SYNTHESIS AND CONFORMATION OF AZACYCLOHEXANES

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BY

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To my family and my wife

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SUMMARY

In this thesis, the ring conformations of azacyclohexanes are studied using the 1,3,5-triazacyclohexanes and 3,7-diazabicyclo[3.3.1]nonanes as model structures.

A review is presented of the synthesis of mono-, di-, tri- and tetraazcyclohexanes and of studies of their conformations in solution and in the solid state.

The synthesis of the 1,3,5-trisubstituted 1,3,5-triazacyclohexanes (106), (107), (108), (110), (111), (112), (113), (114), (115), (116), (118) and (122) has been undertaken by condensation of formalin or paraformaldehyde with the corresponding aryl/alkylamines in an inert solvent, toluene, benzene or ethanol, sometimes with addition of strong base. Compound (117) was formed using the reported reaction of 4-nitroaniline with dimethylsulphoxide in presence of phosphorus pentoxide.

Condensation of 2-trifluoromethylaniline with paraformaldehyde and of 4-nitroaniline with formalin gave the N,N'-diaryldiaminomethanes (122) and (123) probably as the result of steric hindrance in the former and decreased nitrogen basicity in the latter. Attempts to prepare the triazacyclohexane (119) by

increasing reaction time and temperature gave the 2:1 adduct (122). Condensation of 2-trifluoromethylaniline with DMSO / P_2O_5 failed to give either (119) or (122).

X-ray crystal structure analysis revealed that compounds (106) to (108), (110) to (113), and (114) exist in the solid state as chair conformations in which the nitrogen substituents adopt diaxial-equatorial substituents, whereas, for compounds (115) and (116), the nitrogen substituents are diequatorial-axial. The existence of eight of the ten 1,3,5-triazacyclohexanes studied as the aae conformers is considered to be a manifestation of the rabbit-ear (or generalised anomeric) effect. That the other two 1,3,5-triazacyclohexanes adopt, in the solid state, the aee conformers is most likely the result of crystal packing forces rather than of a major energy difference between the aae and aee conformers. The nitrogen atoms of all ten compounds are pyramidal and the syn-diaxial substituents are displaced apart. The triazacyclohexane (117) as the pyridine solvate adopts a twist-boat conformation with one nitrogen atom planar and the two other nitrogen substituents anti to each other. The diaryldiaminomethane (122) adopts a skewed conformation around the $N-CH_2$ bonds with the trifluoromethyl groups remote from each other. The crystal structure of diaryldiaminomethane (123) was not refined.

Compounds (182)-(186) were formed by reaction of the sulphonyl chlorides (RSO_2Cl) with diazaadamantanone (144) or the diamine (181). An alternative approach to 3,7-diazabicyclo[3.3.1]nonanes by nucleophilic substitution of tetraiodide (189) by 4-fluoroaniline has led to the monocyclic piperidine (190).

In the solid state, 3,7-diazabicyclo[3.3.1]nonanes (182) and (184) were found to adopt a twin-chair conformation with somewhat pyramidal character of the nitrogen atoms. The alternative boat-chair conformation was adopted by (183), and (185) exists in both twin-chair and boat-chair conformations in the solid state. Again, the different conformational preferences are considered to be due to crystal packing forces and not to marked differences in energy between the twin-chair and the boat-chair conformations.

The piperidine (190) adopts the chair conformation with N atom pyramidal and with the equatorial orientation on the piperidine ring of all three substituents.

Chapter 1

Review

Synthesis and Conformational Analysis of Six-Membered Saturated Heterocycles Containing Nitrogen.

Review

Synthesis and Conformational Analysis of Six-Membered Saturated Heterocycles Containing Nitrogen.

Saturated heterocyclic compounds are of interest because they offer a variety of possibilities for the study of ring conformation by spectroscopy and X-ray crystal structure analysis[1]. Because of the presence of a lone pair, or lone pairs, of electrons on the heteroatom(s), the heterocycles additionally allow for the study of the conformational effects of non-bonding electrons. Two such effects which are widespread in structural chemistry are the "rabbit-ear" effect and the "anomeric" effect. The former[2a] refers to the repulsion in six-membered rings between lone pairs of syn-axial electrons on non-adjacent atoms, through which the conformation (1) is disfavoured. The latter effect has been recognised[2b] in six-membered saturated heterocycles (2) containing oxygen and sulfur where an electronegative group (eg. alkoxy or halogen), adjacent to the heteroatom, prefers to adopt the axial orientation, remote from the lone pairs, despite its

stereochemical proximity to syn-axial hydrogens. This preference is considered[3] to arise from a through-bond orbital interaction **(Fig. 1)** between the axial non-bonding orbital of the heteroatom and the σ^* antibonding orbital of the C-X bond, resulting in introduction of double bond character into the ring C-Z bond and weakening of the C-X bond. Since both effects can also be perceived as arising from unfavourable parallel alignment of lone-pair dipoles, the rabbit-ear effect can be regarded as a manifestation of the generalised anomeric effect.

In this review, discussion will be limited to six-membered rings containing one, two, three and four nitrogen heteroatoms. For these heterocycles, the orientation of nitrogen substituents can potentially be altered both by conformational change within the ring and by nitrogen inversion. The presence of a N atom in the ring will modify the positions of conformational equilibria compared to cyclohexane.

Piperidines (Azacyclohexanes)

Piperidine (3) is of importance because of its common occurrence in the alkaloids. Piperidines may be prepared by thermally induced cyclisation of aliphatic

1,5-diamines[4], by radical cyclisations[5] of 1,5- or 1,6-aminoalkenes (10) or (11) **(Scheme 1)** or by catalytic hydrogenation of the corresponding pyridines[6].

The conformational equilibrium of piperidine **(Scheme 2)** has been the subject of prolonged controversy. The N-H orientation can be altered by conformational ring inversion (processes A and B) or by the lower-energy configurational nitrogen inversion (processes C and D).

Considerable evidence has been collected in support of preference for both the N-H axial and N-H equatorial conformations. Barton and Cookson[7] predicted a predominance of the N-H axial conformation of piperidine by analogy with the stereochemistry of carbanions, a conclusion supported by force field calculations[8]. Aroney and LeFevre[9], from the study of Kerr constants and molecular polarizabilities, concluded that the N-H axial conformer of (3) was preferred to the extent of more than 80 % in benzene solution and suggested that, in the usual conformational sense, the N lone-pair exhibits a greater steric requirement than the hydrogen atom. This work, however, has been criticized because of insufficient accuracy in the bond polarizabilities used in the calculations[10]. An attempt was made by Lambert[11] to determine by low temperature ^{1}H NMR the N-H

orientation in piperidine by its effects on the chemical shift difference $\Delta_{ae}(\alpha)$ between the axial and equatorial protons on the adjacent carbon atoms C-2 and C-6. The measured Δ_{ae} (0.44 ppm) was found to differ significantly from that for N-methylpiperidine (4) (0.94 ppm), in which the nitrogen substituent was regarded (see later) as being equatorial (axial lone pair). This led to the conclusion that the N-H of (3) is axial (equatorial lone pair) but these conclusions were later regarded[12-13] as invalid. Changes in the ^{1}H and ^{13}C shieldings on the addition of paramagnetic shift reagent were interpreted[14] in terms of an axial preference and an empirical correlation of the absolute chemical shift with the number of skew lone pair/hydrogen interactions led to the same conclusion[15]. The evidence thus adduced in support of the predominance of the axial N-H conformer of (3) is generally insubstantial.

In contrast, the microwave spectrum of (3) shows lines that can be attributed to both the equatorial and the axial conformations in which the equatorial predominates (ca. 60% at 25°)[16]. An energy difference[17] of 3.1 kJ mol^{-1} corresponds to an equatorial-axial ratio of 3.5 to 1 at 20°. An infrared analysis of the N-H stretching frequencies (6500 cm^{-1}) of (3) reveals two bands which were assigned[18] to the N-H equatorial and

axial conformations, the equatorial conformation being lower in enthalpy by 2 ± 0.4 kJ mol^{-1}. The gas-phase molecular structure of (3), studied by electron diffraction, was interpreted[19] as showing that the molecule has a chair conformation with an N-H equatorial and with the possibility of a minor amount of the N-H axial. Vibrational analysis in the vapour state was interpreted[20] as demonstrating that (3) exists predominantly in the N-H equatorial conformation and from calorimetric data an energy difference of ca. 2.5 kJ mol^{-1} favouring the N-H equatorial conformer was found. Low temperature NMR measurements on dried piperidine show two conformations at -172° in the ratio of 85:15 (ΔG 1.5 kJ mol^{-1}), the predominant form assigned[21] as possessing the equatorial N-H. From a line shape analysis at -142°, a first-order rate constant (major form to minor form) of 240 ± 20 s^{-1} was calculated[21] and using absolute rate theory, a free energy of activation ($\Delta G^{\ddagger}$) of 25.5 ± 1 kJ mol^{-1} has been obtained for the $N\text{-}H_e \rightleftharpoons N\text{-}H_a$ process (e = equatorial, a = axial). Total energies were calculated[22] for (3) and (4), the equatorial conformers assigned as the more stable. The free energy barrier for ring inversion in (3) was measured[23] by dynamic ^1H NMR spectroscopy to be 43.5 kJ mol^{-1}.

Thus, the evidence is stronger in favour of the

existence of piperidine as mainly the conformation with the equatorial N-H.

Allinger[24] and Katritzky[25] studied the dipole moments of 4(4-chlorophenyl)piperidine (12) and its N-methyl derivative (13), assigning the equatorial conformations to be more stable by 1.68-2.1 kJ mol^{-1} (12) and 7.1 kJ mol^{-1} (13) respectively. Dipole moment measurements were also taken to indicate a conformational free-energy difference of 2.7 kJ mol^{-1} for an N-methyl group in the piperidine ring system in favour of the equatorial methyl group[26].

From analysis of cobalt(III)-porphyrin shifted ^{1}H NMR spectra[27] and low temperature ^{13}C NMR spectra[28], 4-substituted piperidines (14) are claimed to prefer a conformation with the substituent equatorial but with a significant proportion (15-48%) of the axial conformation in the equilibrium. In these publications, no reference was made to the orientation of the N-H bond. Indeed, this system does not create a satisfactory model for the uncomplexed piperidine base, as coordination of the piperidine nitrogen is likely to affect both the nitrogen configurational equilibrium and the ring conformational equilibrium.

Kinetically controlled protonation[29-30] **(Scheme 3)** of (4) and kinetically controlled nitrene-trapping[31] **(Scheme 4)** were used to measure the conformational free energy difference for the interconversion of the conformations. The measured value (ca. 11.5 kJ mol^{-1}) is larger than that (7 kJ mol^{-1})[32] for methylcyclohexane and this difference was explained by the closer proximity of the axial N-Me group of (4) to the syn-axial hydrogens on C-3 and C-5. Dynamic ^{1}H NMR measurements[33] gave the barrier to ring inversion in (4) as $\Delta G^{\ddagger}$ at -28° = 49.6-50.4 kJ mol^{-1}. Dipole moment measurements in cyclohexane were used to estimate ΔG° of 4 kJ mol^{-1} and 6 kJ mol^{-1} for the equilibrium **(Scheme 5)** where R = Et (5) (83.3% e R) and R = i-Pr (6) (92% e R) respectively[26].

For N-chloropiperidine (7), the ^{13}C NMR spectrum shows[34] signals for both $N\text{-}Cl_a$ and $N\text{-}Cl_e$ conformers at -98°, and the free energy difference for the $N\text{-}Cl_e \rightarrow N\text{-}Cl_a$ equilibrium was calculated to be 6.3 ± 0.4 kJ mol^{-1}. This is claimed to demonstrate an increased preference for the conformation bearing the equatorial chlorine substituent compared with chlorocyclohexane, for which the conformational free energy difference is 2.1 kJ mol^{-1}. The free-energy of activation ($\Delta G^{\ddagger}$) for nitrogen inversion of (7) has been estimated as 43 ± 1 kJ mol^{-1} ($N\text{-}Cl_a \rightarrow N\text{-}Cl_e$) or 49 ± 1 kJ mol^{-1} ($N\text{-}Cl_e \rightarrow N\text{-}Cl_a$). NMR

measurements indicate that the N-fluoro substituent of (8)[35] and the N-SO_2Me of (9)[36] exist mainly in the equatorial orientation. NMR chemical shifts and coupling constants[37] were interpreted as indicating a strong preference for the oxygen substituent of N-alkylpiperidine-N-oxides (15) to adopt the axial orientation of the N-O bond. Where the piperidine ring is substituted on the C-2 and C-6 positions, as in (16) and (17), a planar equatorial nitrogen substituent can adopt an orientation either in the molecular mirror plane or at right angles to it, depending on the steric requirement of the substituent[38].

For N-benzoylpiperidine (18), it is claimed that the planarity of the N atom can be adduced from ^{13}C NMR analysis[39].

From UV/visible absorption data, it has been inferred[40] that a through-bond interaction between functional groups via the intervening sigma bonds in a bridged N-aryl piperidine derivative (19), having an electronegative substituent at C-4, stabilizes the axial orientation of the aryl group. It is claimed that this stereochemical preference was verified by X-ray crystal structure analysis, although the X-ray data were not presented.

Crystallographic studies of N-substituted piperidines (eg. 1,2,5-trimethyl-4-hydroxy-4-phenylpiperidines and 1-(1-phenylcyclohexyl)piperidine) have clearly established[41-44] that the ring adopts a chair conformation with nitrogen substituents equatorial.

On balance, the evidence in favour of the existence of piperidine and N-substituted piperidines as mainly the equatorial N-H or N-substituent conformers would appear to be stronger. There are many publications which clearly establish from X-ray crystal structure analysis of highly substituted piperidines that the N-substituent bond is equatorial in the solid state.

Hexahydropyridazines (1,2-Diazacyclohexanes).

1,2-Diazacyclohexanes can be prepared **(Scheme 6)** by Diels-Alder reaction[45] of diethyl azidodicarboxylate with conjugated, substituted dienes, followed by catalytic hydrogenation and other desired structural modification. An alternative synthesis **(Scheme 7)** is nucleophilic-addition-with-elimination reaction[46] of hydrazines with activated 1,4-diacid derivatives.

The effect of introducing a second N atom at the 2-

position of a piperidine ring raises the nitrogen inversion barriers to a point where they are comparable with that for ring inversion.

Three types of inversion barriers were recognised[47] in 1,2-diazacyclohexanes : (i) high energy (50.4 kJ mol^{-1}) configurational nitrogen inversion where the nitrogen substituents pass within close proximity of each other; (ii) intermediate energy (40.2 kJ mol^{-1}) ee→aa ring inversions; (iii) low energy (34 kJ mol^{-1}) N-inversions without passing.

For 1,2-disubstituted 1,2-diazacyclohexanes, e.g. (20), there are four different possible conformational changes[48] **(Scheme 8)**, two different ring inversions and two different nitrogen inversions. The processes which involve the passing of methyl groups, i.e. the four identical N inversions and the two identical ring inversions which cross the heavy line bisecting **Scheme 8**, are of high energy and will be slow compared with the lower energy interconversions which do not cross the line. It is claimed that this energy difference accounts for the appearance of the $N-CH_2$ signal as an AB double doublet in the ^1H NMR spectrum while the $N-CH_3$ signal is a singlet.

From ^{13}C NMR measurements, (20) is claimed[49] to exist in solution as a mixture of the diequatorial-methyl (ee) form (21) and the axial-equatorial (ae) (22) with the former slightly predominating. The diaxial-methyl (aa) form (23) was apparently not detected. The data are interpreted as showing that (21) is about 1.3 kJ mol^{-1} more stable than (22), and that $\Delta G^{\ddagger}$ for the two different N inversions possible for (20) differ by about 20 kJ mol^{-1}, principally caused by lone-pair...lone-pair repulsion. The favouring of the ee conformer over the ae conformer of (20) by 1.3 kJ mol^{-1} in solution is estimated[50], by variable-temperature photoelectron spectroscopy, to increase to 6 ± 0.35 kJ mol^{-1} in the vapour phase.

In the case of the two isomeric 1,2,3,6-tetramethyl-1,2-diazacyclohexanes only ae conformations (24) and (25) are assigned[49] by ^{13}C NMR to be present in solution. 1,6-Diazabicyclo[4.4.0]decane appears to favour the ee conformation (26) [ΔG^{o} at -49^{o} trans $\rightleftharpoons$ cis > 10 kJ mol^{-1}], a result supported by photoelectron spectroscopy[51].

From variable temperature ESR spectra, the cations of (20), the separated (24) and (25), 1,2,3,3,6,6-hexamethylhexahydropyridazine (27) and 3,4-dimethyl-3,4-diazabicyclo[4.4.0]decane (28) are reported[52] to exist

in half-chair conformations.

X-ray crystal structure analysis of (28) shows[53] both methyl groups occupy equatorial positions in the solid state. The CN-NC and the MeN-NMe torsion angles are 65° and 64° respectively, indicating that the ring is more puckered (about the N-N bond) than the cyclohexane ring. In contrast, 2,3-dimethyl-2,3-diazatricyclo [8.4.0.$0^{4,9}$] tetradec-9-ene (29) has the ae conformation and the dihedral angles, 67° for CN-NC, and 72° for MeN-NMe, however, also indicate an increased puckering of the heterocyclic ring relative to cyclohexene.

The preferred conformation of hydrazine has the lone pair orbitals gauche[53a]. Observation of the ae conformation in 1,2-diazacyclohexanes is therefore not unexpected.

Hexahydropyrimidines (1,3-Diazacyclohexanes).

1,3-Diazacyclohexanes have been synthesised[54-55] from appropriately substituted trimethylene diamines and aldehydes or dibromomethane[56].

The introduction of a heteroatom β to the N-H group

of piperidine is claimed[57] to result in the predominance of the ae conformation (30). Two possible explanations for this effect are (i) attraction between the lone-pair and the N-H in the N-H axial conformer (30), and (ii) dipolar repulsion (rabbit ear effect, see p. 1) between the two lone-pairs in the ee conformer (31). In contrast, conformational analysis by molecular mechanics[58] predicts a preference for the ee form.

IR measurements[57,59] on the N-methyl derivative (32) are interpreted as indicating the presence of an axial N-H group, as (35), and the same conclusion was reached[60] from analysis of the CH-NH coupling constants in the ^{1}H NMR spectrum at low temperatures. For the N,N'-dimethyl derivative (33), low temperature ^{13}C NMR measurements[61] were taken to indicate the presence of both ae and ee conformers at -150^{o} with predominance of the ee conformation (36) **(Scheme 9)**. This result is in agreement with estimates based on molecular mechanics, which show 66.4% of the ee conformation[58], and with dipole moment measurement[62]. Comparisons[63] of the Δ_{ae} and J_{gem} of (36/37) with those of model compounds (38) and (39) indicate that the conformational equilibrium on nitrogen in (36/37) lies part-way between the ee and ae extremes and that there is only a small difference in free energy between these ae and ee conformers. Calculation of the equilibrium position from comparison

of the chemical shift of axial protons with the values in (38) and (39) is in agreement with the predominance of (36)[64]. The chemical shifts are , however, sensitive to the effect of the 5-substituents and, as previously noted, such chemical shift comparisons are generally unreliable[65].

For the ring-inversion of (33), the $\Delta G^{\ddagger}$ has been estimated[54] by ^{1}H NMR to be 47.5 ± 1.7 kJ mol^{-1} at -29 ± 4°. From variable temperature ^{13}C NMR studies of (33), the $\Delta G^{\ddagger}$ for the conversions of ee → transition state and ae → transition state have been estimated[66] to be 32 and 29 kJ mol^{-1} respectively and the corresponding values for (34) are 29 and 26.5 kJ mol^{-1}.

^{1}H NMR studies of 1,3-diazacyclohexanes (40-43), bearing a 2-methyl or 2-benzyl substituent, were interpreted[55] in terms of an axial hydrogen and equatorial substituent.

From molecular mechanics calculations on (44), it can be inferred[58] that the presence of a 2-methyl group stabilizes the ae conformation (45) (83.4% ae). This result is in agreement with the conclusions reached from ^{13}C NMR measurements[66]. The proportion of the conformation with C-substituent equatorial has been

claimed to decrease[58] as the size of the N-substituent increases. The proportion of the population of (44) with the conformation in which C-substituent is axial is 15.4% according to molecular mechanics and 9.5-11.2% according to ^{13}C NMR studies[61].

Changes observed in the ^{1}H NMR spectra of bis-(1-hexahydropyrimidyl)methane, as the temperature is lowered are explained[67] in terms of the existence of two diastereoisomeric sets of conformations interconvertible by a ring inversion process, viz. the meso set (46) which shows an AB double doublet for the bridging methylene group and the racemic set (47) which shows a singlet. Two AB double doublets for the ring $N-CH_2-N$ groups are observed in both cases.

Dipole moment measurements[68,69] were used to assign the predominant conformation of (48) as that with the axial nitro group and both R groups (R = benzyl and R = cyclohexyl) equatorial. The measurement of geminal coupling constant values is claimed[70] to support this conclusion.

It should be noted that the above solution studies have not been corroborated by solid state evidence, and that the conformational preferences are affected by the presence of C-substituents.

In the solid state[71], the pyrimidine ring of 1,3,5,5-tetranitrohexahydropyrimidine (49) adopts the chair conformation with diaxial N-nitro groups.

Piperazines (1,4-Diazacyclohexanes).

Piperazine (51) is prepared[72] **(Scheme 10)** by the catalytic (Raney nickel) cyclodehydration of N-(2-hydroxyethyl) ethenediamine (50) or diethylenetriamine. 1-t-Butyl-4-alkylpiperazines (53) and (54) have been synthesised[73] **(Scheme 11)** by condensation of primary alkylamines with t-butyl-di(2-chloroethyl)amine (57).

Analysis of the N-H stretching vibrations of N-t-butylpiperazine (52) were interpreted[59] as indicating the predominance of the N-H equatorial conformer. An equilibrium value of 63 : 27, equatorial : axial N-H **(Scheme 12)** was estimated[59] by dipole moment measurement in cyclohexane solution at 25°.

From dipole moment measurements[74] of the 1-alkyl-4-t-butylpiperazines (53) and (54) in cyclohexane, it is claimed that the N-methyl and N-ethyl groups **(Scheme 13)** occupy the equatorial orientation.

Kinetically controlled protonation of N,N'-dimethylpiperazine[75] (55) was interpreted as indicating that the N-Me groups prefer the equatorial over the axial orientation by about 12.5 ± 0.2 kJ mol^{-1} which is close to the value found in N-methylpiperidine (4).

Molecular mechanics[76] calculations suggest that piperazine derivatives should be more stable as ee conformers. The more highly N-substituted the molecule, the greater is the proportion of ee conformers. The N-H piperazines are predicted to have 14-20% of the N-H aa conformation.

Electron diffraction studies[77] on (55) show a flatter chair than in cyclohexane, with both N-methyl groups equatorial. The ring inversion barriers[78] in the piperazines have been estimated as $\Delta G^{\ddagger}$ 43.3 kJ mol^{-1} for piperazine (51) and 48 kJ mol^{-1} for N-methylpiperazine (56) and these values are almost identical to those for the piperidines, 43.7 kJ mol^{-1} for (3) and 50 kJ mol^{-1} for (4).

In the solid state, the 1,4-dibenzoyl-2,5-dialkylpiperazines (58), in which the alkyl groups are <u>cis</u> to each other, exist in twist boat conformations (59) whereas ^{13}C NMR spectra indicated that the <u>trans</u> (60) isomers have a chair conformation with diaxial

alkyl groups[79]. In these molecules the N atoms are approximately planar. X-ray crystal structure analysis[80] shows that N,N'-di(aryl)piperazine N,N'-dioxide (61) exists in the chair form with equatorial aryl groups and axial N-oxide bonds.

Hexahydro-1,3,5-triazines(1,3,5-Triazacyclohexanes)

1,3,5-Trisubstituted-1,3,5-Triazacyclohexanes (62) **(Scheme 14)** are commomly prepared by the reaction of equimolar quantities of aqueous formaldehyde and an aliphatic or aromatic primary amine, sometimes in the presence of hydroxide ion, formally giving aldimines which rapidly trimerize[81]. Alternatively, this condensation may be effected in anhydrous conditions by heating the amine with paraformaldehyde in an inert solvent or with dimethyl sulphoxide in the presence of phosphorus pentoxide to generate formaldehyde in situ. The tribenzyl compound (63) was formed[81] **(Scheme 15)** by treating the quaternary salt of hexamethylene tetramine (75) with benzyl iodide in hot alkali. The triphenyl compound (64) has been prepared[81] by heating aniline with (75) or methylchloromethylsulphate as sources of formaldehyde.

From the condensation of arylamines with

formaldehyde, it has been possible to isolate the 1:1 N-methyleneaniline (76)[82], the 2:1 bis(anilino)methane (77)[83], and the cyclic 4:4 adducts (1,3,5,7-tetraazacyclooctanes) (78)[83,84] as well as the cyclic 3:3 triazacyclohexanes (62) . Although (77), (78) and (62) are formally oligomers of (76), it is thought that hydroxyamines of the type (80) are the reactive intermediates of the oligomerisation. Sometimes, higher molecular weight products ("polymer") are formed in arylamine / formaldehyde condensations.

The N-methyleneanilines (76) have been characterised[82] in cases where oligomerisation has been hindered by the presence of large substituents on the ortho positions of the phenyl ring.

The formation of bis(anilino)methanes[83] (2:1 adducts) (77) appears to be favoured when strong electron withdrawing groups are present on the phenyl ring, reducing the basicity of the amine group. The formation of such adducts is observed for 2-, 3- and 4-nitroaniline, for 2- and 4-alkoxycarbonylaniline and for 4-cyanoaniline. The 4:4 cyclic adducts (78) have been characterised[84,83] in some cases and the solid state conformation has been determined by X-ray analysis for (79).

From dipole moment measurements in solution, 1,3,5-trimethyl-1,3,5-triazacyclohexane (65) has been claimed[85] to exist in two equally populated conformations in which the methyl groups are arranged aae (81) and aee (82). The dipole moment data are interpreted as indicating that for 1,3,5-triethyl-1,3,5-triazacyclohexane (66) the monoaxial conformer (82) is slightly favoured and that 1,3,5-tri-t-butyl-1,3,5-triazacyclohexane (67) exists as approximately 85% in the aee conformer (82).

Low temperature ^{1}H and ^{13}C NMR measurements[86,87] are claimed to show the predominance of the aee (82) conformation of (65) in solution. The barriers to ring inversion and nitrogen inversion were estimated[86] respectively as $\Delta G^{\ddagger}$ 55.5 ± 0.8 kJ mol^{-1} at -5° and 30.2 ± 0.4 kJ mol^{-1} at -123.5°. The aee (82) is also claimed as the main solution conformation of the triethyl (66)[87], triisopropyl (68)[87] and trimethoxy (69)[88] derivatives. This result is apparently supported by photoelectron spectroscopy[89] of (65)-(68) and (84).

The barriers to ring and nitrogen inversion of 1,3,5-triazacyclohexanes have been shown[87] to decrease with increasing size of substituent.

^{13}C NMR spectra of α-tripiperideine (84) and β-

tripiperideine (85) at low temperature is interpreted as showing the predominant conformations as those with one axial N-alkyl substituent. The $\Delta G^{\ddagger}$ of 47 ± 0.4 kJ mol^{-1} observed for interconversion in (84) has been assigned to inversion of one ring and a N atom[90].

In the solid state, 1,3,5-triphenyl-1,3,5-triazacyclohexane (64)[91] exists in a chair conformation with the aae orientation of substituents. The torsion angles around N(1)-C(2), C(2)-N(3) and N(3)-C(4) bonds are respectively -58.8°, +57.4° and -56.4° (average 57.5°). The bond angles at N atoms indicate their pyramidal geometry.

The solid-state conformation of the tribenzyl compound (63) is temperature dependent[92]. Below -23°, X-ray analysis shows that (63) exists as a single aae conformer but, at higher temperatures, nitrogen inversion in the solid results in the co-existence of the aae and the aee conformations, the proportion of the latter increasing with rise in temperature.

In the solid state, 1,3,5-triacetoxy-1,3,5-triazacyclohexane (70) adopts the aaa conformation (83) with an average ring torsion angle[93] of 44°. The short O...O intramolecular axial separations of 2.82-2.97 A°

suggest that intramolecular dipole-dipole attractions between the axial substituents may exert a stabilising influence on the triaxial conformation, in addition to the effect of crystal packing forces.

The 1,3,5-tri(phenylsulfonyl) derivative (71) adopts aee stereochemistry in the crystal[94] whereas axial/equatorial assignment for the 1,3,5-tris(methylsulfonyl) compound (72) is inapplicable as it possesses two planar nitrogens and one flattened pyramidal nitrogen.

The 1,3,5-triacetyl derivative (73), with delocalised N lone pairs, has planar geometry at all three N atoms[95].

The 1,3,5-trinitro derivative (74) has been studied both on its own[96] and in a complex with tetrahydrothiophene 1,1-dioxide[97]. In both, two of the N atoms of the ring have pyramidal geometry with diaxial stereochemistry in the free compound and axial-equatorial stereochemistry in the complex, whereas the third N atom of the ring has planar geometry.

It will be demonstrated later in this thesis that eight 1,3,5-triazacyclohexanes exist as the aae conformation in the solid state. The existence of this

conformation cannot thus be regarded simply as an accident of crystal packing forces but must be a consequence of the "rabbit ear" effect (see p 1) which disfavours the aee conformation through 1,3 dipolar alignment of N lone pairs. It is most likely that the aae is also a major conformation in the solution equilibrium, an observation which contradicts some solution assignments (see above). It will be shown that two of the 1,3,5-triazacyclohexanes studied in the present work adopt the aee conformation in the solid state. This is considered to be the result of crystal packing and indicative of a small energy difference between the aae and aee conformers.

Conclusions discussed in this review regarding di-, tri- and tetra-azacyclohexane conformations, based solely on solution measurements, must thus be regarded as tenuous until fully substantiated by a sufficient number of X-ray analyses.

Hexahydro-1,2,4,5-tetrazines (1,2,4,5-Tetraazacyclohexanes).

1,2,4,5-Tetraalkylhexahydro-1,2,4,5-tetrazines can be prepared by the 2:2 condensation of formaldehyde with 1,2-dialkylhydrazines as in the formation of tetra-N-methyl- (86)[98] and tetra-N-ethylhexahydro-1,2,4,5-

tetrazine (87)[99] respectively from 1,2-dimethyl- and 1,2-diethyl hydrazine. A C-substituted derivative (88) was prepared by replacing formaldehyde by acetaldehyde[100]. The fused hexahydro-1,2,4,5-tetrazines (90)[101] and (91)[99] are formed **(Scheme 16)** by reaction of formaldehyde with hexahydropyridazine (93) and 1,2,3,6-tetrahydropyridazine (94).

In solution 1,2,4,5-tetraalkylhexahydro-1,2,4,5-tetrazines may exist in three conformational sets **(Scheme 17)** in which there is no 1,3-diaxial arrangement of substituents and within which interconversion is by nitrogen inversion.

The low temperature ^{1}H NMR spectrum of (86) at -87° appears to show[102] an AB double doublet for the N-CH_2-N and 1:1 doublet for the methyl groups. These results were interpreted in terms of predominance of the aeae conformation (96) (set II), in contrast with the conclusion from dipole moment studies[103] which supported the predominance of the aaee conformation (98) (set III). The ^{1}H NMR spectrum, vibrational spectra and dipole moment measurement are claimed to demonstrate[104] that the tetramethyl derivative (86) exists as set III **(Scheme 17))** with the predominance of the aeee conformation (97) (70%) over aaee (98) (30%) which are

rapidly interconverting, whereas the tetraethyl derivative (87) exists as a mixture of set II [aeae (96), 65%] and set III [aeee (97), 33% and aaee (98), 2%] **(Scheme 17)** which are also rapidly interconverting. The saturated tricyclic compound (90) is considered[99,104] to exist mainly in the eeee conformer (99) (set I) and the unsaturated compound (92) as three conformers with 67% aeee (100) (set III), 20% aeae (101) (set II) and 13% eeee (102) (set I) respectively.[104,105]. From ^{13}C NMR[100] measurement, 1,2,3,4,5,6-hexamethyl-1,2,4,5-tetrazine (88) is assigned to be the conformation (103) with the C-methyl groups diequatorial and the N-methyl groups symmetrically aeae (set II).

In the solid, state 1,2-dimethylhexahydro-1,2,4,5-tetrazine (104)[106] exists in a chair conformation with equatorial N-methyl groups and axial N-hydrogen atoms (cf. (98), set III, **Scheme 17**). 1,4-Dimethyl-2,5-dibenzyl-1,2,4,5-tetraazacyclohexane exists in the aeae chair conformation (105) (cf. set II, **scheme 17**) with the benzyl and methyl groups in axial and equatorial orientations respectively. The same conformation was found for the tetrabenzyl derivative (89)[107]. In the solid state, the saturated and unsaturated tricyclic compounds (90) and (91) exist in chair conformations with eeee (99) (cf. set I, **scheme 17**) and aeee (100) (cf. (97) set III) orientations respectively[107].

Chapter 2

Synthesis and Conformational Study of 1,3,5-Trisubstituted-1,3,5-Triazacyclohexanes

Introduction

The 1,3,5-triazacyclohexanes (62) have been known since 1884 when the 1,3,5-triphenyl derivative (64) was prepared independently by Tollens[108] and Paterno[109] by condensation of aniline with formalin.

Numerous patent claims have been made covering the diverse uses (only a few illustrative references[110-119] are cited) of 1,3,5-triazacyclohexanes as adhesion promoter, anticorrosive, biocide (acaricide, antiviral, bacteriocide, fungicide, herbicide, insecticide, nematocide), dye constituent, polymer auxiliary (activator, catalyst, constituent of flame-resistant and oxidation-resistant polymers, cross-linking enhancer, hardening accelerator, moulding binder, reinforcement constituent), in colour photographic processing, in thermal imaging and in fabric and leather finishing. Some patent claims cover improved methods of synthesis of 1,3,5-triazacyclohexanes and their use as synthetic precursors of active compounds.

While the conformations of 1,3,5- trialkyl-1,3,5-triazacyclohexanes have been widely studied (see pp 17-22) the conformations of the triaryl compounds have received comparatively little attention. In the current work, it was proposed to synthesize a series of 1,3,5-

triaryl-1,3,5-triazacyclohexanes, bearing electron-withdrawing or electron-donating substituents at varing positions on the aryl rings and study the effect of the size and nature of the N-substituents on the heterocyclic ring conformation in the solid state by X-ray crystal structure analysis. It was expected that this analysis would also provide definitive information on the axial-equatorial preference of the nitrogen lone pairs. Lone pair delocalisation would be manifest in the bond angles around the nitrogen atoms, in the N-C(Ar) bond lengths and in the rotational attitude of the aryl ring planes. It was hoped that the results would be of general significance within the wider field of six-membered saturated heterocycles. Noting that ring and nitrogen inversion barriers[87] within 1,3,5-triazacyclohexanes decrease with increasing size of N-substituent, it was considered unlikely that conformational data would be easily derived from variable-temperature solution NMR measurements.

Discussion

1,3,5-Tri-(2-fluorophenyl)-1,3,5-triazacyclohexane (106) was prepared by the condensation of formalin with 2-fluoroaniline in the presence of sodium hydroxide. The 3- and 4- fluorophenyl compounds, (107) and (108) were formed by reaction of paraformaldehyde with 3-fluoroaniline in benzene and formalin with 4-fluoroaniline in ethanol without added stong base.

(106), (107) and (108) were obtained as crystalline products in 81, 79 and 69% yield respectively. The microanalytical figures were consistent with the molecular formula $C_{21}H_{18}F_3N_3$. The mass spectra of (106) and (107) showed molecular ions at m/z 369 but this peak was absent from the mass spectrum of (108). All three spectra showed base peaks at m/z 123 corresponding to the daughter ion $[ArNCH_2]^+$. The IR spectra showed C-H aryl stretching absorptions at 3015-3070 cm^{-1} and strong aromatic ring breathing in the 1487-1610 cm^{-1} region. In the solution state, facile conformational inversion of (106), (107) and (108) results in averaging of the ^1H NMR, signals of the axial and equatorial CH_2 hydrogen atoms, which appear as a narrow singlet at δ 4.92 **(Fig. 2)**, 4.91 **(Fig. 4)** and 4.76 **(Fig. 6)** respectively. The ^{13}C NMR spectrum **(Fig. 3)** of (106) showed seven

absorptions, two singlets at δ 69.56 and 121.25 due to C(2) and C(11) and five doublets at δ 115.86 (J_{CCF} = 20.83 Hz) due to C(9), at δ 123.28 (J_{CCCF} = 8 Hz) due to C(10), at δ 124.35 (J_{CCCF} = 3.47 Hz) due to C(12), at δ 136.48 (J_{CCF} = 8.96 Hz) due to C(7) and at δ 155.67 (J_{CF} = 245.10 Hz) due to C(8). The ^{13}C NMR spectrum **(Fig. 5)** of (107) showed also seven absorptions, a singlet at δ 67.84 due to C(2) and six doublets at δ 104.55 (J_{CCF} = 24.61 Hz) due to C(8), at δ 107.73 (J_{CCF} = 21.44 Hz) due to C(10), at δ 112.91 (J_{CCCCF} = 2.52 Hz) due to C(12), at δ 130.37 (J_{CCCF} = 9.76 Hz) due to C(11), at δ 149.98 (J_{CCCF} = 9.56 Hz) due to C(7) and at δ 163.55 (J_{CF} = 244.82 Hz) due to C(9). Five absorptions appeared in the ^{13}C NMR spectrum **(Fig. 7)** of (108), a singlet at δ 70.44 due to methylene C(2) and four doublets at δ 115.64 (J_{CCF} = 22.14 Hz) due to C(9) and C(11), at δ 119.87 (J_{CCCF} = 7.75 Hz) due to C(8) and C(12), 144.97 at δ (J_{CCCCF} = 2.42 Hz) due to C(7) and at δ 157.84 (J_{CF} = 240.50 Hz) due to C(10).

An attempt was made to examine the conformation of (108) in solution in CD_2Cl_2-CF_2Cl_2-$(CD_3)_2CO$ (1:1:1) by low-temperature ^1H NMR spectrometry. Marked broadening of both aryl and methylene resonances was observed as the temperature was taken below -70° but the coalescence temperature for the methylene signal had not been reached by -135°. A similar observation was reported

for (109) which failed to exhibit separation between axial and equatorial H signals down to -80°. This behaviour has been ascribed[120] to fast ring inversion as a result of the suggested near planarity of the N atoms of (109). In contrast, the methylene protons of the 1,3,5-trialkyl-1,3,5-triazacyclohexanes displayed[86] an AB NMR spectrum at low temperature (-90°).

In the solid state, all three monofluorophenyl derivatives **(Fig. 49-51)**, like the unsubstituted phenyl[91] compound, exist in the chair conformation with diaxial-equatorial substituents but the 2- and 3-fluoro substituents of (106) and (107) exert an additional non-bonded influence on the orientation of the aryl planes. Conformational parameters for (106)-(108) are listed in **Table 1**. In the 4-fluorophenyl compound (108), the equatorial aromatic ring is in the ideal perpendicular orientation, the angle which the aromatic ring makes with the symmetry plane of the trizacyclohexane ring being close to 90°. This is in the same orientation as the equatorial aryl group of (64), and in this conformation there is a maximum overlap between the N lone-pair and the π-orbitals of the aromatic ring, as shown by the shorter N-C(Ar) bond length of (108) compared with those of (106) and (107). In the 3-fluorophenyl compound (107), the equatorial aromatic

ring is inclined from the perpendicular orientation, the angle between the aromatic ring and the symmetry plane of the triazacyclohexane ring being 64.7°. The plane of the equatorial 2-fluorophenyl of (106) forms an angle of only 22.5° with the symmetry plane of the heterocycle. The change in the orientation of the aryl ring from 2- to 3- to 4-fluorophenyl clearly depends on the decreasing repulsion between the equatorial hydrogen atoms at C-2 and C-6 of the heterocyclic ring and the atoms bonded to the aryl ring ortho to the N-C(Ar) bond. This non-bonded steric interaction is a maximum when the fluorine substituent occupies the aryl 2-position and minimum when it occupies the 4-position. When the fluorine substituent is in the aryl 3-position it exerts a buttressing effect on the adjacent aryl C-2 hydrogen atom increasing (relative to the 4-fluorophenyl case) its non-bonded steric interaction with the heterocyclic ring hydrogens.

The conformational comparisons of (106) and (108) can be made with phenylcyclohexane where two limiting orientations of the phenyl group are possible, with the plane of the aromatic ring either perpendicular or parallel to the symmetry plane of the substituted cyclohexane ring[121]. Force-field calculations[121] and NMR measurements[122-124] have established that in the equatorial conformation (120) the phenyl group of

phenylcyclohexane favours the parallel orientation to avoid repulsive interactions between the ortho H atoms of the phenyl and the equatorial H atoms at C-2 and C-6 of the cyclohexane whereas in the axial conformation (121) the perpendicular orientation is preferred to avoid interactions between an ortho H atom of the phenyl and the axial H atoms at C-3 and C-5 of the cyclohexane. Detailed study of the force-field calculations for the axial conformer shows that the preferred angle between the phenyl ring and the symmetry plane of the cyclohexane is actually ca. 65° rather than 90° with a variation in energy over this angular range of only ca. 0.84 kJ mol^{-1}. In 1,3,5-triphenyl-1,3,5-triazacyclohexane (64) the perpendicular orientation of a phenyl group maximises overlap between the phenyl π-orbitals and the adjacent N lone-pair orbital in both axial and equatorial conformations. In comparing (64) and (120) we note that the equatorial-perpendicular conformation of phenylcyclohexane has been calculated to be higher in energy than the equatorial-parallel conformation by ca. 16.4 kJ mol^{-1}. The H(ortho)...H(2e,6e) interactions for an equatorial phenyl in (64) are similar to those in (120), and an unfavourable H(ortho)...H(1a) interaction of the equatorial-parallel phenyl in (120) is replaced by a less unfavourable H(ortho)...N(lone-pair) interaction in

the equatorial-parallel rotamer of (64). It follows that the N lone-pair-phenyl π-orbital overlap requires a favourable energy term in excess of ca. 16.8 kJ mol^{-1} for the equatorial-perpendicular conformation to be preferred over the equatorial-parallel conformation in (64). Since the barrier to rotation about the N-C(Ar) bond has been estimated from spectroscopic measurements to be 24 kJ mol^{-1} in aniline[125] and 21.5 kJ mol^{-1} in N,N-dimethyl-aniline[126] but has been calculated by ab initio MO methods to be as low as 11.5 kJ mol^{-1} in aniline[127], the preferred orientation of an equatorial phenyl group in (64) and related compounds is a matter of some interest. The crystallographic results for (64) show that the equatorial phenyl group in that compound adopts the perpendicular orientation in the crystal[91].

The effect of the 2-, 3-, and 4-fluoro substituents on the orientation of the axial aryl rings is less pronounced than for the equatorial aryl groups. The orientation angle changes from 61-65° in the 4- and 3-fluorophenyl compounds (108) and (107) to 44-46° in the 2-fluorophenyl compound (106).

The nitrogen atoms of (106), (107) and (108) have distinctly pyramidal geometry. The N-C(2-fluorophenyl) bond of (106) is inclined at 48.5° to the CH_2-N-CH_2 plane at N(5) where the equatorial aryl ring is attached

and at 35.9° and 33.7° for the nitrogens bearing the axial groups. The N-C(3-fluorophenyl) equatorial bond of (107) is inclined at 32.6° to the CH_2-N-CH_2 plane, indicating that there is some overlap of the N lone-pair electrons with the aryl π system. The two axial N-C aryl bonds are inclined at 36.7° and 37.4° to the CH_2-N-CH_2. The N-C(4-fluorophenyl) bonds of (108) are inclined at 36.9°, 37.4° and 37.4° to the CH_2-N-CH_2 planes at the equatorial bond, and at the two axial bonds respectively **(Table 1)**. The largest out-of-plane angle, 48.5°,is for the equatorial 2-fluorophenyl ring which is close to the parallel orientation, i.e the aryl plane is parallel to the symmetry plane of the heterocyclic nucleus and the nitogen lone-pair electrons do not overlap with the π-system of the aryl ring. For comparison, spectroscopic studies on aniline[125,128] indicate that the angle between the NH_2 and C_6H_5N planes is ca. 37.5°. In N,N-dimethylaniline[129] the angle between the ring plane and that containing the two N-CH_3 bonds is 27°, whereas for N-methylaniline[130] and for 4-fluoroaniline[131] the corresponding angles are 20° and 46.4° respectively. Since the out-of-plane angle in a tetrahedral arrangement is 54.7°, the N-C(axial) bonds in (106)-(108) are not parallel to each other but are splayed outwards by 17-21° from the positions in an ideal chair conformer, ameliorating the non-bonded

interaction between the axial aryl groups. In the triazacyclohexane rings the torsion angles around the N-C bonds are in the range 52.7-59.5, mean 56.5°, compared with 55.9° for the cyclohexane ring[132] and 60° for the ideal chair conformation. The CH_2-N bond lengths are 1.443-1.479, mean 1.460 Å, similar to those in the tribenzyl compound (63) which are 1.445-1.480, mean 1.463 Å. The CH_2-N bonds are shorter than the C-C bonds in cyclohexane[132] 1.528 Å. The CH_2-N-CH_2 angles are somewhat smaller than N-CH_2-N, the former are in the range 108.2-110.7, mean 109.7°, the latter in the range 110.5-113.0, mean 111.9°.

The N and F atoms are not quite coplanar with the phenyl ring. The N atoms deviate from the phenyl planes by 0.024-0.139, mean 0.084 Å, whereas the F atoms have displacements of only 0.005-0.029, mean 0.014 Å. These departures from coplanarity correspond to out-of-plane angles of 0.2-1.2, mean 0.6°, for the F-C(Ar) bonds and 0.9-5.6, mean 3.4°, for the N-C(Ar) bonds.

The molecular geometry of aniline has recently been computed[127] by ab initio gradient MO methods. For the equilibrium conformation in which the dihedral angle between the N lone-pair orbital and the aromatic π-orbitals is 0°, the N-C(Ar) bond was estimated to be inclined at 2.4° to the aromatic plane. For the higher-

energy conformation in which the dihedral angle is 90°, the N atom does not deviate from the aromatic plane. In agreement with this, the minimum out-of-plane angle for the N-C(Ar) bonds in (106)-(108) (see **Table 1**) is for the equatorial-parallel bond in the 2-fluoro derivative (106), where the dihedral angle between the N lone-pair orbital and the aromatic π-orbitals is 67.5°. This involves concomitantly the most pyramidal of the N atoms and the one with the longest N-C(Ar) bond (1.427 Å). The ab initio calculations for fluorobenzene indicate no departure from planarity[133].

In substituted benzene rings, the ring angle at a substituent is related to the electron-donating or withdrawing character of the substituent[134-137]. The ring angles at electron withdrawing substituents have been shown to be greater than 120°. The observed values for (106), (107) and (108) are in the range 121.2-123.8°, mean 122.8° compared with the ring angle at F in fluorobenzene[134] of 122.9° and at N in nitrobenzene[134] of 122.2°. This enlargement of the ring angle arises from the carbon atom where F is attached being pushed towards the ring centre. The values obtained support the conclusions[134] based on microwave spectroscopy and electron diffraction data and confirm the prediction made in 1962 by Bak et al.[138] "that no kind of ordinary

monosubstitution, such as by halogens, aliphatic chains, OCH_3, $COCH_3$, CHO, COOH, CF_3, etc., is likely to cause benzene ring distortions exceeding about 0.005 A^o for the carbon-carbon distances and 2-3° for the valence angles". Where electron-donating substituents are present, the aryl ring angle at the substitued carbon atom has been shown to be less than 120°. For (106), (107) and (108), the ring angles at the aryl carbons attached to N are in the range 115.5-117.8°, mean 116.9° which may be compared with the ring angles at the carbon atoms bearing an NH_2 or $N(CH_3)_2$ in aniline[134], (118.7°) and N,N,N',N'-tetramethyl-4-phenylenediamine[139], (117.0 (2)°)*. An attempt has been made[140-141] to explain the larger ring angle at an aromatic carbon atom in terms of hybridization effects. In a carbon atom the 2s electrons experience a greater effective nuclear charge and are therefore held more tightly than the 2p electrons. Because of this it is more favourable energetically to have carbon orbitals with less than average s-character directed towards the most electron-withrawing substituents and orbitals with more than average s-character directed towards the least electron-withdrawing substituents, rather than to have a set of entirely equivalent orbitals.

* The final figure is the standard deviation

The investigation of the 2- and 4-chlorophenyl compounds (110), (111) support the results obtained for the 2- and 4-fluoro compounds. (110) And (111) were prepared by the reaction of formalin with 2-chloroaniline and 4-chloroaniline in toluene and EtOH respectively.

The structural assignments of (110) and (111) were established by their microanalytical data, consistent with the molecular formula, $C_{21}H_{18}Cl_3N_3$, and their spectroscopic properties. In both cases, molecular ion peaks are not observed in the mass spectra but peaks corresponding to daughter ions 2/3 M and 1/3 M are present at m/z 282, 280, 278 and 141, 139. The IR spectra show peaks at 3060, 2905 for (110) and 3020 cm^{-1} for (111) for C-H aryl stretching, in addition to strong peaks at 1486, 1478 for (110) and 1596, 1496 cm^{-1} for (111) of the aromatic ring. In solution, facile conformational interconversion in both compounds results in averaging of the ^1H NMR signals of the axial and equatorial CH_2 hydrogen atoms, which appear as a narrow singlet at δ 4.70 (110) **(Fig. 8)** and 4.78 (111) **(Fig. 10)**. The aromatic resonances of (110) are complex whereas those of (111) appear as a double doublet (J = 9 Hz).

The triazacyclohexane derivatives (110) and (111) adopt the aae chair conformation in the solid state **(Fig. 52-53)** with diaxial repulsion between aryl groups preferred to that between lone-pairs of electrons.

Conformational parameters for (110) and (111) are listed in **Table 2**. In (111) the angle between the equatorial aromatic ring and the symmetry plane of the triazacyclohexane is 90° and in this conformation there is a maximum overlap between the N(3) lone-pair and the π-orbitals of the aromatic ring. In (110), in contrast, the equatorial aromatic ring lies in the symmetry plane of the molecule so that there is no overlap between the N(3) lone-pair and the π-orbitals of the aromatic ring. The change in orientation can be attributed to the severe overcrowding that would arise for the chlorine atom in (110) if the molecule adopted the conformation of (111).

The substituent position also affects the axial aryl groups, since the orientation angle θ changes from 68.1° in (111) to 44.2° in (110), in accord with the results for the 2-and 4-fluorophenyl compounds.

The N atoms of (110) and (111) are distinctly pyramidal in character, the N-C(Ar) bonds being inclined

to the CH_2-N-CH_2 planes at 32.3-48.9° (**Table 2**). The out-of-plane angle in a tetrahedral arrangement of bonds is 54.7° and the out-of-plane angles of 32.3-35.3° indicate that the N-C(axial) bonds in (110) and (111) are bent outwards by 19-22° from the positions in an ideal chair conformer, alleviating the repulsion between the axial aryl groups. The largest out-of-plane angle, 48.9°, is for the equatorial aryl group at N(3) in the 2-chlorophenyl compound (110), with zero lone-pair / π-orbital overlap.

The N-C(Ar) bond here is 1.433 (4) Å, a little longer than the other N-C(Ar) bonds of 1.405 (8)-1.415 (3) Å in these molecules. The molecular geometry of aniline has been derived by ab initio gradient MO methods and the N-C bond length estimated[127] to increase from 1.415 to 1.449 Å as the dihedral angle between the lone-pair orbital of the pyramidal N atom and the aromatic π-orbitals changes from 0° to 90°.

Atom N(3) of the 2-chlorophenyl compound (110) lies in the plane of the equatorial aryl group, whereas the other N atoms of (110) and (111) deviate from their aryl planes by 0.101(2)-0.158(5) Å, corresponding to out-of-plane angles of 4.1-6.5° for the N-C(Ar) bonds. The MO calculations for aniline[127] found that the C-N bond lies

in the aromatic plane when the dihedral angle between the N lone-pair orbital and the aromatic π-orbitals is 90° and that the out-of-plane angle for the C-N bond increases to 2.4° when the dihedral angle between the orbitals is 0°. The maximum out-of-plane angle for the N-C(Ar) bonds in (110) and (111) is at N(3) **(Fig. 54)** in the 4-chlorophenyl compound, where the N lone-pair / π-orbital dihedral angle is 0°, in qualitative agreement with the MO calculations.

The CH_2-N-CH_2 angles are 109.3-110.8(2)° for (110) and 108.7-110.6(5)° for (111) and the N-CH_2-N angles are 112.0-113.4(3)° for (110) and 110.5-112.0(6)° for (111). Similar small differences were observed (vide infra) in the heterocyclic ring angles of 2-, 3- and 4-fluorophenyl compounds (106), (107) and (108). The torsion angles around the C-N bonds in the triazacyclohexane rings are 55.0-56.7(2)° for (110) and 55.6-58.9(5)° for (111) which differ slightly from those in fluoro compounds (106), (107) and (108) (52.7-59.5)°, mean (56.5)°.

1,3,5-Tri(2-methoxyphenyl)-1,3,5-triazacyclohexane (112)[114] was prepared by heating 2-anisidine and paraformaldehyde in an inert solvent (xylene) in presence of NaOH. The 1,3,5-Tri(4-methoxyphenyl) compound (113) was prepared from formalin and 4-

anisidine in EtOH.

The structures of (112) and (113) were confirmed by elemental analysis and ^{1}H NMR spectra **(Fig. 12, 14)** which showed sharp methoxy singlets at δ 3.82 and 3.72 and methylene resonances at δ 4.86 and 4.66 respectively, indicating that rapid conformational inversion, resulting in signal averaging, is likely to be taking place in solution.. For (113), the aromatic resonances appear as an AB double doublet (J = 9 Hz). For both (112) and (113) the mass spectra showed no molecular ion but the peak of highest-mass at m/z 135 was assigned to $[CHO_3C_6H_4NCH_2]^+$ (M/3).

The 2- and 4-methoxyphenyl compounds again both adopt the aae chair conformation **(Fig. 54-55)**. Conformational details of the molecules are listed in **Table 3.**

The N atoms of (112) and (113) have pyramidal geometry with the N-C(Ar) bonds inclined at 30.8-44.9 (2)° to their CH_2-N-CH_2 planes. The N-C(axial) bonds of (112) and (113) are bent outwards by 15-24° from the positions in an ideal chair conformer, reducing the interactions between the axial aryl groups.

The angle θ (**Table 3**) for (113) is in the range 62.4-63.6 (3)°, indicating that the dihedral angle between the N lone-pair orbital and the aromatic π-orbitals is ca. 26-28°, whereas in (112) θ is 32.8-40.0 (3)° and the lone-pair / π-orbital dihedral angle is increased to 50-57°.

The N atoms deviate from the phenyl planes by 0.036-0.160 (3) Å and the O atoms deviate by 0.004-0.079 Å, giving out-of-plane angles of 1.4-6.5 (3), mean 4.4°, for the N-C(Ar) bonds and 0.2-3.3 (3), mean 1.1°, for the O-C(Ar) bonds.

The packing of molecules of (112) in the unit cell is rather more compact than that of (113), since V/Z for (112) is 520 $(Å)^3$ and V/Z for (113) is 539 $(Å)^3$.

1,3,5-Tri-(4-tolylmethyl)-1,3,5-triazacyclohexane (114) was obtained[142] by reaction of 4-tolylmethylamine with formalin under reflux in EtOH.

The molecular formula $C_{27}H_{33}N_3$ was determined from microanalysis and ^1H NMR spectrum **(Fig. 16)** which showed singlets at δ 2.31, 3.41 and 3.62 of the CH_3, CH_2 and $N-CH_2-N$ respectively and a double doublet at δ 7.08 and 7.22 (J = 9 Hz) for the aromatic ring. The ^{13}C NMR spectrum **(Fig. 17)** showed (from DEPT scan) a methyl and

two methylene carbon adsorptions at δ 21.09, 56.73 and 73.66. The aryl carbon resonances appeared as a singlet at δ 128.84 for the H-C(Ar) and two quaternary carbons at δ 135.32 and 136.45.

1,3,5-Tri-(4-tolylmethyl)-1,3,5-triazacyclohexane (114) formed triclinic prisms, with space group $P\bar{1}$. In the solid state, the molecule adopts the aae chair conformation **(Fig. 56)**, in common with the 1,3,5-tri-aryl compounds (106-113) and 1,3,5-tri-benzyl-1,3,5-triazacyclohexane (63).

The N atoms of (114) have distinctly pyramidal bonding geometry, the exocyclic N-C bonds being inclined at 45.3° (2), 45.5° (2) and 53.5° (2) to the CH_2-N-CH_2 planes at N(1), N(3) and N(5), respectively. The out-of-plane angle for the equatorial N(5)-C(23) bond is close to the value of 54.7° for tetrahedrally arranged bonds whereas the out-of-plane angles for the axial N(1)-C(7) and N(3)-C(15) bonds are distinctly smaller and these bonds are bent outwards from ideal axial positions by ca. 9°, a displacement that relieves the 1,3-diaxial repulsion. Other geometrical responses to the repulsion between the axial substituents of N(1) and N(3) involve the N(1)-C(2)-N(3) ring angle of 116.8° (2) being distinctly larger than the other N-C-N ring angles

of 111.5° (2) and 112.0° (2) and the N(1)-C(2) and N(3)-C(2) ring torsion angles of -50.6° (2) and 50.6° (3) being substantially smaller than the N(5)-C(4) and N(5)-C(6) ring torsion angles of 61.1° (2) and -60.7° (2) . These molecular adjustments result in unexceptional 1,3-diaxial H...H and C...C separations : the H(7A)...H(15B) distance is 2.33 (3), H(7B)...H(15A) is 2.65 (3) and C(7)...C(15) is 3.246 (3) Å.

The flatter pyramids at the nitrogen atoms N(1) and N(3) of (114) indicate some rehybridization to give more s character to the bonds at these atoms and, in accord with this, the N-C ring bonds at N(1) and N(3) , 1.449-1.456 (3) Å, are slightly shorter than those at N(5), 1.466-1.477 (3) Å. Similar minor differences between the ring bonds at equatorial and axial sites occur in the tribenzyl[91] compound (63).

As before, the CH_2-N-CH_2 angles in the triazacyclohexane ring of (114) are all slightly smaller than tetrahedral, 108.0 (2)-109.4° (2), and the $N-CH_2-N$ angles are larger than tetrahedral, 111.5° (2)-116.8° (2). The $N-CH_2-C$ angles of the substituent groups are greater than tetrahedral, 112.4° (2)-113.8° (2). The torsion angles around the exocyclic $N-CH_2$ bonds deviate from ideal values of 60° and 180° to reduce steric

interactions : e.g. the torsion angle defined by C(6)-N(1)-C(7)-C(8) is -76.4° (3), that by C(4)-N(3)-C(15)-C(16) is 81.6° (3) and that by C(6)-N(5)-C(23)-C(24) is 71.7° (3).

1,3,5-Tri(4-tolyl)-1,3,5-triazacyclohexane (115) was prepared by the reaction of formalin and 4-toluidine in EtOH.

The structure of (115) was assigned on the basis of microanalysis which corresponded to the formula, $C_{24}H_{27}N_3$, and ^1H NMR **(Fig. 18)** in which two singlets at δ 2.22 and 4.74 were assigned to methyl and methylene protons repectively. The aryl resonances appeared as a double doublet at δ 6.39 and 7.64 (J = 9 Hz). The methyl and methylene carbon signals appeared as a quartet and a triplet at δ 15.2 and 64.2 respectively in the ^{13}C NMR spectrum **(Fig. 19)**. The aryl carbon resonances appeared as two doublets at δ 112.68 and 124.38 for the methine carbon and two singlets at δ 125.03 and 141.08 for the quaternary carbons.

Compound (115) gave crystals in a triclinic system with space group $P\bar{1}$. In contrast to the previous structures discussed, 1,3,5-tri(4-tolyl)-1,3,5-triazacyclohexane (115) exists, in the solid state, as a chair conformation with aee orientation of the aryl

substituents **(Fig. 57)**. The three N atoms of (115) are more uniformly pyramidal than those of (106)-(113) since (115) does not have syn diaxial repulsions between substituents : the N-C(Ar) bonds of (115) form out-of-plane angles with the CH_2-N-CH_2 planes of between 38.4° and 39.7° **(Table 4)** (cf., eg.36.9° - 37.4° for (108)). The N atoms are not coplanar with the phenyl ring. The out-of-plane angles between the N-C(Ar) bond and the phenyl planes are in the range 5.18°-6.16°, mean 5.66°.

For comparison, the ideal aniline conformation has C_s symmetry with the N lone pair of electrons in the symmetry plane perpendicular to the phenyl plane to allow maximal orbital overlap. If each lone pair orbital in (115) is assumed to bisect the C-N-C angle in Newman projection along the N-C(Ar) bond, the departure from the ideal aniline conformation is calculated to be 6° at N(1), 19° at N(3) and 2° at N(5) of (115) **(Fig. 58)**.

The N-C(Ar) bond lengths, 1.414 Å-1.432 Å, mean 1.426 Å are slightly larger than the N-C bond length in aniline (1.402 Å). This is consistent with the slightly greater degree of pyramidal character at the N atoms of the triazacyclohexanes.

The observation of these different conformations for closely related compounds suggests that the difference in energy between the aae and aee conformations of 1,3,5-triaryl-1,3,5-triazacyclohexanes is small. The absence of any unambiguous evidence for the eee conformation in these compounds emphasizes the important role of the lone pairs of electrons on the N atoms.

1,3,5-Tricyclohexyl-1,3,5-triazacyclohexane (116) was synthesised in 74% yield by the reaction of paraformaldehyde and cyclohexylamine in benzene.

The assigned structure of (116) was consistent with the microanalytical figures corresponding to the molecular formula $C_{21}H_{39}N_3$. The mass spectrum showed the M/3 peak at m/z 111. The presence of the cyclohexyl substituents was verified by the appearance of a complex methylene multiplet **(Fig. 20)**, of a relative integrated intensity 10H, at δ 0.95-2.00 and a methine envelope (1H) at δ 2.30-2.50. Distinct from these, the heterocyclic methylene groups gave rise to a sharp singlet , of relative intensity 2H, at δ 3.56. The methylene of the cyclohexyl substituents appeared as three singlets at δ 25.65, 26.13 and 30.24 in the ^{13}C NMR spectrum **(Fig. 21)**. The methine and methylene carbon resonances attached to nitrogen appeared as singlets at

δ 58.39 and 68.27 respectively.

In the solid state, the heterocyclic and the carbocyclic rings of (116) exist in chair conformations **(Fig. 58)**. With respect to the heterocycle, the N-C(cyclohexyl) bonds are oriented aee, as was observed for the tri(4-tolyl) compound (115) but not for the N-aryl compounds (106)-(113). These results suggest the 1,3-diaxial repulsions within the 1,3,5-triazacyclohexanes increase in the order aryl/aryl < lone-pair/lone-pair < C_6H_{11}/C_6H_{11}. This is in agreement with the greater steric requirements of cyclohexyl rings in comparison with aryl or 4-tolylmethyl substituents. All three cyclohexyl rings of (116) have the C-N exocyclic bonds equatorial.

The N atoms of (116) have distinctly pyramidal geometry, the N-C (cyclohexyl) bond being inclined at 52.2 (2), 46.7 (2) and 46.1 (2)° to the CH_2-N-CH_2 plane at N (1), N (3) and N (5), respectively. The average out-of-plane angle, 48.3°, is close to the corresponding angle at N(5) in the 2-fluorophenyl compound (106), 48.5°, at N(3) in the 2- chlorophenyl compound (110), 48.9° and in the tribenzyl derivative, 48.1° but differ from the other out-of-plane angles in (106)-(111), 32.3-37.4° **(Table 1-2)**.

In the triazacyclohexane ring of (116), the C-N torsion angles are in the range 55.8 (2)-61.4 (2), mean 59.3°. The C-C torsion angles in the cyclohexyl rings are rather smaller, 52.7 (2)-57.3 (2), mean 55.4°, with no distinction between axial (mean 55.8°) and equatorial (mean 55.3°) rings.

The N-C(cyclohexyl) bond lengths of (116) are 1.447 (2)-1.484 (2), mean 1.467 Å, similar to those in the 1,3,5-tribenzyl compound which are 1.445 (2)-1.480 (2), mean 1.463 Å. The C-N ring bonds, 1.447 (2)-1.465 (2), mean 1.460 Å are slightly shorter than the exocyclic bonds, 1.473 (2)-1.484 (2), mean 1.479 Å and those at the equatorial sites N(1) and N(5) are slightly longer than those at the axial site N(3). The CH_2-N-CH_2 angles are 106.9 (2)-109.1 (2), mean 107.9° which are smaller than those for fluoro and chloro compounds (106)-(108) and (111)-(112) and the N-CH_2-N angles are 110.5 (2)-112.9 (2), mean 111.6° which are close to those of (106)-(108) and (111)-(112).

In the cyclohexyl rings the C-C-C angles range from 109.1 (2) to 113.2 (2), mean 111.2°. The smallest angles, 109.1, 109.6, 109.7°, are at the cyclohexyl positions directly bonded to the N atoms [i.e. C(7), C(13), C(19)], indicating that a steric effect is

involved. Though the H-C-H angles of the cyclohexyl groups, 102.7 (17)-110.3 (19)°, are subject to fairly large errors, the mean value of 107.0° is undoubtedly significantly smaller than tetrahedral. The C-C bond lengths are 1.504 (3)-1.533 (2), mean 1.520 Å. The thirty-three C-H bonds of the cyclohexyl groups range from 0.90 (2) to 1.04 (3) Å and the mean length, 0.98 Å, is the customary 0.1 Å shorter than C-H internuclear distances determined by spectroscopy or neutron diffraction methods.

1,3,5-Tri(4-nitrophenyl)-1,3,5-triazacyclohexane (117) was prepared[143] by the reaction of 4-nitroaniline with DMSO and phosphorus pentoxide.

Recrystallisation from pyridine furnished (117) as small yellow needles, the melting point of which (275-276°, decomp.) differed significantly from the literature[143] value (286-287° decomp.). These crystals, however, gave microanalytical data consistent with the molecular formula, $C_{21}H_{18}N_6O_6$, and possessed satisfactory spectroscopic characteristics. There were five distinct absorptions in the ^{13}C NMR spectrum **(Fig. 23)**, two of which were due to aromatic quaternary carbons at δ 138.88 and 153.35, two to aromatic methine carbons at δ 111.76 and 128.19 and one to aliphatic

methylene carbons at δ 51.02, as shown by DEPT scans. The aromatic proton resonances **(Fig. 22)** appeared as an AB double doublet (J = 10 Hz) at δ 8.09 and 7.21 and the ring methylene protons as a sharp singlet at δ 5.35.

Slow crystallisation of (117) from pyridine over several weeks inside a desiccator over silica gel gave yellow, lustrous prisms, m.p. 290-291° (decomp.), which showed ^{1}H NMR absorptions **(Fig.24)** closely similar to those of the above needles accompanied by pyridine resonances. The prisms were assigned as a 1:1 pyridine solvate, $C_{21}H_{18}N_6O_6.C_5H_5N$ from microanalytical figures and the ^{1}H NMR integration.

1,3,5-Tri(4-nitrophenyl)-1,3,5-triazacyclohexane (117) formed in a monoclinic system with space group $P2_1/n$. X-ray crystal structure analysis of the prisms showed that the unit cell contained four molecules of 1,3,5-tri(4-nitrophenyl)-1,3,5-triazacyclohexane and four molecules of pyridine **(Fig. 59)**. The pyridine molecules were contained in spiral channels and the pyridine N atoms were found to be ordered, probably due to crystal packing forces. In the pyridine molecules the N-C bonds, 1.300, 1.312 (5) Å, are a little shorter than the C-C bonds, 1.327-1.430 (6), mean 1.368 Å.

Since the pyridine molecules were not totally

enclosed in the complex, they should, in principle, be able to diffuse from the crystal. Indeed, the crystal faces, on long standing, were observed to become clouded through the accumulation of amorphous material. The possible total enclosure of the guest molecule by an appropriately substituted 1,3,5-triazacyclohexane host would provide a future extension to this field of study.

In the crystals of the complex, 1,3,5-tri(4-nitrophenyl)-1,3,5-triazacyclohexane (117) adopts a twist boat conformation **(Fig. 60)**. The torsion angles **(Table 5)** around the C-N bonds in the triazacyclohexane ring are, -25.3° (2),-41.3°, 70.3°, -27.7°, -35.8° and 66.0° which vary slightly from the torsion angles **(Table 5)** of an ideal cyclohexane twist-boat[144] viz -31°,-31°,65°,-31°,-31° and 65°. It should be noted that 1,3-dihydroxymethyl-5-t-butylcyclohexane (formally aae with equatorial t-Bu substituent) shows a similar departure from the ideal twist-boat where the torsion angle **(Table 5)** are -20.2°, -38.8°, 62.2°, -22.6°, -38.1° and 61.1°[145]. This may be the result of crystal packing forces or is perhaps indicative of a certain amount of twisting about the geometrically perfect twist form.

The exocyclic N-C(Ar) bond lengths are 1.356, 1.382, and 1.400 (2) Å, with the shorter bond associated

with the smallest N-C(Ar) out-of-plane angle (3.3°) and the longest bond associated with the largest out-of-plane angle (29.5°). The correlation demonstrates that the quinonoid character of a 4-nitroaniline fragment decreases as the bonding pattern at N(amino) becomes more pyramidal. The N-C(Ar) bonds in the 2, 3, and 4-fluorophenyl compound (106)-(108) are generally a little longer, 1.398-1.427 (3), mean 1.416 Å consistent with the larger N-C(Ar) out-of-plane angles in these compounds. The $N-CH_2$ bond lengths in the triazacyclohexane nucleus, 1.442-1.474 (3), mean 1.461 Å, are very similar to those in the 2, 3, and 4-fluorophenyl compounds (106)-(108), 1.443-1.479 (4), mean 1.460 Å. The CH_2-N-CH_2 angles of (117) are 110.6-112.5° (2), mean 111.6°, and the $N-CH_2-N$ angles are 108.3-108.9° (2), mean 108.5°. As for (106)-(108) and (111)-(112) the CH_2-N-CH_2 angles of (117), 110.6-112.5 mean 111.6° are a little larger than the tetrahedral angle and the $N-CH_2-N$ angles, 108.3-108.9° (2) mean 108.5°, are a little smaller.

The N-C(Ar) bonds of the triazacyclohexane nucleus of (117) are tilted at 21.2°, 29.5° and 3.3° (3)° to the CH_2-N-CH_2 planes at N(1), N(3) and N(5), respectively. Thus, N(1) and N(3) are moderately pyramidal, while N(5) is virtually planar. These out-of-plane angles are smaller than the out-of-plane angles in the other

triaryl triazacyclohexanes.

For comparison, strain energy calculations for cyclohexane, indicate that the twist-boat conformation is about 21 kJ mol^{-1} higher in energy than the chair[146] and at normal temperatures, the twist-boat form is confined to substituted cyclohexanes in which syn-axial interactions in the chair form are relieved by conformational inversion to the twist-boat form[147] (e.g. trans-1,3- and cis-1,4-di-t-butyl-cyclohexanes).

The conformation found in a solid is not necessarily the predominant conformation of a set of molecules in solution or in the vapour phase. Unambiguous examples of packing forces influencing molecular conformation are provided by polymorphic forms of crystals[148]. Two crystalline forms of humulene nitrosite (124), for example, contain distinctly different conformers[149]. Incorporation in an inclusion compound may cause a molecule to adopt a conformation that differs from the minimum-energy conformation because of the constraints of the host-guest interactions[150]. The compound 3,3,6,6-tetramethyl-1,2,4,5-tetrathiane (125), for example, crytallizes in the twist-boat conformation[151] whereas the inclusion compound it forms with hexakis(4-t-

buthylphenylthiomethyl)benzene contains the chair conformer[152] and calculations by molecular mechanics indicate[153] that the chair form is less stable than the twist-boat form by 3 kJ mol^{-1}. The adoption of the twist-boat conformation by the 1,3,5-tri-4-nitrophenyl-1,3,5-triazacyclohexane molecule in the pyridine inclusion compound may represent another example of a response to host-guest interactions and crystal packing forces. It was not possible to judge the significance of the host-guest interaction by comparison of the crystal structure of the complex with that of the uncomplexed (117), as the needles of the latter were too small for X-ray analysis.

1,3,5-Tri(3-trifluoromethylphenyl)-1,3,5-triazacyclohexane (118) was prepared by the reaction of paraformaldehyde and 3-trifluoromethylaniline in benzene.

The microanalytical figures for (118) correspond to the molecular formula, $C_{24}H_{18}N_3F_9$. In the ^1H NMR spectrum **(Fig. 25)**, the methylene protons appeared as a singlet at δ 4.96. In the ^{13}C NMR spectrum **(Fig. 26)** the methylene carbon absorbed as a singlet at δ 68.5 and the trifluoromethyl carbon gave rise to a quartet centred at δ 123.9 with C-F coupling constant of 272.6 Hz. Of the two aryl quaternary carbons, the lower

field, a singlet at 148.7, was assigned as the N-$\underline{C}$(Ar) and the higher field, a quartet at δ 131.6 with J_{CCF} of 32.0 Hz, to the F_3C-$\underline{C}$(Ar). The aryl methine carbons ortho to $-CF_3$ substituent appeared as quartets at δ 114.4 and 118.0 with J_{CCCF} couplings of 4.0 and 3.8 Hz respectively. The two remaining aryl methine carbons absorbed as singlets at δ 120.9 and 129.8.

The crystallisation from petroleum-ether (60-80°)-hexane gave colourless needles, the X-ray crystal structure analysis of which has not yet been undertaken.

N,N'-Bis(2-trifluoromethylphenyl)diaminomethane (122) was prepared from paraformaldehyde and 2-trifluoromethylaniline in an attempt to form 1,3,5-tri(2-trifluoromethylphenyl)-1,3,5-triazacyclohexane. Attempts to prepare 1,3,5-tri(2-trifluoromethylphenyl)-1,3,5-triazacyclohexane (119) have failed after investigating numerous variations of time, temperature, solvent and mole ratios of reagents.

For (122), the microanalytical figures were consistent with the molecular formula, $C_{15}H_{12}F_6N_2$. The ^1H NMR spectrum **(Fig. 27)** showed a triplet (J = 5 Hz) at δ 4.78 assigned to the aminal methylene protons, coupled to the N-H protons, which gave rise to a

deuterium-exchangeable absorption at δ 4.88. The mass spectrum gave the molecular ion at m/z 333 and the IR spectrum **(Fig. 29)** showed an N-H stretching absorption at ca. 3380-3540 cm^{-1}. As for (118), N,N'-bis(2-trifluoromethylphenyl)diaminomethane (122) showed eight resonances in the ^{13}C NMR spectrum **(Fig. 28)**. For (122), the methylene carbon singlet appeared at δ 54.5, up-field relative to that for (118). The N-C(Ar) resonance of (122), in this case ortho to the CF_3 substituent, appeared as a narrow quartet at δ 143.8 with J_{CCCF} of ca. 3 Hz and the methine carbon ortho to CF_3 as a quartet at δ 126.85 showing a fluorine coupling of 5.4 Hz. The trifluoromethyl resonance of (122) possessed a chemical shift, δ 125.0, and coupling constant, J_{CF} 272.4, virtually identical to those of (118). For (122), the aryl carbon bearing the CF_3 substituent appeared as a quartet at δ 114.5 with fluorine coupling, J_{CCF}, of 29.4 Hz. The remaining three aryl methine carbons of (122) absorbed as singlets.

In the solid state, N,N'-di-(2-trifluoromethylphenyl)diaminomethane (122) adopts a skewed conformation around both $N-CH_2$ bonds **(Fig. 61)**. The C(11)-N(1)-C(2)-N(3) and C(4)-N(3)-C(2)-N(1) torsion angles are 63.5° (4) and 63.3° (4). The $N-CH_2$ bond is rotated out of the plane of the adjacent phenyl ring to a small extent, the C(16)-C(11)-N(1)-C(2) and C(9)-C(4)-

N(3)-C(2) torsion angles being 8.2° (4) and 6.5° (4). The bond angles in the chain linking the phenyl groups are distinctly greater than tetrahedral, 123.1 (4) at N(1), 113.6 (3) at C(2) and 124.9° (4) at N(3).

The $N-CH_2$ bonds, 1.459 (6) and 1.439 (6) Å, are ca. 0.07 Å longer than the N-C(Ar) bonds, 1.372 (4) and 1.374 (4) Å. Similar values for N-C(Ar) bonds have been observed in N,N-dialkylanilines with electron-withdrawing substituents on the phenyl rings : e.g. 1.362 Å in 4-dimethylaminoazobenzene-2'-carboxylic acid[154], 1.358 Å in 4-dimethylamino-3-nitrocinnamic acid[155], 1.368 Å in N,N-di-n-propyl-2,6-dinitro-4-chloroaniline[156].

In the trifluoromethyl groups the F-C-F angles are all distinctly smaller than tetrahedral, 105.2 (4)-106.4 (4), mean 105.7°. The C-F bond lengths are 1.318 (5)-1.337 (6), mean 1.330 Å. The shorter H...F distance between the H atoms at N(1) and N(3) and the F atoms of the adjacent CF_3 groups are H(N1)...F(4) 2.36 (3), H(N1)...F(5) 2.35 (4), H(N3)...F(1) 2.58 (3), and H(N3)...F(2) 2.31 (3) Å. These contacts may represent intramolecular hydrogen bonds since there is no intermolecular hydrogen bonding.

N,N'-Bis(4-nitrophenyl)diaminomethane (123) was prepared from formalin and 4-nitroaniline in attempt to form 1,3,5-tri(4-nitrophenyl)-1,3,5-triazacyclohexane (117).

The structural assignment of (123) was established by its microanalytical data, consistent with the molecular formula, $C_{13}H_{12}N_4O_4$, the melting point (230.5-231°) which is close to the literature value (230-232°)[157] and the IR spectrum **(Fig. 31)** which shows the NH absorption at 3372 cm^{-1}. The NH signal in the ^1H NMR spectrum **(Fig. 30)** appeared as a singlet at δ 2.55 and the methylene protons as a sharp singlet at δ 4.7.

Crystallisation from methylated spirit gave needles, the crystal structure of which was not refined.

Abbreviations

The following abbreviations and symbols have been used.

br	broad
b.p.	boiling point
ar	aryl
Bz	benzyl ($PhCH_2$)
d	doublet
m	multiplet and minute
q	quartet
s	singlet
t	triplet
u.v	ultra-violet
NMR	nuclear magnetic resonance
t.l.c.	thin layer chromatography
Hz	hertz
h	hour
lit.	literature
m.p.	melting point
m/z	mass to charge ratio.
Pr	1-propyl
iPr	2-propyl
Ts	4-toluenesulphonyl ($MeC_6H_4SO_2$)
a	axial
e	equatorial

dil.	dilute
DEPT	distortionless enhacement by polarisation transfer.

General Experimental

Formalin was of concentration 37-39% (w/w) and ethanol absolute (99.8%, v/v). Benzene was dried over sodium wire. Dichloromethane was purified and dried by shaking with portions of concentrated sulphuric acid until the acid layer remained colourless, washing with water, 5% w/v sodium hydroxide and drying over $CaCl_2$. After distillation, the dichloromethane was stored in a brown bottle with Linde type 4A molecular sieves. Toluene was distilled and dried over sodium wire. Pyridine was distilled and stored over sodium hydroxide pellets. Tetrahydrofuran was refluxed with Cu_2Cl_2 overnight followed by distillation over potassium hydroxide pellets. The peroxide possibly present in tetrahydrofuran was destroyed by refluxing with sodium metal and benzophenone under argon gas. Methanol was dried by addition of a few grams of magnesium turnings and iodine to 100 ml of MeOH. The mixture was refluxed till the colour of iodine disappeared, then a further 600-800 ml MeOH was added. The mixture was refluxed for 1/2 h and the MeOH distilled off. Dimethylsulphoxide was stored over 4A molecular seives.

Organic solutions were dried with anhydrous sodium sulphate and solvents were removed using a Buchi Rotavapor coupled to a water aspirator.

Quoted yields are not regarded as optimum.

Melting points were recorded on a Reichert hot-stage apparatus unless otherwise specified.

^{1}H NMR spectra were recorded at 90 MHz on a Perkin-Elmer R32 spectrometer and at 200 MHZ on BRUKER AM and WP 200 SY instruments. ^{13}C NMR spectra were recorded at 25.15 MHz on a Varian XL-100 F.T. spectrometer or at 50.3 MHz on BRUKER AM and WP 200 SY spectrometers. The spectra were determined in $CDCl_3$ solutions, unless otherwise stated. Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane as internal reference.

IR spectra were recorded on a Perkin-Elmer 580 spectrophotometer on chloroform solutions or KBr disks. The peaks of medium to high intensity are reported as ϑ_{max} in inverse centimetres.

Mass spectra were run on a VG upgraded Kratos MS12 instrument.

Analytical TLC was carried out on Merck precoated plastic plates. Spots were visualised by UV light and

by staining with iodine.

Synthesis Experimental

1,3,5-Tri(2-fluorophenyl)-1,3,5-triazacyclohexane (106)

2-Fluoroaniline (2.23 g, 20 mmol) was stirred overnight at ambient temperature with water (10 ml), potassium hydroxide (1.15 g, 20.5 mmol) and an excess of formalin (6 ml). The reaction mixture was extracted with ether and the ether layer dried and evaporated to yield (106) as an oil which solidified on standing. Recrystallisation from petroleum spirit (b.p. 60-80°) gave needles (1.99 g, 81%), m.p. 176-178°. (Found: C, 68.26; H, 4.84; N, 11.24; F, 15.43. $C_{21}H_{18}F_3N_3$ requires C,68.28; H, 4.91; N, 11.38; F, 15.43%); m/z 369 (2, M), 246 (32, M-$FC_6H_4NCH_2$) and 123 (100%, $FC_6H_4NCH_2$); ϑ_{max} 3070, 3015, 2830, 1501, 1239, 1225, 1200, 1042, 736 and 668 cm^{-1}; δ_H 4.92 (s, 6H, CH_2) and 6.8-7.5 (m, 12H, Ar); δ_C 69.56 (C(2), from DEPT scan) 115.86 (d, J_{CCF} = 20.83 Hz, C(9)), 121.25 (s, C(11)), 123.28 (d, J_{CCCF} = 8 Hz, C(10)), 124.35 (d, J_{CCCF} = 3.47 Hz, C(12)), 136.48 (d, J_{CCF} = 8.96 Hz, C(7)) and 155.67 (d, J_{CF} = 245.10 Hz, C(8)).

1,3,5-Tri(3-fluorophenyl)-1,3,5-triazacyclohexane (107)

3-Fluoroaniline (2.23 g, 20 mmol) was stirred and heated (bath temperature slowly raised from 90° to 102°) with paraformaldehyde (0.63 g, 21 mmol) in anhydrous benzene (30 ml) with azeotropic removal of water, using a Dean and Stark apparatus. The remaining benzene was removed in vacuo and the solid residue recrystallised from hexane to yield (107) as leaflets (1.94 g, 79%), m.p. 84-85°. (Found: C, 68.20; H, 4.76; N, 11.40. $C_{21}H_{18}F_3N_3$ requires C, 68.28; H, 4.91; N, 11.38%); m/z 369 (1, M), 246 (8, M-$FC_6H_4NCH_2$) and 123 (100%, $FC_6H_4NCH_2$); ϑ_{max} 3025, 2830, 1610, 1585, 1487, 1256, 1198, 1140, 985 and 687 cm^{-1}; δ_H 4.91 (s, 6H, CH_2) and 6.5-7.4 (m, 12H, Ar); δ_c 67.84 (C(2), from DEPT scan), 104.55 (d, J_{CCF} = 24.61 Hz, C(8)), 107.73 (d, J_{CCF} = 21.44 Hz, C(10)), 112.91 (d, J_{CCCCF} = 2.52 Hz, C(12)), 130.37 (d, J_{CCCF} = 9.76 Hz, C(11)), 149.98 (d, J_{CCCF} = 9.56 Hz, C(7)) and 163.55 (d, J_{CF} = 244.82 Hz, C(9)).

1,3,5-Tri(4-fluorophenyl)-1,3,5-triazacyclohexane (108)

Formalin (10 ml) was added with stirring to a solution of 4-fluoroaniline (5.56 g, 50 mmol) in EtOH

(20 ml). The precipitated (108) (4.27 g, 69%) recrystallised from ether as needles or prisms, m.p. 161-162°. (Found: C, 68.25; H, 4.84; N, 11.32; F, 15.39. $C_{21}H_{18}F_3N_3$ requires C,68.28; H, 4.91; N, 11.38; F, 15.43%); m/z 123 (93, $FC_6H_4NCH_2$), 121 (1, FC_7H_4N), 95 (100, FC_6H_4) and 76 (10%, C_6H_4); ϑ_{max} 3030, 2835, 1510, 1238, 1225, 1161, 1104, 829 and 622 cm^{-1}; δ_H 4.76 (s, 6H, CH_2), 6.70-7.10 (m, 12H, Ar); δ_c 70.44 (C(2), from DEPT scan), 115.64 (d, J_{CCF} = 22.14 Hz, C(9), C(11)), 119.87 (d, J_{CCCF} = 7.75 Hz, C(8), C(12)), 144.97 (d, J_{CCCCF} = 2.42 Hz, C(7)) and 157.84 (d, J_{CF} = 240.50 Hz, C(10)).

1,3,5-Tri(2-chlorophenyl)-1,3,5-triazacyclohexane (110)

Aqueous formaldehyde (6.5 ml) was added with stirring to a solution of 2-chloroaniline (7.5 g, ca. 60 mmol) in toluene (30 ml). The mixture was stirred for 6 h at 45°, the organic phase was separated and subjected to azeotropic distillation. The resulting colourless precipitate was recrystallised from benzene to yield (110) (4.94 g, 60%) as needles, m.p. 224-225° (Reichert hot stage), 210-211° (Gallenkamp) (lit. 210°)[84]. (Found: C, 60.31; H,4.33; N, 10.06. $C_{21}H_{18}N_3Cl_3$ requires C, 60.21; H, 4.33; N 10.03%); m/z 282 (0.6), 280 (4), 278 (5.8, $C_{14}H_{12}N_2Cl_2$), 142 (21) and 139 (100%, C_7H_6NCl);

ϑ_{max}(KBr) 3060, 2905, 2825, 1588, 1486, 1478, 1389, 1217, 940 and 754 cm^{-1}; δ_H 4.7 (s, 6H, CH_2) and 6.7-7.2 (m, 12H, Ar), δ_c, 70.50 (CH_2), 111.89, 118.51 (Cl-C(Ar)), 123.40, 124.59, 127.33, 130.38 (Ar) and 145.73 (N-C(Ar)).

1,3,5-Tri(4-chlorophenyl)-1,3,5-triazacyclohexane (111)

Formalin (6 ml) and 4-chloroaniline (6.39 g, 50 mmol) were allowed to react for 12 h in EtOH (25 ml). The crystalline product (needles) was collected and washed with a little EtOH to yield substantially pure (111) (4.83 g, 69%) which was recrystallizsed from ether-petroleum spirit (b.p.60-80°) (1:1), m.p.141.5-142.5°(lit.142°)[158]. (Found: C, 60.16; H, 4.18; N, 9.89. $C_{21}H_{18}N_3Cl_3$ requires C, 60.21; H, 4.33; N 10.03%); m/z 280 (0.5), 278 (1, $C_{14}H_{12}N_2Cl_2$), 142 (3), 141 (32, C_7H_5NCl), 140 (36, C_7H_4NCl) and 139 (100%, C_7H_6NCl); ϑ_{max} 3020, 1596, 1496, 1097 and 825 cm^{-1}; δ_H 4.78 (s, 6H, CH_2), 6.86 (d, J = 9 Hz, 6H, Ar) and 7.15 (d, J = 9 Hz, 6H, Ar); δ_c 68.70 (CH_2), 118.99, 129.15 (Ar), 128.25 (Cl-C(Ar)) and 148.95 (N-C(Ar)).

1,3,5-Tri-(2-methoxyphenyl)-1,3,5-triazacyclohexane (112)

2-Anisidine (6.16 g, 50 mmol) was stirred for 3 h at 46° (oil bath temp.) with paraformaldehyde (1.58 g, 52.5 mmol) in xylene containing 0.05 g of NaOH. The xylene was removed under vacuum (oil pump) and the residue recrystallised from acetone to give (112) (5.94 g, 88%) as needles m.p. 166-168°. (Found: C, 71.17; H, 6.79; N, 10.35. $C_{24}H_{27}N_3O_3$ requires C, 71.08; H, 6.71; N, 10.36%); m/z 135 (71, $CH_3OC_6H_4NCH_2$), 134 (20, $CH_3OC_6H_4NCH$), 121 (5, $CH_3OC_6H_4N$), 107 (11, C_7H_7O), 92 (44, C_6H_4O), 76 (9, C_6H_4) and 66 (100%); ϑ_{max} 3000,2838, 1595, 1500, 1465, 1454, 1245, 1196, 1175, 1112, 1030, 1000, 940 and 770 cm^{-1}; δ_H 3.82 (9H, s, CH_3), 4.86(6H, s, CH_2), 6.67-7(12H, m, Ar); δ_c 55.23 (q, CH_3), 69.62 (t, CH_2), 110.99, 120.95, 121.05, 122.94 (d, Ar), 138.43 (N-C(Ar)) and 152.31 (O- C(Ar)).

1,3,5-Tri(4-methoxyphenyl)-1,3,5-triazacyclohexane (113)

Formalin (8 ml) was added with stirring to a solution of 4-anisidine (6.18 g, ca. 50 mmol) in EtOH (20 ml) at ambient temperature. After 1 h the precipitate was filtered off and dried in vacuo to yield (113) (4.88 g, 72%) which recrystallised from EtOH as needles, m.p. 133°. (Found: C, 70.99; H, 6.85; N,

10.25. $C_{24}H_{27}N_3O_3$ requires C, 71.08; H, 6.71; N, 10.36%); m/z 135 (68, $CHOC_6H_4NCH_2$), 134 (4, $CH_3OC_6H_4NCH$), 121 (9, C_7H_7NO), 120 (100, C_7H_6NO,), 107 (2, C_7H_7O) and 92 (48, C_6H_4O); ϑ_{max} 2957, 2835, 1510, 1246, 1185, 1157, 1036, 987, 940 and 825 cm^{-1}; δ_H 3.72 (9H, s, CH_3), 4.66 (6H, s, CH_2), 6.76 (ca. 6H, d, J = 9 Hz, Ar) and 7.00 (ca. 6H, d, J = 9 Hz, Ar); δ_c 55.51 (q, CH_3), 71.13 (t, CH_2), 114.47, 120.09 (d, Ar), 142.67 (N-C(Ar)) and 154.53 (O-C(Ar)).

1,3,5-Tri(4-tolylmethyl)-1,3,5-triazacyclohexane (114)

A solution of 4-tolylmethylamine (1.22 g, 10 mmol) and formalin (1 ml) in EtOH (30 ml) was refluxed for 2 h. On cooling a pure sample of (114) collected as needles (1.13 g, 84%), m.p. 141-143° (lit. 134-135.5°)[153]. (Found: C, 80.80; H, 8.45; N, 10.54. $C_{27}H_{33}N_3$ requires C, 81.16; H, 8.33; N, 10.52%); m/z 133 (8, $CH_3C_6H_4CH_2NCH_2$), 105 (100, $CH_3C_6H_4CH_2$) and 91 (4, $CH_3C_6H_4$); ϑ_{max} 3012, 2958, 2886, 2848, 2794, 2758, 1512, 1305, 1313, 1336, 1345, 1260, 1170, 1151, 988, 900, 865 and 800 cm^{-1}; δ_H 2.31 (s, 9H, CH_3), 3.41 (s, 6H, CH_2), 3.62 (s, 6H, N-CH_2-N), 7.08 (d, ca. 6H, J = 9 Hz, Ar), and 7.22 (d, ca. 6H, J = 9 Hz, Ar); δ_c 21.09 (CH_3, from DEPT scan), 56.76 (C-CH_2-N), 73.71 (N-CH_2-N), 128.84 (s,

H-C(Ar)), 135.32 and 136.45 (C-C(Ar)).

1,3,5-Tri(4-tolyl)-1,3,5-triazacyclohexane (115)

A solution of 4-toluidine (5.57 g, ca. 50 mmol) in EtOH (50 ml) was cooled in an ice bath at 0°, vigorously stirred and an excess of formalin (12 ml) added. After 30 m the resulting precipitate was filtered off, washed with cold EtOH and dried in vacuo to yield (115) (4.8 g, 79%) which was recrystallised from petroleum spirit (60-80°) as colourless needles m.p. 128-130° (lit. 128-129°)[159]. (Found: C, 80.69; H, 7.34; N, 11.86. $C_{24}H_{27}N_3$ requires C, 80.63; H, 7.61; N, 11.76%); m/z 119 (100, $CH_3C_6H_4NCH_2$), 118(61, $CH_3C_6H_4NCH$), 91 (97, C_7H_7), 77 (3, C_6H_5), and 65 (15%, C_5H_5); ϑ_{max} 3012, 2925, 1612, 1512, 1399, 1386, 1230, 990, 942 and 815 cm^{-1}; δ_H 2.22 (9H, s, CH_3), 4.74 (6H, s, CH_2) and 6.39-7.04 (12H, dd, J = 9 Hz, Ar); δ_c 15.2 (q, CH_3), 64.2 (t, CH_2), 112.68, 124.38 (d, Ar), 125.03 (C-C(Ar)) and 141.08 (N-C(Ar)).

1,3,5-Tricyclohexyl-1,3,5-triazacyclohexane (116)

Cyclohexylamine (2.98 g, 30 mmol) and paraformaldehyde (1.08 g, 36 mmol) were refluxed in dried benzene (30 ml) in oil bath at ca. 90° for 2 h.

The water which formed was removed gradually. The remaining benzene was removed in vacuo, the resulting an oil purified by crystallization from EtOH to give (116) (2.48 g, 74%) as needles m.p. 74-75° (lit. 75°)[160]. (Found: C, 76.09; H, 11.60; N, 12.25. $C_{21}H_{39}N_3$ requires C, 75.68; H, 11.78; N, 12.60%); m/z 111 (2.4, $C_6H_{11}NCH_2$), 97 (1, $C_6H_{11}N$), 83 (42, C_6H_{11}) and 55 (100%, C_4H_7); ϑ_{max} 3030, 3000, 2925, 2856, 2830, 1450, 1328, 1208, 1174, 1160, 1133, 1107, 1007, 920, 898 and 885 cm^{-1}; δ_H 0.95-2.00 (m, 30H, CH_2), 2.30-2.50 (s, 3H, N-CH), 3.56 (s, 6H, N-CH_2-N); δ_c 25.65, 26.13, 30.24 (CH_2, from DEPT scan), 58.39 (N-CH) and 68.27 (N-CH_2-N).

1,3,5-Tri(4-nitrophenyl)-1,3,5-triazacyclohexane (117)

Phosphorus pentoxide (3.6 g) was added, with stirring and cooling in ice to anhydrous dimethylsulphoxide (15 ml). After 15 m, 4-nitroaniline (2.76 g, 20 mmol) was added and the resulting clear solution was stirred for 48 h during which time a solid separated. The mixture was diluted with methanol, filtered and the residue (1.29 g, 43%) recrystallised from pyridine to give (117) as yellow needles m.p. (decomp.) 275-276° (Reichert) 279-280° (Gallenkamp) (lit. 286-287 decomp.)[142]. (Found: C,56.11; H, 4.11; N,

18.82. $C_{21}H_{18}N_6O_6$ requires C, 55.99; H, 4.03; N, 18.66%); m/z 300 (2, $C_{14}H_{12}N_6O_2$) 150 (100, $O_2NC_6H_4NCH_2$), 149 (7, $O_2NC_6H_4NCH$), 136 (1, $O_2NC_6H_4N$) 122 (3, $O_2NC_6H_4$), 104 (20, $C_6H_4NCH_2$), and 76 (34%, C_6H_4); ϑ_{max} 2998, 2957, 2835, 1596, 1510 (NO), 1330, 1296 (NO), 1233, 1116, 950, 835 and 752 cm^{-1}; δ_H (d_6-DMSO) 5.34 (s, 6H, CH_2), 7.21 (d, 6H, J = 10 Hz, Ar) and 8.70 (d, 6H, J = 10 Hz, Ar); δ_c (DMSO) 51.02 (CH_2), 111.76, 128.19 (Ar), 138.88 (N-C(Ar)) and 153.35 (O_2N-C(Ar)).

Slow crystallisation (more than 6 weeks) from anhydrous pyridine in a desiccator over silica gel gave the 1:1 pyridine inclusion compound as deep yellow prisms, m.p. (decomp.) 290-291° (Reichert) 280-281° (Gallenkamp). (Found: C, 58.84; H, 4.10; N, 18.41. $C_{21}H_{18}N_6O_6.C_5H_5N$ requires C, 58.97; H, 4.38; N, 18.52%); δ_H (d_6-DMSO) 5.33 (6H, bs, CH_2), 7.18 (ca. 6H, d, J = 10 Hz, Ar) and 8.10 (ca. 6H, d, J = 10 Hz, (Ar)) partly obscured by pyridine resonances at δ_H 7.36 (ca. 2H, br), 8.16 (ca.1H, brs) and 8.57 (2H, brd).

1,3,5-Tri(3-trifluoromethylphenyl)-1,3,5-triazacyclohexane (118)

3-Aminobenzotrifluoride (4.83, 30 mmol) and paraformaldehyde (0.94 g, 31.3 mmol) were refluxed in dried benzene (30ml) in oil bath at ca.90° for 4 h. The

water which formed was removed gradually using a Dean and Stark apparatus. The remaining benzene was removed in vacuo and the resulting oil (4.93 g) solidified on standing. The solid was crystallized from 1:1 petroleum spirit (60-80°)-hexane to give (118) as colourless needles (3.5 g, 67%), m.p.:68-70°. (Found: C, 55.39; H, 3.32; N,8.10. $C_{24}H_{18}N_3F_9$ requires C, 55.41; H, 3.49; N, 8.09%); m/z 519 (1, M), 346 (6, M-$CF_3C_6H_4NCH_2$) and 173 (100%, $CF_3C_6H_4NCH_2$); ϑ_{max} 1608, 1491, 1447, 1441, 1371, 1341, 1323, 1316, 1226,1160, 1112, 999, 948, 801 and 699 cm^{-1}; δ_H 4.96 (s, 6H, CH_2) and 7.2-7.45 (m, 12H, Ar); δ_c 68.5 (C(2) from DEPT scan)), 114.4 (q, J_{CCCF} = 4.0 Hz, H-C(Ar)), 118.0 (q, J_{CCCF} = 3.8 Hz, H-C(Ar)), 120.9 (s, H-C(Ar)), 123.9 (q, J_{CF} = 272.6 Hz, C(13), CF_3), 129.8 (s, H-C(Ar)), 131.6 (q, J_{CCF} = 32.0 Hz, C(9), F_3C-C(Ar)) and 148.7 (s, C(7), N-C(Ar)).

N,N'-Bis(2-trifluoromethylphenyl)diaminomethane (122).

To a solution of 2-aminobenzotrifluoride (3.23 g, 20 mmol) in benzene (20 ml) at ca. 98° paraformaldehyde (0.65 g, ca. 22 mmol) was added portion wise during 40 m with azeotropic removal of water, using a Dean and Stark apparatus. At the end of the addition a clear solution was obtained. It was kept for an additional 30 m at ca.

98°. Complete solvent removal under vacuum (water pump) in an oil bath at 70° gave an oil as product which solidified at ambient temperature to colourless needles, which were recrystallised from hexane to yield (122) (3.27 g, 94%) m.p. 106-108°. (Found: C, 53.80; H, 3.65; N, 8.30. $C_{15}H_{12}F_6N_2$ requires C, 53.89; H, 3.62; N, 8.38%); m/z 334 (2, M), 174 (14, $F_3C_7H_4NHCH_2$), 173 (86, $F_3C_7H_4NHCH$), 172 (81, $F_3C_7H_4NHC$), 162 (2), 161 (100) and 145 (78%, $F_3C_7H_4$); ϑ_{max} 3480 (NH), 3010, 1612, 1585, 1470, 1327, 1270, 1164, 1105 and 1031 cm^{-1}; δ_H 4.78 (t, 2H, NH), 4.88 (d, 2H, CH_2) and 6.65-7.60 (8H, m, Ar); δ_C 54.5 (CH_2), 112.6 (s, H-C(Ar)), 114.5 (q, J_{CCF} = 29.4 Hz F_3C-C(Ar)), 117.5 (s, H-C(Ar)), 125.0 (q, J_{CF} = 272.4 Hz CF_3), 126.85 (q, J_{CCCF} = 5.4 Hz H-C(Ar)), 133.2 (s, H-C(Ar)) and 143.8 (q, J_{CCCF} = ca. 3 Hz N-C(Ar)).

N,N'-Bis(4-nitrophenyl)diaminomethane (123).

4-Nitroaniline (2.07 g, 15 mmol) and formalin (3 ml) were stirred in THF (30 ml) for 4 h. The yellow precipitate was filtered off and dried to yield (123) (0.95 g, 45%). Recrystallisation from EtOH:acetone gave needles m.p. 230.5-231 (lit. 230-232°)[157]. (Found: C, 54.06; H, 4.04; N, 19.23. $C_{13}H_{12}N_4O_4$ requires C, 54.18; H, 4.19; N, 19.44%); m/z 150 (100, $O_2NC_6H_4NCH_2$), 138 (67, $O_2NC_6H_4NH_2$) and 92 (23%, C_6H_6N); ϑ_{max} 3372 (NH),

1600, 1534 (NO), 1502, 1470, 1320 (NO), 1300, 1265, 1190, 1144, 1110, 1096 and 835 cm^{-1}; δ_H 2.55 (s, 2H, NH), 4.70 (s, 2H, CH_2), 6.85 (d, J = 9 Hz, Ar) and 8.04 (d, J = 9 Hz, Ar).

Crytallographic Experimental

Data were collected on Enraf-Nonius CAD 4 diffractometers at ambient temperature using Cu-K_α and Mo-K_α radiations. Cell dimensions were derived from least-squares analysis of the setting angles of 25 reflections. The crystal structures were elucidated by the direct phasing program MITHRIL[161]. Fourier, least-squares, geometry and ORTEP calculations were performed with the GX package of programs[162].

Crystallographic Data

1,3,5-Tri(2-fluorophenyl)-1,3,5-triazacyclohexane (106)

$C_{21}H_{18}F_3N_3$, M = 369.42, monoclinic, a = 6.683 (3), b = 20.728 (2), c = 13.739 (2) Å, β = 112.79 (2)°, V = 1755 Å^3, D_c = 1.40 g cm^{-3}, Z = 4, F(000) = 768, μ(Cu-Kα) = 9.2 cm^{-1}, space group $P2_1/c$, 2945 reflexions for which $I > 2.5\ \sigma(I)$, R = 0.046, R_w = 0.072 with $w = 1/\sigma^2(|F|)$.

1,3,5-Tri(3-fluorophenyl)-1,3,5-triazacyclohexane (107)

$C_{21}H_{18}F_3N_3$, M = 369.42, orthorhombic, a = 13.629 (2), b = 12.798 (3), c = 20.586 (2) Å, V = 3591 Å^3, D_c = 1.37 g cm^{-3}, Z = 8, F(000) = 1536, μ(M_o-Kα) = 1.13 cm^{-1}, space group Pbca, 1643 reflexions for which $I > 2.5\ \sigma(I)$, R = 0.036, R_w = 0.042 with $w = 1/\sigma^2(|F|)$.

1,3,5-Tri(4-fluorophenyl)-1,3,5-triazacyclohexane (108)

$C_{21}H_{18}F_3N_3$, M = 369.42, orthorhombic, a = 14.412 (2), b = 20.395 (2), c = 12.100 (2) Å, V = 3557 Å^3, D_c = 1.38 g cm^{-3}, Z = 8, F(000) = 1536, μ(Cu-Kα) = 9.0 cm^{-1},

space group Cmca, 1294 reflexions for which $I > 2.5\ \sigma(I)$, R = 0.051, R_w = 0.060 with $w = 1/\sigma^2(|F|)$.

1,3,5-Tri(2-chlorophenyl)-1,3,5-triazacyclohexane (110)

$C_{21}H_{18}Cl_3N_3$, M = 418.80, orthorhombic, a = 20.899 (4), b = 12.466 (3), c = 7.372 (1) Å, V = 1921 $Å^3$, D_c = 1.45 g cm^{-3}, Z = 4, F(000) = 864, μ = 0.49 mm^{-1}, λ (Mo-$K\alpha$) = 0.71069 Å, space group Pnma, 1581 independent observed reflexions for which $I > 2.5\ \sigma(I)$, R = 0.040, R_w = 0.049, with $w = 1/\sigma^2(|F|)$.

1,3,5-Tri(4-chlorophenyl)-1,3,5-triazacyclohexane (111)

$C_{21}H_{18}Cl_3N_3$, M = 418.80, orthorhombic, a = 5.689 (2), b = 21.874 (3), c = 15.789 (3) Å, V = 1965 $Å^3$, D_c = 1.42 g cm^{-3}, Z = 4, F(000) = 864, μ = 4.3 mm^{-1}, λ (Cu-$K\alpha$) = 1.5418 Å, space group Pbcm, 1190 independent observed reflexions for which $I > 2.5\ \sigma(I)$, R = 0.053, R_w = 0.073, with $w = 1/\sigma^2(|F|)$.

1,3,5-Tri-(2-methoxyphenyl)-1,3,5-triazacyclohexane (112)

$C_{24}H_{27}N_3O_3$, M = 405.53, triclinic, a = 8.582 (2), b = 8.996 (2), c = 15.357 (3) Å, α = 94.90 (1), β = 93.27 (1), γ = 117.59 (1)°, V = 1041 (1) $Å^3$, D_c = 1.29 g cm^{-3}, Z = 2, F(000) = 432, μ (Mo-Kα)= 0.09 mm^{-1}, λ (Mo-Kα) = 0.71069 Å, space group $P\bar{1}$, 3691 independent observed reflexions for which I > 2.5 σ(I), R = 0.038, R_w = 0.050, with w = $1/\sigma^2(|F|)$.

1,3,5-Tri-(4-methoxyphenyl)-1,3,5-triazacyclohexane (113)

$C_{24}H_{27}N_3O_3$, M = 405.53, orthorhombic, a = 15.518 (2), b = 16.427 (2), c = 8.460 (1) Å, V = 2157 (1) $Å^3$, D_c = 1.25 g cm^{-3}, Z = 4, F(000) = 864, μ (Cu-Kα) = 0.68 mm^{-1}, λ (Cu-Kα) = 1.5418 Å, space group $Pca2_1$, 2111 independent observed reflexions for which I > 2.5 σ(I), R = 0.027, R_w = 0.036, with w = $1/\sigma^2(|F|)$.

1,3,5-Tri-(4-tolylmethyl)-1,3,5-triazacyclohexane (114)

$C_{27}H_{33}N_3$, M = 399.62, triclinic, a = 6.020 (2), b = 15.326 (2), c = 13.009 (1) Å, α = 97.00 (1), β = 98.05

(1), γ = 90.55 (2)°, V = 1179 (1) Å^3, D_c = 1.13 g cm^{-3}, Z = 2, F(000) = 432, μ (Mo-Kα)= 0.07 mm^{-1}, λ (Mo-Kα) = 0.71069 Å, space group $P\bar{1}$, 2713 independent observed reflexions for which I > 2.5 σ(I), R = 0.047, R_w = 0.056, with w = $1/\sigma^2(|F|)$.

1,3,5-Tri(4-tolyl)-1,3,5-triazacyclohexane (115)

$C_{24}H_{27}N_3$, M = 357.53, monoclinic, a = 11.550 (5), b = 5.931 (4), c = 29.359 (3) Å, β = 98.53 (3)°, V = 1989 Å^3, D_c = 1.19 g cm^{-3}, Z = 4, F(000) = 768, μ(Cu-Kα) = 5.5 cm^{-1}, space group $P2_1/c$, 2248 reflexions for which I > 2.5 σ(I), R = 0.078, R_w = 0.071 with w = $1/\sigma^2(|F|)$.

1,3,5-Tricyclohexyl-1,3,5-triazacyclohexane (116)

$C_{21}H_{39}N_3$, M = 333.6, triclinic, a = 19.322 (3), b = 10.076 (2), c = 5.291 (2) Å, α = 77.81 (2), β = 84.48 (2), γ = 85.69 (2)°, V = 1001 (1) Å^3, D_c = 1.11 g cm^{-3}, Z = 2, F(000) = 372, μ = 0.07 mm^{-1}, λ (Mo-Kα) = 0.71069 Å, space group $P\bar{1}$, 3641 independent observed reflexions for which I > 2.5 σ(I), R = 0.058, R_w = 0.084, with w = $1/\sigma^2(|F|)$.

1,3,5-Tri(4-nitrophenyl)-1,3,5-triazacyclohexane (117)

$C_{21}H_{18}N_6O_6$ C_5H_5N, M = 529.57, monoclinic, a = 9.848 (3), b = 10.636 (3), c = 23.216 (4) Å, β = 93.110 (20)°, V = 2428 (2) $Å^3$, D_c = 1.449 g cm^{-3}, Z = 4, F(000) = 1104, λ(Mo-Kα) = 0.7107 Å μ = 0.12 mm^{-1}, space group $P2_1/n$, 2248 reflexions for which I > 2.5 σ(I), R = 0.039, R_w = 0.050 with $w = 1/\sigma^2(|F|)$.

N,N'-Bis(2-trifluoromethylphenyl) diaminomethane (122)

$C_{15}H_{12}F_6N_2$, M = 334.29, monoclinic, a = 20.018 (3), b = 4.942 (2), c = 30.497 (3) Å, β = 106.18 (1)°, V = 2909 (1) $Å^3$, D_c = 1.527 g cm^{-3}, Z = 8, F(000) = 1360, λ(Mo-Kα) = 0.71069 Å μ = 0.16 mm^{-1}, space group C2/c, 1604 independent observed reflexions for which I > 2.5 σ(I), R = 0.048, R_w = 0.071 with $w = 1/\sigma^2(|F|)$.

Chapter 3

Synthesis and Conformational Study of 3,7-Diazabicyclononanes

Introduction

The study of 3,7-diazabicyclo[3.3.1]nonanes (3,7-DABNs) (bispidines) is of importance because of interest in their pharmacological properties[163] and because of the occurrence of the 3,7-DABN nucleus in the more complex ring system of the quinolizidine alkaloids[164-165], which occur in leguminosae plants such as laburnum and lupin. Examples of quinolizidine alkaloids are sparteine (126), lupanine (127), anagyrine (128), aphylline (129), and cytisine (130). The bispidines are found to possess useful biological activities[166], such as antiarrhythmic, local anaesthetic, antiphlogistic and antithrombic and the quinolizidines have[167] antiarrhythmic, uterotonic, depressant, oxytocic, diuretic, stimulant, hypotensive, hypoglycemic, teratogenic and hallucinogenic properties.

The synthesis of the quinolizidines may be approached[168] **(Scheme 18)** by S_N2' reaction of diethyl malonate with the vinyl dihydropyridine (131) which is accompanied by elimination of acetic acid to give (132, R = Et). The diacid (132, R = H) undergoes a combined Michael-Mannich reaction with benzylamine and formaldehyde to afford (133). Reduction gives carbinol (134, R = CH_2OH) which is converted to the bromide (134, R = CH_2Br), which cyclised to the pyridinium salt (135) on neutralisation. (135) is oxidized by alkaline

ferricyanide to the pyridone from which the benzyl group is cleaved by acid to afford d,l-cytisine (130).

The structurally simpler 3,7-DABNs may be prepared via the Mannich reaction, by ring fission of diazaadamantanones or by intramolecular cyclizations.

Mannich condensation of phenyl-substituted acetones, paraformaldehyde and a primary aliphatic amine affords[169] **(Scheme 19)** 3,7-DABNs (136). Dibenzyl ketones have been used as the ketone component in the Mannich reaction to prepare 1,5-diaryl-3,7-DABN-9-ones (137) **(Scheme 19)**. 3,7-DABNs have been prepared[169-172] in which the aryl groups are phenyl, 4-chlorophenyl, 4-anisyl, or 2-methoxyphenyl groups.

Replacement of phenyl-substituted acetones by acetone dicarboxylic acid and its esters provides[173] **(Scheme 20)** doubly activated methylene groups as in the synthesis of (138) and (139).

Unsymmetrically N,N'-disubstituted-3,7-DABNs (140-141) can be prepared[174-175] **(Scheme 21)** in one step from the readily available piperidin-4-ones (142) and (143) by condensation with formaldehyde and a primary amine.

Diazaadamantanone (144), prepared from dibenzyl ketone, formaldehyde and ammonium acetate, undergoes ring opening with electrophiles to yield 3,7-DABN-9-ones. Thus, (144) reacts[176-178] **(Scheme 22)** with acetic anhydride or acetyl chloride to form 3,7-diacetyl-1,5-diphenyl-3,7-DABN-9-one (145), with 4-toluenesulfonyl chloride to form (146) and with nitrous acid to form (147). 5,7-Di(phenylthio)-1,3-diazaadamantane (148) cleaved **(Scheme 23)** by acetic anhydride to yield (149) which may be desulphurised and hydrolysed to give[179] alcohol (150) unsubstituted at C (1) and C (5).

The C(9) carbonyl groups of 1,5-diaryl-3,7-DABN-9-ones and of diazaadamantanone (144) are stereochemically hindered[180-181] and fail to react with certain carbonyl reagents. However, 1,5-unsubstituted-3,7-DABN-9-one (151) can be reduced[174] successfully to (152).

The basic properties of the 3,7-DABNs proved to be interesting because all known 3,7-DABNs titrate as monoamines and none of them form stable disalts as the common aliphatic diamines do. This behaviour of the 3,7-DABNs was interpreted as indicating the formation, on protonation, of an adamantane-like structure (153)[174] where hydrogen bonding stabilises the monoprotonated form. As shown by X-ray crystal structure analysis[182] the $N(3)-H...N^{+}(7)$ interaction seems to play an

important role in stabilising the twin-chair conformation of the monoprotonated dimethyl derivative (154), the neutral form of which exists in the boat-chair conformation[183].

The lone pairs on N(3) and N(7) of the 3,7-DABNs can coordinate to metal cations such as Cu^{2+} and Ni^{2+} to form stable complexes of the form $M(DABN)_2$[184]. Through such complexation, sparteine can be employed for partial asymmetric induction in the Grignard and Reformatsky reactions. For example, Reformatsky reaction **(Scheme 24)** between benzaldehyde and ethyl bromoacetate in the presence of Zn and (-)-sparteine gave an optical yield ca. 95% of the chiral hydroxyester (156) via the postulated intermediate (155) in which preferred orientation of the bulky aryl group ensures reaction in one stereochemical sense only[185].

In the twin-chair conformation of 3,7-disubstituted 3,7-DABNs, where the N atoms come close together, three arrangements of the R groups can be considered, the R groups both equatorial (exo) (157), both axial (endo) (158), and one axial one equatorial (159). For all three, severe non-bonded interaction occurs between the endo lone-pairs (157), between the endo R groups (158) or between a lone pair and an R group (159) and the

alternative boat-chair conformation may become favoured (if the interaction is repulsive for (158) and (159)).

A number of structural studies of 3,7-DABNs and of alkaloids containing the 3,7-DABN skeleton by both solution measurements and X-ray crystal structure analysis have been undertaken. From solution ^{13}C NMR measurements[186], the conformations of multiflorine perchlorate (160), seco-(11,12)-12-dehydromultiflorine perchlorate (161) and of seco-(11,12)-12-dehydromultiflorine (162) have been assigned as possessing the twin-chair DABN (half-chair ring A; for (160) chair ring D), whereas multiflorine (163), as the free base exists in the boat-chair conformation, with chair ring D and half-chair ring A. In (160), a weak intramolecular hydrogen bond of an adamantane like character is thought to stabilize the DABN twin-chair conformation whereas in (163) repulsions between the β hydrogen pairs at C(8) and C(12), C(12) and C(17), and C(17) and C(14) are claimed to destabilise the twin-chair DABN.

The alkaloid derivatives, α-isosparteine monohydrate[187] (164), 7-hydroxy-β-isosparteine perchlorate (165)[188] and sparteine-N(16)-oxide sesquiperchlorate (166)[189] were found to adopt the twin-chair conformation in the solid state with distances

between the N atoms of 3.01, 2.68 and 3.198 A° respectively. Lupanine hydrochloride dihydrate (167)[190] and 13-oxolupanine (168)[191] adopt the same conformation in the crystal as in (163).

A boat-chair conformation has been proposed[192] for 3,7-dialkyl-1,5-diphenyl-3,7-DABN-9-one (169) and (170), based on the comparison of the dipole moment of (169) (3.34 D) with diazaadamantanone (144) (1.94 D) in which the two piperidone rings are necessarily fixed in a chair conformation. A rapid boat-chair ⇌ chair-boat equilibrium **(Scheme 25)** was proposed to explain the ambient temperature ^{1}H NMR spectra of (169) and (170) which shows only one AB double doublet, rather than two, for the methylene protons.

Independent measurements of ^{1}H and ^{13}C NMR spectra of 3-alkyl-7-methyl-3,7-DABN-9-ones (172) led to the assignment[193] of the solution conformation as the twin-chair with the nitrogen substituents occupying equatorial positions. In view of the results cited in the previous paper and of X-ray observations (see below), it is more likely that compounds (172) exist in solution as fluxional boat-chair species.

X-ray crystal structure analysis of several N,N'-

dialkyl derivatives e.g. (169)[183] and (171)[194] have shown that these compounds adopt the boat-chair conformation, in which the N-R group is exo in the chair ring, rather than the alternative twin-chair in which significant non-bonded steric interaction would occur between N(3) and N(7). 1,5-Diphenyl-3,7-DABN-9-ones (147), (173) and (174) bearing electron-withrawing substituents on the N atoms exist[195] as the twin-chair conformation with approximately planar bonding patterns at the nitrogens, the N(3) and N(7) distances being 2.719, 2.803 and 2.730 Å respectively. In contrast, the bis (tosyl) derivative (146) has the boat-chair conformation with a distinctly pyramidal arrangement of bonds at the N atoms. The ^{1}H NMR spectra of (147), (173) and (174) remained unchanged when recorded at temperatures down to -70°.

Recent X-ray studies show a twin-chair conformation for 3-ethoxycarbonyl-7-methyl-1,5-diphenyl-3,7-DABN-9-one (175) in which the molecule has two different bonding patterns at the N atoms. The results demonstrate the existence of an attractive nucleophile-electrophile interaction in (175)[196].

Recent studies led to the tenuous conclusion that the pyramidal or planar bonding pattern of the N atoms is related to the preference for the DABN ring system to adopt the boat-chair or twin-chair conformation. When

the geometry at nitrogen is markedly pyramidal, the boat-chair was found to be favoured whereas the presence of planar nitrogen atoms was apparently associated with the adoption of the twin-chair conformation. Where the nitrogen substituents are alkyl, the lone-pair electron density is concentrated in the endo region, as in (178), creating a repulsion which disfavours the twin-chair conformation. When the geometry at nitrogen is planar the lone-pair electron density is distributed equally between lobes in the endo and exo regions, as in (179). In the latter, the endo-endo repulsion is released and the twin-chair conformation becomes favoured over the alternative boat-chair. The substituents which favour the twin-chair conformation are acyl which in addition induce an sp^2 hybridization at nitrogen leading to delocalization of the lone-pair electron density away from nitrogen thus reducing further the N(3)...N(7) electron repulsion.

To continue this study, it was proposed to synthesise further DABNs bearing N-sulphonyl substituents as these derivatives were likely to have nitrogen bonding patterns intermediate between the approximately planar arrangements of the N-acyl compounds (147), (173) and (174) and the distinctly pyramidal arrangement of N-alkyl compounds (169) and

(171). It was naively considered that a limiting out-of-plane angle (α) could be reached above which the ring system would be likely to adopt a boat-chair and below which a twin-chair conformation. It will be shown in the Discussion section that this was an over simplistic expectation.

As an alternative method of controlling the nitrogen hybridisation, it was proposed to synthesise 3,7-DABNs with aryl groups, directly bonded to nitrogen, the aryl groups to carry electron-withdrawing and electron-donating substituents.

Discussion.

3,7-Bis(methanesulphonyl)-1,5-diphenyl-3,7-diazabicyclo[3,3,1]nonan-9-one (182) was prepared by sulphonylation of (181) with methanesulphonyl chloride in the presence of pyridine **(Scheme 26)**.

Compound (182) was obtained in 61% yield as prismatic crystals which belonged to space group $P\bar{1}$ of the triclinic system. The microanalytical figures were consistent with the molecular formula $C_{21}H_{24}N_2O_5S_2$ and the mass spectrum showed the molecular ion at m/z 448. The IR spectrum **(Fig. 34)** possessed three strong absorptions, two at 1153 and 1333 cm^{-1} due to sulphonyl stretching and one at 1725 cm^{-1} due to carbonyl stretching. The presence of the methyl groups was confirmed by the appearance of a singlet at δ 3.13 in the ^1H NMR spectrum **(Fig. 32)** and the skeletal methylene groups gave rise to a double doublet (J = 12 Hz) at δ 3.97 and 4.22 (cf. (169) and (170)). The ^{13}C NMR spectrum **(Fig. 33)** showed six absorptions. Methyl and methylene carbons, assigned from DEPT scan, absorbed at δ 36.08 and 56.23 respectively. The quaternary carbon peak at δ 52.73 corresponds to C(1) and C(5) and three aryl resonances appeared at δ 127.63, 128.0 and 137.87. The carbonyl carbon absorption was not observed

in the spectrum.

In the solid state, compound (182) proved to have a twin-chair conformation **(Fig. 62)** with an N(3)...N(7) distance of 2.756 (2) Å and with somewhat pyramidal N atoms. The values of 30.3 and 30.8° **(Table 6)** for the out-of-plane angles (α) of (182) are considerably larger than those previously observed for twin-chair 3,7-DABNs **(Table 7)** in which the R groups are acyl ((173) and (174)) (α values in the range 3.7 to 8.5°) or nitroso (147) (α = 1.2 and 1.6°)[195] and a little larger than those for the chair ring of (146) (24.9°)[195] and for the acyl nitrogen of (175) (26.4°)[196].

The N-S bond lengths **(Table 6)** in (182), 1.635 and 1.628 Å are rather shorter than the sum (1.78 Å) of the covalent radii of nitrogen and sulphur. For comparison, the N-S bond lengths in 4-aminobenzene sulphonacetamide[197] and in 2-naphthyl sulphonyl hydrazine[198] are 1.653 and 1.619 Å. The CH_2-N-CH_2 angles **(Table 6)** of 114.7 and 116.9° are larger than those (108.2-110.8°) in the hexahydrotriazines (see Chapter 2), probably as a result of flattening of the six-membered rings to relieve non-bonded interactions between N(3) and N(7).

The lone pair electron density on N(3) and N(7) in

(182) is not significantly concentrated in the endo-endo lobes to create a repulsion which disfavours the twin-chair conformation but is not so strongly delocalised as to create a planar bonding arrangement at the N atoms. Thus, the bonding pattern at the N atoms is indeed intermediate between the approximately planar acyl nitrogens cited above and the distincly pyramidal[196] (α = 49.1, 47.7 and 50.6, 54.5) N atoms of the boat-chair N,N'-dialkyl derivatives (169) and (171) **(Table 7)**. In the knowledge that (182) exists as the twin-chair in the solid state, it is most likely that this is also the solution conformation. The NMR observations, already described, are in agreement with this assignment. It is noteworthy, however that (169) and (170), which were assigned as fluxional boat-chair conformations in solution, show the same NMR characteristics as (182) and raises the difficulty of conformational assignment by NMR measurements alone.

3,7-Bis(α-toluenesulphonyl)-1,5-diphenyl-3,7-diazabicyclo[3,3,1]nonan-9-one (183) was prepared by reaction of (181) with α-toluenesulphonyl chloride in the presence of pyridine and crystallised in the monoclinic system with space group $\underline{P}\ 2_1/\underline{n}$. The microanalytical data were consistent with the molecular formula, $C_{33}H_{32}N_2O_5S_2.1/2\ CHCl_3$, for a solvated crystal

and the mass spectrum exhibited the molecular ion peak at m/z 600. The IR spectrum **(Fig. 37)** possessed bands at 1736, 1345 and 1152 cm^{-1} for the carbonyl and the two sulphonyl stretching vibrations. The methylene protons of the bicyclic skeleton appeared in the ^{1}H NMR spectrum **(Fig 35)** as a double doublet (J = 12.5 Hz) at δ 3.63 and 4.02. A singlet at δ 4.42 and a multiplet at δ 7.00-7.50 were assigned to the benzylic methylene and aromatic resonances respectively. The ^{13}C NMR spectrum **(Fig. 36)** showed the skeletal and benzylic methylene carbon absorptions respectively at δ 56.59 and 58.31, assigned from DEPT scan, a quaternary C(1), C(5) absorption at δ 54.58 and a carbonyl carbon resonance at δ 206.28.

In contrast to the bis(methanesulphonyl) derivative (182), the bis(α-tolylsulphonyl) compound (183) adopts the boat-chair conformation **(Fig. 63)** in the solid state with the distance of 3.329 (4) Å between N(3) and N(7). The N-S bond lengths of 1.632 Å **(Table 6)** for the chair ring is intermediate between the two values observed for (182), whereas the N-S bond length of 1.626 Å for the boat ring is shorter. The CH_2-N-CH_2 angles of (183) are 114.7° and 115.2° respectively, which are close to the values observed for (182).

The out-of-plane angles **(Table 6)** of 10.4° for the chair ring and 15.6° for the boat ring of (183) are the smallest by comparison to those of other N-sulphonyl DABNs **(Tables 6 and 7)**. This suggests that there is some degree of overlap between the nitrogen lone pairs and the sulphonyl orbitals (cf. amides) but both N-S bonds are not commensurately shortened.

3,7-Bis(benzenesulphonyl)-1,5-diphenyl-3,7-diazabicyclo[3,3,1]nonan-9-one (184) was formed **(Scheme 27)** by reaction of benzene sulphonyl chloride with diazaadamantanone (144).

The structure of (184) was assigned on the basis of microanalysis which corresponded to the formula, $C_{31}H_{28}N_2O_5S_2$, mass spectrum which showed the molecular ion at m/z 572 and the ^1H NMR spectrum **(Fig. 38)** in which two doublets (J = 10 Hz) at δ 3.69 and 4.23 and a multiplet at δ 7.1-7.9 were assigned to methylene protons and aromatic resonances respectively. The C(1) and C(5) carbon atoms gave rise to the quaternary carbon signal at δ 53.20 in the ^{13}C NMR spectrum **(Fig. 39)** and were distinguished from the methylene carbon resonances at δ 56.85 by DEPT scan. The presence of the carbonyl group was verified by the ^{13}C resonance at δ 206.11 and by the stretching vibration at 1740 cm^{-1} in the IR spectrum **(Fig. 40)**.

The bis(benzenesulphonyl) compound (184), which formed triclinic prisms with space group $P\bar{1}$, exists in the solid state in the twin-chair conformation **(Fig. 64)**. Conformational parameters for (182) are listed in **Table 6**. The N-S bonds are inclined to the CH_2-N-CH_2 planes at 23.5° and 17.2° which are smaller than the out-of-plane angles in (182) (α = 30.8° and 30.3°) and larger than the out-of-plane angles of the twin-chair conformations with N-acyl groups (α varies between 1.2° and 6.3°)[196] **(Table 7)**.

The N-S bond lengths of 1.615 and 1.608 Å are the shortest of any of the N,N'-disulphonyl derivatives of 3,7-diazabicyclo[3.3.1]nonane studied and, taken with the above out-of-plane angles of 23.5° and 17.2°, indicate that there is some degree of overlap between the N lone-pair and the d orbital of sulfur atom. It is noteworthy, however, that (184), with the shortest N-S bond lengths, does not also have the smallest out-of-plane angles α (possessed by (182), vide supra).

3,7-Bis(4-methoxybenzenesulphonyl)-1,5-diphenyl-3,7-diazabicyclo[3,3,1]nonan-9-one (185) was synthesised both by the ring fission of (144) (60% yield) and by the sulphonylation of (181) (84% yield) with 4-

methoxybenzenesulphonyl chloride. The crystals of (185) gave microanalytical data consistent with the molecular formula, $C_{33}H_{32}N_2O_7S_2$, and the mass spectrum showed a molecular ion at m/z 632. The absorptions of the carbonyl and sulphonyl stretching appeared at 1738, 1344 and 1155 cm^{-1} **(Fig. 43)**. In the ^{13}C NMR spectrum **(Fig. 42)**, the quaternary carbon resonances appeared at δ 53.17, the methyl and methylene carbon resonances at δ 55.67, 56.85 and carbonyl resonance at δ 206.29. The methylene proton resonances in the ^{1}H NMR spectrum **(Fig. 41)** appeared as a double doublet (J = 13 Hz) at δ 3.7 and 4.19. The aromatic proton resonances appeared as an AB double doublet (J = 8 Hz) at δ 7.04 and 7.77 and a multiplet at δ 7.14-7.5.

In the crystal, monoclinic prisms with space group P $2_1/a$, both the twin-chair **(Fig. 65)** and boat-chair **(Fig. 66)** conformations of (183) were observed in 1:1 ratio. The N(3)...N(7) distance for the twin-chair conformation is 2.716 Å, which is shorter than for (182). For the boat-chair conformation the N(3)...N(7) distance of 3.391 Å is longer than for (183). The twin-chair form of (185) has one long (1.649 Å) N-S bond whereas, for the boat-chair form, both N-S bonds are long (1.638 and 1.665 Å, the latter being the longest of any of the N-sulphonyl derivatives studied. The CH_2-N-CH_2 angles of 114.4, 113.9° for the twin-chair of (185)

and 114.4, 112.3° for the boat-chair are generally smaller than those observed for (182), (183), (184).

All the N atoms of (185) are pyramidal rather than planar, the N-S bonds being inclined to the CH_2-N-CH_2 planes at 25.1, 37°, for the twin-chair and 24.4, 45.6° for the boat-chair. For comparison, the out-of-plane angles in the N-(arylsulphonyl)-3-azabicyclo[3.3.1]nonanes are on average[199] 32°. The largest out-of-plane angle of 45.6° corresponds to the longest N-S bond length of 1.665 Å for the boat ring of boat-chair (185). These values indicate that there is a little delocalisation of this sulphonamide N lone pair. In contrast, the N atom of the chair ring of the boat-chair (185) shows some degree of delocalisation of the lone pair since its out-of-plane angle is 24.4°.

3,7-Bis(4-nitrobenzenesulphonyl)-1,5-diphenyl-3,7-diazabicyclo[3,3,1]nonan-9-one (186) was synthesised by the reaction of (181) and 4-nitrobenzenesulphonyl chloride in pyridine. The structural assignment of (186) was established from the microanalytical figures, consistent with its molecular formula, $C_{31}H_{26}N_4O_9S_2$ and from spectroscopic properties but the mass spectrum did not show the molecular ion peak. The IR spectrum **(Fig. 46)** possessed a carbonyl stretching absorption at 1735

cm^{-1} and sulphonyl stretching absorptions at 1350 and 1165 cm^{-1} and the ^{1}H NMR in (d_5-pyridine) **(Fig. 44)** showed a double doublet (J = 12 Hz) at δ 3.68 and 4.36 for the methylene proton resonances. The C(1), C(5) quaternary resonance appeared at δ 52.35 in the ^{13}C NMR spectrum **(Fig. 45)**. The methylene carbons at δ 56.15 were identified from DEPT scan and a carbonyl resonance appeared at δ 205.46.

It was not possible to grow a suitable crystal of (186) for X-ray analysis as the compound formed fine needles when crystallised from several solvents.

From the above solid-state measurements, it can be adduced that the existence of the N,N-disubstituted 3,7-diazabicyclo[3.3.1]nonanes as the twin-chair or boat-chair conformation is not strictly related to the planar or pyramidal nitrogen bonding pattern, as had been previously believed. This is illustrated by comparison of (182) and (183). The nitrogen atoms of the former are more pyramidal (see **Table 6**) and yet it exists, in the solid state, as a twin-chair, in contrast to the latter which adopts the boat-chair conformation. The bis(sulphonamido) derivatives (146) (182), (183), (184) and (185) of 3,7-diazabicyclo[3.3.1]nonane possess broadly intermediate bonding patterns between the planar cases (147), (173), (174) and (175) and the pyramidal

cases (169) and (171) but the sulphonamide nitrogen atoms appear to tolerate a wide variation in the out-of-plane angle α from almost planar (10.4° in (183)) to distinctly pyramidal (45.6° in (185)). Although there is a correlation (see (185)) between the longest sulphonamide N-S bond and the largest out-of-plane angle α, the shortest N-S bonds (see (184)) are not possessed by those sulphonamides with almost planar nitrogen atoms (see (183)). It is thus clear that the out-of-plane angles and the conformations are being determined by crystal packing forces as well as by hybridisation of the nitrogen atoms.

It could be argued that the existence of the 3,7-bis(methyl) (169) and bis(benzyl) (171) derivatives as boat-chair conformations is favoured by the presence of the C(9) carbonyl group which offers little non-bonded steric interaction with the N atom of the boat ring. The replacement of the C(9) carbonyl group by a methylene group was envisaged as a means of destabilising the boat-chair conformation. However, attempted Wolff-Kishner reduction of (171) was unsuccessful because this compound failed to form hydrazones probably due to the steric congestion caused by the phenyl substituents at C(1) and C(5). The treatment of (171) with 1,2-ethanedithiol failed also to

give the dithioketal, intended for Raney nickel desulphurisation.

An approach to the synthesis of the 3,7-diazabicyclononanes (192) and (193) bearing aryl groups directly substituted on the N atoms, followed the reported method for the preparation of 3,7-diphenyl-3,7-diazabicyclononane (191)[200]. Aldol condensation of formalin with 2 moles of diethyl malonate furnished the tetraester (187), which was reduced **(scheme 28)** with lithium aluminium hydride to tetrol (188). Treatment of (188) **(Scheme 28)** with red phosphorus and iodine yielded the tetraiodide (189). Attempts were made to react (189) with 4-fluoroaniline and 4-methoxyaniline. Tetraiodide (189) condensed with 4-fluoroaniline in refluxing toluene to give a mixture of products from which the monocyclic N-(4-fluorophenyl)-3,5-di(iodomethyl)piperidine (190) was isolated in 15% yield by chromatography. Unsuccessful attempts were made to induce the reaction to form the bicyclo[3.3.1]nonane skeleton in tangible yield by increasing the reaction time sequentially to 5 days.

The monocyclic (190) showed a molecular ion at m/z 459 and microanalytical data consistent with the molecular formula, $C_{13}H_{16}I_2FN$. The three distinct methylene carbon resonances observed in the ^{13}C NMR

spectrum **(Fig. 48)** were assigned on the basis of chemical shift, the highest-field signal at at δ 9.36 arising from the iodomethyl groups, C(7) and C(8), the lowest-field at δ 57.11 from the methylene groups, C(2) and C(6), adjacent to the nitrogen atom. The C(4) methylene group gave rise to the signal at δ 38.60. The C(3) and C(5) methine carbon resonances appeared at δ 37.57 which was distinguished from the methylene resonances by DEPT scan. The singlet at δ 147.0 was assigned as due to the quaternary aryl carbon, C(9), which showed no coupling with the fluorine atom, whereas the signal for C(12) was taken as the doublet at δ 157.22 , which showed the strongest fluorine coupling, J_{CF} = 239 Hz. Because of the sequentally weaker couplings with the fluorine atom, the doublets at δ 115.66 with J_{CCF} = 22 Hz and δ 118.65 with J_{CCCF} = 8 Hz were assigned to the aryl methine carbons C(11), C(13) and C(10), C(14) respectively.

Little structural information could be derived from the ^{1}H NMR of (190) at 90 MHz because of poor resolution in the δ 1.5-2.6 region. A 200 MHz NMR spectrum of (190) **(Fig. 47)** showed seven complex absorptions which were assigned on the basis of chemical shift, coupling constants using scale expansion, spin decoupling and solvent shift. The double multiplet at δ 3.7 was

assigned to $H(2)_e$ and $H(6)_e$ (adjacent to nitrogen) because double irradiation of this peak removed the geminal coupling (J = 12.5 Hz) from the $H(2)_a$ and $H(6)_a$ at δ 2.34 leaving the diaxial coupling (J = 12.5 Hz) between $H(2)_a$ and $H(3)_a$ (and between $H(6)_a$ and $H(5)_a$). The complex absorptions at δ 3.15 were assigned to the iodomethyl groups which were assumed to be equatorial. The double multiplets centred at δ 2.15 was assigned to $H(4)_e$. Double irradiation here collapsed the $H(4)_a$ double doublet at δ 0.9 to a triplet which retained the diaxial coupling of (J = 10 Hz) with the axial H(3), H(5). The axial hydrogens at C(3) and C(5) gave rise to the most highly split peak, δ 1.8-2.05 in the spectrum. Double irradiation at ca. δ 1.9 collapsed the δ 3.7 double multiplet ($H(2)_e$ and $H(6)_e$) and the δ 2.3 double doublet ($H(2)_a$ and $H(6)_a$) both to doublets leaving a geminal (J = 10 Hz) coupling. Double irradiation at ca. δ 1.9 also collapsed the double multiplet at δ 2.15 $H(4)_e$ and the double doublet at δ 0.9 $H(4)_a$ both to doublets (J = 10 Hz) and removed a small coupling from the CH_2I signal at δ 3.1. The highest field signal at δ 0.82-0.93 was assigned to $H(4)_a$. Double irradiation of this signal removed a geminal coupling from the double multiplets at δ 2.15 leaving a coupling of ca. 5 Hz between $H(4)_e$ and $H(3)_a$.

The coupling constants observed in the ^1H NMR

spectrum of (190) are thus consistent with the existence of the piperidine ring in solution as a chair conformation with the iodomethyl groups equatorial. The large downfield shift (δ 3.7) shown by the equatorial hydrogen atoms at C(2) and C(6) relative to the corresponding axial resonances (δ 2.32) supports the preferred orientation of the aromatic ring as perpendicular to the symmetry plane of the piperidine ring. In this conformation, the induced diamagnetic ring current deshields the C(2), C(6) equatorial hydrogens. Despite the slight tilt (19°) of the phenyl ring from the perpendicular orientation in the solid state. The aryl hydrogens H(10) and H(14) are, in solution, magnetically equivalent as are H(11) and H(13). In the ^{1}H NMR spectrum in d_6-benzene, the aryl resonances appear as A_2B_2X system (X = F) with a twelve-peak multiplet at δ 6.82 (H(11), H(13)) and a 9-peak multiplet at δ 6.54 (H(10), H(14)) showing apparent couplings of 9 Hz ($J_{ortho} + J_{para}$), 8.3 Hz ($J_{H(11)F,\ H(13)F}$) and 4.6 Hz ($J_{H(10)F,\ H(14)F}$).

Diiodide (190) crystallises in the monoclinic system with space group P $2_1/n$. In the solid state, (190) adopts the chair conformation **(Fig. 67)** with the equatorial orientation on the piperidine ring of all three substituents. This contrasts markedly with the

1,3,5-triaryl-1,3,5-triazacyclohexanes where the diaxial-equatorial orientation of the aryl groups is the most favoured to avoid 1,3 non-bonded interactions between the lone pairs on the N atoms.

The N atom in (190) has pyramidal geometry, the N-C(Ar) bond being inclined at 42.6° (7) to the C(2)-N(1)-C(6) plane of the piperidine ring. The analogous angles at the N atoms in 1,3,5-triaryl-1,3,5-triazacyclohexane are little smaller (see **Table 1-3**) while spectroscopic studies indicate that the N-C(Ar) out-of-plane angle is 46.4° in 4-fluoroaniline[131], 37.5-42.2° in aniline[125] and 27.0° in N,N-dimethylaniline[129]. The N-C(Ar) out-of-plane angles in (108) and (190) are larger than the angles in (64)[91], 30.9-35.2° (7) , and (191)[201], 30.3° and 32.7° (8) ; in conjunction with the spectroscopic results this indicates that the inductive effect of the 4-fluoro substituent is likely to predominate over the competing mesomeric effect to reduce the overlap between the N lone pair and the aromatic π-orbitals.

A conformational comparision can be made with phenylcyclohexane for which force-field calculations and NMR measurements[121-124] have established that the equatorial conformer has the plane of the aromatic ring parallel to the symmetry plane of the cyclohexane to avoid repulsive interactions between the ortho H atoms

of the phenyl and the equatorial H atoms at C(2) and C(6) of the cyclohexane.

In compound (190), the angle between the mean plane defined by atoms N(1), C(9), C(10), C(11), C(12), C(13), C(14), F and that defined by atoms C(4), N(1), C(9), C(12), F is 71 (1)° and the preference for a conformation in which the 4-fluorophenyl group is nearly perpendicular to the symmetry plane of the piperidine can be attributed to a favourable energy term arising from overlap between the N lone pair and the phenyl π-orbitals. A measure of such overlap in anilines is provided by the barrier to rotation around the N-C(Ar) bond and this has been estimated from spectroscopic mesasurements to be 21 kJ mol^{-1} in N,N-dimethylaniline[126], 24 kJ mol^{-1} in aniline and 19 kJ mol^{-1} in 4-fluoroaniline[128]. The small twist away from the ideal perpendicular conformation in (190) has little effect on the overlap between the N lone pair and the π-orbitals of the aromatic ring but increases the $H(10)...H(6)_e$ and $H(14)...H(2)_e$ separations (see **Fig. 67**)

The torsion angles for the piperidine ring are in the range 53.4-60.2° (6), with the largest angles adjacent to N(1) and the smallest adjacent to C(4). The bond angles are 110-111.6°(5) , all slightly larger than

tetrahedral and triazacyclohexane (108.2-110.8°) but smaller than those in the bicyclic 3,7-diazabicyclo[3.3.1]nonane (112.3-117.8°).

An unsuccessful attempt was made to prepare (193) by reaction of tetraiodide (189) with 4-methoxyaniline in toluene. A small amount of product was, however, isolated by preparative t.l.c. and the major band gave a parent peak in the mass spectrum at m/z 471 corresponding to the monocyclic product (194).

Synthesis Experimental

1,5-Diphenyl-3,7-diazaadamantan-9-one (144)

A mixture of dibenzyl ketone (21 g, 100 mmol) and ammonium acetate (20 g, 260 mmol) in EtOH (80 ml) was warmed until most of the solid dissolved. Paraformaldehyde (15.2 g, 500 mmol) was added and the mixture refluxed 3 h. After cooling, the resulting precipitate (14.04 g, 46%) was recrystallised from $CHCl_3/CH_3COCH_3$ (1:1) to give (144) as leaflets m.p. 257.5-259° (lit. 257°)[202]; m/z 304 (97, M), 262 (39, M-NCH_2N), 261 (55), 248 (6, M-$C_2H_4N_2$), 234 (15, M-$C_3H_6N_2$) and 103 (100%); ϑ_{max} 2935, 2855, 1709 (CO), 1496, 1444, 1359, 1243, 1184, 1010, 849, 758 and 704 cm^{-1}; δ_H 3.82 (8H, s, CH_2), 4.26 (2H, s, NCH_2N), 7.09-7.45 (10H, m, Ar).

3,7-Bis(benzyl)-1,5-diphenyl-3,7-diazabicyclo[3,3,1]nonan-9-one (171)

Dibenzyl ketone (8.4 g, 40 mmol), benzylamine (8.57 g, 80 mmol) and paraformaldehyde (6 g, 200 mmol) were refluxed 4 h in EtOH and the resultant precipitate was

filtered, dried and recrystallised from EtOH to yield (171) (8 g, 42%) m.p. 162.5-163° (lit. 161-162°)[169]; m/z 473 (1, M), 382 (1, M-C_7H_7) and 91 (100%, C_7H_7); ϑ_{max} 3062, 3018, 2820, 2400, 1725 (CO), 1495, 1224, 1202, 930, 790, 720 and 702 cm^{-1}; δ_H 3.10 (4H, d, J = 11 Hz, CH_2), 3.55 (4H, d, J = 11 Hz, CH_2), 3.73 (4H, s, N-CH_2-N) and 7.15-7.45 (20H, m, Ar).

3,7-Bis(ethoxycarbonyl)-1,5-diphenyl-3,7-diazabicyclo[3,3,1]nonan-9-one (173)

(144) (10.28 g, ca. 34 mmol) was refluxed 1 h in ethyl chloroformate (90 ml). The ethyl chloroformate was removed in vacuo and the residue dissolved in dioxane/water (1:1) (100 ml). On cooling and further addition of water, the light brown semi-solid which formed was filtered off and recrystallised from EtOH to yield (173) (7.67 g, 52%) as prisms m.p. 171-174° (lit. 174-175°)[203]; m/z 436 (7.5, M), 335 (4, M-CH_2NCOOEt), 234 (11%, M-2CH_2NCOOEt) and 103 (100%); ϑ_{max} 2988, 1700 (CO), 1484, 1440, 1290, 1277, 1236, 1177, 1016, 756 and 700 cm^{-1}; δ_H 1.32 (6H, t, CH_3), 3.6-3.9 (4H, d, CH_2), 4.22 (4H, q, CH_2O), 4.8-5.3 (4H, m, CH_2) and 7.2-7.5 (10H, m, Ar).

3,7-Bis(methoxycarbonyl)-1,5-diphenyl-3,7-diazabicyclo[3,3,1]nonan-9-one (180)

(144) (5 g, 16.4 mmol) was refluxed 1 h in methyl chloroformate (45 ml). The methyl chloroformate was removed in vacuo and the residue was taken up in dioxane/water (1:1)(50 ml). After cooling and further addition of water, the precipitate which formed was filtered and dried to yield (180) (3.62 g, 54%) which recrystallised from $CH_3OH/CHCl_3$ (3:1) as prisms m.p. 192-194°. (Found: C, 67.71; H 6.02; N, 6.89. $C_{23}H_{24}N_2O_5$ requires C, 67.63; H, 5.92; N, 6.86%); m/z 408 (24, M), 393 (2, M-CH_3), 349 (4, M-$COOCH_3$), 321 (4, M-$CH_2NCOOCH_3$), 306 (5, 321-CH_3), 290 (1, M-2$COOCH_3$), 234 (13, M-2$CH_2NCOOCH_3$) and 103 (100%); ϑ_{max} 3008, 2960, 2868, 1700 (CO), 1690 (CO), 1475, 1445, 1414, 1294, 1281, 1272, 758 and 708 cm^{-1}; δ_H 3.67 (4H, d, J = 13 Hz, CH_2), 3.7 (6H, s, OCH_3), 4.7-5.2 (4H, m, CH_2) and 7.15-7.45 (10H, m, Ar); δ_c 53.02 (C(1), C(5)), 53.25 (OCH_3) 55.70 (CH_2, from DEPT scan), 127.42, 127.79, 128.29, 136.14 and 155.71 (Ar) and 207.57 (s, C(9)).

1,5-Diphenyl-3,7-diazabicyclo[3,3,1]nonan-9-one (181) (a)

(180) (10.21 g, 25 mmol) was refluxed 4 h in 10%

methanolic NaOH (250 ml) in an oil bath at 84°. The mixture was cooled, made neutral with glacial acetic acid (40 ml) and refluxed a further 15 m. Water (250 ml) was added and the resulting solution treated with 20% aqueous NaOH (100 ml). The precipitate which collected overnight was filtered off, washed with water and dried. Recrystallisation from MeOH gave (181) (4.39 g, 60%) as colourless needles m.p. 202-204° (lit. 205-206°)[203]; m/z 292 (9, M), 263 (6, M-CH_2NH), 249 (24, M-CH_2NCH_2), 234 (11, M-$2CH_2NH$) and 103 (100%); ϑ_{max} 3404 (NH), 2940, 2918, 2860, 1683 (CO), 1497, 1444, 1299, 1229, 1178, 876, 815, 756 and 705 cm^{-1}; δ_H 2.4-2.65 (2H, br s, NH), 3.69-3.9 (8H, dd, CH_2) and 7.16-7.4 (10H, m, Ar).

(181) (b)

(173) (1.2 g, 2.80 mmol) was refluxed 3 h in 10% methanolic NaOH (25 ml) with water (2 ml) added. The mixture was cooled, made neutral with glacial acetic acid and refluxed further 15 m. Water (25 ml) was added and the resulting solution treated with 20% aqueous NaOH (10 ml). The precipitate which collected was filtered off, washed with water and dried to yield (181) (0.69 g, 79%). Recrystallisation from MeOH gave (181) (4.39 g, 60%) as colourless needles. Melting point, NMR and IR

were identical to (181) prepared by method (a).

3,7-Bis(methanesulphonyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (182)

(181) (0.147 g, 0.5 mmol) was stirred at room temperature for 24 h with methanesulphonyl chloride (0.147 g, 2.5 mmol) and anhydrous pyridine (0.5 ml) in CH_2Cl_2 (30 ml). The solution was washed with dil. HCl, dried and the solvent removed in vacuo. Recrystallisation of the residue (0.188 g) from acetone yielded (182) (0.138 g, 61%) as prisms m.p. 315-316° (Gallenkamp). (Found: C, 56.24; H, 5.44; N, 6.17. $C_{21}H_{24}N_2O_5S_2$ requires C, 56.24; H, 5.39; N; 6.25%); m/z 448 (7.6, M), 369 (18, M-SO_2CH_3) and 341 (8, M-$CH_2NSO_2CH_3$); ϑ_{max} 3006, 2926, 2864, 1725 (CO), 1701, 1500, 1462, 1448, 1333 (SO), 1191, 1153 (SO), 1144, 990, 815, 806, 700 and 518 cm^{-1}; δ_H 3.13 (6H, s, CH_3), 3.97 and 4.22 (8H, dd, J = 13 Hz, CH_2) and 7.3-7.55 (10H, m, Ar); δ_c 36.08 (CH_3, from DEPT scan), 52.73 (C(1), C(5)), 56.23 (CH_2, from DEPT scan), 127.63, 128.01 and 137.87 (Ar).

3,7-Bis(α-toluenesulphonyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (183)

(181) (0.3 g, 1.03 mmol) was stirred overnight with α-toluenesulphonyl chloride (0.391 g, 2.06 mmol) and

anhydrous pyridine (1 ml) in CH_2Cl_2 (20 ml). The solution was washed with dil. HCl, dried and the solvent removed in vacuo. Recrystallisation of the precipitate from MeOH/$CHCl_3$ (1:1) yielded (183) (0.3 g, 47%) as colourless plates m.p. 225-226°. (Found: C, 60.93; H, 4.66; N, 4.11. $C_{33}H_{32}N_2O_5S_2.1/2\ CHCl_3$ requires C, 60.93; H, 4.96; N, 4.24%); m/z 600 (0.8, M), 445 (7, M-$SO_2CH_2C_6H_5$), 417 (0.5, M-$CH_2NSO_2CH_2C_6H_5$), 290 (0.6, M-$2SO_2CH_2C_6H_5$) and 91 (100%, C_7H_7); ϑ_{max} 3020, 1736 (CO), 1345 (SO), 1221, 1200, 1152 (SO), 1126 and 700 cm^{-1}; δ_H 3.63 (ca. 4H, d, J = 12.5 Hz, CH_2), 4.02 (ca. 4H, d, J = 12.5 Hz, CH_2), 4.42 (4H, s, CH_2) and 7.00-7.50 (20H, m, Ar); δ_c 54.58 (C(1), C(5)), 56.59 (CH_3, from DEPT scan), 58.31 (CH_2 from DEPT scan), 126.72, 127.74, 127.94, 128.36, 129.21, 129.30, 130.67, 138.33 (Ar) and 206.28 C(9).

3,7-Bis(benzenesulphonyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (184)

A solution of NaOH (2 g) in water (10 ml) was added to (144) (1.52 g, 5 mmol) and benzenesulphonyl chloride (2.65 g, 15 mmol) in $CHCl_3$ (20 ml). The mixture was stirred for 10 h and refluxed (bath temp. 80°) for 1/2 h. After acidification with dil. HCl the mixture was extracted with $CHCl_3$ and the organic layer separated and

dried. Removal of solvent gave (184) which recrystallised from EtOH/$CHCl_3$ (1:2) as prisms (1.87 g, 65%), m.p. 265-266°. (Found: C, 64.95; H, 4.95; N, 4.90. $C_{31}H_{28}N_2O_5S_2$ requires C, 65.00; H, 4.93; N, 4.89%); m/z 572 (4, M), 431 (36, M-$SO_2C_6H_5$), 290 (2, M-$2SO_2C_6H_5$) and 77 (100%, C_6H_5); ϑ_{max} 3018, 1740 (CO), 1448, 1350 (SO), 1216, 1212, 1174 (SO), 1091, 744 and 579 cm^{-1}; δ_H 3.69 (4H, d, J = 10 Hz, CH_2), 4.23 (4H, d, J = 10 Hz, CH_2) and 7.1-7.9 (20H, m, Ar); δ_c 53.20 (C(1), C(5)), 56.85 (CH_2, from DEPT scan), 126.78, 127.41, 127.94, 128.49, 129.52 (Ar), 133.44, 136.15, 137.95 (Ar) and 206.11 C(9).

3,7-Bis(4-methoxybenzenesulphonyl)-1,5-diphenyl-3,7-diazabicyclo[3.3.1]nonan-9-one (185) (a)

(181) (0.146 g, 0.5 mmol) was stirred at room temperature 24 h with 4-methoxybenzenesulphonyl chloride (0.248 g, 1.2 mmol) and pyridine (0.5 ml) in CH_2Cl_2 (20 ml). The solution was washed with dil. HCl, dried and the solvent removed in vacuo. The residue of crystalline compound (0.392 g) was recrystallised from EtOH/$CHCl_3$ (5:1) to yield (185) (0.251 g, 84%) as prisms m.p. 199-200° (Gallenkamp), 213-214° (Reichert hot stage). (Found: C, 62.63; H, 5.29; N, 4.26. $C_{33}H_{32}N_2O_7S_2$ requires C, 62.64; H, 5.098; N, 4.43%); m/z 632 (5.4, M), 461 (89.5, M-$CH_3OC_6H_4SO_2$), 433 (7, M-

$CH_3OC_6H_4SO_2N$), 419 (4.5, M-$CH_3OC_6H_4SO_2NCH_2$), 418 (10, M-$2CH_3OC_6H_4$), 290 (4.6, M-$2CH_3OC_6H_4SO_2$), 262 (18.5, M-$2CH_3OC_6H_4SO_2N$), 248 (41, $C_{18}H_{16}O$), 234 (26, $C_{17}H_{14}O$), 220 (8, $C_{16}H_{12}O$) and 206 (6%, $C_{15}H_{10}O$); ϑ_{max} 3060, 2940, 2840, 1738 (CO), 1597, 1567, 1498, 1462, 1446, 1344 (SO), 1308, 1262, 1155 (SO), 1093, 837 and 560 cm^{-1}; δ_H 3.7 (4H, d, J = 13 Hz, CH_2), 3.91 (6H, s, OCH_3), 4.19 (4H, d, J =13 Hz, CH_2), 7.04 (4H, d, J = 8Hz, Ar), 7.14-7.5 (10H, m, Ar) and 7.77 (4H, d, J = 8Hz, Ar); δ_C 53.17 (C(1), C(5)), 55.67 (CH_3, from DEPT scan), 56.85 (CH_2), 114.68, 126.77, 127.40, 127.84, 128.44, 129.68, 138.31, 163.47 (Ar) and 206.29 C(9).

(185) (b)

A solution of NaOH (2 g) in water (10 ml) was added to (144) (1.52 g, 5 mmol) and 4-methoxybenzenesulphonyl chloride (3.1 g, 15 mmol) in $CHCl_3$ (20 ml). The mixture was stirred for 10 h and refluxed (bath temp. 80°) for 1/2 h. After acidification with dil. HCl, the mixture was extracted with $CHCl_3$ and the organic layer separated and dried. Removal of solvent gave (185) which recrystallised from EtOH/$CHCl_3$ as prisms (1.89 g, 60%). Melting point and spectroscopic analysis were identical to (185) prepared by method (a).

3,7-Bis(4-nitrobenzenesulphonyl)-1,5-diphenyl-3,7-diazabicyclo[3,3,1]nonan-9-one (186)

(181) (0.28 g, 0.99 mmol) was stirred overnight with 4-nitrobenzenesulphonyl chloride (0.443 g, 2.00 mmol) and anhydrous pyridine (1 ml) in CH_2Cl_2 (50 ml). The solution was washed with dil. HCl, dried and the solvent removed in vacuo. Recrystallisation of the precipitate from MeOH/$CHCl_3$ (1:1) yielded (186) (0.48 g, 76%) as small needles m.p. 295-296° (Gallenkamp). (Found: C, 56.24; H, 3.79; N, 8.59. $C_{31}H_{26}N_4O_9S_2$ requires C, 56.19; H, 3.95; N, 8.46%); m/z 476 (31.0, M-$SO_2C_6H_4NO_2$), 448 (3.0, M-$CH_2NSO_2C_6H_4NO_2$), 290 (3.0, M-$2SO_2C_6H_4NO_2$) and 262 (17.5%, M-$2NSO_2C_6H_4NO_2$); ϑ_{max} 3105, 2864, 1735 (CO), 1650, 1530 (NO), 1383, 1350 (SO), 1313 (NO), 1167 (SO), 1090, 1010, 986 and 855 cm^{-1}; δ_H (d_5-pyridine) 3.68 (4H, d, J = 12 Hz, CH_2), 4.36 (4H, d, J = 12 Hz, CH_2), and 7.30-7.40 (10H, m, Ar), 8.16 (4H, d, J = 9 Hz, Ar) and 8.41 (4H, d, J = 9 Hz, Ar); δ_c 52.35 (C(1), C(5)), 56.15 (CH_2 from DEPT scan), 124.74, 127.79, 127.96 and 129.12 (CH, Ar), 136.34, 141.64 and 150.05 (quaternary C, Ar) and 205.46 C(9).

Diethyl 2,4-di(ethoxycarbonyl) glutarate (187)

A mixture of diethyl malonate (160 g, 1 mol) and

formalin (43 ml, 37-39%) were cooled to 0° by immersion in ice and diethylamine (2.5 g, 3.7 ml) was added. The mixture was allowed to come to room temperature and remain for 15 h after which it was stirred under reflux at 110° (oil bath) for 6 h. The aqueous layer was separated and the residue distilled under reduced pressure (vacuum oil pump) to yield (187) (95.82 g, 58%) b.p. 138°/0.05 mm (lit. 190-200°/12 mm; 210-215°/20 mm)[205]; m/z 287 (5, M-OEt), 197 (1, M-3OEt), 186 (1, M-2COOEt), 113 (1, M-3COOEt) and 40 (1.5%, M-4COOEt); ϑ_{max} 2984, 2940, 2908, 1750 (CO), 1734 (CO), 1465, 1446, 1370, 1300, 1270, 1250, 1154, 1098, 1037 and 855 cm^{-1}; δ_H 1.25 (12H, t, CH_3), 2.45 (2H, t, CH_2), 3.47 (2H, t, CH) and 4.18 (8H, q, CH_2O).

1,5-Dihydroxy-2,4-di(hydroxymethyl)pentane (188)

Lithium aluminium hydride (20 g, 0.52 mol) was added in portions to stirred anhydrous THF (350 ml) at room temperature and a solution of tetraester (187) (58.38 g, 0.175 mol) in dry THF (100 ml) was added dropwise during 2 h. The mixture was refluxed (bath temp. 80°) under nitrogen and constant stirring for 12 h. To decompose unreacted lithium aluminium hydride, 20ml water, 20ml 15% aqueous NaOH, and 60ml water were successively added with stirring. The precipitate was

filtered off, and digested with EtOH. The tetrol was extracted from the precipitate with THF in a Soxhlet apparatus for 24 h. Rotatory evaporation of the THF solution gave a viscous oil which solidified on cooling in ice. Recrystallisation of the solid from EtOH/acetone (1:1) yield (188) (19.48 g, 68%) as prisms m.p. 129-130° (lit. 130-132°)[205]; m/z 128 (1, $C_7H_{14}O_2$), 116 (10.3, $C_6H_{12}O_2$), 113 (1.3, $C_7H_{13}O$) and 96 (1.4%, C_7H_{12}); ϑ_{max} 3200-3350, 2938, 2850, 1470, 1377, 1200, 1120, 1088, 1079, 1030, 976, 946 and 683 cm^{-1}; δ_H 1.15 (2H, t, CH_2), 1-1.33 (2H, CH), 3.26-3.7 (8H, CH_2O) and 4.15-4.36 (4H, OH).

1,5-Diiodo-2,4-di(iodomethyl)pentane (189)

Red phosphorus (9.45 g) and iodine (117 g) were stirred and heated at 90° for 1 h. The tetrol (188) (12 g, 73 mmol) was added in small portions and the mixture heated at 120° for 5 h, cooled in ice, and decomposed with 75 ml ice-cold water. The resulting precipitate was filtered washed with water and recrystallised from CCl_4 to give the tetraiodide (189) (37.01 g, 84%) m.p.103° (lit.103-103.5°)[200]. m/z 604 (2, M), 477 (28, $C_7H_{12}I_3$), 350 (1.6, $C_7H_{12}I_2$) and 96 (9%, C_7H_{12}); ϑ_{max} 2927, 1430, 1287, 1258, 1197, 1187, 850, 790, 648, 626 and 621 cm^{-1}; δ_H 1.49 (4H, brs, CH-CH_2-CH) and 3-3.6 (8H, m, CH_2O).

N-(4-fluorophenyl)-3,5-di(iodomethyl)piperidine (190)

1,5-Diiodo-2,4-di(iodomethyl)pentane (189) (6.04 g, 10 mmol) and 4-fluoroaniline (6.67 g, 60 mmol) were stirred under reflux in toluene (60 ml) in an oil bath at 127° for 72 h. The precipitated ammonium salt was filtered off, washed with hot benzene and the filtrate stripped of solvent.

A solution of the residue (7.4 g, containing 4-fluoroaniline) in dichloromethane was evaporated to dryness under suction (Buchi Rotavapor) in the presence of silica gel HF 254 (15 g) and the dried material placed on top of dry-packed column of silica gel HF 254 (120 g, 4 cm x 23 cm) contained in a porosity 3 column fitted with a vacuum side-arm. The column was eluted under suction with $CHCl_3$/petroleum spirit (60-80°) mixtures of increasing polarity: 1:10 (3 x 100 ml), 1:9 (10 x 50 ml, ca.300 ml), 1:8 (4 x 50 ml, 150 ml), 1:7 (4 x 50 ml, 150 ml), 1:6 (5 x 50 ml, 200 ml), 1:5 (4 x 50 ml, 150 ml), 1:4 (14 x 25 ml, 300 ml), 1:3 (6 x 30 ml, 160 ml) and 1:2. Combined fractions (31-44) gave (190) as an oil purified by crystallisation twice from EtOH to yield (0.69 g) as needles m.p. 73-75°. (Found: C, 34.13; H, 3.32; N, 2.99. $C_{13}H_{16}NFI_2$ requires C, 34.00;

H, 3.48; N, 3.05%); m/z 459 (0.5, M), 332 (13, $C_{13}H_{16}NFI$), 205 (1.7, $C_{13}H_{16}NF$), 177 (0.6, $C_{11}H_{12}NF$), 164 (0.6, $C_{10}H_{11}NF$), 163 (5.5, $C_{10}H_{10}NF$), 162 (7.5, $C_{10}H_9NF$), 161 (6.2, $C_{10}H_8NF$), 149 (1.6, C_9H_8NF), 147 (6.2, C_9H_6NF), 137 (100, C_8H_8NF), 123 (15.2, C_7H_6NF), 122 (18, C_7H_5NF) and 121 (36.7%, C_7H_4NF); ϑ_{max} 3028, 3020, 1505, 1458, 1440, 1412, 1140, 1130, 1120, 723 and 663 cm^{-1}; δ_H 0.82-0.93 (1H, dd, J = 13 Hz, H_a of CH_2), 1.8-2.05 (2H, m, 2CH), 2.06-2.23 (1H, dm, J = 13 Hz, H_e of CH_2), 2.29-2.35 (2H, dd, J = 12.5 Hz, H_a, of CH_2N), 3-3.22 (4H, m, CH_2I), 3.66-3.72 (2H, dm, J = 12.5 Hz, H_e of NCH_2) and 6.8-7.1 (4H, m, Ar); δ_c 9.36 (C(7), C(8)), 37.57 (C(3), C(5)), 38.60 (C(4)), 57.11 (C(2), C(6)), 115.66 (d, J_{CCF} = 22 Hz, C(11), C(13)), 118.65 (d, J_{CCCF} = 7.5 Hz, C(10), C(14)) and 157.22 (d, J_{CF} = 239 Hz, C(12)).

Crystallographic Data

3,7-Bis(methanesulphonyl)-1,5-diphenyl-3,7-diazabicyclo[3,3,1]nonan-9-one (182)

$C_{21}H_{24}N_2O_5S_2$, M = 448.60, triclinic, a = 11.389 (2), b = 10.870 (2), c = 9.852 (2) Å, α = 65.15 (2), β = 72.10 (2), γ = 84.12 (1)°, V = 1053 Å^3, D_c = 1.415 g cm^{-3}, Z = 2, F(000) = 472, μ(Mo-Kα) = 2.87 cm^{-1}, space group P$\bar{1}$, 4473 reflexions for which I > 2.5 σ(I), R = 0.038, R_w = 0.060 with w = $1/\sigma^2(|F|)$.

3,7-Bis(α-toluenesulphonyl)-1,5-diphenyl-3,7-diazabicyclo[3,3,1]nonan-9-one (183)

$C_{33}H_{32}N_2O_5S_2.1/2\ CHCl_3$, M = 660.36, monoclinic, a = 14.475, b = 23.776 , c = 9.651 (3) Å, β = 107.15 (3)°, V = 3174 Å^3, D_c = 1.38 g cm^{-3}, Z = 4, F(000) = 1380, μ(Mo-Kα) = 3.38 cm^{-1}, space group P$2_1/n$, 3319 reflexions for which I > 2.5 σ(I), R = 0.049, R_w = 0.057 with w = $1/\sigma^2(|F|)$.

3,7-Bis(benzenesulphonyl)-1,5-diphenyl-3,7-diazabicyclo[3,3,1] nonan-9-one (184)

$C_{31}H_{28}N_2O_5S_2.CHCl_3$ M = 692.15, Triclinic, a =

10.878 (5), b = 11.208 (2), c = 15.097 (3) Å, α = 110.89 (2), β = 111.04 (3), γ = 90.10 (3)°, V = 1587.Å^3, D_c = 1.448 g cm^{-3}, Z = 2, F(000) = 716, μ(Mo-Kα) = 4.62 cm^{-1}, space group P 1 .4706 reflexions for which I > 2.5 σ(I), R = 0.054, R_w = 0.065 with w = $1/\sigma^2(|F|)$.

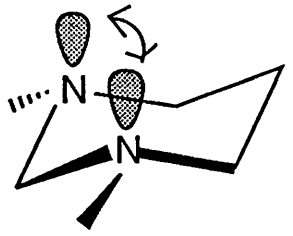
3,7-Bis(4-methoxybenzenesulphonyl) 1,5-diphenyl-3,7-diazabicyclo[3,3,1]nonan-9 one (185)

$C_{33}H_{32}N_2O_7S_2$, M = 600, monoclinic, a = 16.114 (3), b = 19.714 (6), c = 19.193 (6) Å, β = 97.31 (2)°, V = 6048 Å^3, D_c = 1.39 g cm^{-3}, Z = 8, F(000) = 2656, μ(Mo-Kα) = 2.30 cm^{-1}, space group P $2_1/a$, 4230 reflexions for which I > 2.5 σ(I), R = 0.043, R_w = 0.039 with w = $1/\sigma^2(|F|)$.

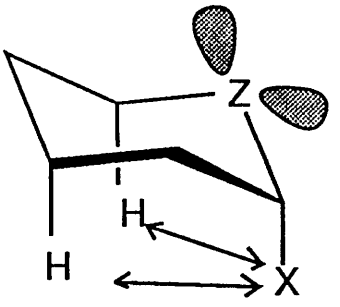
N-(4-fluorophenyl)-3,5-di(iodomethyl)piperidine (190)

$C_{13}H_{16}FI_2N$, M = 459.12, monoclinic, a = 16.771 (3), b = 8.522 (2), c = 10.782 (2) Å, β = 103.18 (2)°, V = 1500 Å^3, D_c = 2.02 g cm^{-3}, Z = 4, F(000) = 856, μ(Mo-Kα) = 4.2 cm^{-1}, space group P $2_1/n$, 2377 reflexions for which I > 2.5 σ(I), R = 0.048, R_w = 0.059 with w = $1/\sigma^2(|F|)$.

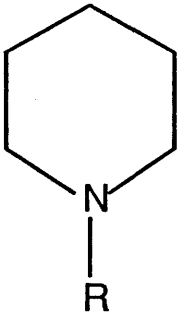
Formulae and Schemes



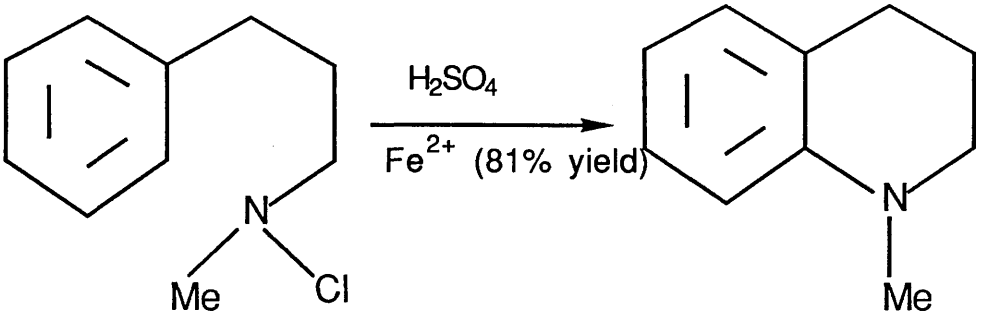
(1)



(2) (Z = O or S)
(X = halogen or OR)



(3) R = H
(4) R = Me
(5) R = Et
(6) R = iPr
(7) R = Cl
(8) R = F
(9) R = SO_2Me



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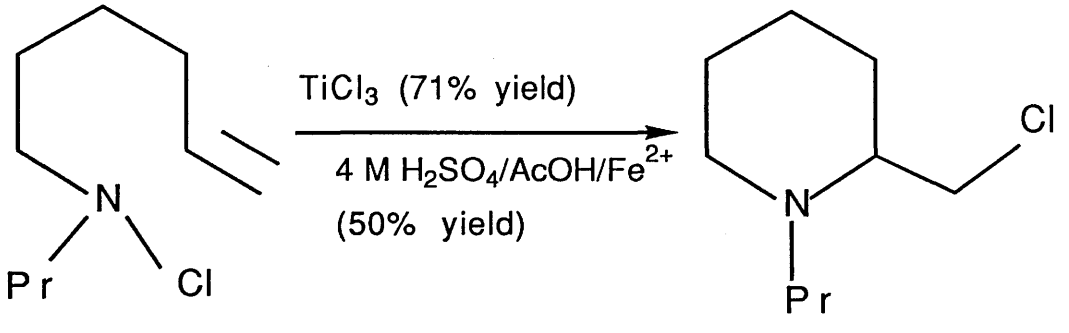
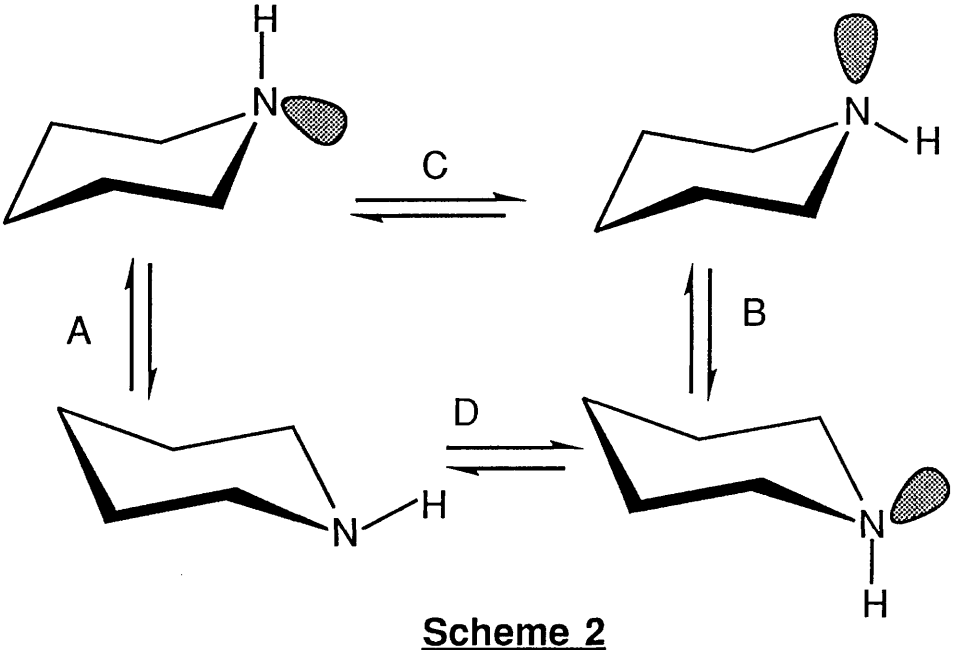
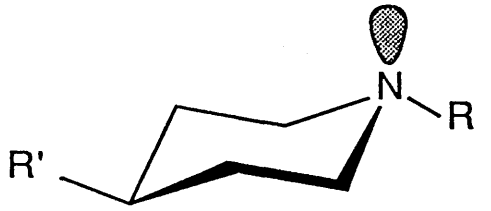


(11)

Scheme 1



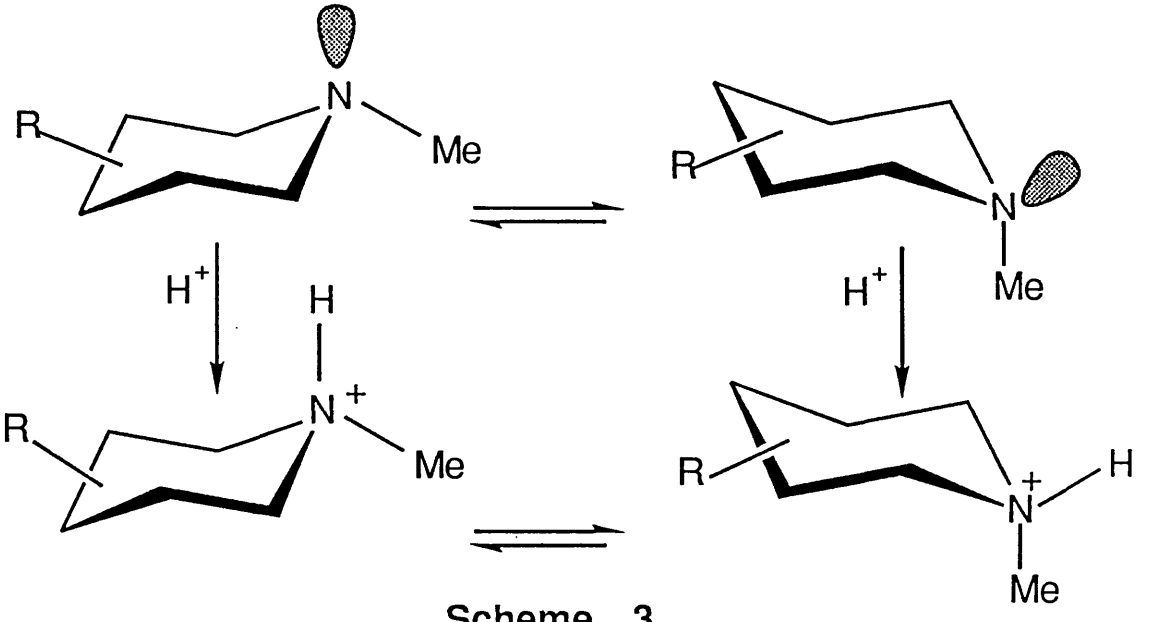
Scheme 2



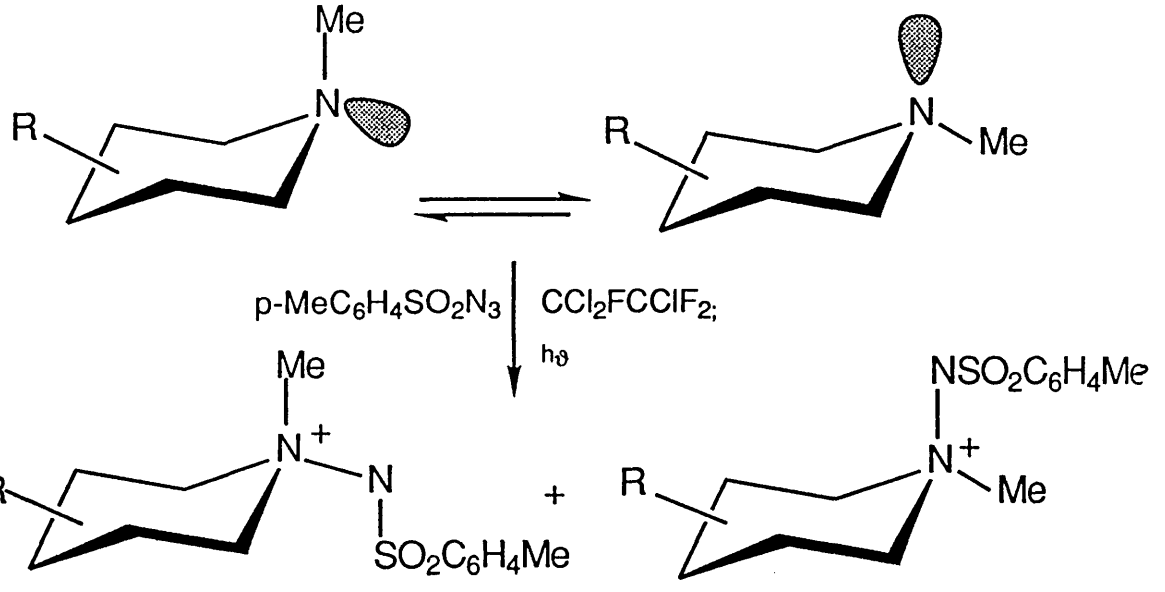
(12) R = H, R' = 4-ClC_6H_4

(13) R = Me, R' = 4-ClC_6H_4

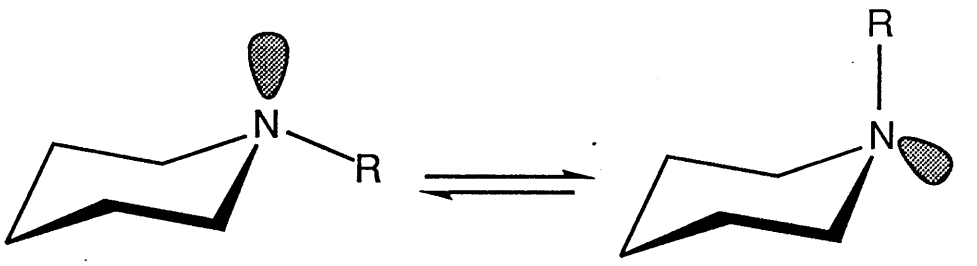
(14) R = H or Me, R' =OMe, Me, Cl, Br or OH



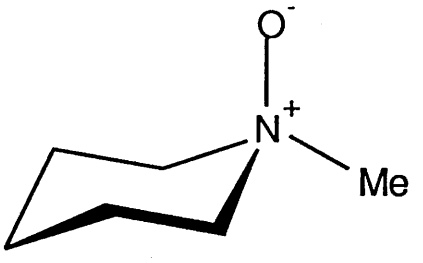
Scheme 3



Scheme 4



Scheme 5 (5) R = Et
(6) R = i-Pr



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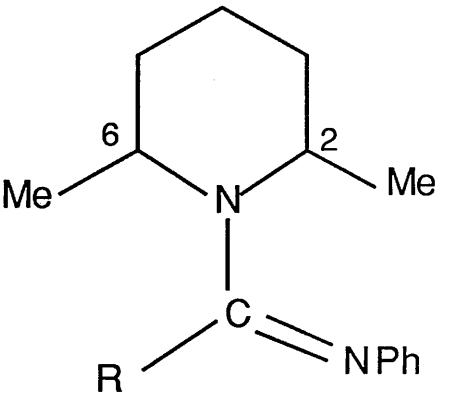
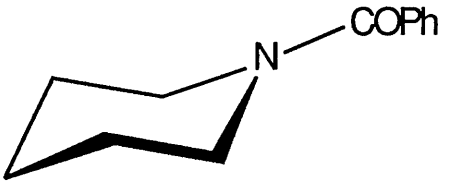


(16) R = Ph
(17) R = Bu^t



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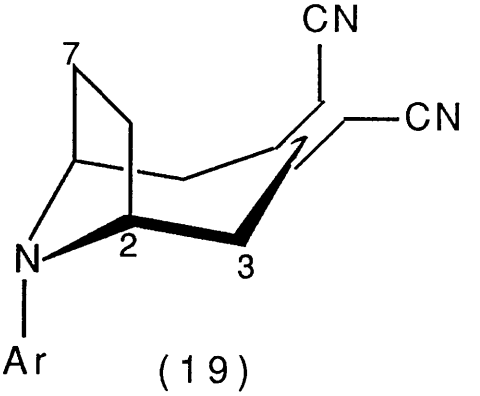

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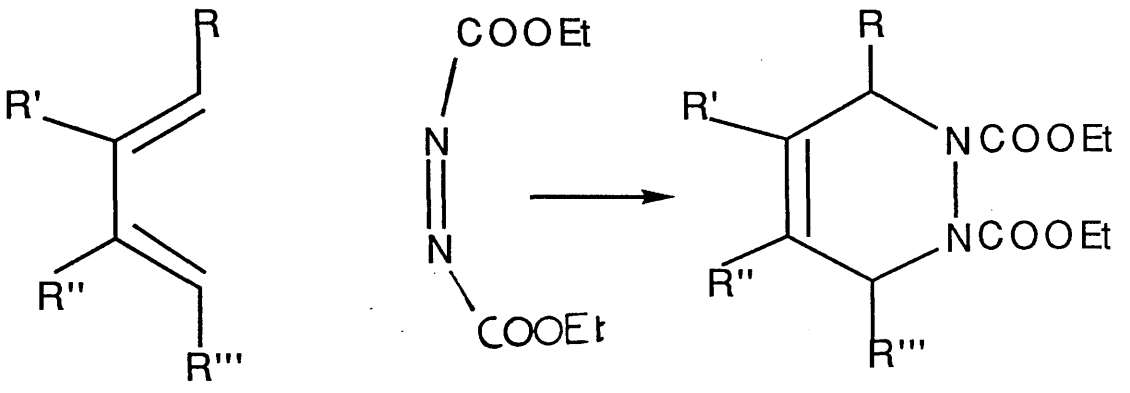
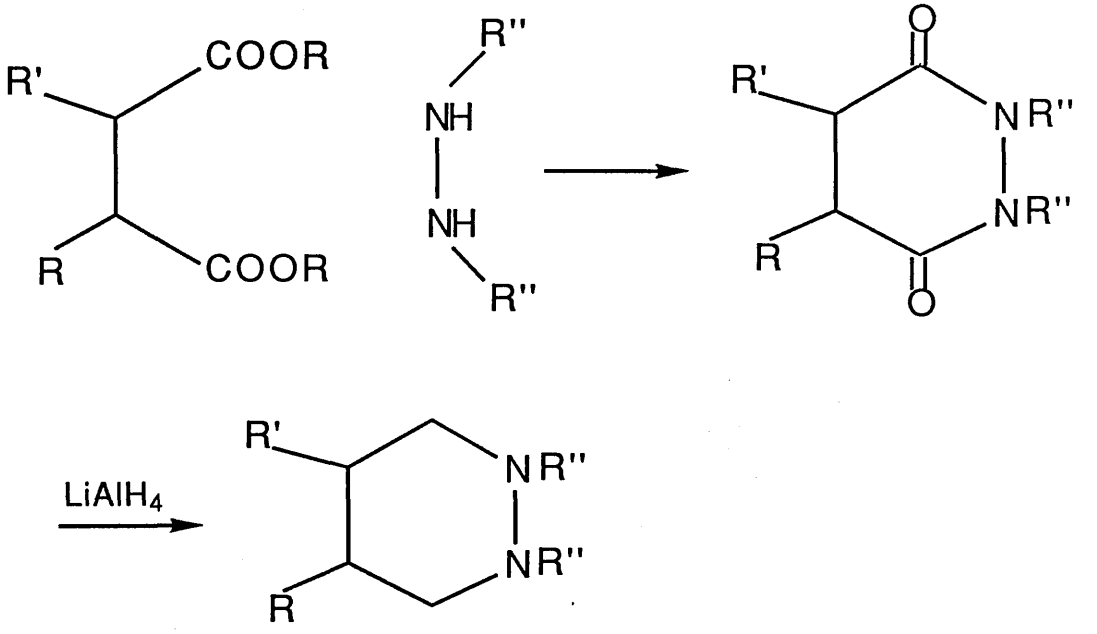
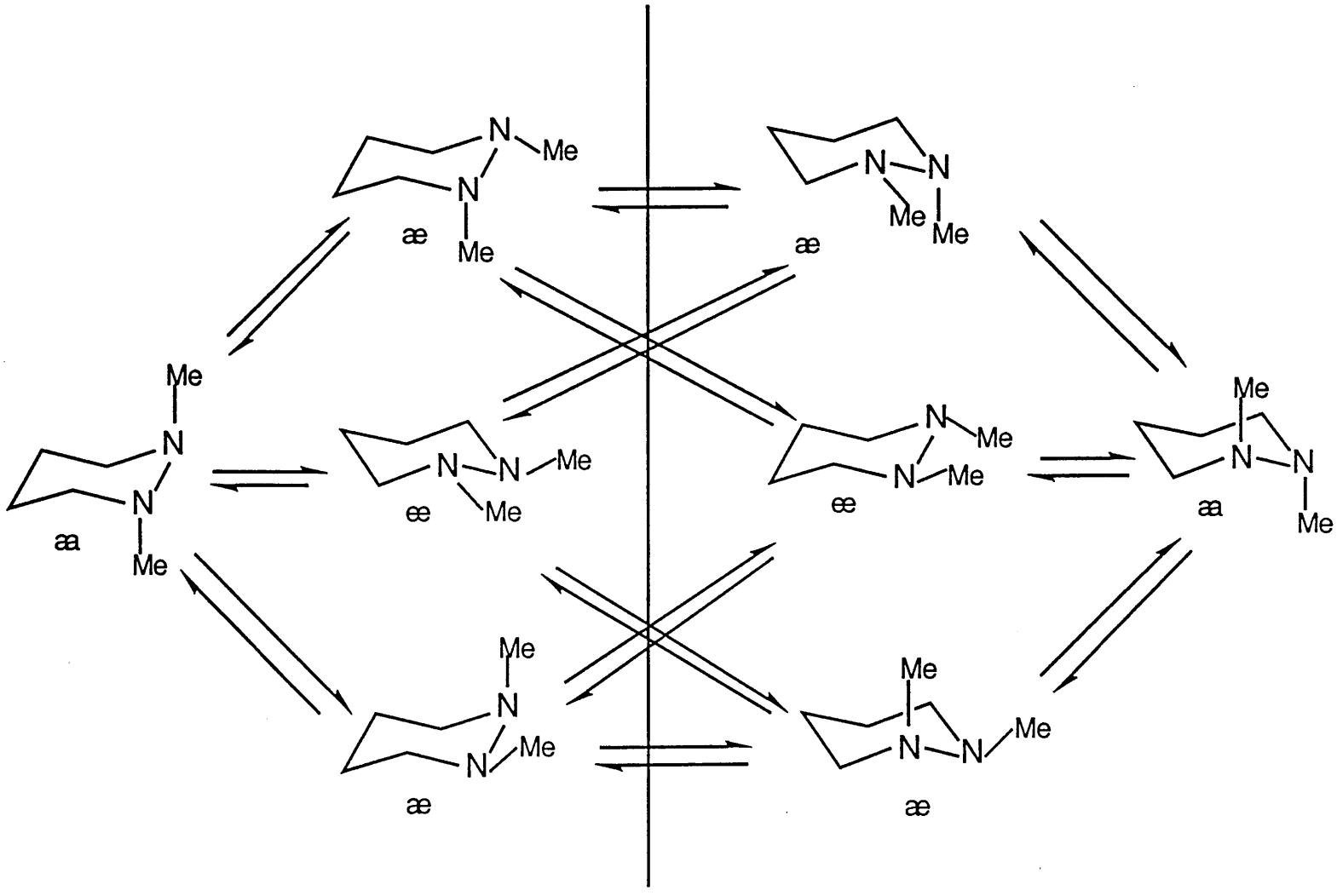


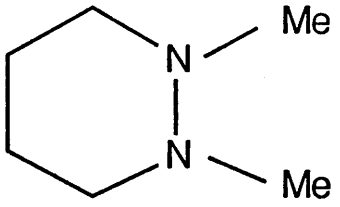
Scheme 6



Scheme 7



Scheme 8



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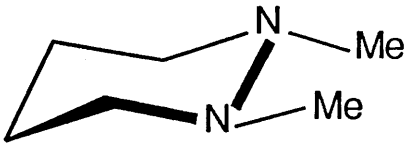

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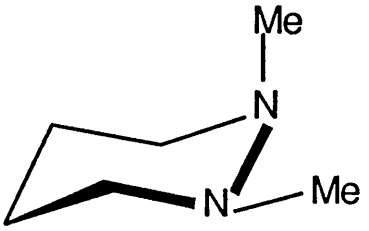

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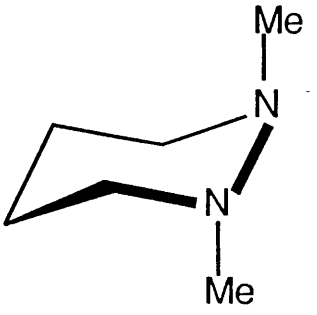

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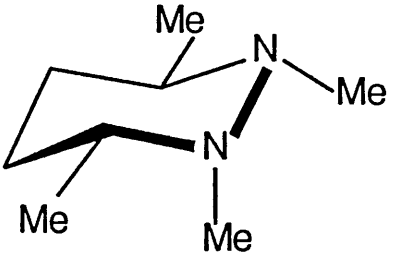

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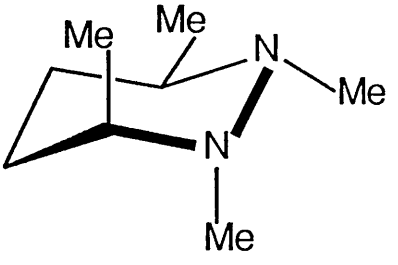

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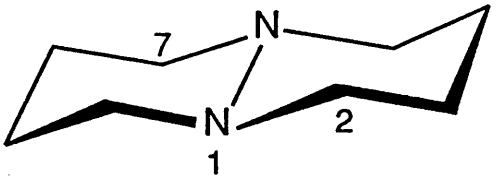

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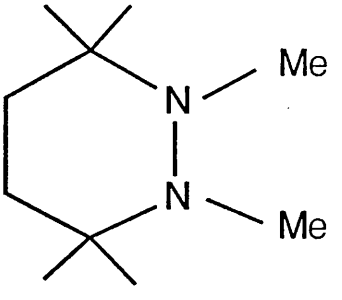

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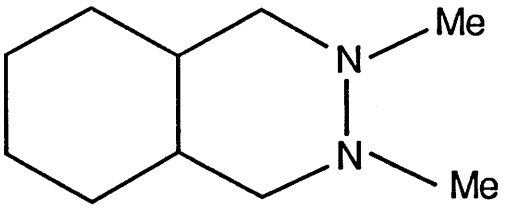

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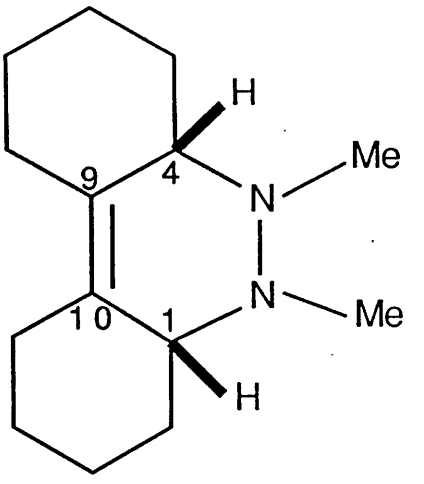

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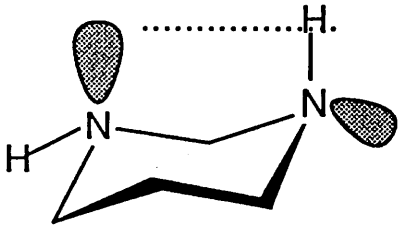

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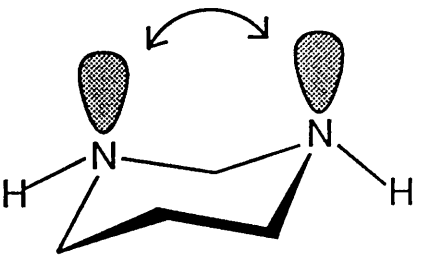

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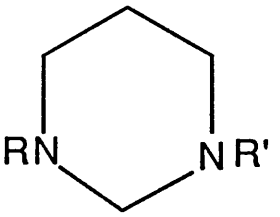
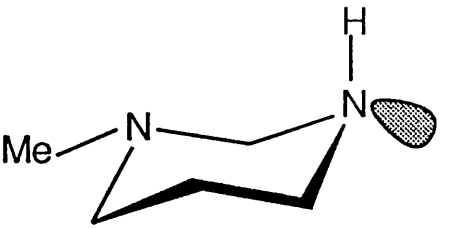


(32) R = Me, R' = H
(33) R = R' = Me
(34) R = R' = Et



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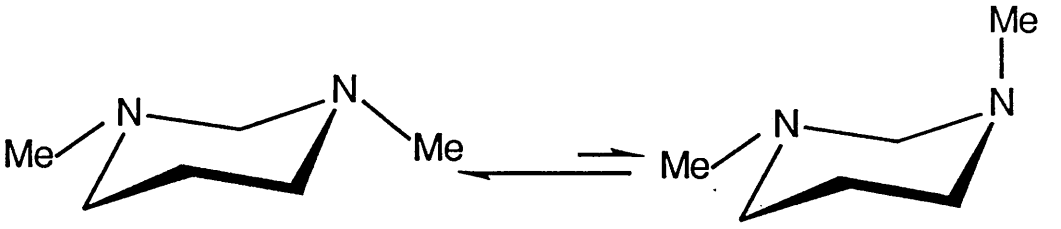
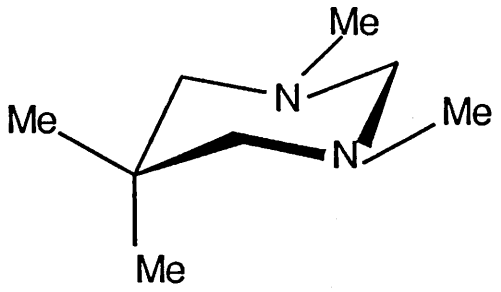


(36) (37)

Scheme 9



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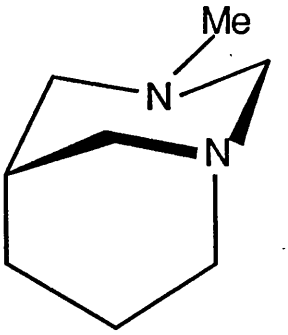

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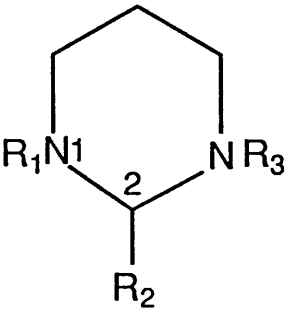
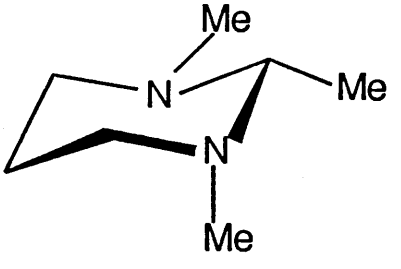


(40) $R_1 = R_3 = H$, $R_2 = Me$
(41) $R_1 = R_2 = Me$, $R_3 = H$
(42) $R_1 = R_3 = H$, $R_2 = Bz$
(43) $R_1 = (CH_2)_4NCHMe$, $R_2 = Me$, $R_1 = H$
(44) $R_1 = R_2 = R_3 = Me$



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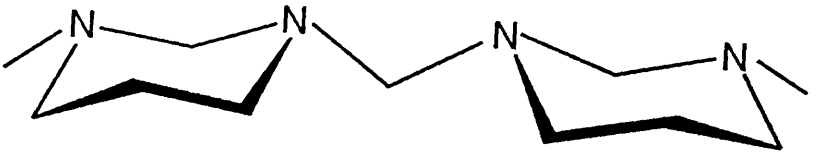

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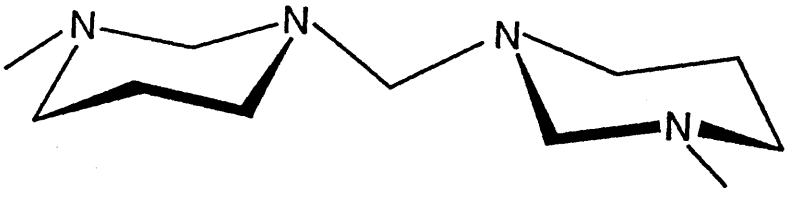

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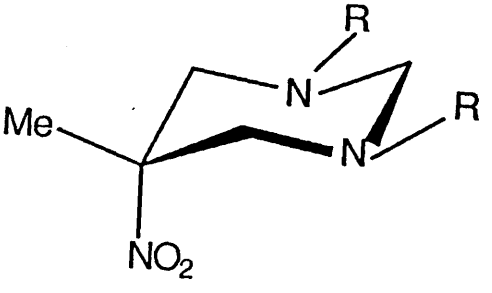

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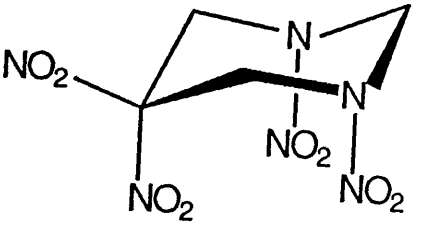

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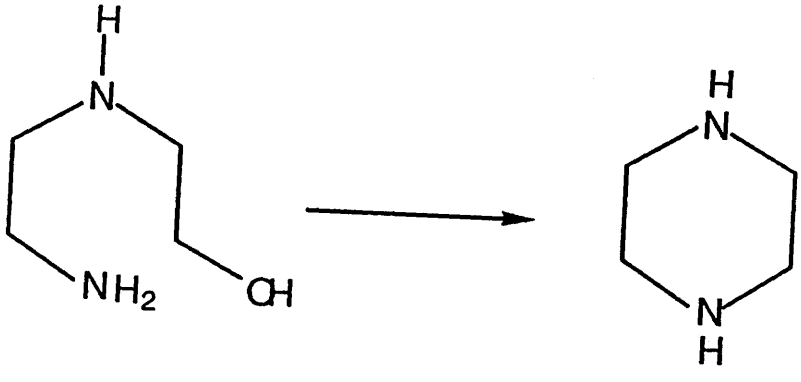
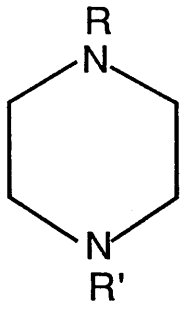
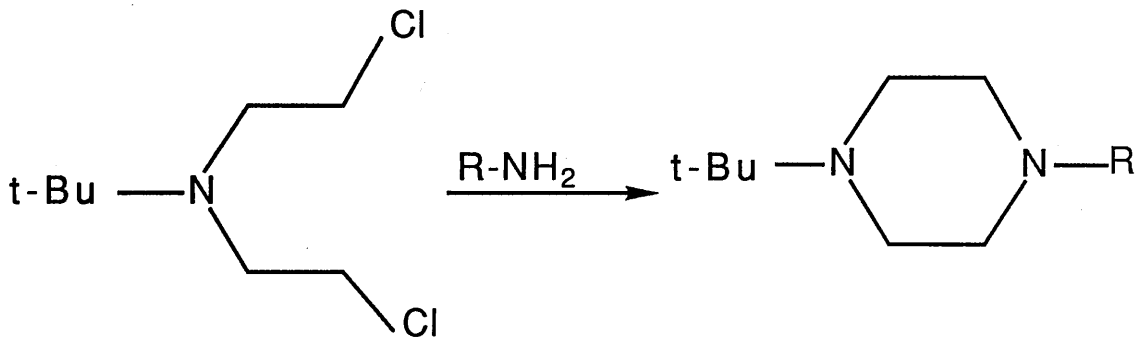


(50) (51)

Scheme 10



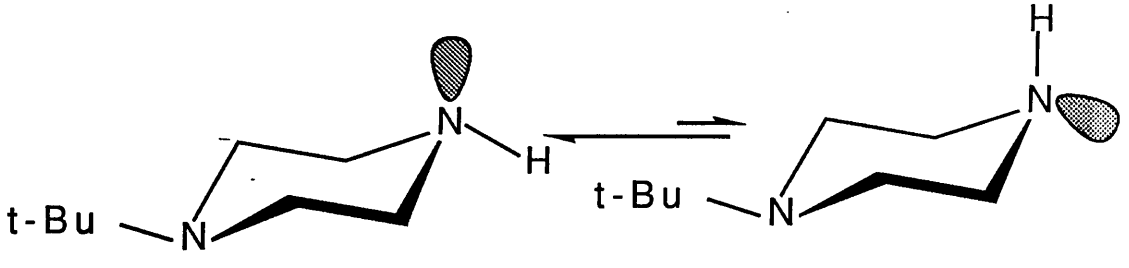
(51) R = R' = H
(52) R = H, R' = t-But
(53) R = Me, R' = t-But
(54) R = Et, R' = t-But
(55) R = R' = Me
(56) R = Me, R' = H



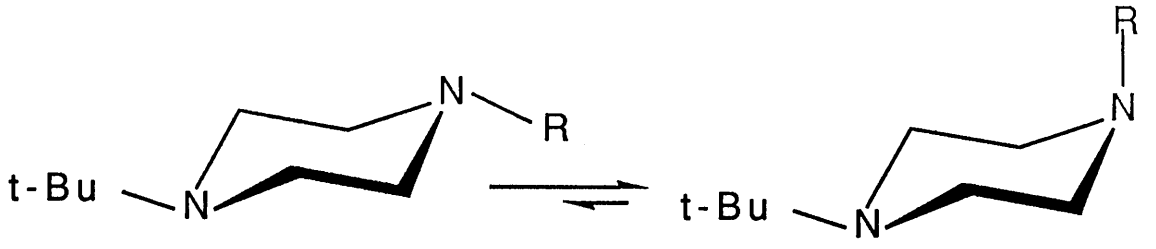
(57)

(53) R = Me
(54) R = Et

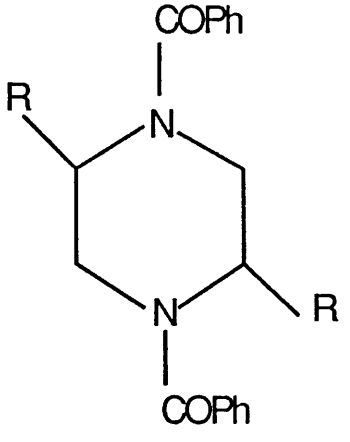
Scheme 11



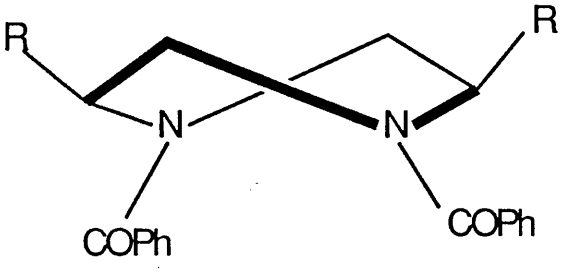
Scheme 12



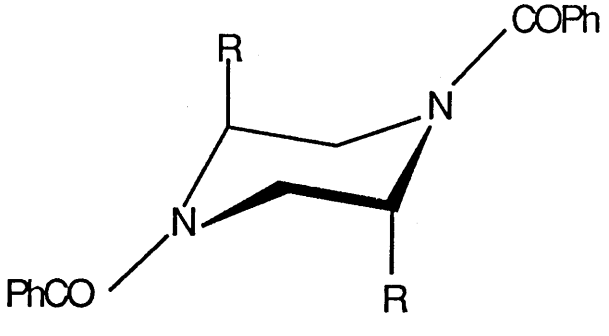
Scheme 13



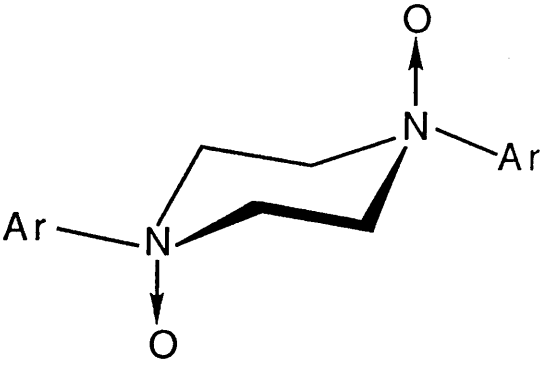
(58) R = Me or Et



(59) R = Me or Et

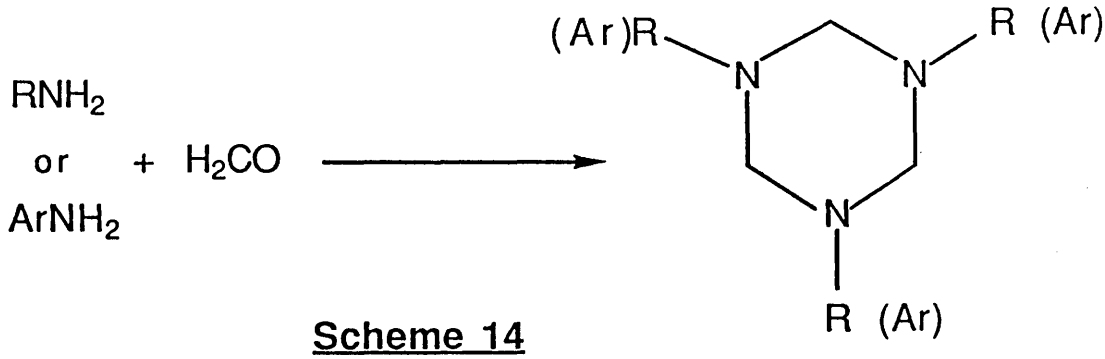


(60) R = Me or Et



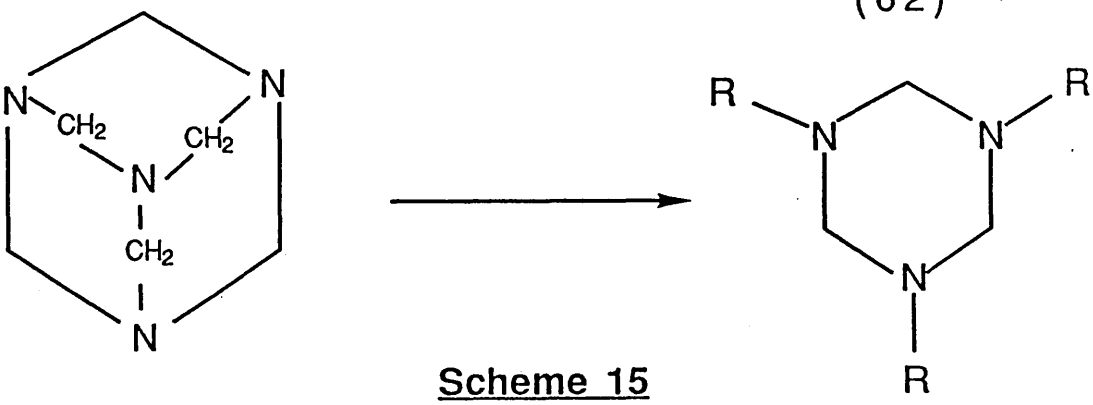
(61)

Ar = 2-MeC_6H_4
4-MeC_6H_4
4-ClC_6H_4



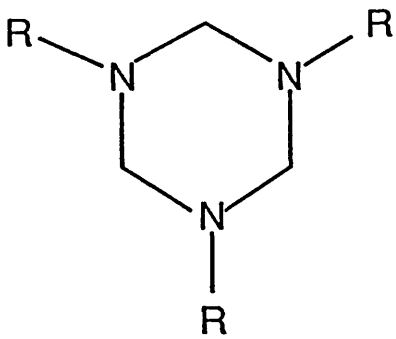
(62)

Scheme 14

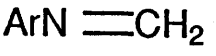


(75)

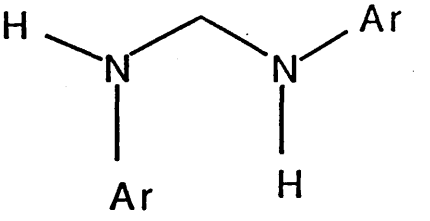
Scheme 15



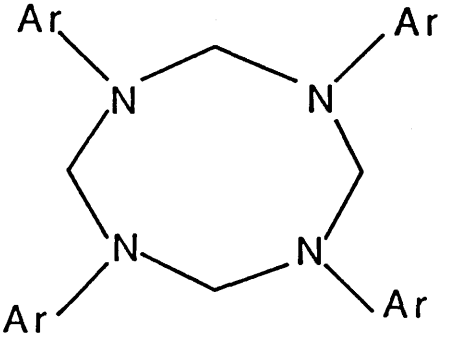
(63) R = Bz
(64) R = Ph
(65) R = Me
(66) R = Et
(67) R = t-Bu
(68) R = i-Pr
(69) R = OMe
(70) R = OCOMe
(71) R = $SO_2C_6H_5$
(72) R = SO_2CH_3
(73) R = COMe
(74) R = NO_2



(76)



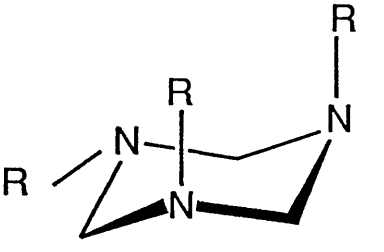
(77)



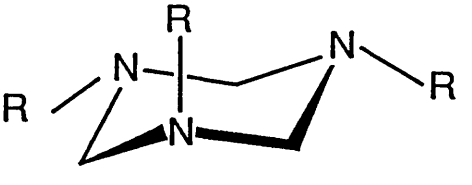
(78) Ar = 3-MePh
Ar = 4-MePh
Ar = 4-t-BuPh
Ar = 3-FPh

(79) Ar = Ph

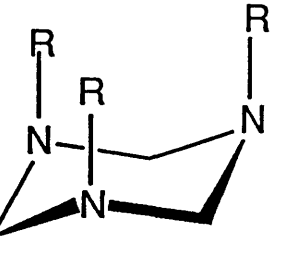
(80)



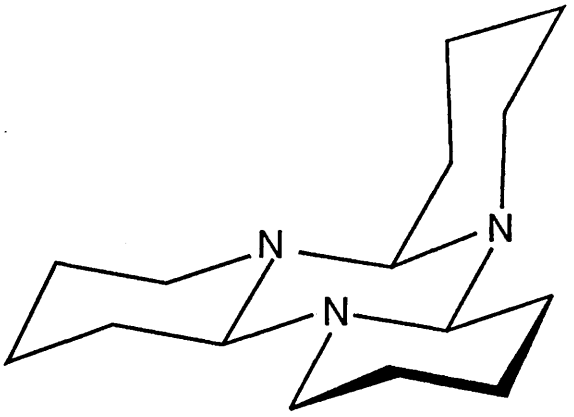
(81)



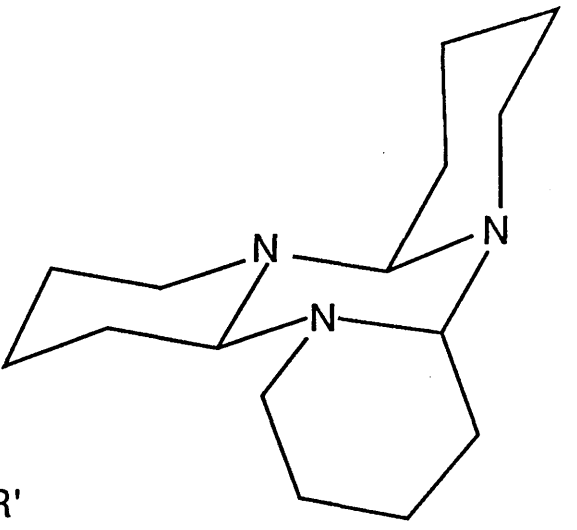
(82)



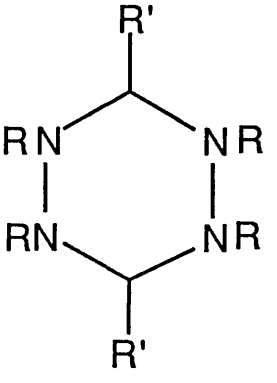
(83)



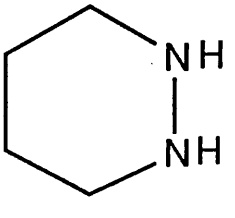
(84)



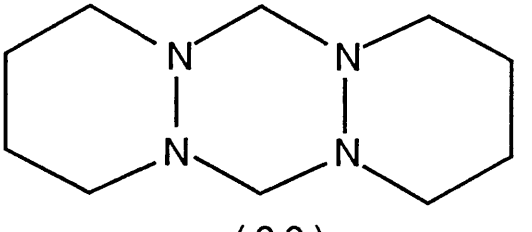
(85)



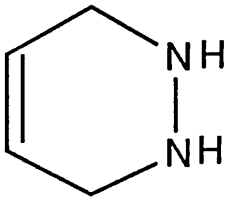
(86) R = Me, R' = H
(87) R = Et, R' = H
(88) R = R' = Me
(89) R = Bz, R' = H



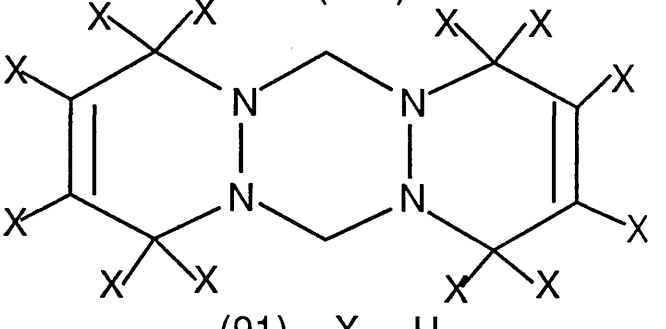
(93)



(90)



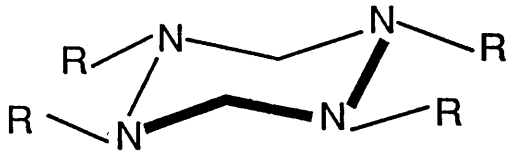
(94)



(91) X = H
(92) X = D

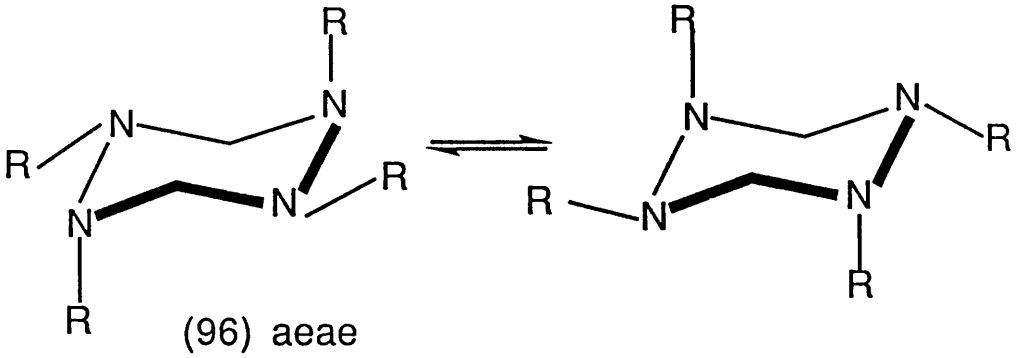
Scheme 16

Set I

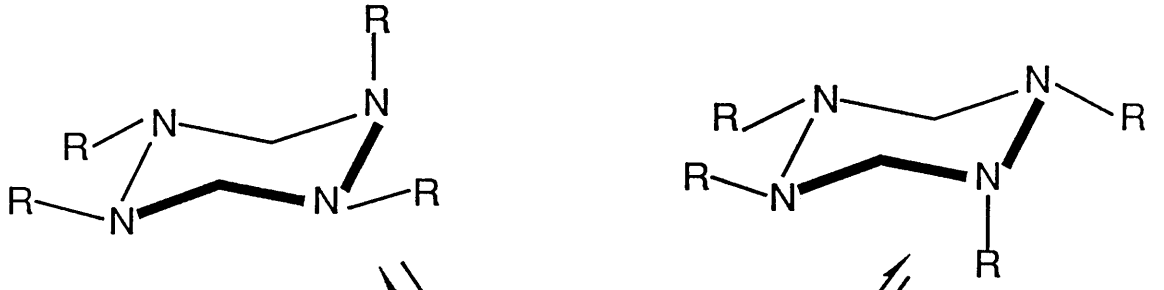


(95) eeee

Set II

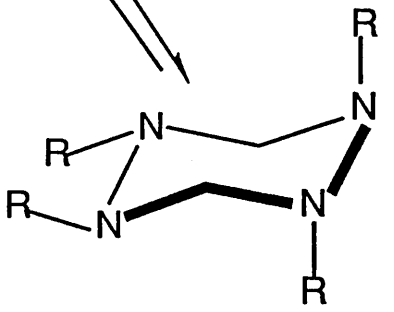


(96) aeae



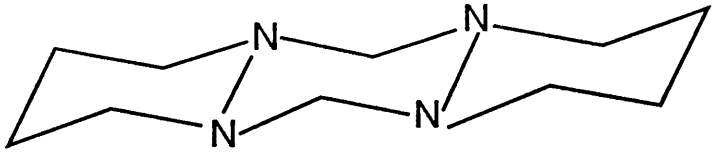
(97) aeee

Set III

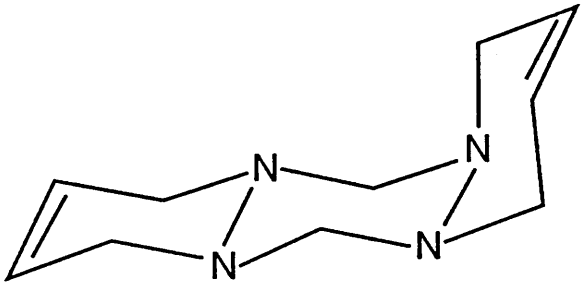


(98) aaee

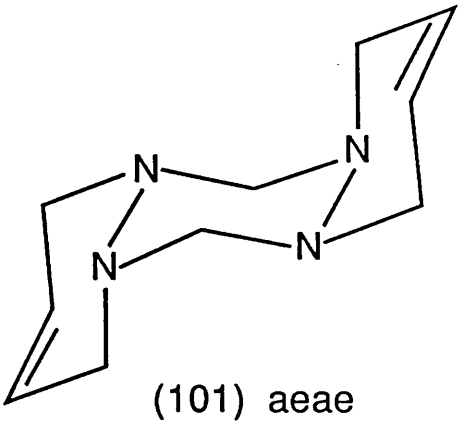
Scheme 17



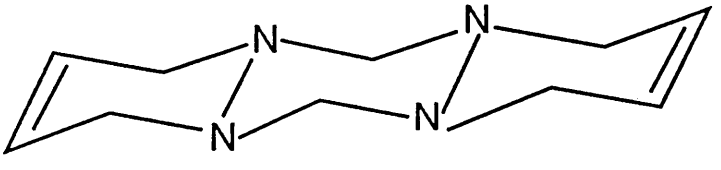
(99) eeee



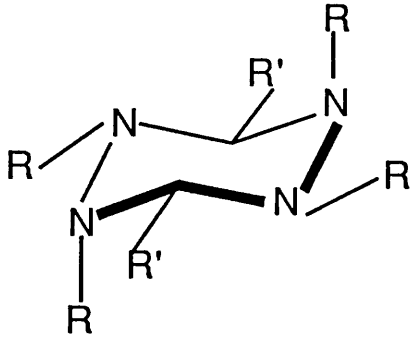
(100) aeee



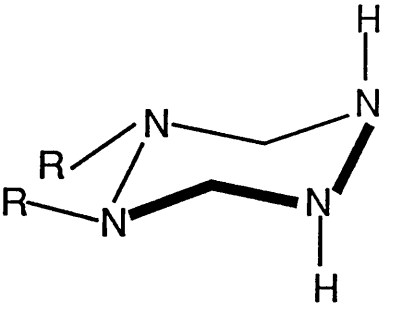
(101) aeae



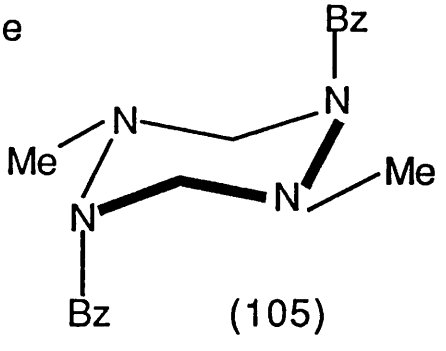
(102) eeee



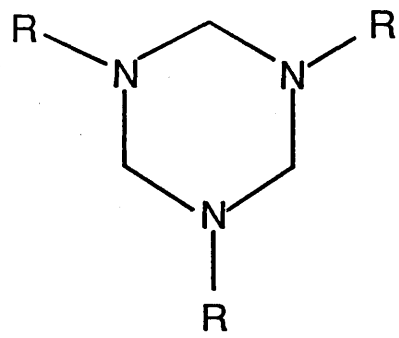
(103) R = R' = Me



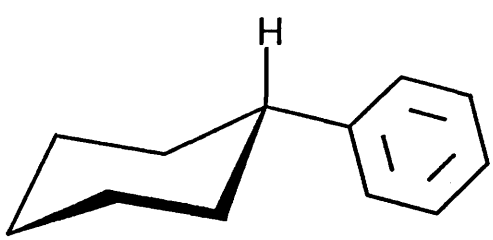
(104) R = Me



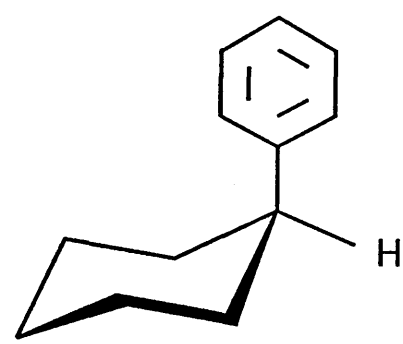
(105)



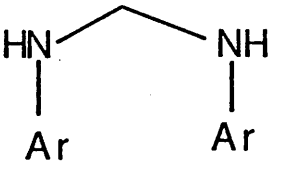
(106) R = 2-FC_6H_4
(107) R = 3-FC_6H_4
(108) R = 4-FC_6H_4
(109) R = 4-$CH_3C_6H_4SO_2$
(110) R = 2-ClC_6H_4
(111) R = 4-ClC_6H_4
(112) R = 2-$CH_3OC_6H_4$
(113) R = 4-$CH_3OC_6H_4$
(114) R = 4-$CH_3C_6H_4CH_2$
(115) R = 4-$CH_3C_6H_4$
(116) R = C_6H_{11}
(117) R = 4-$NO_2C_6H_4$
(118) R = 3-$CF_3C_6H_4$
(119) R = 2-$CF_3C_6H_4$



(120)

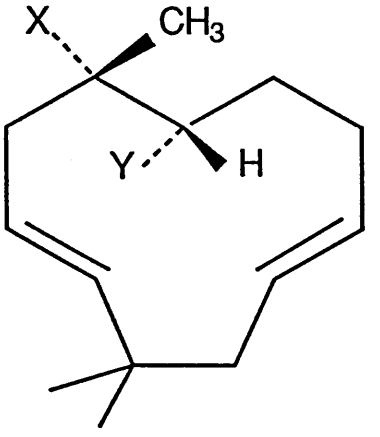


(121)

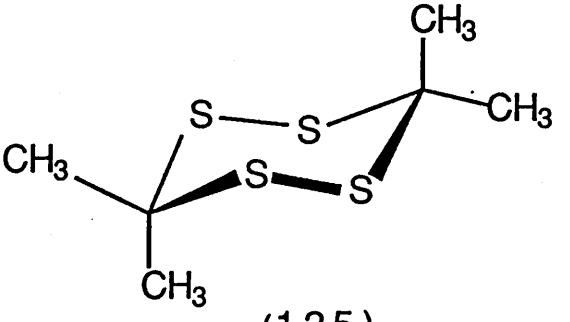


(122) R = 2-$CF_3C_6H_4$

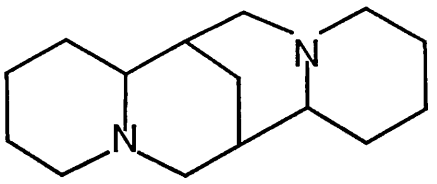
(123) R = 4-$NO_2C_6H_4$



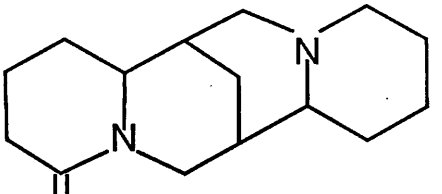
(124) X = NO, Y = NO_2



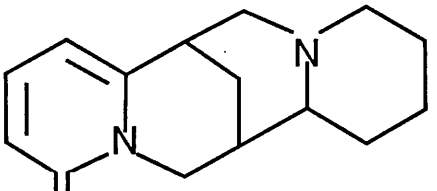
(125)



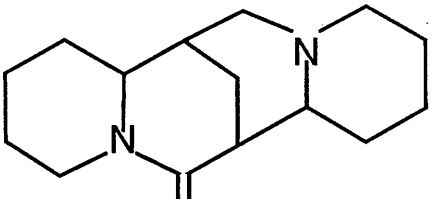
(126)



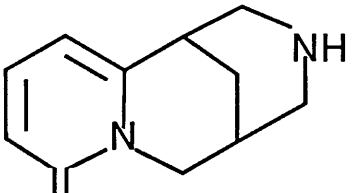
(127)



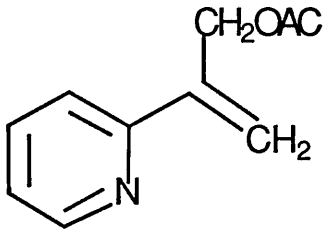
(128)



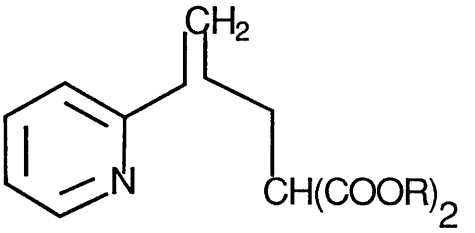
(129)



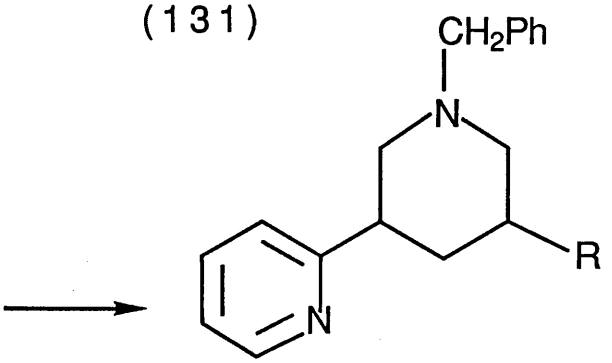
(130)



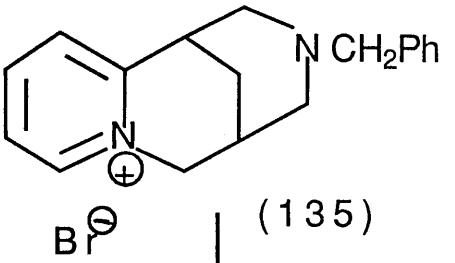
(131)



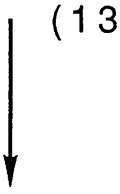
(132) R = Et
R = H



(133) R = COOH
(134) R = CH_2OH
R = CH_2Br

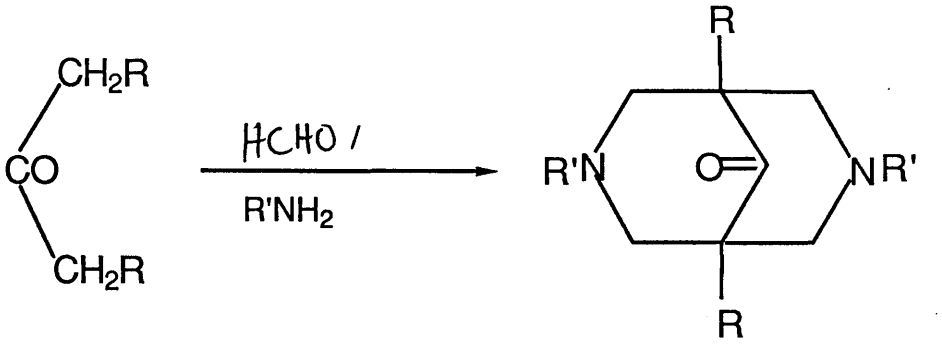


(135)



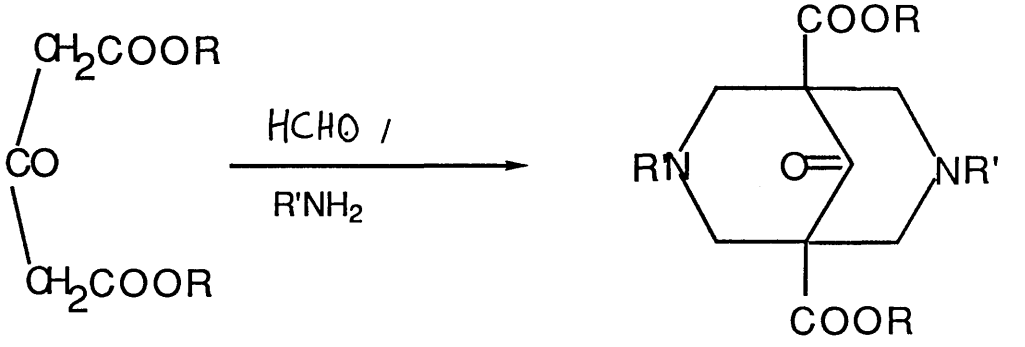
(130)

Scheme 18



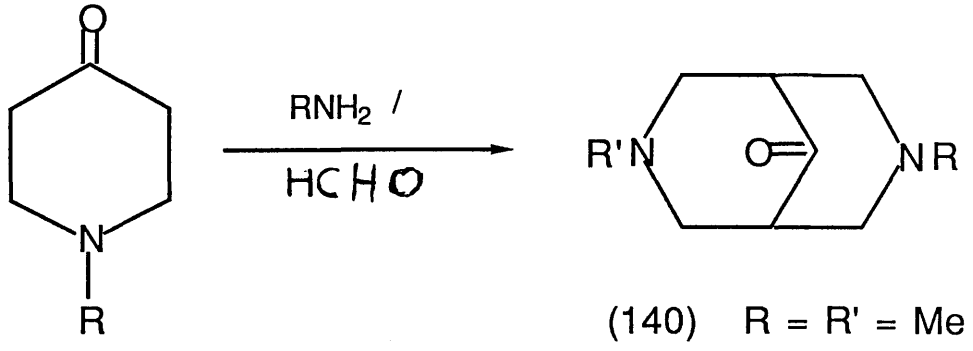
(136) R = Ph, R' = H, Me, Pr or BZ
(137) R = Ar, R' = alkyl

Scheme 19



(138) R = R' = Me
(139) R = Et, R' = Me

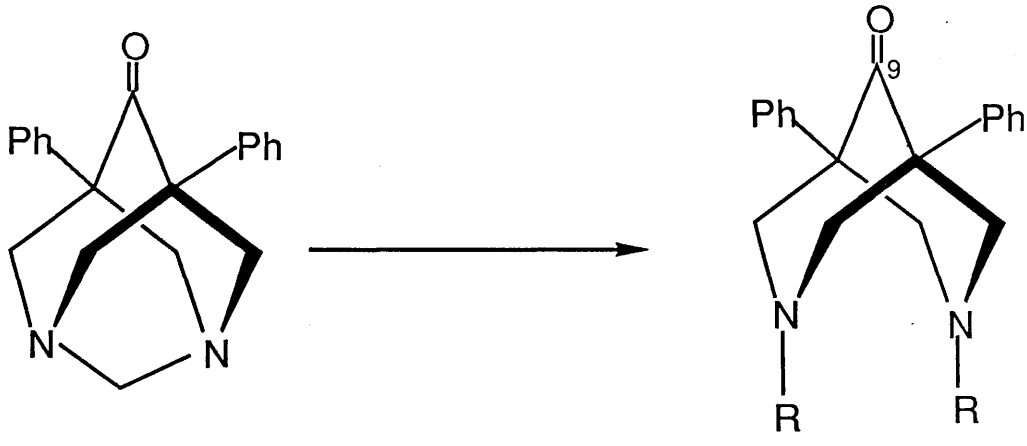
Scheme 20



(140) R = R' = Me
(141) R = Me, R' = Bz

(142) R' = Me
(143) R' = Bz

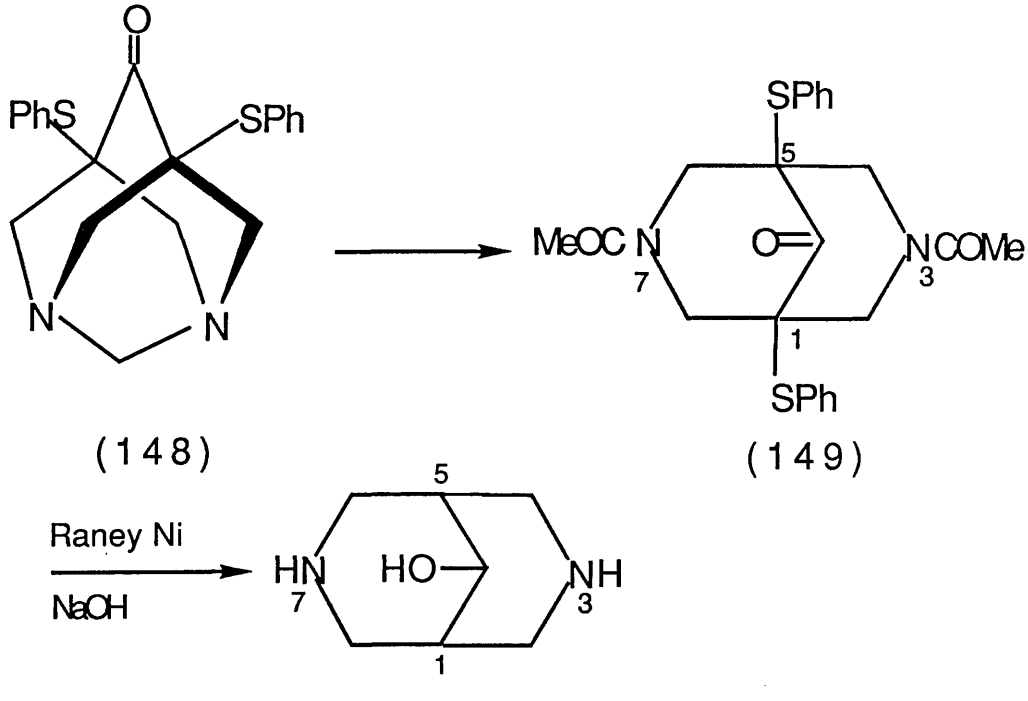
Scheme 21



(144)

(145) R = CH_3CO
(146) R = Ts
(147) R = NO

Scheme 22

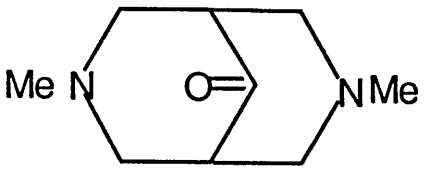


(148)

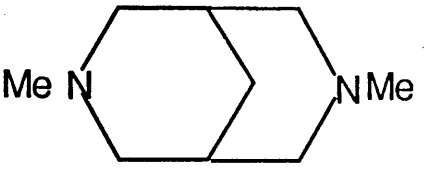
(149)

(150)

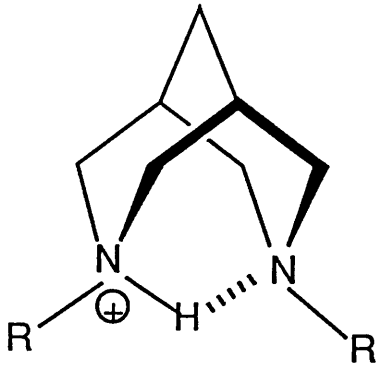
Scheme 23



(151)



(152)



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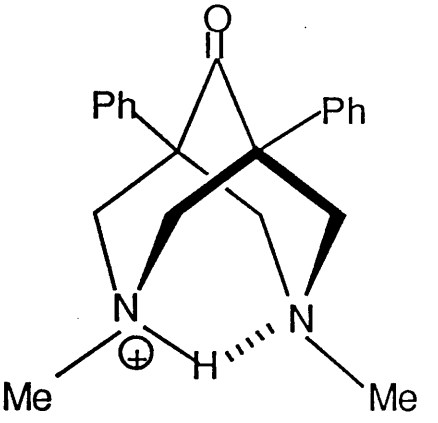
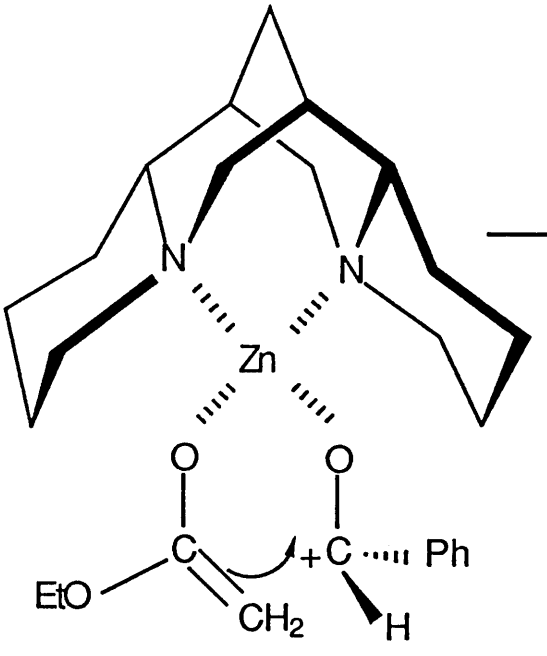
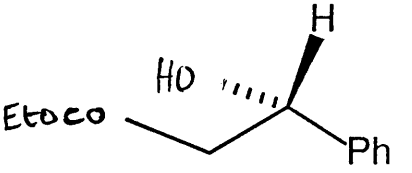


(154)

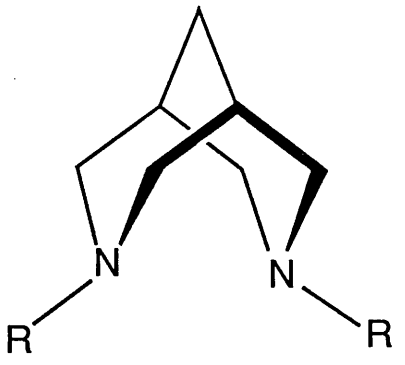


(155)

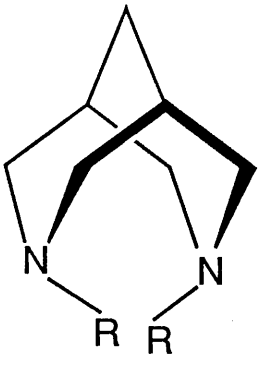


(156)

Scheme 24



(157)



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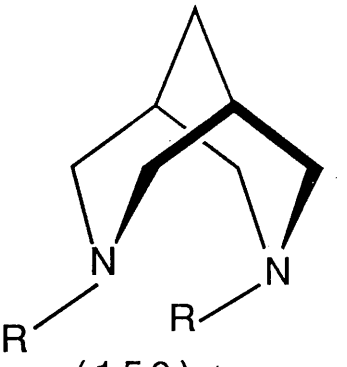
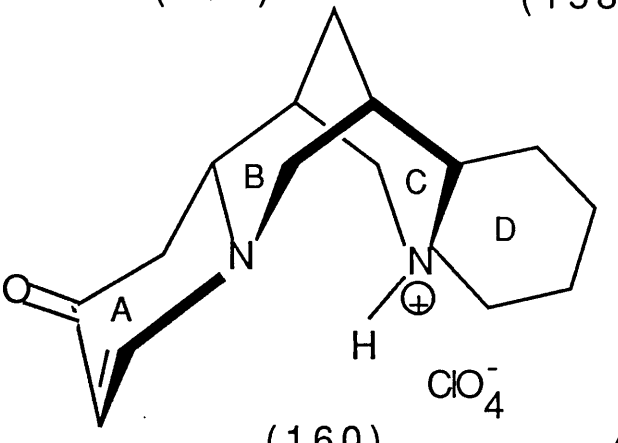


(159)



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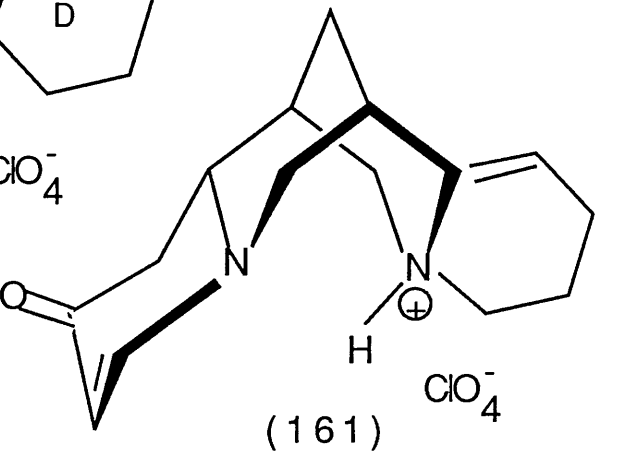
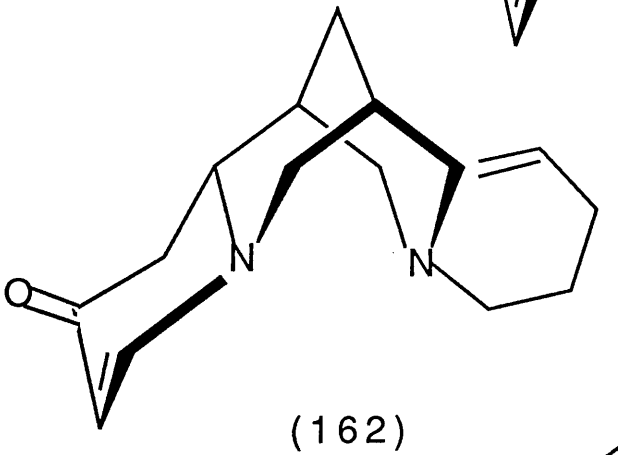
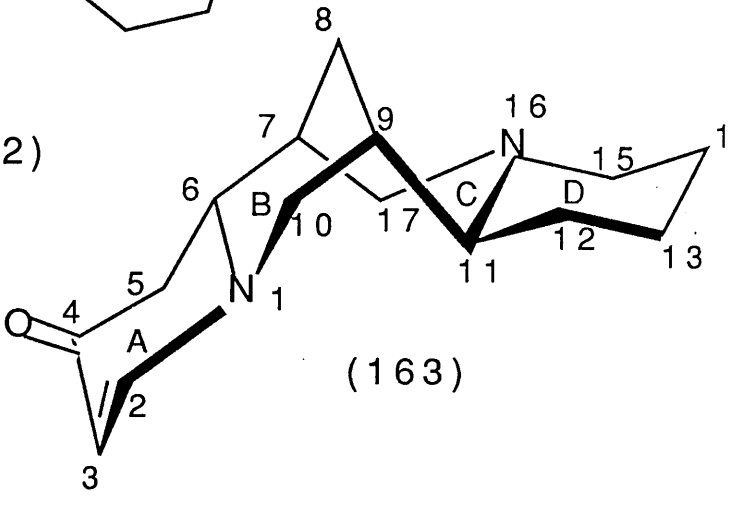


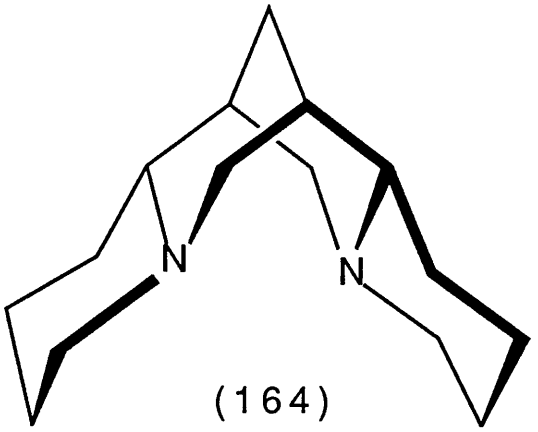
(161)



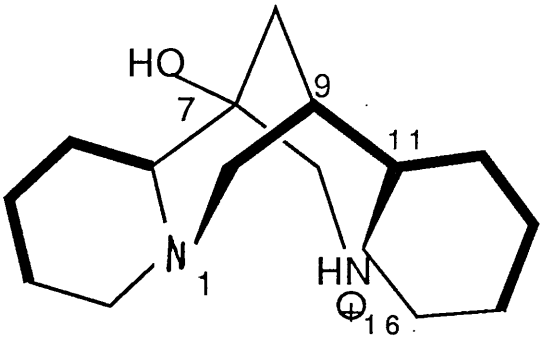
(162)



(163)

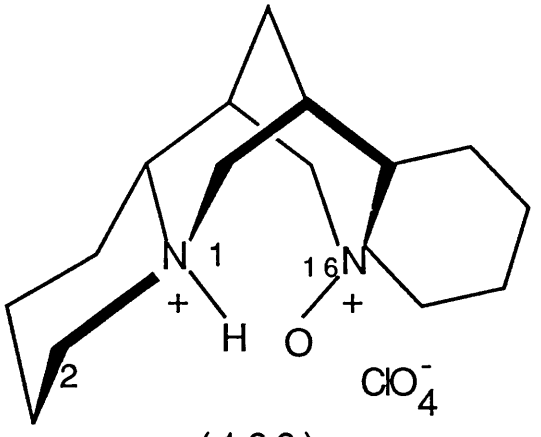


(164)



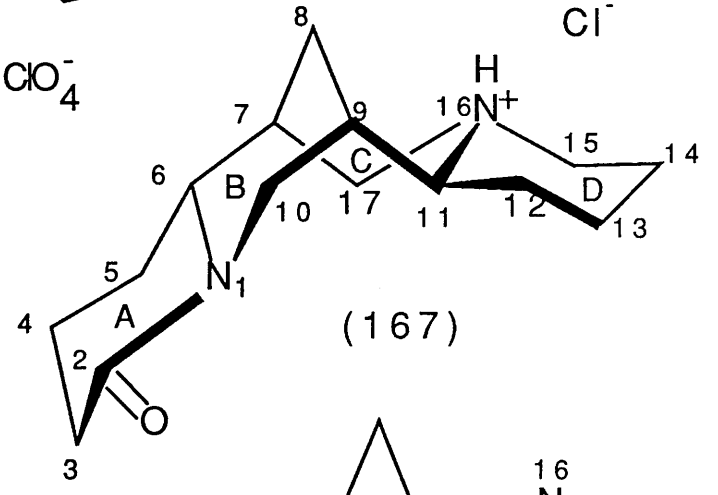
ClO_4^-

(165)

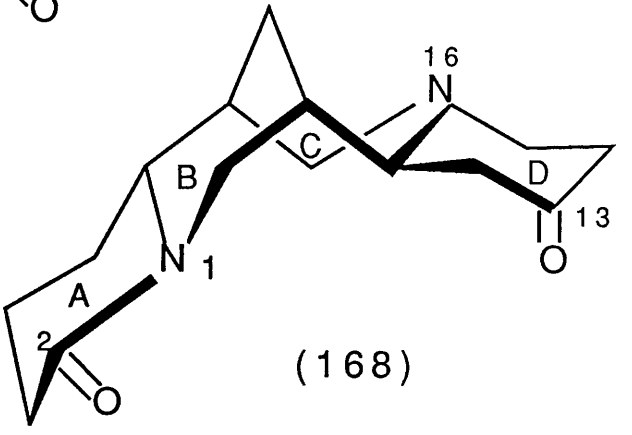


ClO_4^-

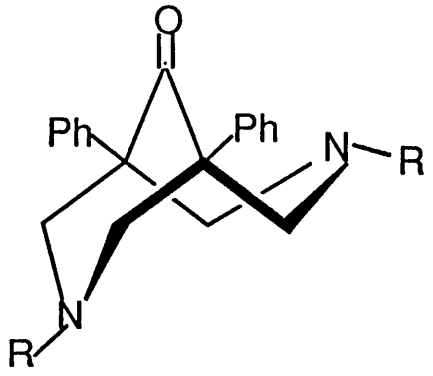
(166)

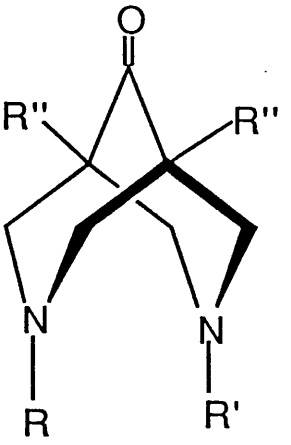


(167)



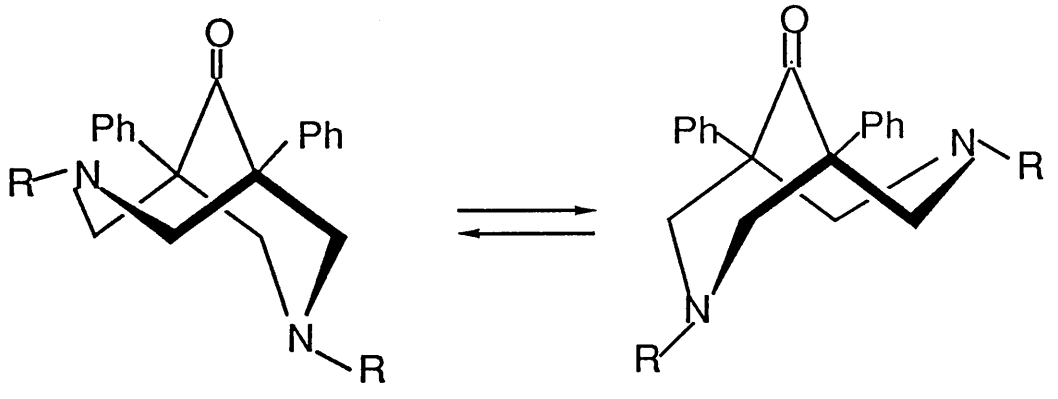
(168)





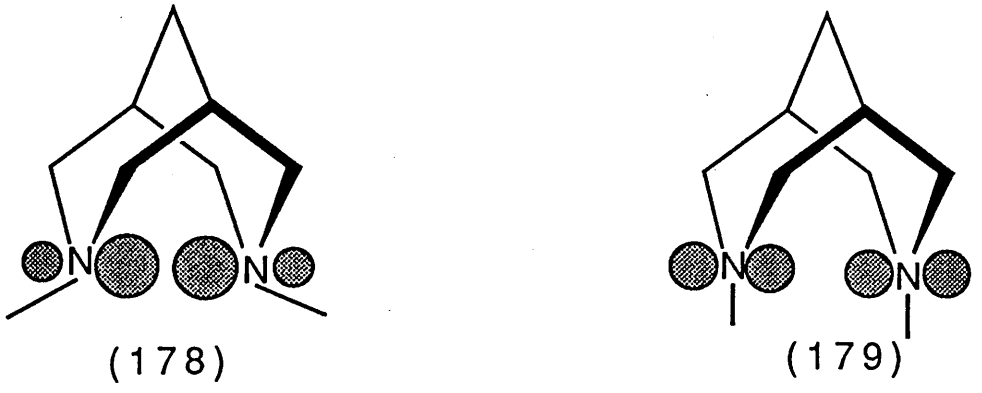
(169) R = Me
(170) R = Bu^t
(171) R = Bz

(172) R = Me, R' = Alkyl, R'' = H
(173) R = R' = COOEt, R'' = Ph
(174) R = R' = CF_3CO, R'' = Ph
(175) R = COOEt, R' = Me, R'' = Ph

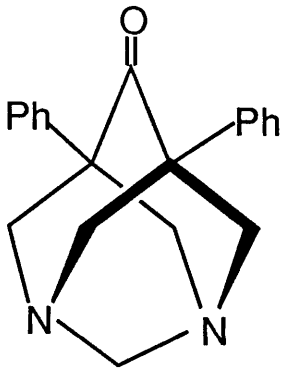


(176) (177)

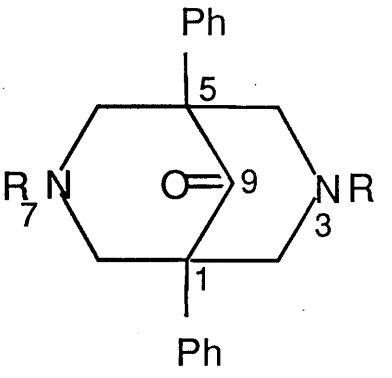
Scheme 25



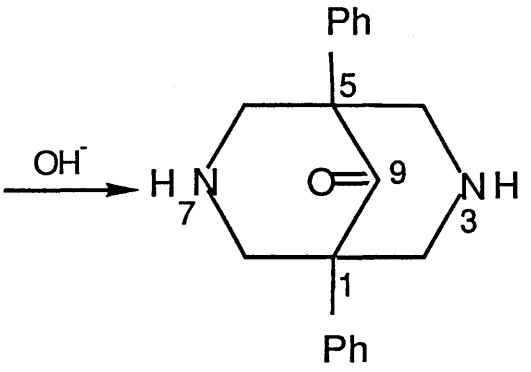
(178) (179)



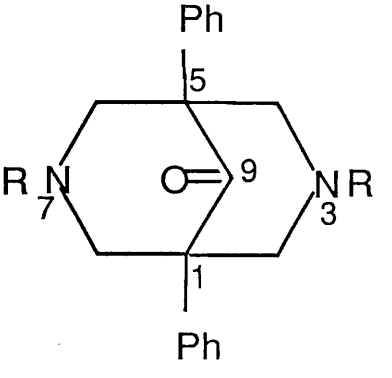
(144)



(173) R = EtOOC
(180) R = MeOOC

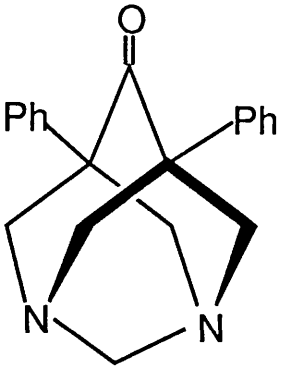


(181)



(182) R = SO_2Me
(183) R = $SO_2CH_2C_6H_5$
(185) R = $SO_2C_6H_4OMe$
(186) R = $SO_2C_6H_4NO_2$

Scheme 26



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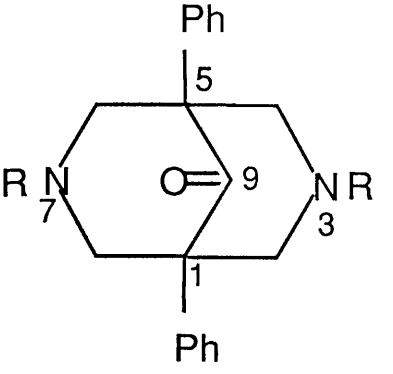
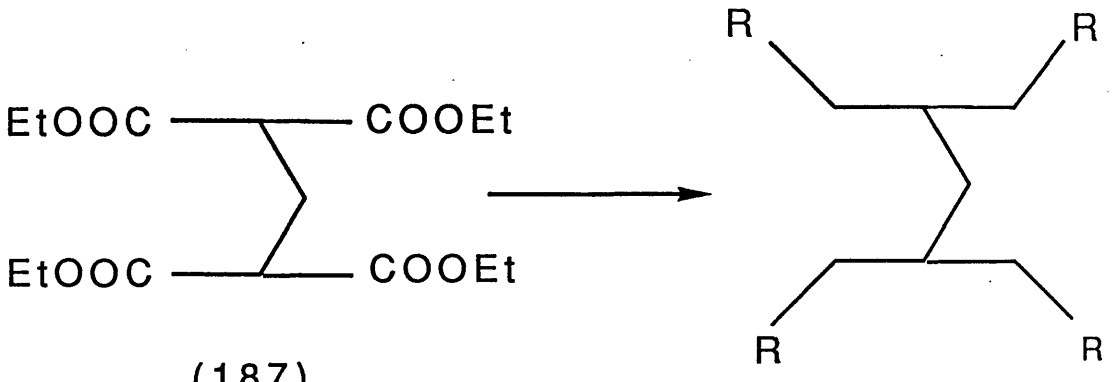


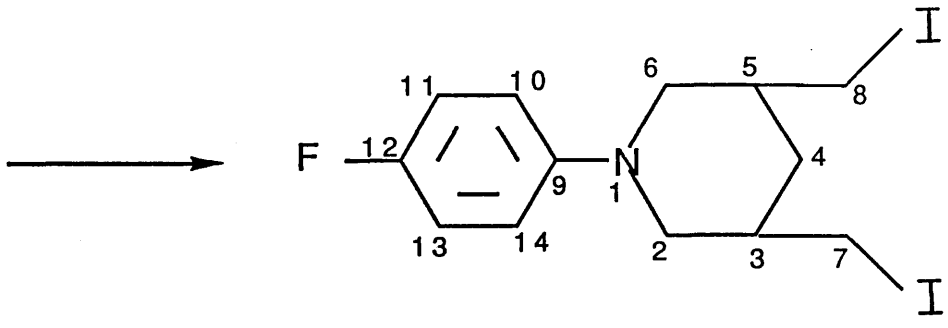
(184) R = $SO_2C_6H_5$
(185) R = $SO_2C_6H_4OCH_3$

Scheme 27



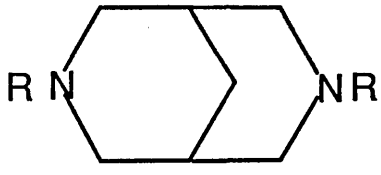
(187)

(188) R = OH
(189) R = I

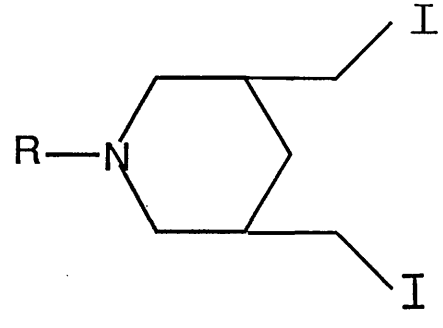


(190)

Scheme 28



(191) R = Ph
(192) R = 4-FC_6H_4
(193) R = 4-$CH_3OC_6H_4$



(194) = 4-$H_3COC_6H_4$

Figures

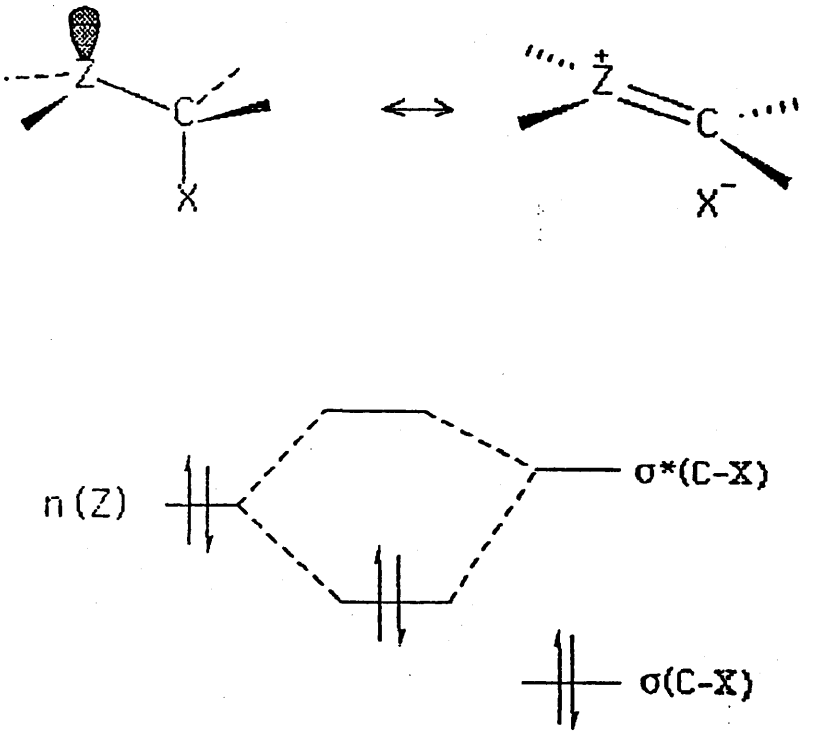


Fig. 1

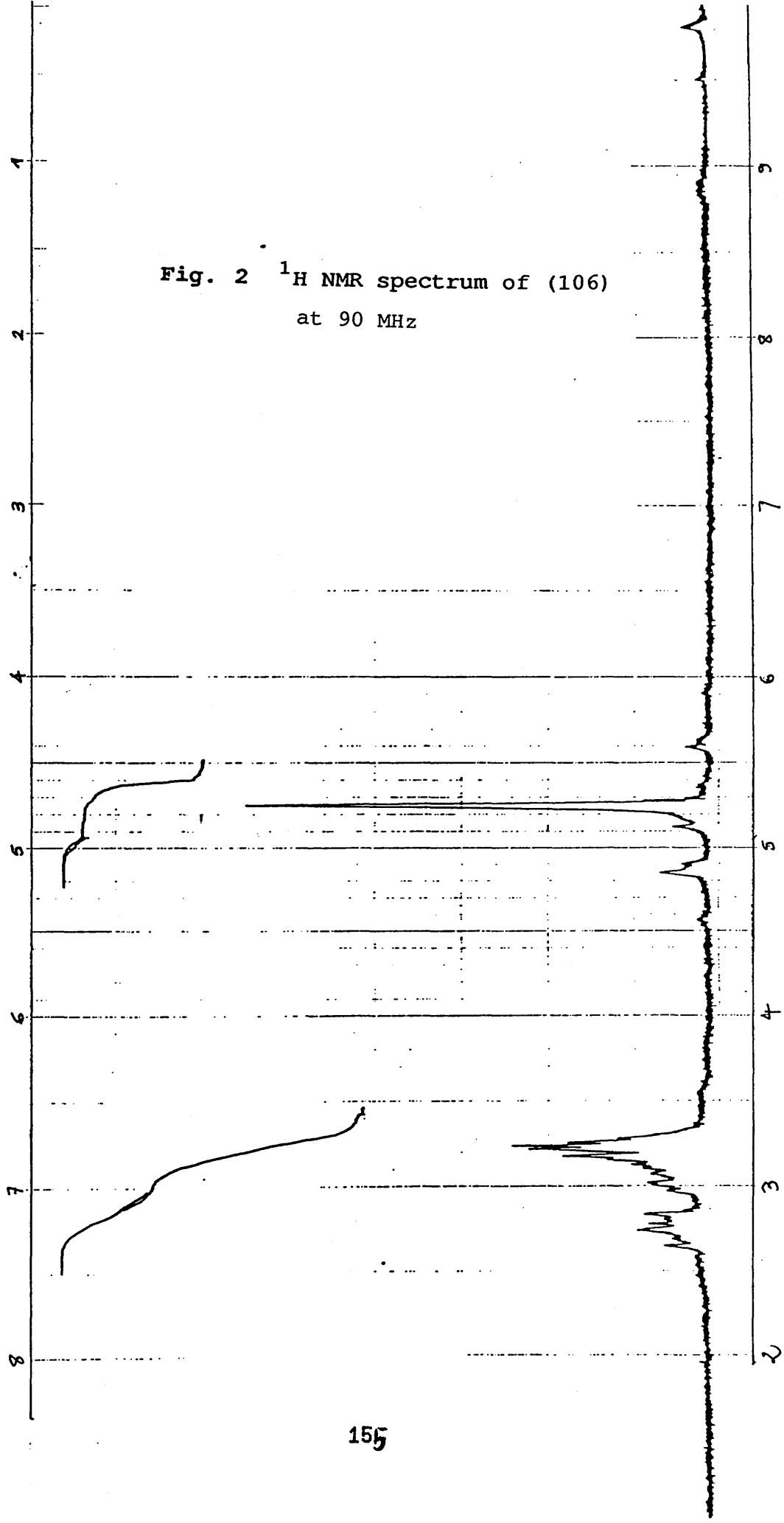


Fig. 2 ^{1}H NMR spectrum of (106)
at 90 MHz

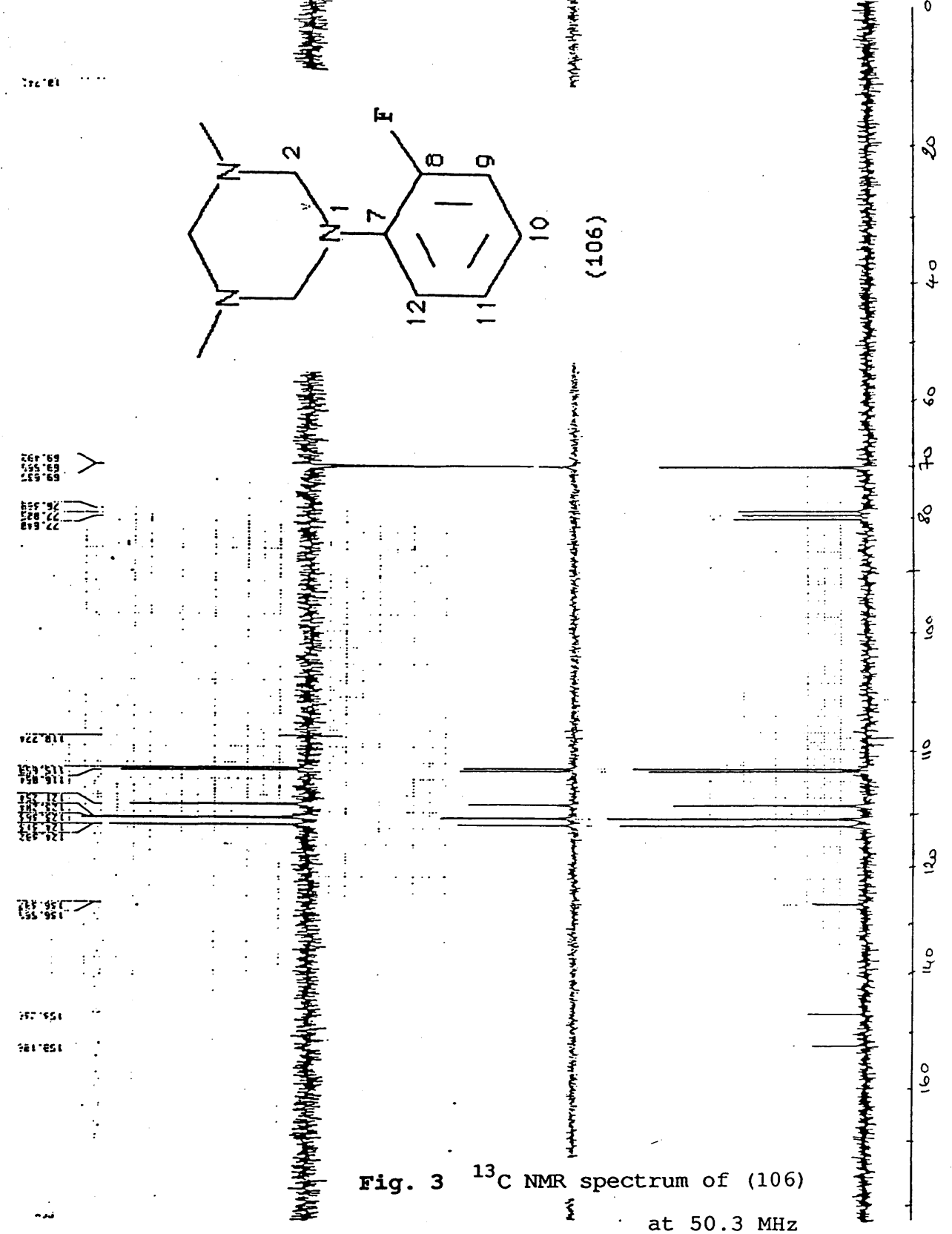


Fig. 3 ^{13}C NMR spectrum of (106) at 50.3 MHz

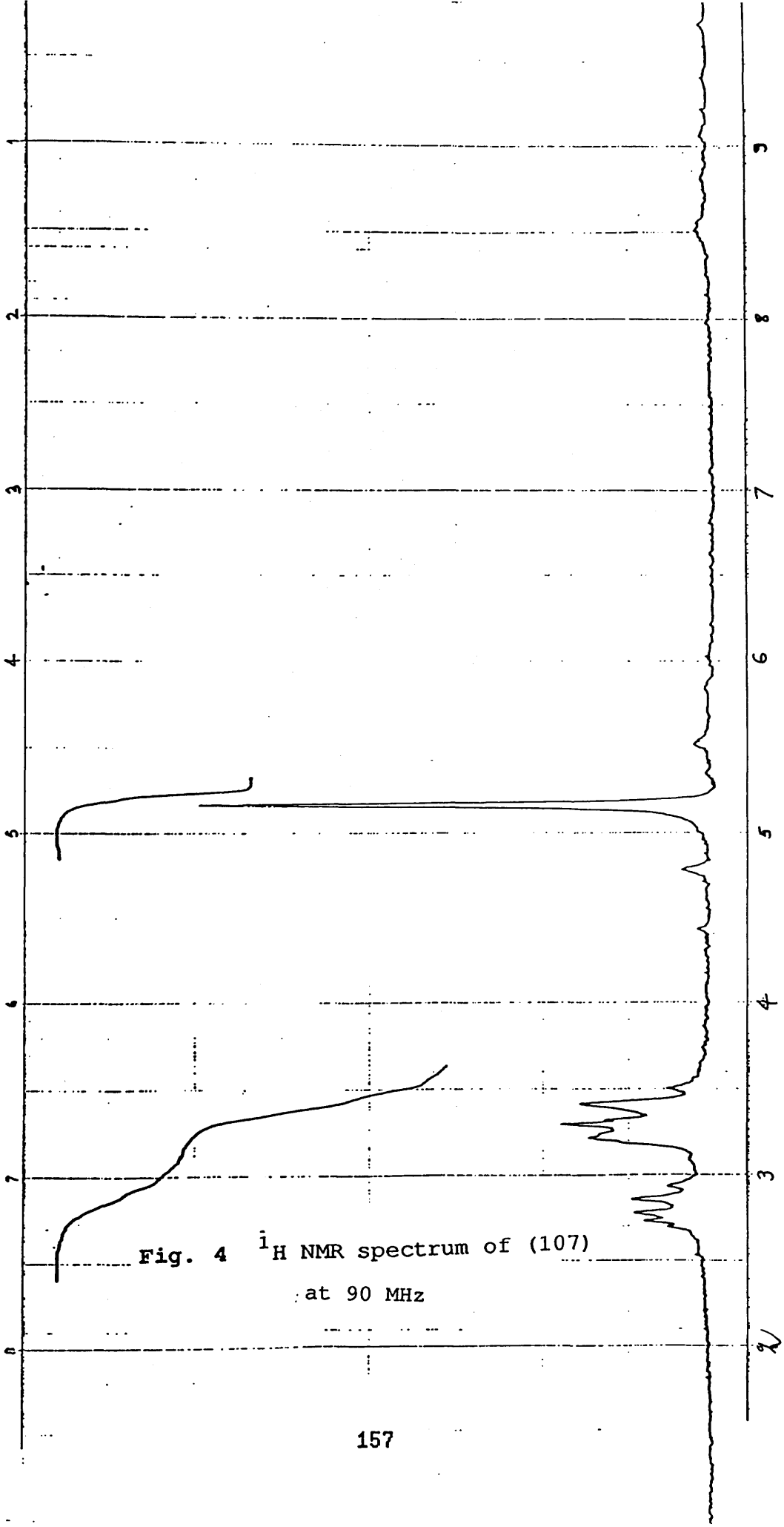


Fig. 4 ^{1}H NMR spectrum of (107) at 90 MHz

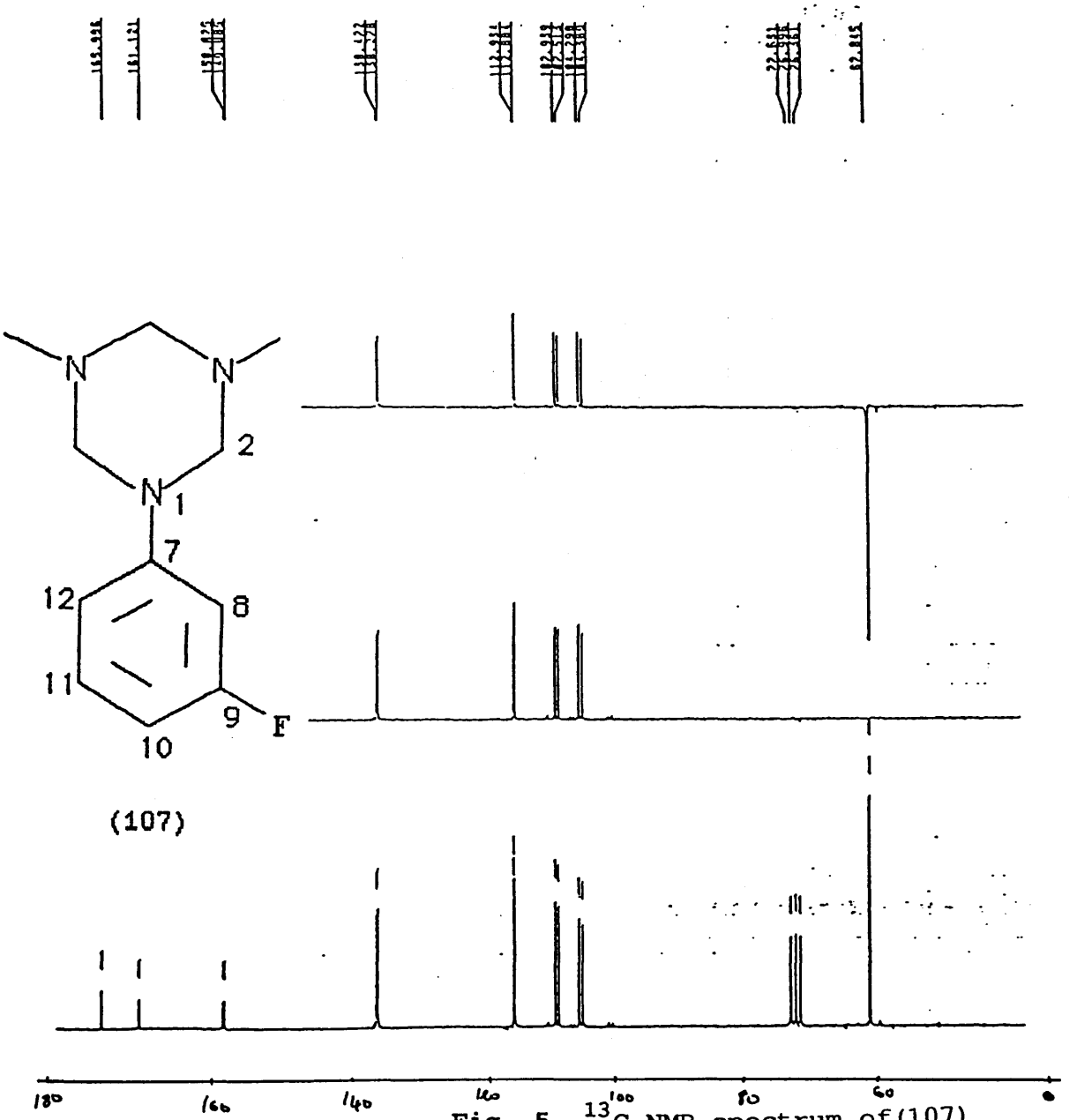


Fig. 5 ^{13}C NMR spectrum of(107)

at 50.3 MHz

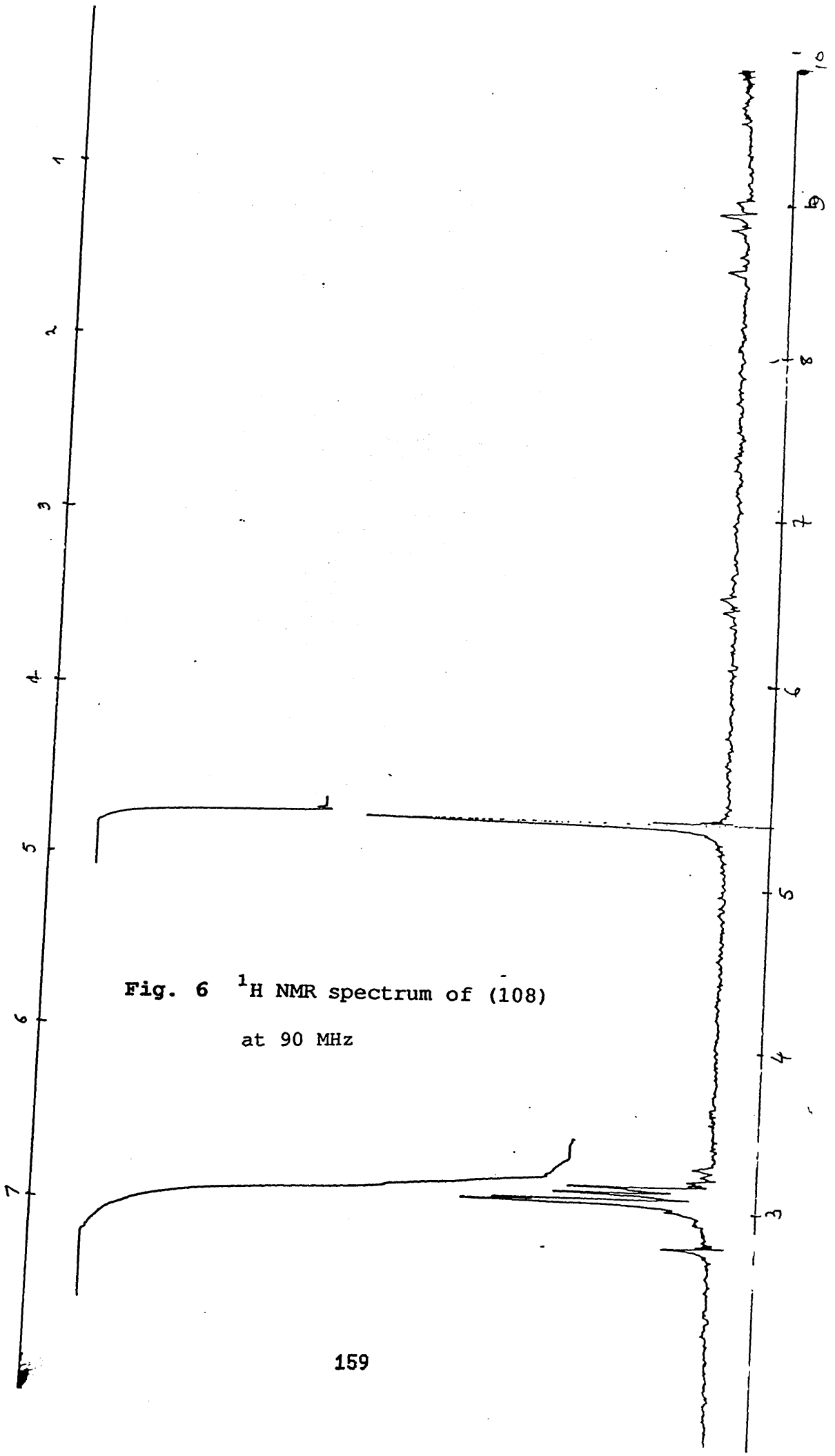


Fig. 6 ^{1}H NMR spectrum of (108)

at 90 MHz

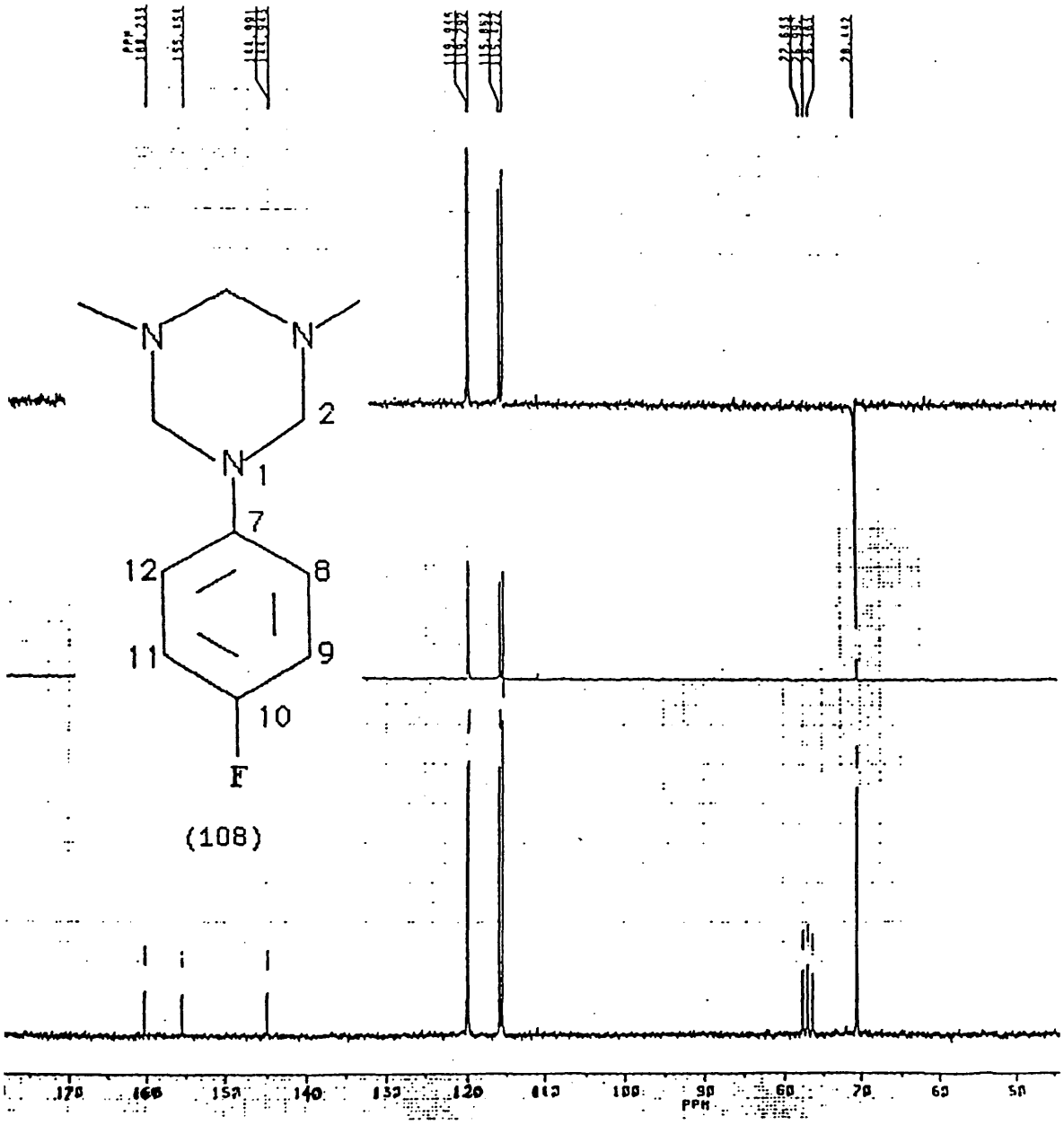


Fig. 7 ^{13}C NMR spectrum of (108) at 50.3 MHz

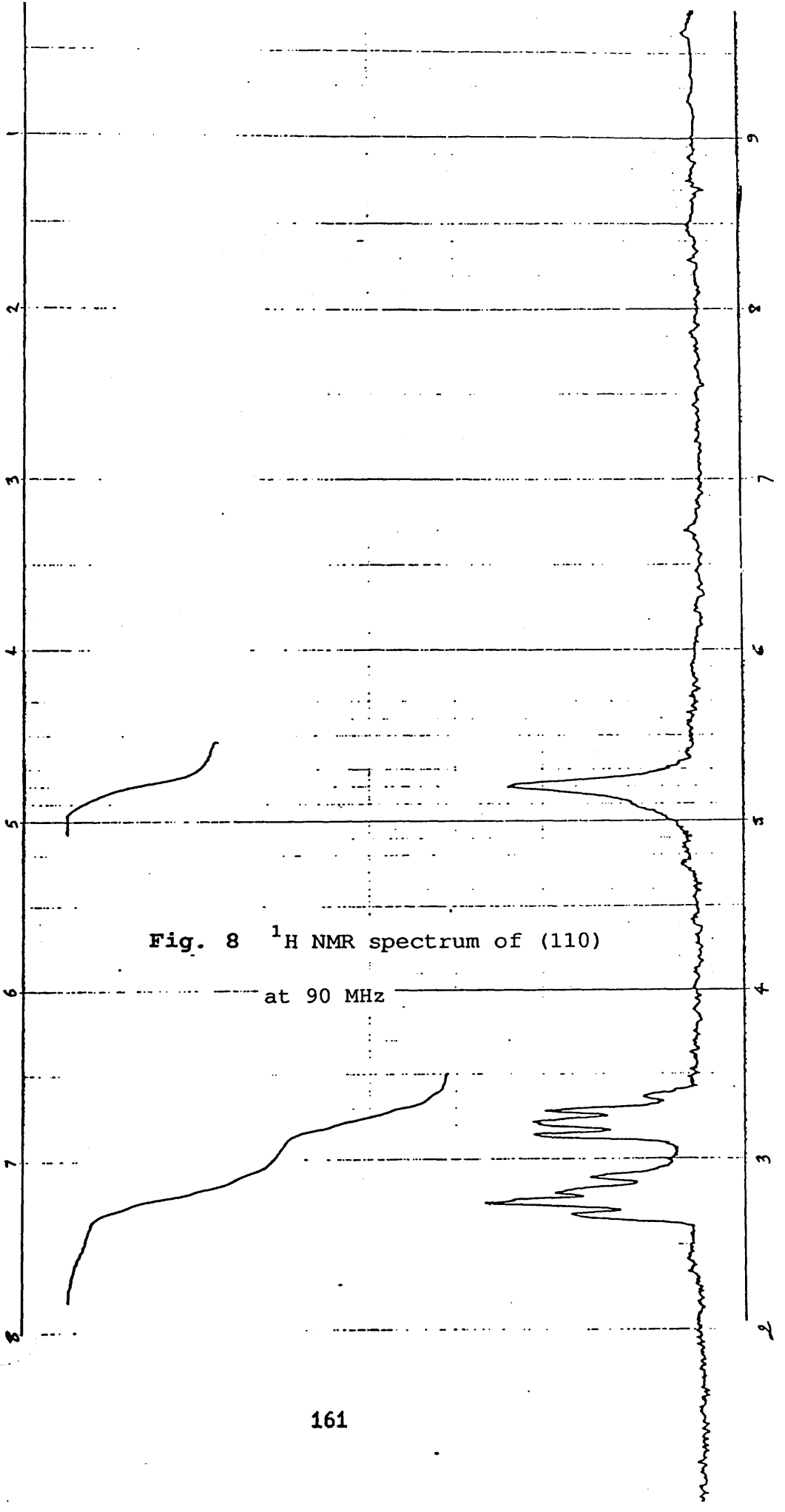


Fig. 8 ^{1}H NMR spectrum of (110) at 90 MHz

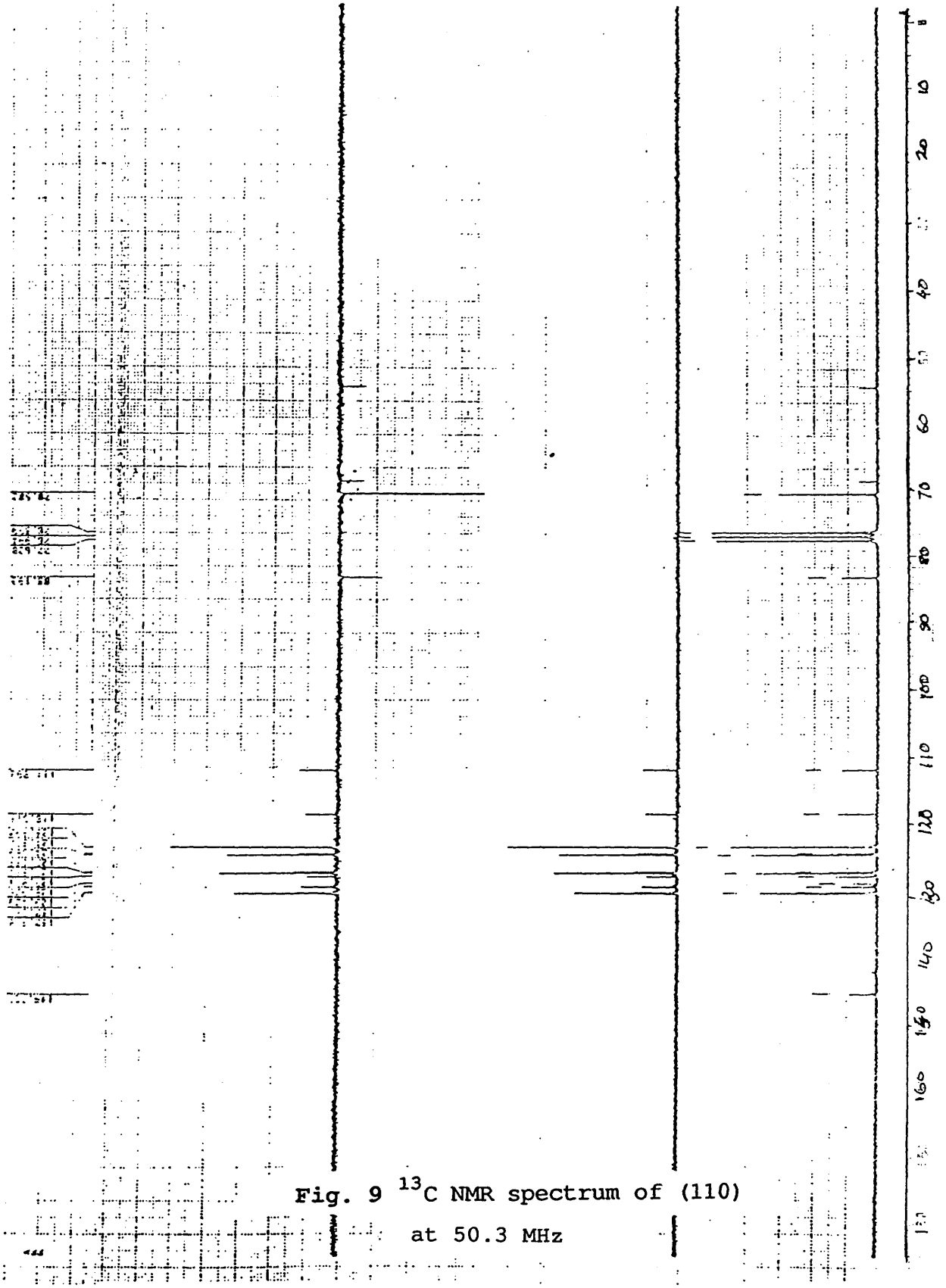


Fig. 9 ^{13}C NMR spectrum of (110) at 50.3 MHz

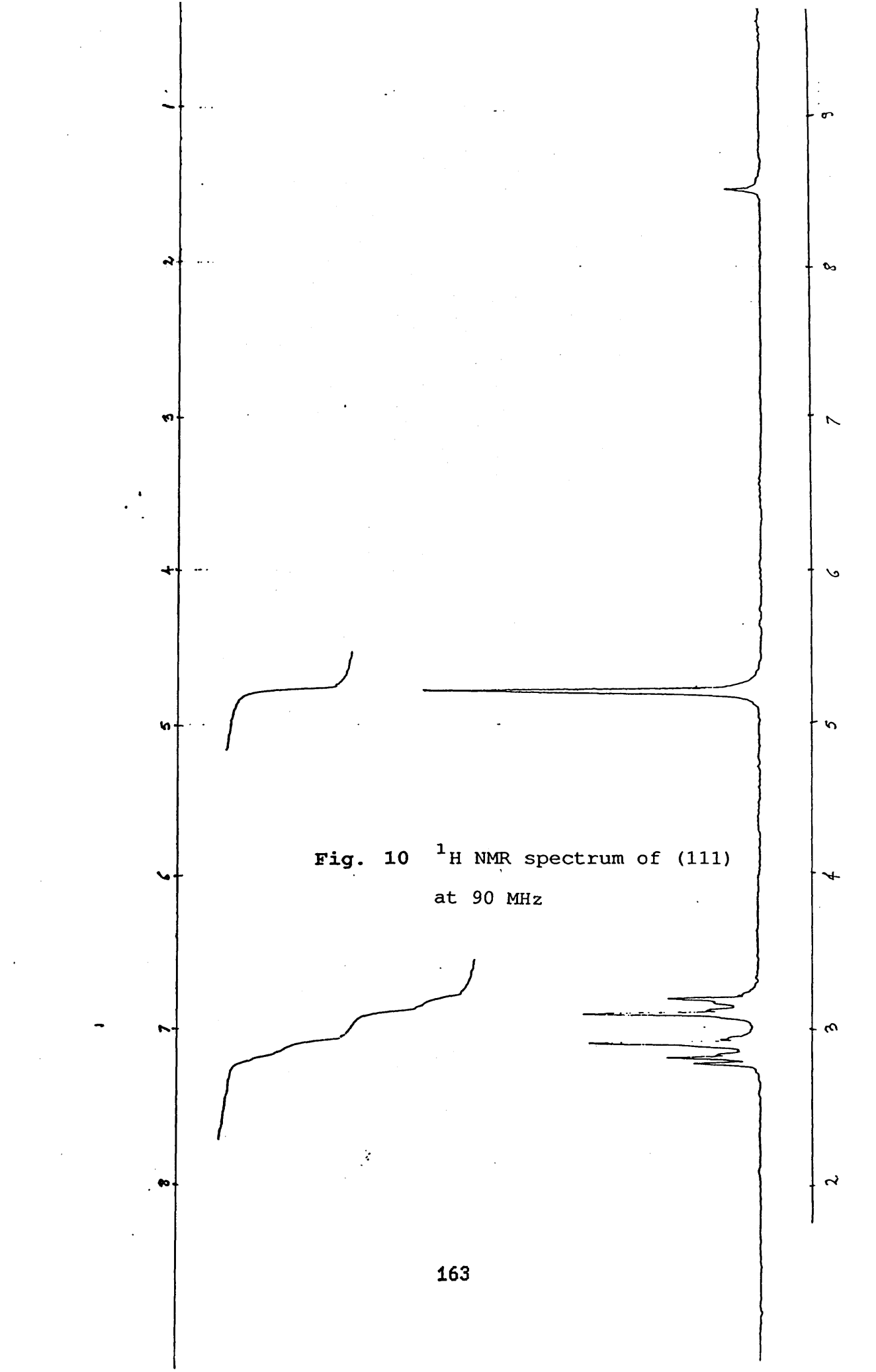


Fig. 10 ^{1}H NMR spectrum of (111) at 90 MHz

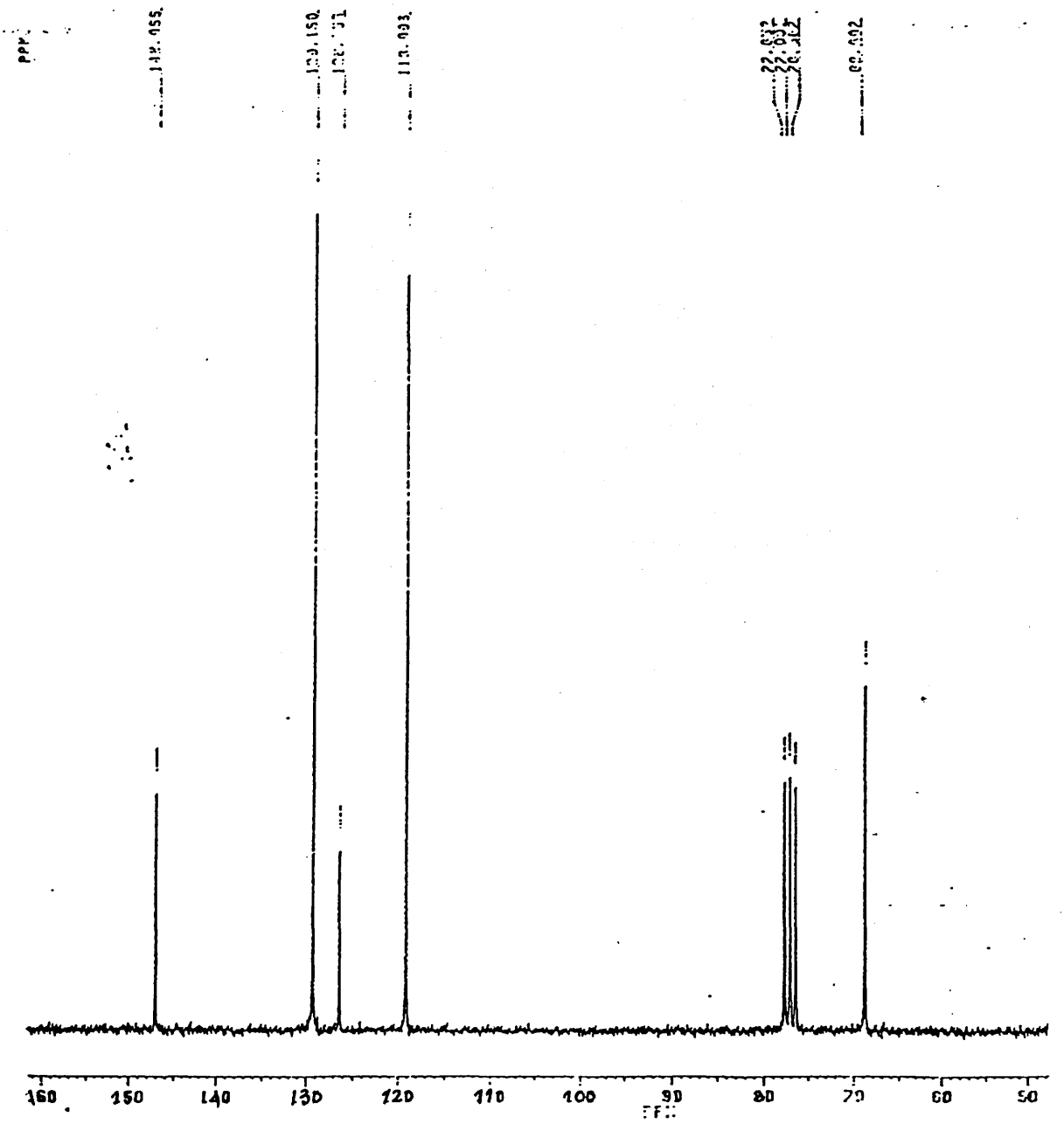


Fig. 11 ^{13}C NMR spectrum of (111) at 50.3 MHz

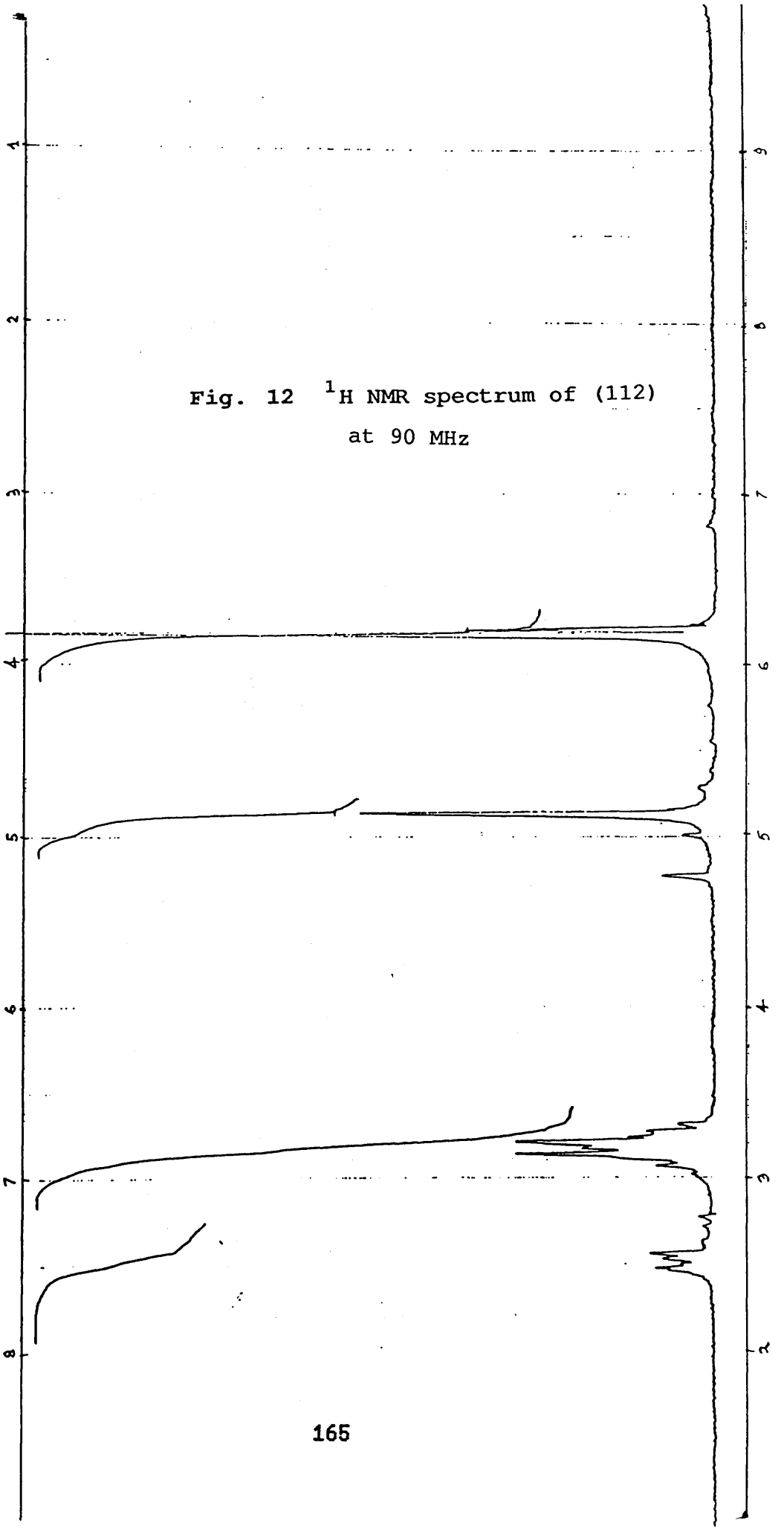


Fig. 12 ^{1}H NMR spectrum of (112) at 90 MHz

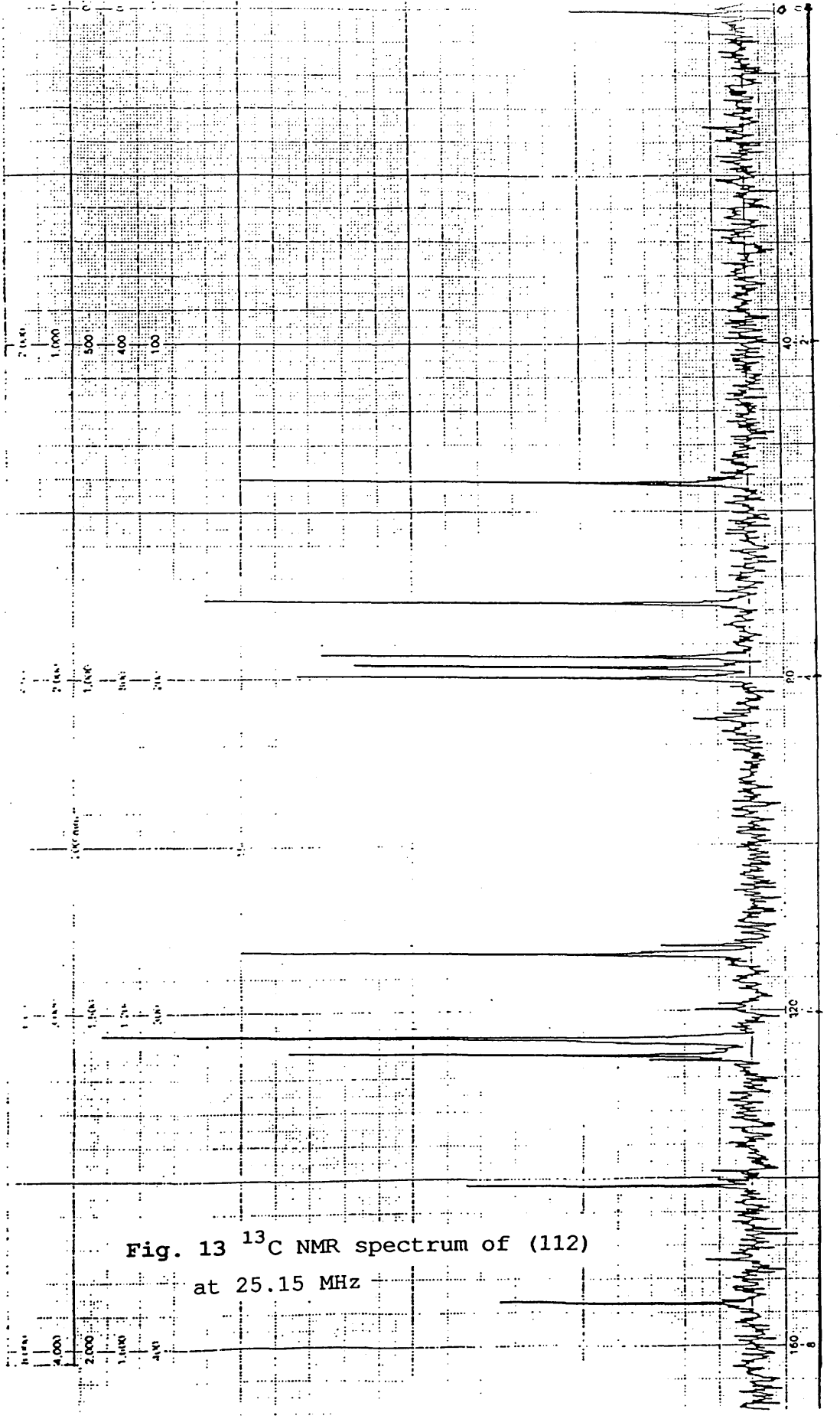


Fig. 13 ^{13}C NMR spectrum of (112) at 25.15 MHz

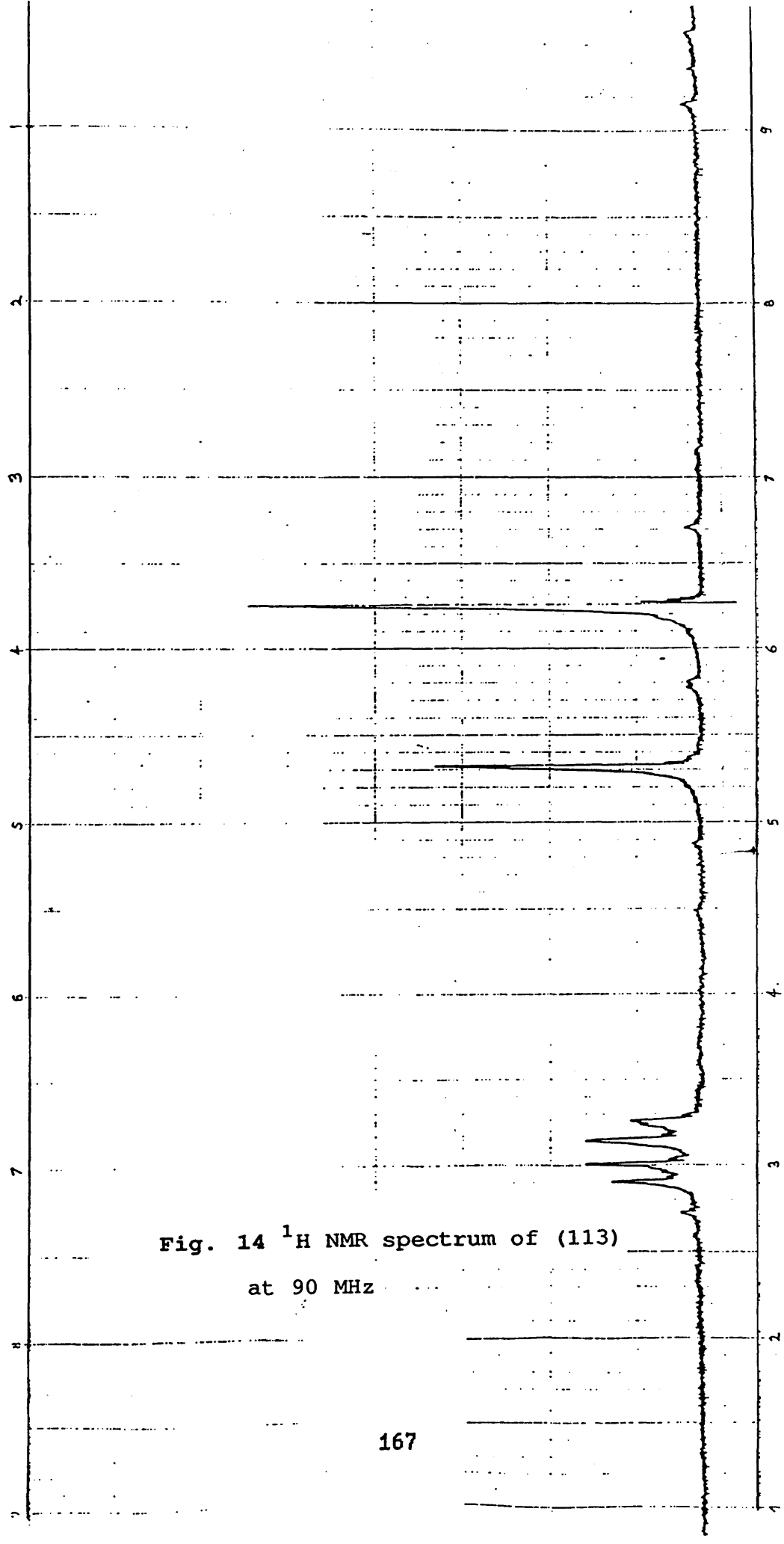


Fig. 14 ^{1}H NMR spectrum of (113) at 90 MHz

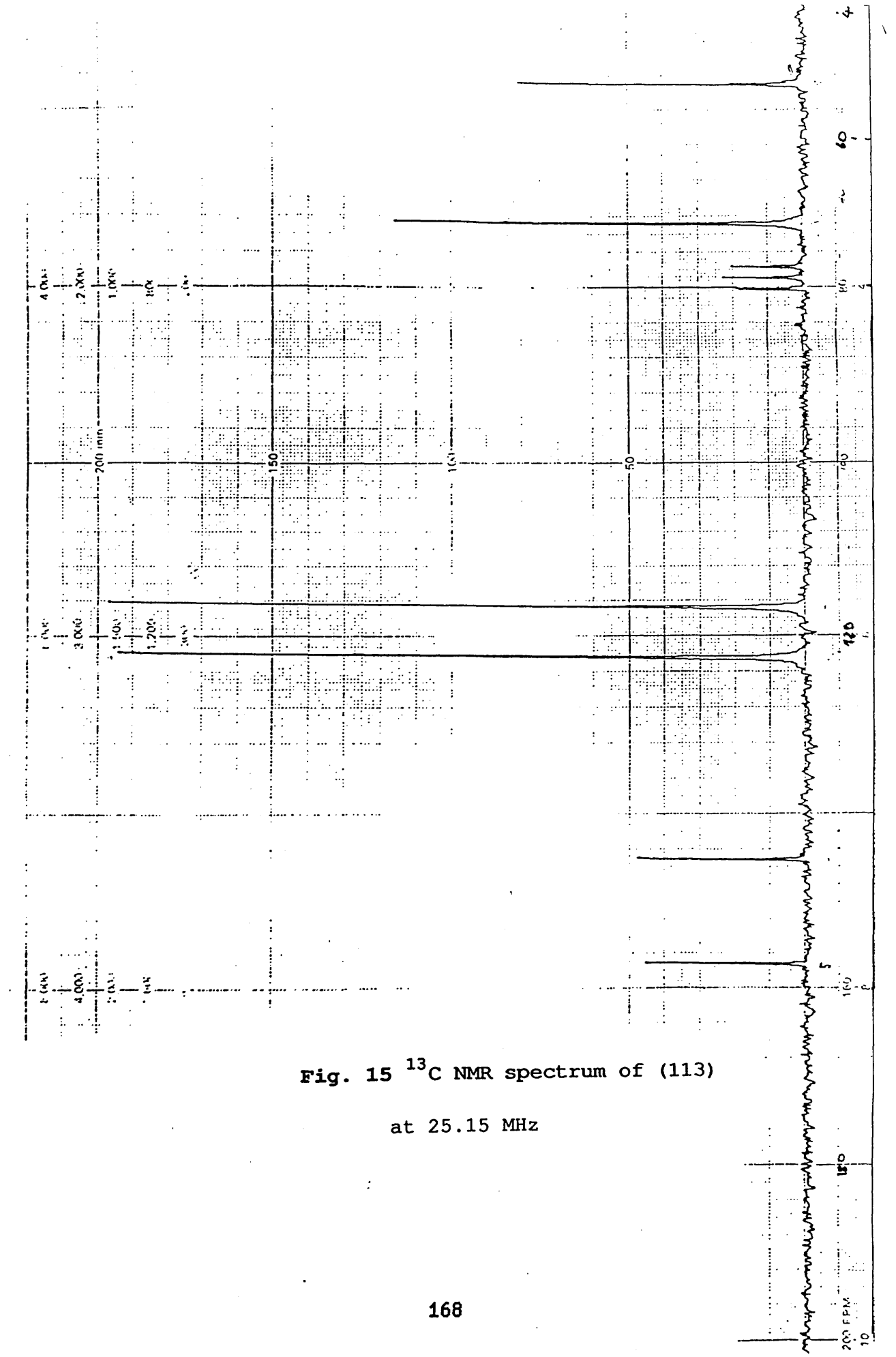


Fig. 15 ^{13}C NMR spectrum of (113)

at 25.15 MHz

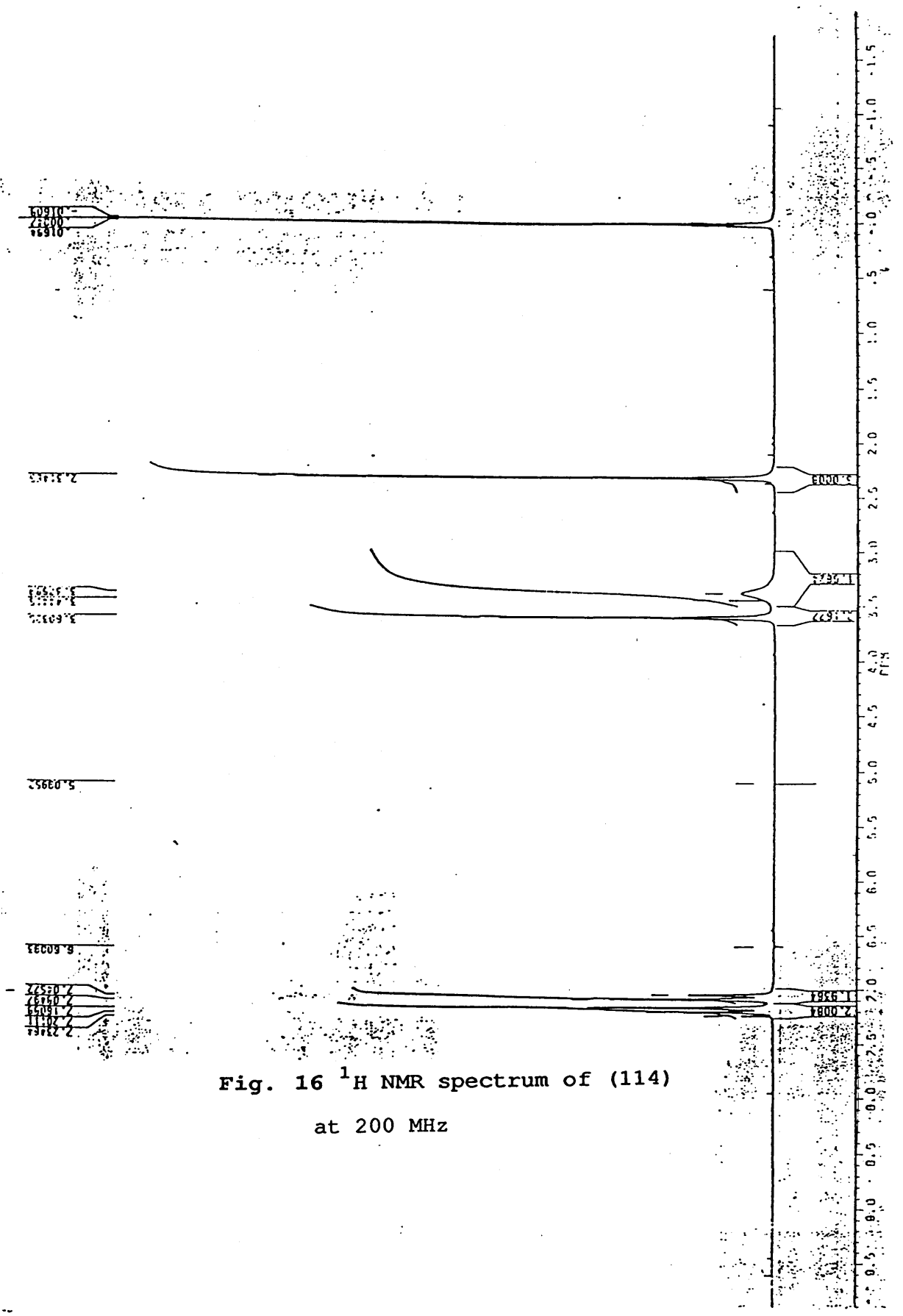


Fig. 16 ^{1}H NMR spectrum of (114)

at 200 MHz

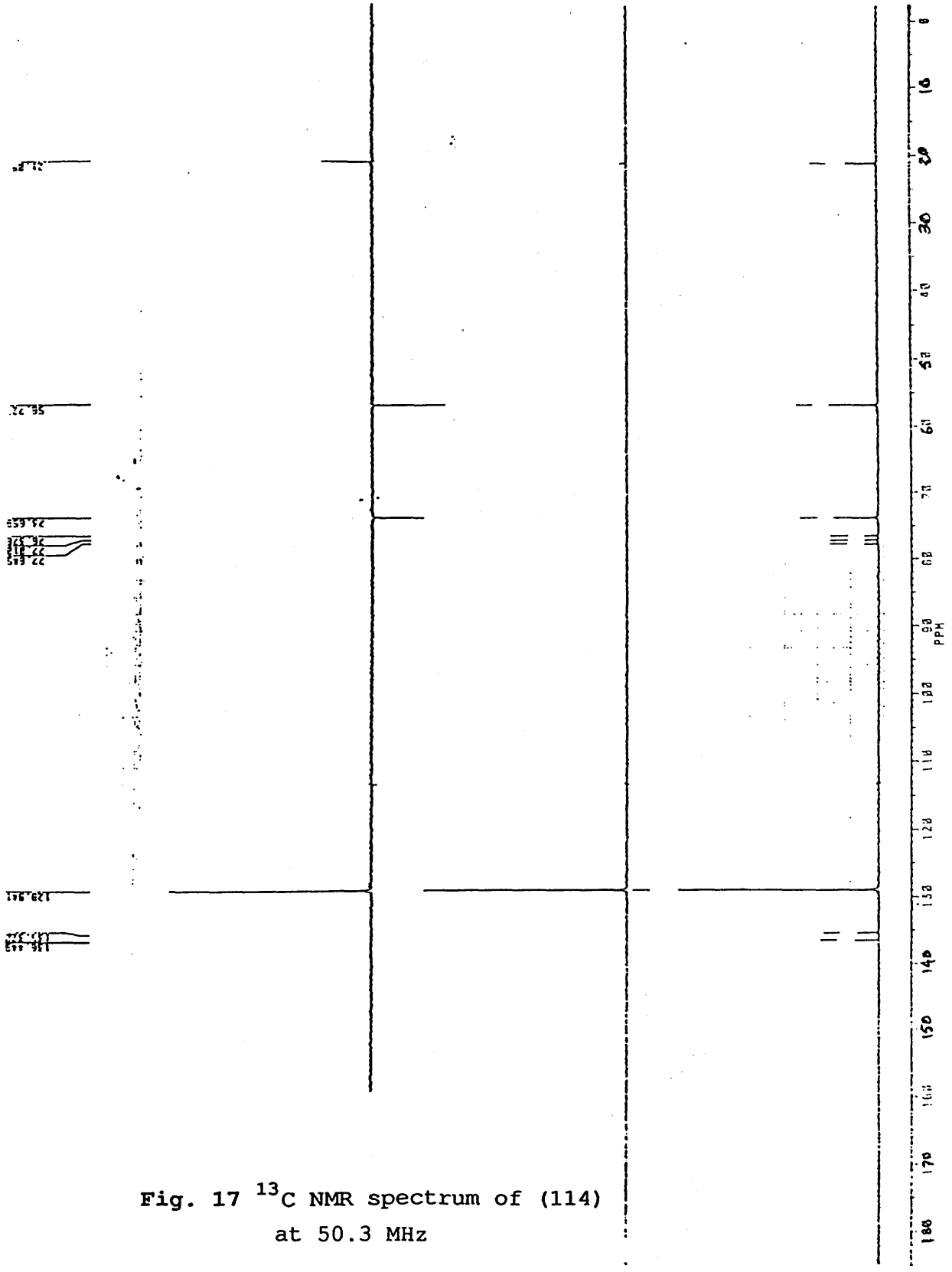


Fig. 17 ^{13}C NMR spectrum of (114) at 50.3 MHz

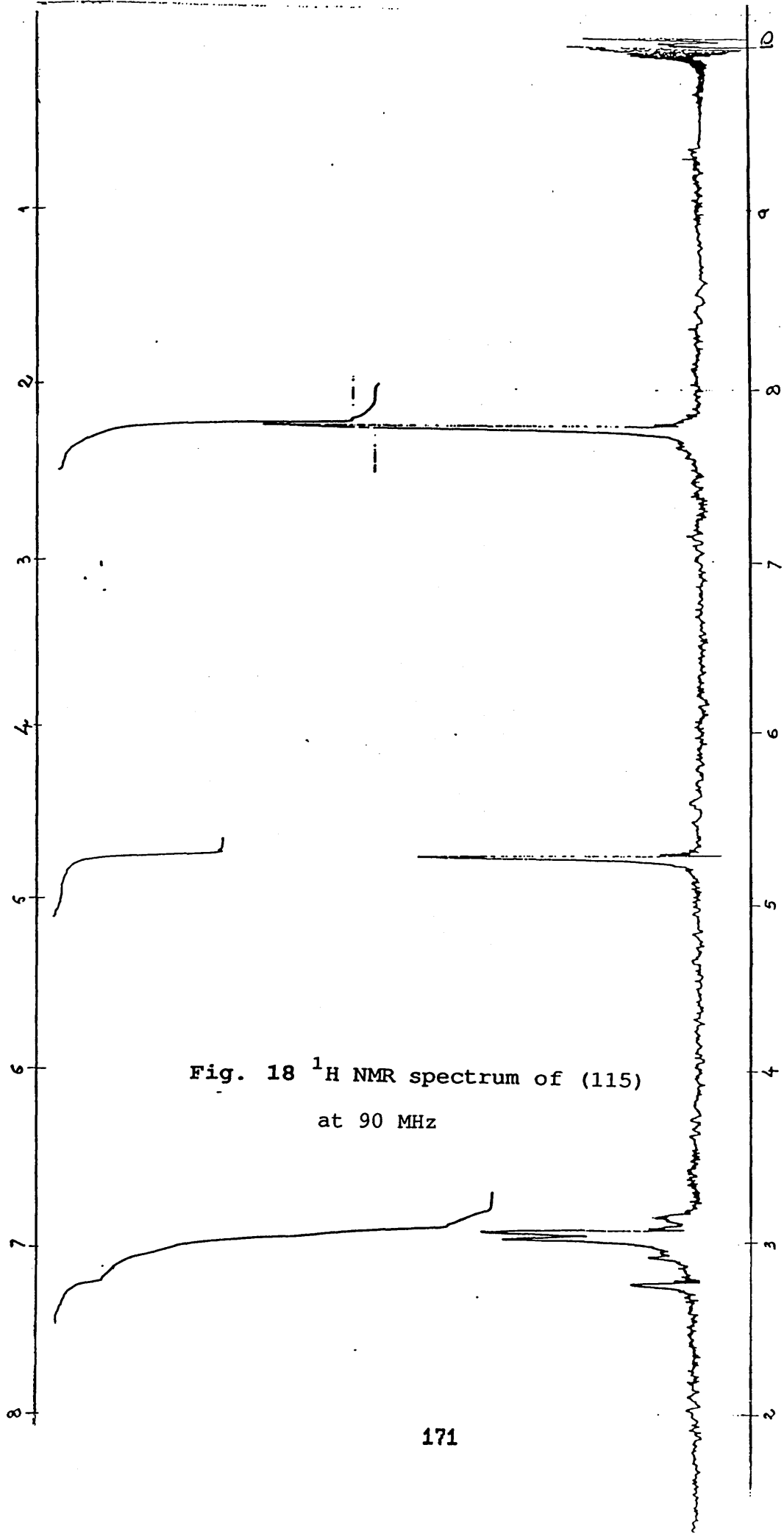


Fig. 18 ^{1}H NMR spectrum of (115)

at 90 MHz

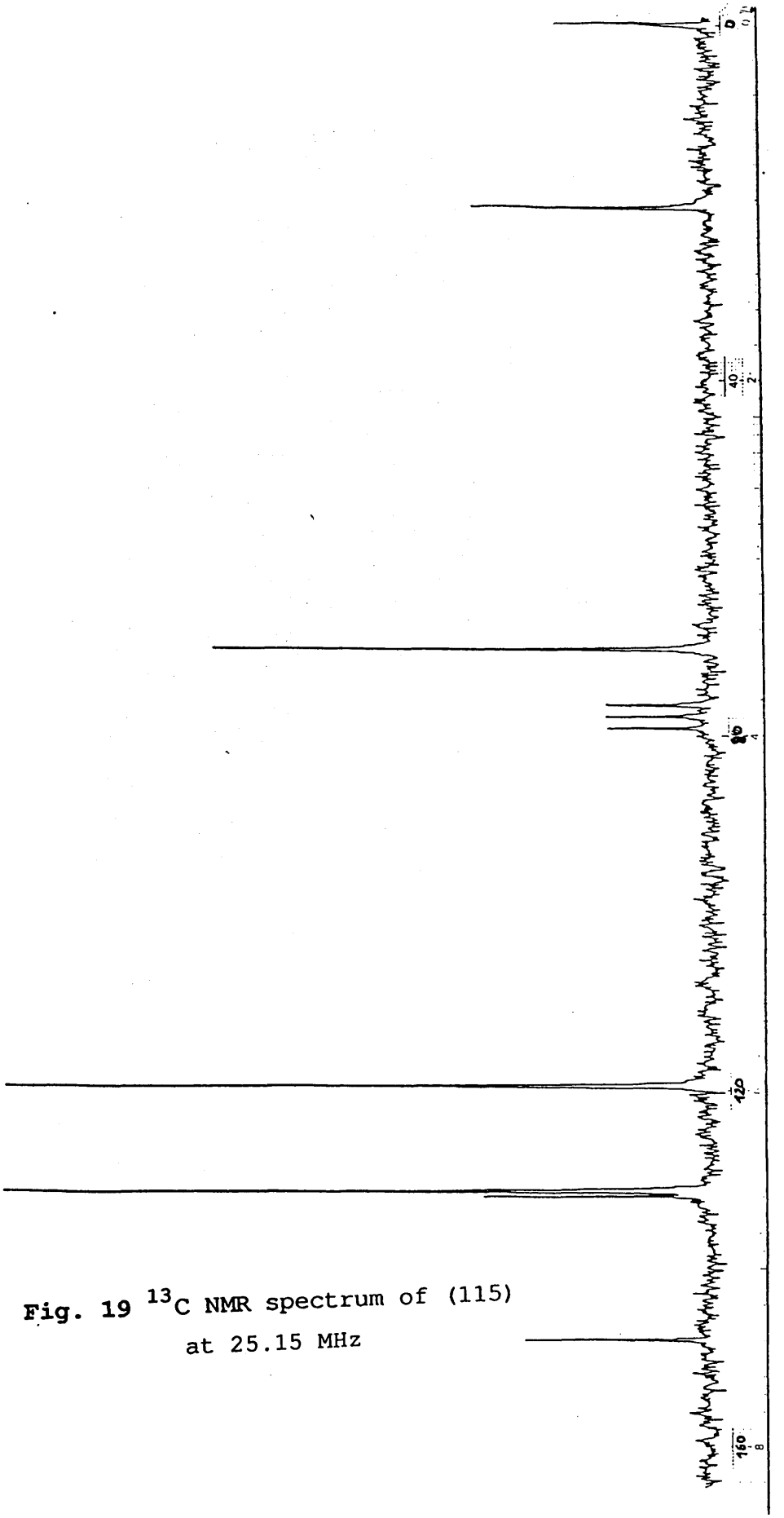


Fig. 19 ^{13}C NMR spectrum of (115) at 25.15 MHz

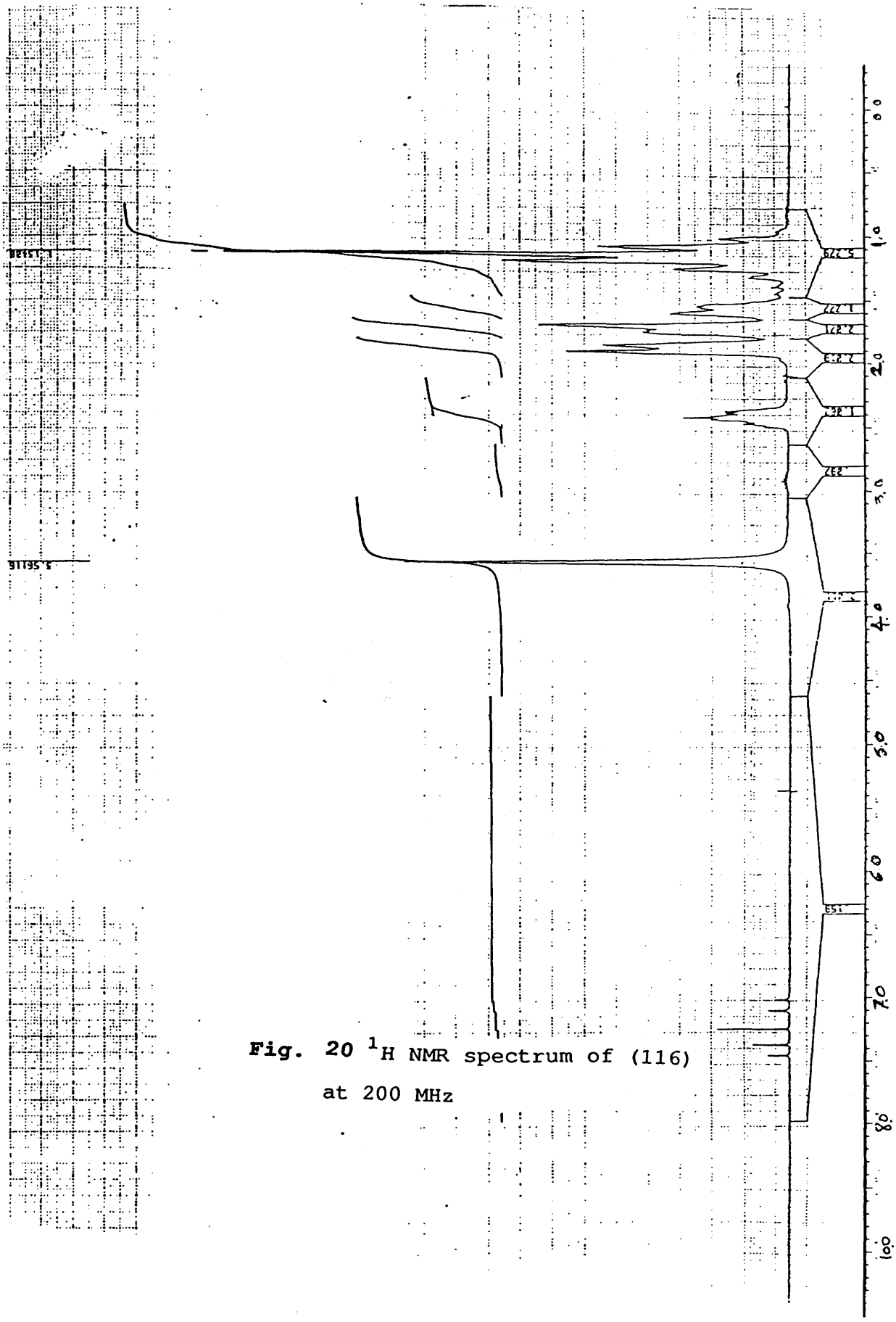


Fig. 20 ^{1}H NMR spectrum of (116) at 200 MHz

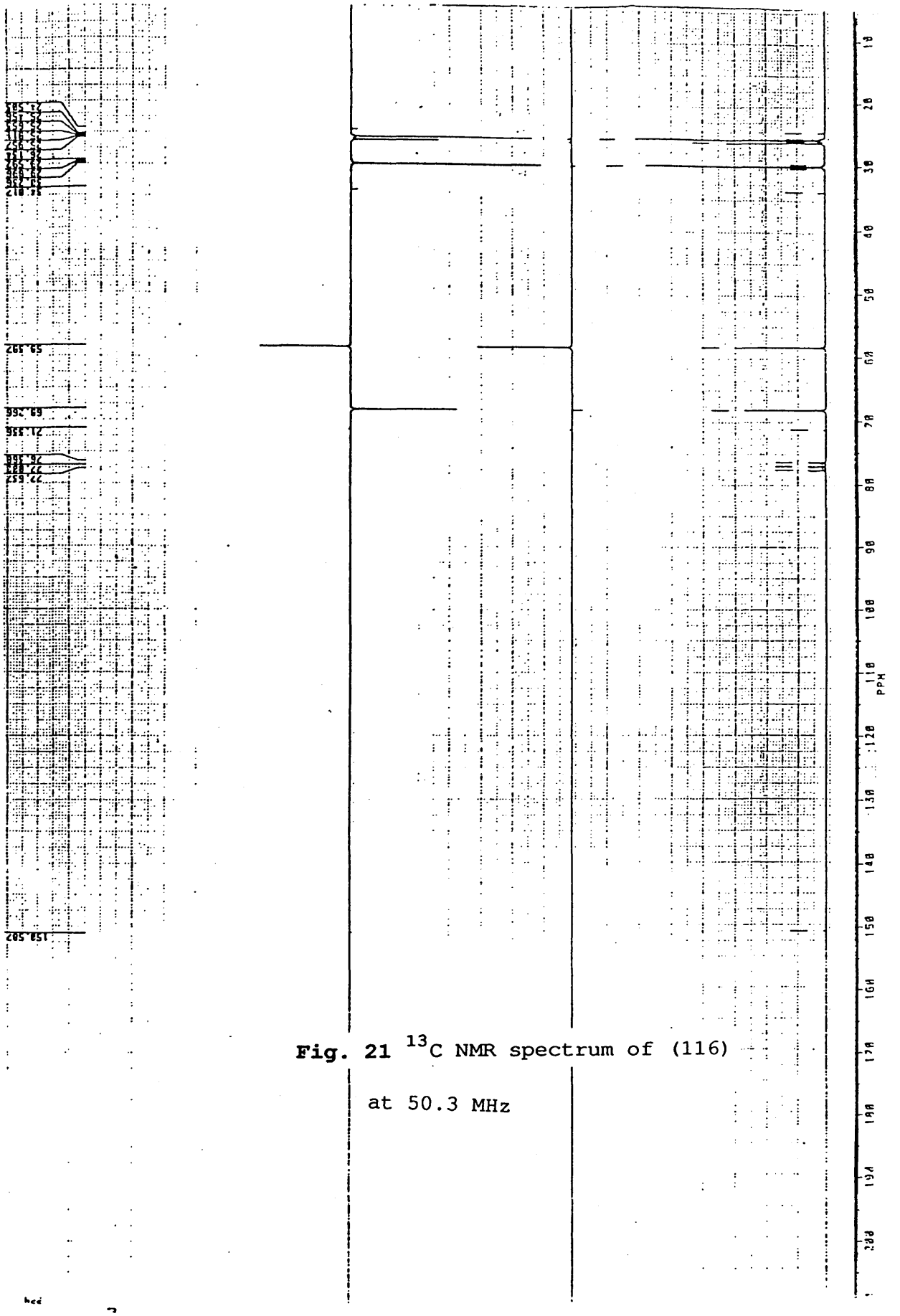


Fig. 21 ^{13}C NMR spectrum of (116)

at 50.3 MHz

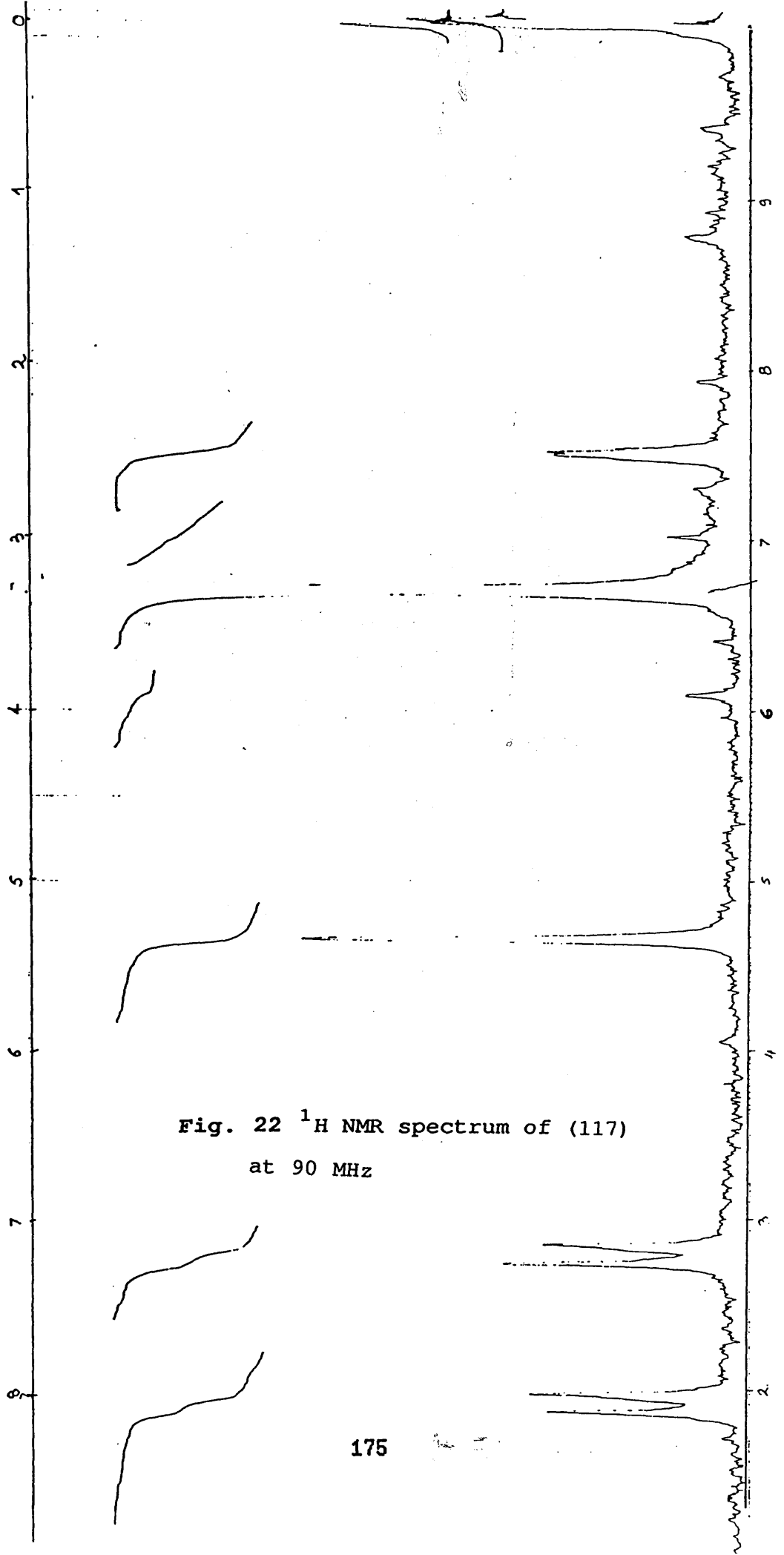


Fig. 22 ^{1}H NMR spectrum of (117) at 90 MHz

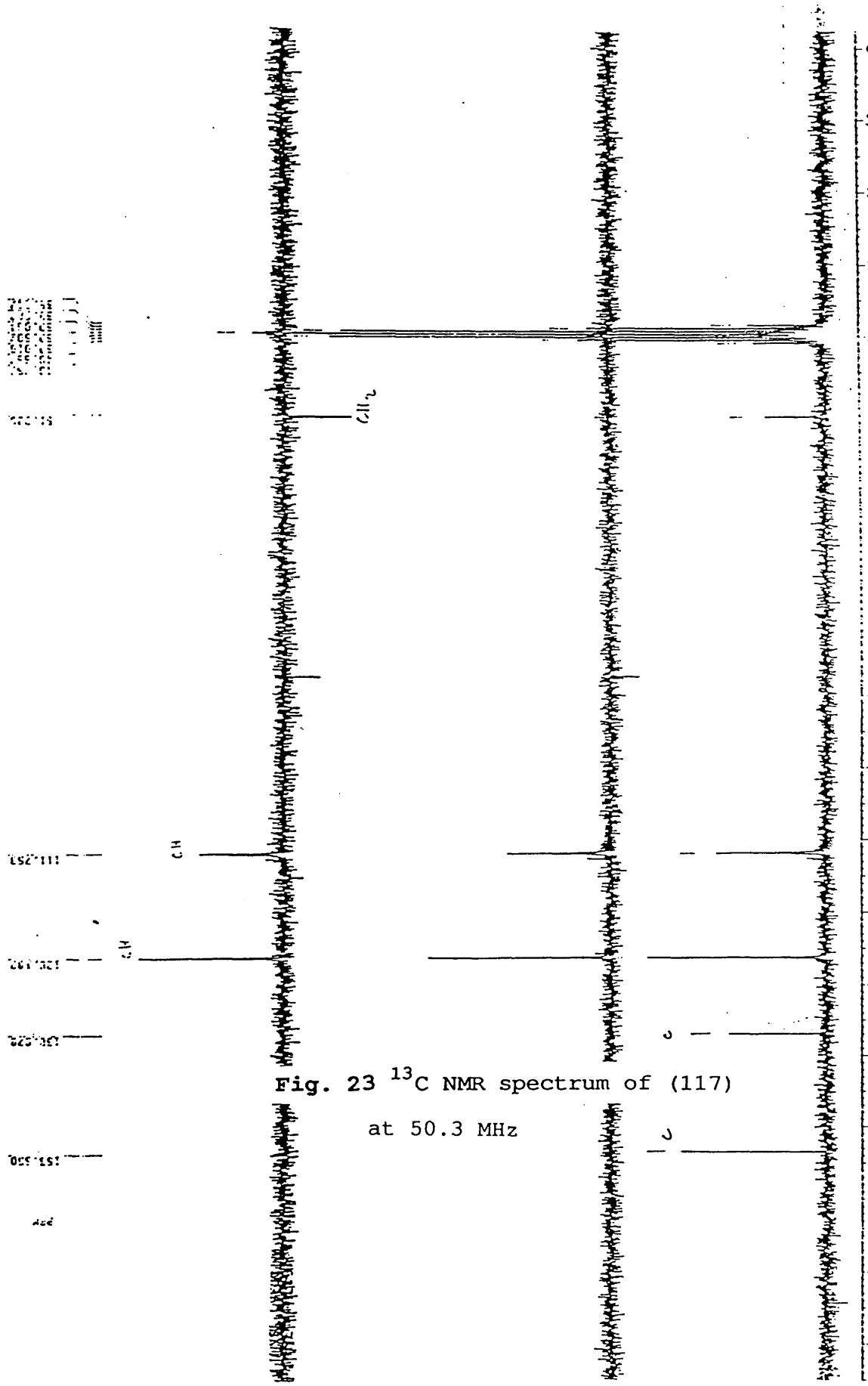


Fig. 23 ^{13}C NMR spectrum of (117) at 50.3 MHz

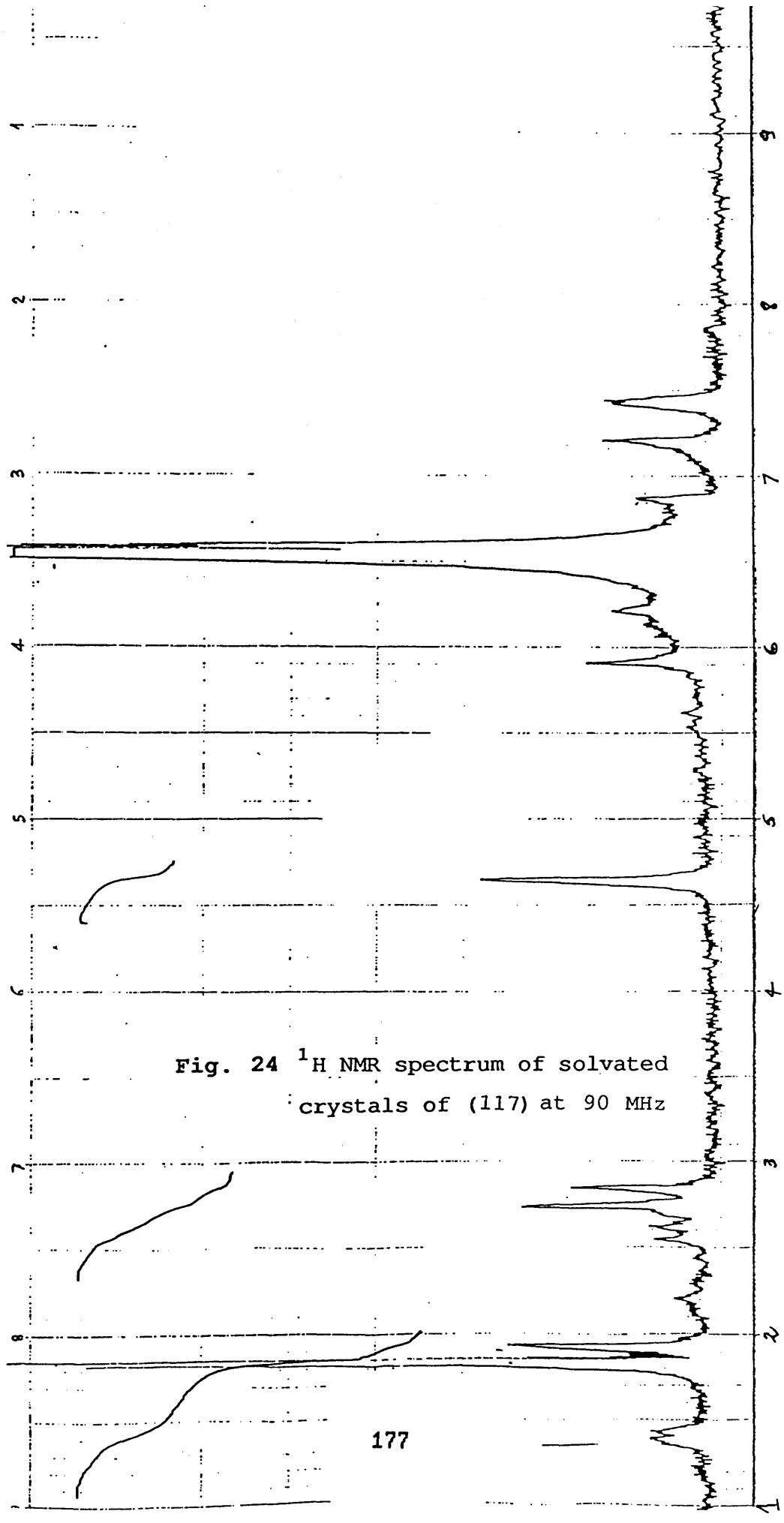


Fig. 24 ^{1}H NMR spectrum of solvated crystals of (117) at 90 MHz

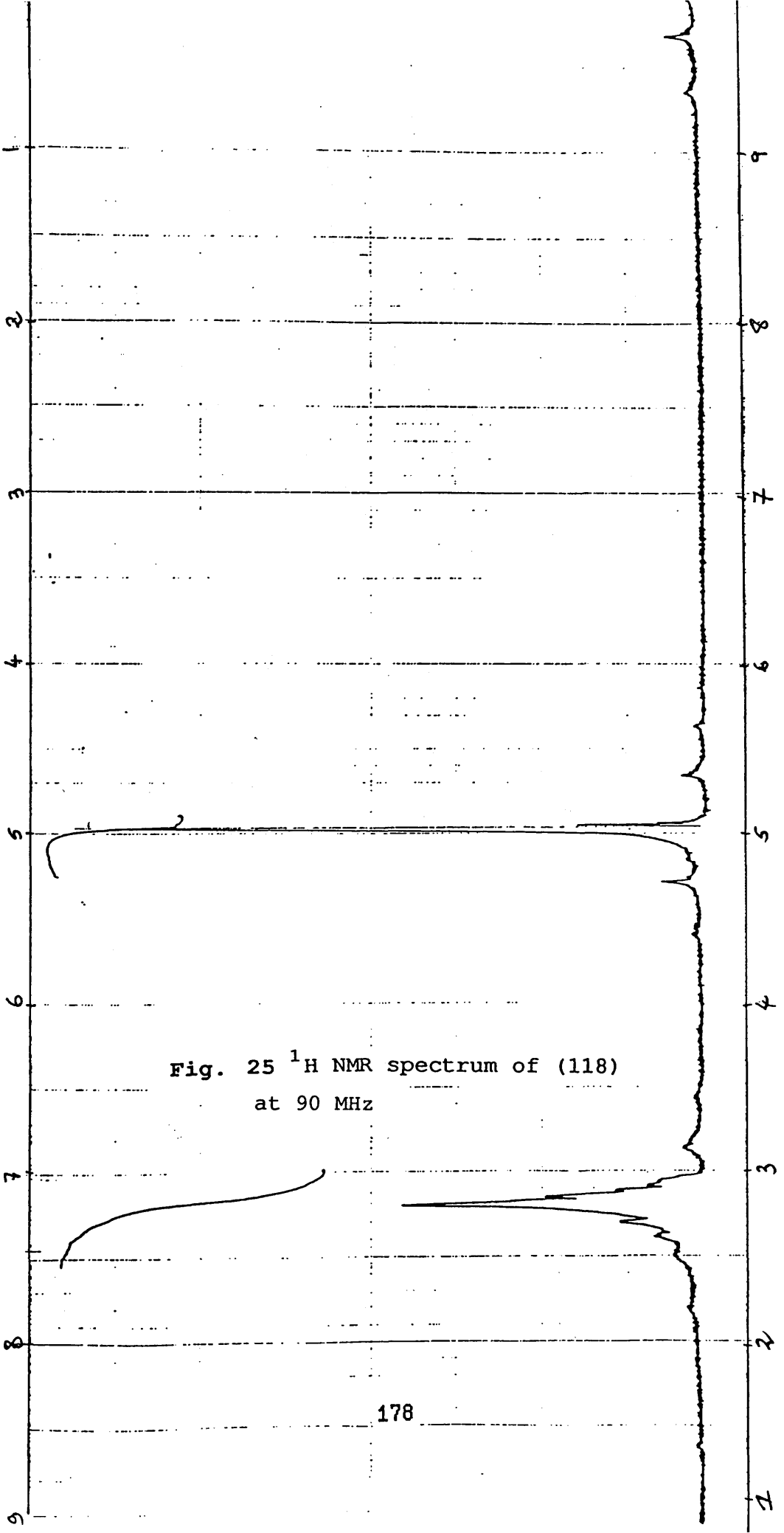


Fig. 25 ^{1}H NMR spectrum of (118)
at 90 MHz

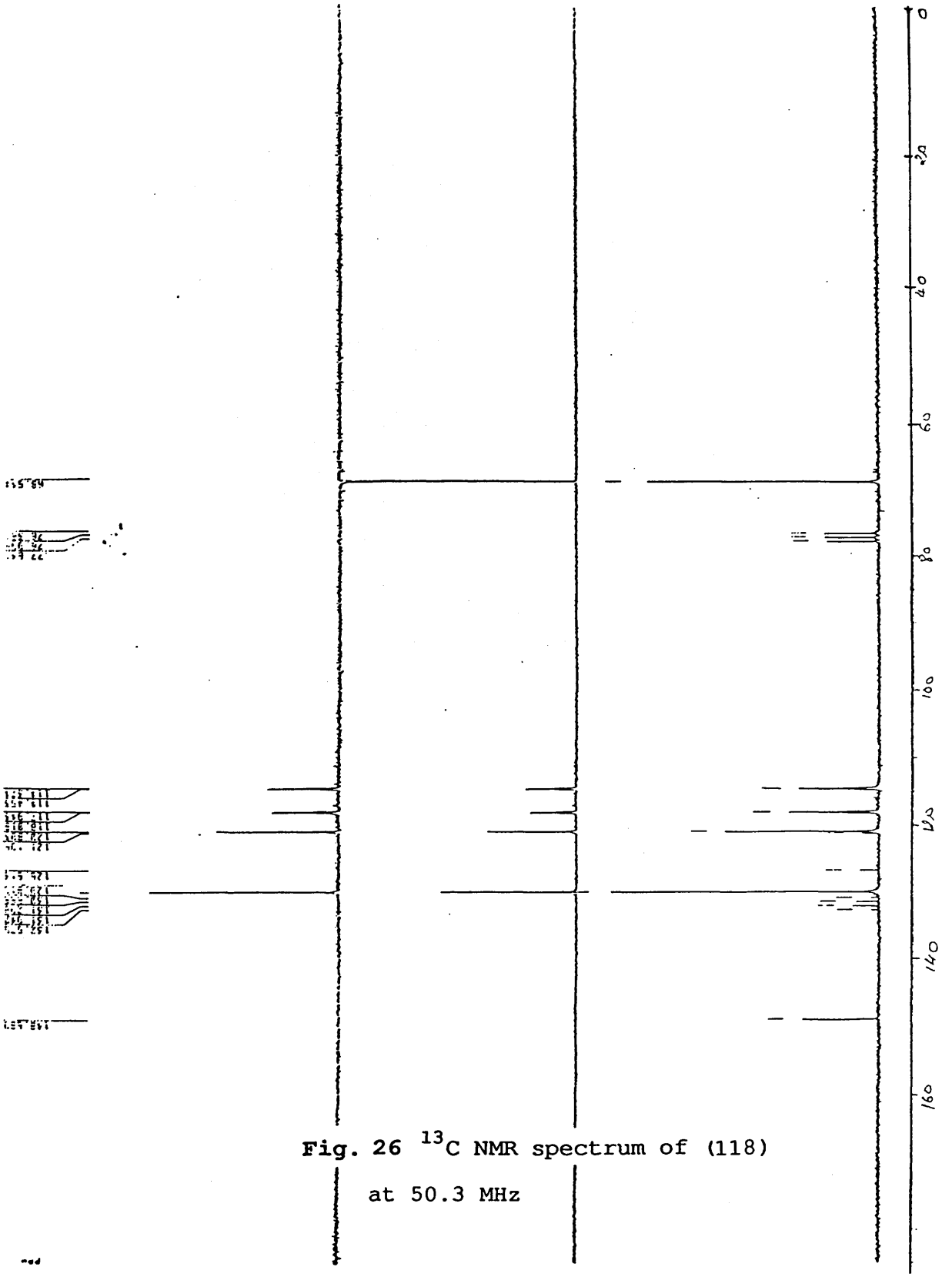


Fig. 26 ^{13}C NMR spectrum of (118) at 50.3 MHz

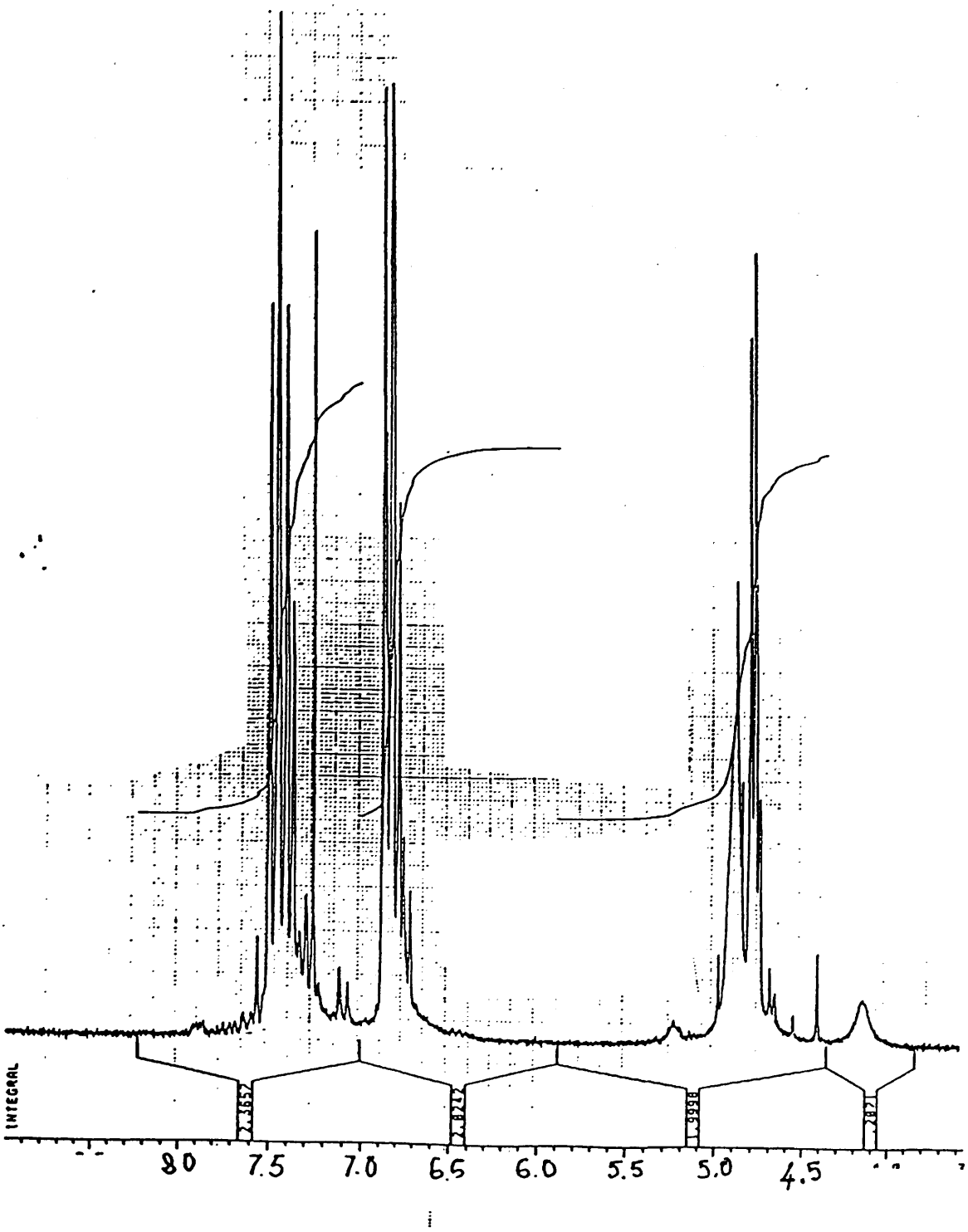


Fig. 27 ^{1}H NMR spectrum of (122)

at 200 MHz

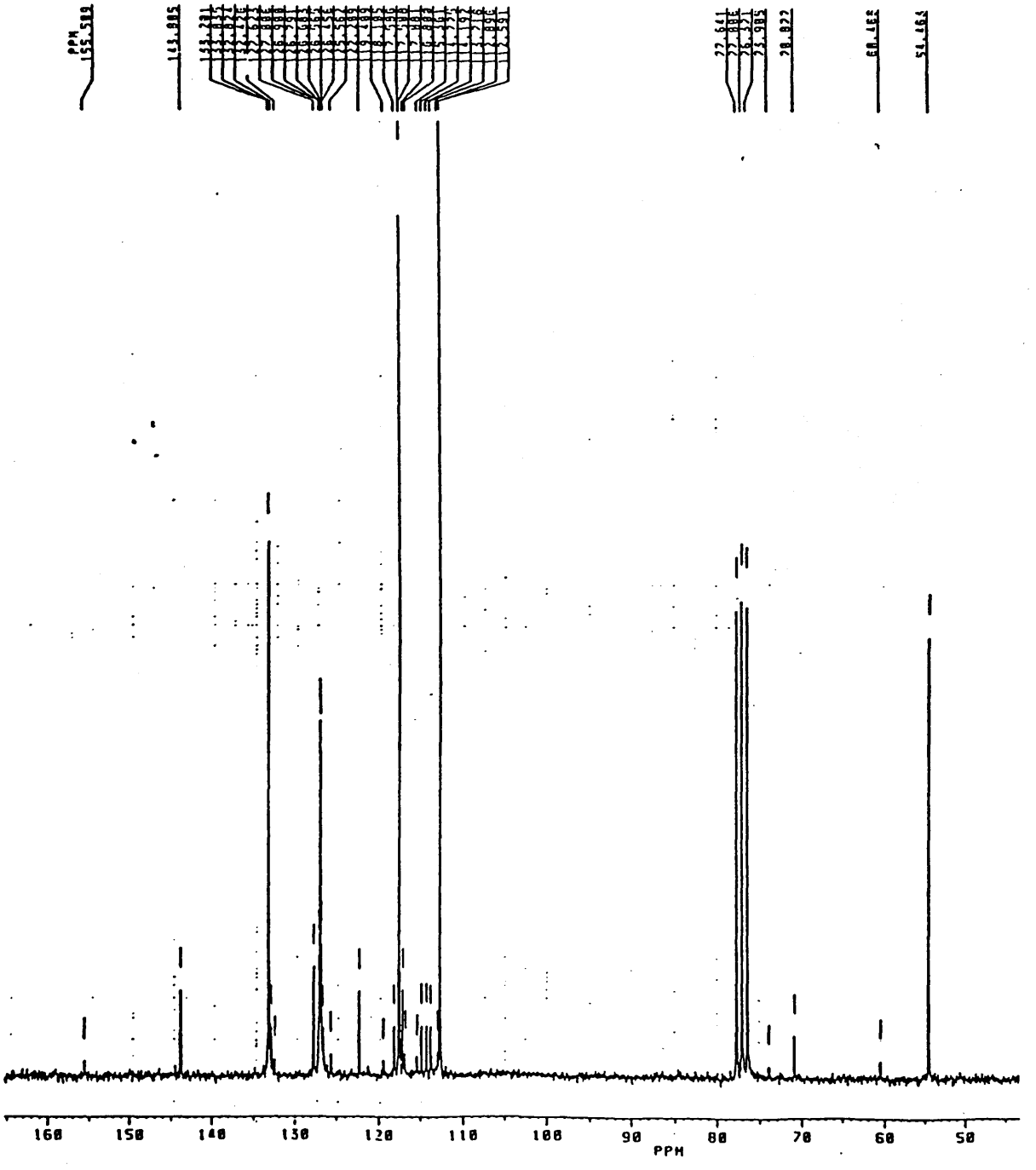


Fig. 28 ^{13}C NMR spectrum of (122) at 50.3 MHz

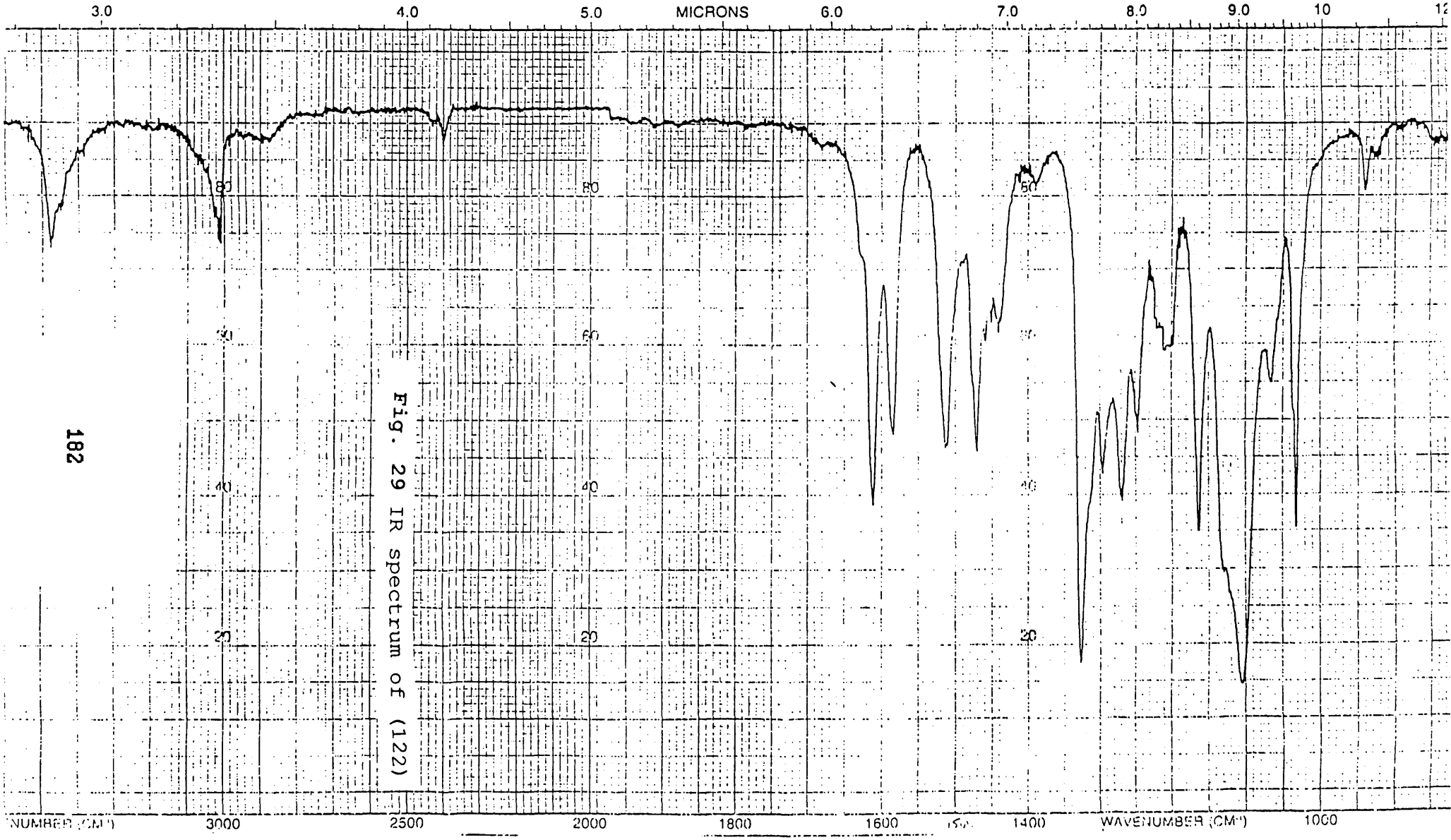


Fig. 29 IR spectrum of (122)

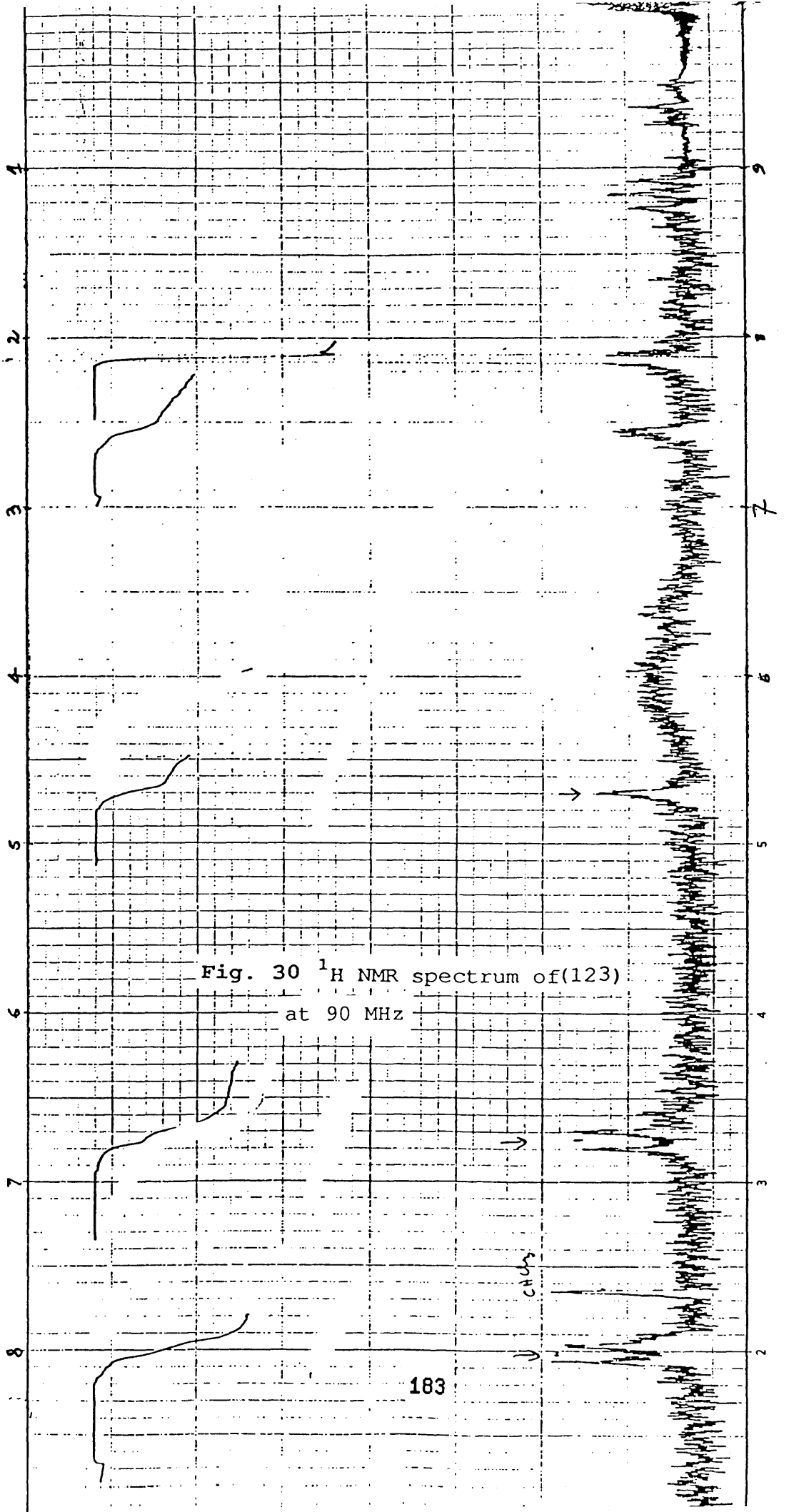


Fig. 30 ^{1}H NMR spectrum of(123) at 90 MHz

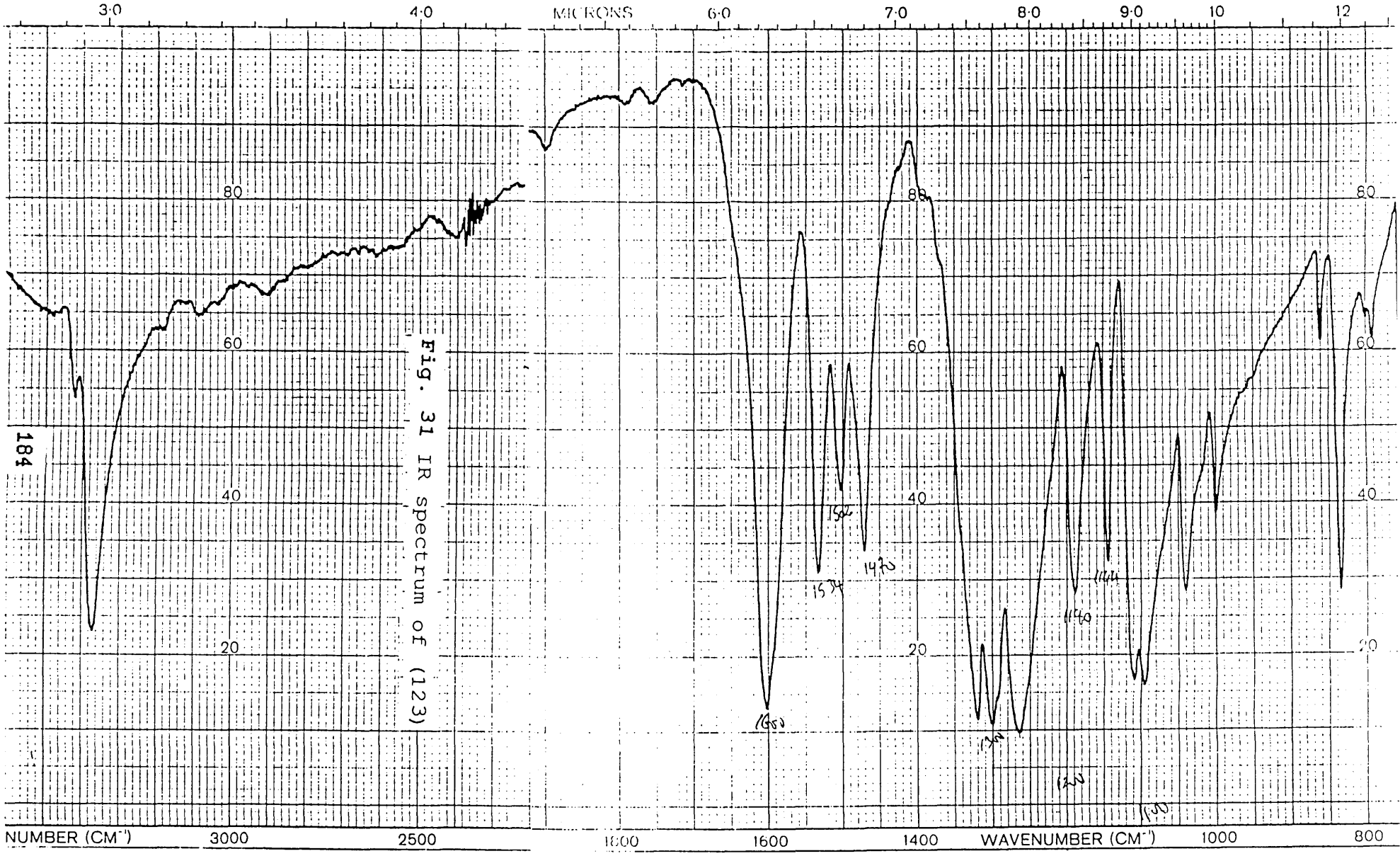


Fig. 31 IR spectrum of (123)

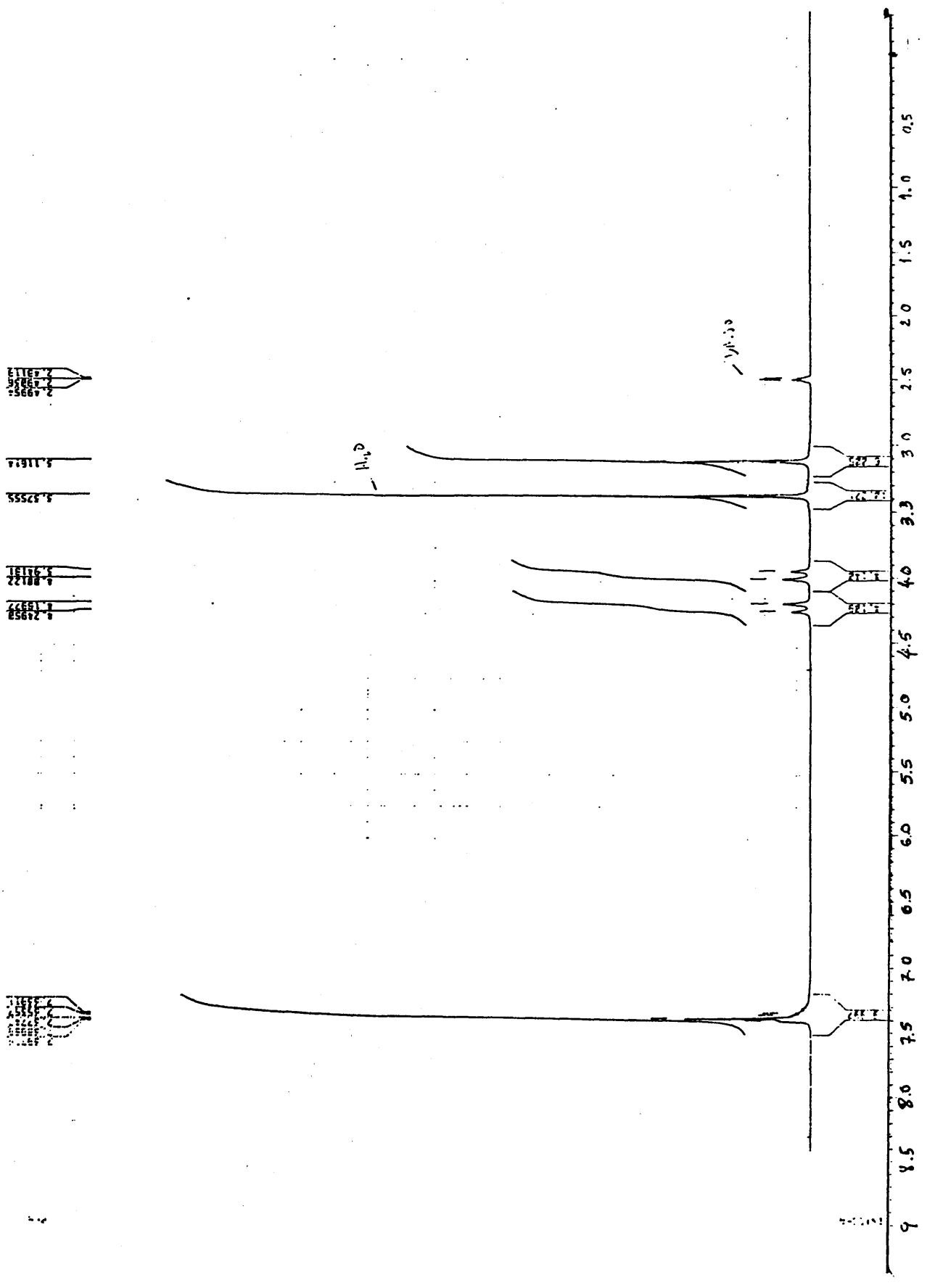


Fig. 32 ^{1}H NMR spectrum of (182) at 200 MHz

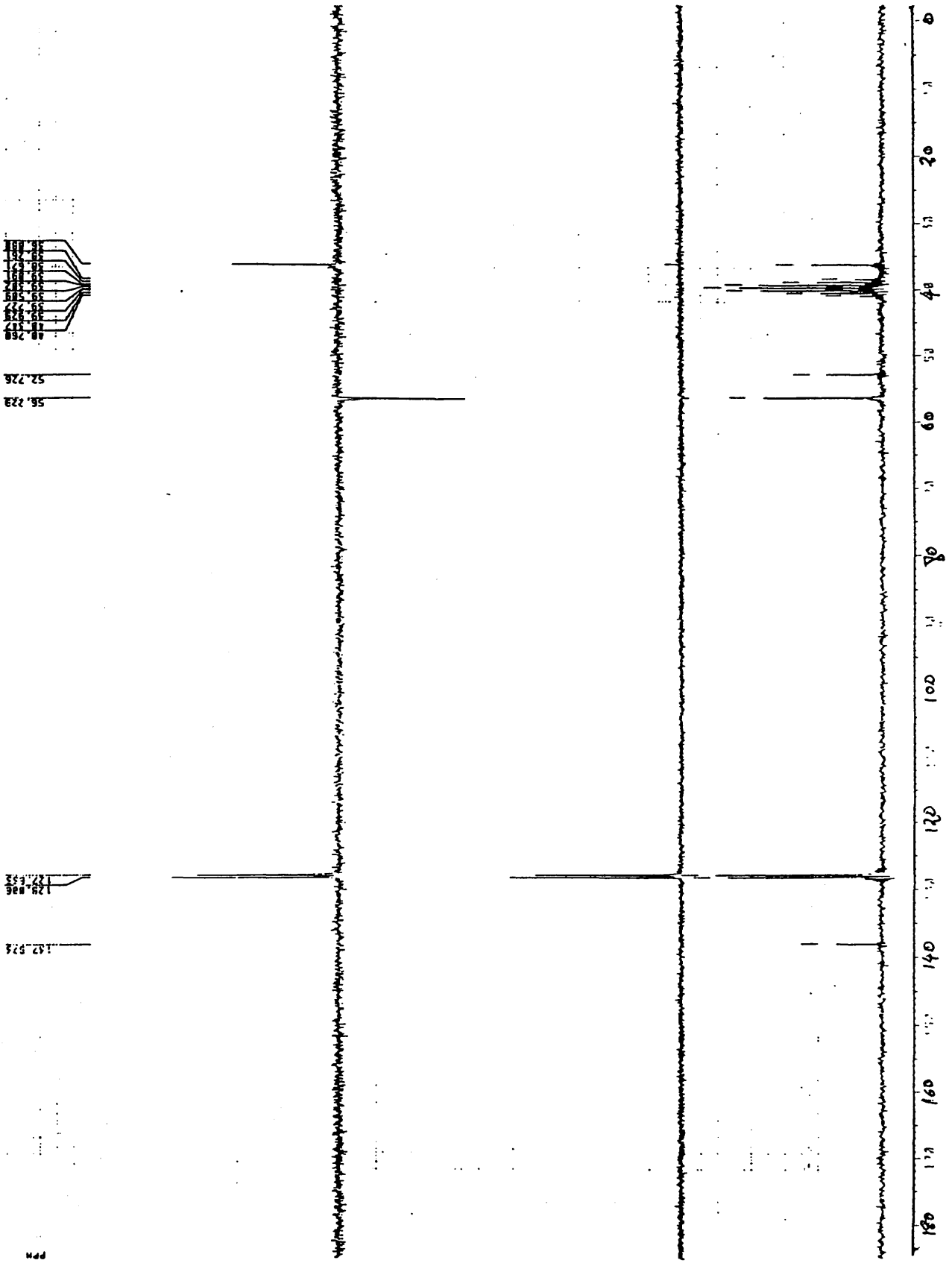


Fig. 33 ^{13}C NMR spectrum of (182) at 50.3 MHz

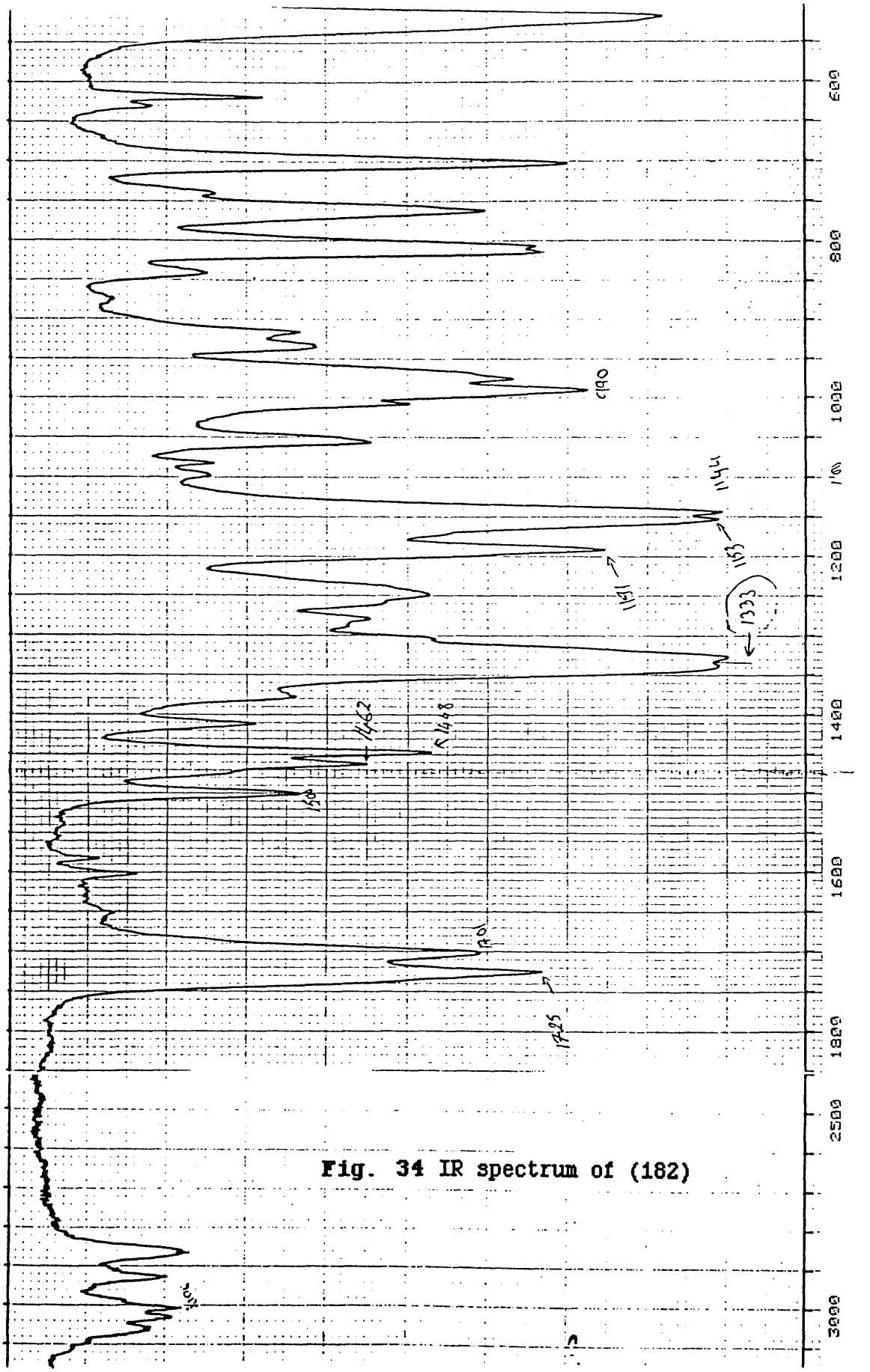


Fig. 34 IR spectrum of (182)

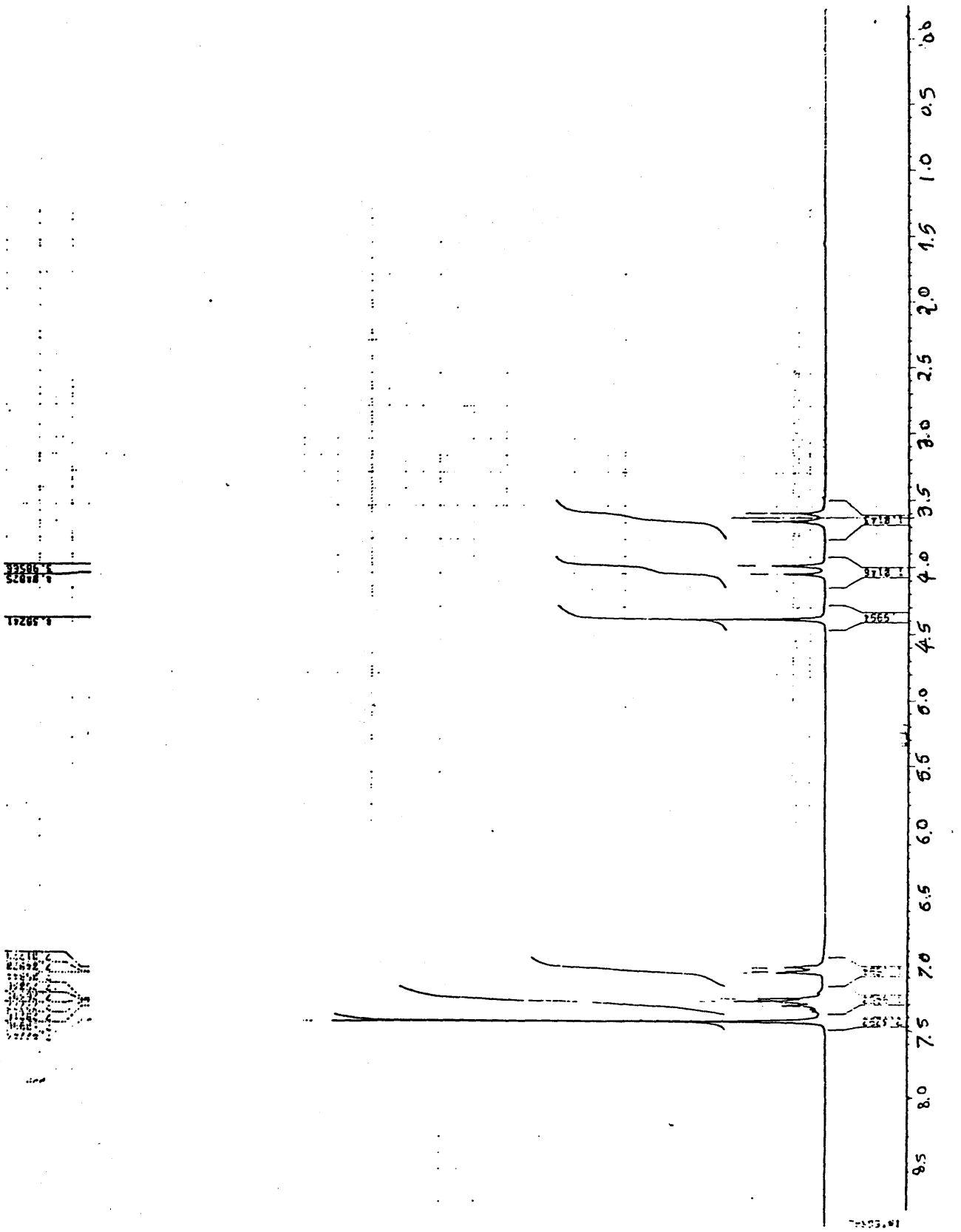


Fig. 35 ^{1}H NMR spectrum of (183) at 200 MHz

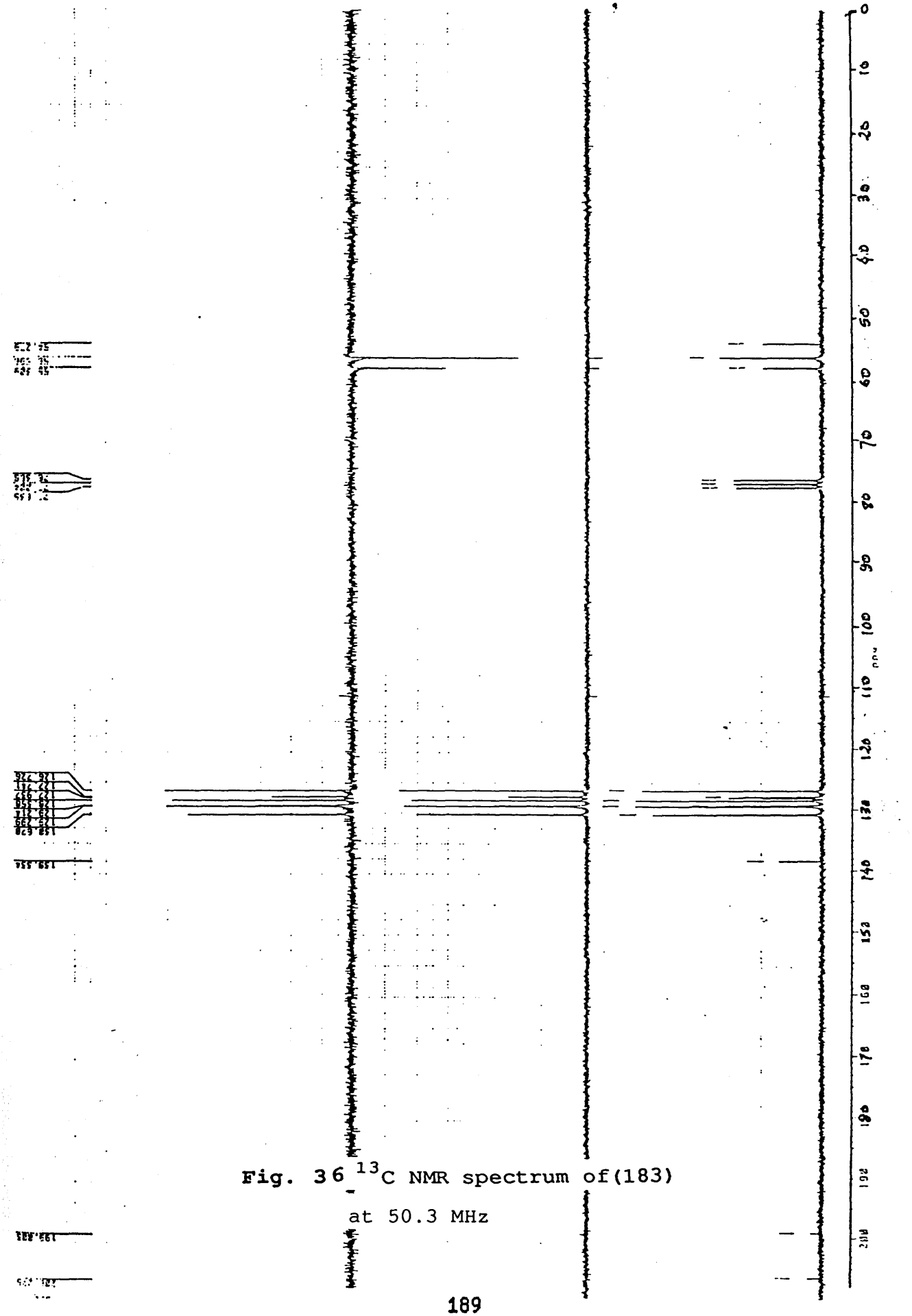


Fig. 36 ^{13}C NMR spectrum of(183)
at 50.3 MHz

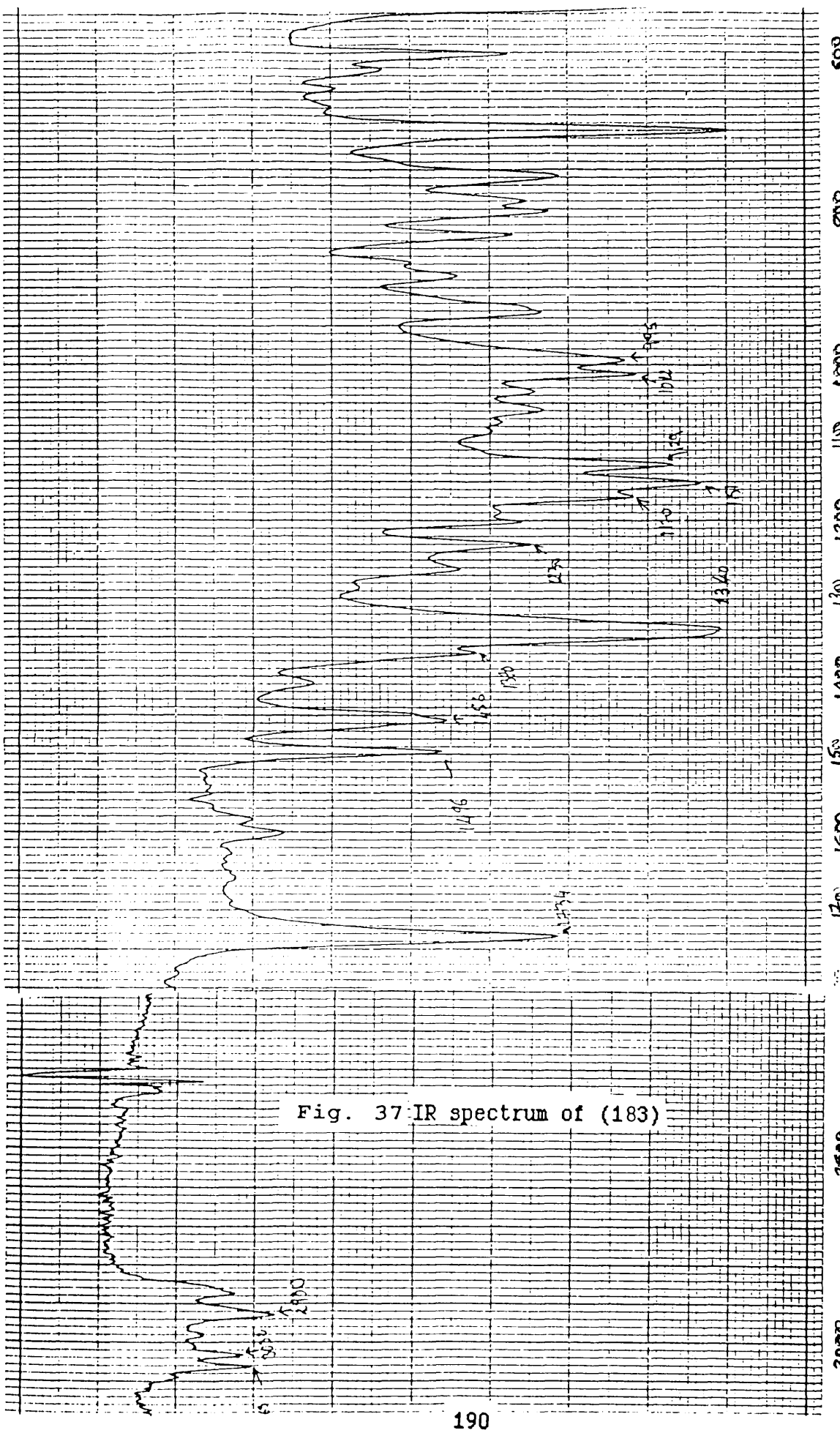


Fig. 37 IR spectrum of (183)

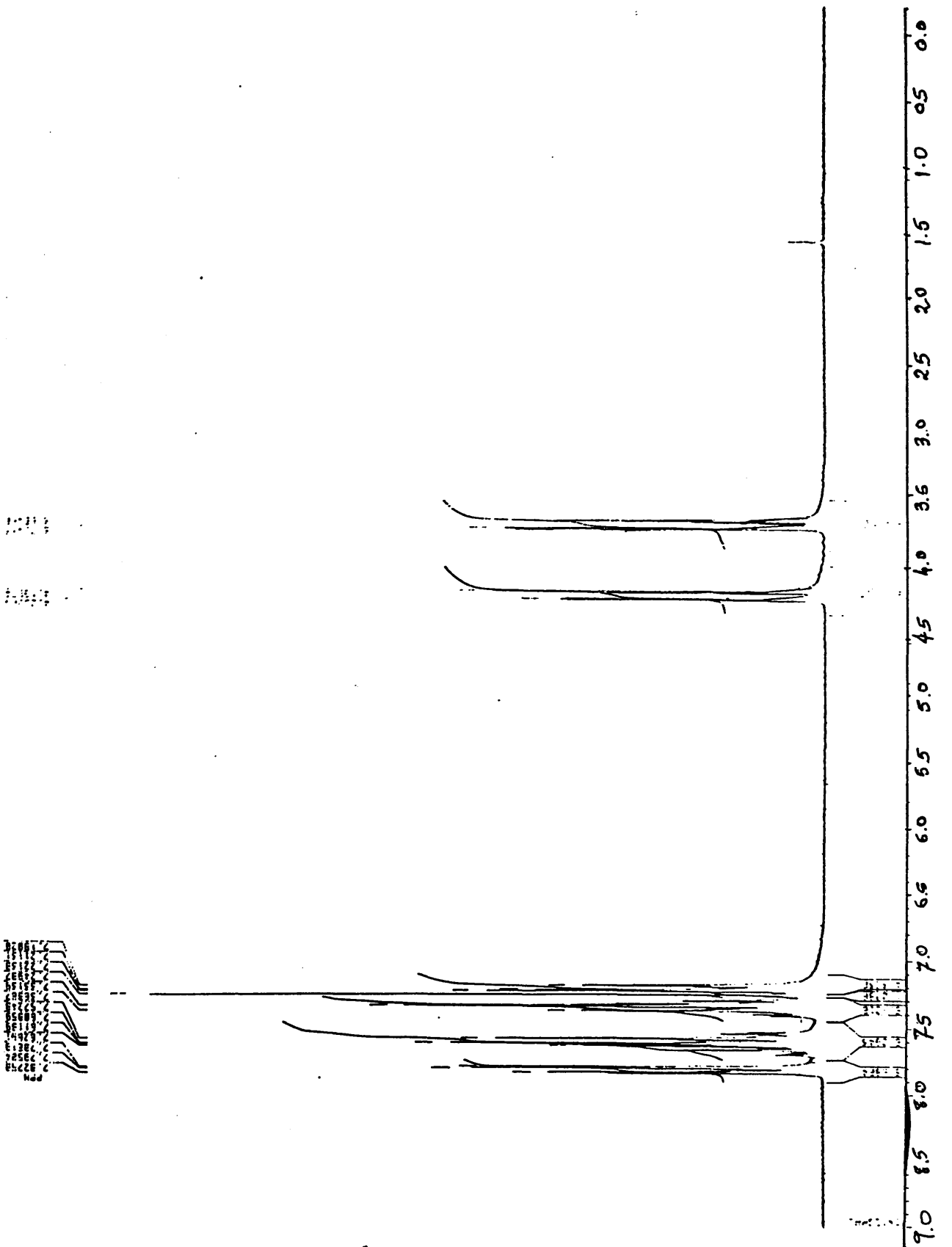


Fig. 38 ^{1}H NMR spectrum of(184) at 200 MHz

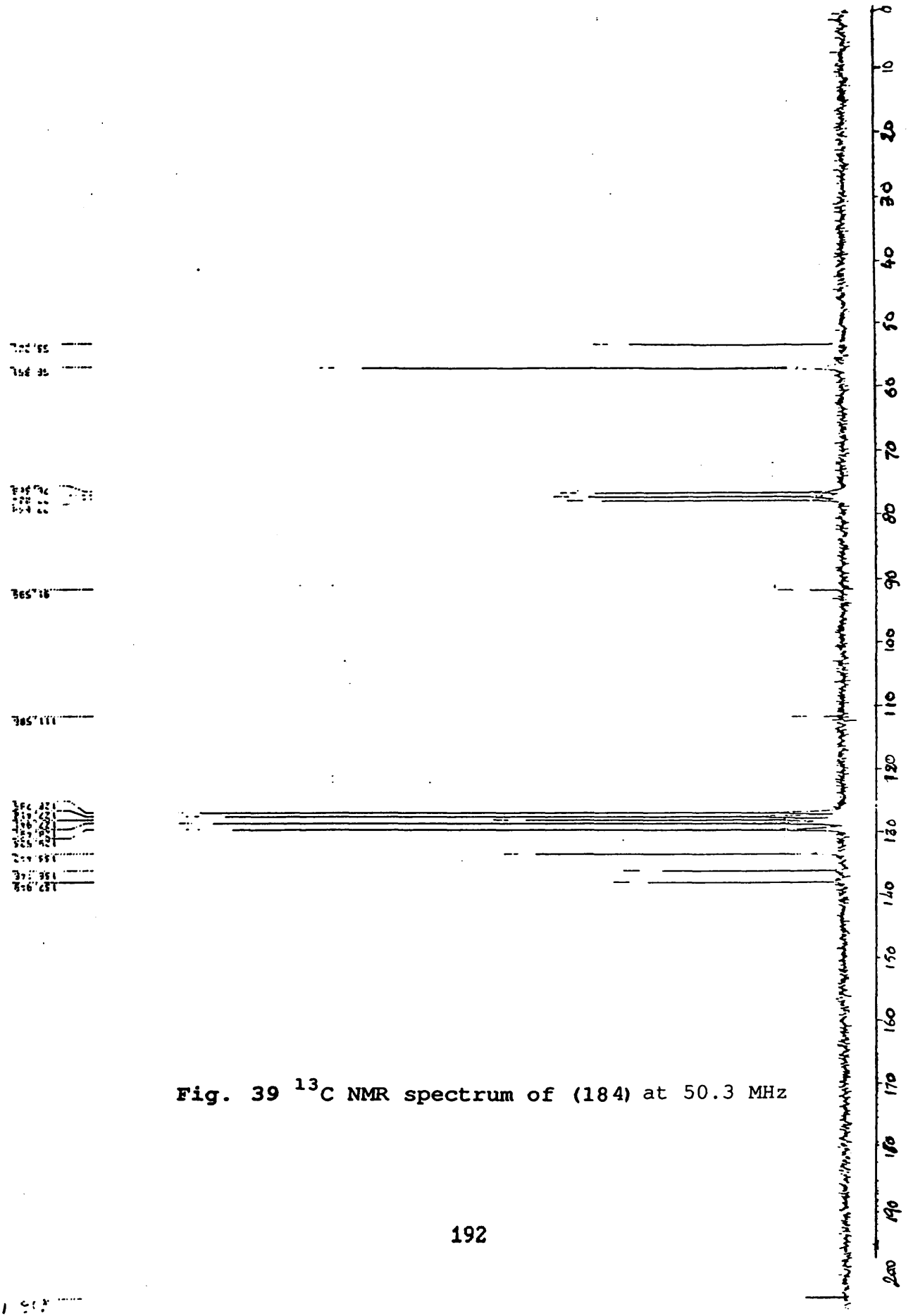


Fig. 39 ^{13}C NMR spectrum of (184) at 50.3 MHz

Fig. 40 IR spectrum of (184)

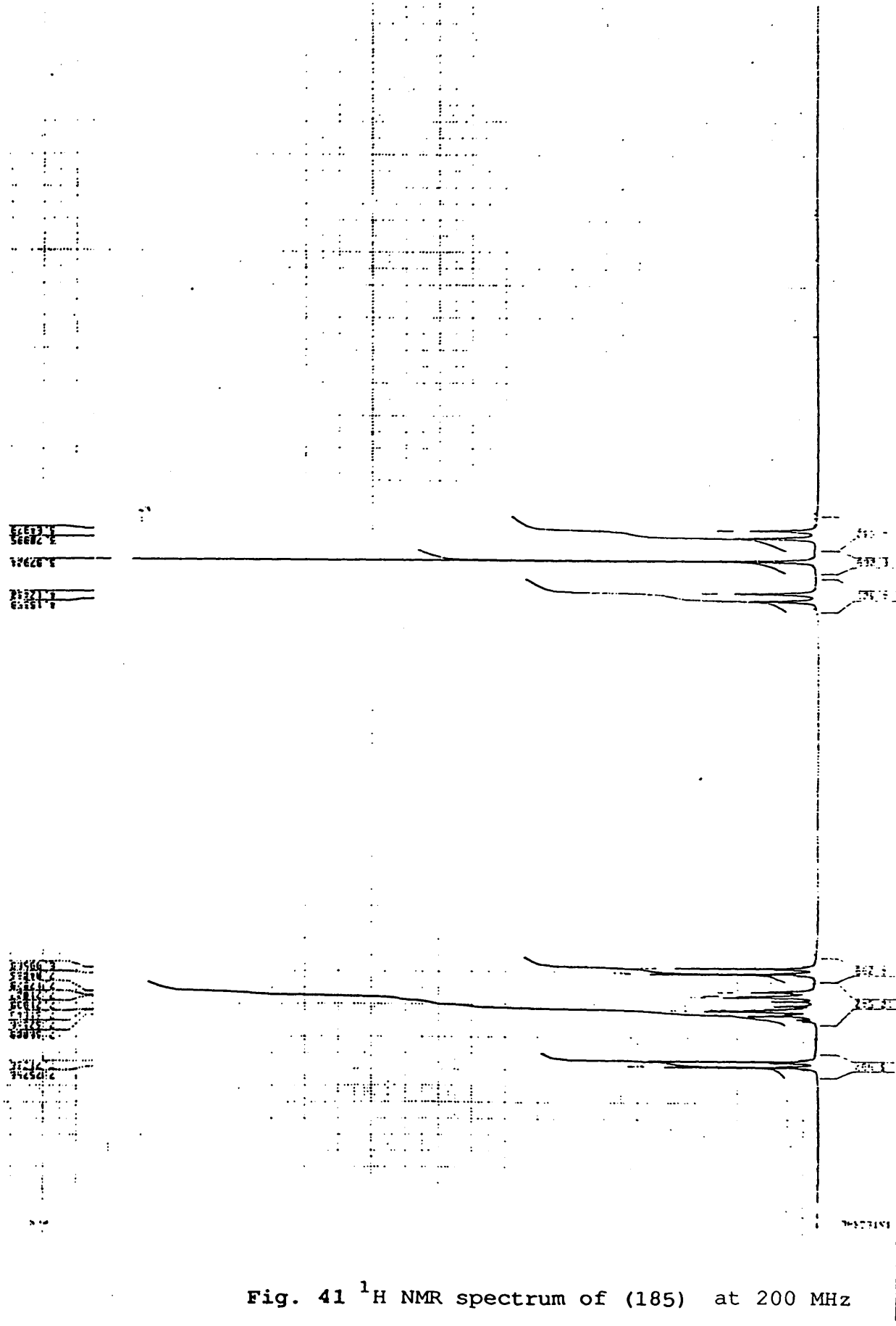


Fig. 41 ^{1}H NMR spectrum of (185) at 200 MHz

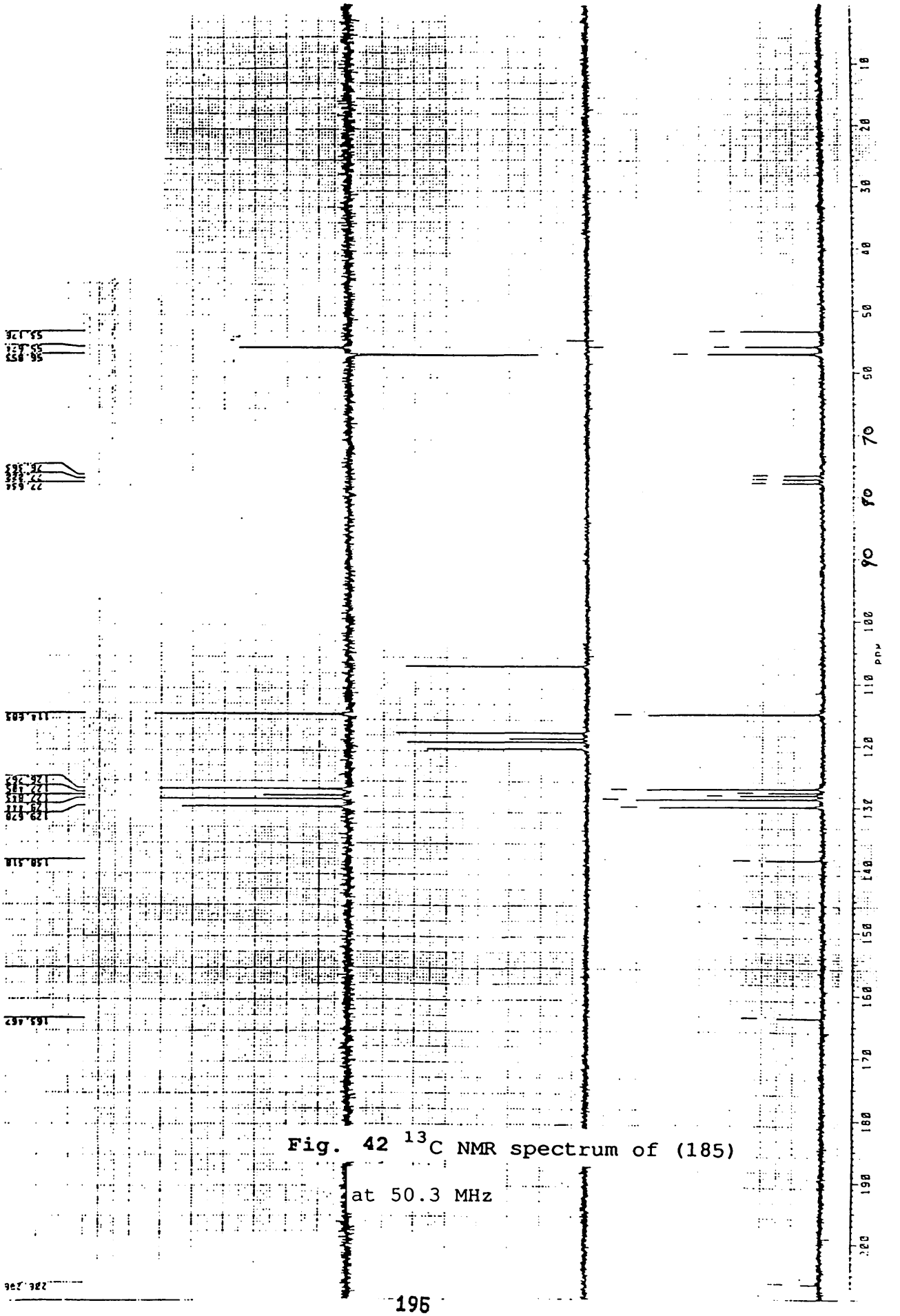


Fig. 42 ^{13}C NMR spectrum of (185) at 50.3 MHz

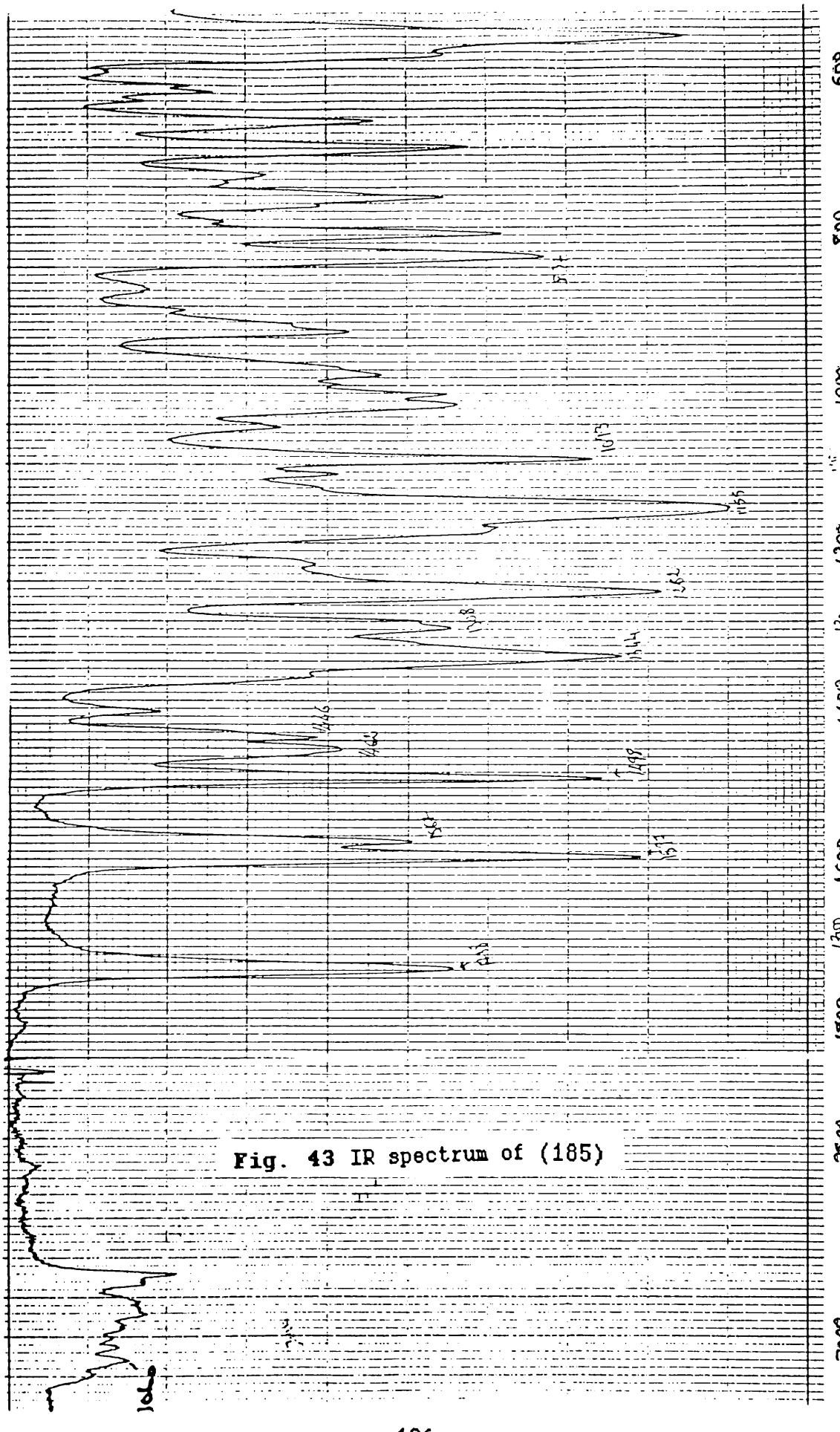


Fig. 43 IR spectrum of (185)

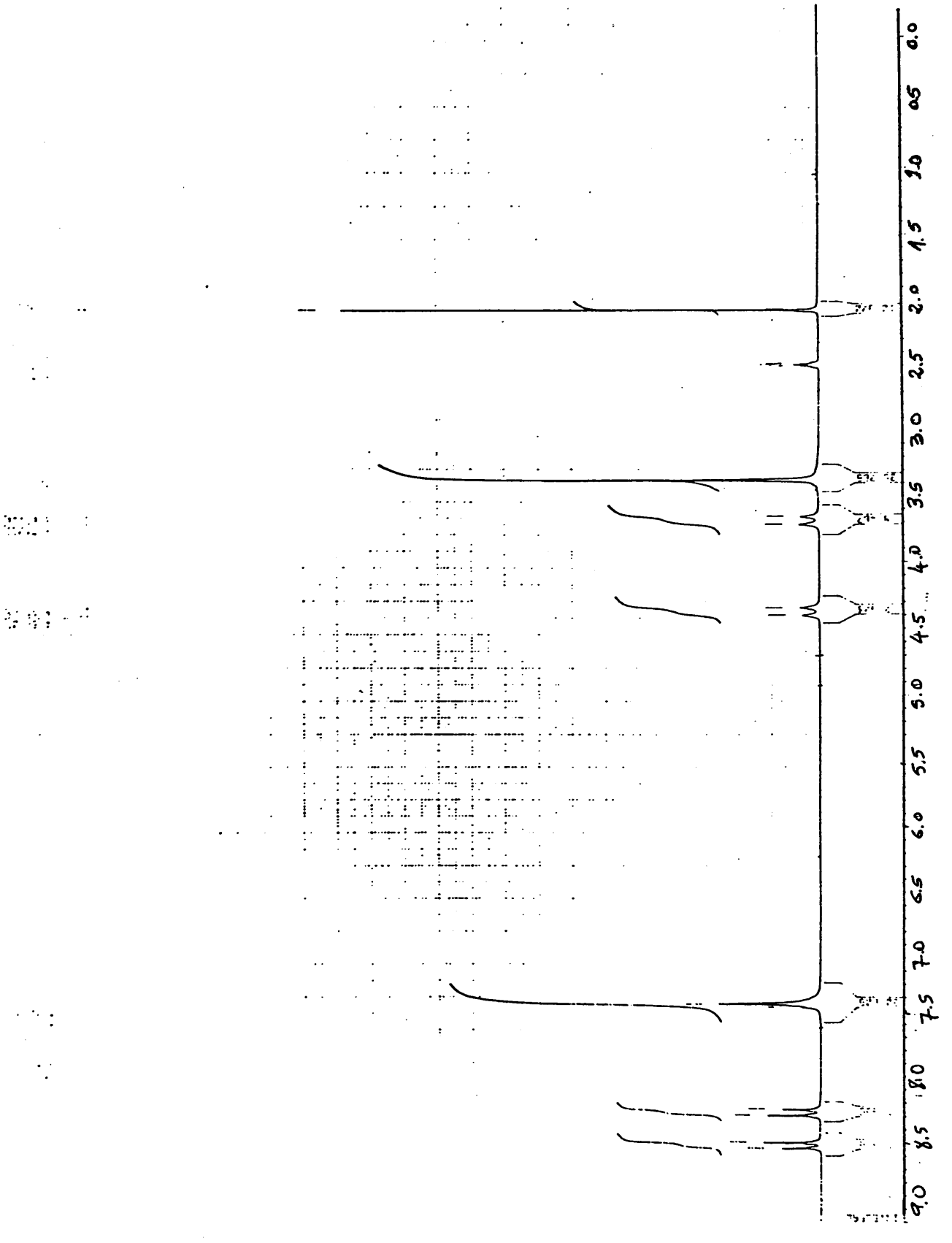


Fig. 44 ^{1}H NMR spectrum of (186) at 200 MHz

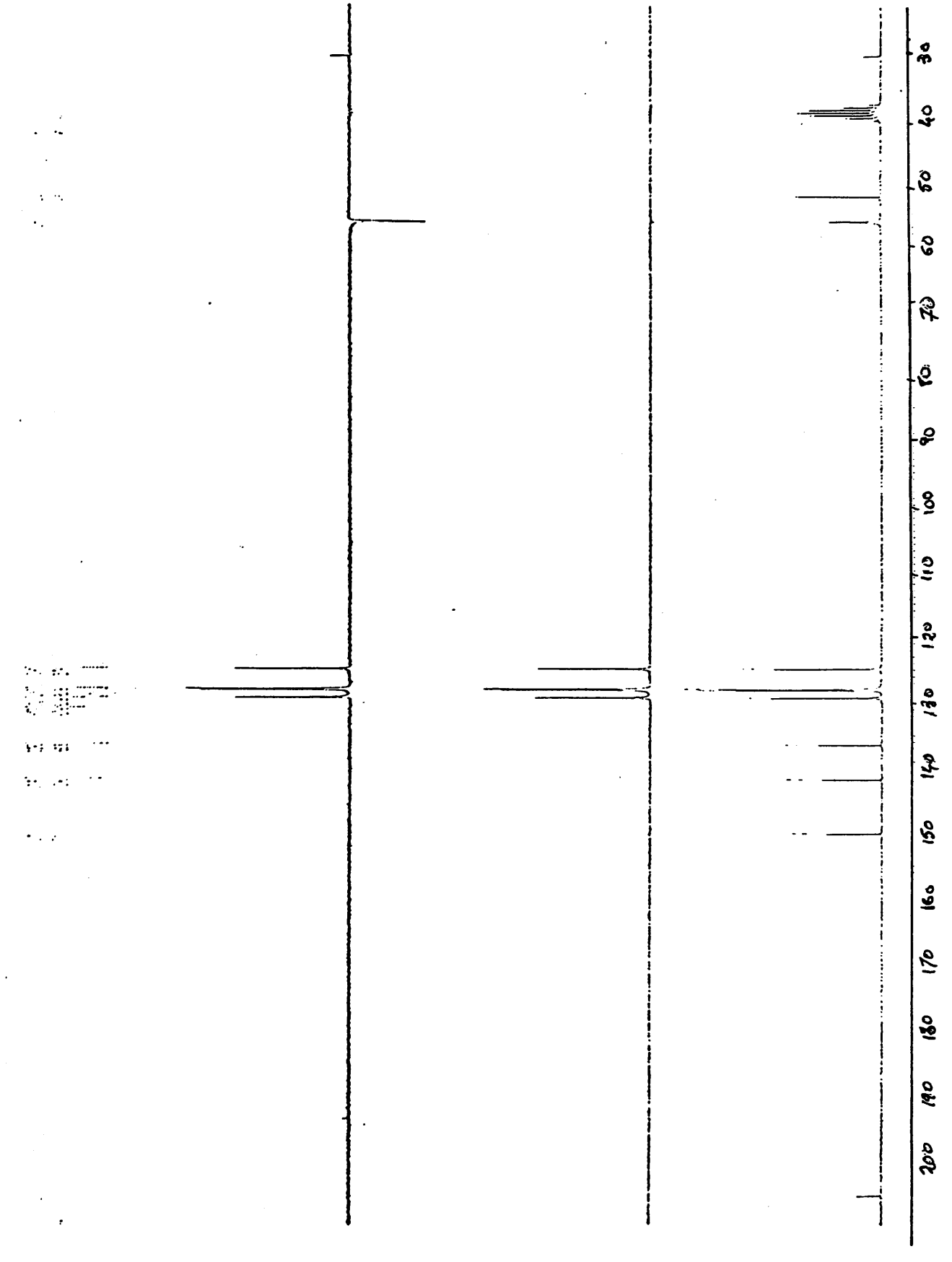


Fig. 45 ^{13}C NMR spectrum of (186) at 50.3 MHz

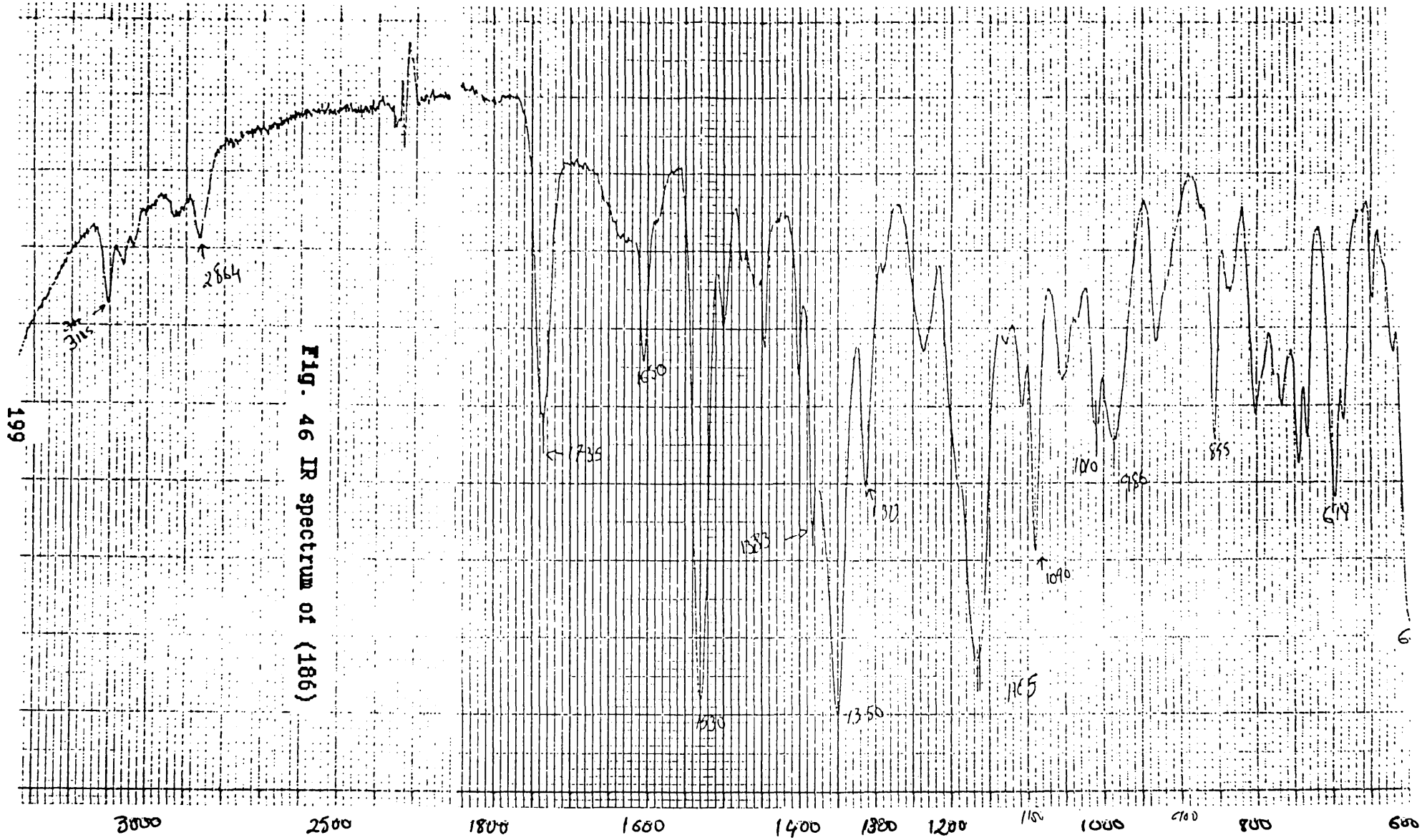


Fig. 46 IR spectrum of (186)

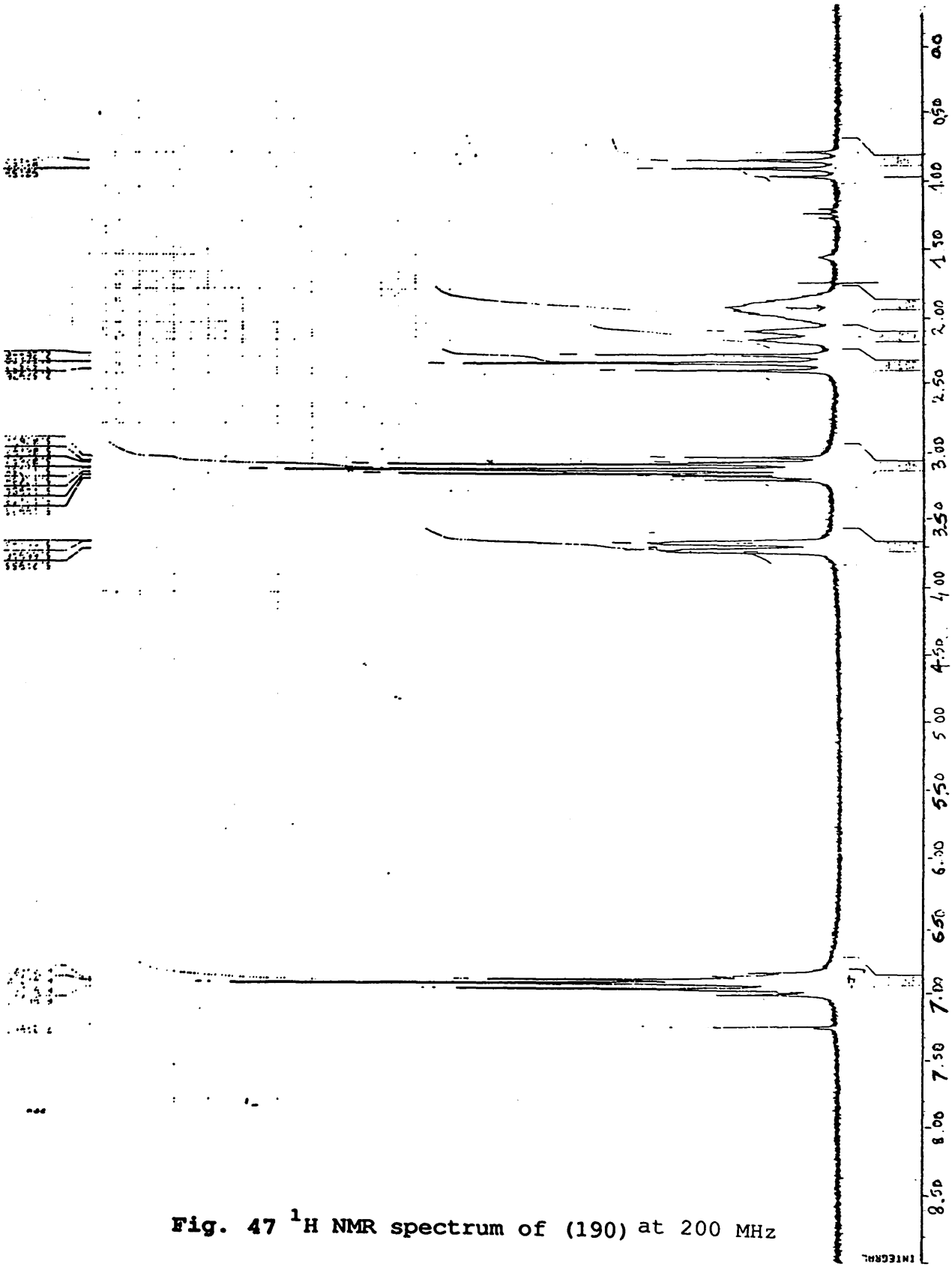


Fig. 47 ^{1}H NMR spectrum of (190) at 200 MHz

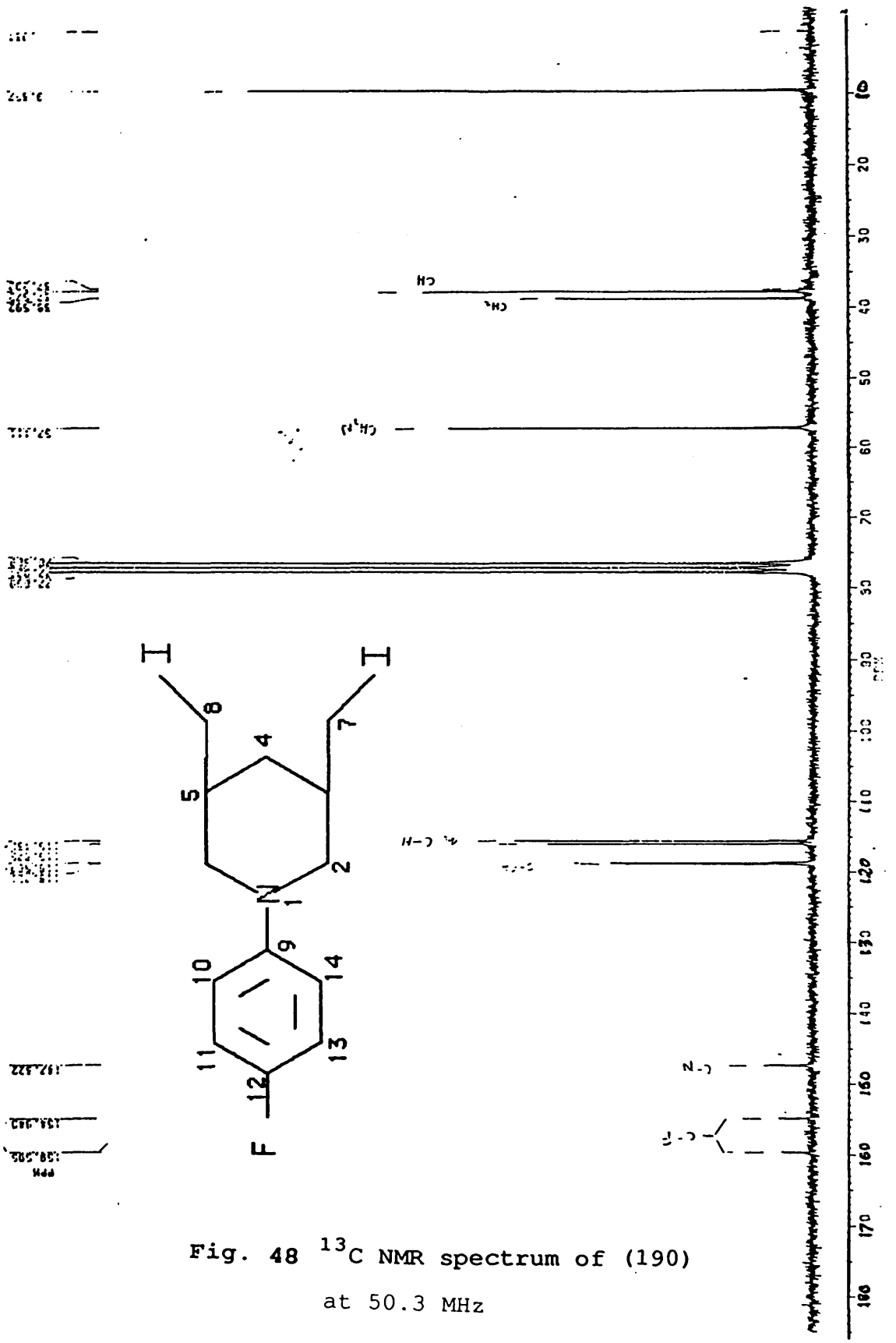


Fig. 48 ^{13}C NMR spectrum of (190)

at 50.3 MHz

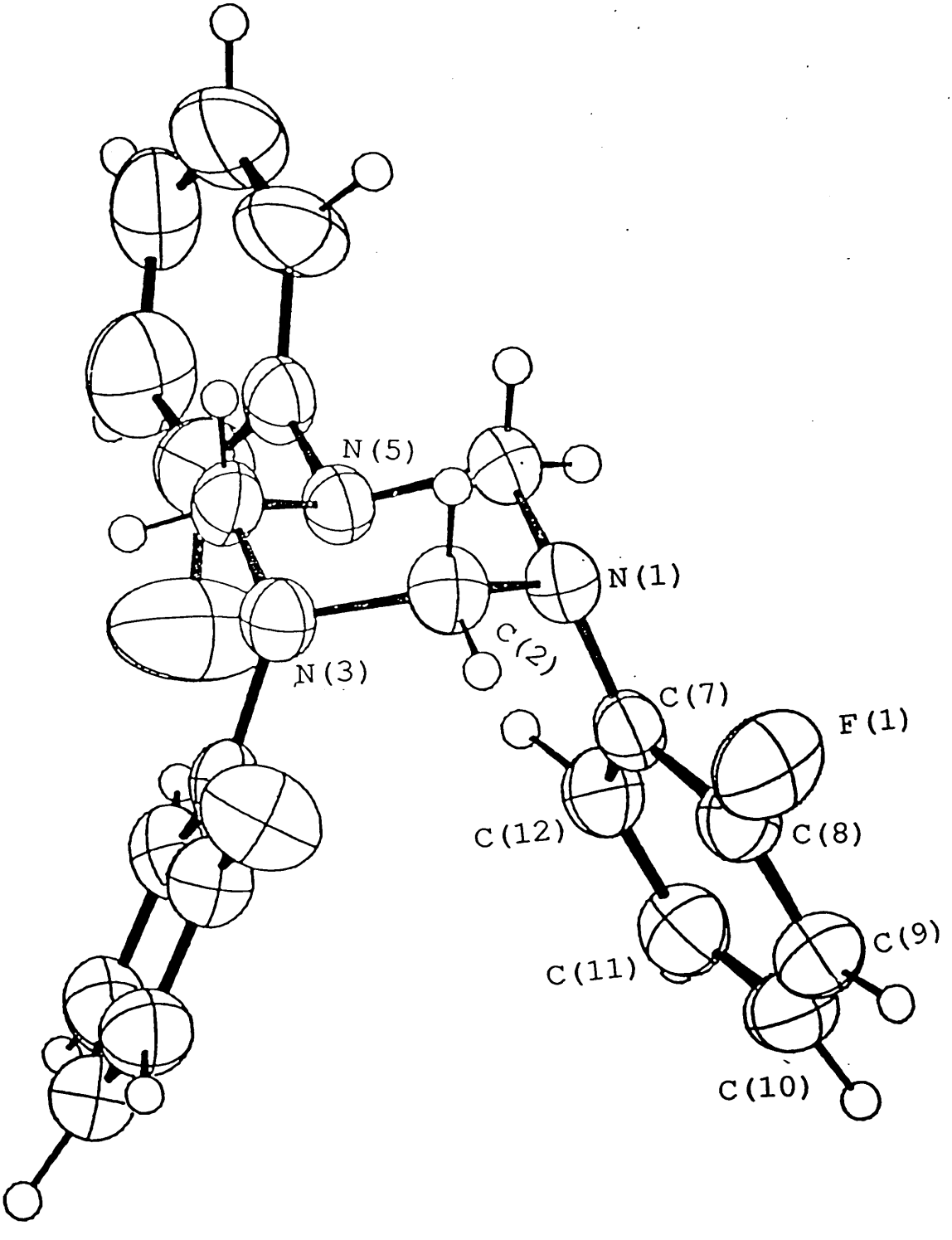


Fig. 49 Ortep diagram of (106)

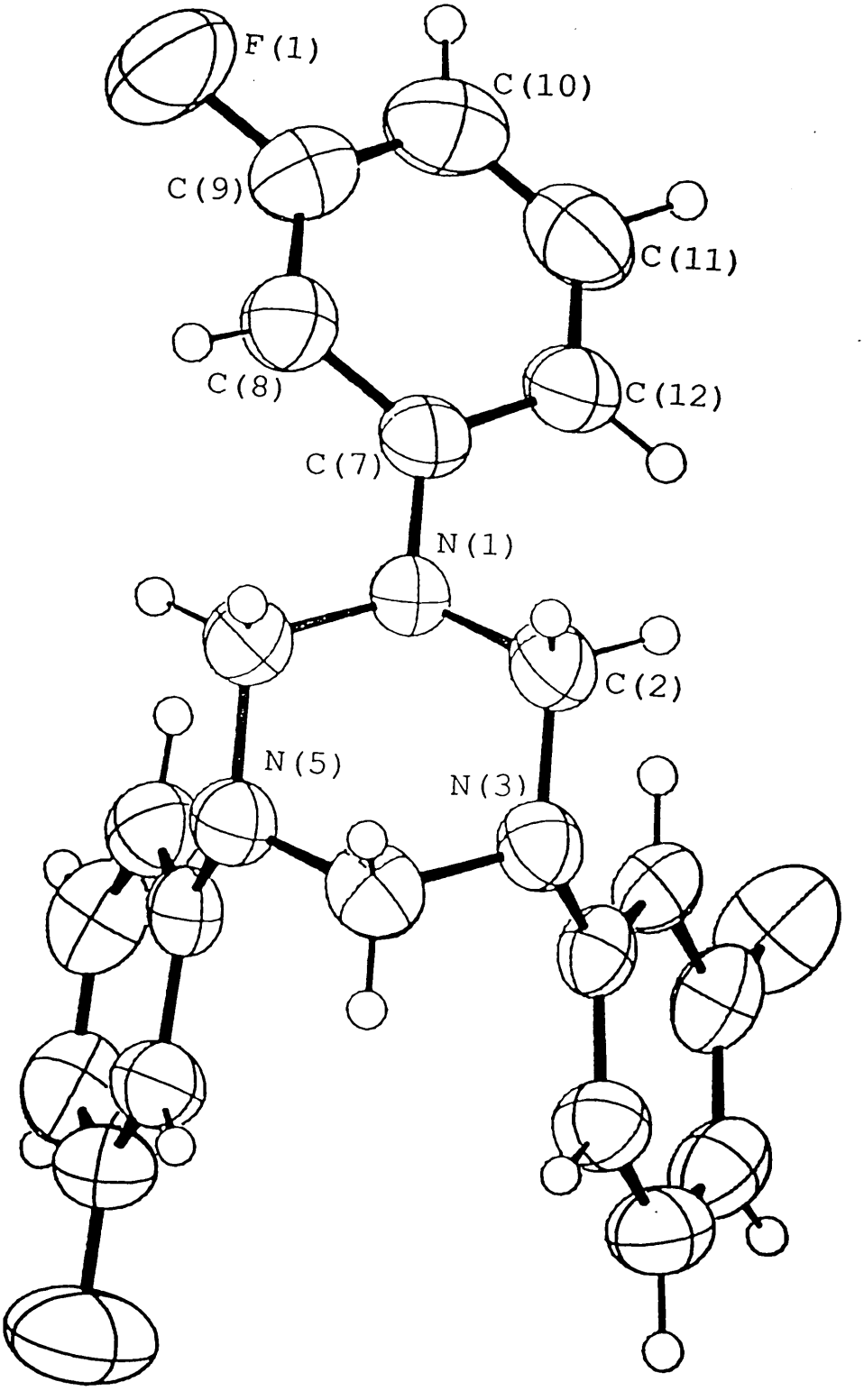


Fig. 50 Ortep diagram of (107)

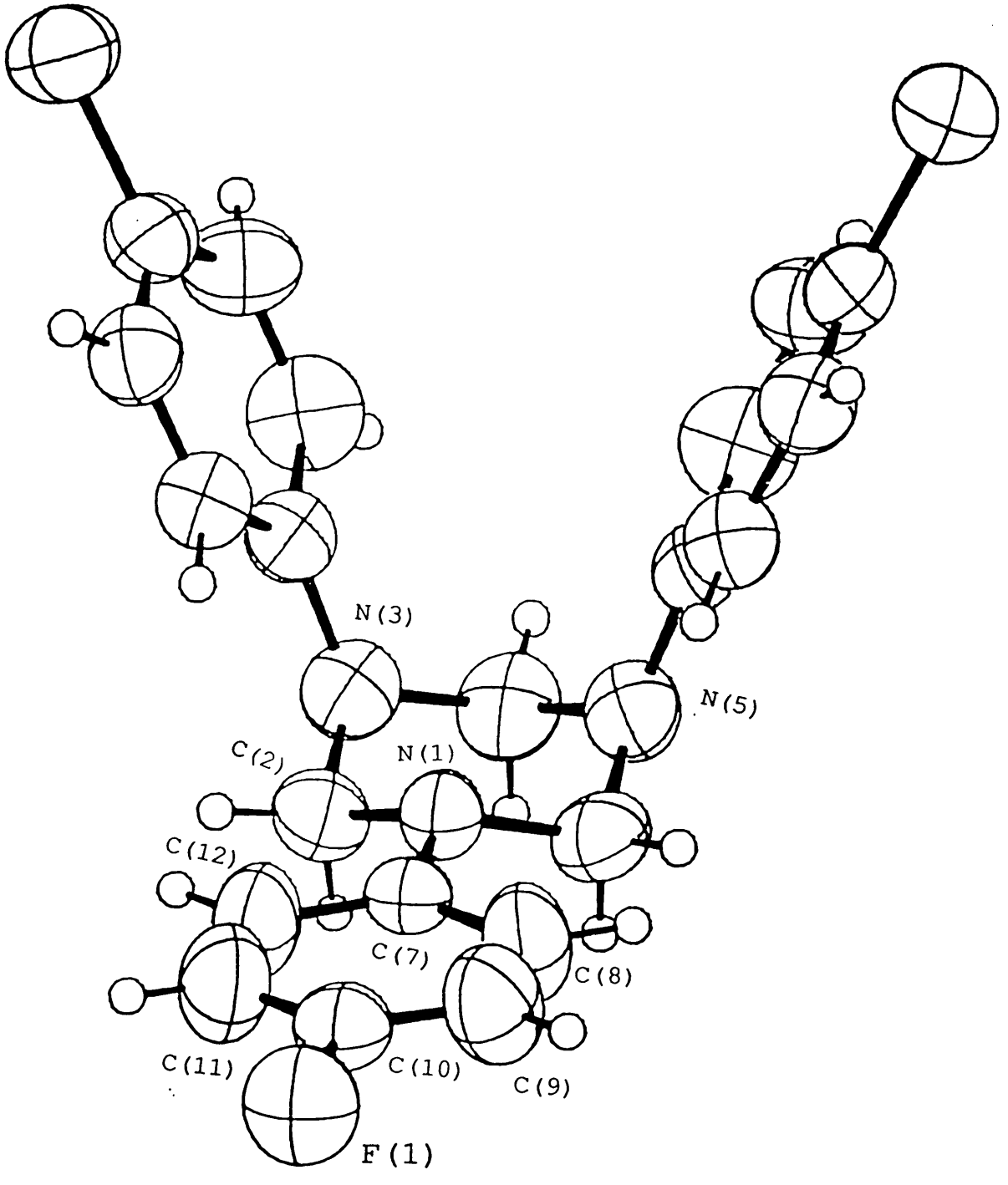


Fig. 51 Ortep diagram of (108)

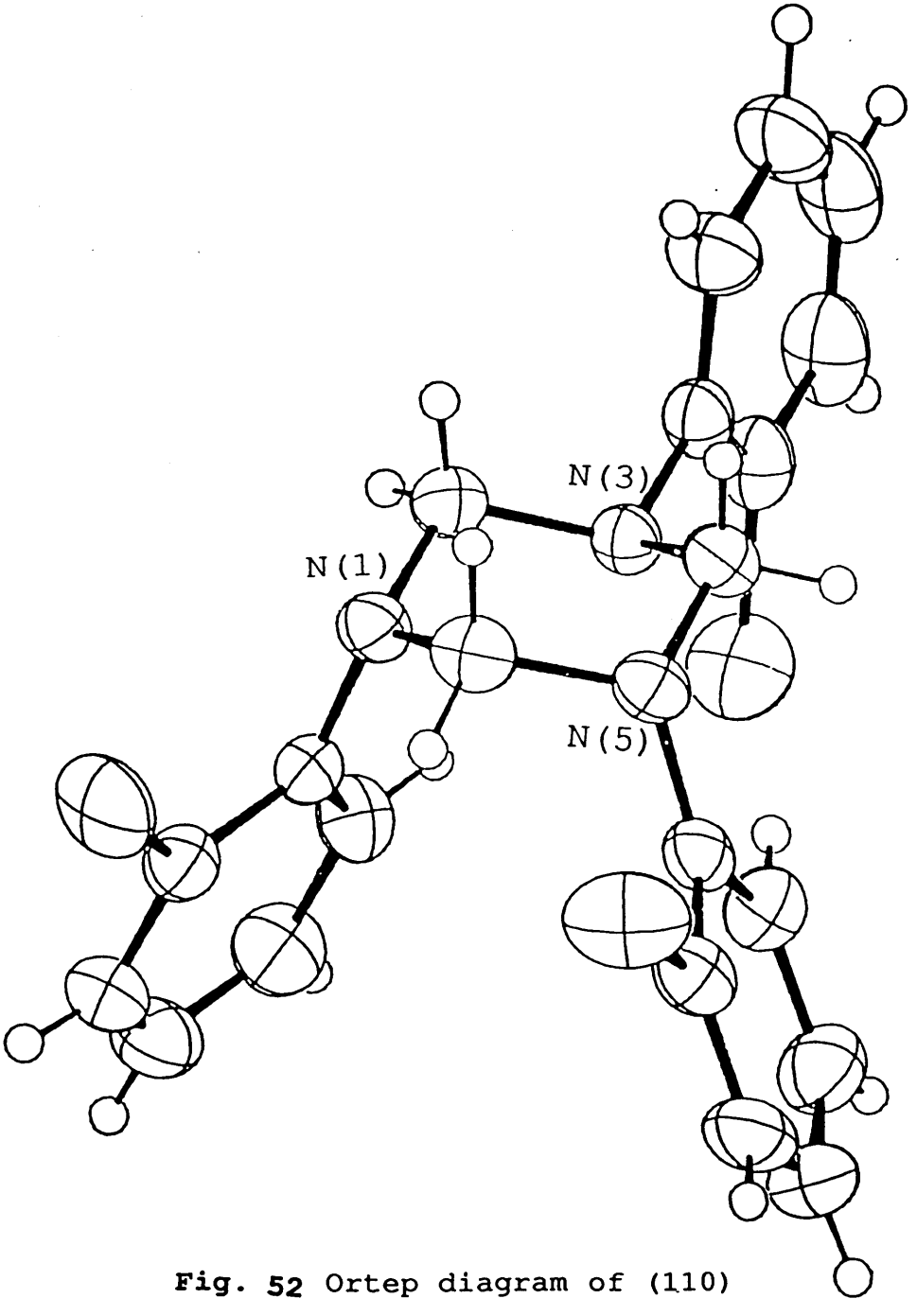


Fig. 52 Ortep diagram of (110)

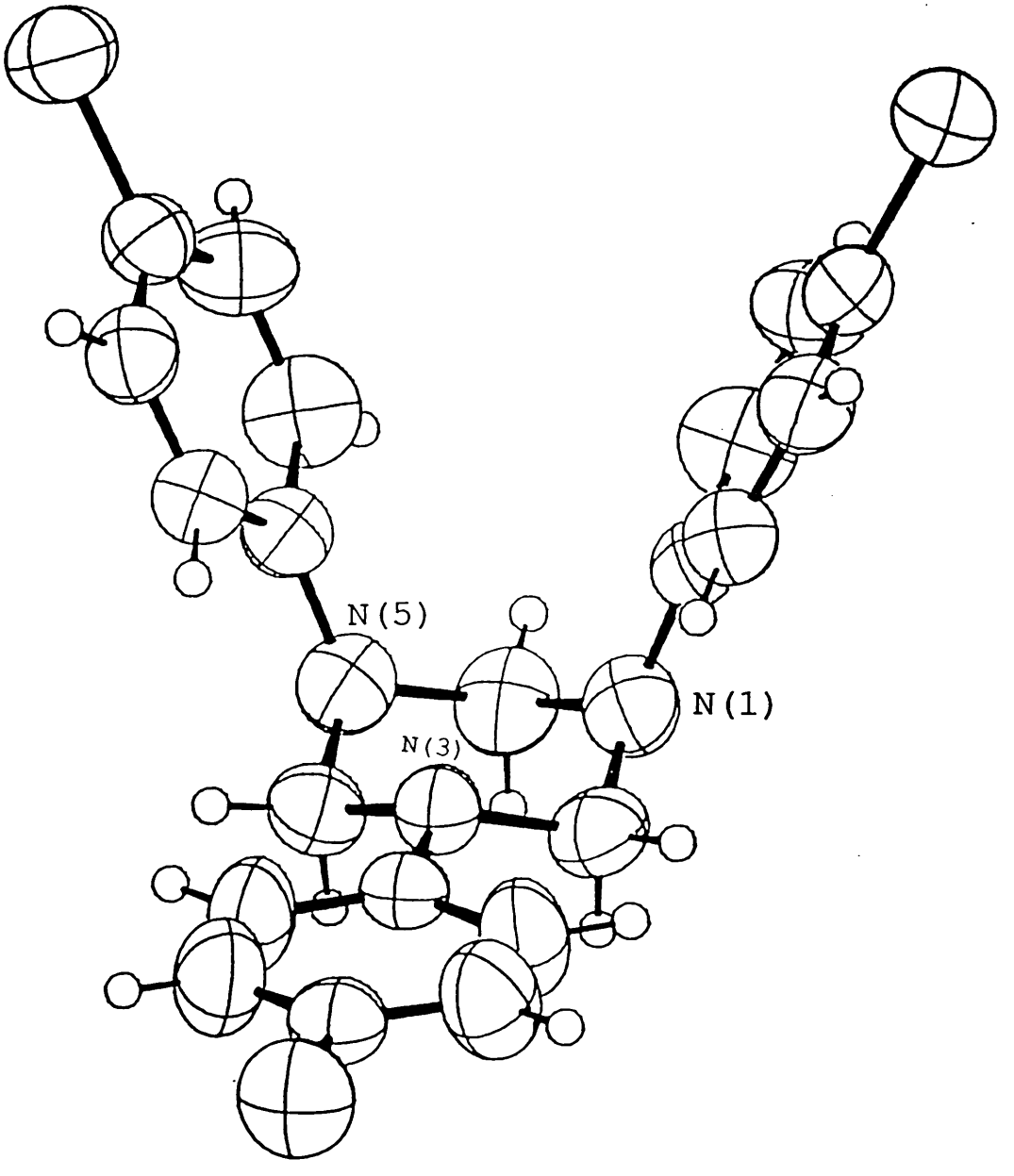


Fig. 53 Ortep diagram of (111)

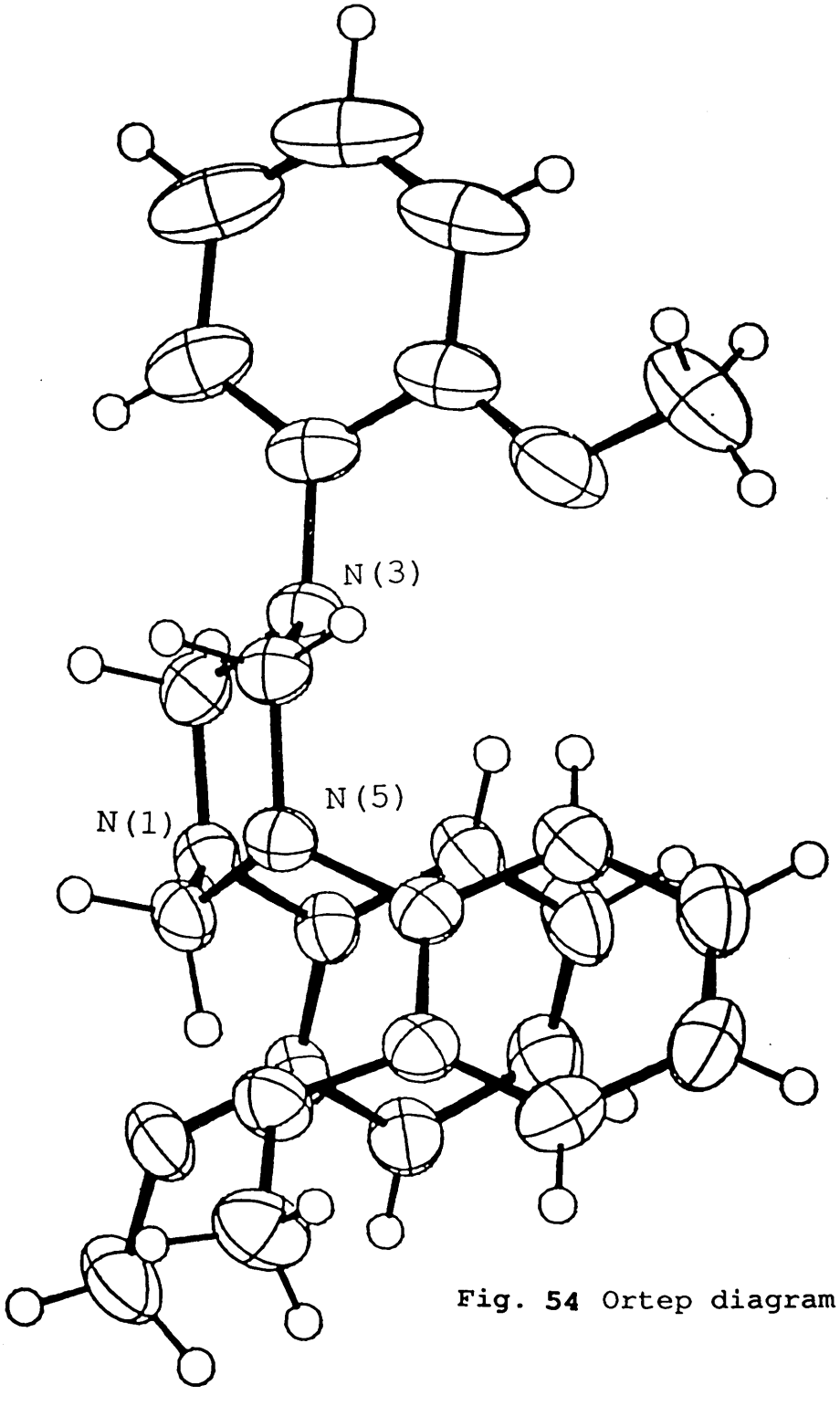


Fig. 54 Ortep diagram of (112)

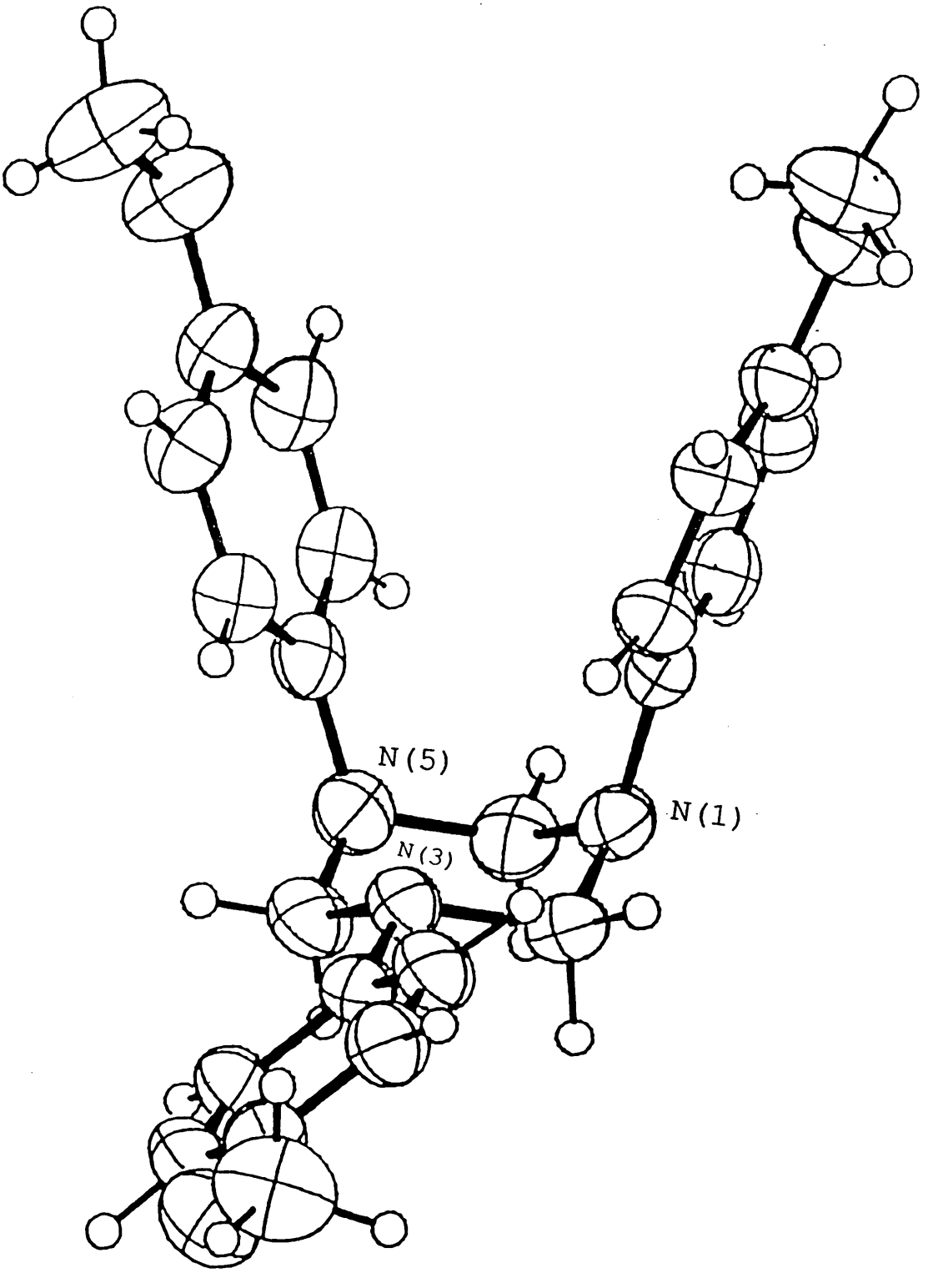


Fig. 55 Ortep diagram of (113)

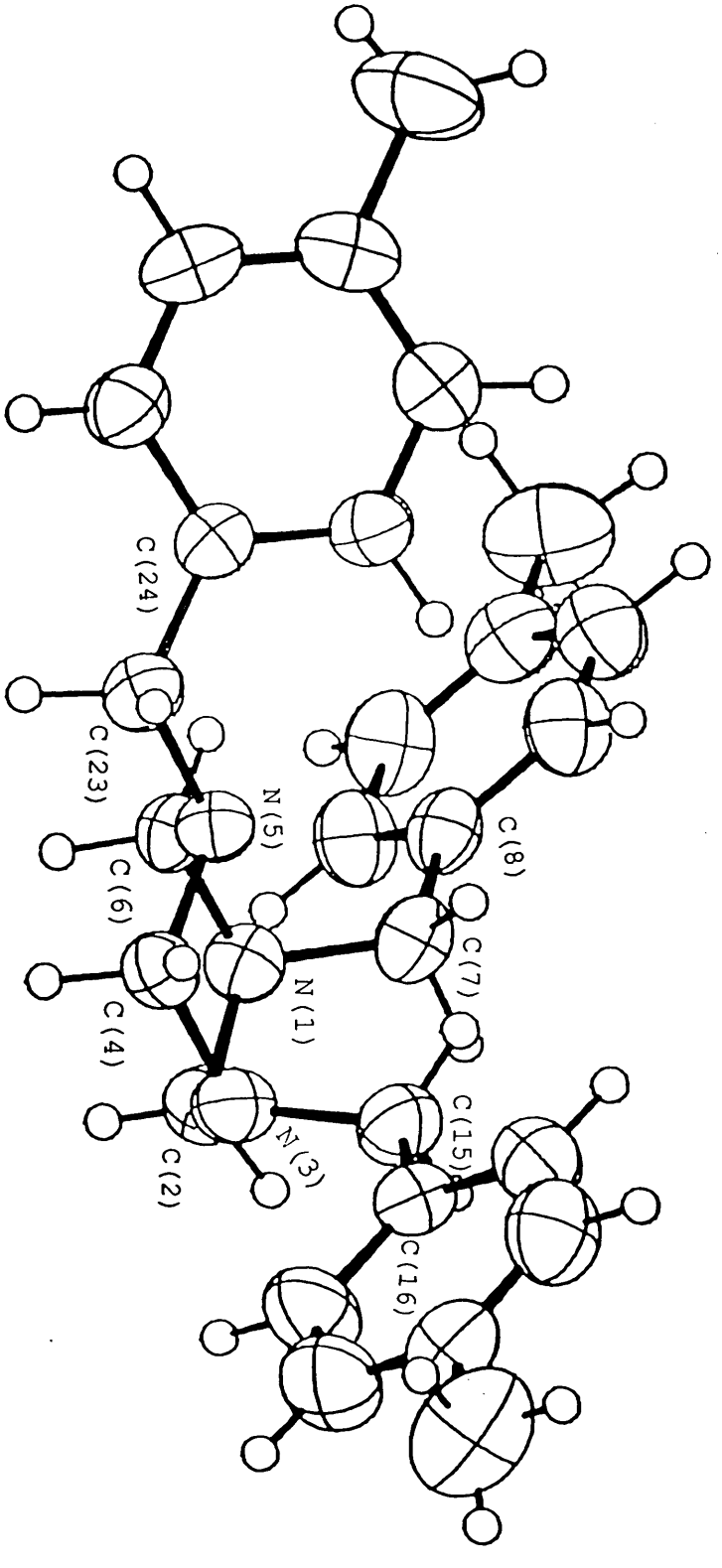


Fig. 56 Ortep diagram of (114)

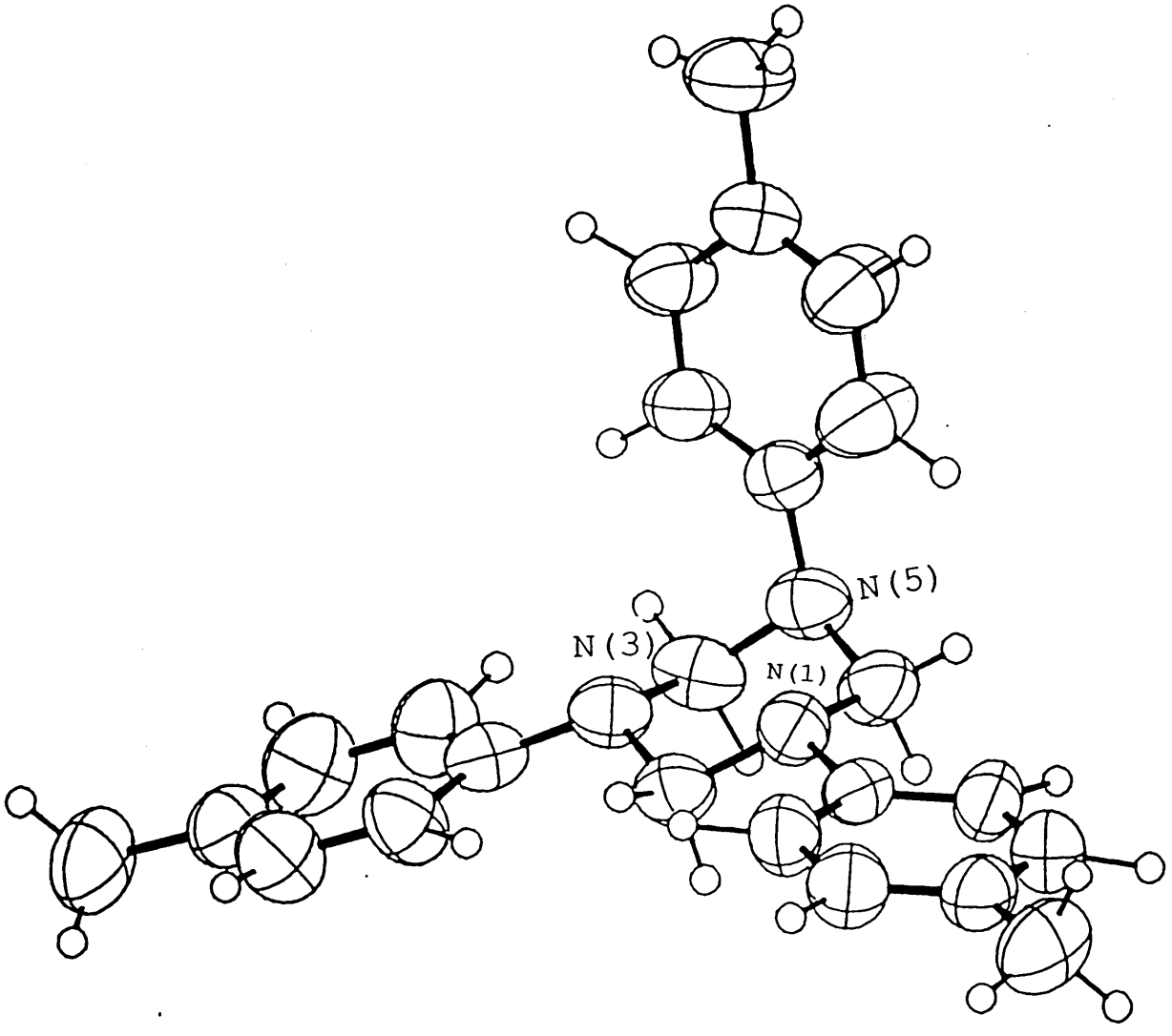


Fig. 57 Ortep diagram of (115)

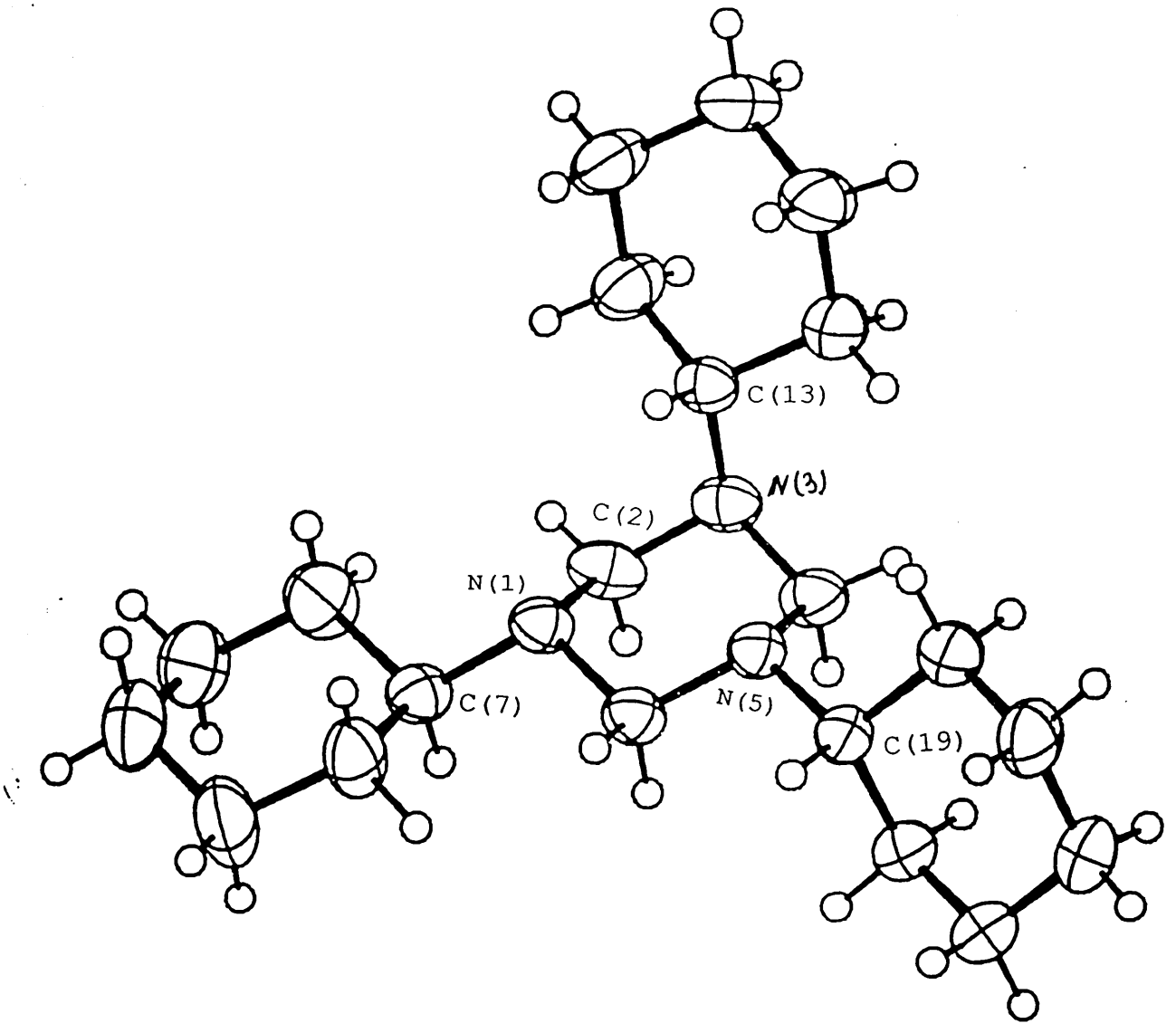


Fig. 58 Ortep diagram of (116)

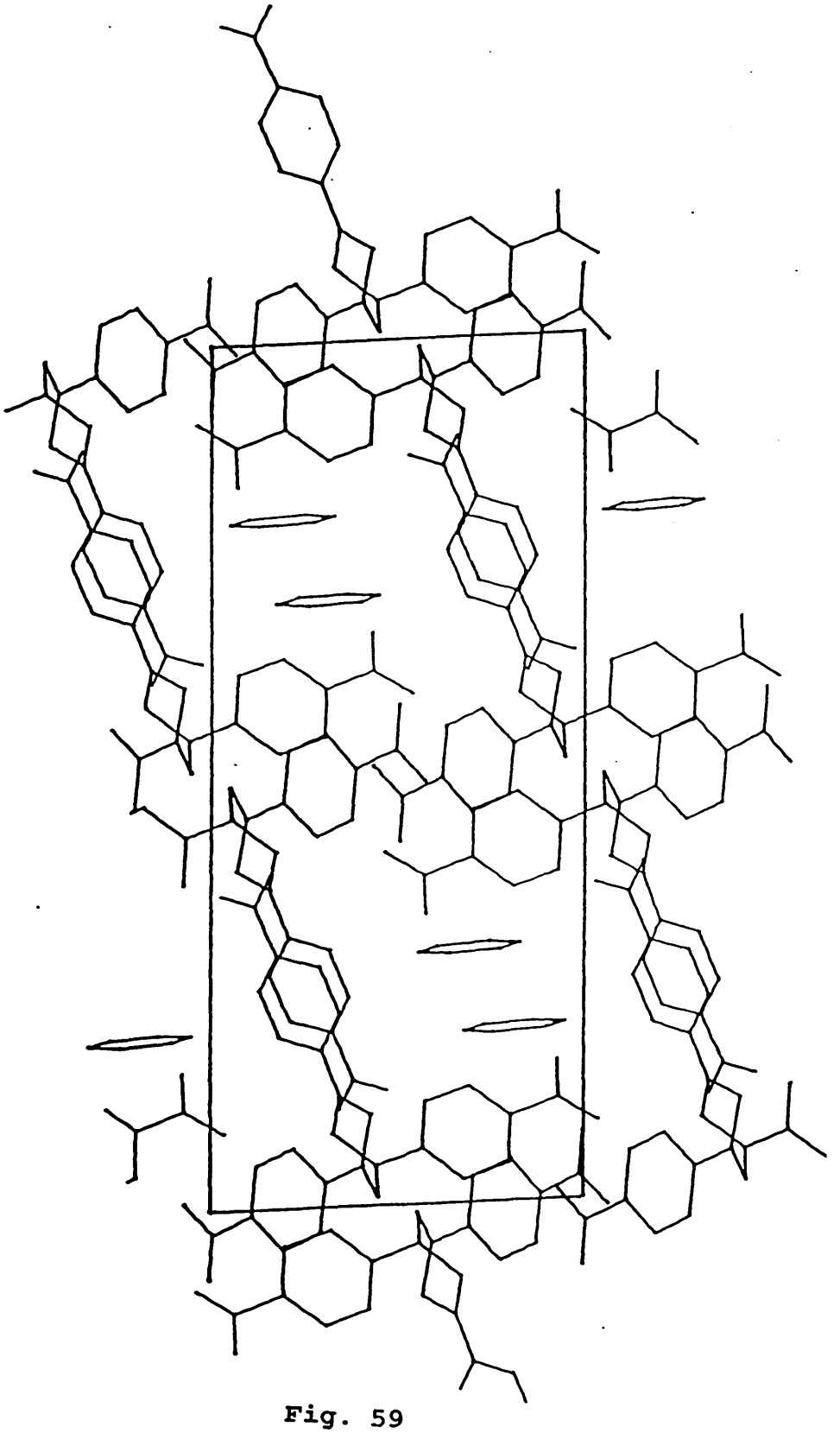


Fig. 59

Crystal packing diagram of solvated crystals of (117)

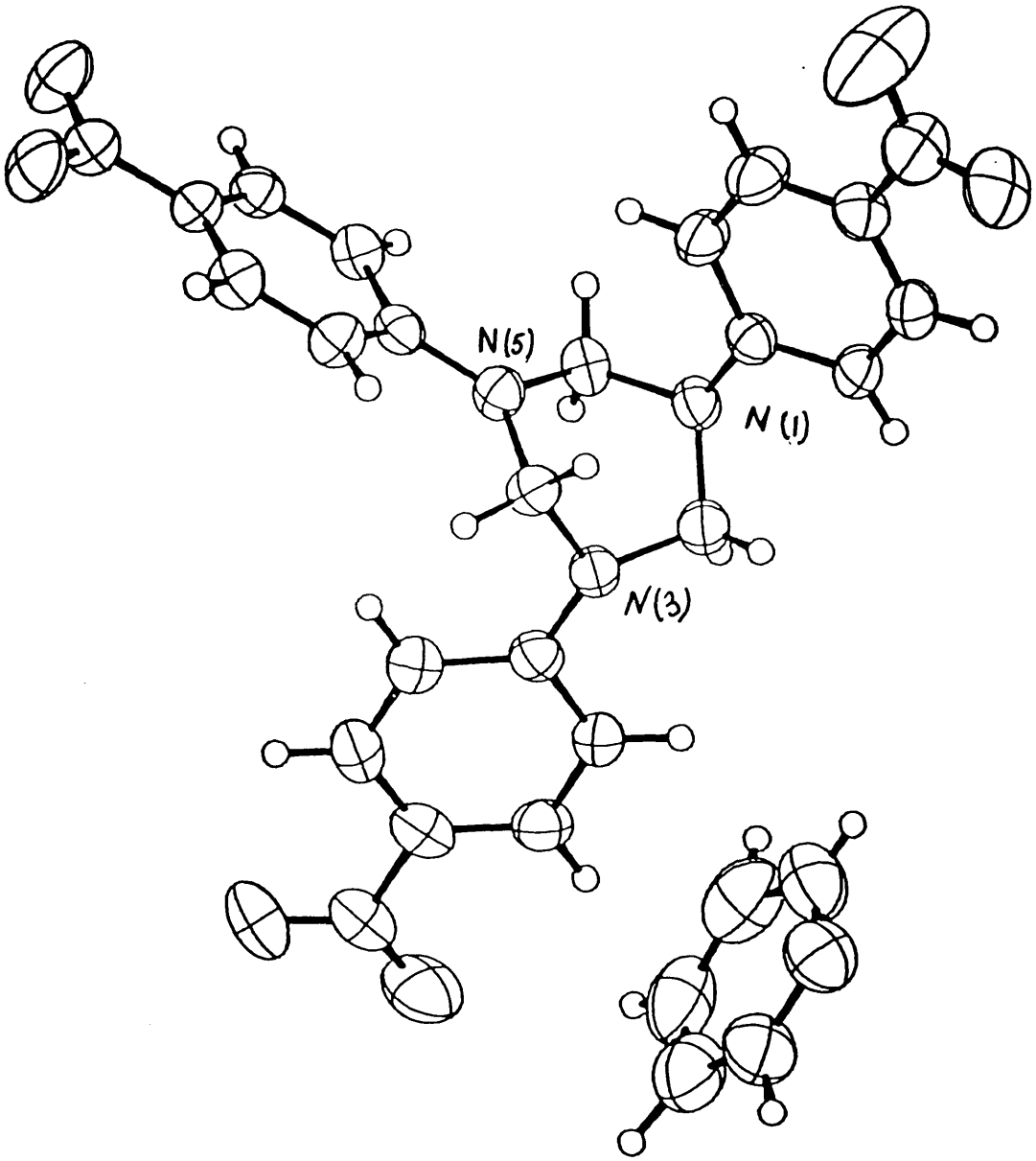


Fig. 60 Ortep diagram
of solvated crystals of (117)

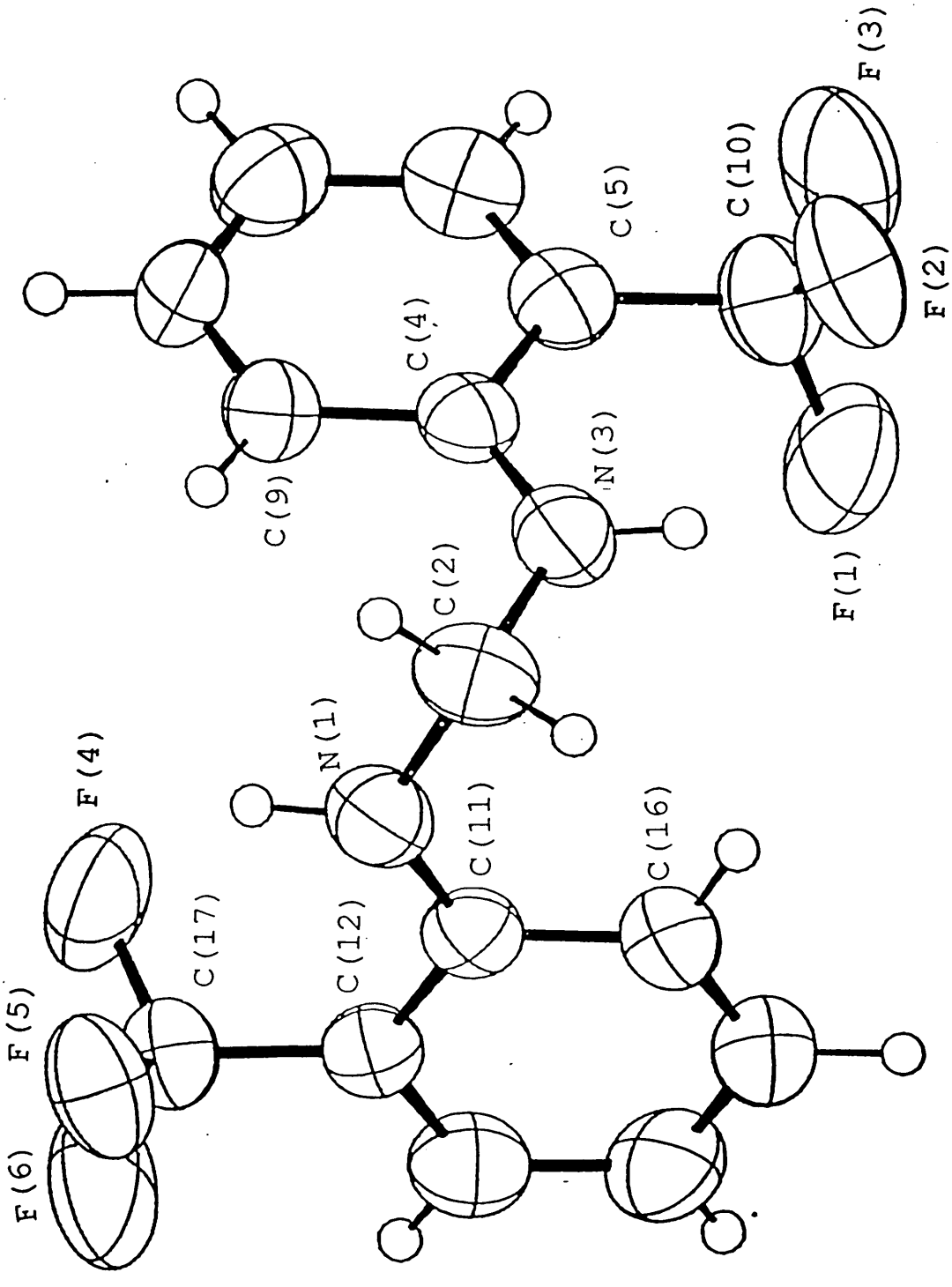


Fig. 61 Ortep diagram of (122)

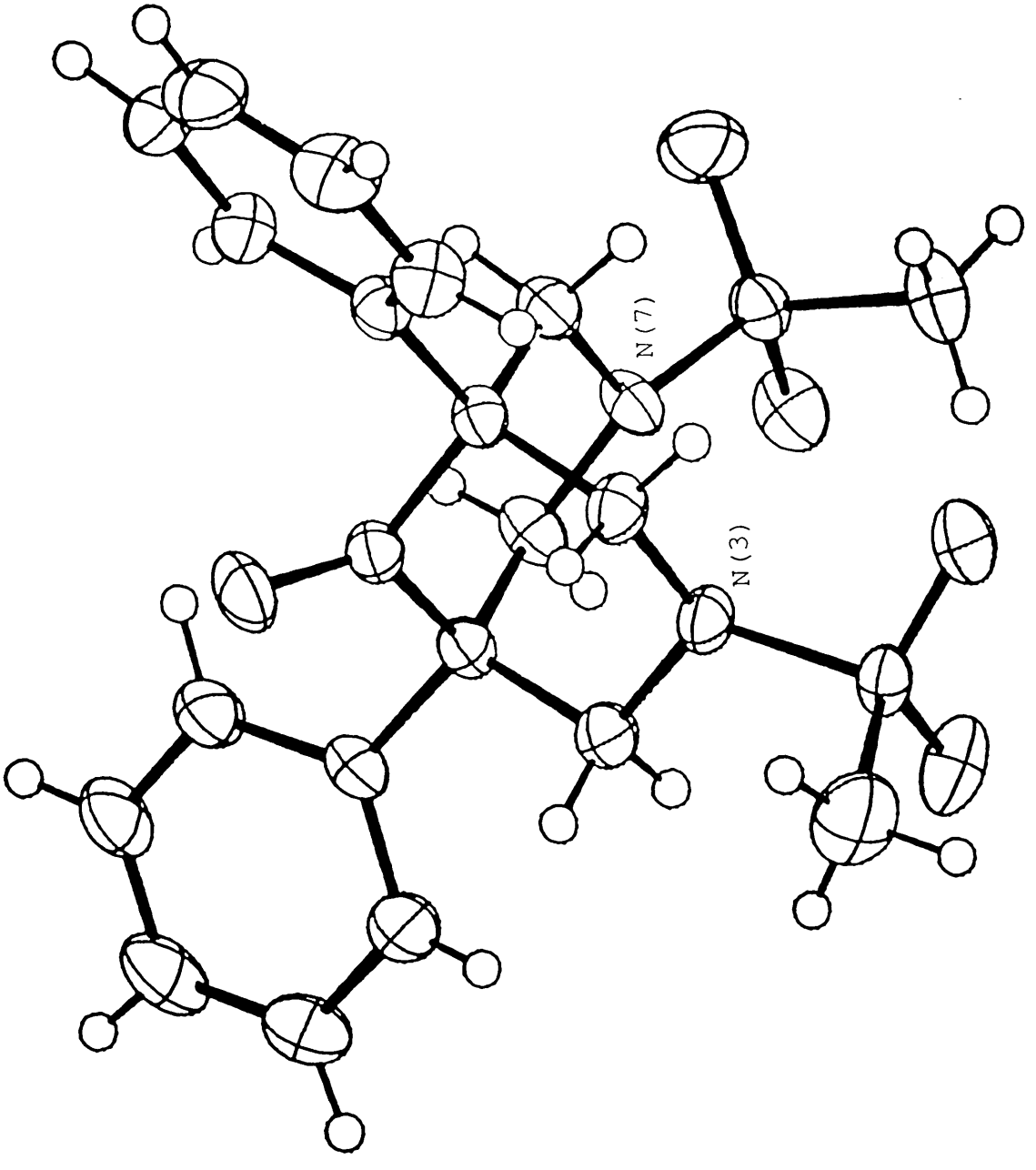


Fig. **62** Ortep diagram of (182)

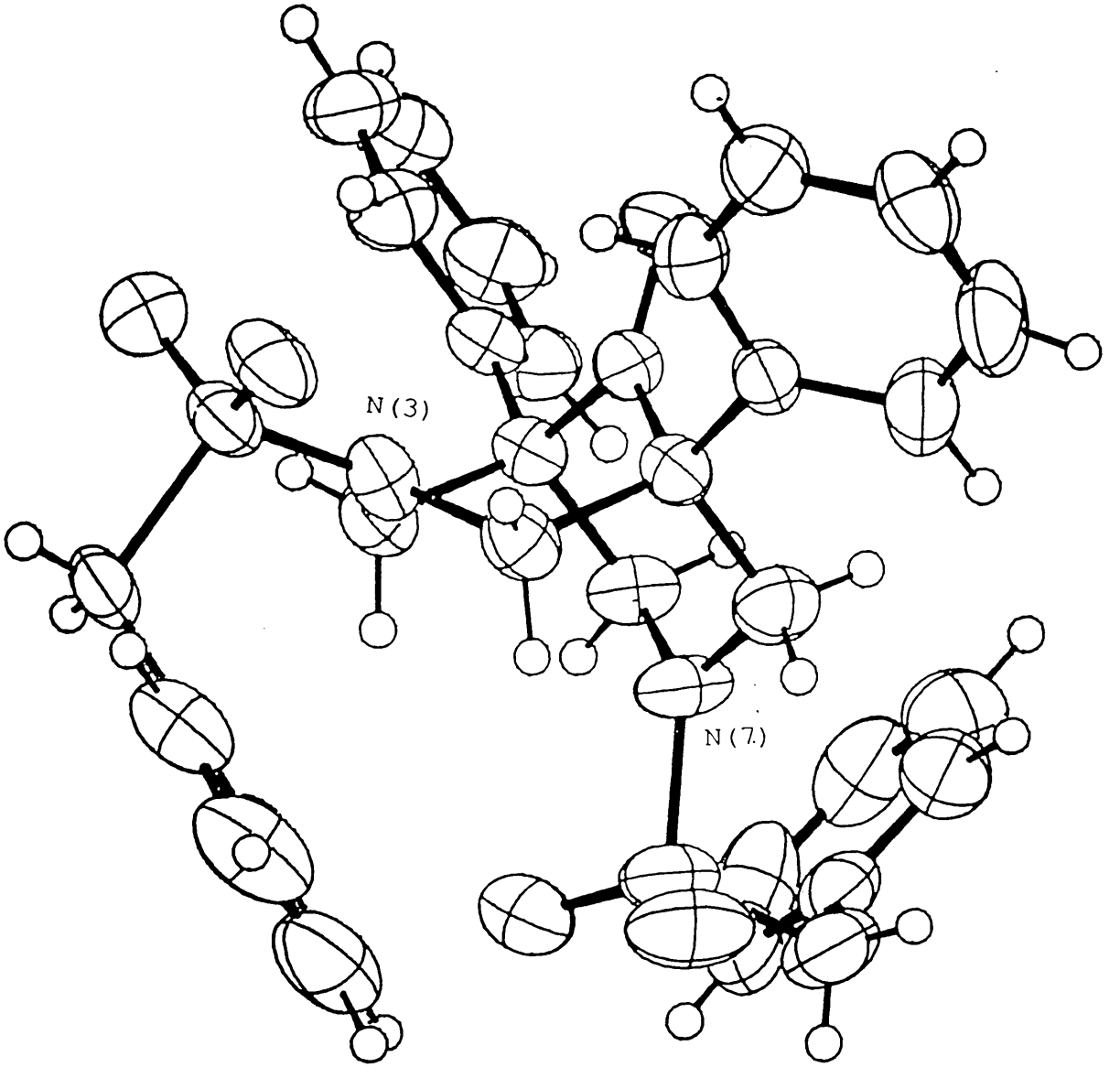


Fig. 63 Ortep diagram of (183)

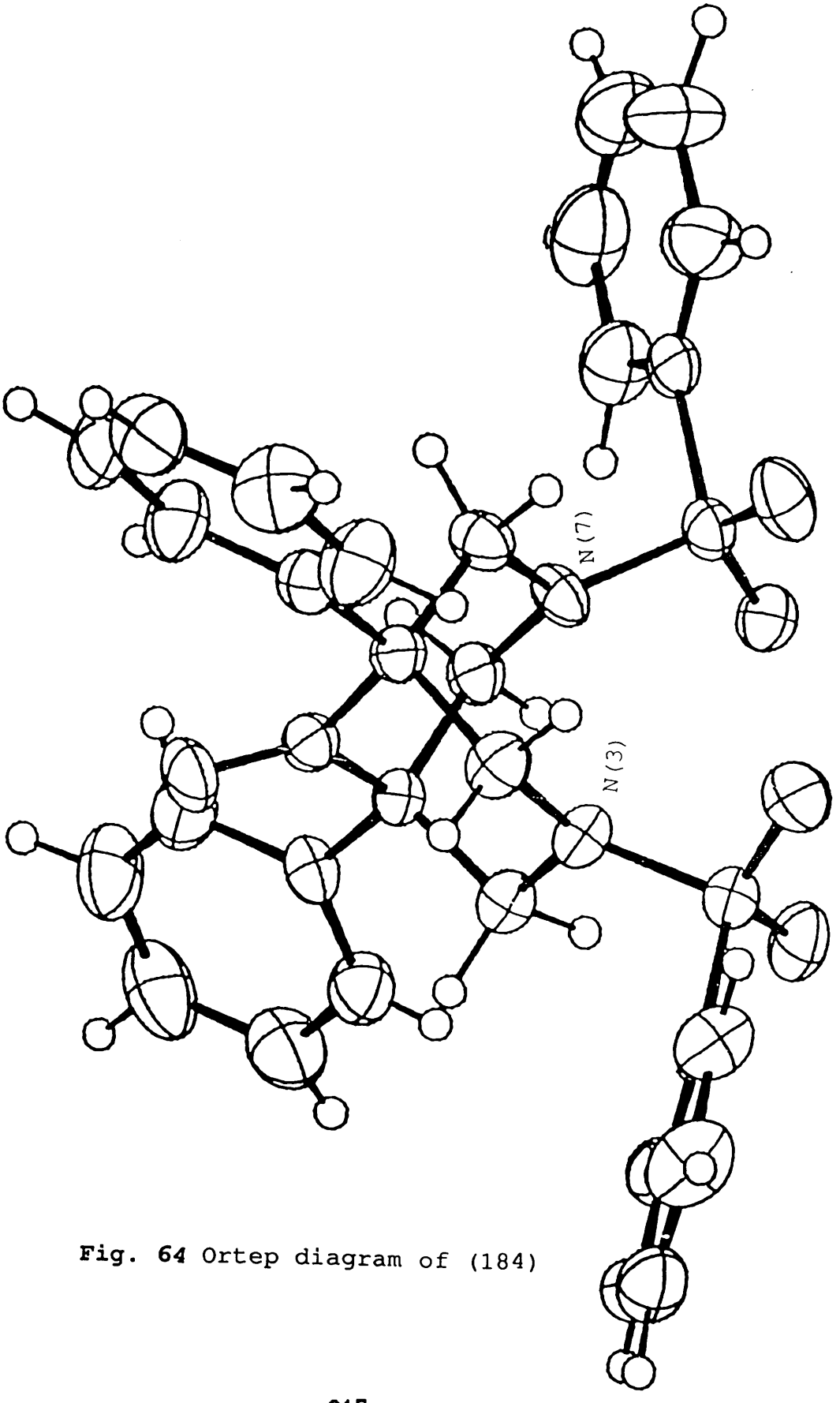


Fig. 64 Ortep diagram of (184)

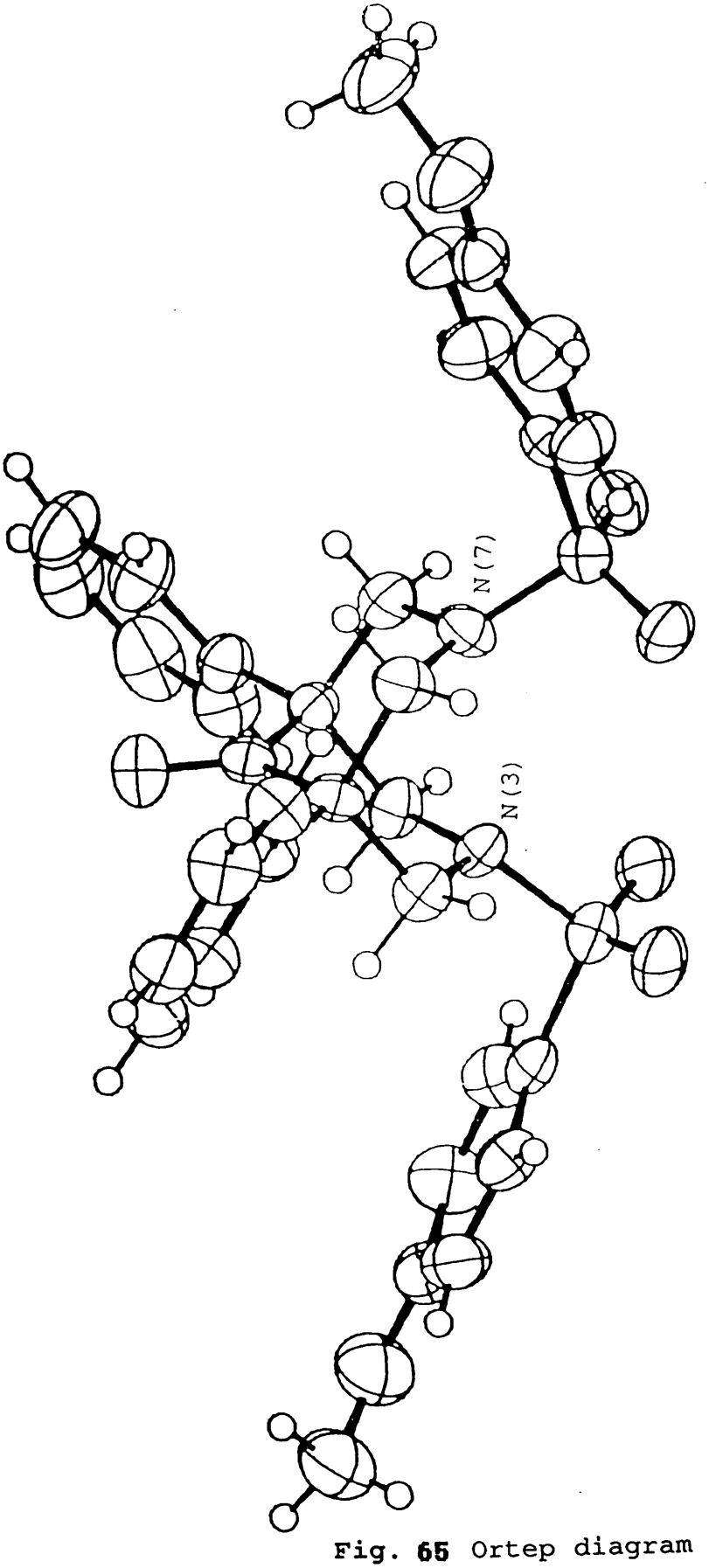


Fig. 65 Ortep diagram of (185)

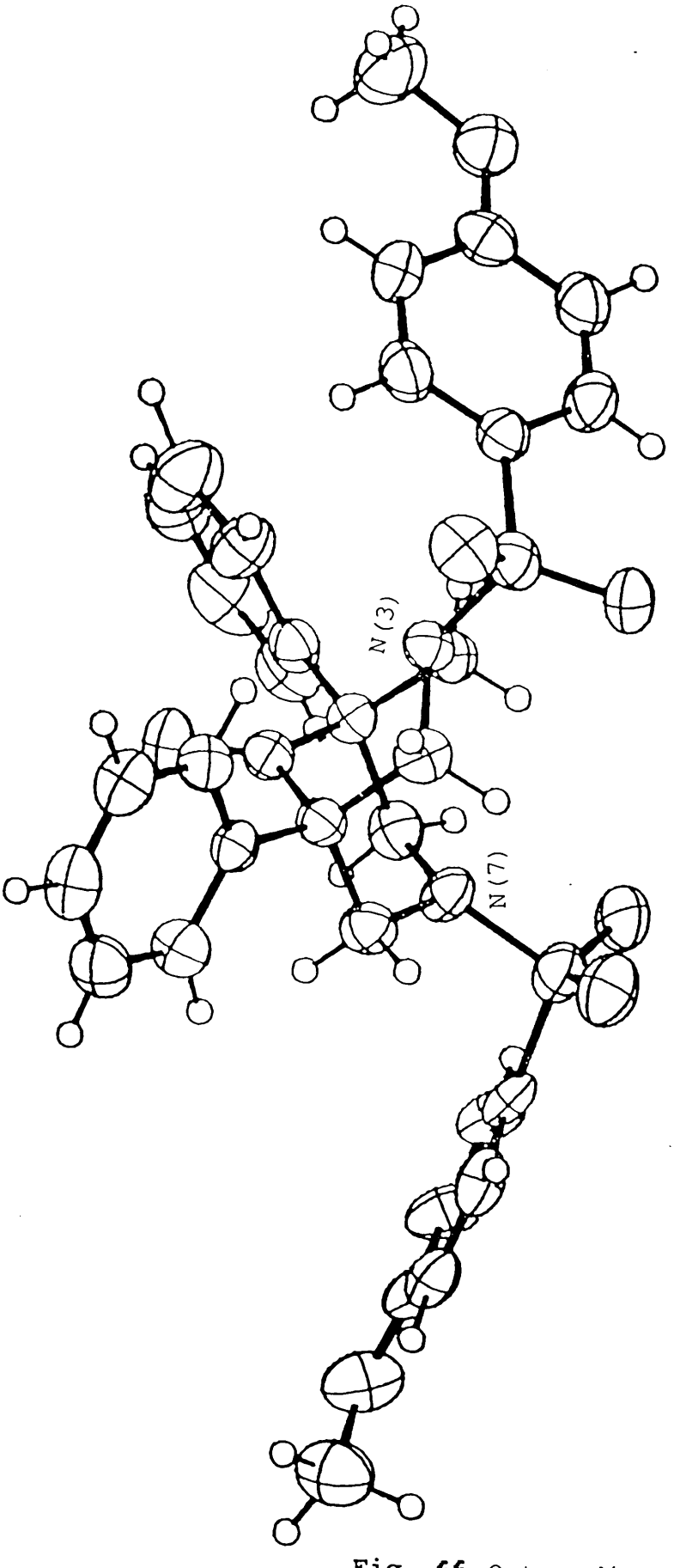


Fig. 66 Ortep diagram of (185)

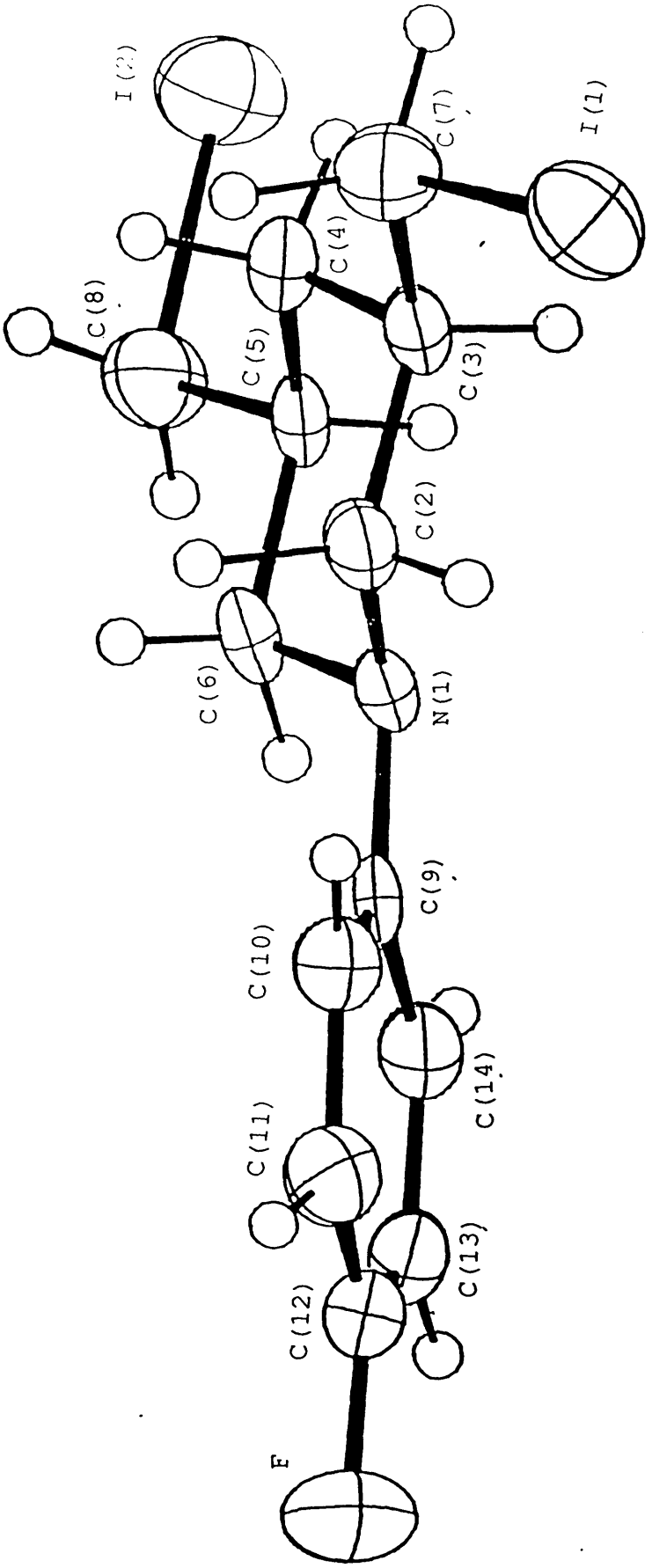
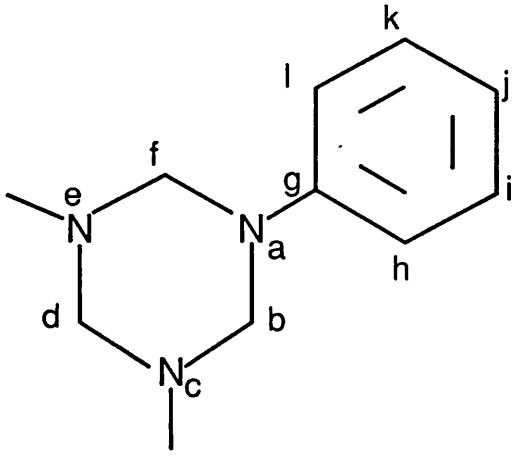


Fig. 67 Ortep diagram of (190)

Tables

Table 1 Conformational parameters for 1,3,5-trifluorophenyl 1,3,5-triazacyclohexanes (106), (107) and (108). a = axial e = equatorial

Compound		θ(°)	α(°)	β(°)
(106)	N(1) a	45.7	35.9	5.4
	N(3) a	44.1	33.7	5.6
	N(5) e	22.5	48.5	0.9
(107)	N(1) e	54.7	32.6	4.8
	N(3) a	64.3	36.7	2.1
	N(5) a	65.3	37.4	2.9
(108)	N(1) e	90.0	36.9	4.6
	N(3) a	61.3	37.4	2.2
	N(5) a	61.3	37.4	2.2



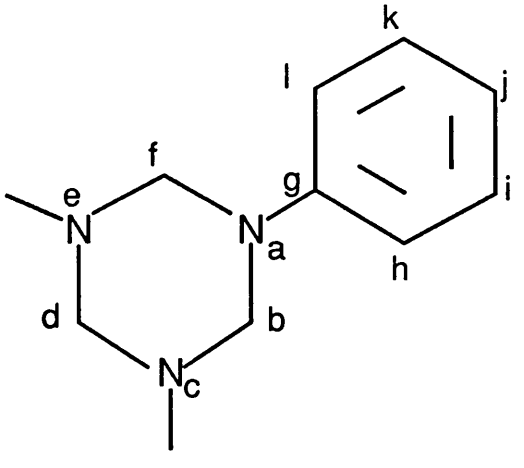
θ is angle between planes dagj and aghijkl

α is angle between bond a-g and fab

β is angle between bond a-g and ghijkl

Table 2 Conformational parameters for 1,3,5-trichlorophenyl 1,3,5-triazacyclohexanes (110) and (111). a = axial e = equatorial

Compound		θ(°)	α(°)	β(°)
(110)	N(1) a	44.2 (4)	35.3 (3)	4.1 (3)
	N(3) e	0.0	48.9 (3)	0.0
(111)	N(1) a	68.1 (6)	32.3 (5)	5.2 (5)
	N(3) e	90.0	35.5 (5)	6.5 (5)



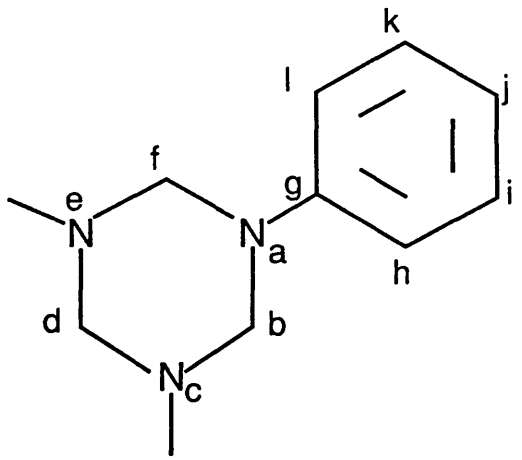
θ is angle between planes dagj and aghijkl

α is angle between bond a-g and fab

β is angle between bond a-g and ghijkl

Table 3 Conformational parameters for 1,3,5-trimethoxyphenyl 1,3,5-triazacyclohexanes (112) and (113). a = axial e = equatorial

Compound		θ(°)	α(°)	β(°)
(112)	N(1) a	38.4	30.8	5.3
	N(3) e	40.03 (4)	44.9 (3)	3.7 (3)
	N(5) a	32.8	35.5	6.0
(113)	N(1) a	63.6	35.0	6.5
	N(3) e	63.3 (3)	43.1 (2)	3.5 (3)
	N(5) a	62.4	39.5	1.4



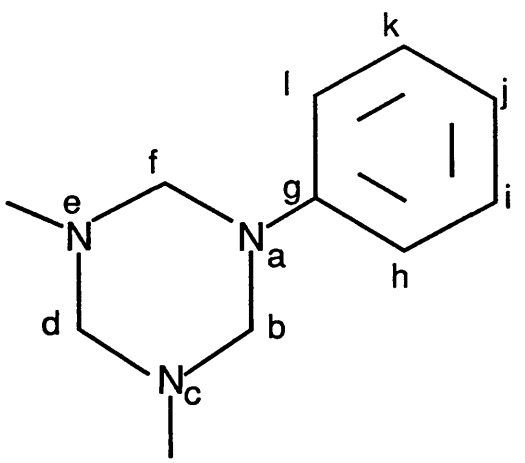
θ is angle between planes dagj and aghijkl

α is angle between bond a-g and fab

β is angle between bond a-g and ghijkl

Table 4 Conformational parameters for 1,3,5-tritolyl 1,3,5-triazacyclohexane (115).
a = axial e = equatorial

Compound		θ(°)	α(°)	β(°)
(115)	N(1) e	6	38.42	5.18
	N(3) e	19	39.68	6.16
	N(5) a	2	38.94	5.66



θ is angle between planes dagj and aghijkl

α is angle between bond a-g and fab

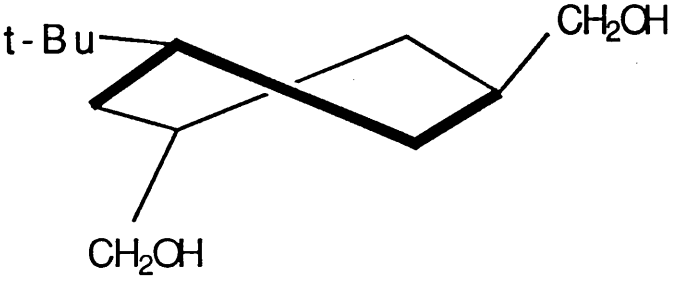
β is angle between bond a-g and ghijkl

Table 5

Torsional angles in twist-boat six-membered rings.

Column **A**:torsion angles measured by X-ray crystal structure analysis of 1,3,5-tri-4-nitrophenyl-1,3,5-triazacyclohexane (117).

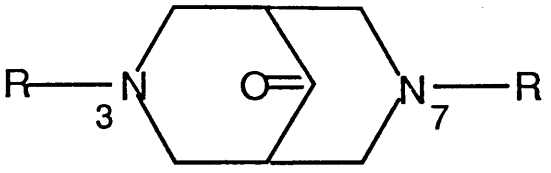
Column **B**:torsion angles for 1,3-dihydroxymethyl-5-t-butylcyclohexane as reported[145] from X-ray crystal structure analysis.



Column **C**:predicted angles for ideal twist-boat cyclohexane.

Bond	**A**	**B**	**C**
1-2	-25.3 (2)°	-20.2°	-31°
2-3	-41.3	-38.8	-31
3-4	70.3	62.2	65
4-5	-27.7	-22.6	-31
5-6	-35.8	-38.1	-31
6-1	66.0	61.1	65

Table 6



α is the angle between CH_2-N-CH_2 planes and N-S bond

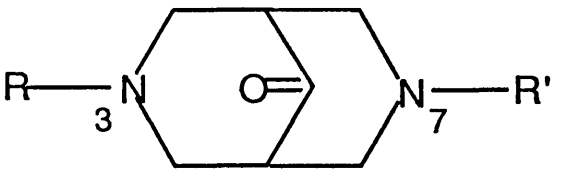
Chair ring

Compound	R	C-N-C angle ()°	(α)°	N-S bond Å
(182)	SO_2CH_3	114.7 116.9	30.8 30.3	1.635 1.628
(183)	$SO_2CH_2C_6H_5$	115.2	10.4	1.632
(184)	$SO_2C_6H_4$	117.8 115.1	23.5 17.2	1.615 1.608
(185)	$SO_2C_6H_4OMe$	Twin-chair 114.5 113.9 Boat-chair 114.4	25.1 37.0 24.4	1.618 1.649 1.638

Boat ring

(183)	$SO_2CH_2C_6H_5$	114.7	15.6	1.626
(185)	$SO_2C_6H_4OMe$	Boat-chair 112.3	45.6	1.665

Table 7



α is the angle between CH_2-N-CH_2 planes and N-S bond

Chair ring

Compound	R	$(\alpha)^o$	R'	$(\alpha)^o$
(146)	$SO_2C_6H_4CH_3$	24.9		
(147)	NO	1.2	NO	1.6
(169)	Me	50.6		
(171)	CH_2Ph	49.1		
(173)	COOEt	3.7	COOEt	6.3
(174)	$COCF_3$	4.2	$COCF_3$	8.5
(175)	COOEt	26.4	Me	49.6

Boat ring

(146)			$SO_2C_6H_4CH_3$	32.5
(169)			Me	54.5
(171)			CH_2Ph	47.7

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