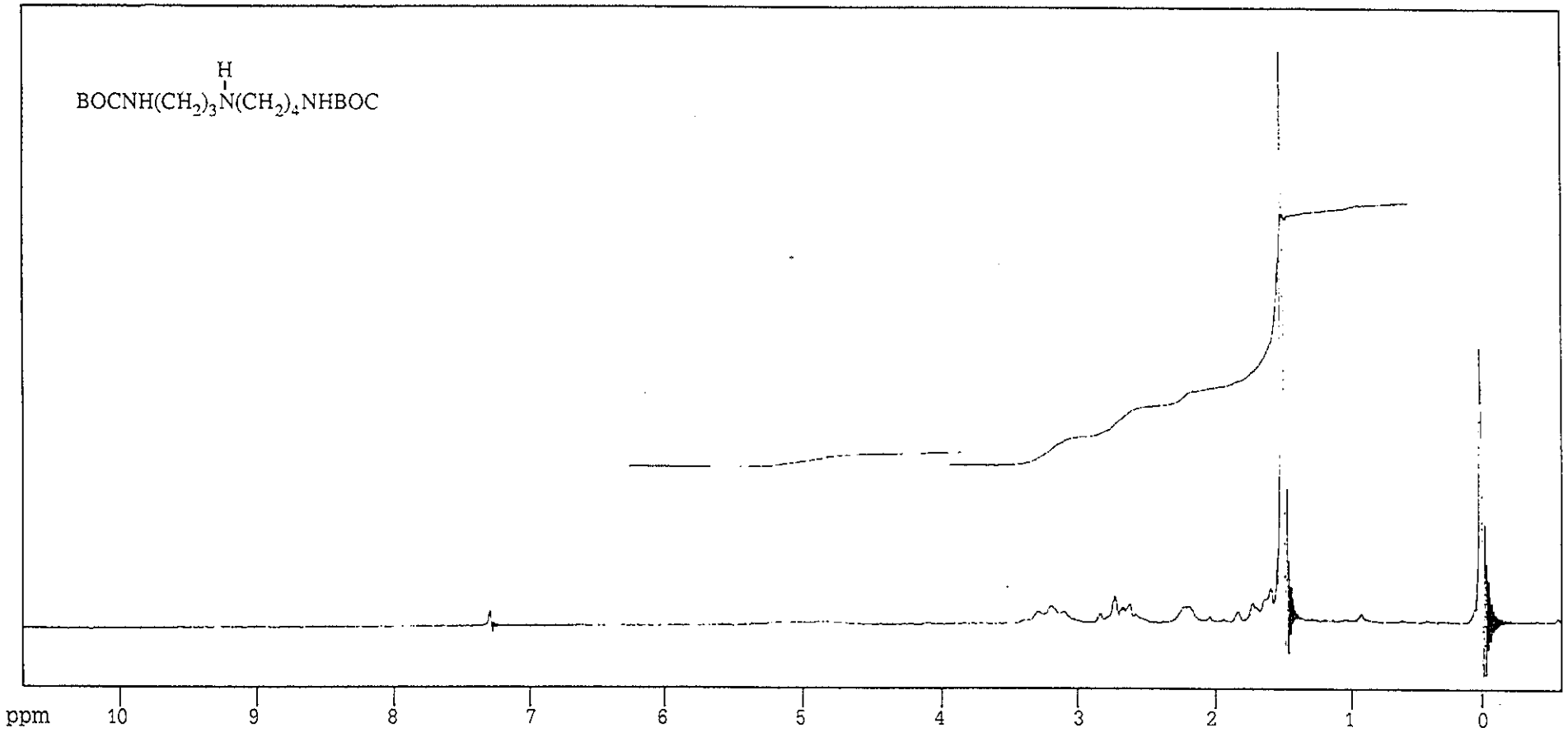


Figure 20 NMR spectrum of N^1, N^8-di(*tert*-butyloxycarbonyl)spermidine (124)

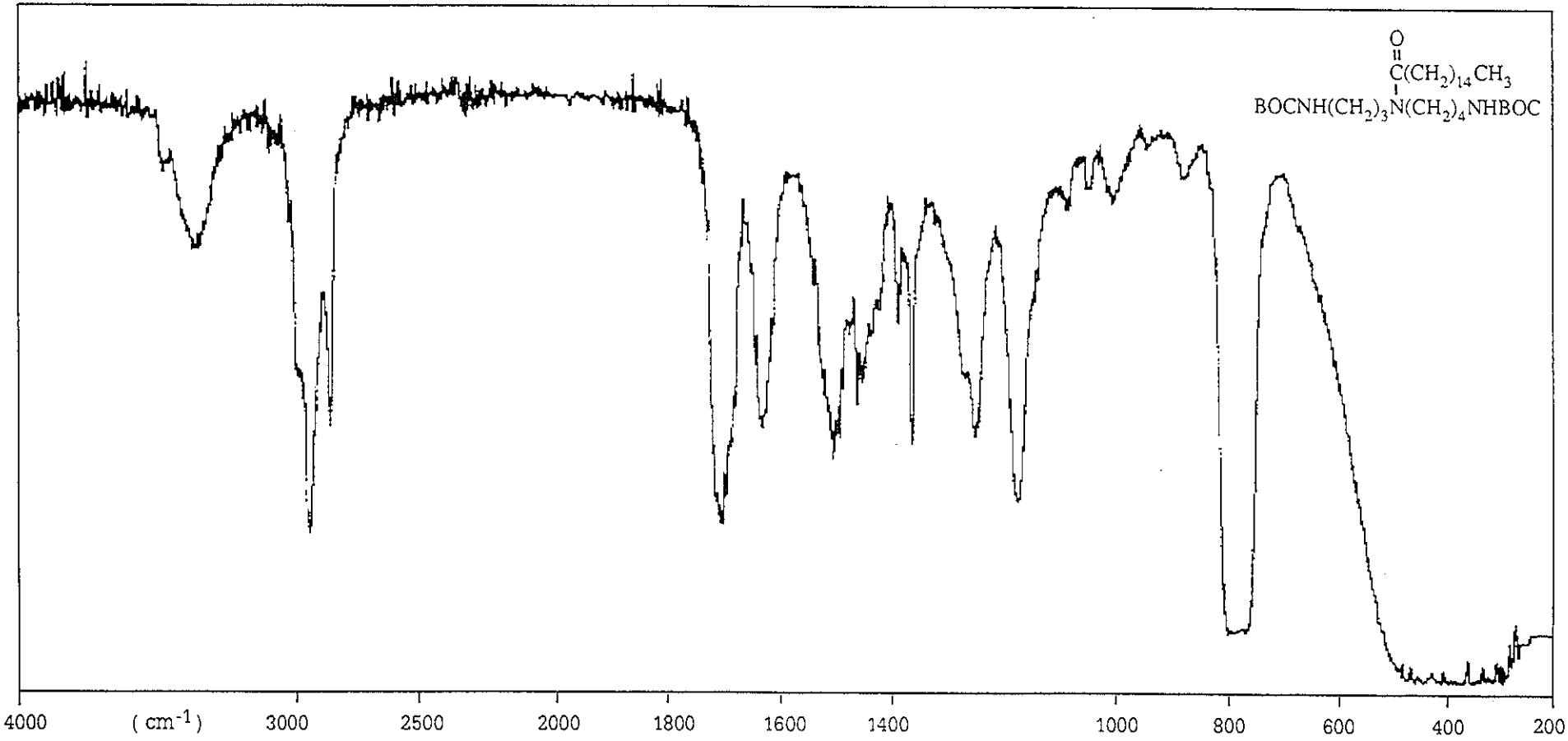


Figure 21 IR spectrum of N^1, N^8-di-(tert-butyloxycarbonyl)-N^4-palmitoyl spermidine (163)

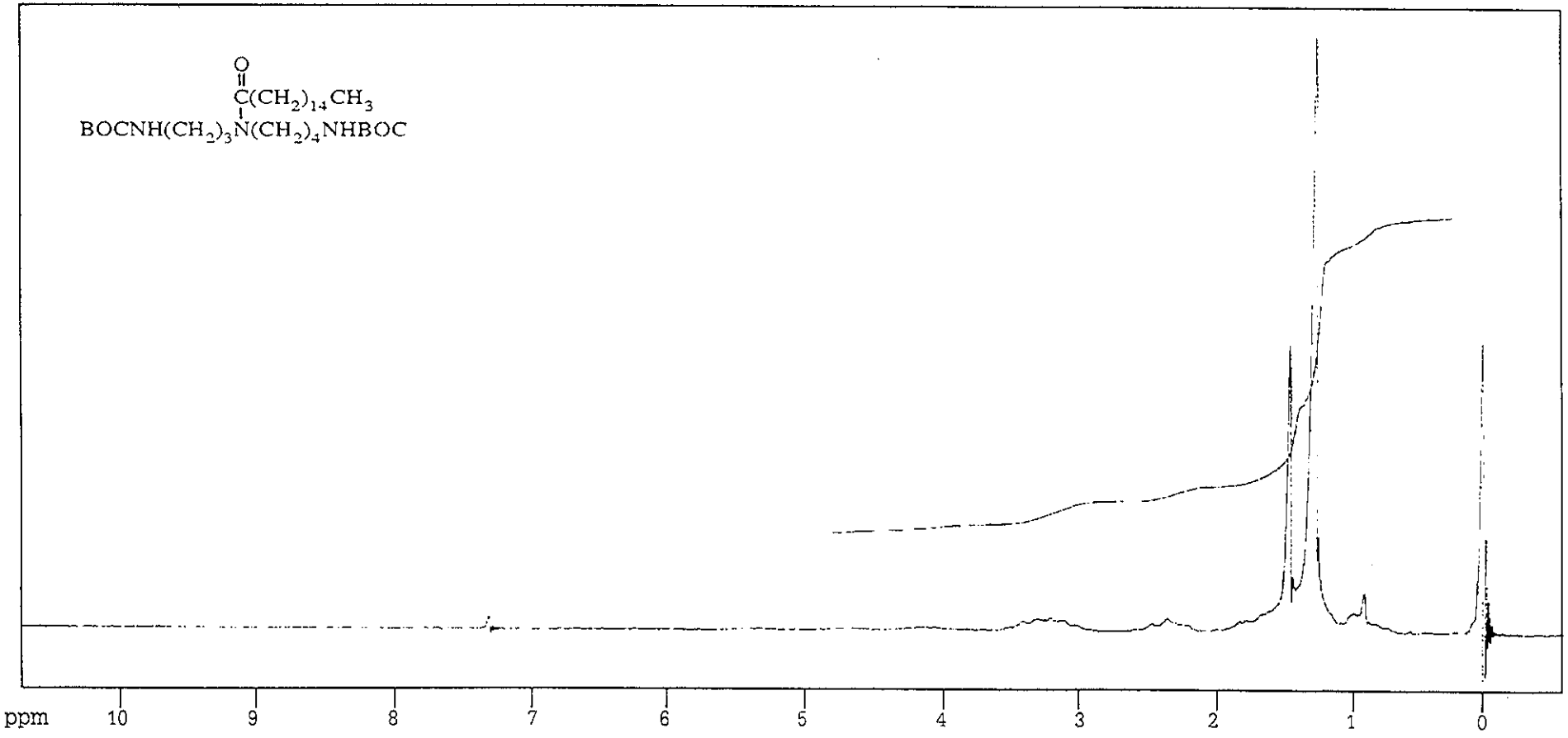


Figure 22 NMR spectrum of N^1, N^8-di(*tert*-butyloxycarbonyl)-N^4-palmitoylspermidine (163)

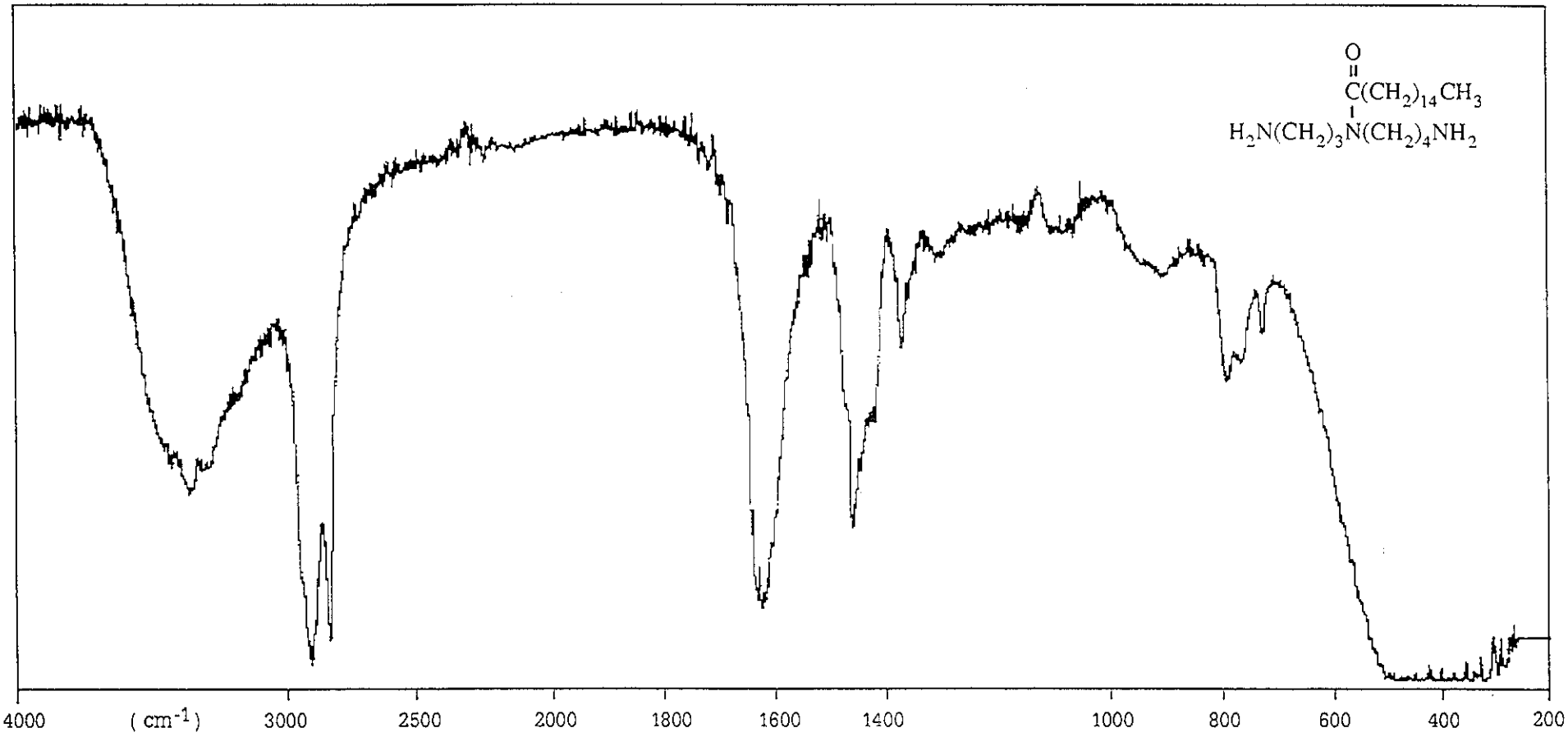


Figure 23 IR spectrum of N^4-palimitoylspermidine (164)

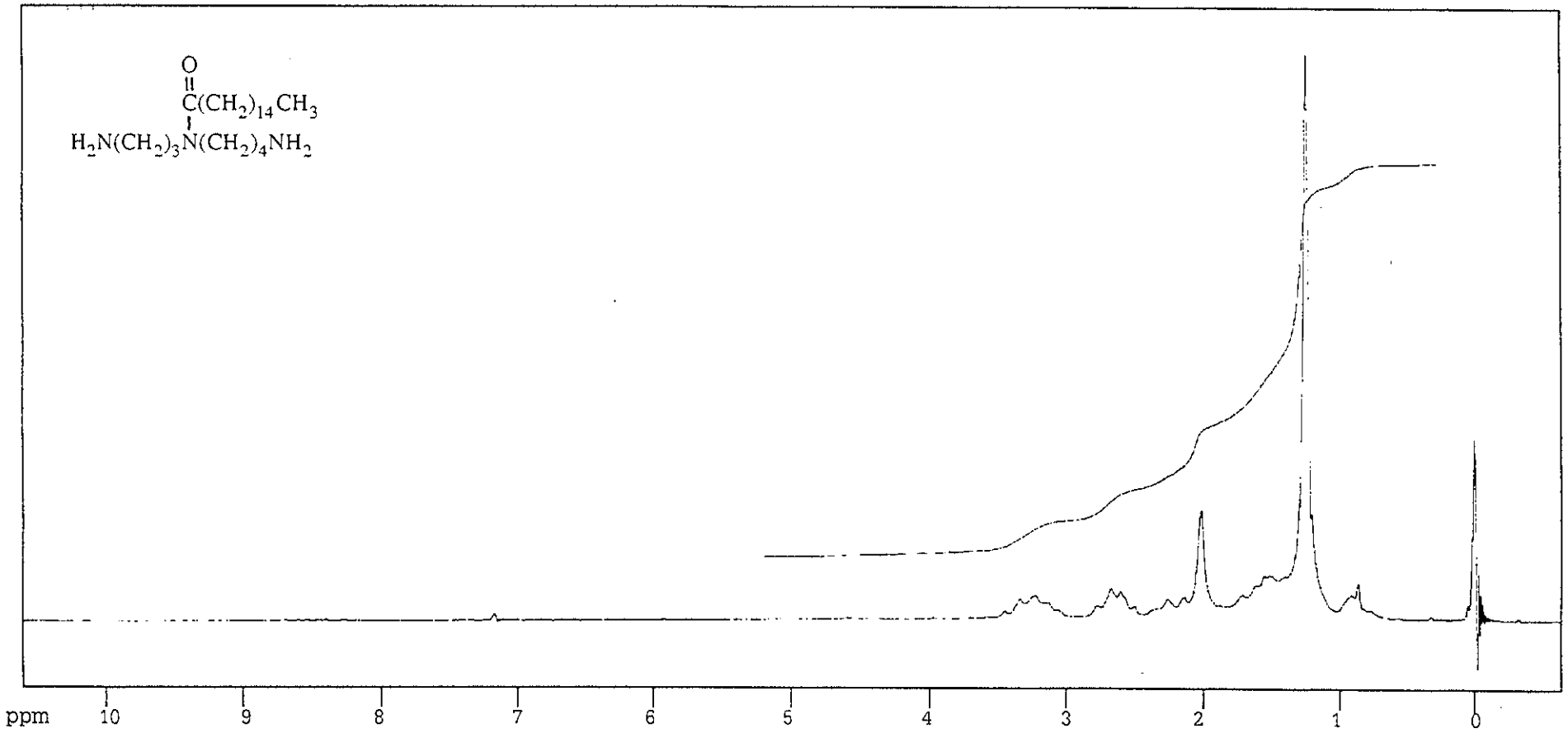


Figure 24 NMR spectrum of N^4-palimitoylspermidine (164).

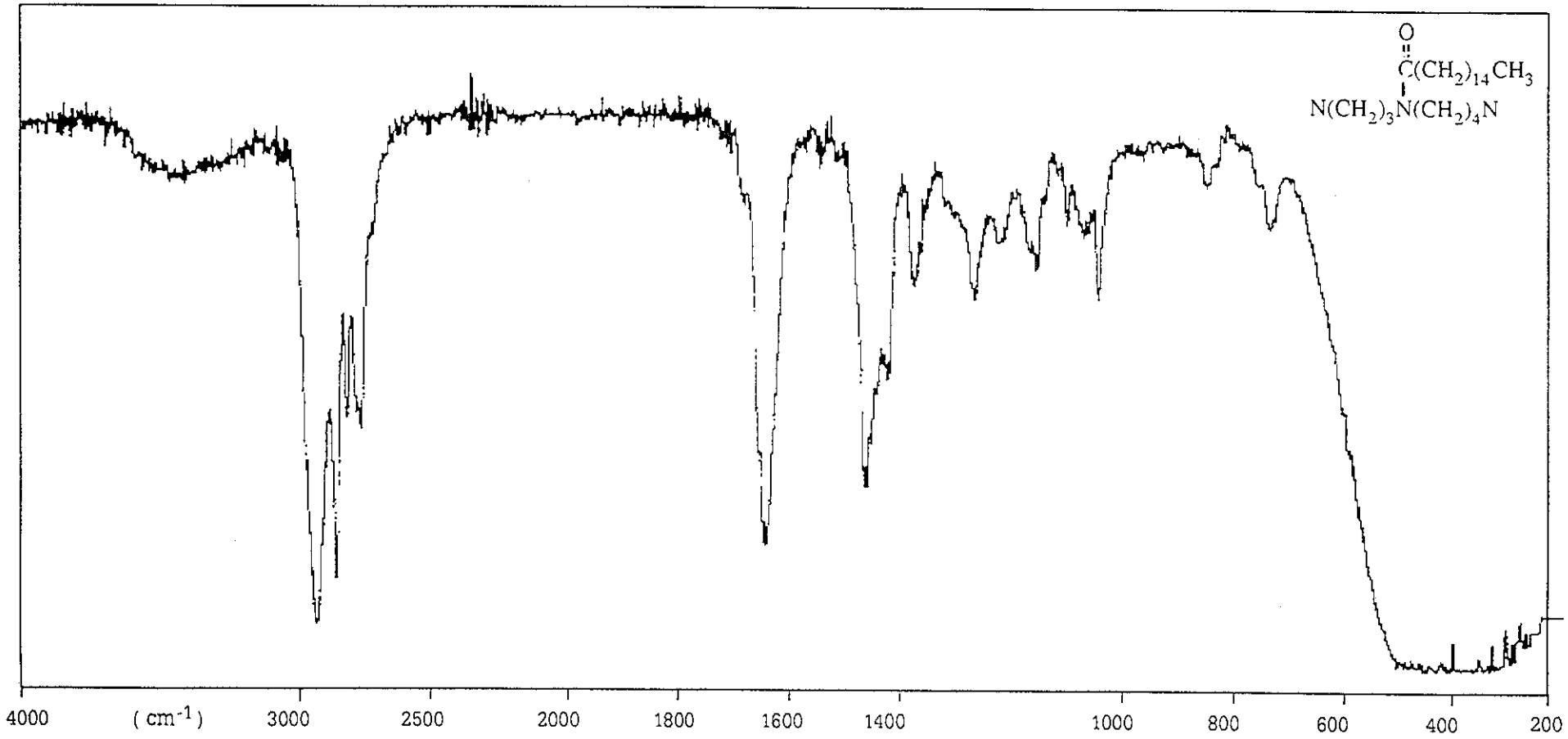


Figure 25 IR spectrum of solapalmitine homologue (165)

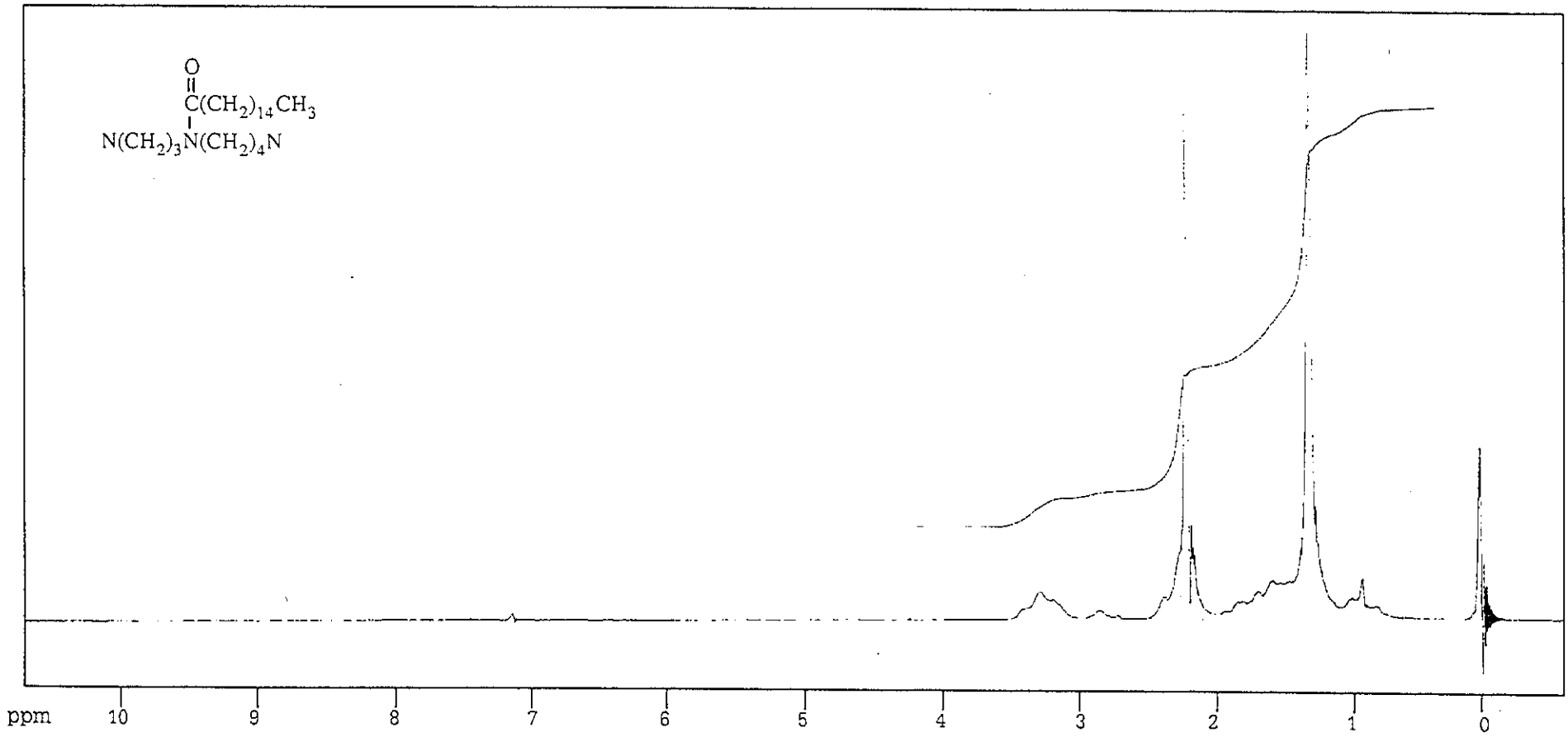


Figure 26 NMR spectrum of solapalmitine homologue (165)

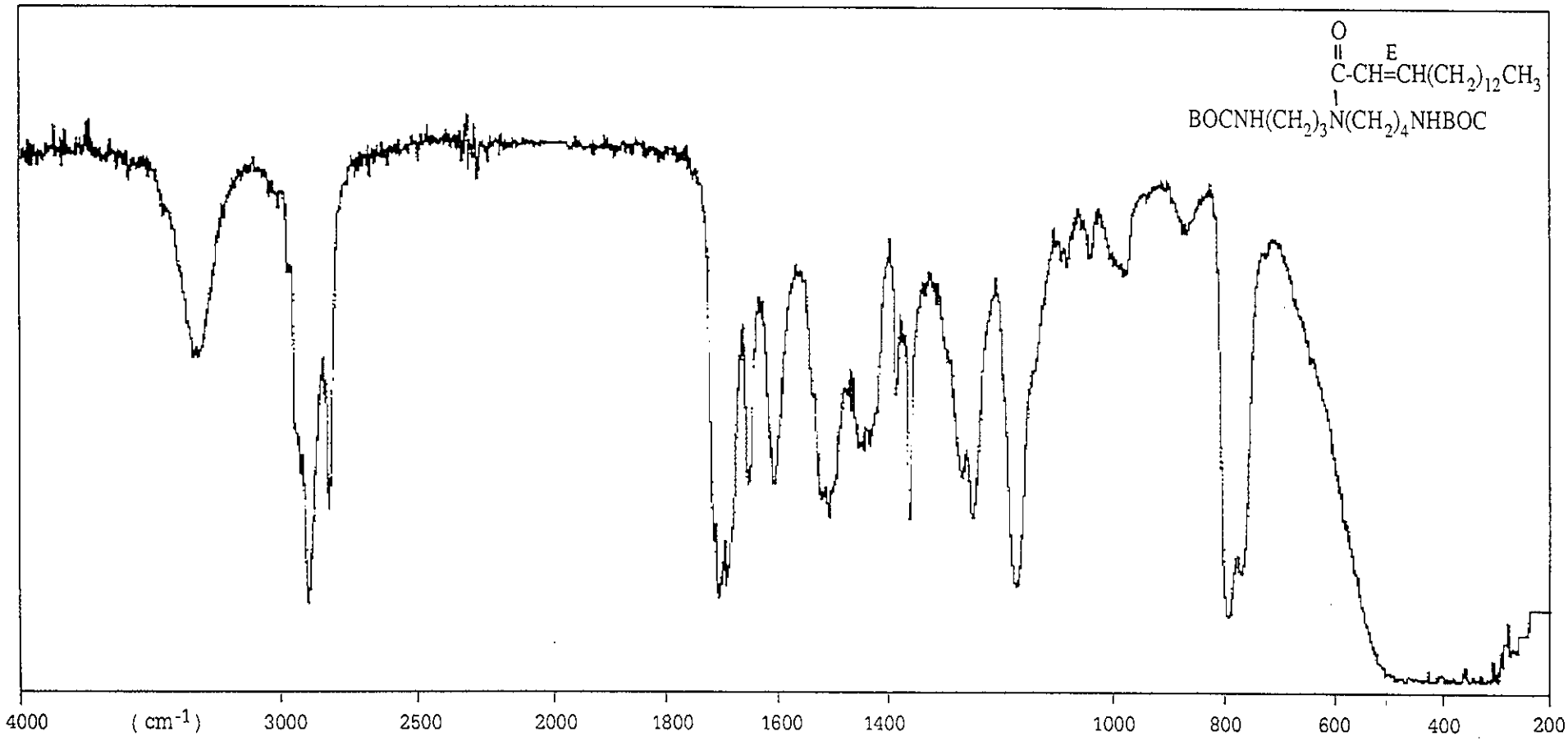


Figure 27 IR spectrum of N^1,N^8-di(*tert*-butyloxycarbonyl)-N^4-(*trans*-2-hexadecenoyl)spermidine (166)

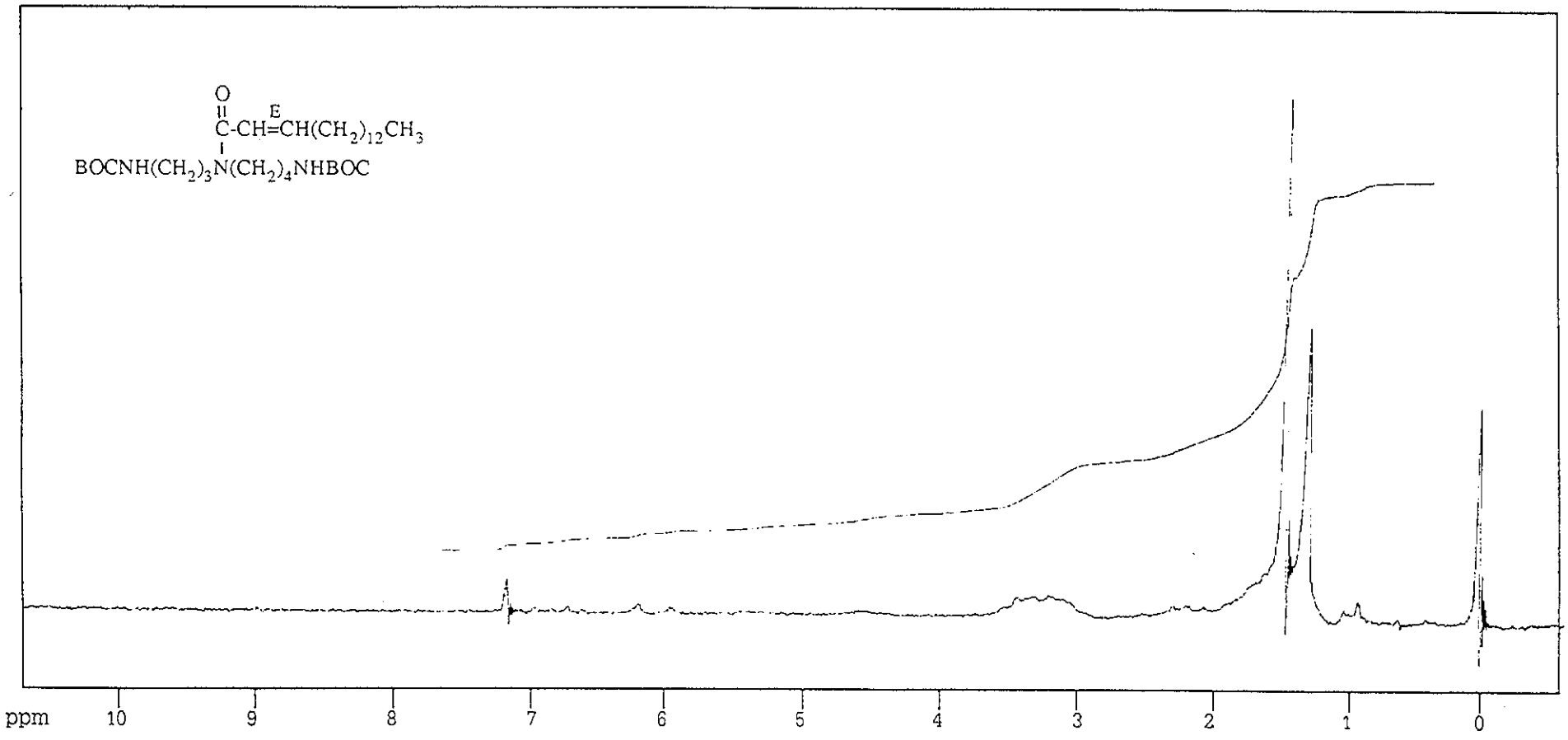


Figure 28 NMR spectrum of N^1,N^8-di(*tert*-butyloxycarbonyl)-N^4-(*trans*-2-hexadecenoyl)spermidine (166)

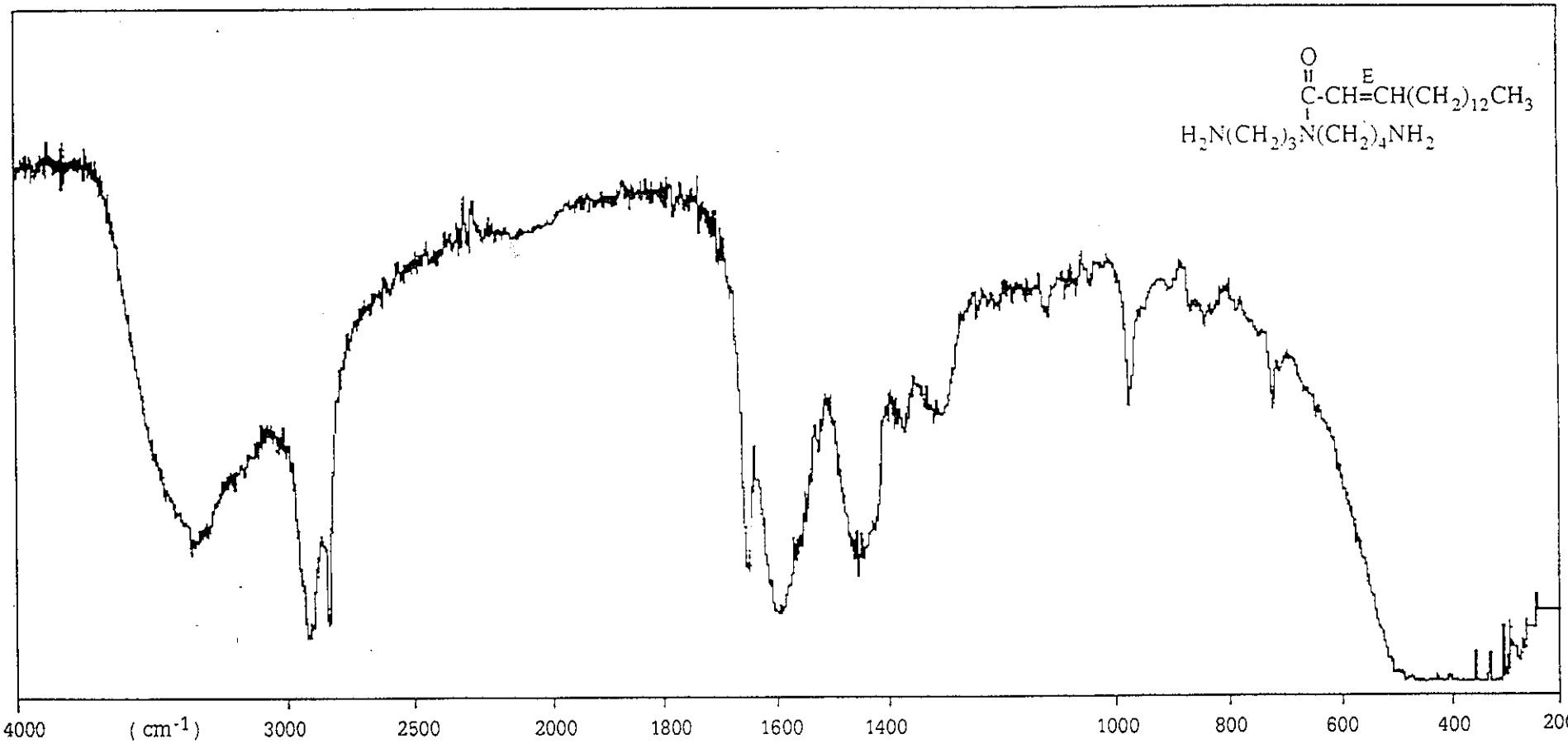


Figure 29 IR spectrum of N^4-*trans*-2-hexadecenoylspermidine (167)

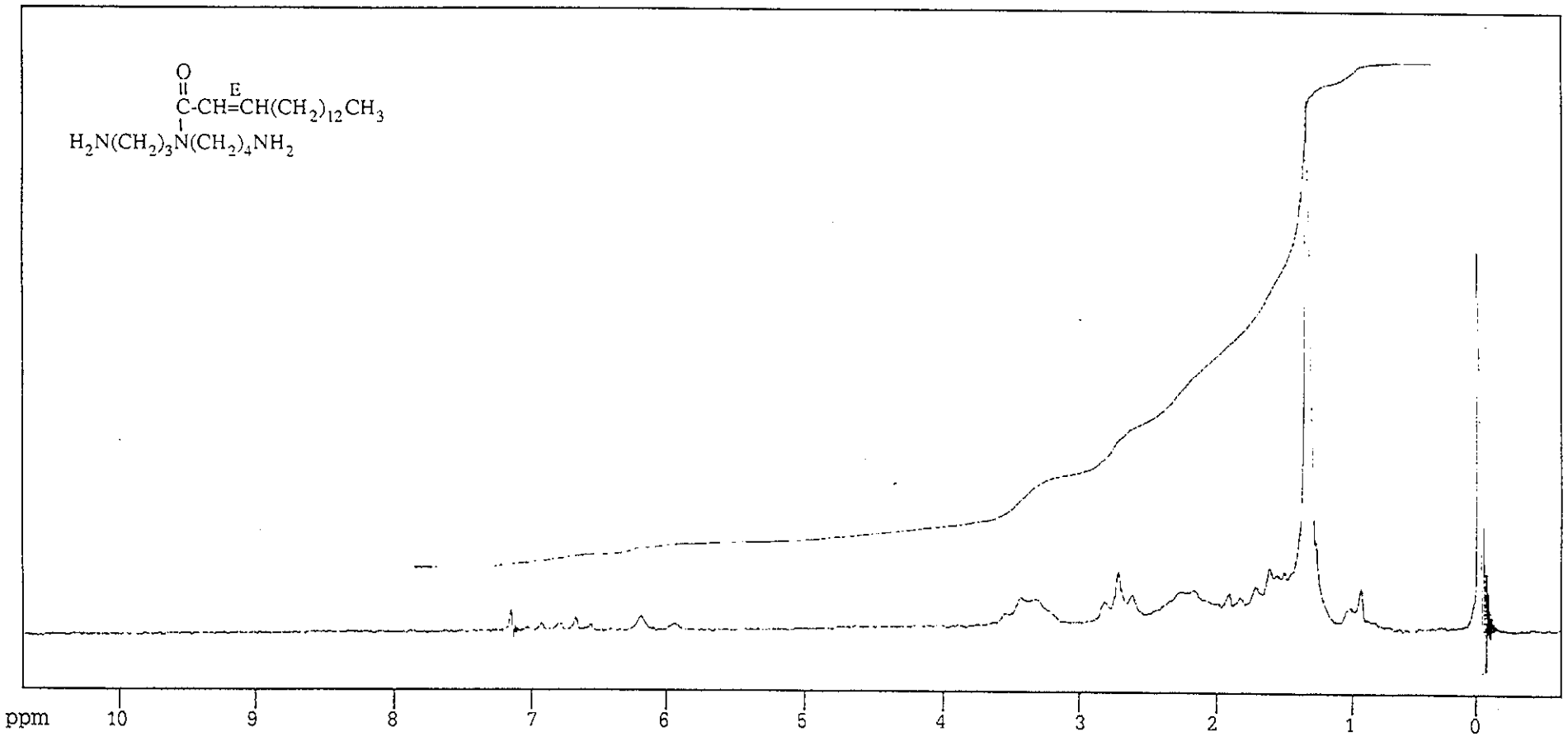


Figure 30 NMR spectrum of N^4-*trans*-2-hexadecenoylspermidine (167)

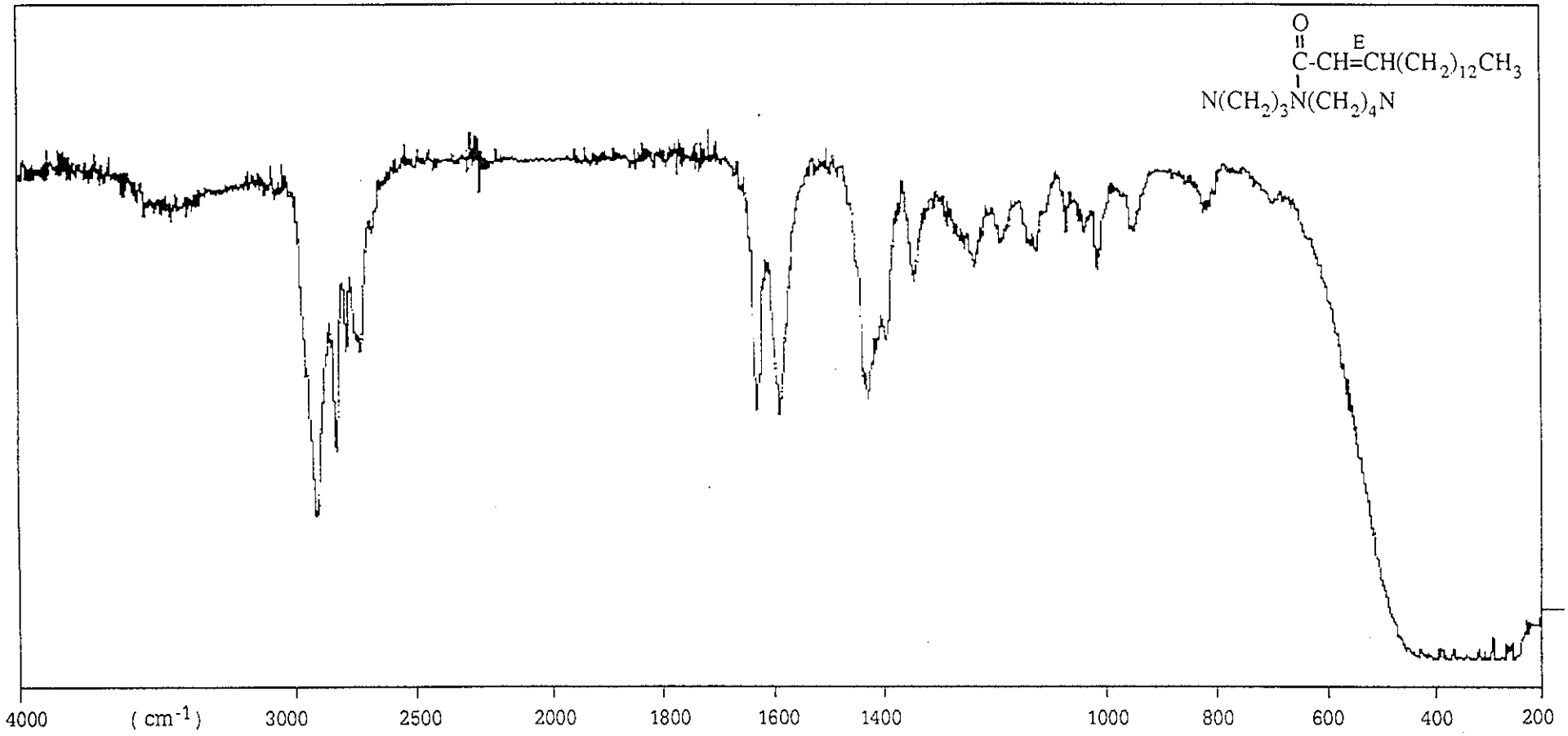


Figure 31 IR spectrum of solapalmitenine homologue (168)

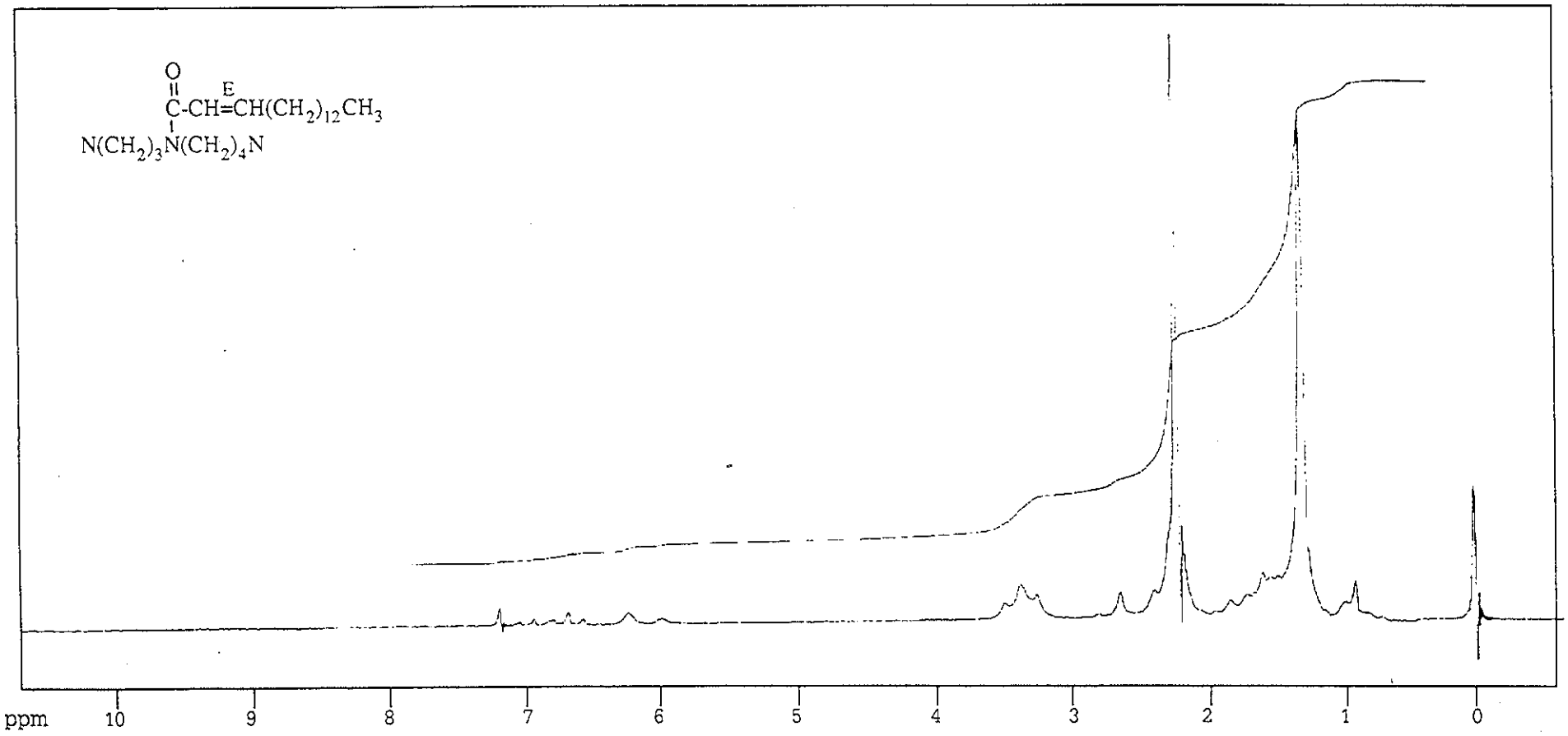


Figure 32 NMR spectrum of solapalmitenine homologue (168) .

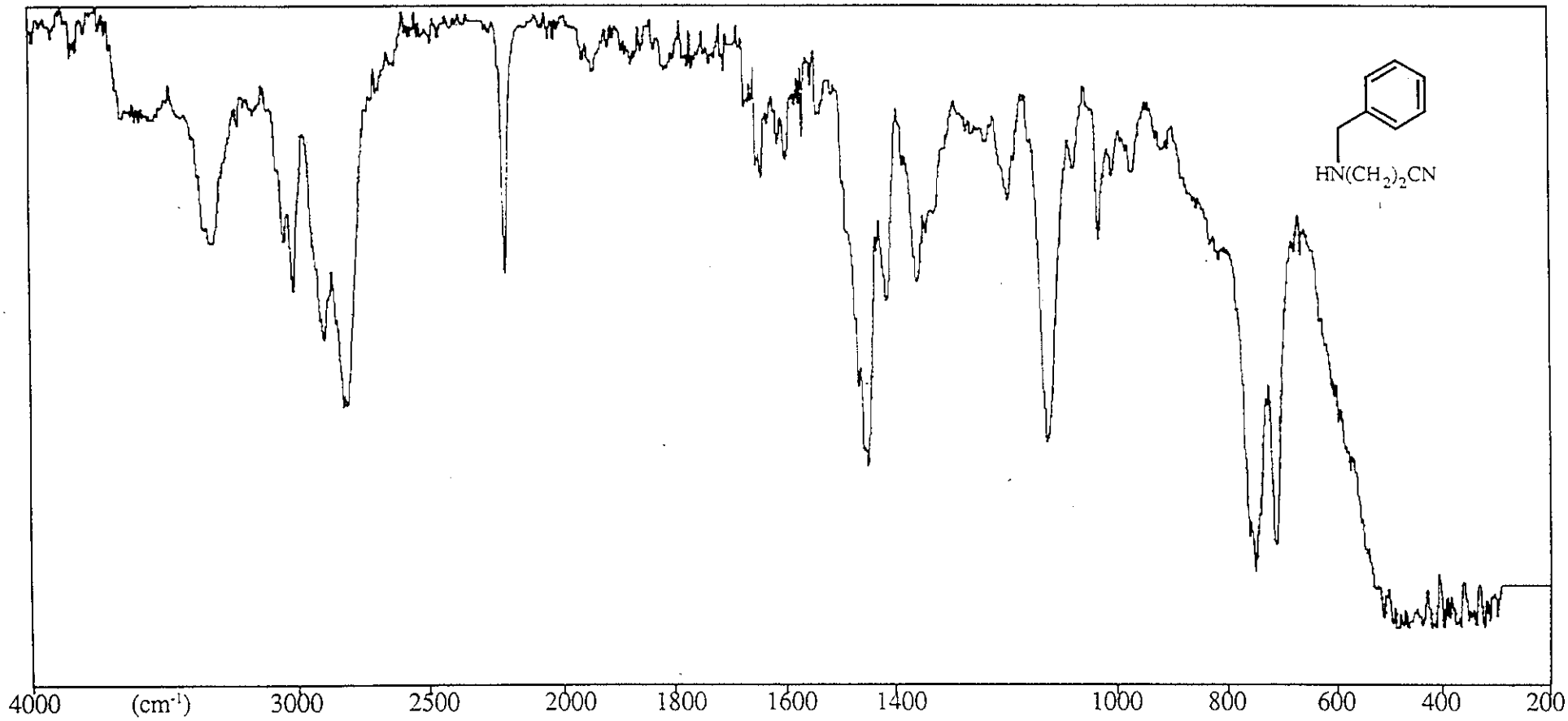


Figure 33 IR spectrum of N-(2-cyanoethyl)benzylamine (169)

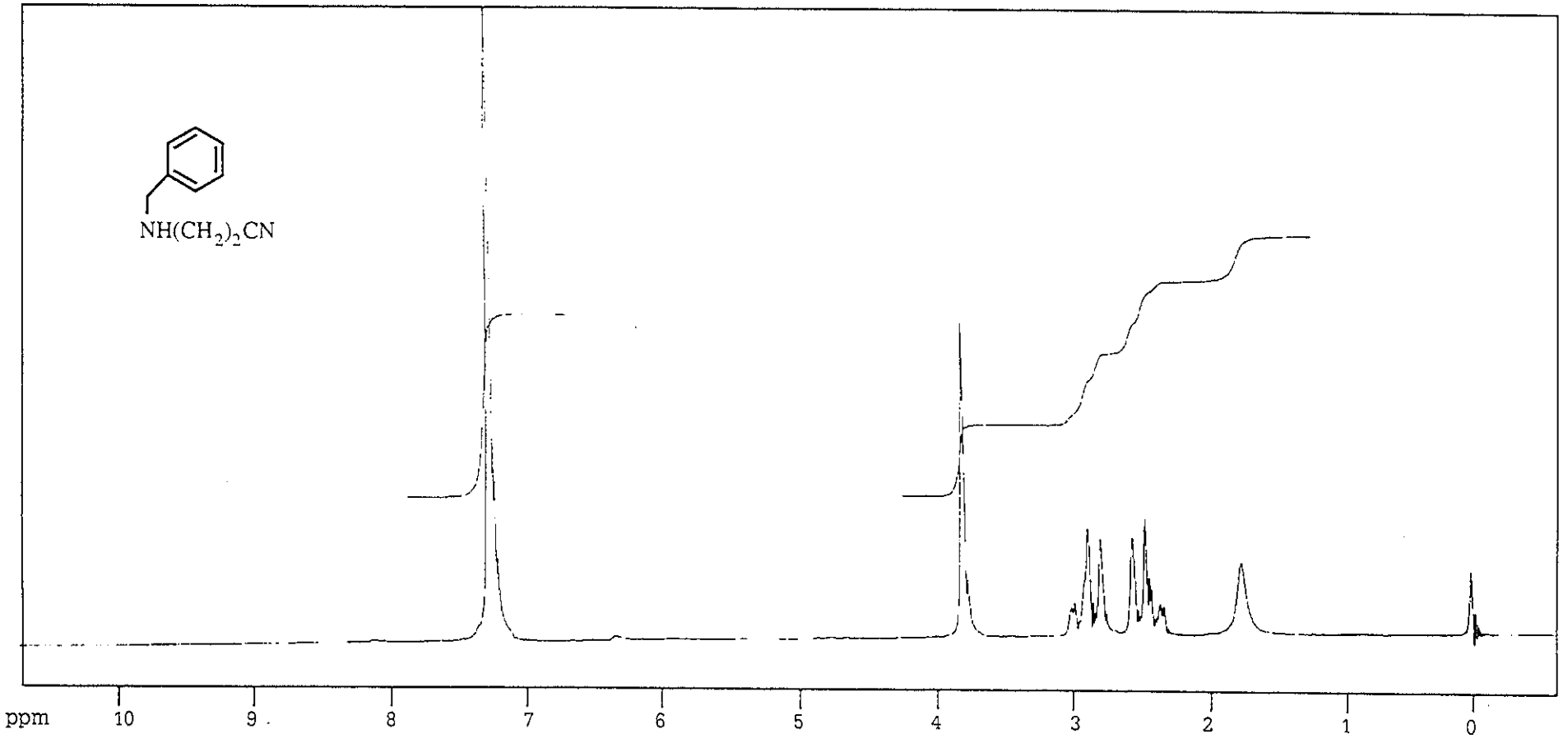


Figure 34 NMR spectrum of N-(2-cyanoethyl)benzylamine (169)

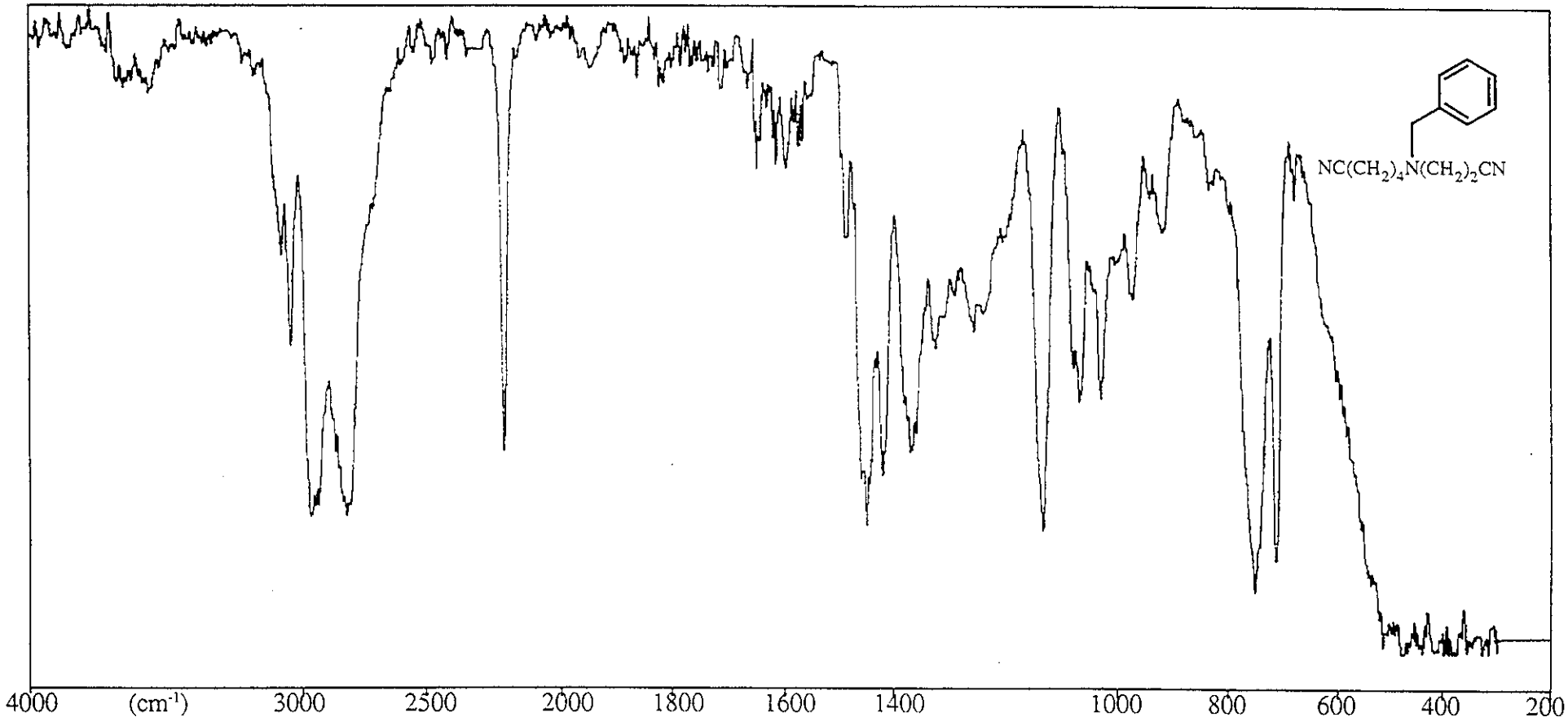


Figure 35 IR spectrum of N-(2-cyanoethyl)-N-(4-cyanobutyl)benzylamine (170)

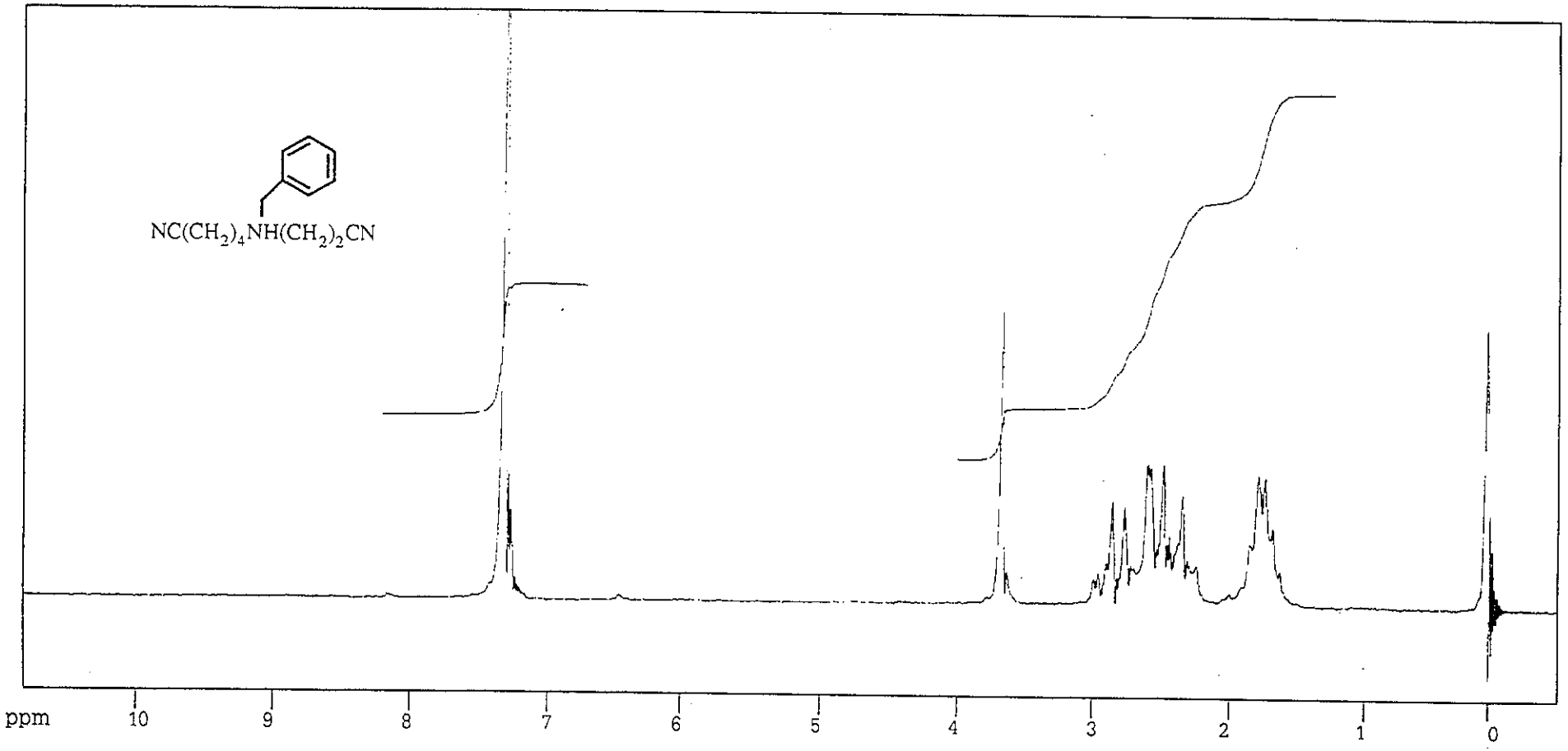


Figure 36 NMR spectrum of N-(2-cyanoethyl)-N-(4-cyanobutyl)benzylamine (170)

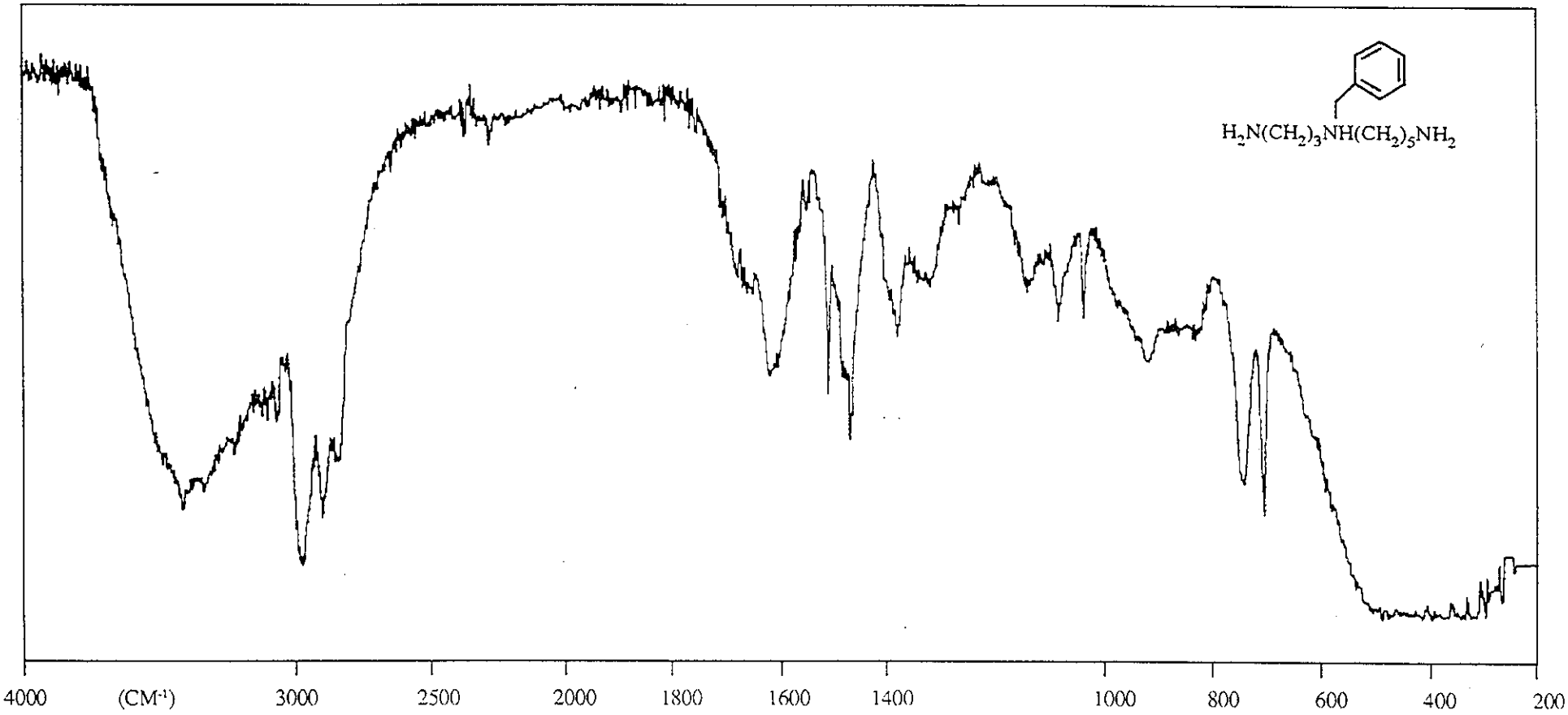


Figure 37 IR spectrum of N^5-benzylhomospermidine (171)

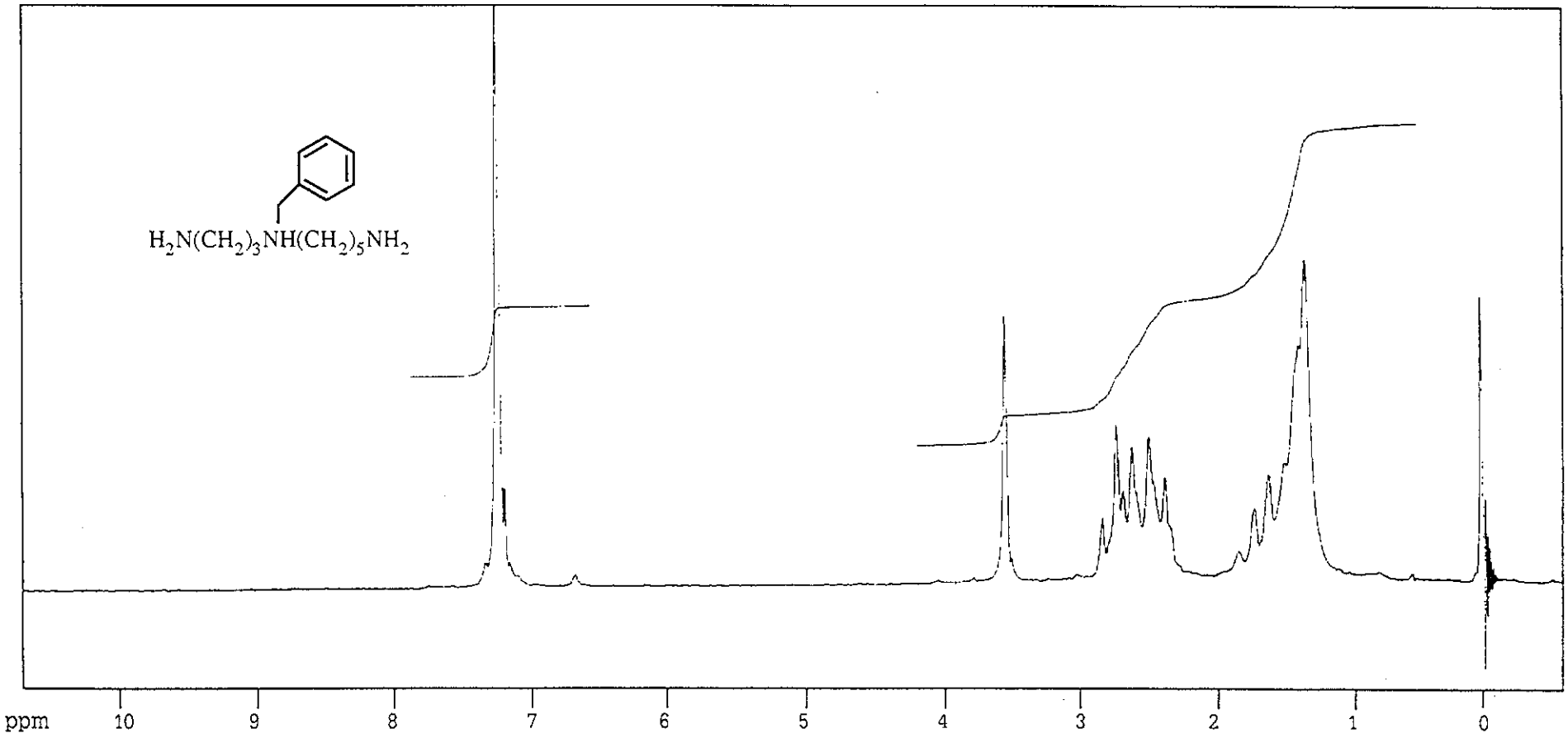


Figure 38 NMR spectrum of N^5-benzylhomospermidine (171)

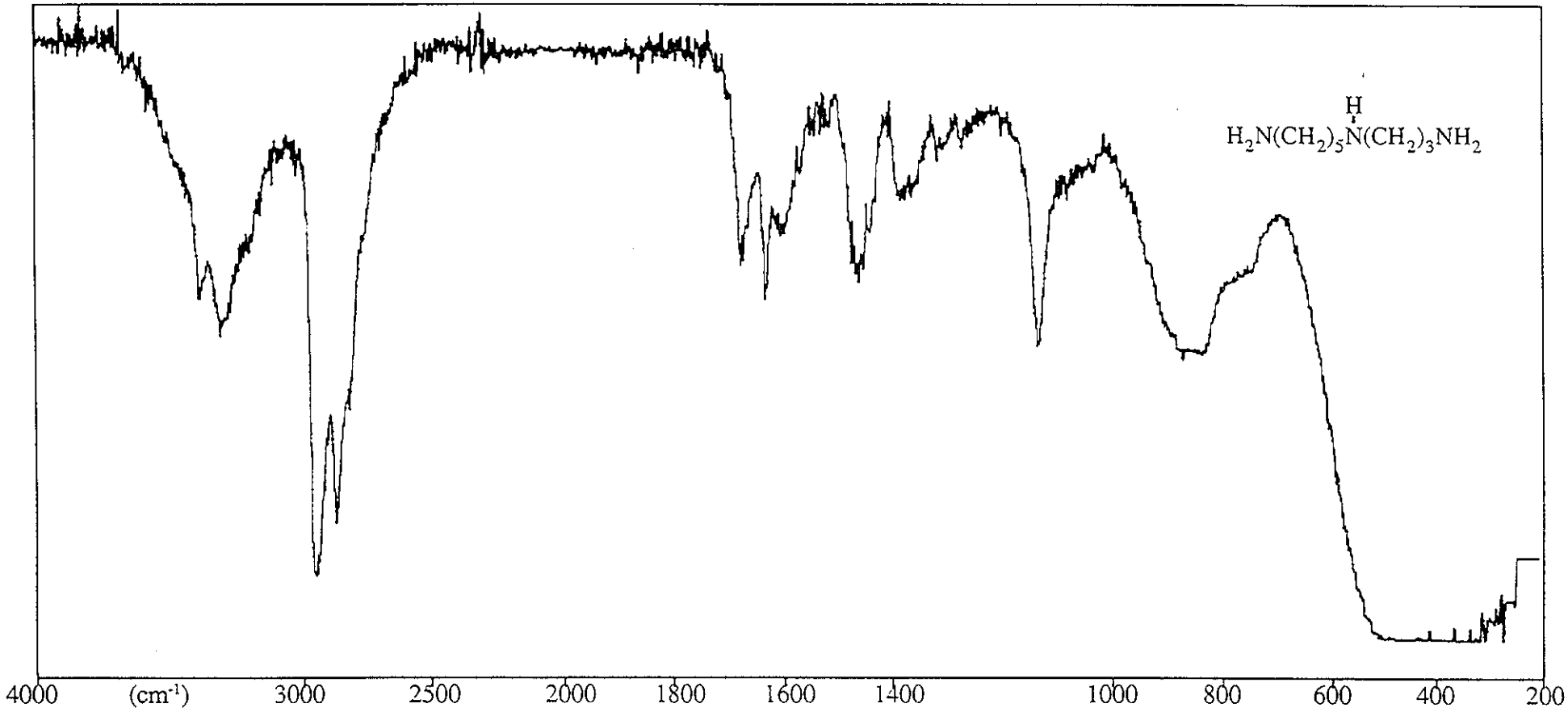


Figure 39 IR spectrum of unsymmetrical homospermidine (67)

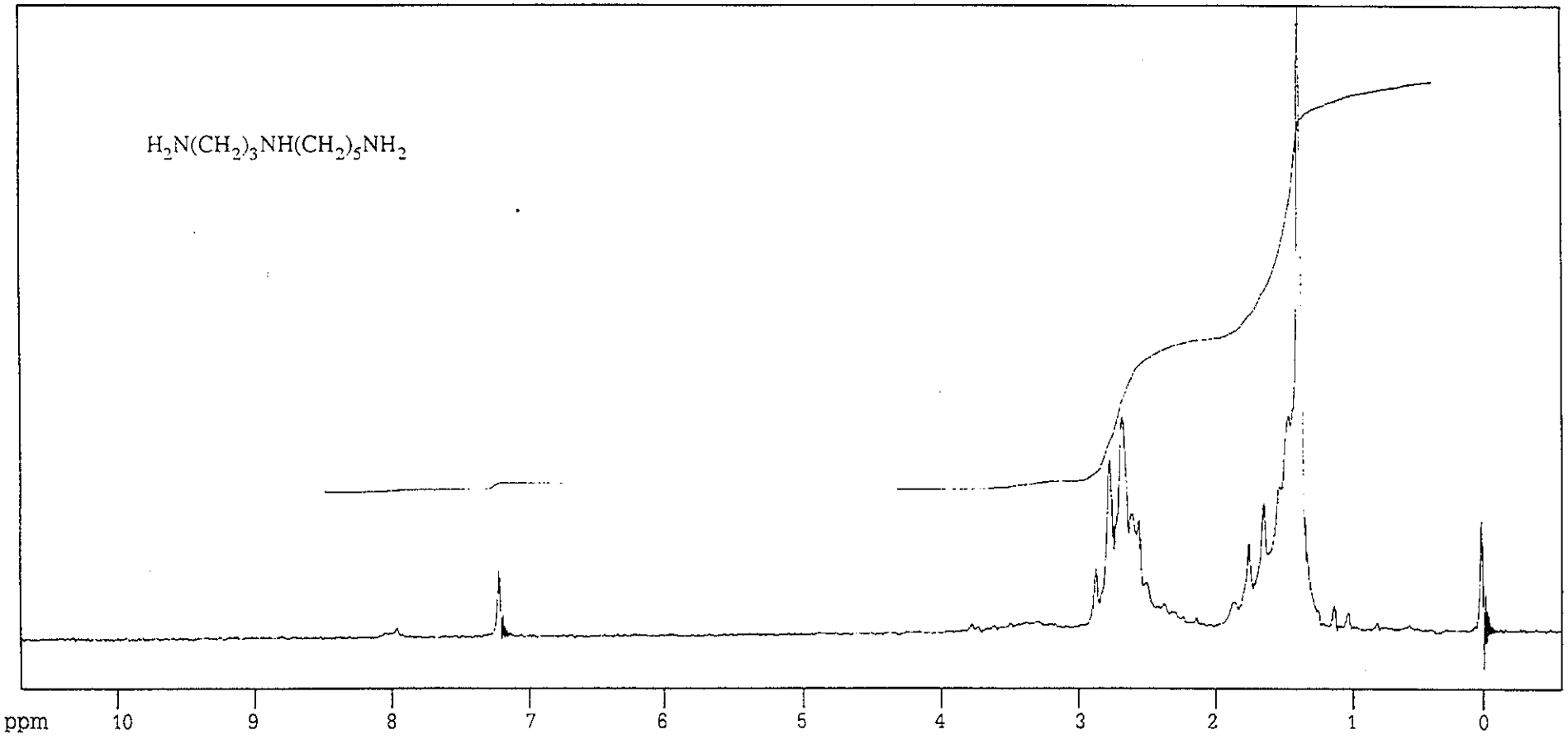


Figure 40 NMR spectrum of unsymmetrical homospermidine (67)

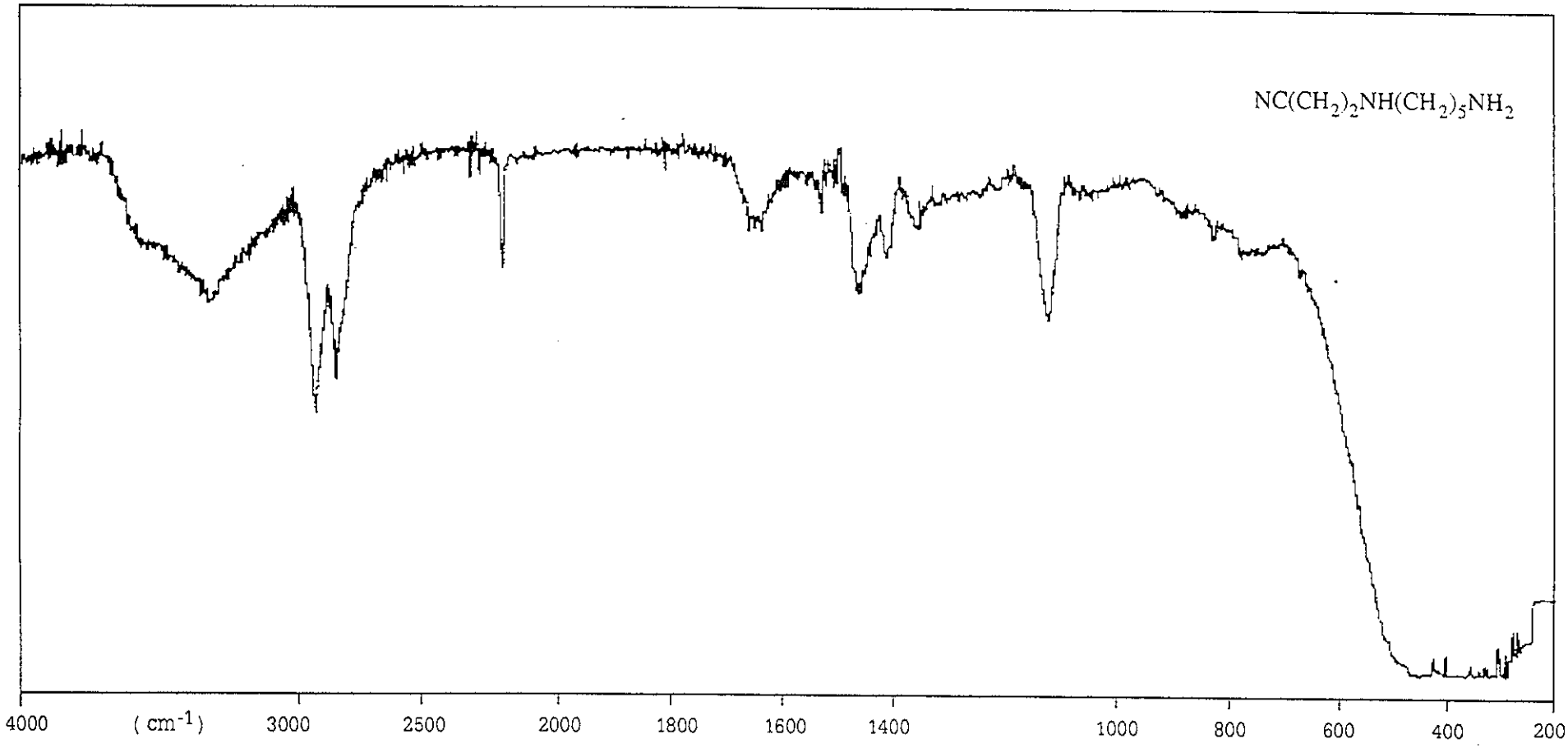


Figure 41 IR spectrum of 3-[(5-aminobutyl)amino]propanenitrile (173)

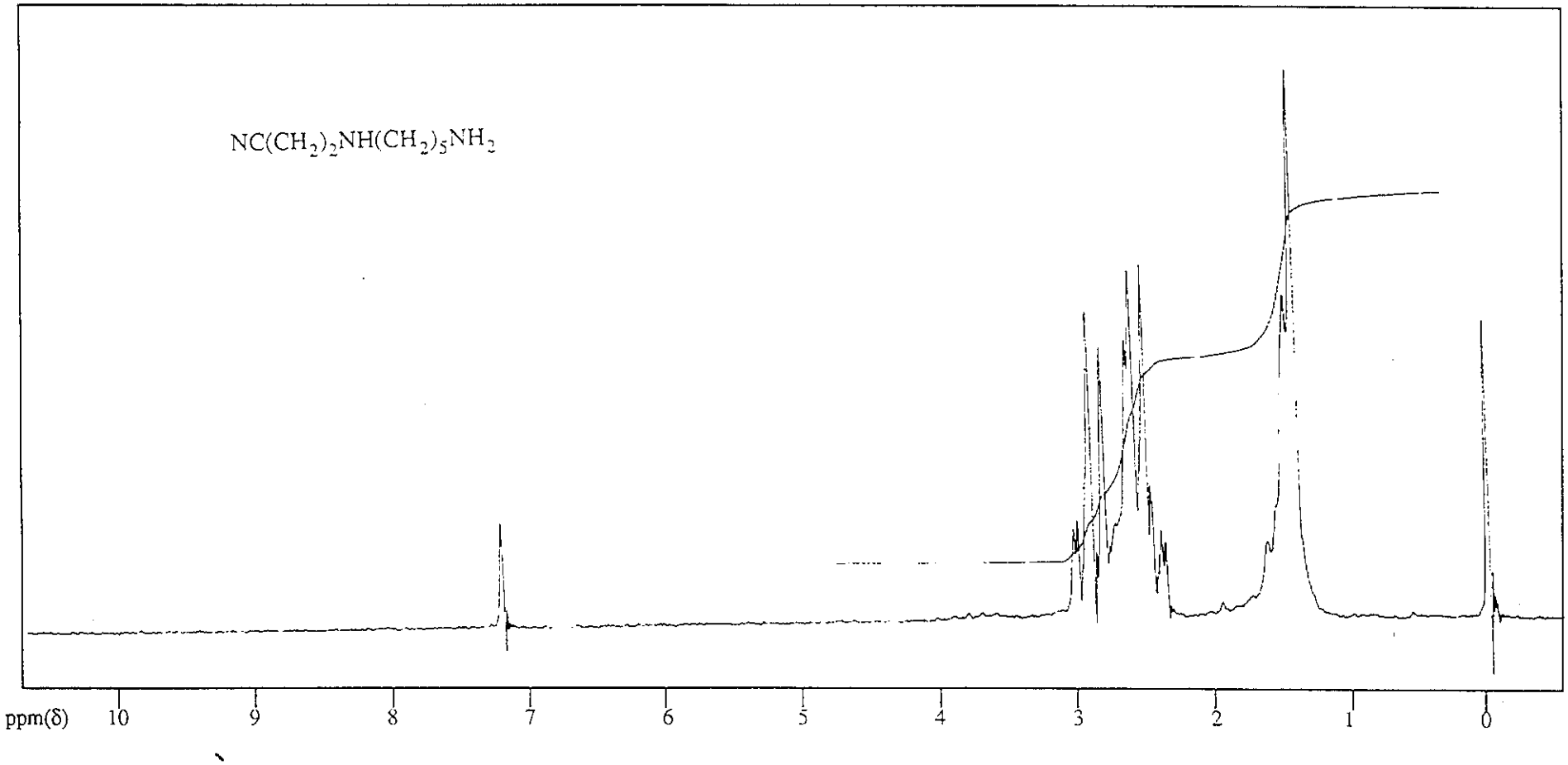


Figure 42 NMR spectrum of 3-[(5-aminobutyl)amino]propanenitrile (173).

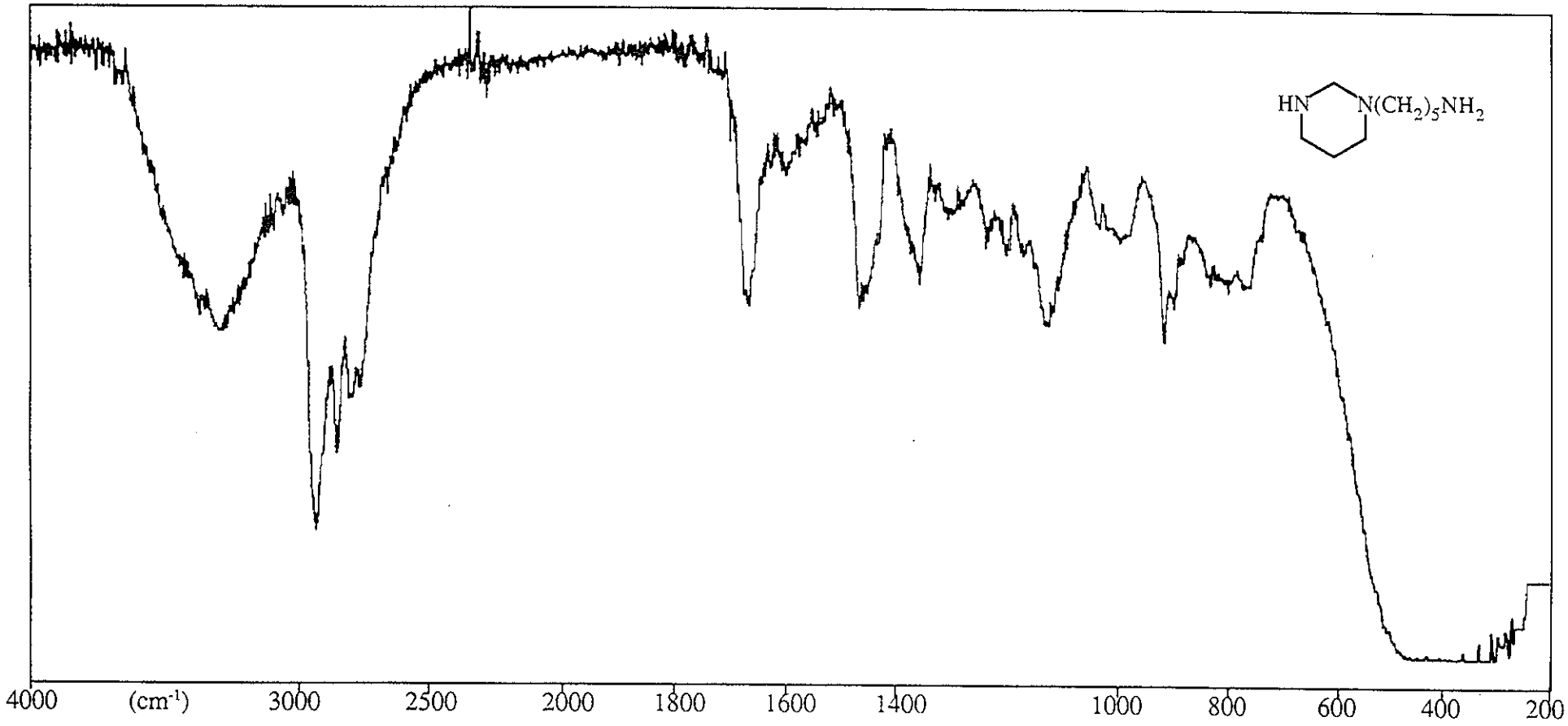


Figure 43 IR spectrum of hexahydropyrimidine (174)

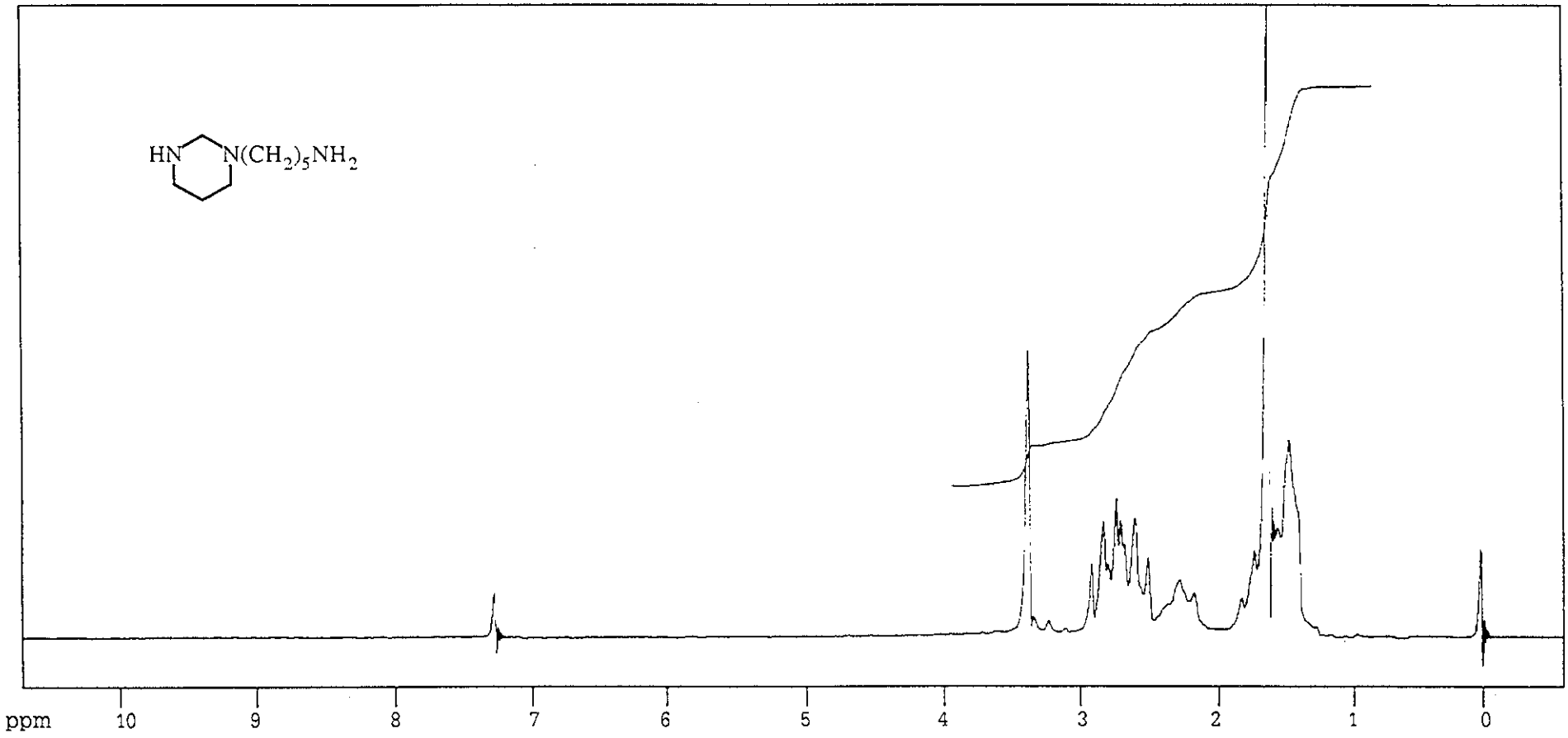


Figure 44 NMR spectrum of hexahydropyrimidine (174)

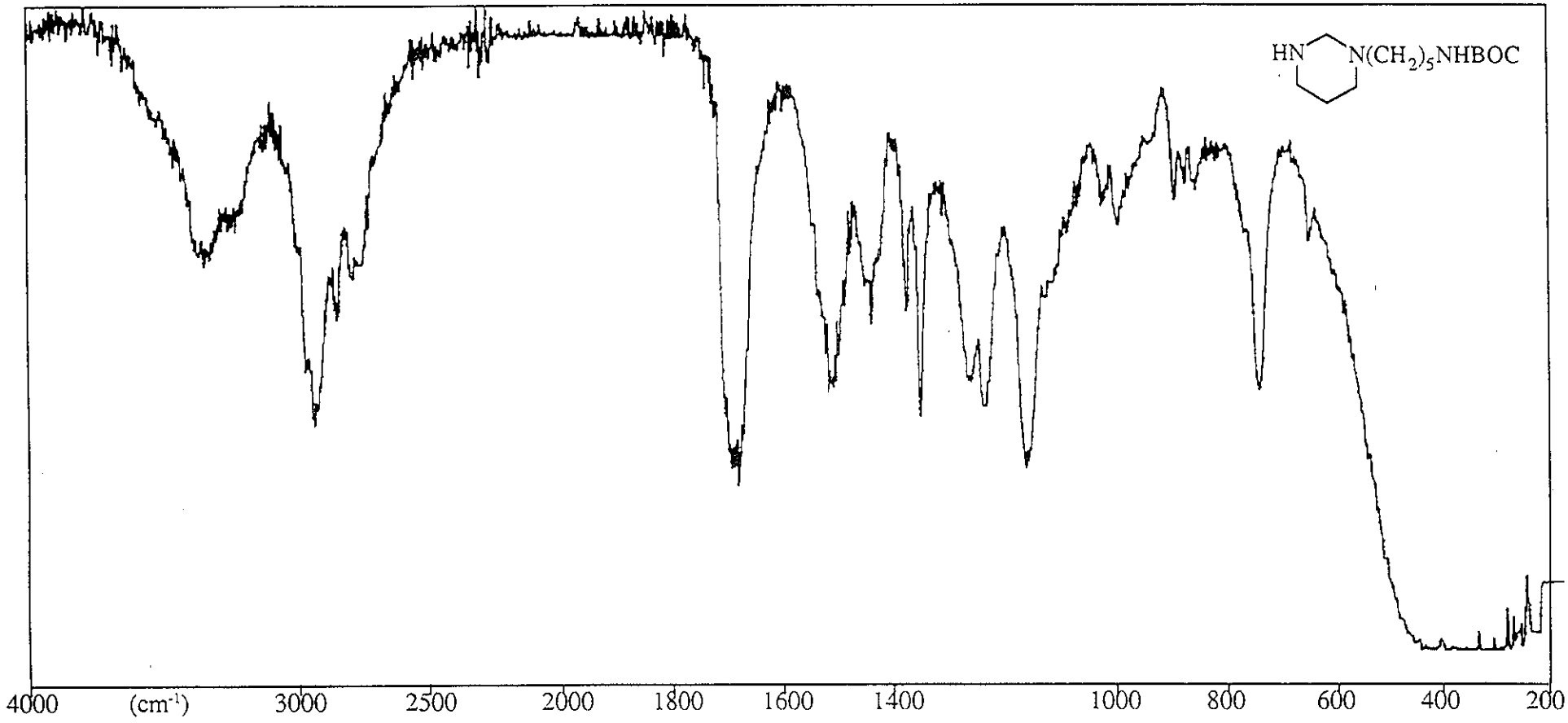


Figure 45 IR spectrum of N^9-(*tert*-butyloxycarbonyl)hexahydropyrimidine (175)

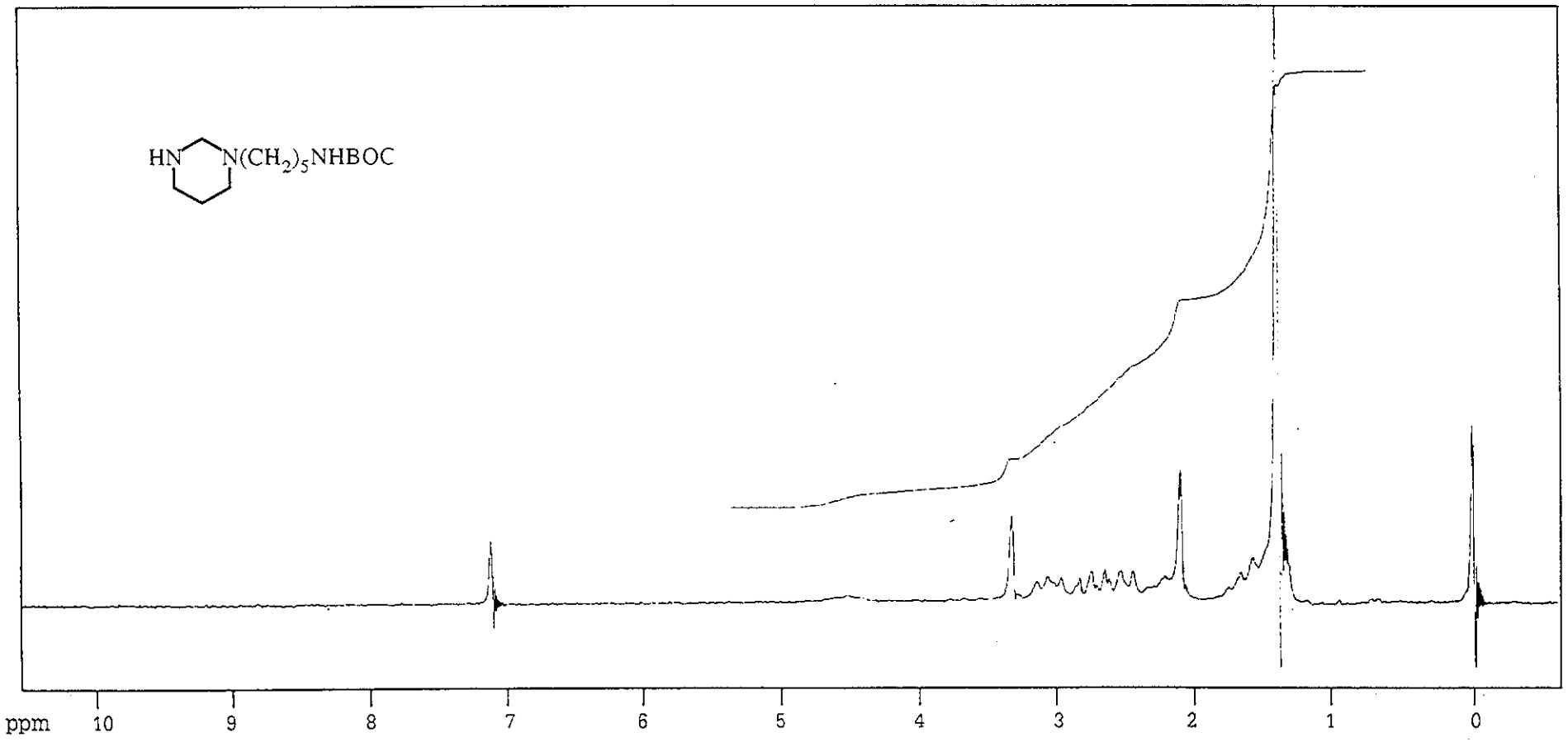


Figure 46 NMR spectrum of N^9-(*tert*-butyloxycarbonyl)hexahydropyrimidine (175)

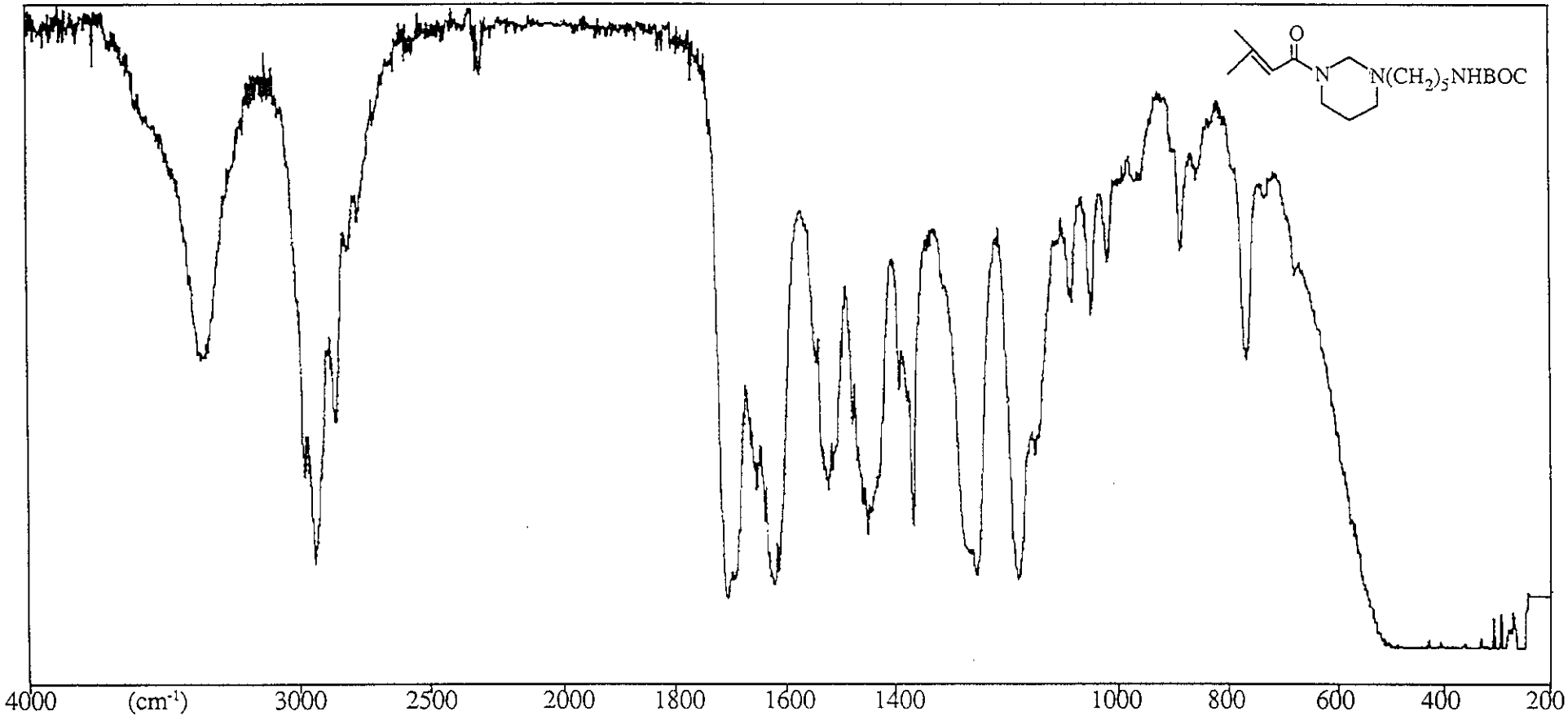


Figure 47 IR spectrum of N^1-(3-methylbut-2-enamido)-N^9-(*tert*-butyloxycarbonyl)hexahydropyrimidine (177)

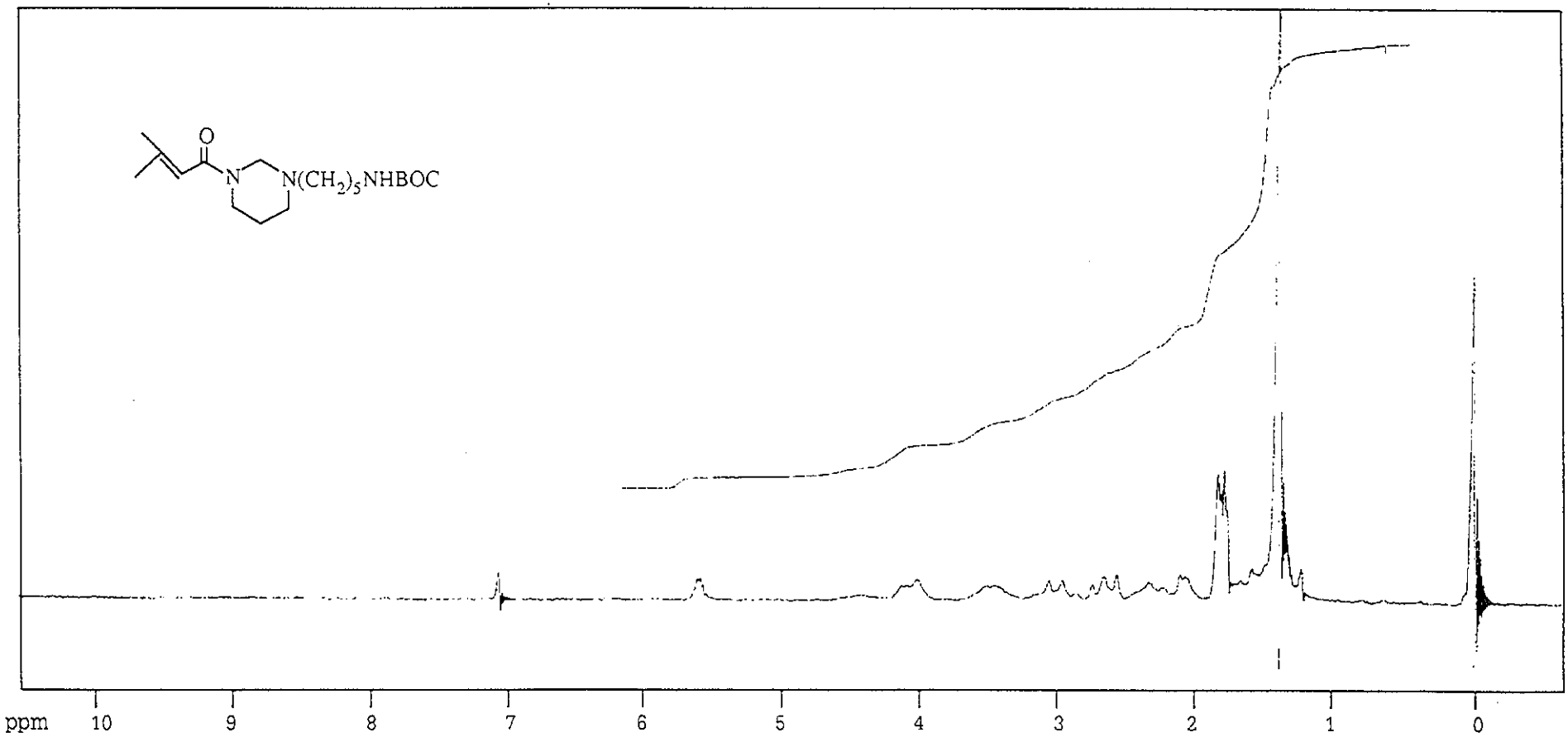


Figure 48 NMR spectrum of N^1-(3-methylbut-2-enamido)-N^9-(*tert*-butyloxycarbonyl)hexahydropyrimidine (177)

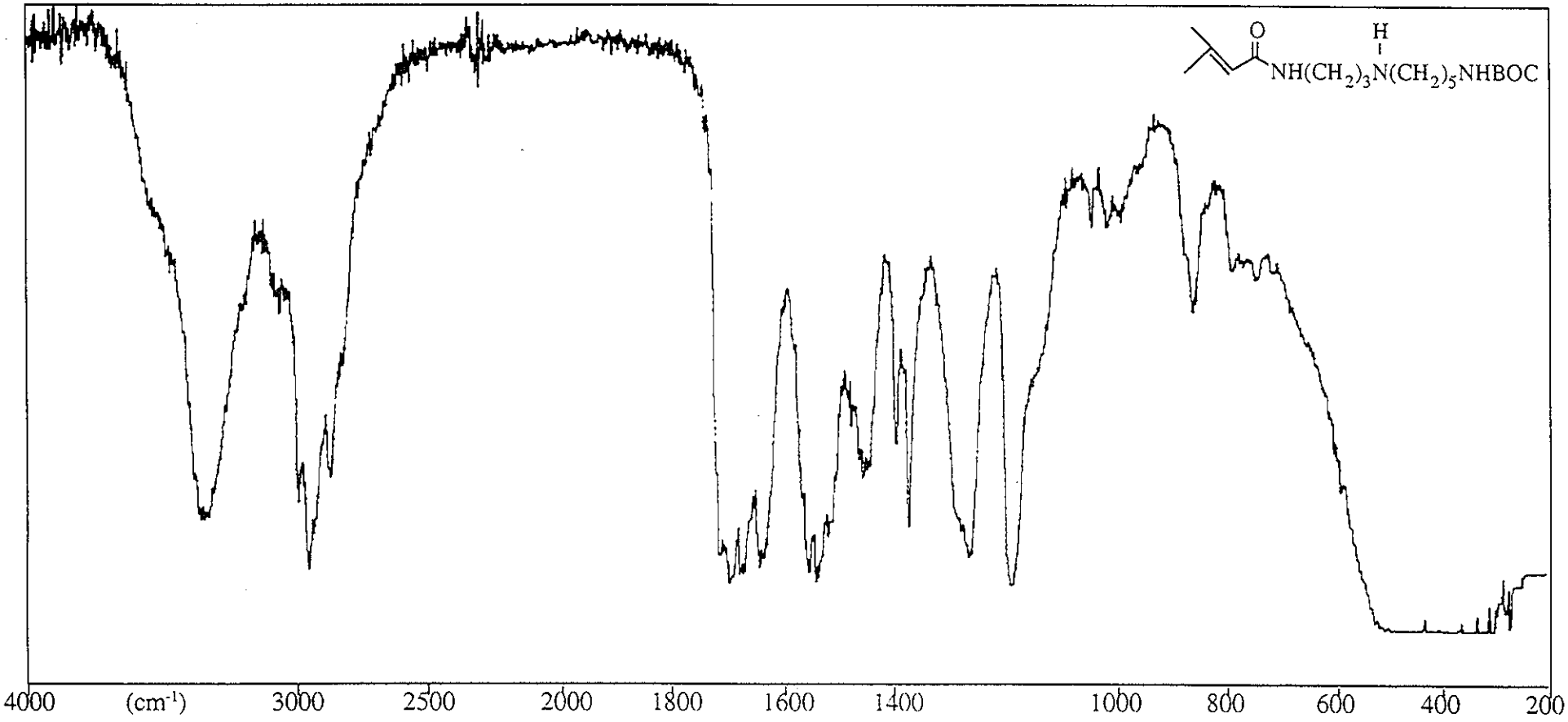


Figure 49 IR spectrum of N-(*tert*-butyloxycarbonyl)-N^1-[3-(3-methylbut-2-enamido)propyl]-1, 5-diaminopentane (178)

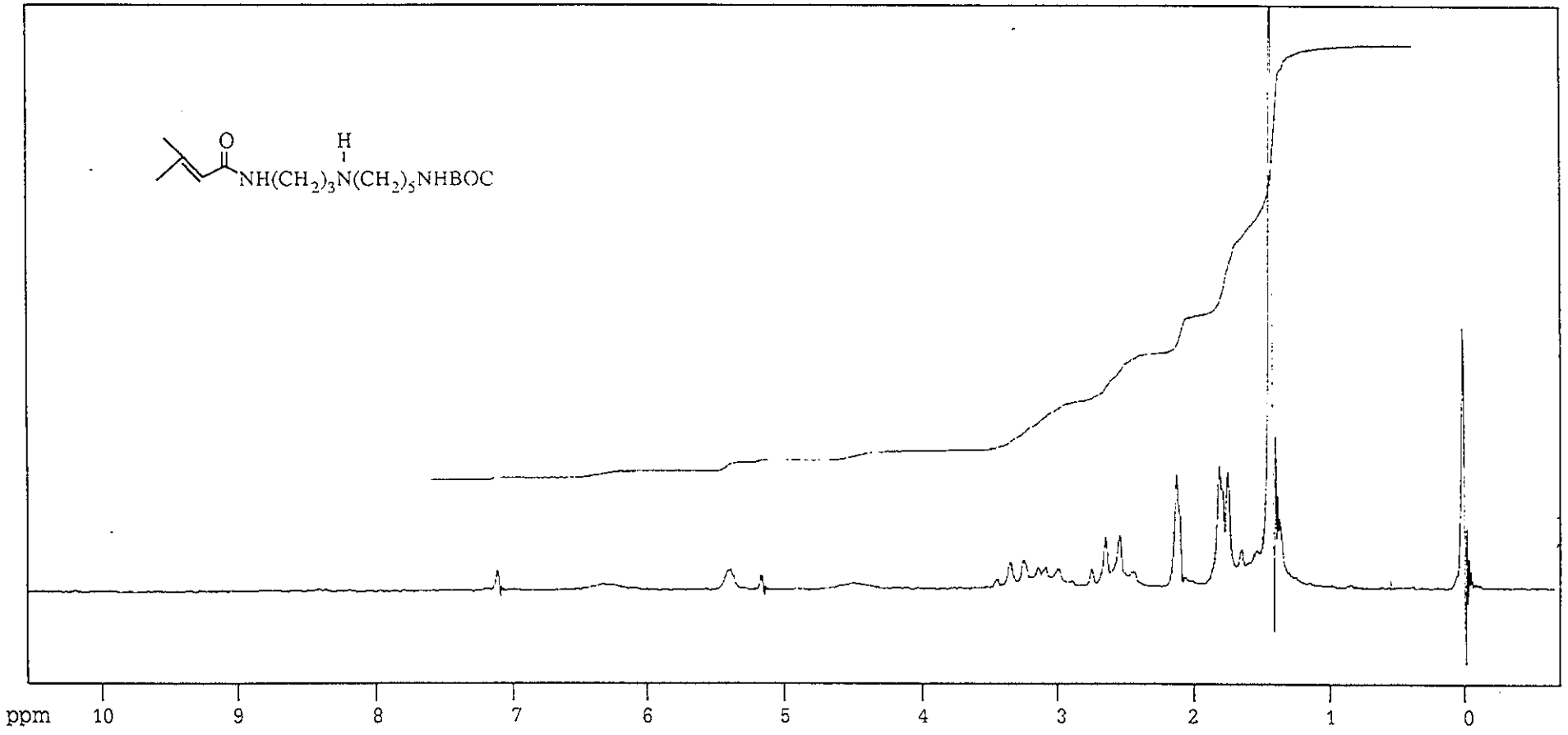


Figure 50 NMR spectrum of N-(*tert*-Butyloxycarbonyl)-N^1-[3-(3-methylbut-2-enamido)propyl]-1, 5-diaminopentane (178)

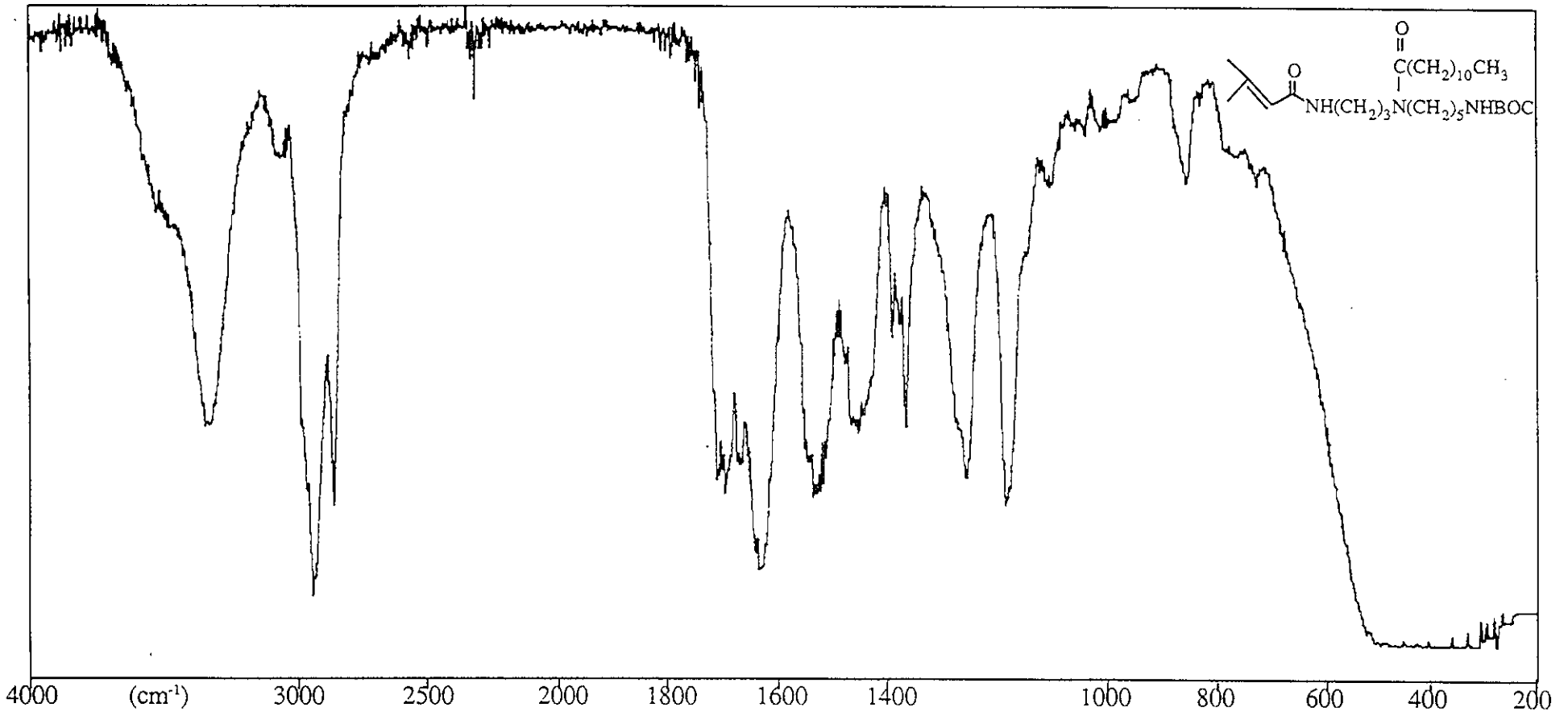


Figure 51 IR spectrum of N-[5-(*tert*-butyloxycarbonylamino)pentyl]-N-[3-(3-metylbut-2-enamido)propyl] dodecanamide (179)

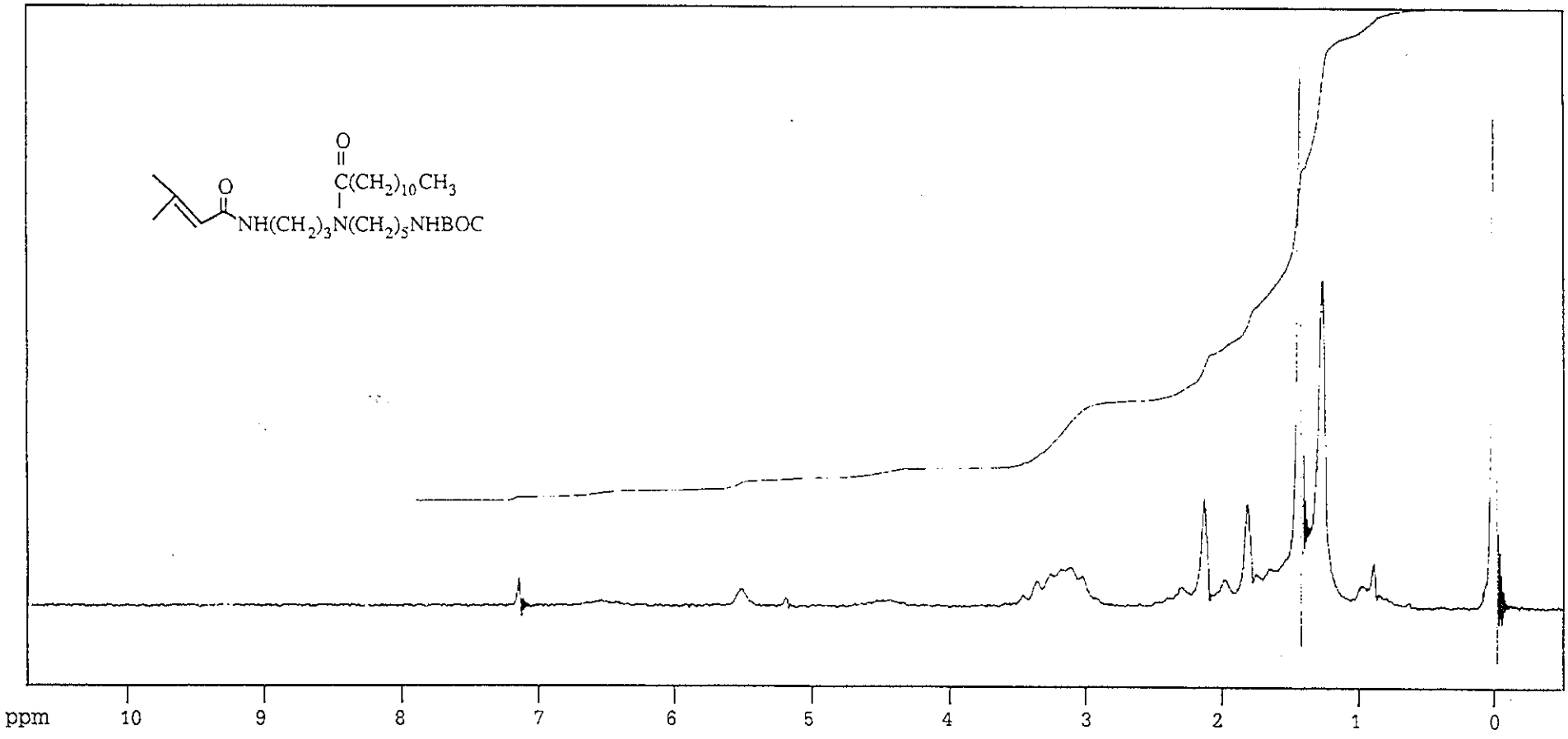


Figure 52 NMR spectrum of N-[5-(*tert*-butyloxycarbonylamino)pentyl]-N-[3-(3-metylbut-2-enamido)propyl] dodecanamide (179)

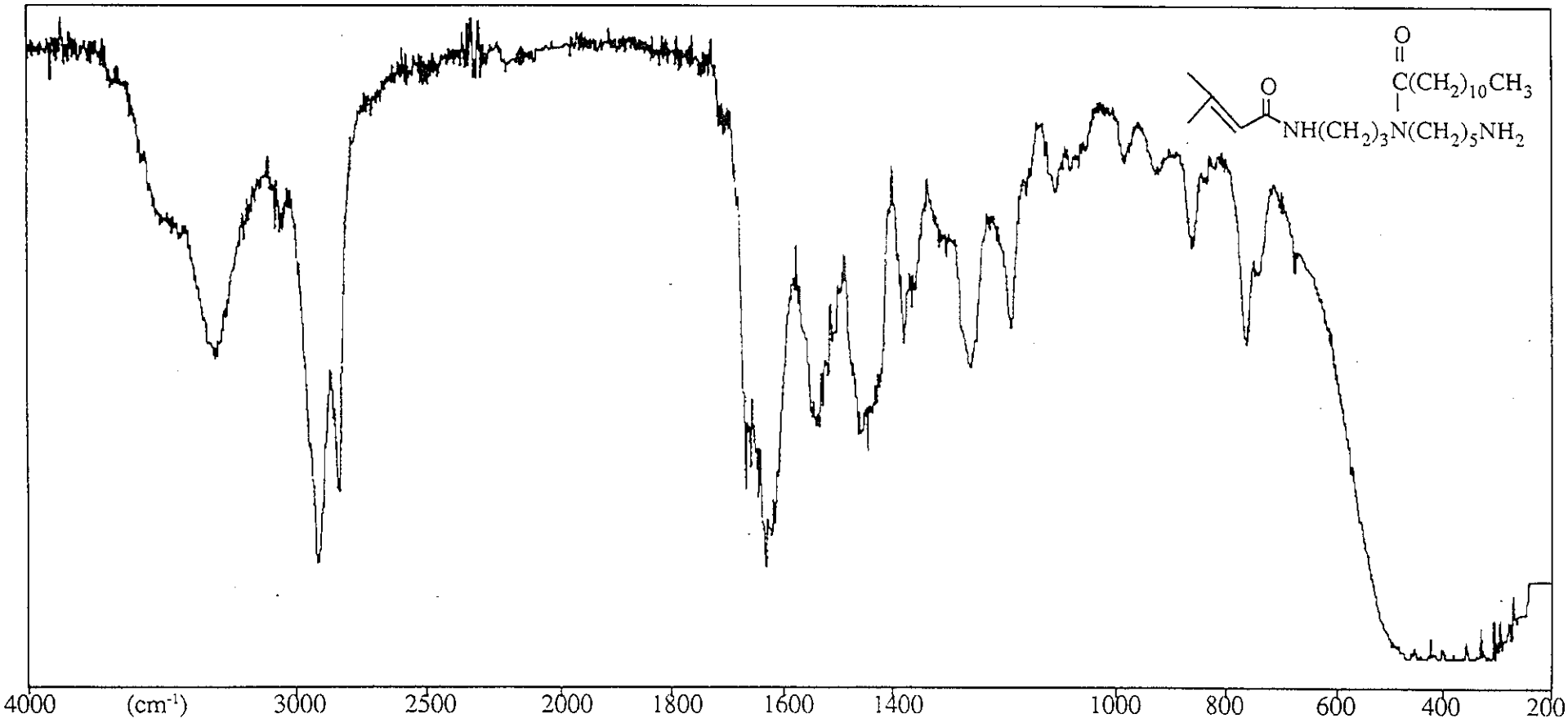


Figure 53 IR spectrum of N-(5-aminopentyl)-N-[3-(3-metylbut-2-enamido)propyl]dodecanamide (180)

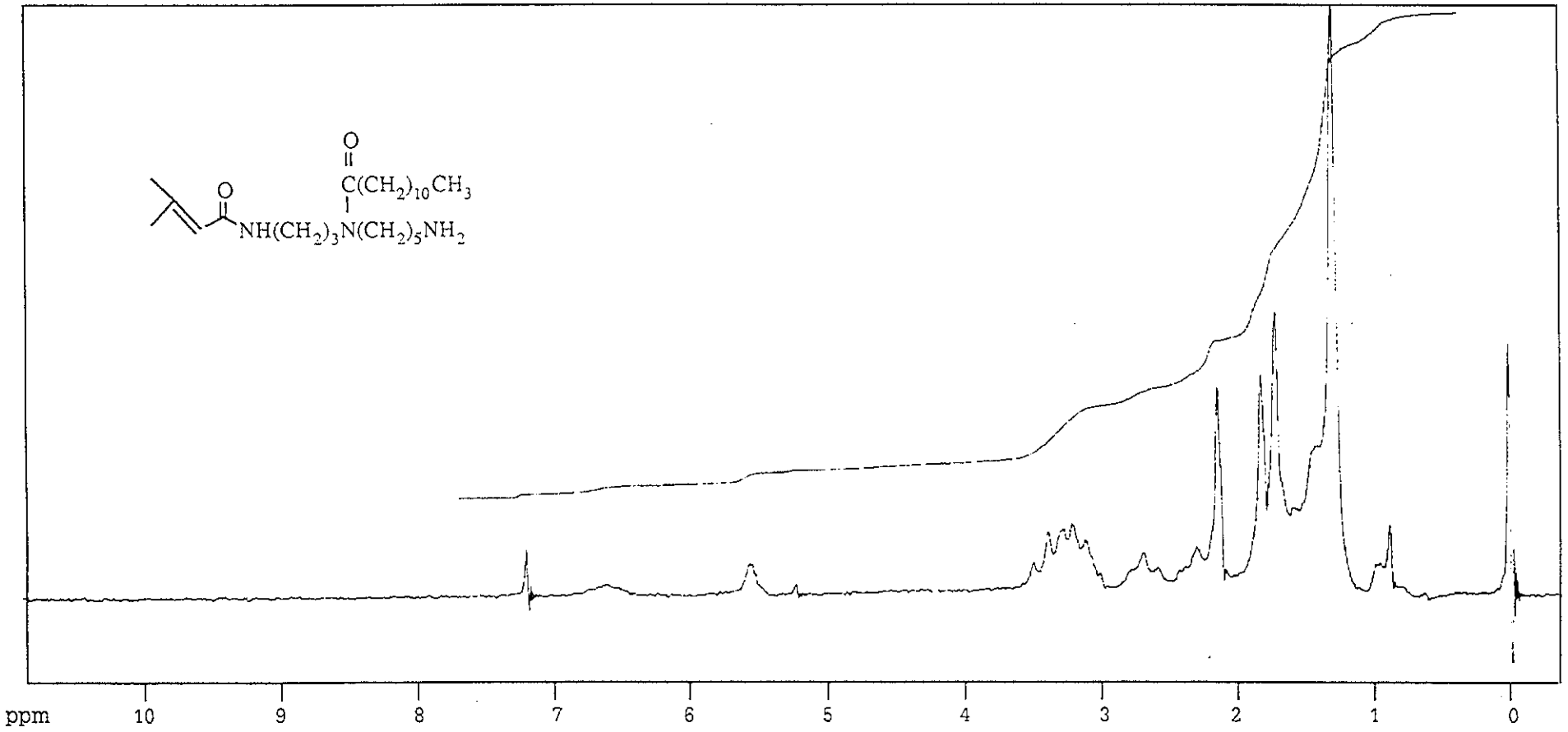


Figure 54 NMR spectrum of N-(5-aminopentyl)-N-[3-(3-metylbut-2-enamido)propyl]dodecanamide (180)

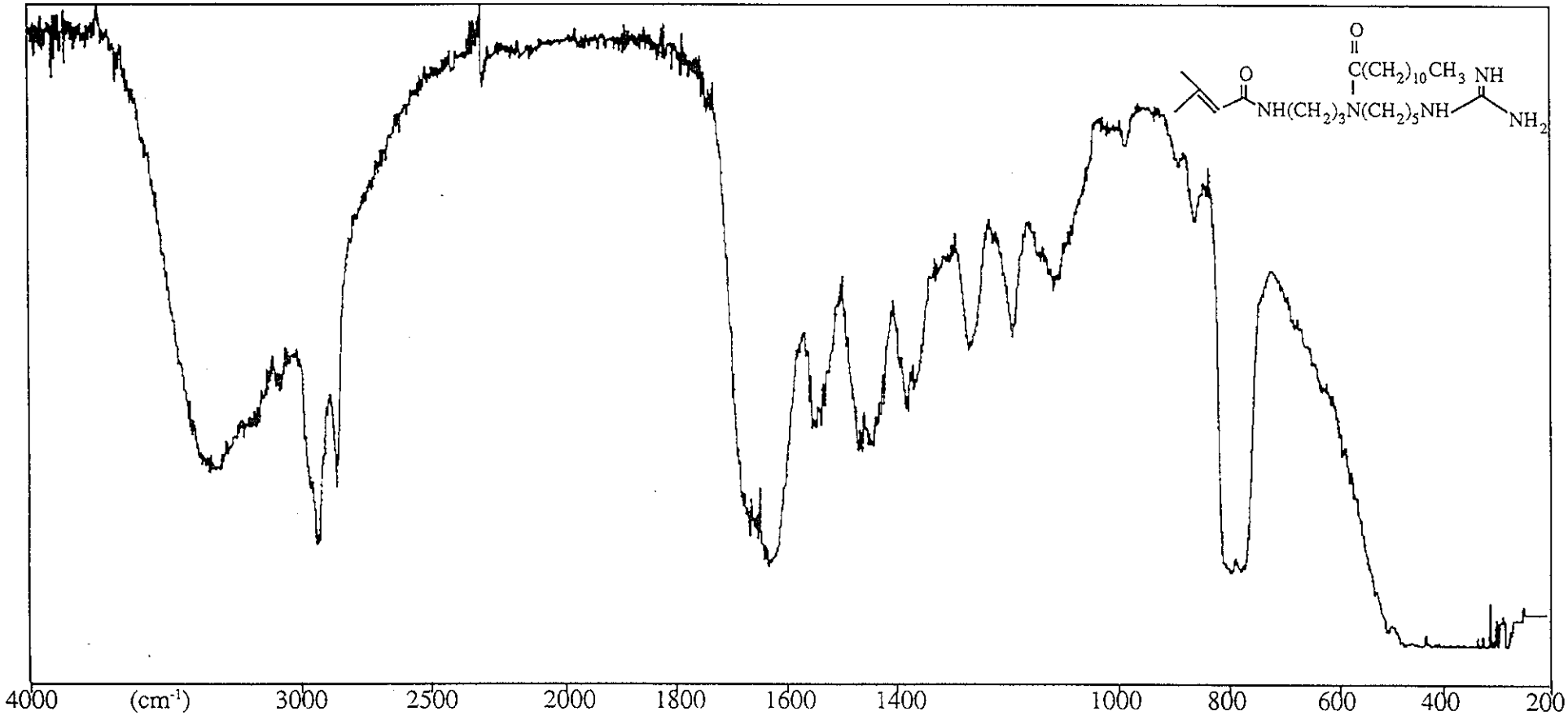


Figure 55 IR spectrum of N-(5-guanidinopentyl)-N-[3-(3-metylbut-2-enamido)propyl]dodecanamide (73)

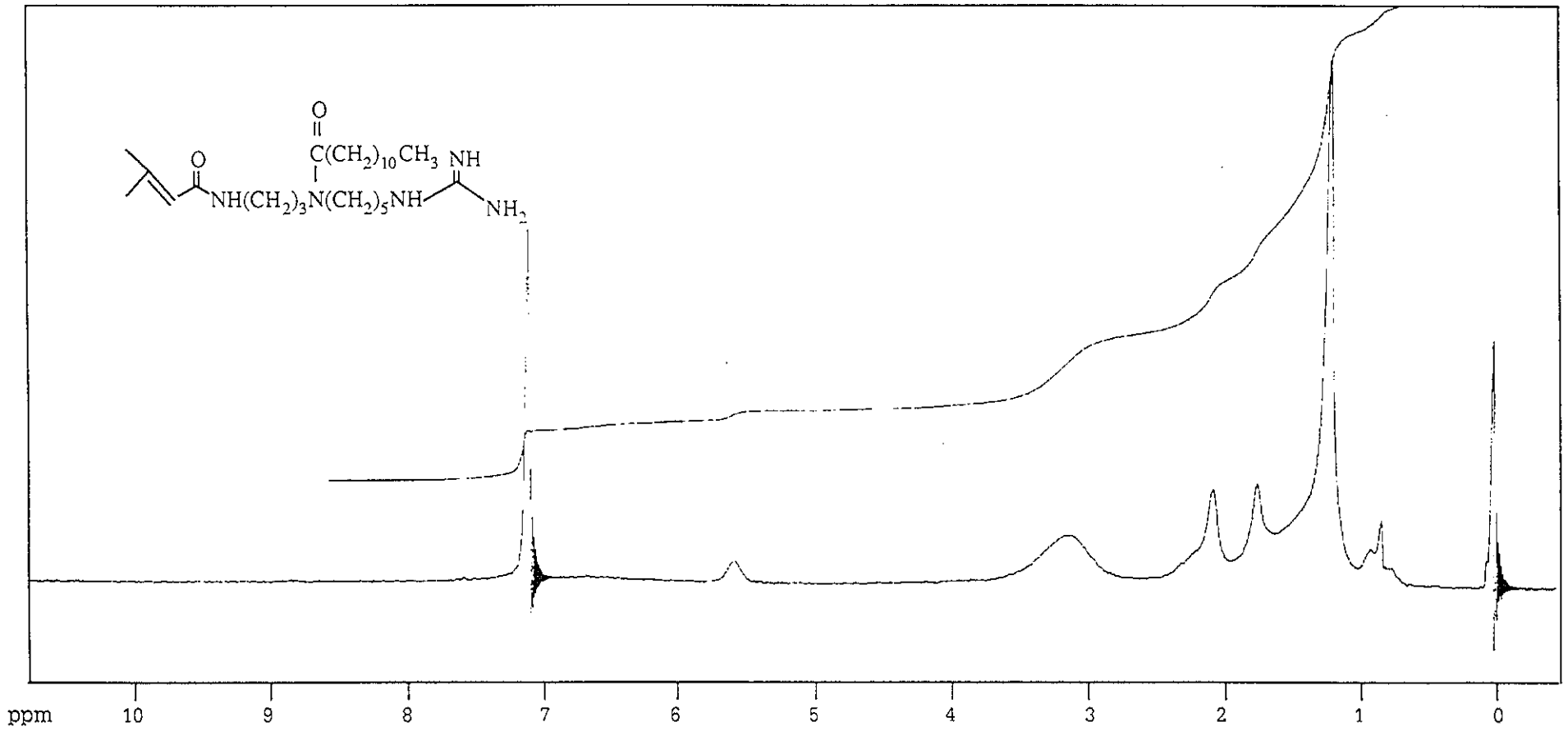


Figure 56 NMR spectrum of N-(5-guanidinopentyl)-N-[3-(3-metylbut-2-enamido)propyl]dodecanamide (73)

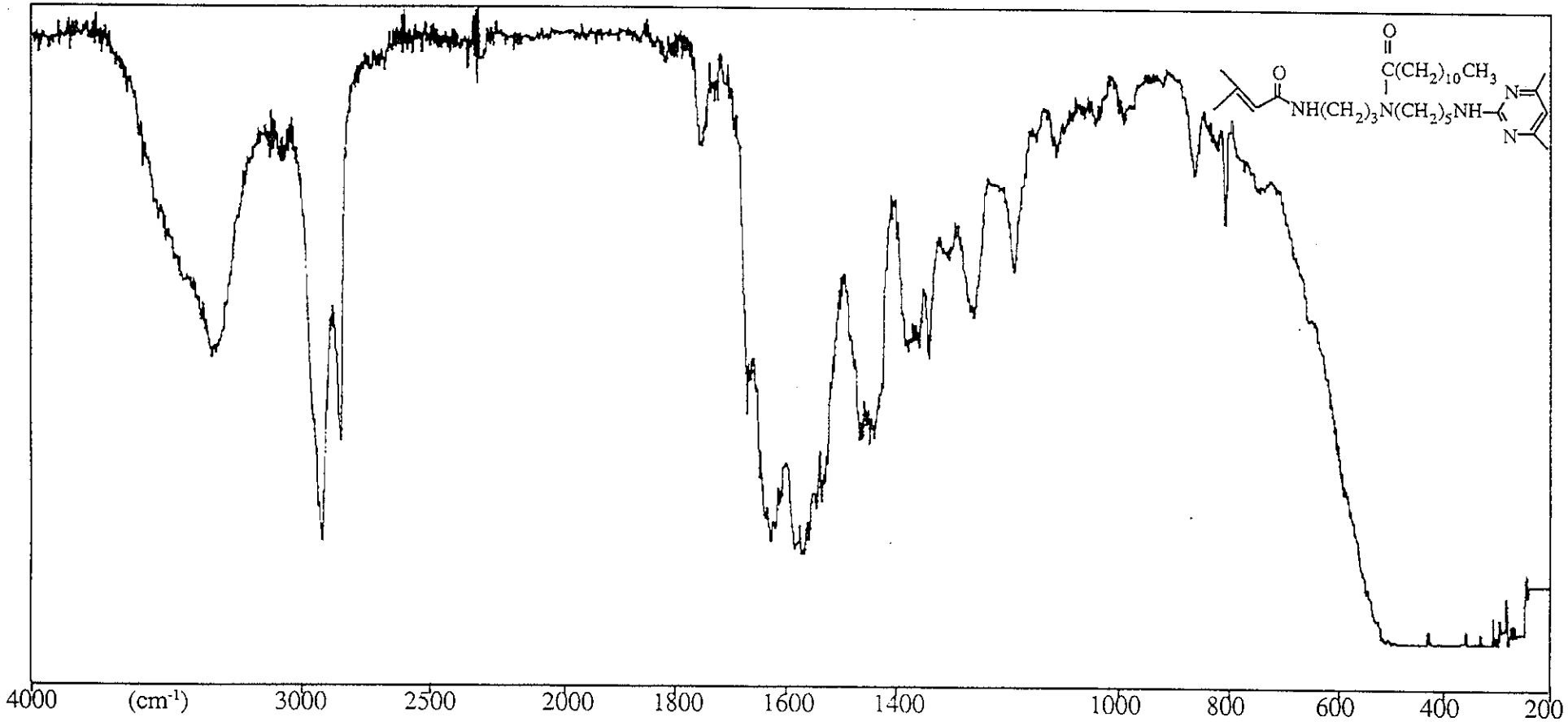


Figure 57 IR spectrum of N-[5-(4, 6-dimethylpyrimidin)-2-ylamino)pentyl]-N-[3-(3-metylbut-2-enamido)propyl] dodecanamide (83)

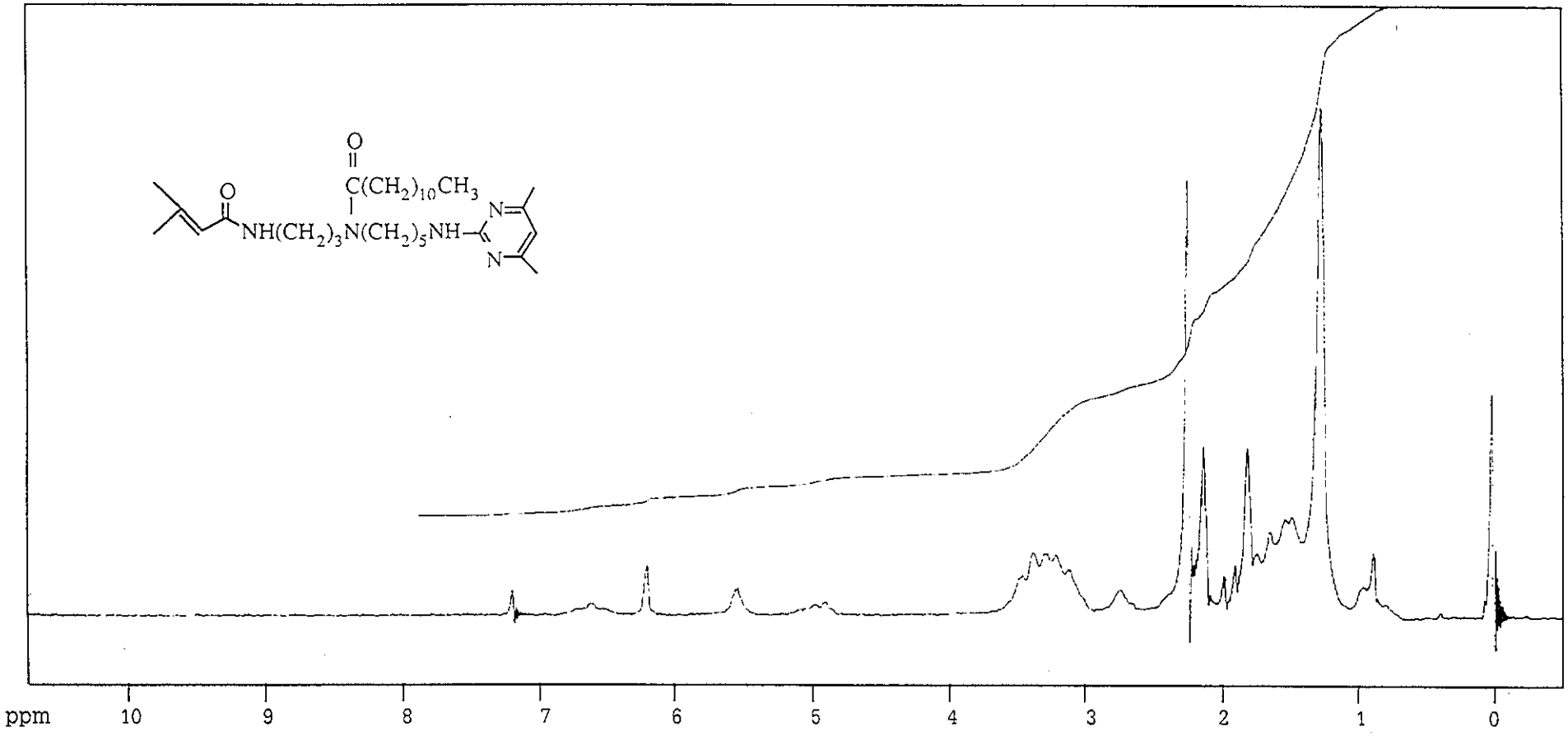


Figure 58 NMR spectrum of N-[5-(4, 6-dimethylpyrimidin)-2-ylamino)pentyl]-N-[3-(3-metylbut-2-enamido) propyl] dodecanamide (83)

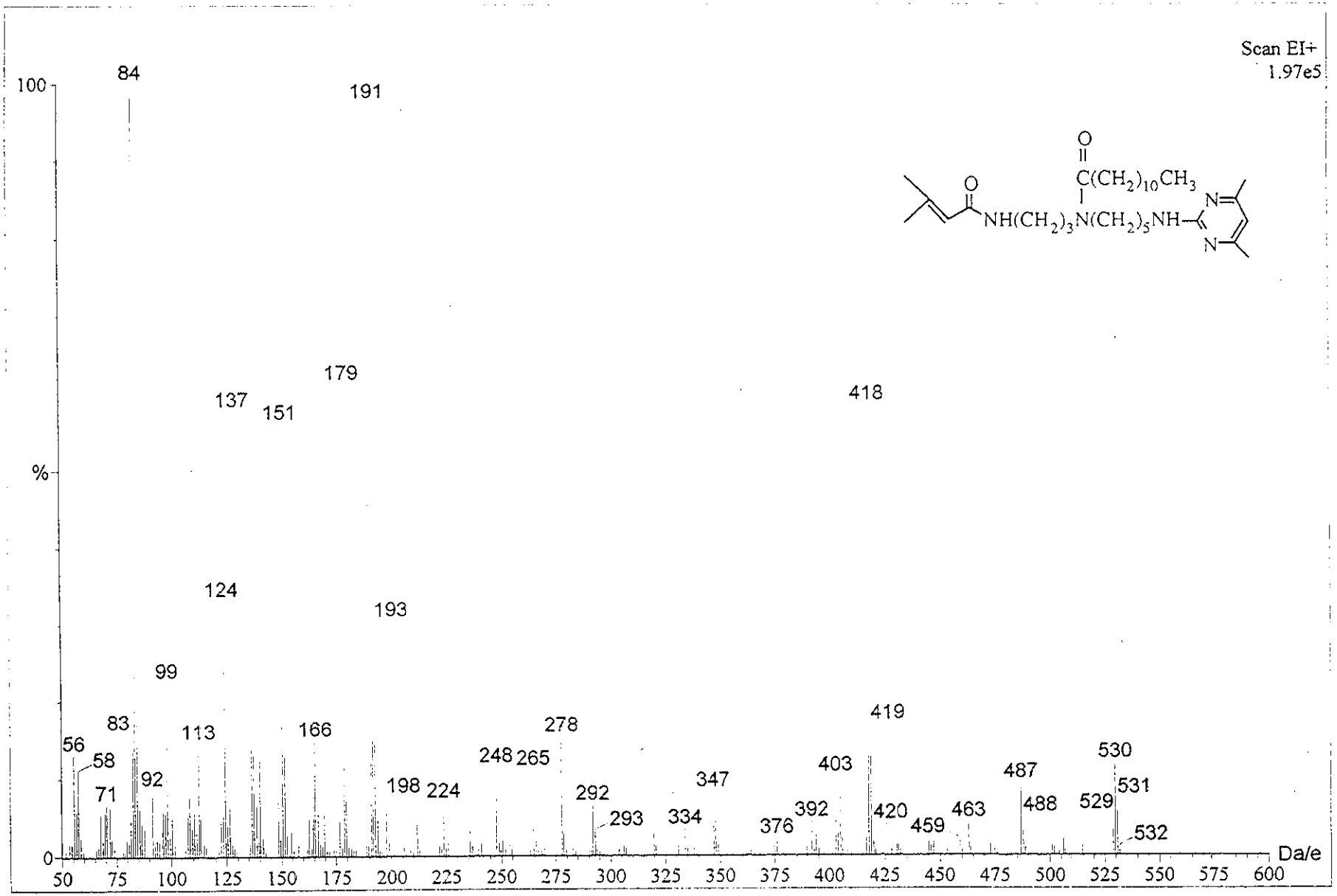


Figure 59 MS spectrum of N-[5-(4, 6-dimethylpyrimidin)-2-ylamino)pentyl]-N-[3-(3-metylbut-2-enamido) propyl]dodecanamide (83)

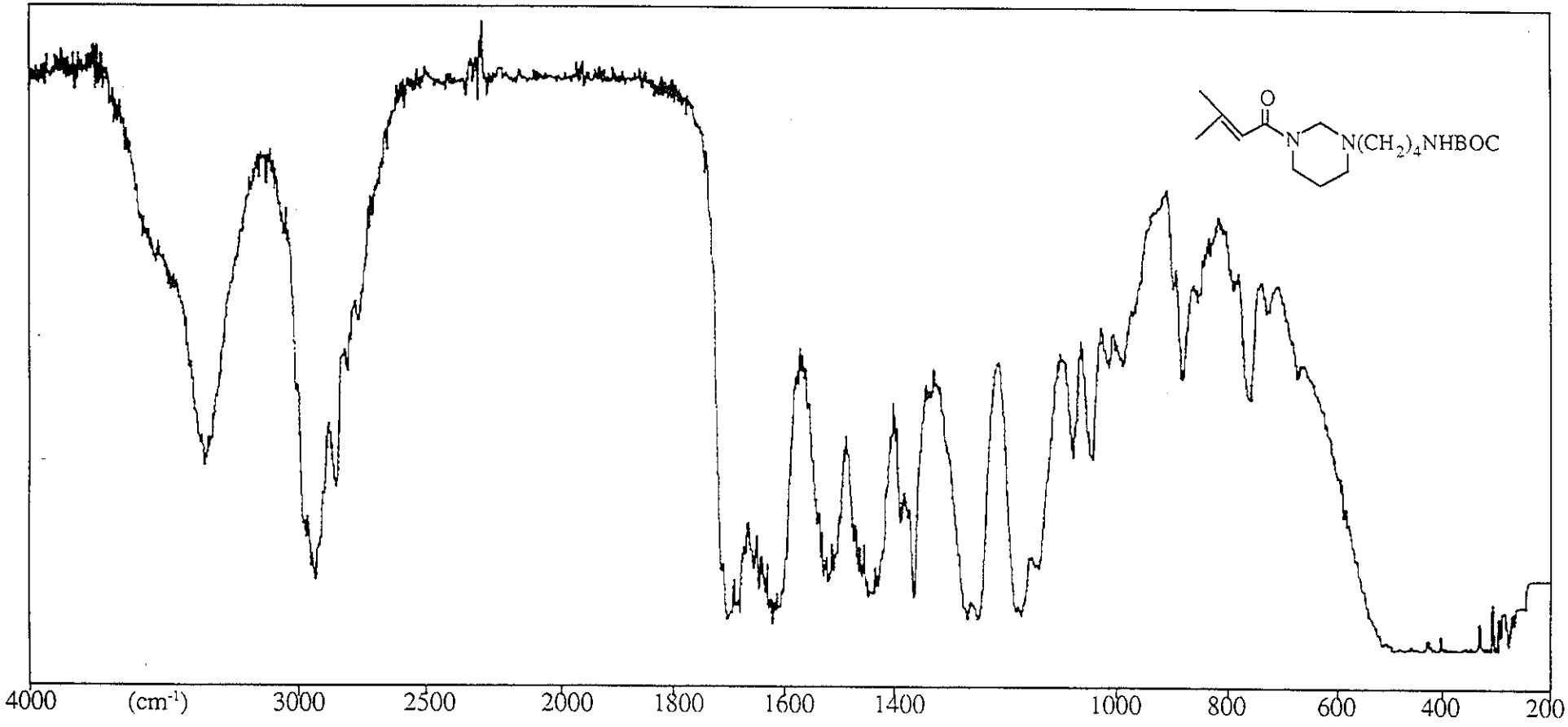


Figure 60 IR spectrum of N^1-(3-(3-methylbut-2-enamido)-N^8-(*tert*-butyloxycarbonyl)hexahydropyrimidine (184)

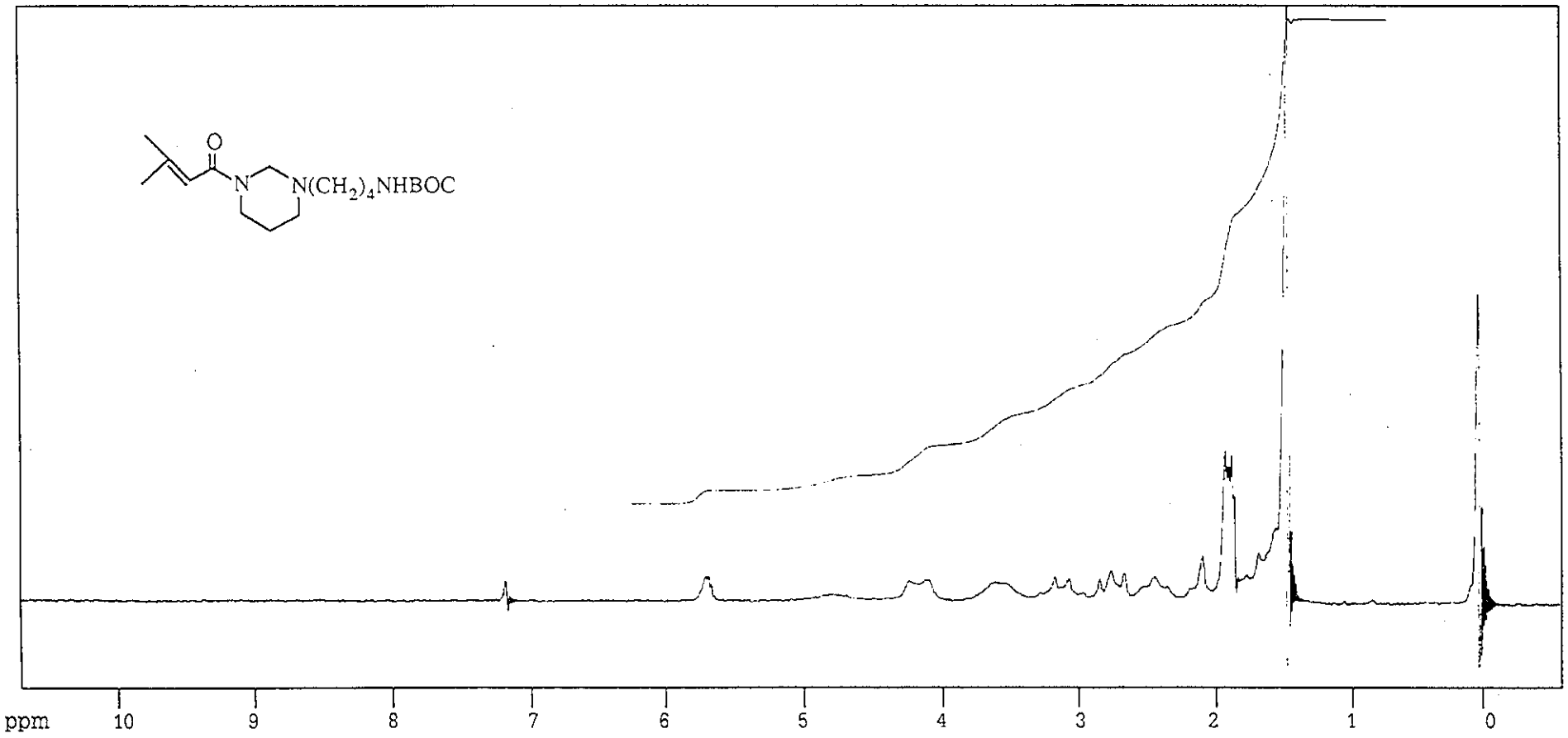


Figure 61 NMR spectrum of N^1-(3-(3-methylbut-2-enamido)-N^8-(*tert*-butyloxycarbonyl)hexahydropyrimidine (184)

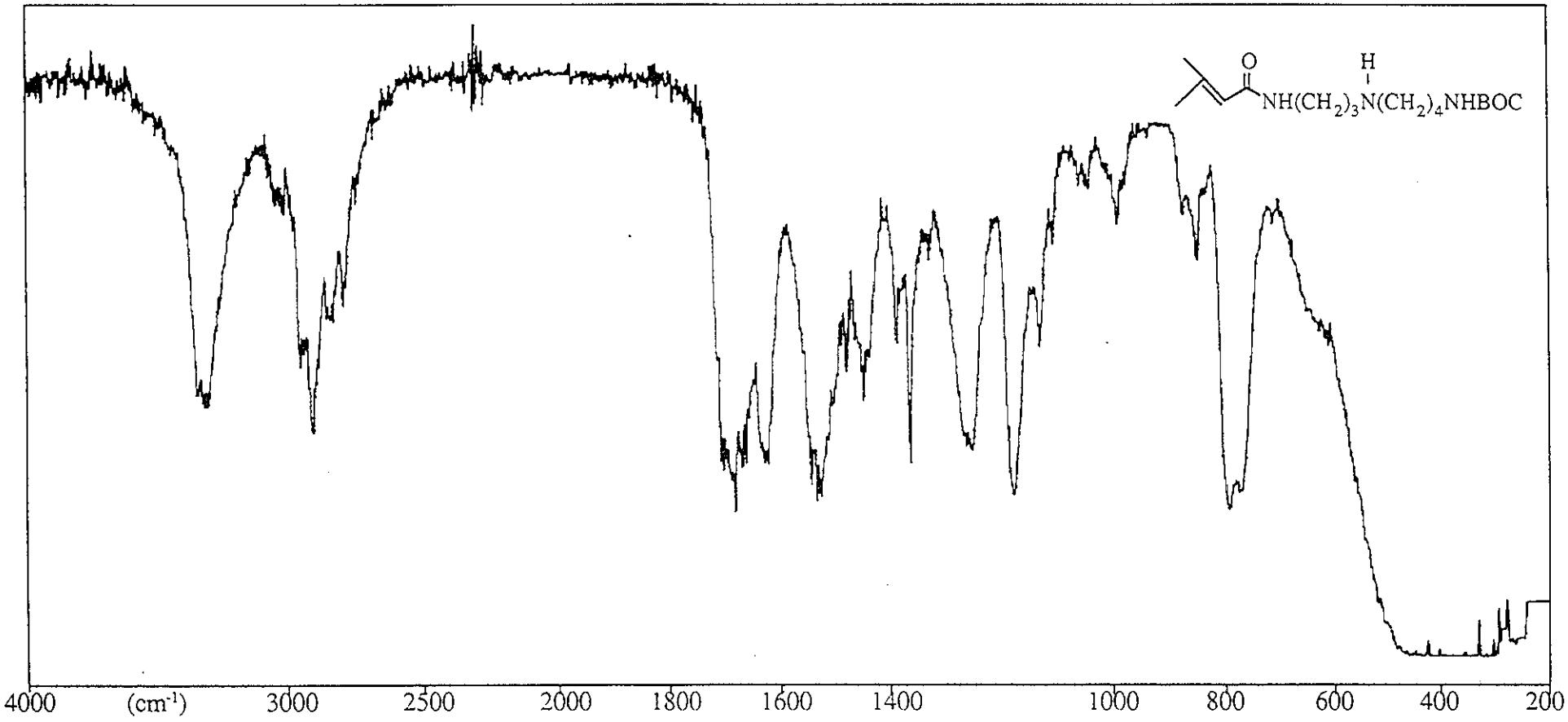


Figure 62 IR spectrum of N-(*tert*-butyloxycarbonyl)-N^1-[3-(3-methylbut-2-enamido)propyl]-1,4-diaminobutane (185)

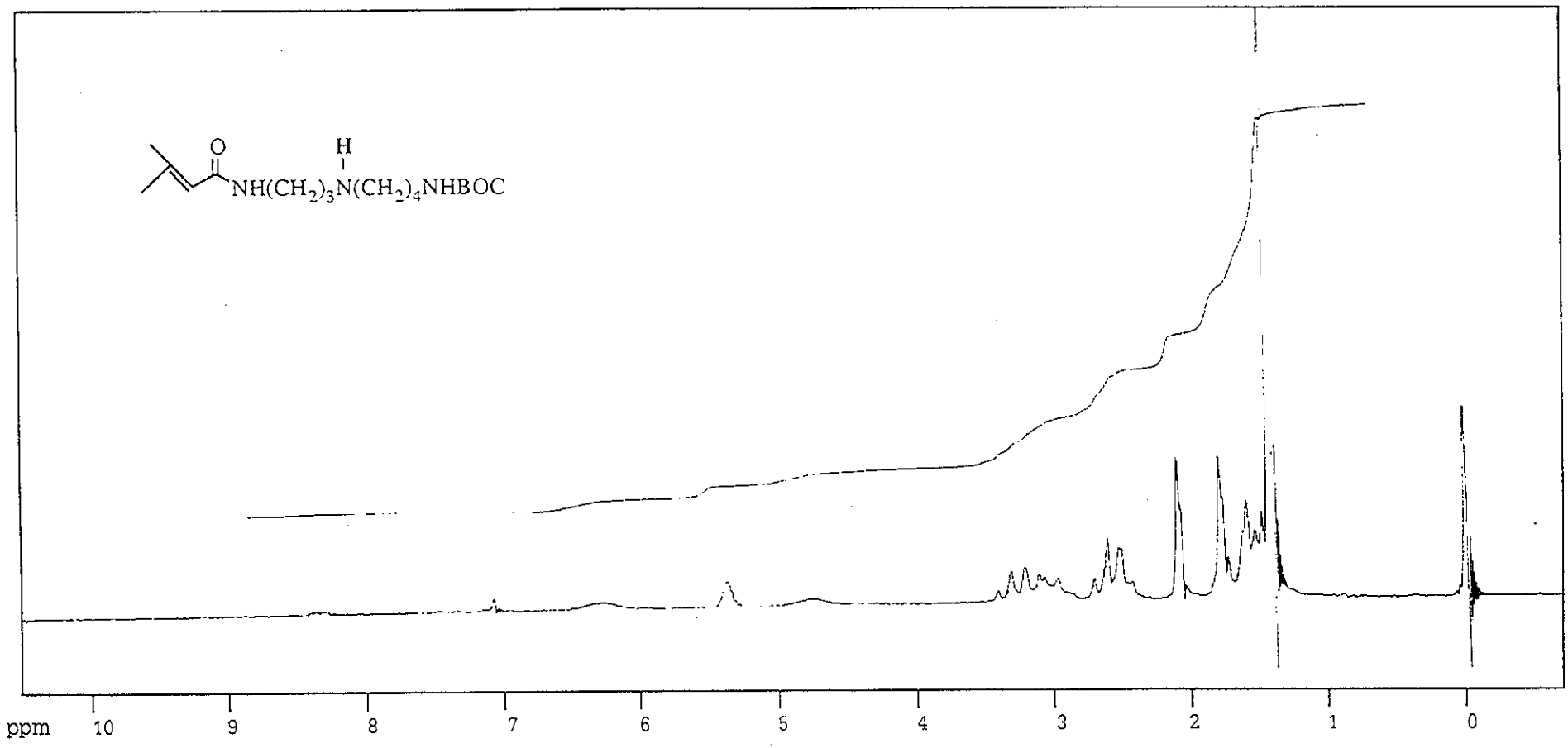


Figure 63 NMR spectrum of N-(*tert*-butyloxycarbonyl)-N^1-[3-(3-methylbut-2-enamido)propyl]-1,4-diaminobutane (185)

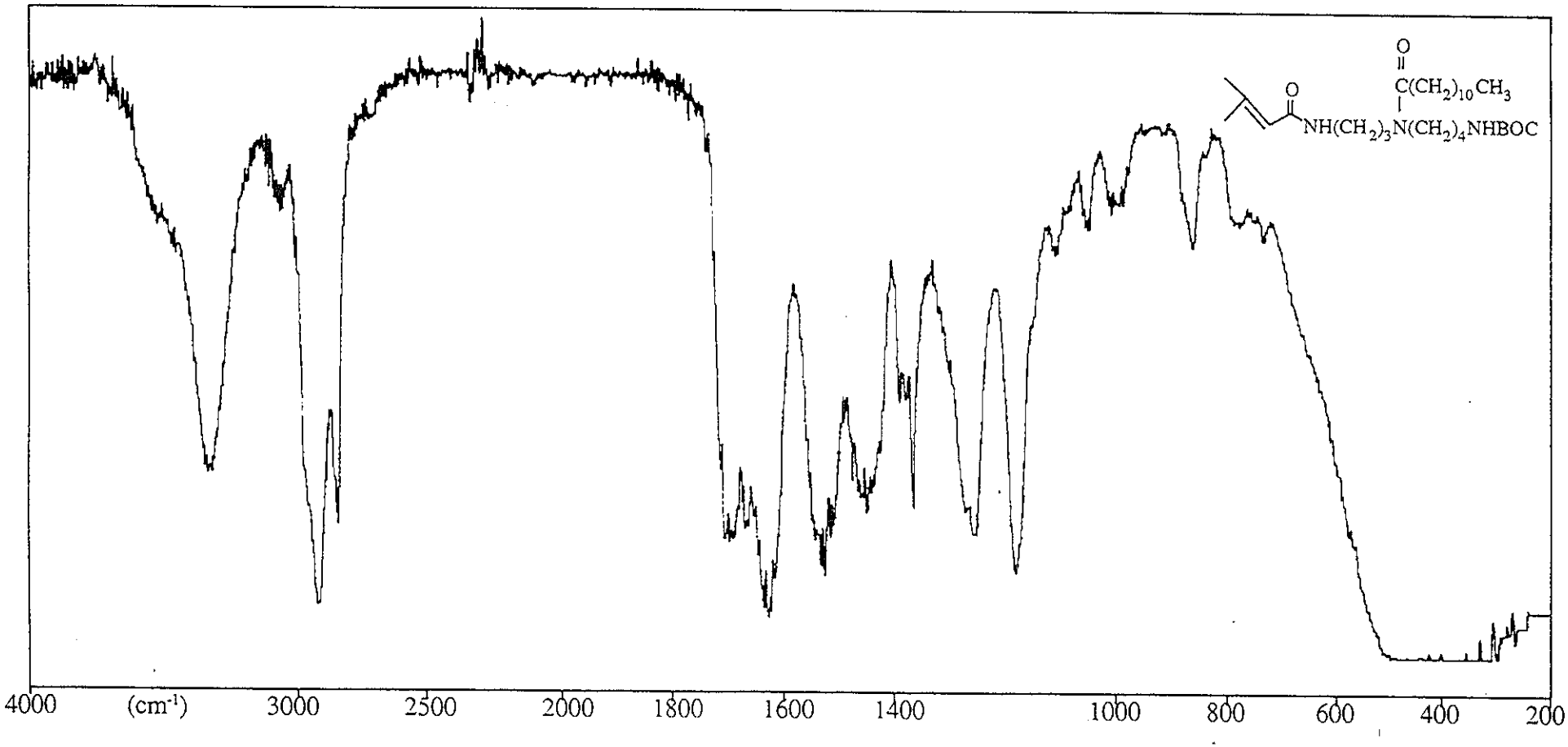


Figure 64 IR spectrum of N-[4-(*tert*-butyloxycarbonylamino)butyl]-N-[3-(3-methylbut-2-enamido)propyl] dodecanomide (186)

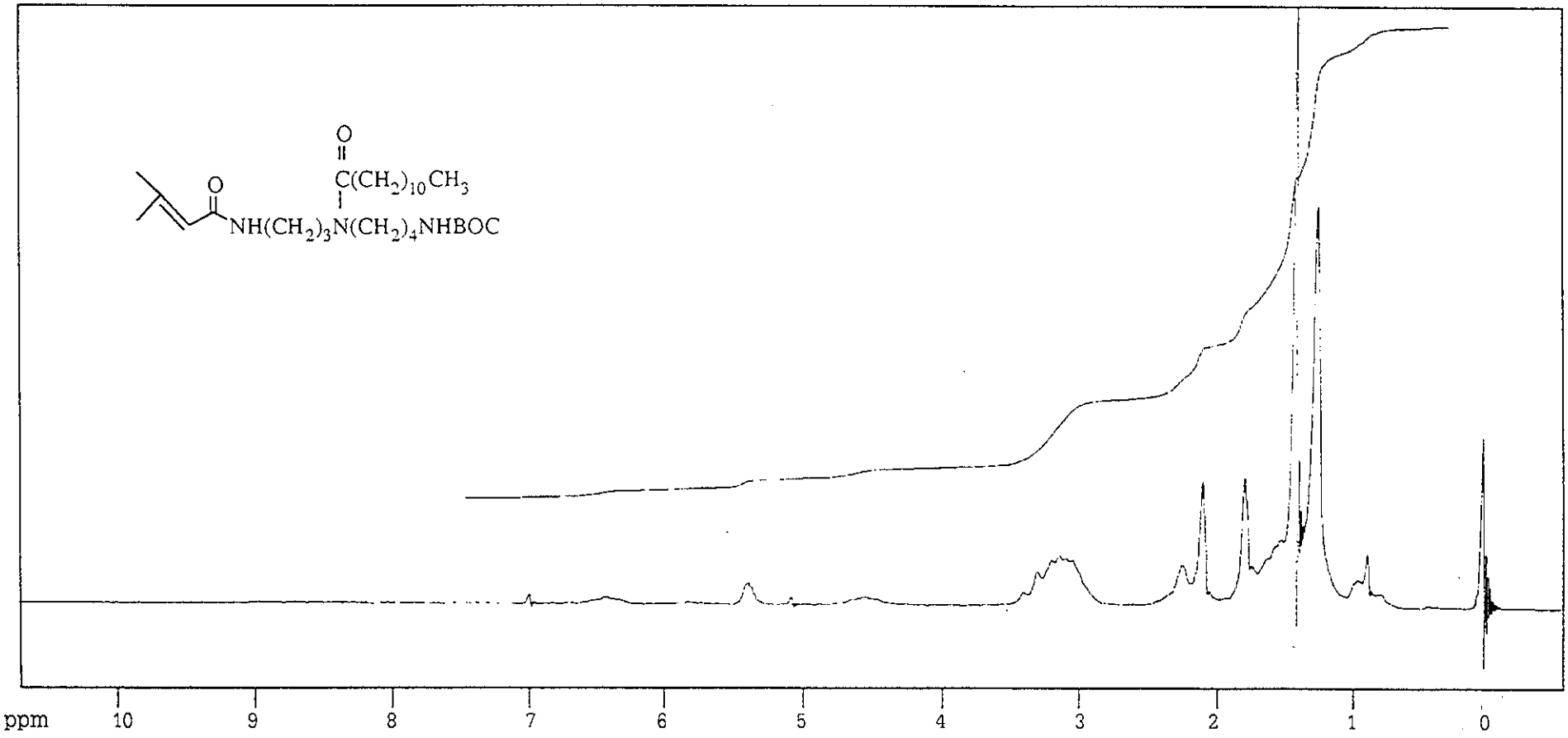


Figure 65 NMR spectrum of N-[4-(*tert*-butyloxycarbonylamino)butyl]-N-[3-(3-methylbut-2-enamido)propyl] dodecanomide (186)

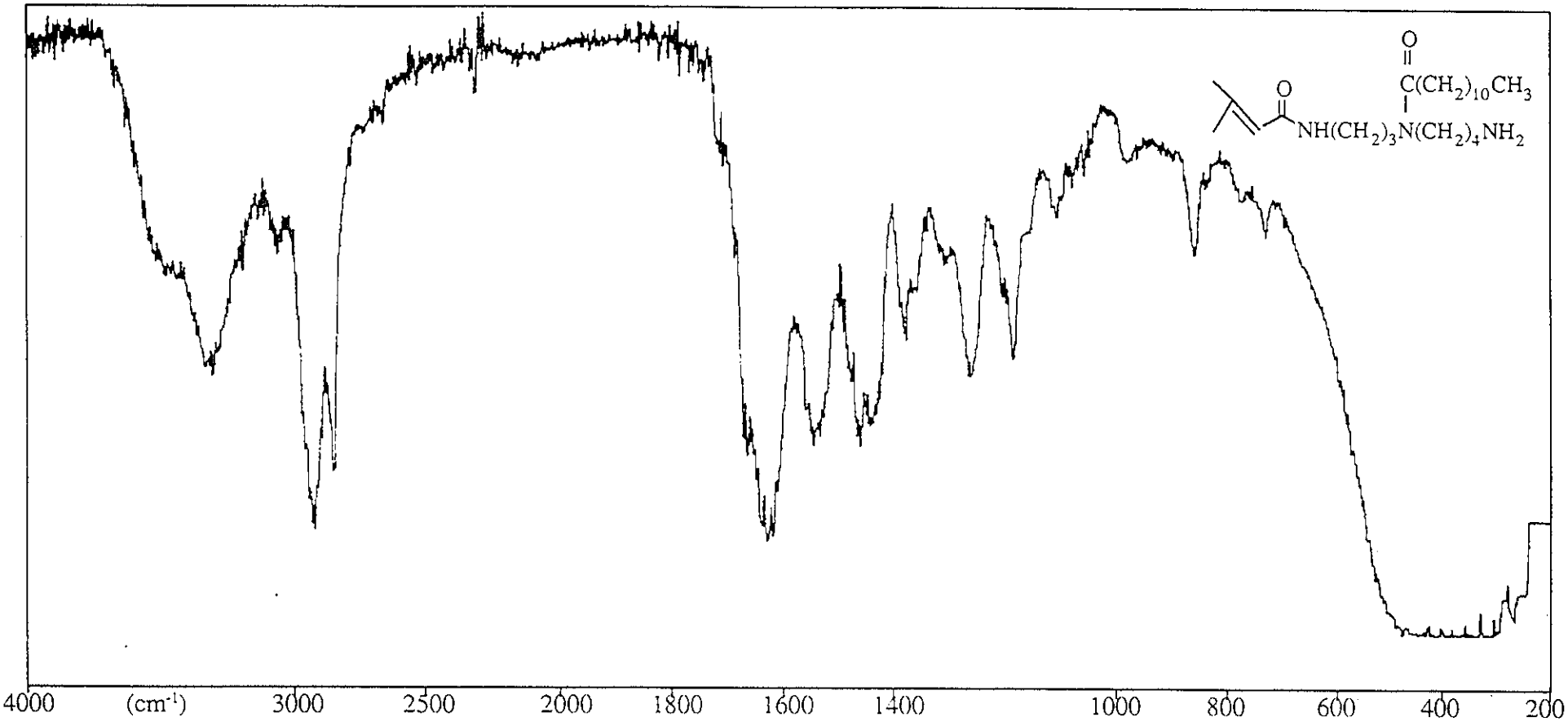


Figure 66 IR spectrum of N-(4-aminobutyl)-N-[3-(3-methylbut-2-enamido)propyl]dodecanamide (187)

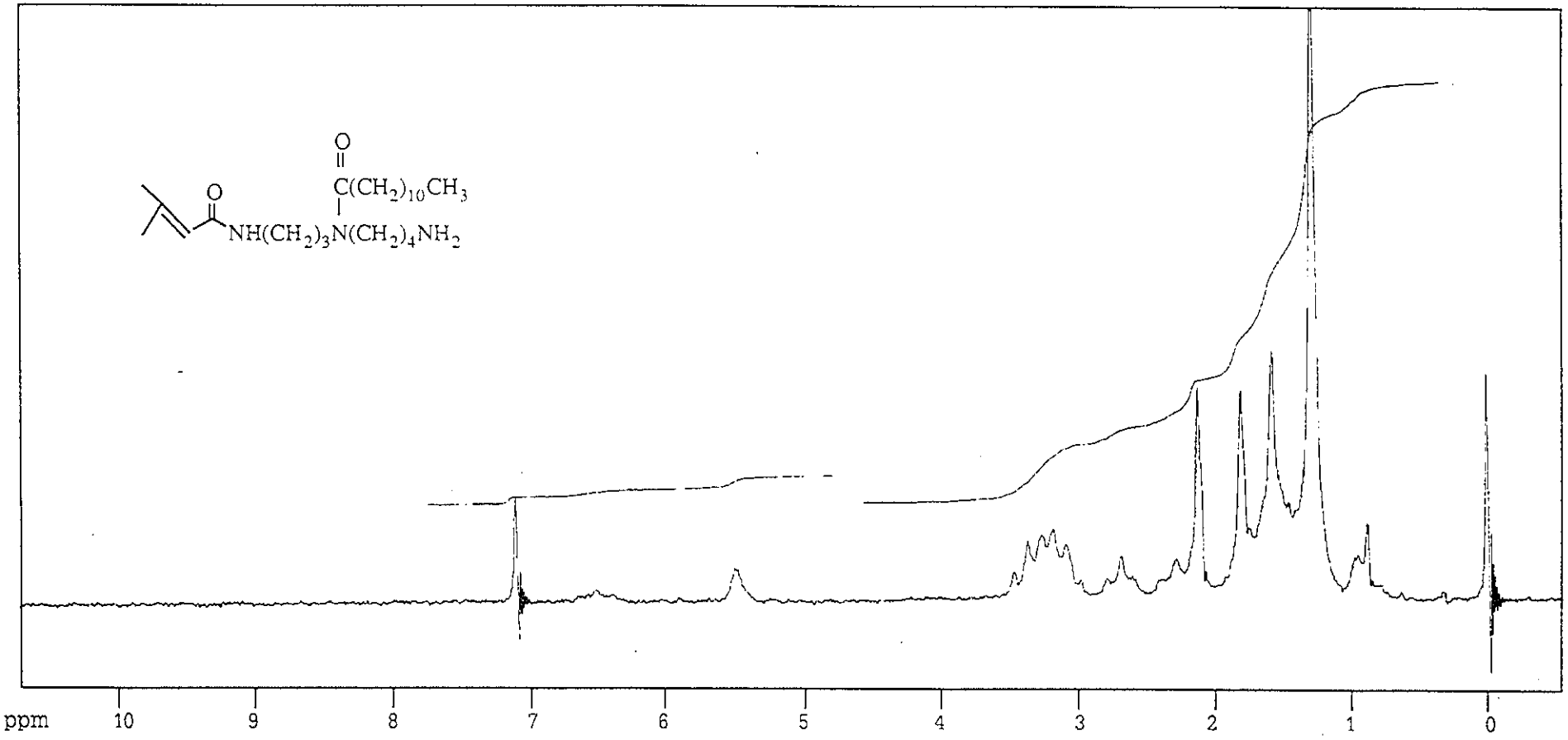


Figure 67 NMR spectrum of N-(4-aminobutyl)-N-[3-(3-methylbut-2-enamido)propyl]dodecanamide (187)

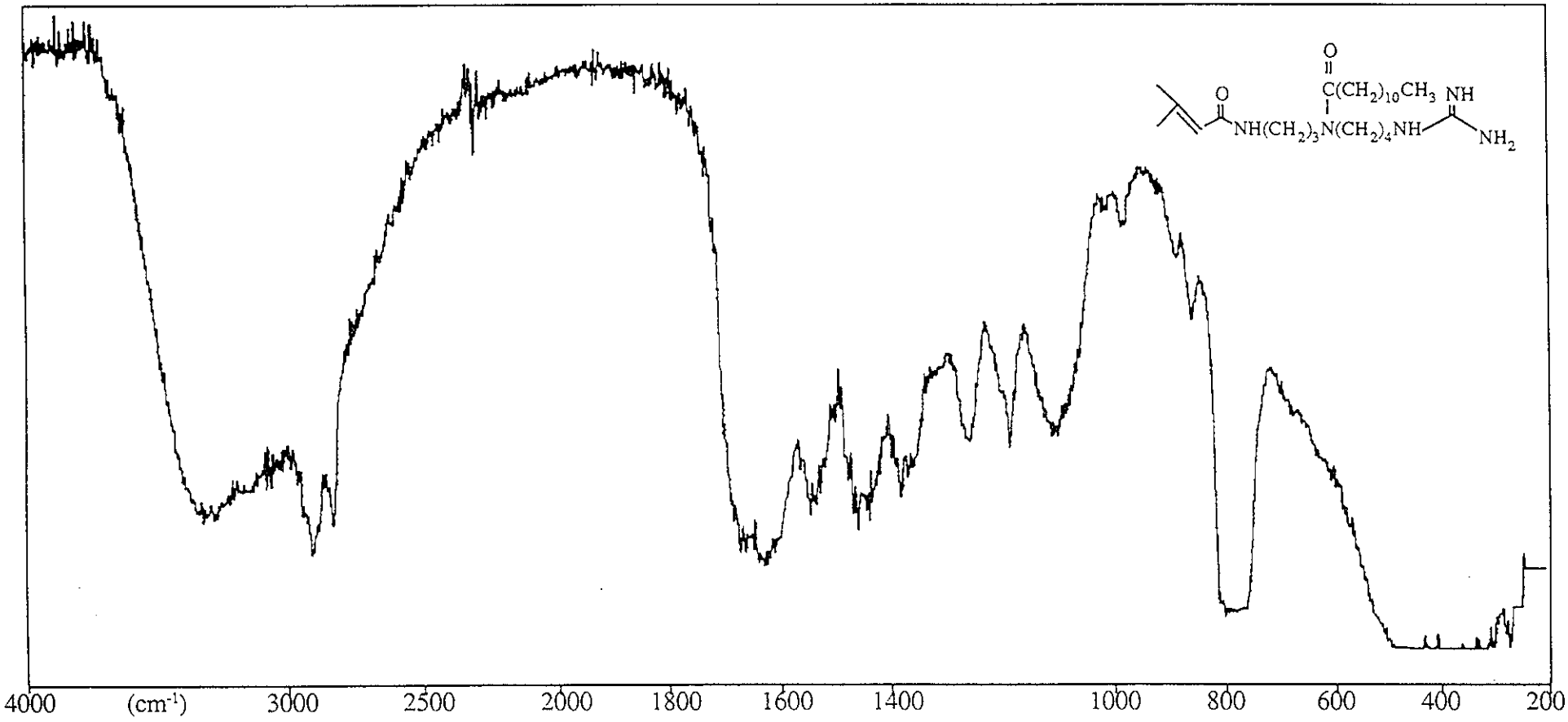


Figure 68 IR spectrum of N-(4-guanidinobutyl)-N-[3-methylbut-2-enamino)propyl]dodecanamide (188)

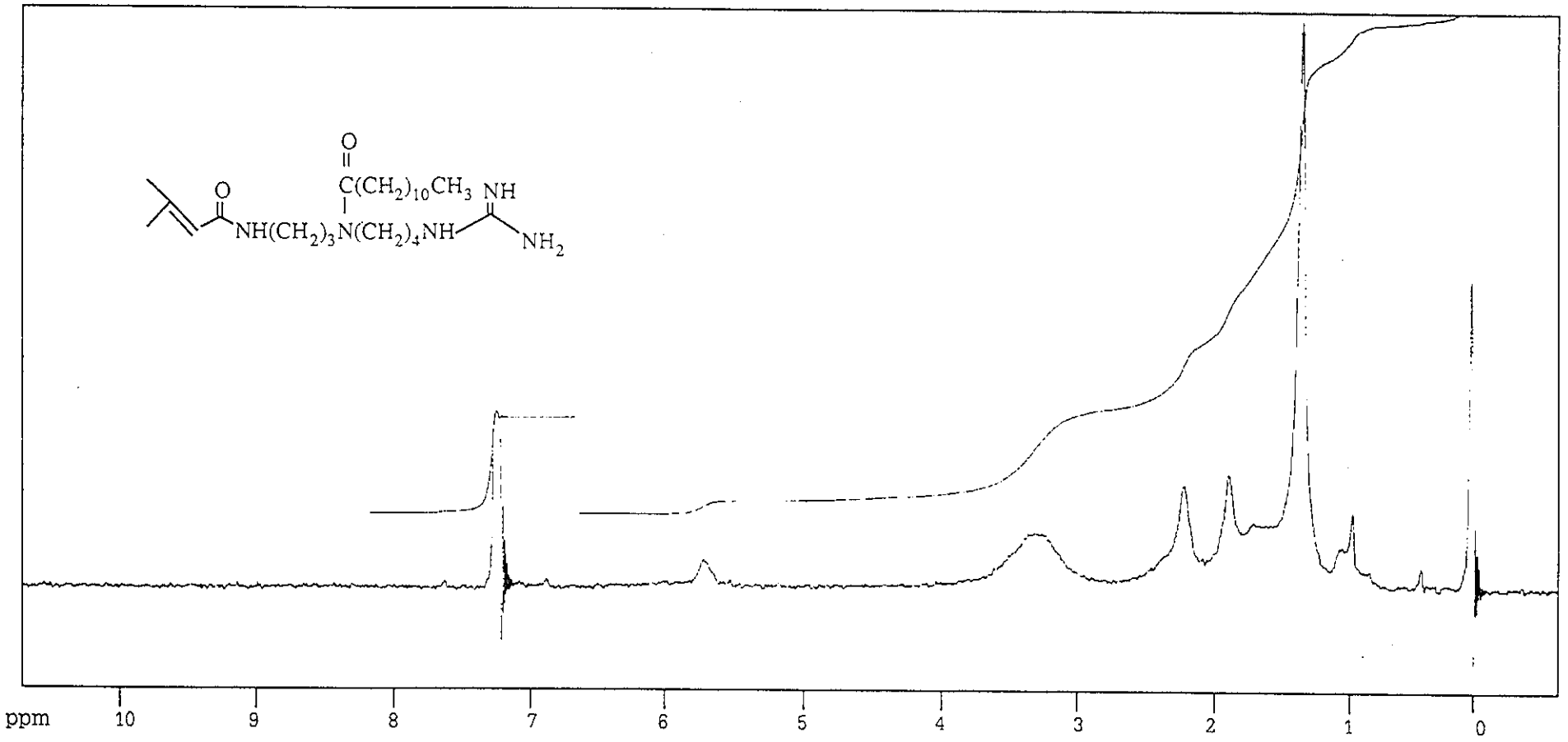


Figure 69 NMR spectrum of N-(4-guanidinobutyl)-N-[3-methylbut-2-enamino)propyl]dodecanamide (188)

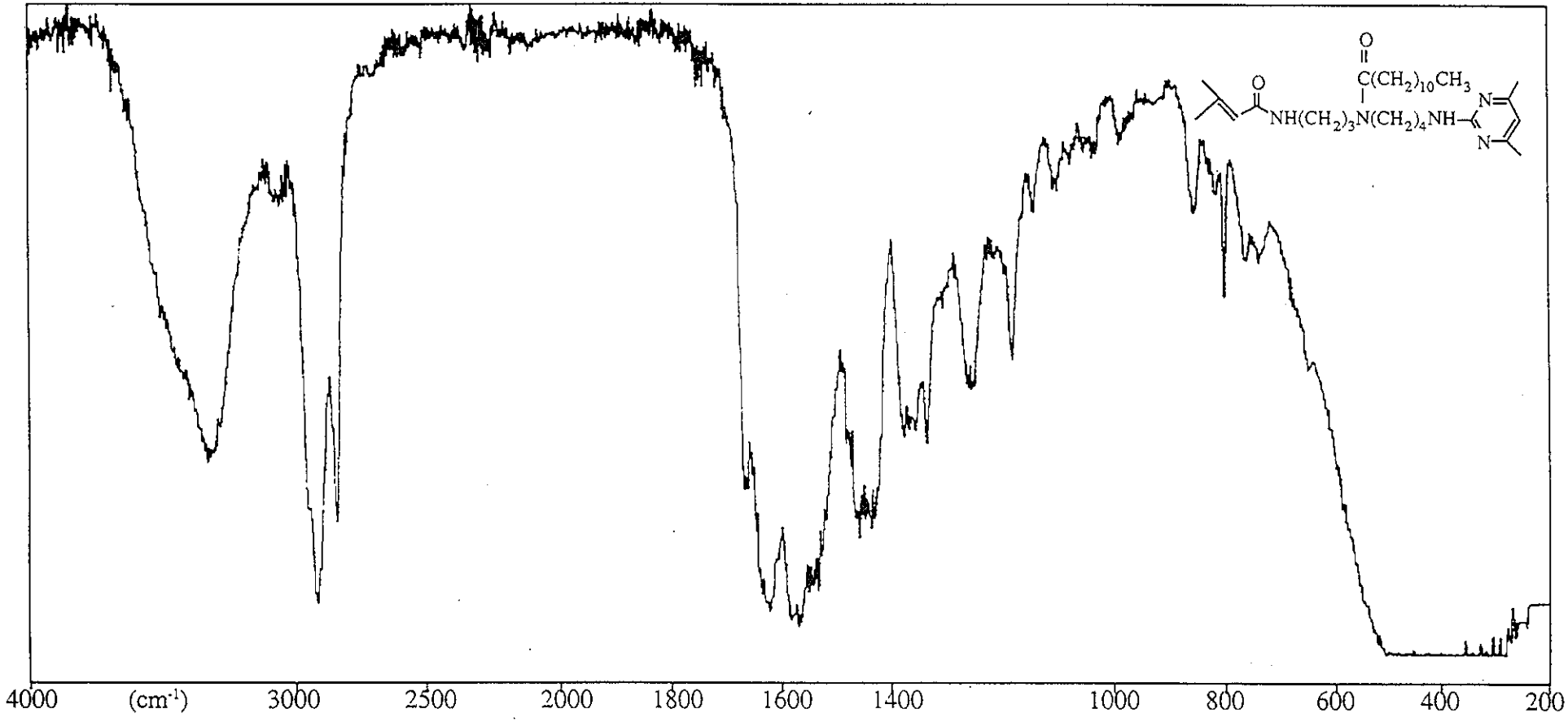


Figure 70 IR spectrum of N-[4-(4,6-dimethylpyrimidin)-2-ylamino)butyl]-N-[3-(3-methylbut-2-enamido)propyl] dodecanamide (189)

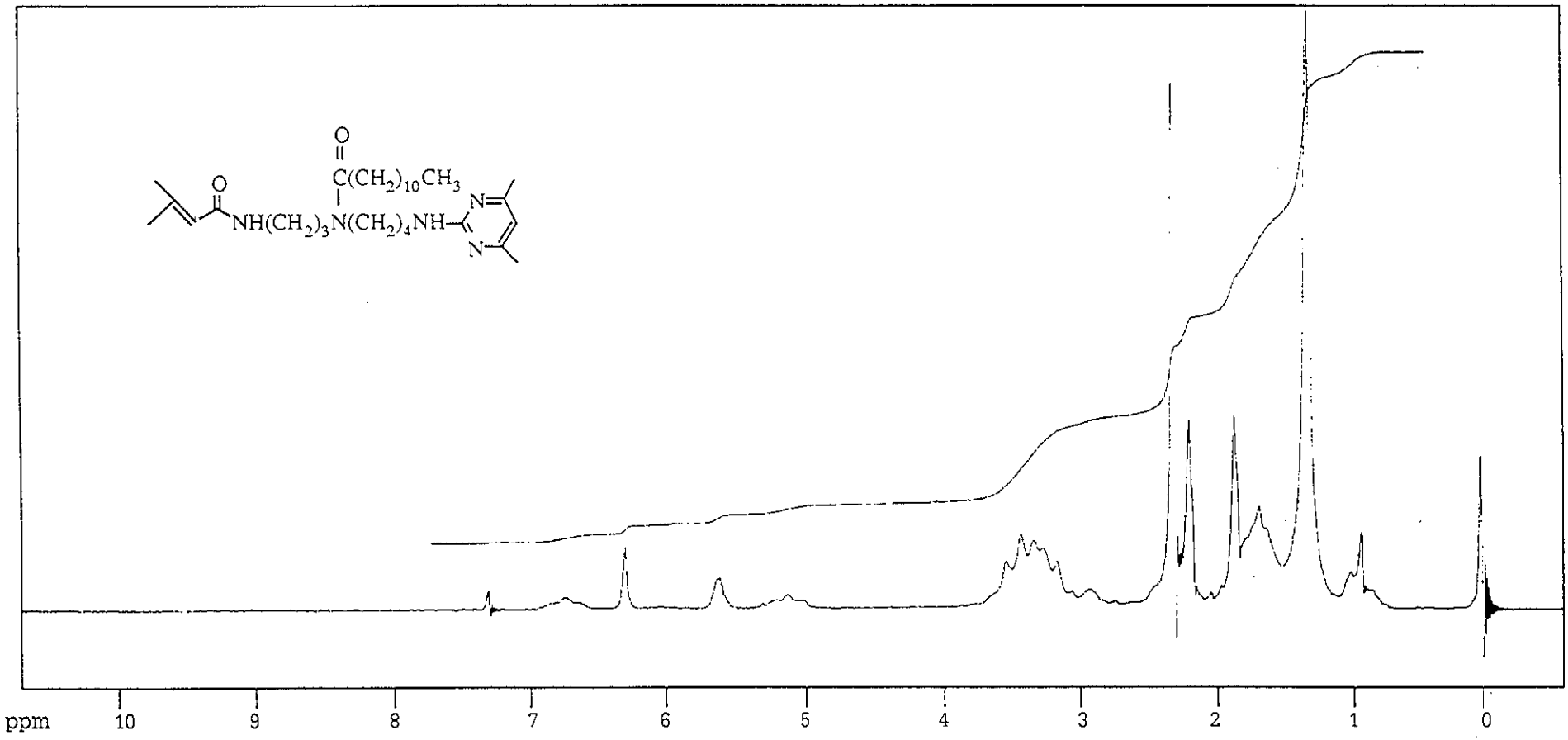


Figure 71 NMR spectrum of N-[4-(4,6-dimethylpyrimidin)-2-ylamino)butyl]-N-[3-(3-methylbut-2-enamido)propyl] dodecanamide (189)

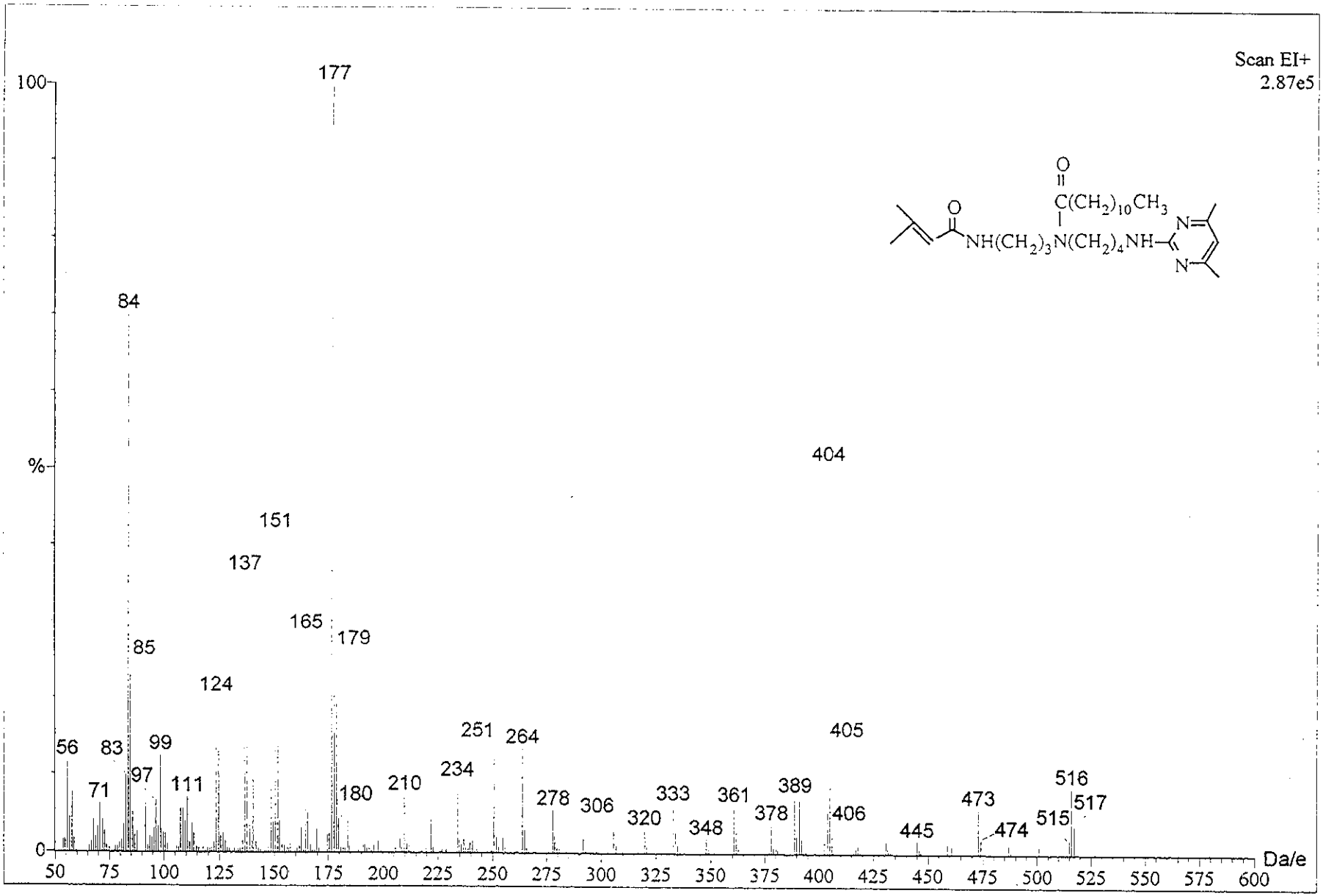


Figure 72 MS spectrum of N-[4-(4,6-dimethylpyrimidin)-2-ylamino)butyl]-N-[3-(3-methylbut-2-enamido)propyl] dodecanamide (189)

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