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APPROACHES TO THE SYNTHESIS OF 3,5-BIS(5-METHINYLPYRROLIDIN-ONYL)PYRAZOLE

presented by

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has been accepted towards fulfillment of the requirements for

MS degree in CHEMISTRY

Eugene W. Hoff
Major professor

Date 22 July 1980

APPROACHES TO THE SYNTHESIS OF 3,5-BIS(5-METHINYLPYRROLIDIN-2-ONYL)PYRAZOLE

By

Alan Curtis Brown

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

MASTER OF SCIENCE

Department of Chemistry

1980

ABSTRACT

APPROACHES TO THE SYNTHESIS OF

3,5-BIS(5-METHINYLPYRROLIDIN-2-ONYL)PYRAZOLE

By

Alan Curtis Brown

The partial synthesis of 3,5-bis(5-methinylpyrrolidin-2-onyl)pyrazole, by the Stevens method[1] is described. Utilizing isoxazole technology, the bis-cycloaddition of the nitrile oxide derived from methyl 4-nitrobutyrate to 1,4-pentadiene gave 3,3'-bis[5-(2-carbomethoxyethyl)isoxazolinyl] methane. This was aromatized by N-bromosuccinimide (NBS) bromination and dehydrobromination to the 3,3'-bis-[5-(2-carbomethoxyethyl)isoxazoloyl]methane. The two isoxazole rings were hydrogenolysed to the bis-β-ketovinylogous amine - using Adam's catalyst (PtO_2) - which consequently ring closed to the bis-lactam by reaction of the amino groups with esters. The remaining β-diketones did not react with hydrazine to form the pyrazole ring of the target molecule.

[1]Stevens, R. V., Tetrahedron, 32, 1599 (1976).

To my wife, Regina, and my new daughter, Megan, without whose support this would not have been possible.

ACKNOWLEDGMENTS

I would like to thank the Department of Chemistry for providing me with financial support. I would also like to express my gratitude to Dr, Eugene LeGoff for his guidance and his group for making my stay at MSU enjoyable.

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INTRODUCTION

Although intense interest in porphyrins has resulted in an abundance of scientific literature,[1] very few expanded porphyrins (platyrins) have been synthesized.[2] The synthesis and study of the platyrin in Figure 1. would be a unique model.

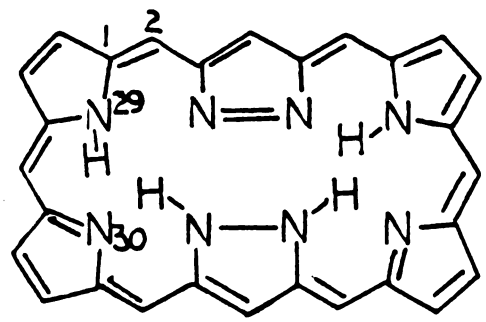


Figure 1. Proposed platyrin

This platyrin should be of interest because of its ability to complex one or two metal atoms. There are potentially interesting electron tranfer and catalytic properties in the use of this molecule. The synthesis of the proposed compound by conventional porphyrin techniques was unsuccessful,[3] and an alternative synthesis was envisioned using the Stevens method.[4]

The object of this project was to construct an intermediate molecule which could be transformed into a bispyrrole and eventually cyclized into the proposed molecule

by the LeGoff-Cheng method.[5]

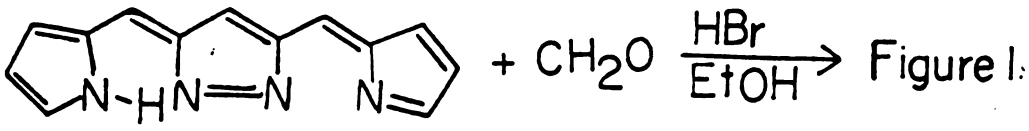
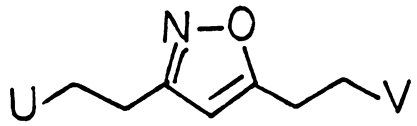


Figure 2. LeGoff-Cheng method

The strategy of the Stevens method involves the manipulation of the isoxazole moiety. The isoxazole has been useful in functional group interchange[6] and the synthesis of β-furanones[7] and porphyrins.[8] The general chemical scheme involves the placement of reactive functionalities on either side of the 3 and 5 positions on the isoxazole, as in 1.



1

These functions are typically esters or ketones. When the isoxazole ring is hydrogenolysed, the β-functionality formed can be used in the formation of the pyrrole rings.

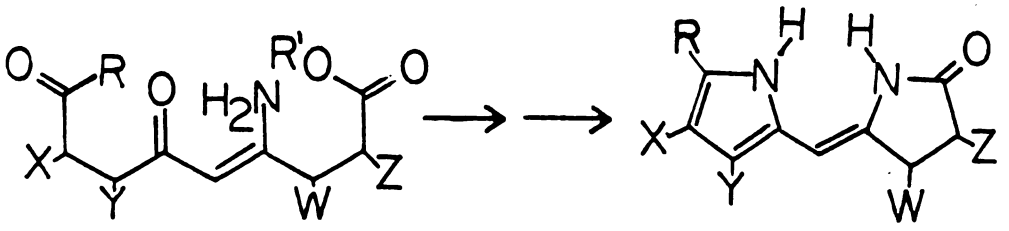
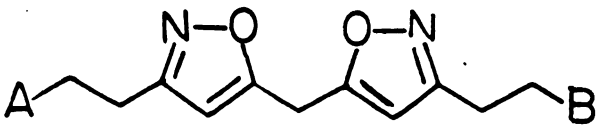


Figure 3. Stevens method

The scheme necessary to synthesize one half of the platyrin would require the use of two isoxazole moieties α to each other as in compound 2.



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The isoxazole ring is most easily made by the cycloaddition of nitrile oxides to alkynes.[9] Thus, the synthesis of compound 4 would necessitate the bis-cycloaddition of an aliphatic nitrile oxide to 1,4-pentadiyne or possibly a 3-substituted 1,4-pentadiyne. This procedure has been done with stabilized nitrile oxides,[10] however, it has been found that most aliphatic nitrile oxides tend to dimerize instead of forming the bis-adduct. A convenient solution to the problem lies in the ability of olefins to react 10^2-10^3 times faster with nitrile oxides. Subsequent dehydrogenation[11] of the resulting isoxazolines should give the desired isoxazoles.

The hydrogenolysis of the isoxazole ring system has been accomplished by a variety of methods.[12] The cleavage of the bis-adduct yields a masked β-tetraketone as an intermediate.

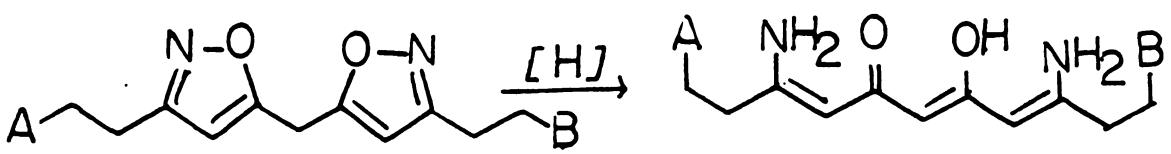
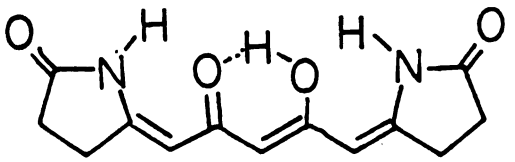


Figure 4. Hydrogenolysis of the bis-isoxazole

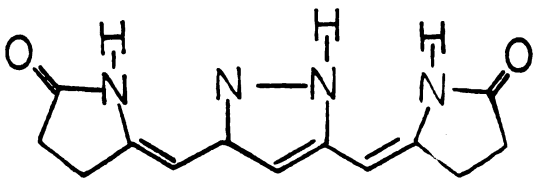
Although not utilized previously in the Stevens type synthesis, these masked β-tetraketones, after acid hydrolysis, form various phenols[13] via aldol condensations. Left

unhydrolysed, if A and B are esters, then the bis-vinylogous lactam 3 will form.



3

The reaction of the above compound with hydrazine forms pyrazole 4, the target compound of this project.



4

Figure 5. Target molecule: 3,5-bis(5-methinyl-pyrrolidin-2-onyl)pyrazole

DISCUSSION AND RESULTS

The first step in the synthesis of the target molecule 4 was a cycloaddition. As mentioned previously, the cycloaddition of aliphatic nitrile oxides to alkynes is not as favorable as nitrile oxide dimerization. Several attempts to add the necessary nitrile oxide derived from methyl 4-nitrobutyrate to both 1,4-pentadiyne and 3-acetoxy-1,4-pentadiyne resulted in 5-10% of the adduct and 70-80% of the nitrile oxide dimer. Yields were estimated by PMR comparison of the aromatic proton to those of the ester.

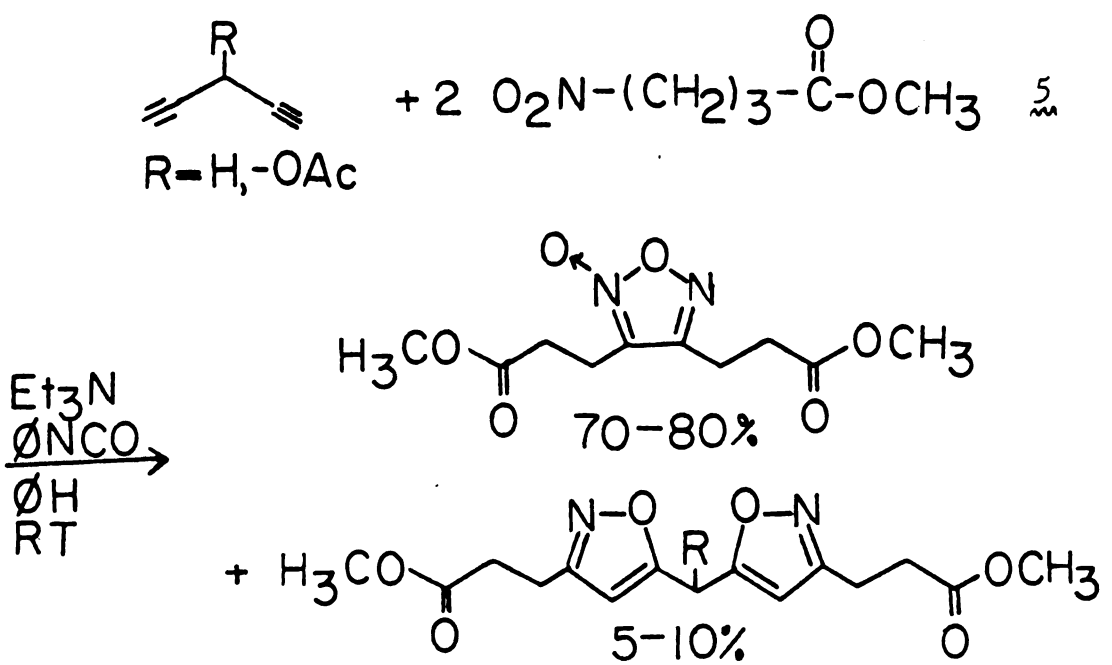
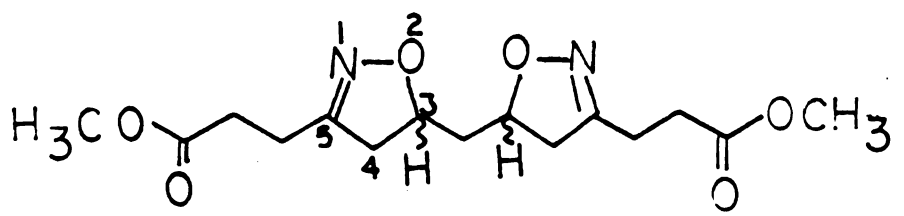


Figure 6. The attempted cycloaddition to the 1,4-pentadiynes

We found that substitution of 1,4-pentadiene for the diyne overcame the low yields of the adduct and the difficulty in the synthesis of the diynes. The cycloaddition of two equivalents of the nitrile oxide to the diene yielded 55-60% of a stable white solid that had the correct parent ion in the mass spectrum. Since there is the possibility of threo and erythro isomers in the 3 positions of both rings, it is reasonable that the melting point was a rather broad 96-9° . The splitting in the bridging methylene, 3 and 4 position protons was indicative of diastereomers, but separation and characterization of these isomers was not investigated.



6

The aromatization of compound 6 was attempted using several recent techniques. Heterogeneous dehydrogenation with both MnO_2[14] and NiO_2[15] proved fruitless. Although small amounts of the mono- and bis-aromatic were isolated, the majority of the 6 was found to be complexed to the metals. Under these conditions, the reaction did not proceed. Although 2,3 dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has been shown to dehydrogenate 3-methyl-5-propyl isoxazoline in good yields[16] in both benzene and dioxane, no yields greater than 2% (estimated by PMR) resulted when starting with

compound 6. Bromination and dehydrobromination using NBS and triethylamine was successful in moderate yields of 40-50%.

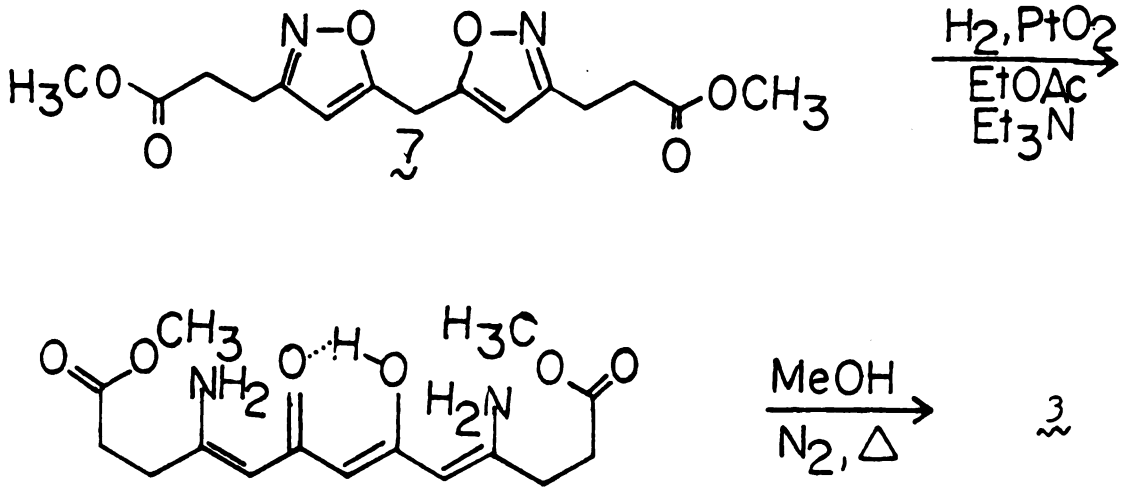
The bromine atom can be attached at the 3 or 4 positions on each ring[17] of compound 6 and therefore, the thin layer chromatogram (TLC) of the dibrominated material was quite complex. Dehydrobromination with the mild base triethylamine, seemed to give the best results. When 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), a stronger base, was used a more complex mixture was produced and led to appreciably lower yields. The product mixture was separated by Still's[18] flash chromatography technique to one spot.

Although the off-white solid gave a good parent ion and degradation pattern in the mass spectrum, the melting point was broad and the PMR had an extraneous absorption at δ = 3.70. The material showed a single spot on the TLC and the decision was made to continue the synthesis with this material.

The hydrogenolysis of the bis-aromatic 7 was best accomplished by Adam's catalyst in 2% triethylamine:ethylacetate. The oily solid that resulted was not characterized extensively except for PMR and mass spectral data. The compound was not stable to air due to spontaneous cyclization to the amide. It was immediately placed into methanol with a catalytic amount of base (triethylamine) and refluxed under nitrogen until the bis-cyclization was complete.

Upon cooling the yellow methanolic solution, a

precipitate of fine yellow solid was obtained. Crystallization from methanol gave a 35% yield of 8 with a melting point of 179-80° . In accordance with it's structure, a parent ion of mass 262 was obtained in the mass spectrum. The PMR exhibited two multiplets centered about δ = 2.52 and



δ = 2.90 which would account for the protons on the lactam ring. The β-diketone exhibited keto-enol tautomerization as seen by a singlet at δ = 3.52 for the keto and two singlets at δ = 5.04 and δ = 5.20 for the E and Z vinyl enol protons. The enol -OH exhibited an absorption as a broad singlet at δ = 9.97. The amide N-H was further downfield at δ = 10.7 as a broad singlet. The infrared spectrum (IR) showed the N-H stretch at 3225 cm^{-1} superimposed on a broad absorption from 2200 cm^{-1} to 3500 cm^{-1}. The ketones and lactam carbonyls exhibited absorptions at 1720 and 1630 cm^{-1} respectively. The yellow-gold solid was sparingly soluble in most organic solvents and exhibited a rather large tailing spot on the TLC (R_f = 0.75) when eluted on a silica gel plate

with 1:1 ethylacetate/hexane.

The reaction of hydrazine with the β-ketones of compound 3 failed. Varied reaction conditions were attempted; slightly alkaline to slightly acidic, several solvents and different temperatures. The products obtained were usually viscous hygroscopic oils which were complex mixtures. The mass spectrum of these showed minor amounts of mass 258 for the product, but mainly consisted of starting material and various other components which were not explicable. The reason for the lack of reaction and side products is probably the abstraction of a proton to form the stabilized enolate. This could further react as a nucleophile or just be very sluggish in its reaction with the hydrazine. The replacement of the acidic hydrogen with an alkyl group to form the enol ether would probably be the answer, but in this project it was not investigated.

EXPERIMENTAL

GENERAL PROCEDURE

The melting points were determined on a Thomas Hoover Uni-melt melting point apparatus and are uncorrected.

The infrared spectra were recorded on a Perkin-Elmer Model 237B or 137 spectrometer. The PMR spectra were obtained on a Varian T-60 or a Bruker 180 or 250 spectrometers with chemical shifts reported in δ (ppm) measured from tetramethylsilane as the internal standard. The ^{13}CMR were obtained on a Varian CFT-20 spectrometer with chemical shifts reported in δ (ppm) from $CDCl_3$ as the internal standard. The UV and visible spectra were recorded on a Unicam SP-800 spectrometer using 1cm quartz cells. A Finnigan 4000 mass spectrometer was used to obtain mass spectra.

1,4-pentadiyne

The literature procedure was followed[18] except the material was not distilled due to its instability at higher temperatures. The purity was estimated by PMR and used in the cycloaddition.

3-hyroxy-1,4-pentadiyne

The literature[19] procedure was followed except that the product was not distilled. The crude oil isolated was multiply extracted with boiling petroleum ether (BP 35-60°) and a white solid was collected upon cooling. Yields were

typically 20-25%, melting point 51-2° .

3-acetoxy-1,4-pentadiyne

Again the literature procedure was followed[20] and the yields were typically 85-90% without distillation and 45-50% with distillation.

Cycloaddition of the nitrile oxide to the above diynes

Typical procedure: In 50 ml dry benzene was placed 14 mmol of the diyne, 29 mmol (4.26 g) methyl 4-nitrobutyrate, 60 mmol (6.5 ml) phenyl isocyanate and 0.25 ml triethylamine. The solution becomes heterogeneous after about 40 minutes and gradually becomes thicker as the reaction proceeds. After stirring for a total of 15-17 hours at room temperature, the solid was collected by filtration and washed with fresh benzene. The solvents were removed in vacuo, leaving a viscous dark brown oil (5.5-6.0 g) which could not be purified. By PMR analysis, yields of isoxazole (mono- and bis-adduct combined) were estimated at 5-10% while the dimer of the nitrile oxide made up 70-80% of the product. This was done by comparison of the aromatic proton at δ = 5.95 to the methyl ester protons at δ = 3.65.

Methyl 4-nitrobutyrate (5)

In a 1000 ml three necked flask fitted with a condenser, Teflon stirrer and addition funnel with pressure equalization sidearm with a nitrogen bleed was placed 500 ml (9.32 mol) nitromethane and 25 ml triethylamine. The solution was heated to 90° and 130 ml (1.44 mol) of methyl acrylate was

added over a one hour period at reflux. The dark mixture was refluxed for 24 hours and cooled. Instead of the usual extractive work up, the mixture was stripped of nitromethane in vacuo and the residue distilled under vacuum through a 5" Vigreaux column. The boiling point was 84-85° at 1 mm. A yield of 55-65 g or 27-31% was obtained: IR (neat): 2950, 1745, 1550, 1460 and 1340 cm^{-1}; PMR ($CDCl_3$): δ 1.58 (d, impurity), 2.0-2.61 (m, 4H, MeC-$C\underline{H}_2$-$C\underline{H}_2$), 3.61 (s, 3H, -$OC\underline{H}_3$), 4.38 (t, 2H, -$C\underline{H}_2NO_2$); mass spectrum: m/e 147 (parent); n_D^{20}: 1.4532.

3,3'bis-[5-(2-carbomethoxyethyl) isoxazolinyl]methane (6)

In a 250 ml three necked round bottom flask fitted with a Teflon stirrer, an addition funnel with a pressure equalization sidearm, a condenser and a nitrogen bleed was placed 10 ml (97 mmol) 1,4-pentadiene, 100 ml dry CCl_4, 10 ml (72 mmol) triethylamine and 44 ml (0.194 mol) phenylisocyanate at 0° . To the stirred solution was added dropwise 28.5 g (0.194 mol) of methyl 4-nitrobutyrate in 60 ml dry CCl_4 over a 5-7 hour period, maintaining the temperature at 0-5° . The thick mixture was stirred an additional 18-20 hours, then cooled to 0°, filtered and the solid washed with 25 ml dry CCl_4. The brown liquors were placed back into the flask with 24 ml (0.220 mol) phenylisocyanate and 8.0 g (55 mmol) more nitro ester in 15 ml CCl_4 was added over a 1-2 hour period at 0° . After stirring overnight again, the mixture was cooled and filtered. The solid cakes were combined and

dried. The solid was slurried in 150 ml CH_2Cl_2 and filtered to separate the product from the sym-diphenylurea. The liquors were stripped to dryness, crushed to a fine powder and slurried in 150 ml isopropanol to remove the last traces of the urea. The solid was filtered and dried. A yield of 20.6 g or 65% was obtained. Recrystallization from CCl_4 gave 18.9 g of a white solid: melting point 96-99° (s.95°); PMR ($CDCl_3$): δ 1.80 (overlapping t, 2H, $-C\underline{H}_2-$), 2.29-3.21 (m, 4H, 4 position), 2.59 (bs, 8H, $-C\underline{H}_2-C\underline{H}_2-$), 3.60 (s, 6H, $-OC\underline{H}_3$), 4.33-4.82 (overlapping q, 2H, 3 position); IR (nujol): 2870, 1740, 1560 and 1200 cm^{-1}; mass spectrum: m/e 326 (parent).

3,3'bis-[5-(2-carbomethoxyethyl) isoxazoyl]methane (7)

In a dry 250 ml three necked flask fitted with a thermometer, a reflux condenser and a serum cap was placed 125 ml dry CCl_4, 2.0 g (6.1 mmol) compound 6, 4.4 g (24.6 mmol) NBS (recrystallized from H_2O) and 0.10 g (catalytic) benzoyl peroxide. The mixture was refluxed with a subsurface nitrogen bleed for 1.25-1.50 hours until the starting material (R_f = 0.34) and monobrominated material (R_f = 0.42) were gone. The TLC silica gel plate was developed with 3:2 ethylacetate/hexane. The reddish mixture was cooled to 20° and the succinimide was filtered off. The CCl_4 liquors were washed with dilute bisulfite, then with $NaHCO_3$, and dried with $MgSO_4$. After removal of the solvent in vacuo, approximately 3.0 g of a red oil was obtained with a TLC containing

4-5 spots with R_f values greater than 0.5. The oil was placed in 25 ml dry THF and 10 ml Et_3N and then refluxed for 24 hours under nitrogen. After cooling to 20°, the brown solid was filtered and washed with fresh THF. A black oily solid (2.5 g) was obtained after removal of the solvent. The TLC showed two spots; R_f = 0.49 (product) and R_f = 0.53 (impurity). After removing the color on an alumina column eluting with ethyl acetate, these were separated on a 5 cm Still's flash chromatography column.[21] This yielded 0.9 g (45.6%) of an off-white solid: melting point 78-81°; PMR ($CDCl_3$): δ 2.47-3.15 (m, 8H, $-C\underline{H}_2-C\underline{H}_2-$), 3.60 (s, 6H, $-OC\underline{H}_3$), 3.70 (s, impurity), 4.10 (s, 2H, $-C\underline{H}_2-$), 5.92 (s, 2H, isoxazole); IR (nujol): 3120, 2950, 1730, 1607, 1180 cm^{-1}; mass spectrum: m/e 322 (parent); UV: 245, 273μm.

β-keto bis-vinylogous lactam (3)

In a 250 ml Paar flask was placed 100 ml dry ethylacetate, 1.3 g (4 mmol) compound 7, 2 ml Et_3N and 0.13 g (catalytic) PtO_2 (Adam's catalyst). The light yellow mixture was hydrogenated at 45 psi for 5-7 hours at room temperature. The light green solution showed one spot by TLC (same solvent system as for compound 7) at R_f = 0.1. After filtration and removal of the solvent, a PMR and a mass spectrum were taken; PMR ($CDCl_3$): δ 2.47 (t, 8H, $-C\underline{H}_2-C\underline{H}_2-$), 3.16 (s, 2H, $C-C\underline{H}_2CO$), 3.60 (s, 6H, $-OC\underline{H}_3$), 4.95 (s, 2H, vinyl), 6.40 (vbs, 2H, $N\underline{H}_2$), 9.55 (vbs, 2H, enol -OH); mass spectrum: m/e 326 (parent).

The above yellow-green oil was dissolved in 25 ml methanol containing 1 ml Et_3N and refluxed under nitrogen until cyclization was complete (usually 4-5 hours). Upon cooling a yellow solid precipitated out and was filtered off. The solid was recrystalized from methanol and cooled slowly to yield 0.37 g (35% yield based on bis-isoxazole) of bright yellow-gold needles: melting point 178-9°(dec 184°); IR (nujol): 3225, 1720, 1630, 1300, 1165 and 1125 cm^{-1}; PMR ($CDCl_3$): δ 2.48-2.54 (m,4H,-$C\underline{H}_2CH_2CO$), 2.86-2.93 (m, 4H, -$CH_2C\underline{H}_2CO$), 3.52 (s,1H, keto), 5.04 (s, 0.3H, enol), 5.20 (s, 0.2H, enol), 5.56 (s, 2H, vinylogous amide), 9.97 (broad s, 0.5H, enol -OH), 10.7 (broad s, 2H, -N$\underline{H}$); mass spectrum: m/e 262 (parent); UV: 297, 362, 392 and 402 μm.

Attempts to synthesis target molecule (4)

Compound (3) 0.02 mmol was dissolved in MeOH or THF and 0.02 mmol of a hydrazine salt (sulfate or dihydrochloride) with enough base (Et_3N, K_2CO_3 or $KHCO_3$) to neutralize the amine salt added. The mixture was heated to reflux for 1-12 hours and cooled.The solids were removed by filtration and the solvents removed in vacuo. A dark brown viscous oil remained. The mass spectrum showed little or none of m/e 258 (parent) but mostly starting material and other ions not matching the hydrazone or identifiable products. The TLC (same system as above) showed many spots which could not be separated by chromatography.

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APPENDIX

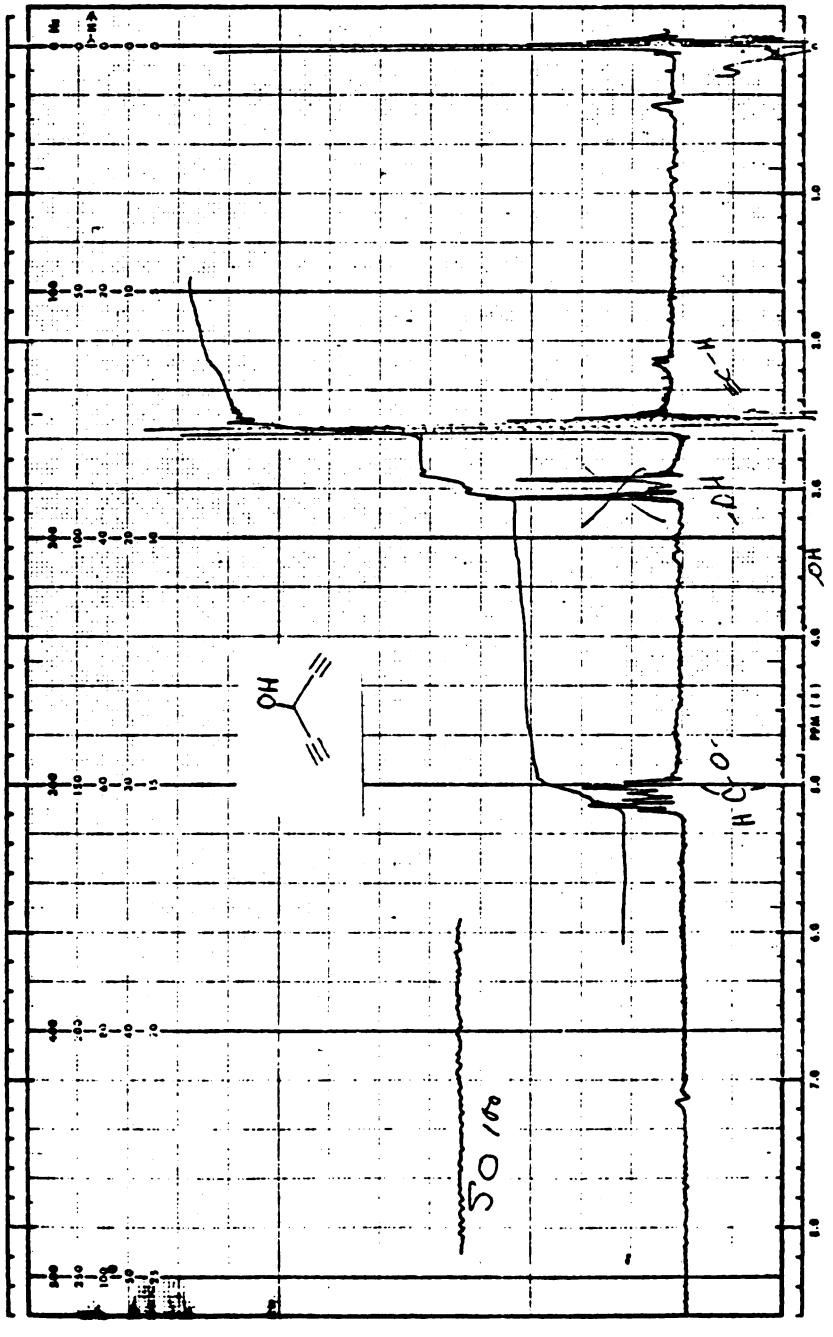

Figure 7. PMR of 3-hydroxy-1,4-pentadiyne

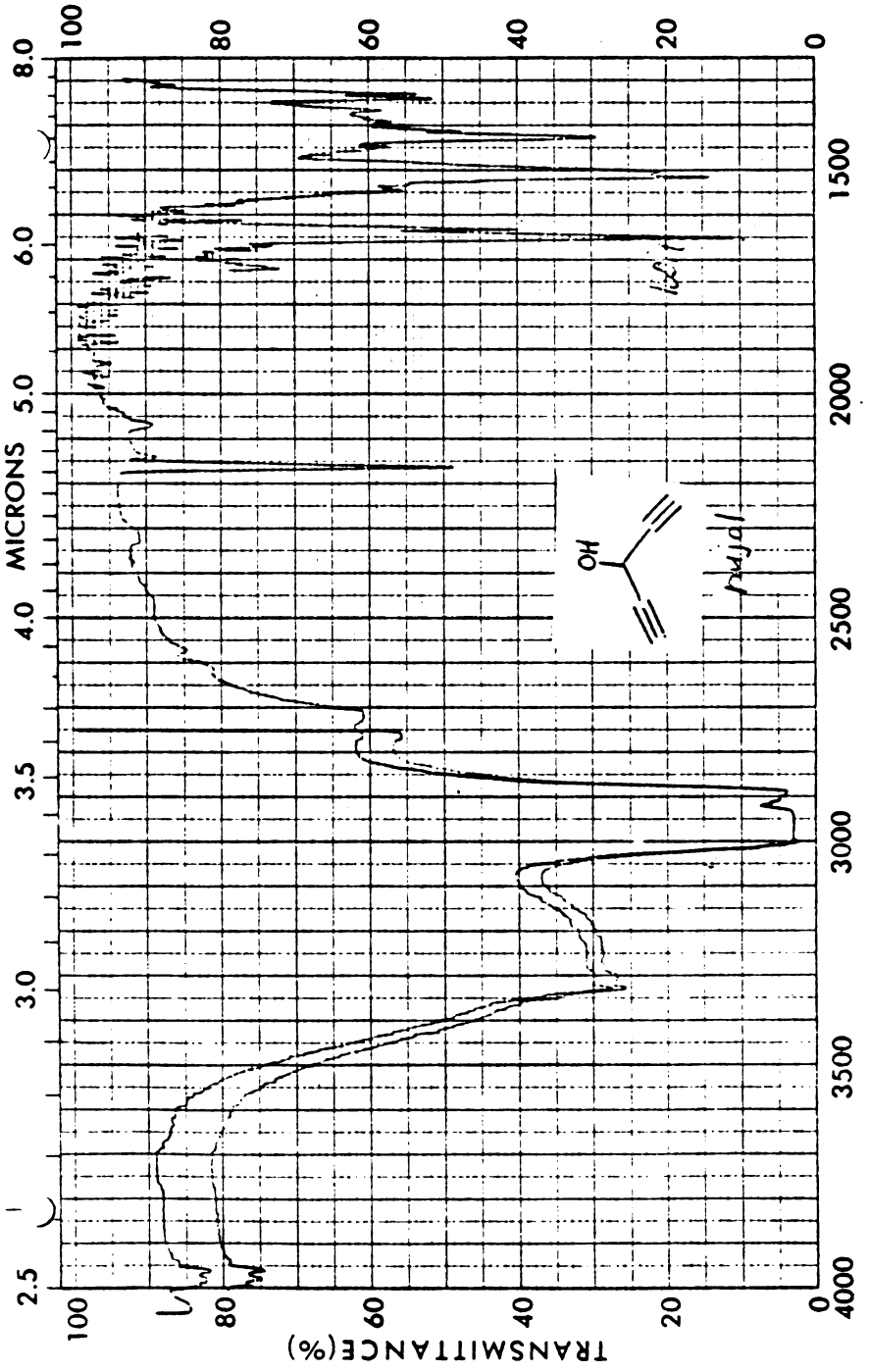

Figure 8. IR (4000-1250 cm^{-1}) of 3-hydroxy-1,4-pentadiyne

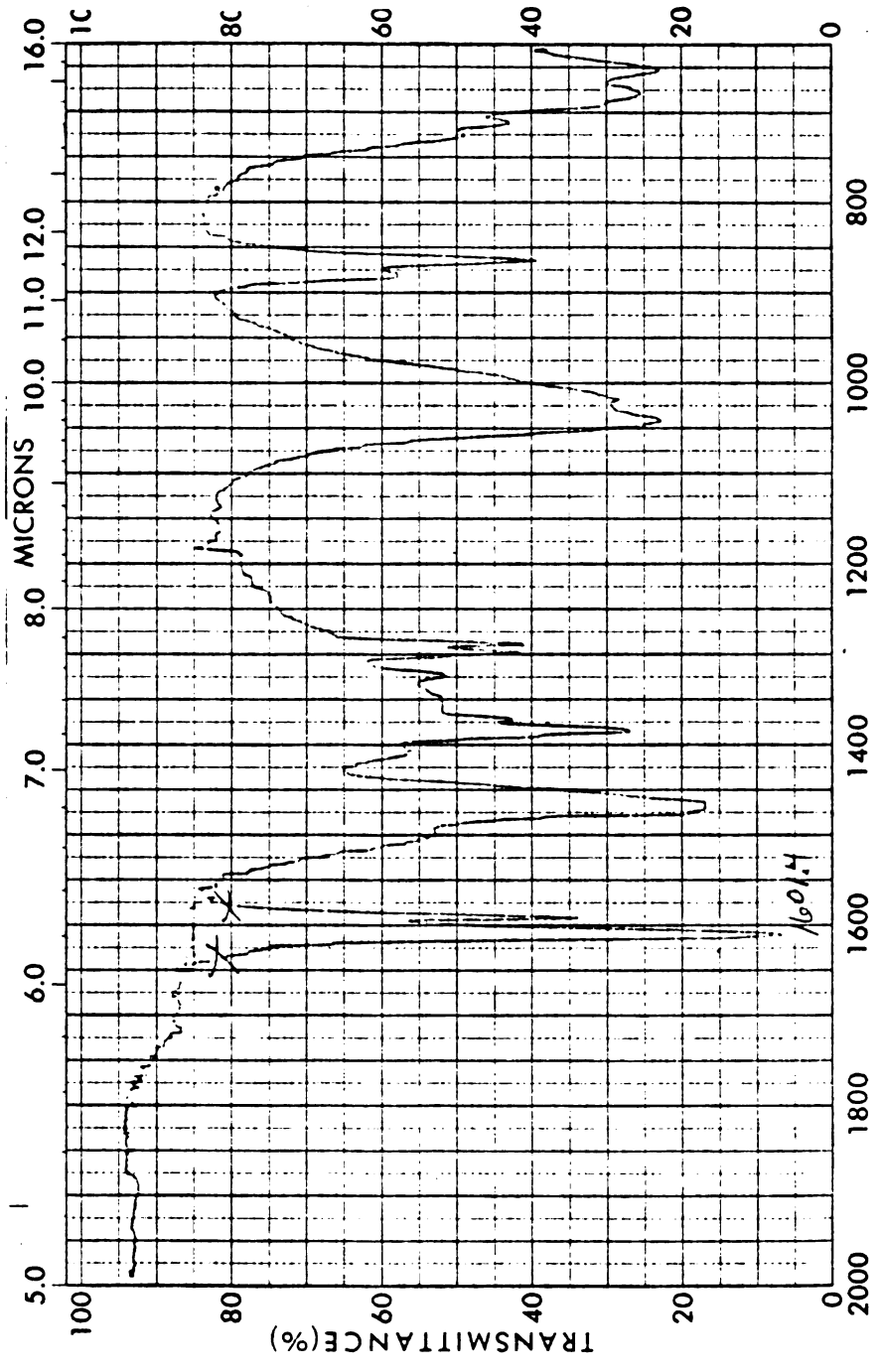

Figure 9. IR (1250-650 cm^{-1}) of 3-hydroxy-1,4-pentadiyne

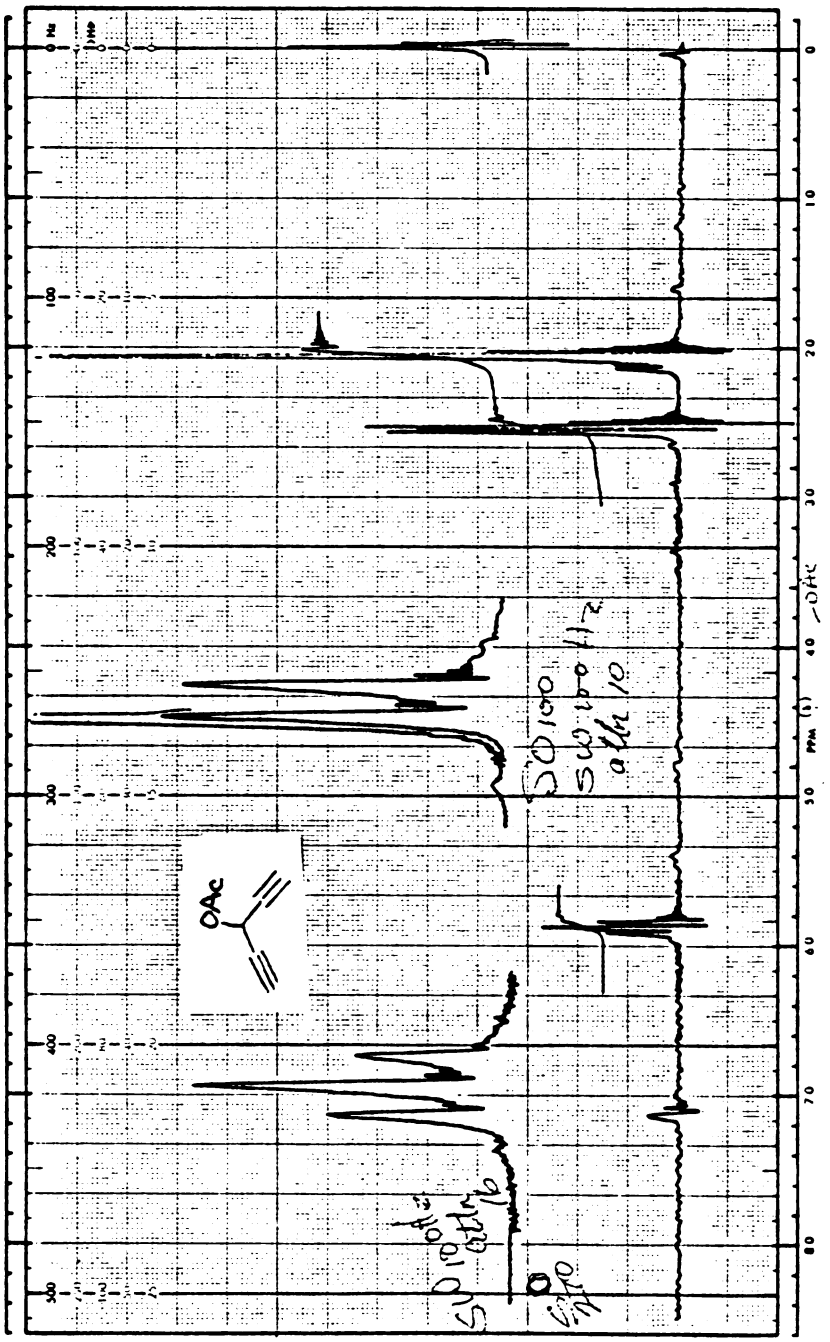

Figure 10. PMR of 3-acetoxy-1,4-pentadiyne

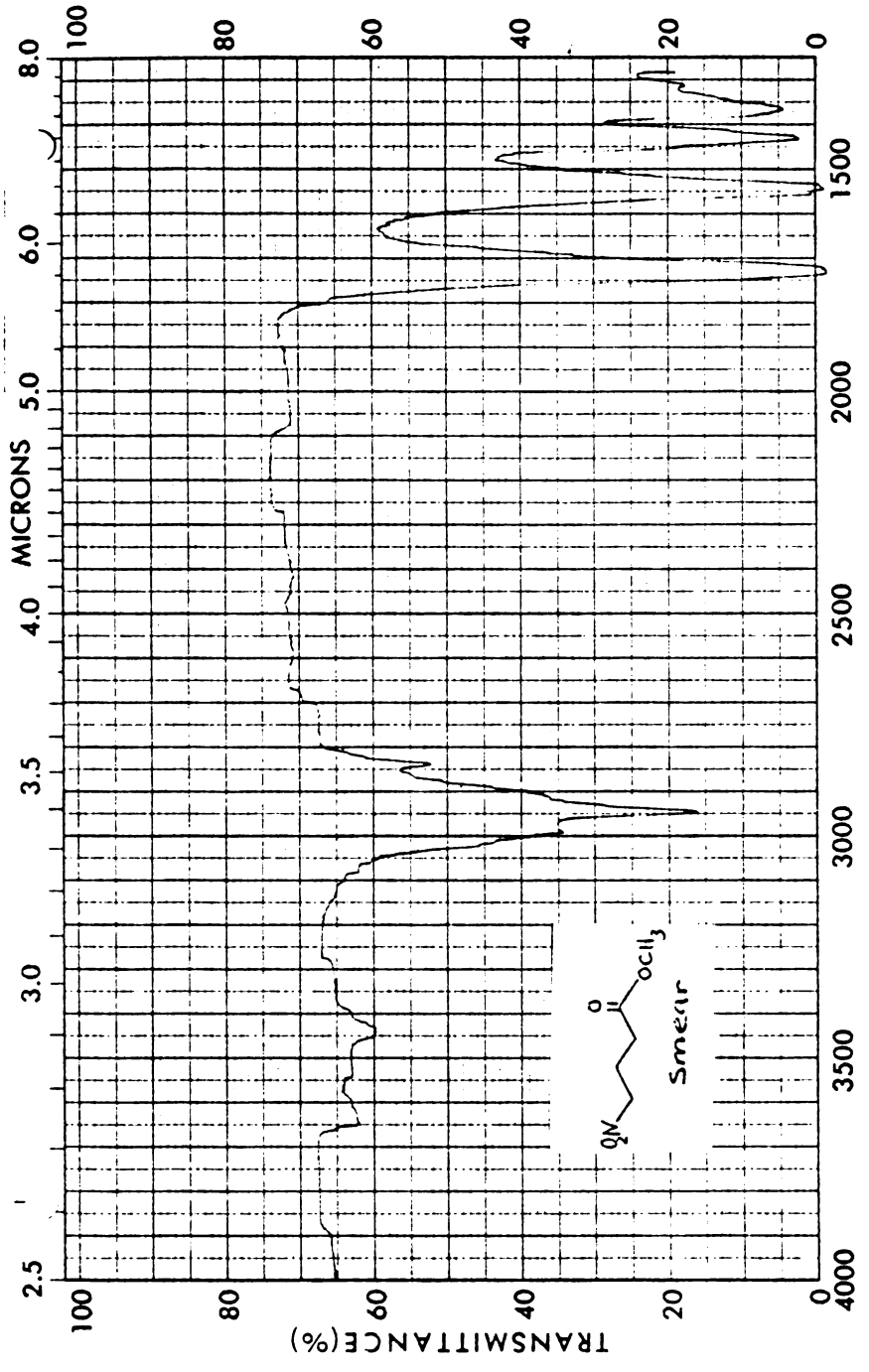

Figure 11. IR (4000-1250 cm^{-1}) of methyl 4-nitrobutyrate

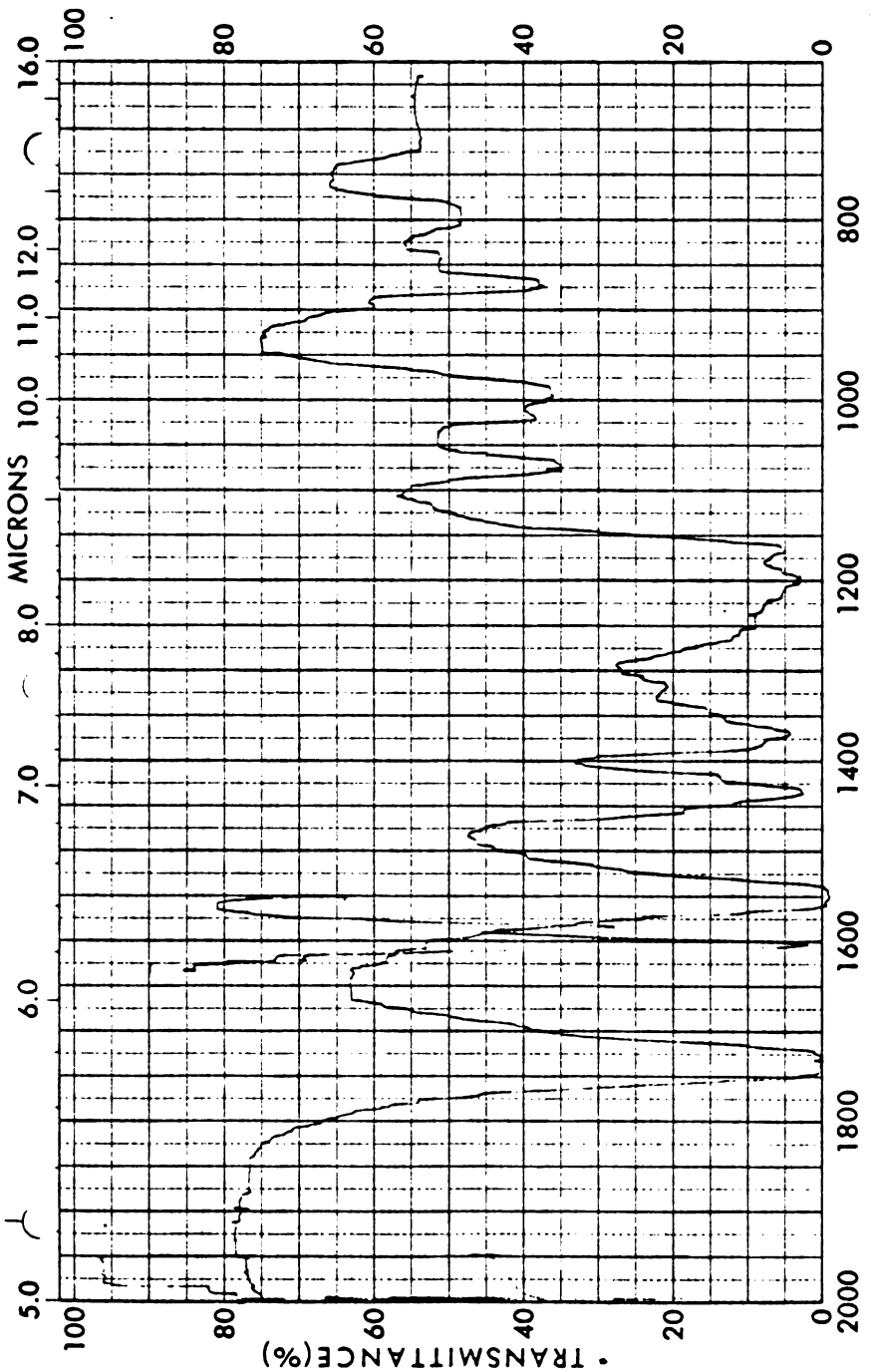

Figure 12. IR (1250-650 cm^{-1}) of methyl 4-nitrobutyrate

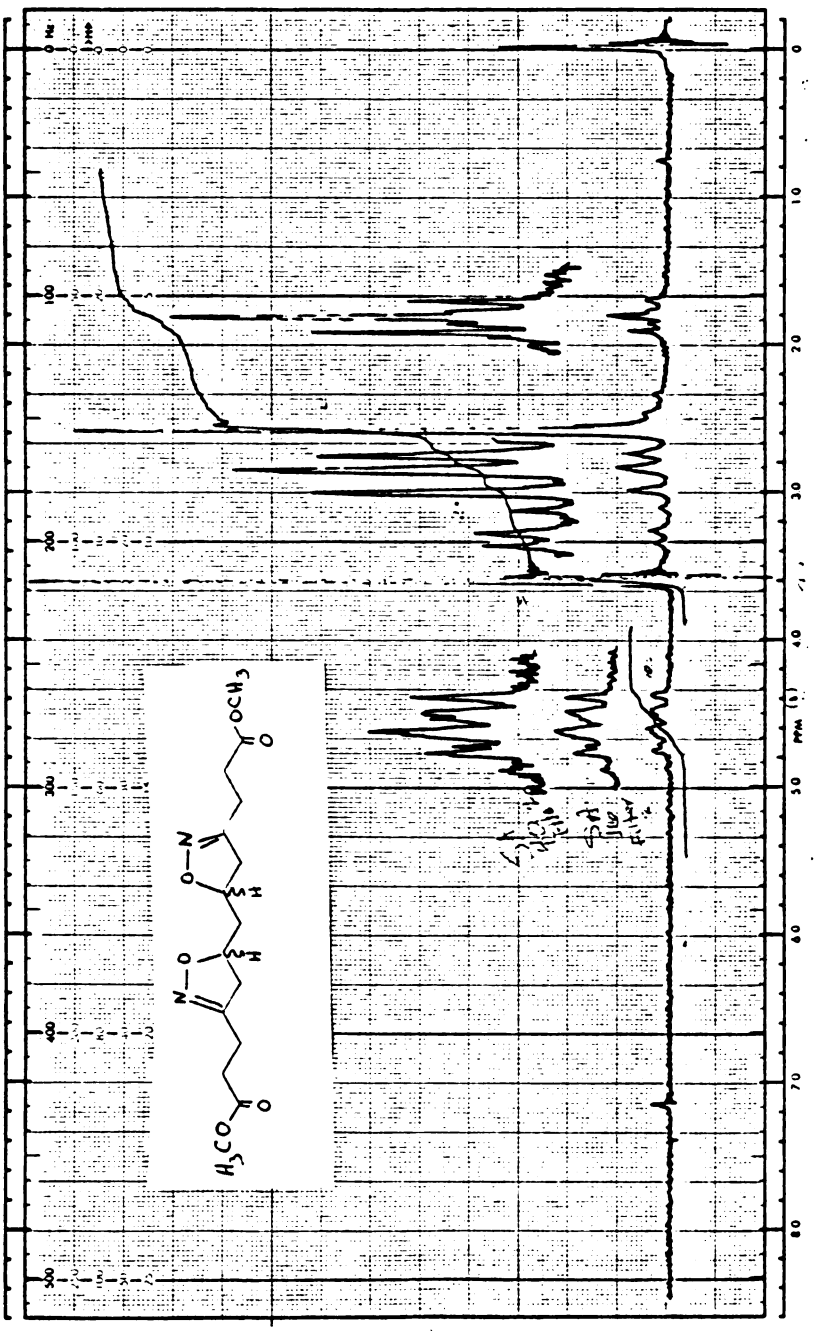

Figure 13. PMR (60 MHz) of bis-isoxazoline (6)

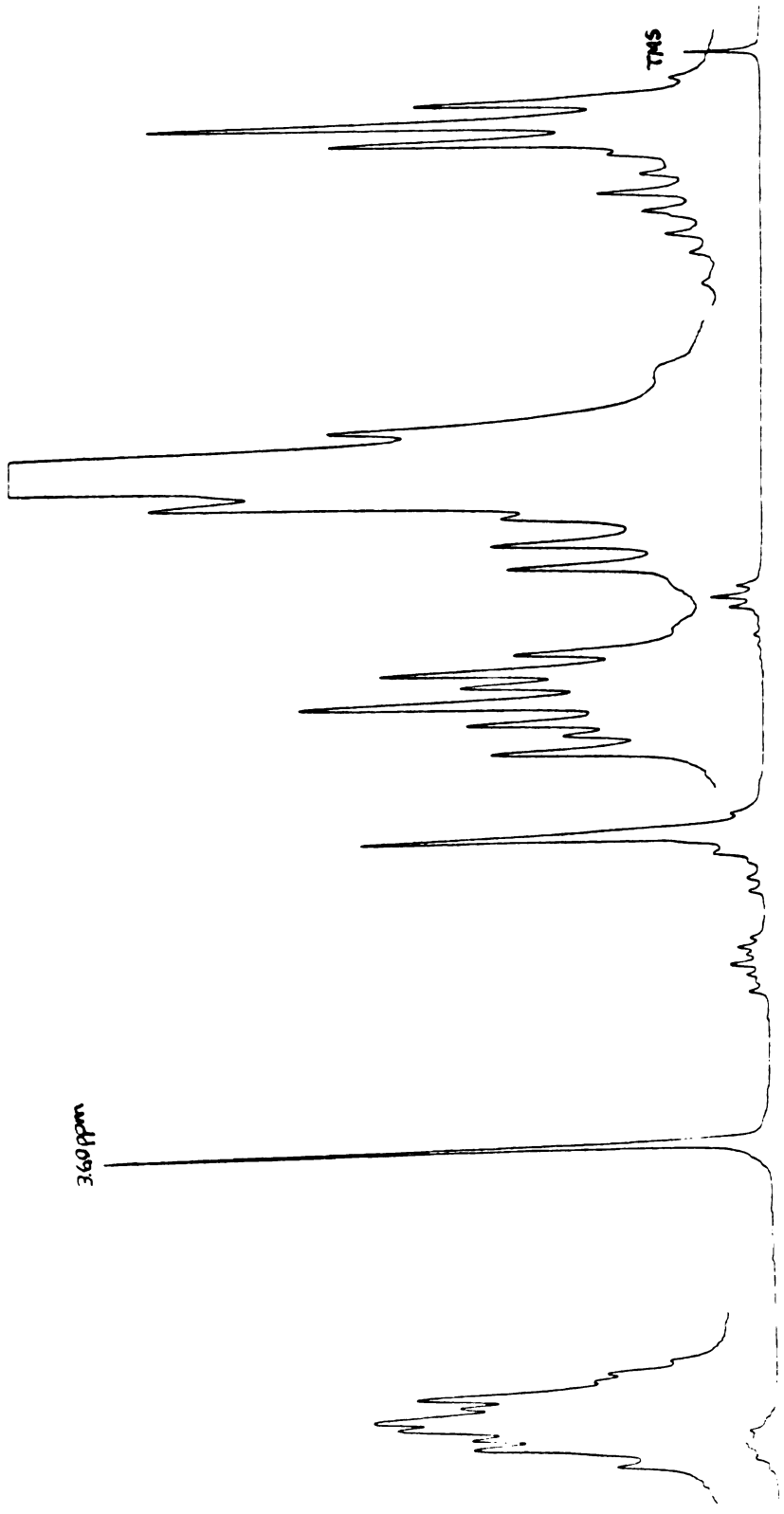

Figure 14. PMR (250 MHz) of bis-isoxazoline (6)

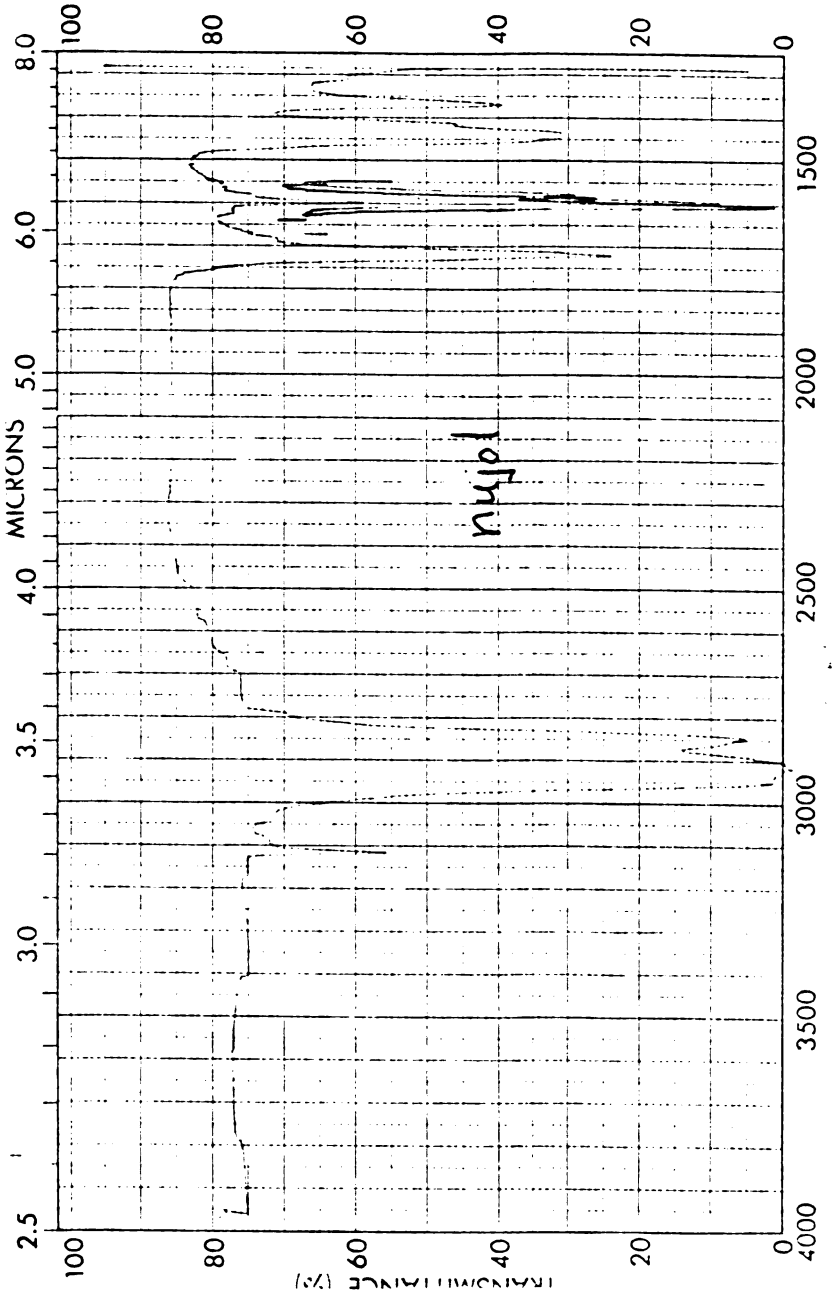

Figure 15. IR (4000-1250 cm^{-1}) of bis-isoxazole (7)

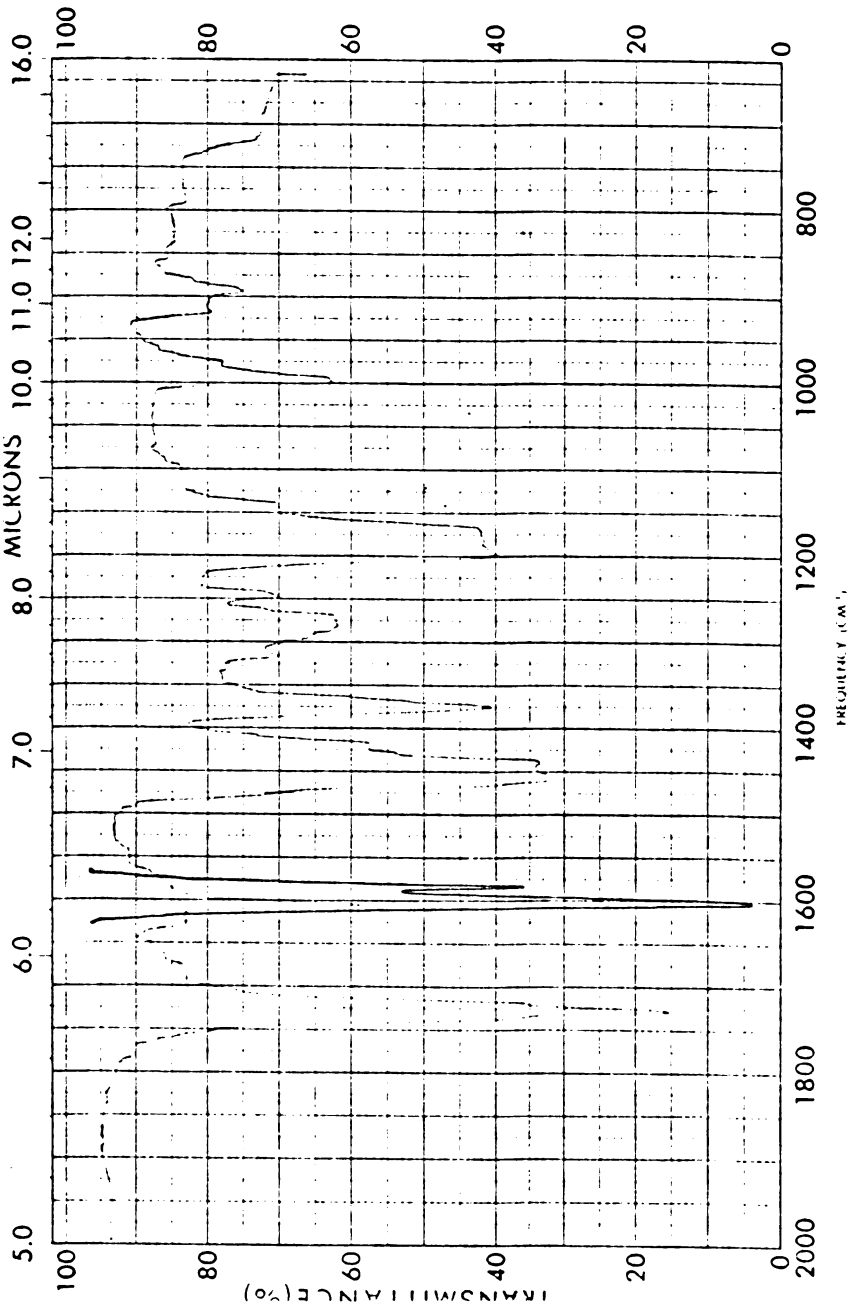

Figure 16. IR (1250-650 cm^{-1}) of bis-isoxazole (7)

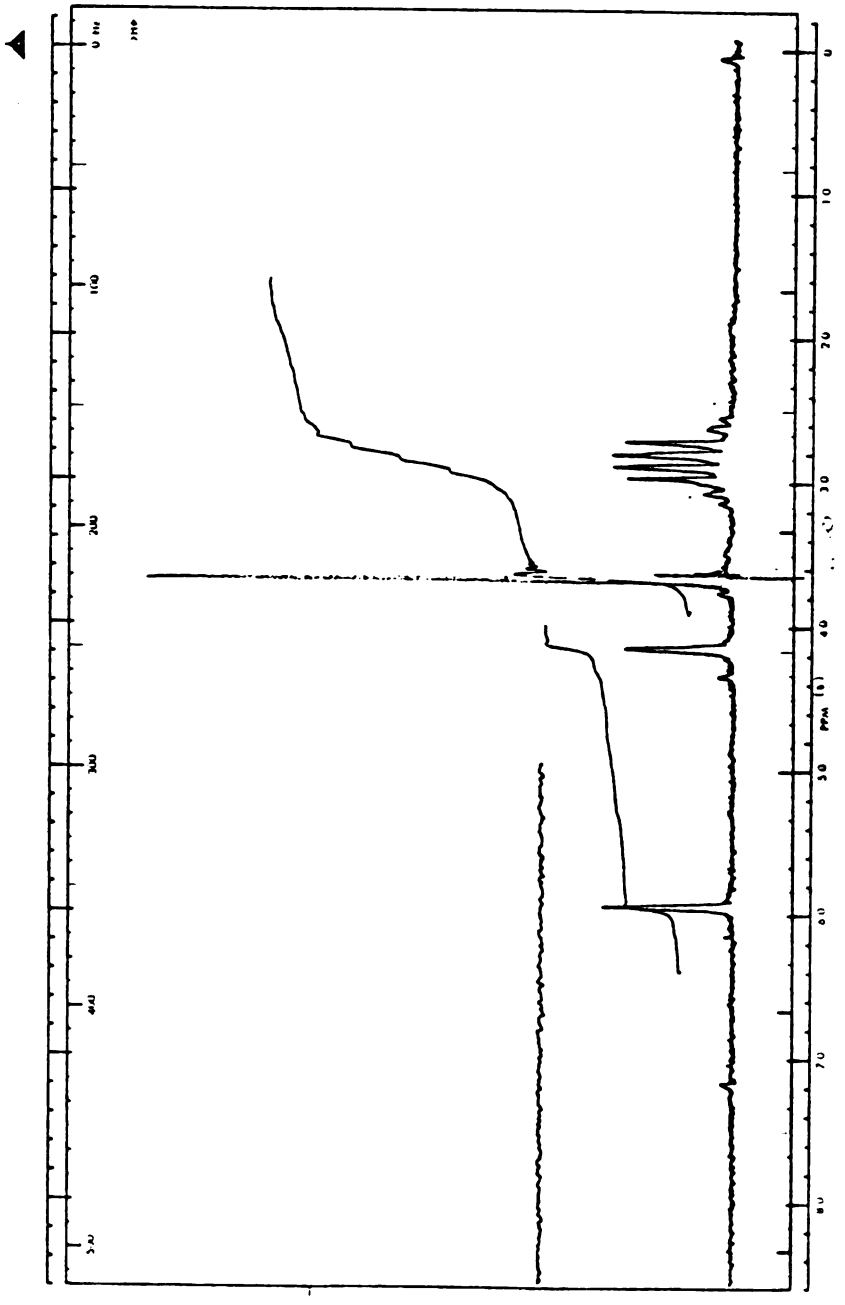

Figure 17. PMR (60 MHz) of bis-isoxazole (7)

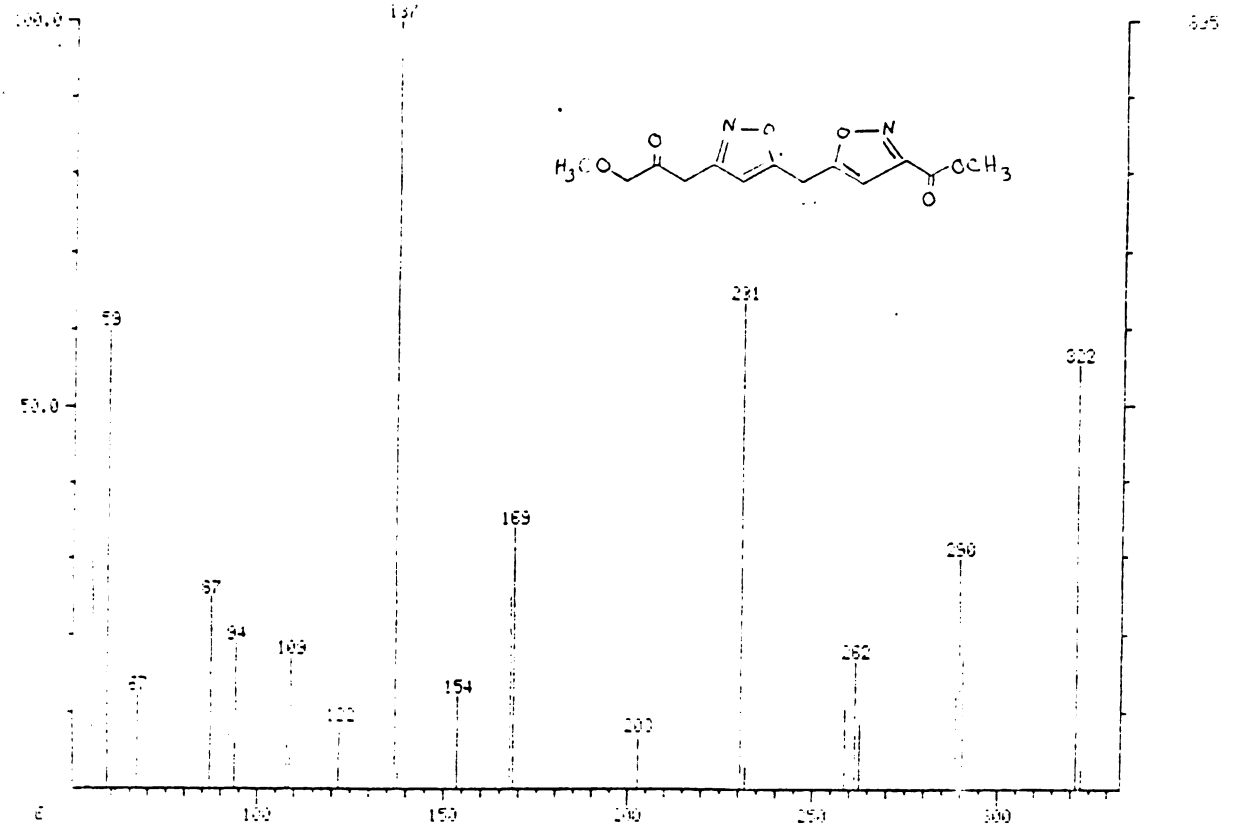

Figure 18. Mass spectrum of bis-isoxazole (7)

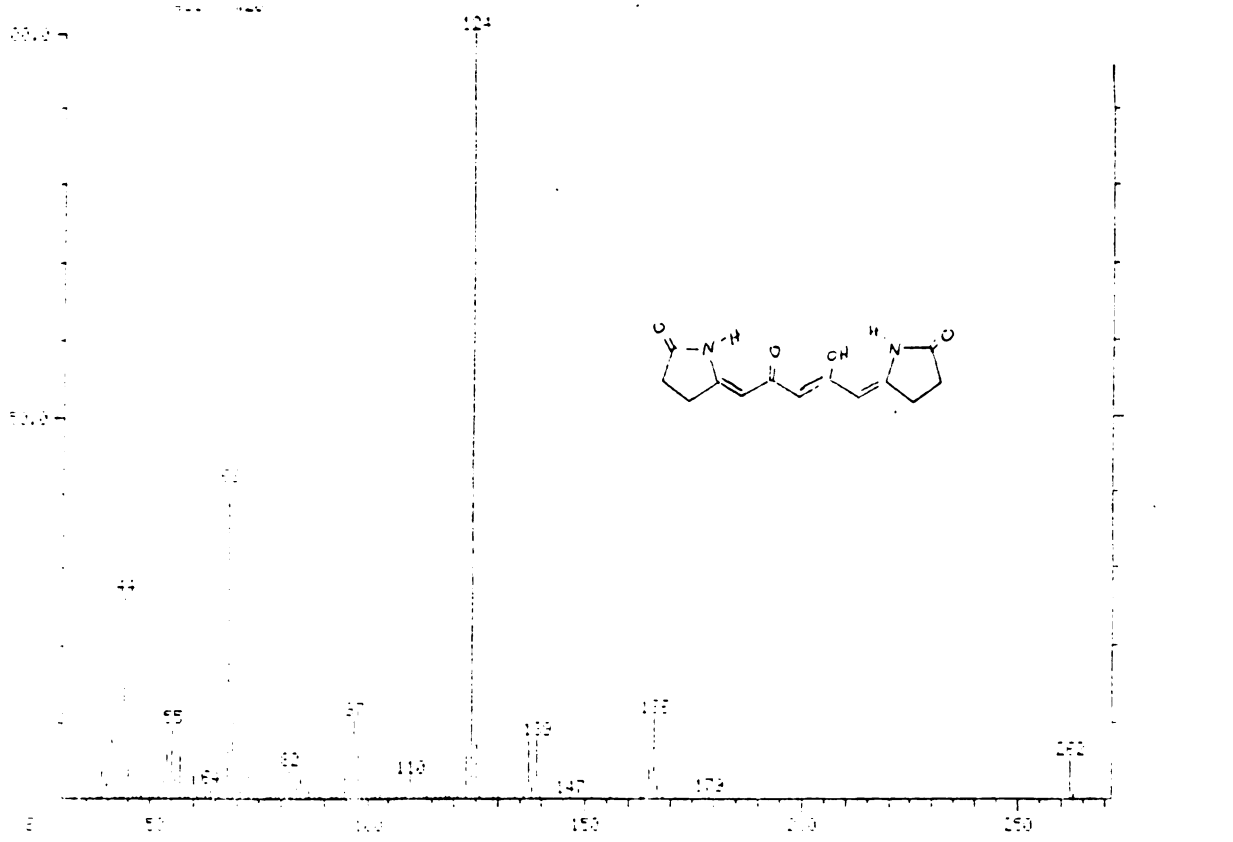

Figure 19.Mass spectrum of β-keto bis-vinylogous lactam (3)

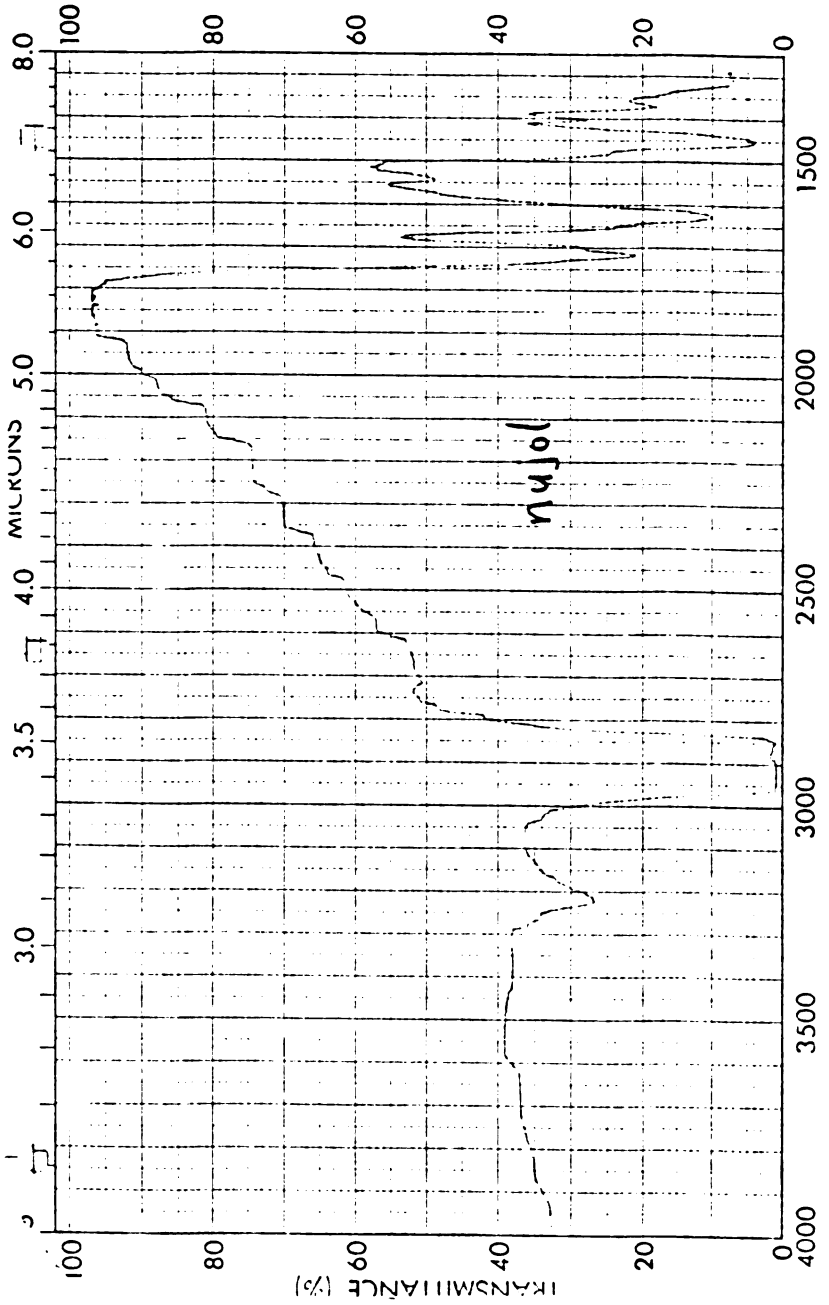

Figure 20. IR (4000-1250 cm^{-1}) of β-keto bis-vinylogous lactam (3)

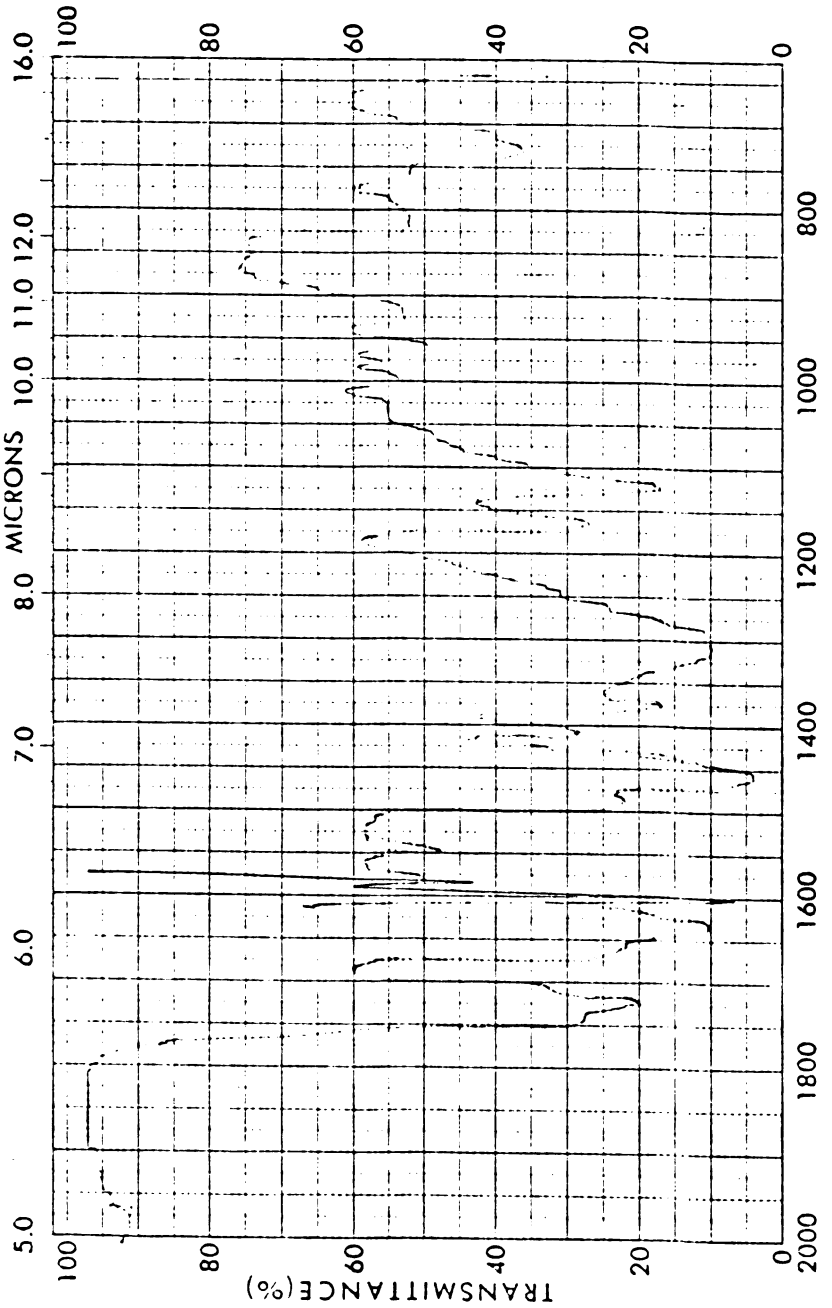

Figure 21. IR (1250-650 cm^{-1}) of β-keto bis-vinylogous lactam (3)

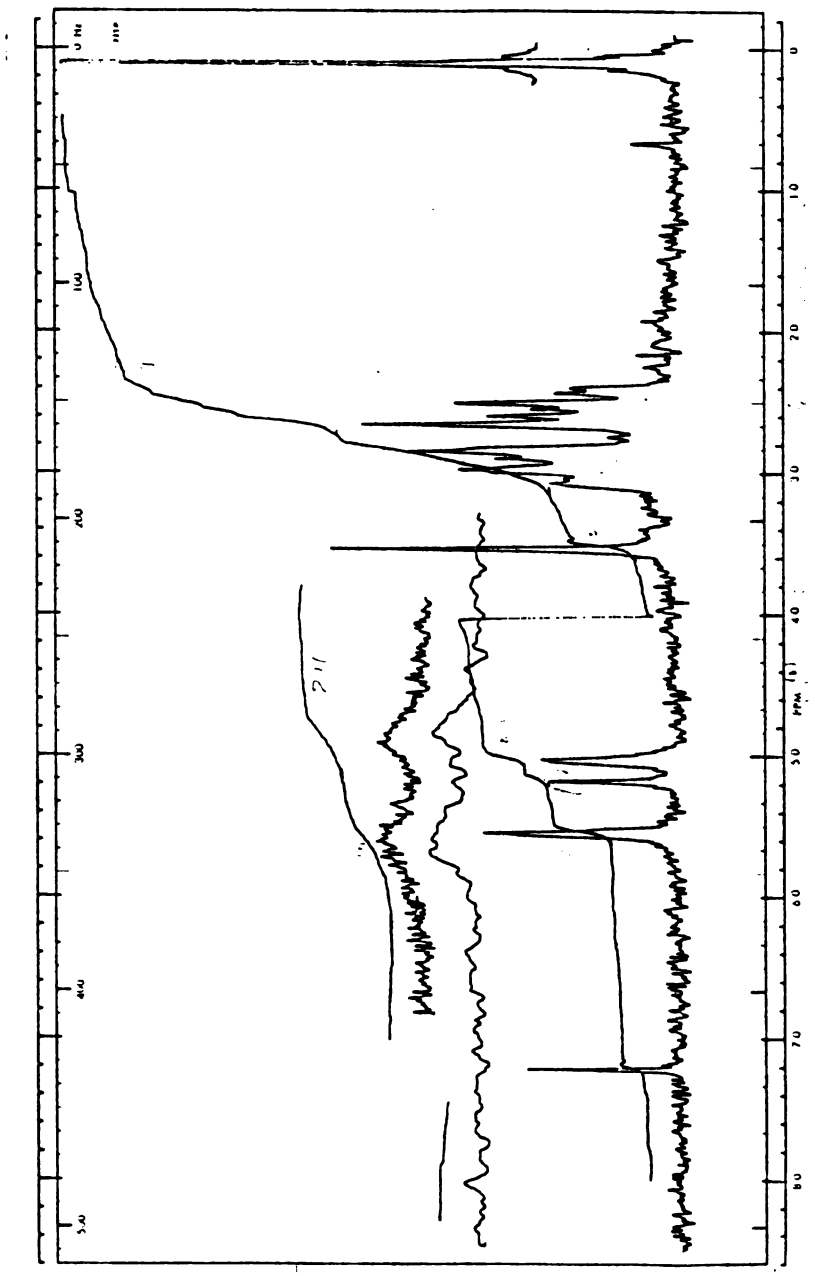

Figure 22. PMR (60 MHz) of β-keto bis-vinylogous lactam (3)