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CUBANE DERIVATIVES FOR PROPELLANT APPLICATIONS

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Work during this program emphasized larger scale preparations of cubane-1,4-dicarboxylic acid and process improvements. In the first step, the reaction solvent was changed to toluene to shorten the reaction time and to avoid the use of the carcinogenic solvent, benzene. In the second step, p-dioxane could not be replaced by another solvent, but only molar amounts were needed. This material was destroyed during the reaction, avoiding disposal problem. In step three, the dehydrohalogenation was improved by using inexpensive sodium hydroxide and ethanol instead of potassium t-butoxide in tetrahydrofuran. In step four, the hydrolysis of the bisketal with HCl in carbon tetrachloride gave high purity monoketal. In step five, the photolytic ring closure to the cage molecule was found to proceed well in methylene chloride, avoiding the use of benzene. In step six, the slow continuous extraction of the caged dione from sulfuric acid was avoided by conversion of the caged monoketal to the tetraacetate. In the seventh step

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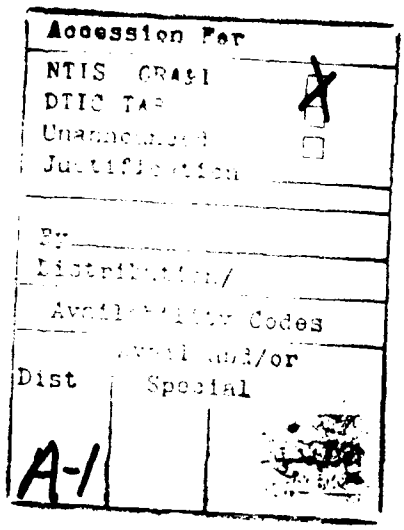
the Favorskii ring contraction of the tetraacetate to form cubane diacid gave improved yields. The eighth and ninth steps required in the original systhesis involving conversion of the diacid to the dimethyl ester, purification and hydrolysis back to the diacid, were eliminated. The synthesis of cubane-1,4-diisocyanate and cubanecarboxylic acid were improved. The synthesis of cubane derivatives containing hydrazino groups was investigated.



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I. INTRODUCTION

Propellant formulations with improved performance are required for Strategic Defense Initiative applications. There is a particular need for non-metal containing propellants with increased specific impulse (Isp) for use in rocket-propelled kinetic energy weapons which would reduce the minimum effective mass of the projectiles. An approach that has been taken to meet the SDI Isp-intensive needs is based on the intrinsic energy that would be released during combustion of energetic cubane derivatives. These advanced materials rely on the high thermodynamic strain energy[1] and inherent high density[2] of cubane (known to be greater than 166 Kcal/mole and 1.3 g/cm^3 for the unsubstituted hydrocarbon). In addition, cubane derivatives have excellent thermal stability making them ideal candidates for incorporation into advanced propellant and explosive formulations. The strain energy will add significantly to the performance of cubane derivatives containing either ring or side-chain energetic functional groups. The presence of the cubyl group is also expected to give high density materials useful for volume-critical applications.

The most readily accessible starting material for the synthesis of energetic cubanes is cubane-1,4-dicarboxylic acid. Functional group transformations of this diacid have yielded energetic derivatives, such as 1,4-dinitrocubane[2] and 1,4-bis(N-nitroamino)cubane[3], demonstrating the feasibility of synthesizing stable, energetic cubane compounds. For example, dinitraminocubane is stable above 200°C by DSC analysis. However, to realize improved performance for SDI applications, oxygen balance at least to the CO level is required. Cubane diacid is the syn-

thetic entry, through metallation chemistry, to tetrafunctional cubane derivatives. The diacid has been converted to both 1,2,4,7- and 1,3,5,7-cubanetetracarboxylic acids from which the energetic molecules 1,2,4,7-cubanetetraammonium tetraperchlorate[4] and 1,3,5,7-tetranitrocubane[5] have been synthesized. Quantities of cubane-1,4-dicarboxylic acid will be to prepare large amounts of energetic cubyl propellants for early testing in a demonstration motor. In addition, ready availability of cubane derivatives will allow commercial applications in polymers and pharmaceuticals.[6]

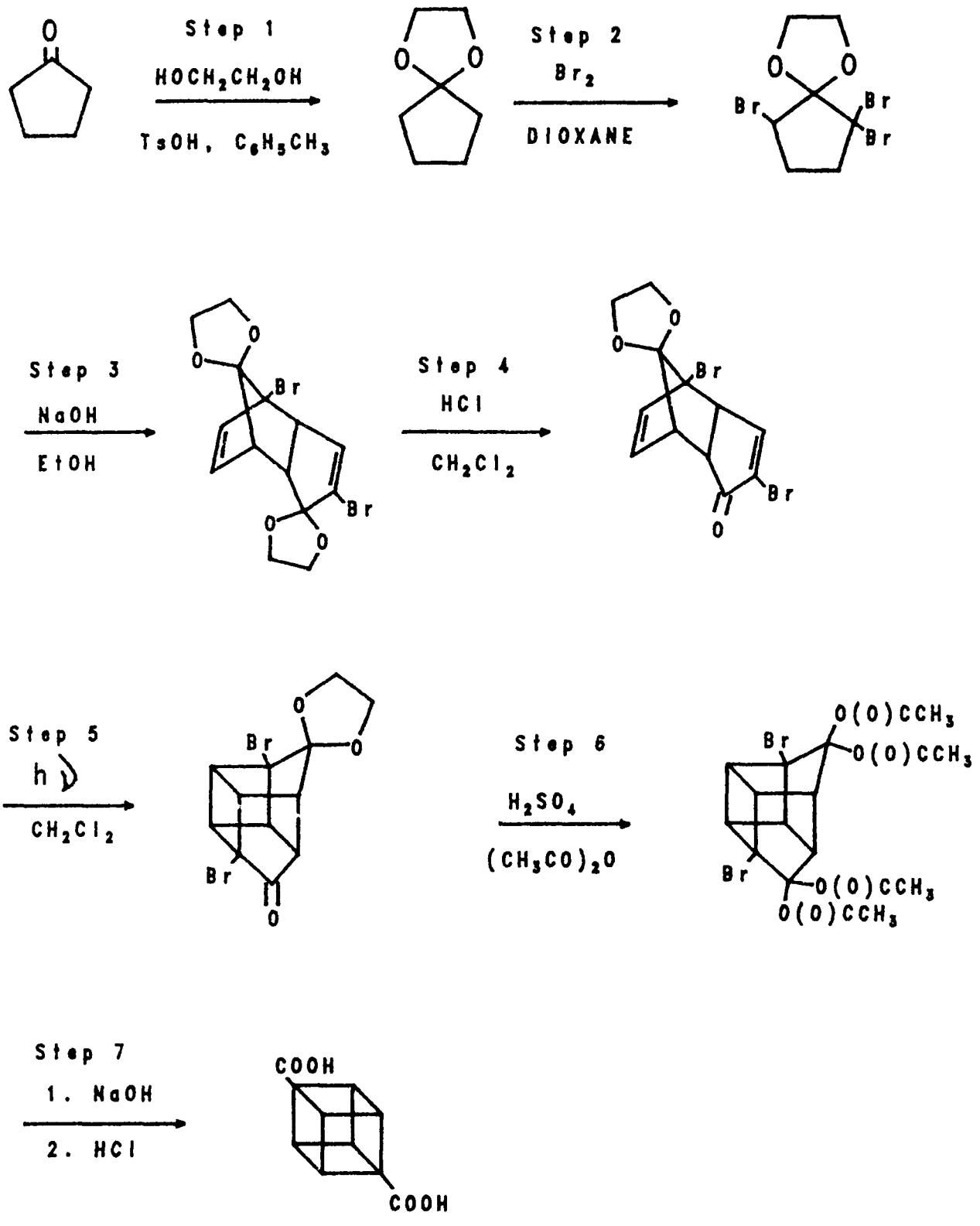
On this program, the scale up of each of the seven steps (Scheme I) required for the synthesis of cubane-1,4-diacid has been investigated. Table I shows a comparison of reaction scales and yields obtained prior to this program and the current best results.

Table I. Synthesis of Cubane-1,4-diacid[a]

Compound	Scale Previous High kg	Scale Phase II High kg	Yield Previous High %	Yield Phase II High %	Yield Phase II Average %
Cyclopentanone Ethylene Ketal	0.39	80	76	95	89
Tribromo ketal	0.28	14	69	85	NI
Bisketal	0.1	7	76	92	55-70(b)
Monoketal	0.106	12	91	95	50-60(c)
Cage Monoketal	0.072	2	89	100	NI(d)
Cage Dione	-	2	71	95	NI
Tetraacetate (e)	-	4	-	90	90
Cubane-1,4-Diacid	0.006	0.285	45	45	30-50(f)
	-	0.800	-	60	52-60(g)

---

a. High value is best single run observed, average is composite yield based on a number of successful runs. NI indicates intermediates which are no longer isolated.
b. Yield of two steps when intermediate is not isolated.
c. After carbon tetrachloride recrystallization
d. 90-95% if isolated for conversion to cage dione
e. New Compound Developed during this Program
f. Yield based on cage dione
g. Yield based on Tetraacetate



SYNTHESIS OF CUBANE-1,4-DICARBOXYLIC ACID

Scheme 1

Also, during this program, cubane diacid was used as a starting point to prepare a number of other cubane derivatives, including cubane-1,4-diisocyanate and the monofunctional acid, cubanecarboxylic acid, which have potential application in energetic polymers. As an adjunct to the scale up work, several new energetic cubane derivatives were prepared, including the first cubyl hydrazines 1,4-bis(hydrazomethyl)cubane and 1,2,4,7-tetra(hydrazomethyl)cubane. The hydrazines were isolated as their di and tetra salts.

Although the focus of the program was concentrated on parameterization of reaction conditions leading to cubane diacid rather than preparation of material, kilograms of the diacid were synthesized. As a result, both the diacid and other cubane derivatives have been provided to laboratories at Aerojet, Morton Thiokol, Stanford Research Institute, Naval Wepons Center, Naval Surface Weapons Center, National Bureau of Standards, Naval Research Laboratories, and several universities.

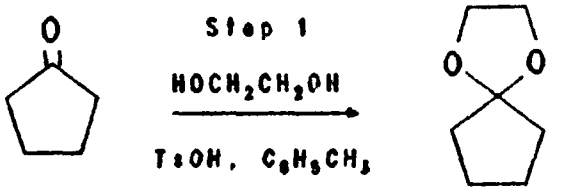
II. DISCUSSION

A. Preparation of Cubane-1,4-dicarboxylic acid.

Cubane-1,4-diacid[8] was first prepared by Eaton, as a key intermediate in his synthesis of the parent hydrocarbon, cubane. The original route was modified by Chapman[9] and was later investigated in some detail on a small scale during Phase I of this program.[10] As a result a nine step synthetic route was established which appeared to be feasible to scale up. Also during that preliminary study, over 100 g of cubane diacid was produced.

In transferring any reaction from laboratory scale to pilot plant scale, engineering problems related to exotherms and material handling must be solved. Environmental issues which are trivial on a small scale must be addressed and frequently reactions must be redesigned with new reagents to avoid unsuitable or unsafe materials. Product analysis and batch control must be addressed.

Cyclopentanone Ethylene Ketal



The original synthesis of cubane involved the bromination of 2-cyclopentenone, but because of the difficulty in preparing this ketone on a large scale, an alternate route was developed based on cyclopentanone employing a ketal protecting group. Cyclopentanone ethylene ketal was first prepared by Salmi[11] and later used for the preparation of cubane derivatives by Chapman.[9] Ketals are formed from ketones and alcohols under acid catalysis. In this case, the ring strain at the spiro carbon causes the ketal formation to be slow. During Phase I, no ketal formation was observed without azeotropic water removal, and even at reflux in benzene, the reaction was 60% complete after 96 hours and only 90% complete after 200 hours. Cyclopentanone was found to polymerize on prolonged heating in the presence of acid, resulting in low yields as the scale was increased.

During this program several improvements were made in the preparation of cyclopentanone ketal. The use of toluene in place of benzene was

found to shorten reaction times due to higher concentration of water in the azeotrope and higher reaction temperatures. At the 100 g scale, the reaction was 90% complete in 16 hours in toluene compared to 1 week in benzene. The ethylene glycol had little solubility in either benzene or toluene. The reaction mixture was difficult to stir in glassware and resulted in bumping. When the reaction was conducted in a 100 gal Pfaudler reactor using toluene, stirring was no longer a problem. For safety considerations, overnight operation was avoided and the azeotrope was removed for approximately 6 hours a day. With these time limitations, optimum yields were obtained when the reaction was stopped after 4-5 days when 85% complete. The unreacted cyclopentanone was recycled and excessive resinous by-product formation was avoided.

Purification of the ketal was complicated by rapid deketalization in the presence of moisture. No feasible method for the removal of the 0.5% *p*-toluenesulfonic acid catalyst from the reaction mixture was found since the ketal was converted completely to the ketone by a water wash. As a result, the unreacted ethylene glycol layer was separated and the mixture was distilled. Toluene (bp 110°C), cyclopentanone (bp 135°C) and cyclopentanone ethylene ketal (bp 152°C) could not be separated by simple distillation. In smaller runs, distillation with a spinning band column gave cyclopentanone ketal containing 2-3% cyclopentanone and trace amounts of toluene. Approximately 4 liters of purified cyclopentanone ketal per day could be prepared by this method. Subsequently, the ketal was distilled through a 4" x 6' bubble plate column and 20 liters per day of ketal containing 2-5% cyclopentanone was produced. The results are summarized in Table II.

Table II. Cyclopentanone Ethylene Ketal

Cyclopentanone kg (mole)	Ethylene Glycol kg (mole)	Toluene L	Time h	Yield (a) kg (%)
0.4 (0.47)	0.47 (0.76)	0.7	8	0.038 (96)
4.0 (47)	5.4 (73)	7	24	4.8 (79)
4.0 (47)	5.4 (73)	7	24	5.3 (93)
12 (142)	14.5 (234)	21	32	10 (55)
16 (190)	16 (260)	26	35	18 (74)
16 (190)	16 (260)	26	30	8 (33)(b)
80 (952)	100 (1613)	120	35	80 (66)
75 (893)	96 (1550)	120	24	70 (61)
68 (748)	73 (1177)	120	32	84.8 (88)(c)

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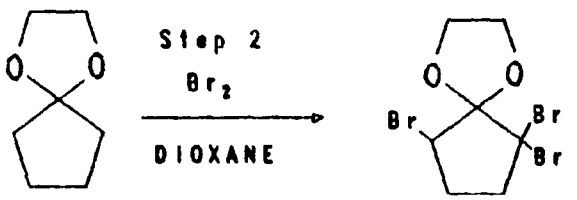
a. Isolated yield based on converted cyclopentanone
b. Rapid water wash before distillation
c. 3 distillations

Bromination of Cyclopentanone Ketal



Cyclopentanone ethylene ketal reacts with bromine to form 2,2,5-tribromocyclopentanone ethylene ketal (tribromo ketal) under very limited reaction conditions. Chapman[9] reported attempts to brominate the ketal with pyridinium bromide perbromide, trimethylphenylammonium perbromide or molecular bromine in a number of solvents. Only bromination in dioxane gave satisfactory results. In this work, a number of alternative ethers such as diethyl ether, tetrahydrofuran and dimethoxyethylene were also found to be ineffective.

Since dioxane, a cancer suspect agent, could not be replaced by another reagent, it was desirable to reduce the amount by dilution with a

cosolvent. It was found that one mole of the ketal, three moles of bromine and approximately one mole of dioxane in methylene chloride gave yields comparable to those in dioxane solution. Optimum results were obtained with a ratio of 1.1 moles of dioxane per mole of ketal in larger scale runs. When the dioxane to ketal molar ratio was below 1:1, incomplete bromination occurred.

The quality of the dioxane was found to be critical. The use of ACS or HPLC grade dioxane from unopened bottles gave yields below 20%; the same material distilled from lithium aluminum hydride gave 70-80% yields. Small amounts of water added to the reaction mixture did not decrease the yield. Although filtration of undistilled dioxane through aluminum oxide sometimes gave satisfactory results, this method of purification was not reliable. Other treatments which would remove peroxides from the dioxane, such as reaction with trimethyl phosphite, also gave inconsistent results.

In reactions involving 45 moles of ketal in a 20 gallon Pfaudler reactor, handling of the bromine became a potential hazard. Initially the bromine was added using 2 liter addition funnels, but subsequently, a teflon metering pump was used to transfer the bromine from the shipment bottles directly into the reactor. The addition of the first mole of bromine was accompanied by a large exotherm and it was necessary to cool the reaction mixture with ice water in the reactor jacket to maintain the temperature below 15°C. After about half of the bromine was added, hydrogen bromide gas evolved at such a rate that the reaction mixture cooled spontaneously to 5-7°C, and the final mole of bromine was then added at a rapid rate.

The course analysis of the bromination was followed glc. At the completion of the bromine addition the reaction was found to be about one-third complete. The second and third bromination steps proceeded very slowly at 15°C, but required 16-18 hours at 20°C and only 2-3 hours at 27°C. When bromination reactions were heated above 30°C even for periods as short as 10 minutes, extensive decomposition occurred and only tars were obtained upon dehydrohalogenation.

As a result of these observations, a procedure was developed in which the the reactor was cooled with ice water during the addition of the first mole of bromine and then warmed with ambient water during the addition of the remaining bromine. After all the bromine had been added, the temperature was slowly increased over several hours to 26-27°C. The heating was then discontinued and the mixture was stirred overnight. The HBr gas evolved in the reaction was trapped with an 8 foot scrubbing column packed with ceramic saddles through which a 10-15% aqueous sodium hydroxide was passed. The loss of some bromine by entrainment with the HBr gas was compensated for by using a slight excess over the theoretical 3 moles.

Work-up of the bromination mixture involved an aqueous wash to remove the residual HBr and bromine and evaporation of the solvent. The aqueous treatment was found to be very exothermic. The reaction mixture was cooled to 10°C, and water and ice were added slowly until the initial exotherm subsided; the reactor temperature was maintained below 15°C. Saturated sodium bisulfite solution was then added with no appreciable exotherm. Finally, the solution was made alkaline with sodium hydroxide solution, and the organic layer was separated and washed with sulfite

solution. Dioxane was not detected in the water washes.

After methylene chloride was removed. The residual oil crystallized to give solid tribromo ketal which was isolated in 55-85% yield. At the 45 mole scale, the pure tribromo ketal was not isolated and the crude reaction product which contained approximately 10% methylene chloride was used directly in the dehydrohalogenation reaction. Use of this oil simplified material handling in the following step.

Table III. Lab Scale Prepartation of Tribromo Ketal

Ketal g (mol)	Bromine g (mol)	Dioxane g (mol)	CH_2Cl_2 L	Temp °C	Time h	Tribromo Ketal g (%)
12.8 (0.1)	5.2 (0.33)	11 (0.13)	0.08	20	22	32 (88)
128 (1.0)	620 (3.9)	130 (1.5)	0.8	20	24	a (90)
256 (2.0)	1040 (6.5)	220 (2.5)	1.6	20	24	576 (79)
128 (1.0)	520 (3.3)	110 (1.3)	0.8	22	60	320 (88)
128 (1.0)	520 (3.3)	110 (1.3)	0.8	22	60	300 (82) (b)

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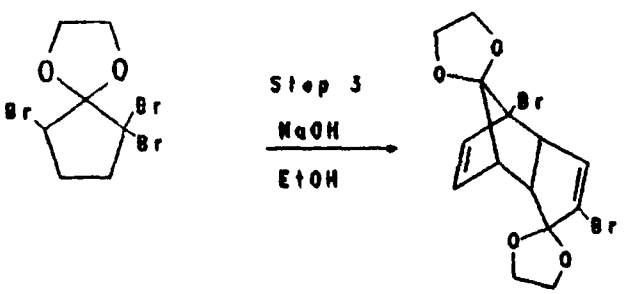
a. glc yield, 34% bisketal isolated
b. Dioxane treated with trimethyl phosphite

Dehydrohalogenation and Dimerization of the Tribromo Ketal to the Bisketal.



Previously the tribromo ketal was reacted with potassium *t*-butoxide in *t*-butanol to form 2-bromocyclopentandienone ethylene ketal which underwent a Diels-Alder dimerization reaction to give *endo*-2,4-dibromodi-

cyclopentadiene-1,8-dione bisethylene ketal (bisketal). The yield was 65-88% when an 80% excess of the base was used. On scale up the cost of potassium *t*-butoxide and *t*-butanol prompted a search for other bases. The use of sodium methoxide or organic bases such as piperidine gave satisfactory results. However, it was found that anhydrous conditions were not required and that sodium hydroxide in ethanol gave results comparable to those obtained with potassium *t*-butoxide.

The purity of the tribromo ketal affected yields of the bisketal. Tribromo ketal which was exposed to bromination temperature exceeding 30°C gives poor yields of bisketal although the glc and nmr analysis showed no significant impurities. Similarly tribromo ketal which contained 10% or more of the dibromo ketal gives very impure bisketal. In both situations the the isolated bisketal was dark-colored, tarry and lachrymatory, and gave emulsions in the next step.

Table IV. Formation of Bisketal from Tribromo Ketal with Time

Time (h)	Bisketal (g)
0.5	0.62
1	1.26
2	1.14
3	1.09

---

30 mL aliquots from a 45 mole run in NaOH/ethanol

In 45 mole runs, 10% methylene chloride was left in the the tribromo ketal to prevent crystallization. This solution was added over 20-30 minutes to ethanolic sodium hydroxide. Addition of the tribromo ketal to cold solutions of sodium hydroxide followed by heating led to uncontrolled

exotherms. After the addition was complete, residual methylene chloride was removed and the reaction mixture was heated at reflux for 3 hours. The course of the reaction was monitored by glc analysis which indicated the presence of unreacted starting materials after 1 hour and partially dehydrohalogenated tribromo ketal after 2 hours. The yield decreases with time, but pure bisketal was not effected by similar treatment in a control study.

Table V. 45 Mol Scale Conversion of Cyclopentanone Ketal to Bisketal

Run #	Bromination Temp °C	Bromination Time h	Dehydrohalogenation Temp °C	Dehydrohalogenation Time h	Yield kg (%)
1	15	20	72	2	3.7 (41)
2	15	17	74	3	6.0 (66)
3	22	17	74	3	3.82 (42)
4	15	17	74	3	3.0 (33)
5	15	17	74	3	5.5 (60)
6	15	17	74	3	2.15 (24) (c)
7	15	17	74	3	6.3 (69)
8	15	17	74	3	5.5 (60)
9	15	17	74	3	6.5 (71)
10	15	17	74	3	4.3 (48) (b)
11	15	17	74	3	3.2 (36) (b)
12	15	17	74	3	4.0 (44) (b)
13	15	17	74	3	4.1 (45) (b)
14	15	17	74	3	4.5 (49) (b)
15	15	17	74	3	4.7 (52) (b)
16	15	17	74	3	6.3 (69)
17	15	17	74	3	2.6 (28)

---

a. Reaction of 5.76 kg (45 mol) of cyclopentanone ketal, 23.4 kg (146 mol) of bromine and 4.9 kg (55.7 mol) of dioxane in 36 L of CH_2Cl_2, followed by dehydrohalogenation with 6.6 kg (165 mol) of NaOH in 140 L of ethanol.
b. Reaction temperature did not exceed 15°C (Winter)
c. Dioxane not freshly distilled

Quenching the dehydrohalogenation-dimerization reaction mixture with water gave an emulsion that required 1-3 days to separate. Water

suspensions of the bisketal were stable for a week, but materials left in the water-ethanol mixture for 3 weeks gave poor yields.

Table VI. Pilot Plant Conversion of Cyclopentanone Ketal to Bisketal

Run #	Scale Mol	Bromination Temp °C	Time h	Yield kg (%)
1	54	25	17	8.1 (75)
2	54	22	17	7.1 (65)
3	54	22	17	1.2 (0) (b)
4	52	22	17	7.1 (68)
5	53	27	3	6.0 (57) (c)
6	46	23	17	7.3 (80)
7	57	25	3	4.6 (40) (d)
8	54	35	2	4.8 (44) (e)
9	57	23	17	5.4 (46)
10	48	22	17	5.4 (57) (f)
11	48	22	17	8.1 (85) (f)
12	49	28	17	5.9 (60)
13	55	26	17	6.4 (58)
14	49	31	17	2.0 (0) (g)
15	51	28	17	7.0 (68)
16	52	27	17	6.5 (57)
17	45	27	17	7.3 (80)
18	56	26	17	4.7 (41)
19	54		17	4.8 (44)
20	50		17	5.5 (55)
21	57	28	17	5.4 (46)
22	53	27	17	5.7 (52)
23	47	27	17	8.1 (85)
24	48	28	17	5.7 (60)

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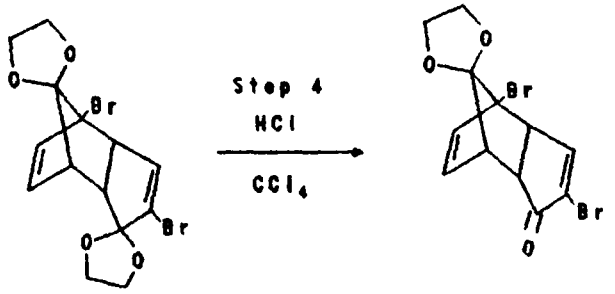
a. A 54 mol scale reaction used 6.8 kg (54 mol) of cyclopentanone ketal, 28.1 kg (176 mol) of bromine and 5.0 kg (57 mol) of dioxane in 30 L of CH_2Cl_2, followed by dehydrohalogenation with 6.6 kg (165 mol) of NaOH in 165 L of ethanol. Other runs were scaled proportionately.
b. Reaction temperature was allowed to go to 35°C for 5 minutes.
c. Bromination and dehydrohalogenation completed in one 10 hour period.
d. Bromination quenched after 1 hour at 25°C.
e. Lachramatory material.
f. Sequential runs with identical material and reaction conditions
g. Black tar.

The light brown material obtained in these reactions was 95% pure by NMR, glc and TGA analysis, and was found to contain essentially no salt or other organic materials; the main impurity was water. The yields of bisketal was generally 65-85% for the combined two steps based on cyclopentanone ketal. On several occasions, two sequential runs using identical reagents and reaction conditions gave yield variations of more than 35% (50-85%)

Overall, the yields from the pilot plant runs were comparable with those from small scale reactions and slightly less than the best results from small scale reactions in which potassium *t*-butoxide was used. However, the cost savings of using sodium hydroxide and ethanol is substantial.

Hydrolysis of Bisketal to *endo*-2,4-Dibromodicyclopentadiene-1,8-dione 8-ethylene ketal (Monoketal).



The photochemical ring closure to form the cage (Step 5) requires an olefin and an ene-one moiety. Therefore, the ketone group in the monocyclic ring of the bisketal must be deprotected by hydrolysis of its ketal blocking group. Reaction of the bisketal with concentrated sulfuric acid gave hydrolysis of both ketals to form a diketone, an undesirable result since the diketone was less stable during photolysis and more

difficult to purify. The difference in reactivity of the two ketals allowed for deblocking of only one ketal under milder conditions. Previously concentrated hydrochloric acid and tetrahydrofuran (THF) were used with good results although the reaction times were long (24-30 hours). The expense and flammability made THF an undesirable solvent.

Deketalization of the bisketal in homogenous solutions of concentrated HCl in refluxing ethanol was complete on a small scale in 1 hour. When the scale was increased to 10 kg, several hours of reflux was needed for completion. During these longer reaction times, small amounts of ethanol became incorporated into the monoketal. The structure of these ethanol containing adducts was not established, but they may have resulted from addition of the ethanol to the double bond, or from displacement of one of the bromo groups by an ethoxy group. Although this incorporation of ethanol never exceeded 2% in the product, the presence of even small amounts were found to lead to poor results in the Favorskii step, as discussed below. This method of deketalization was use for the first year of the program, and gave good results in producing monoketal. However, yields of cubane were low.

The bisketal was also converted to the monoketal in heterogenous mixtures of concentrated HCl and other solvents such as toluene, hexane, cyclohexane, methylene chloride, chloroform or carbon tetrachloride. Good results were obtained with methylene chloride and this solvent was used during the second half of the program. When the bisketal was recrystallized, the deketalization in methylene chloride was found to require 24-48 hours at reflux. However, when crude bisketal was used the reactions were complete in 2-10 hours at room temperature. Small amounts of a

material which acts as a phase transfer agent may be present in the crude bisketal. Dilute acids catalyzed the deketalization at a slower rate; 20% aqueous HCl required 3 days compared to 3 hours for 37% aqueous HCl.

Monoketal prepared in all solvents studied was brown in color, but was otherwise pure by NMR and glc analysis. The color was less pronounced in samples prepared from recrystallized bisketal, but even these materials required further recrystallization. Monoketal which contained colored impurities was found to react slowly in the subsequent photolysis step as discussed below. Solvents such as acetone, ether, methylene chloride, or acetonitrile failed to improve the color of the monoketal. Ethyl acetate, toluene and cyclohexane were more effective, but the best solvent was carbon tetrachloride in which the colored impurities had essentially no solubility. The monoketal solubility in carbon tetrachloride was less than 1 g per 100 g at room temperature and about 3 g per 100 g at reflux, but crystallization from this solvent gave essentially colorless product.

Purification of the crude monoketal was further complicated by its skin irritant properties. As a result, normal production equipment could not be used, and the monoketal was recrystallized in small batches in the hood. At the close of the project, an improved process for the conversion of the bisketal to the monoketal was developed. The crude bisketal was dissolved in refluxing carbon tetrachloride and the hot solution was filtered through diatomaceous earth to remove a small amount of tarry impurity. The solution was refluxed with 1/4 of its volume of concentrated HCl for 3 hours or until the glc analysis indicated that the deketalization was complete. The layers were separated and the carbon tetra-

Table VII. Hydrolysis of Bisketal to Monoketal

Bisketal kg (mol)	HCl L	Solvent L	Time h	Temp °C	Yield kg (%)
0.01 (0.025)	0.01	0.1 (a)	20	25	0.006 (61)
0.0067 (0.017)	0.0067	0.067(a)	24	25	0.0046 (77)
0.0047 (0.012)	0.0052	0.1(b)	2	78	0.0028 (67)
0.00 (0.01)	0.037	1.0(b)	1	25	0.0025 (79)
0.143 (0.36)	0.176	3.2(b)	0.2	78	0.138 (106)
4.0 (9.9)	4.8	90(b)	2	78	2.8 (78)
4.6 (11.4)	3.6	80(b)	1/2	78	1.9 (46)
5.9 (14.5)	4.8	88(b)	0.5	78	2.5 (41)
17.0 (42)	4.8	220(b)	0.5	78	11.8 (78)
2.0 (4.9)	2.4	15(a)	4	90	0.97 (55)
9.5 (23.4)	4.8	220(c)	0.5	45	5.1 (60)
4.0 (99)	4.8	28(c)	120	20	2.0 (56)
4.7 (11.6)	4.8	24(c)	144	20	2.0 (48)
6.3 (15.5)	4.8	20(c)	72	20	3.0 (53)
4.0 (9.9)	2.4	10(c)	48	45	1.2 (34)
2.6 (6.4)	4.8	6(c)	72	45	1.2 (52)
6.0 (14.8)	9.6	24(c)	72	45	4.6 (86)
7.0 (17.2)	12.0	28(c)	100	45	4.2 (76)
6.0 (14.8)	9.6	24(c)	72	45	4.6 (86)
6.3 (15.5)	4.8	20(c)	72	45	4.3 (76)
1.0 (2.5)	2.0	10(d)	2	80	0.53(60)
0.75 (1.87)	2.0	6(d)	3	80	0.3 (45)
2.0 (5.0)	4.0	10(d)	3	80	0.35 (70)
5.7 (14.2)	12.0	40(d)	4	80	2.3 (45)
0.75 (1.87)	2.0	6(d)	3	80	0.27 (40)
1.0 (2.5)	1.5	10(d)	4	80	0.51 (58)
1.5 (3.75)	1.5	10(d)	3	80	0.73 (55)
0.75 (1.87)	2.0	6(d)	3	80	0.31 (46)
0.75 (1.87)	1.1	3(d)	6	80	0.56 (90) (e)
1.0 (2.5)	1.0	6(c)	6	45	0.6 (95)
6.4 (15.7)	12.0	30(c)	17	45	5.2 (90)
7.2 (17.7)	8.0	40(f)	4	80	5.1 (80)
5.0 (12.3)	8.0	40(f)	6	80	2.5 (57)
6.4 (15.7)	10.0	48(f)	4	80	2.5 (44)
5.0 (12.3)	10.0	40(f)	4	80	1.1 (24)

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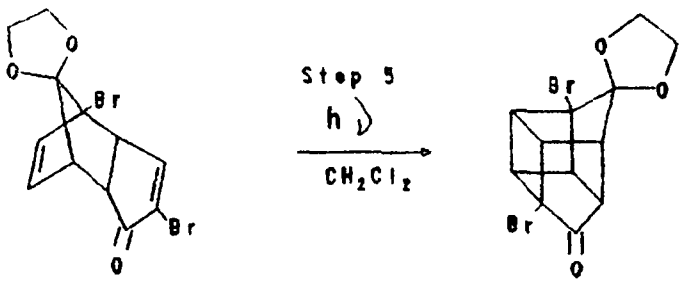
a. THF
b. Ethanol
c. CH_2Cl_2
d. CCl_4
e. CH_2Cl_2 after recrystallization from CCl_4
f. CCl_4 after filtration through diatomaceous earth

chloride was distilled until the volume was reduced by half. The solution of the monoketal was cooled to -20°C and filtered. This method gave nearly colorless monoketal which could be photolyzed rapidly. Also, monoketal produced by this method did not cause skin irritation.

Photochemical Closure of Monoketal to Cage ketal.



The photochemical closure of the monoketal gives 5,9-dibromopentacyclo[5.3.0.0.^{2,5}0.^{3,9}.0^{4,8}]deca-6,10-dione 6-ethylene ketal (cage ketal). During Phase I, exploratory reactions using inexpensive sunlamps and even sunlight gave positive results on a 1 gram scale. These sources of illumination were explored further. A 275 watt Sears sunlamp, gave a 67% conversion of monoketal to cage ketal in 48 hours at the 28 g scale. However, in larger scale reactions, this source of light was too weak to be practical. The rate of reaction of 1-3% per day led to very long reaction times. During these protracted periods, side-reactions diminished the yield. When four lamps were mounted above a reactor containing a solution of 1 kg of monoketal, the reaction proceeded at a rate of approximately 3% per day. After 19 days the material was transferred to a 4 inch column with six lamps. No significant rate enhancement was obtained and the use of sunlamps was abandoned.

Table VIII. Photolysis of Monoketal with 275 W Sunlamps

Monoketal kg (mol)	Methylene Chloride L	Time h	Conversion %	
0.0055 (0.015)	0.09	168	80	(a)
0.0044 (0.012)	0.15	48	0	(b)
0.0028 (0.008)	0.04	48	67	
0.0013 (0.004)(c)	0.01	48	0	
0.0005 (0.0016)(c)	0.005	72	40	
0.001 (0.003)	(d)	32	~1	
0.028 (0.077)	0.45	80	83	
0.028 (0.077)	0.15	80	96	
1.0 (2.76)	20	672	66	(e)

---

a. Sunlight
b. 300 w Blacklight
c. Diketone.
d. Solid state
e. Four Bulbs used.

The use of 175 watt fluorescent bulbs (black lights) was also investigated briefly. This light source was not effective in the ring closure. Sunlight also was found to be too slow on scale up to be useful. Attempts to concentrate the sunlight with mirrors resulted in excessive heating.

The photolysis of solid monoketal was investigated. A crystal of the monoketal did not undergo ring closure when placed in a test tube under nitrogen in sunlight for 8 days. Solid monoketal did undergo ring closure 1 cm from a sunlamp, but the heat from the lamp caused sublimation away from the site of the reaction.

The photochemical closure of monoketal using Hanovia medium pressure lamps was studied. Previously, benzene was used as a solvent. It was found that methylene chloride was a suitable replacement for benzene which cannot be used because of environmental reasons. The monoketal

was not as soluble in methylene chloride at room temperature, but at reflux 15% solutions were obtained. Since the lamps generate substantial heat, efficient cooling jackets and condensers were required to contain the more volatile methylene chloride.

The reaction time for the photochemical closure of a kilogram of monoketal was found to vary from 2 days to a month. Long reaction times were found to result in poor quality product and poor yields. The most important consideration was the purity of the monoketal. Although the purity of monoketal produced in the deketalization step was greater than 99% by nmr and glc analysis, it was beige in color. When this material was dissolved in methylene chloride, solutions of light brown to dark brown color were obtained. Monoketal in the darker solutions underwent ring closure at a slightly slower rate initially, and at a much slower rate after approximately 60% conversion. It appeared that a small amount of highly colored impurity was effectively quenching the photochemical reaction.

Monoketal which had been recrystallized from ethanol or methylene chloride did not react significantly faster than unrecrystallized material. However, a single recrystallization from carbon tetrachloride removed most of the colored material. Although the photolysis of some batches of monoketal still showed a decrease in rate at 60%, the magnitude of the change was smaller in the recrystallized material, and in many cases the reactions proceeded to completion without any inflection (see Graph I). The structure of the colored material was not ascertained.

As the photolysis proceeded, the reaction mixtures became darker and slightly opaque. This problem was overcome by stopping the reaction and filtering the reaction mixture. Activated carbon in the filtration did

Table IX. Photolysis of Monoketal with 450 W Hanovia Lamps[A]

Monoketal kg (mol)	Methylene Chloride L	Time h	Conversion %
1.0 (2.76)	12	192	92
1.5 (4.14)	12	150	90
0.2 (0.5)	0.75	96	88
0.2 (0.5)	0.75	144	85
0.5 (1.4)	3	192	86 (b)
1.0 (2.76)	4	312	88 (c)
1.0 (2.76)	10	192	100 (c)
0.9 (2.5)	4	240	89
0.818 (0.5)	4	288	89
0.9 (2.5)	4	528	95
1.0 (2.76)	6	216	99
1.0 (2.76)	4	144	99
1.0 (2.76)	10	120	100
0.8 (2.2)	4	120	100
1.0 (2.76)	10	312	95
1.0 (2.76)	10	336	95
1.0 (2.76)	4	216	81
1.5 (4.14)	10	>300	90 (d)
1.0 (2.76)	4	>300	90 (d)
0.9 (2.5)	4.5	360	93
1.0 (2.76)	4	>300	88 (d)
0.9 (2.5)	10	312	80
1.0 (2.76)	10	192	80
1.0 (2.76)	10	>300	91 (d)
0.6 (1.66)	10	>300	81 (d)
0.9 (2.50)	4	>300	90 (d)
0.5 (1.4)	4	360	86
0.8 (2.2)	6	>300	90 (d)
0.25 (0.7)	4	>300	90 (d)
0.5 (1.4)	6	>300	90 (d)

a. Monoketal prepared in ethanol.
b. Post treated with carbon
c. Recrystallized from methylene chloride
d. Includes time required for solvent removal.

Table X. Photolysis of Monoketal with 1200 W Hanovia Lamps

Monoketal kg (mol)	Methylene Chloride L	Time h	Conversion %
0.9 (2.5)	10	>100	88 (a)
0.8 (2.2)	4.5	>100	82 (a)
1.0 (2.76)	10	>100	80 (a)
1.0 (2.76)	10	>300	87 (a)
0.8 (2.2)	10	36	99 (b)
1.2 (3.3)	8	40	98 (b)
1.2 (3.3)	8	72	94 (b)
1.2 (3.3)	8	50	97 (b)
1.2 (3.3)	8	56	95 (b)
0.955 (2.6)	8	96	100 (b)
0.64 (1.7)	7	24	100 (b)
0.89 (2.5)	8	125	99 (c)
0.8 (2.2)	8	125	95 (d)
0.5 (1.4)	7	125	88 (d)
0.5 (1.4)	6.5	200	90 (d)
0.96 (2.6)	8	48	99 (d)
1.2 (3.3)	8	96	92 (d)
1.2 (3.3)	8	100	98 (d)
1.5 (4.1)	8	200	94 (d)
0.8 (2.2)	8	48	96 (e)
1.2 (3.3)	8	48	96 (e)
1.2 (3.3)	6	144	96 (e)
0.6 (1.7)	8	244	96 (e)
0.8 (2.2)	8	48	93 (e)
0.8 (2.2)	8	48	92 (e)
0.8 (2.2)	8	48	98 (e)
0.8 (2.2)	8	48	95 (e)
0.8 (2.2)	8	48	96 (e)

---

a. Monoketal prepared in ethanol, recrystallized from methylene chloride
b. Monoketal prepared in methylene chloride, recrystallized from carbon tetrachloride
c. Monoketal prepared in THF, recrystallized from methylene chloride
d. Monoketal prepared in CCl_4
e. Monoketal prepared in CCl_4 after filtration.

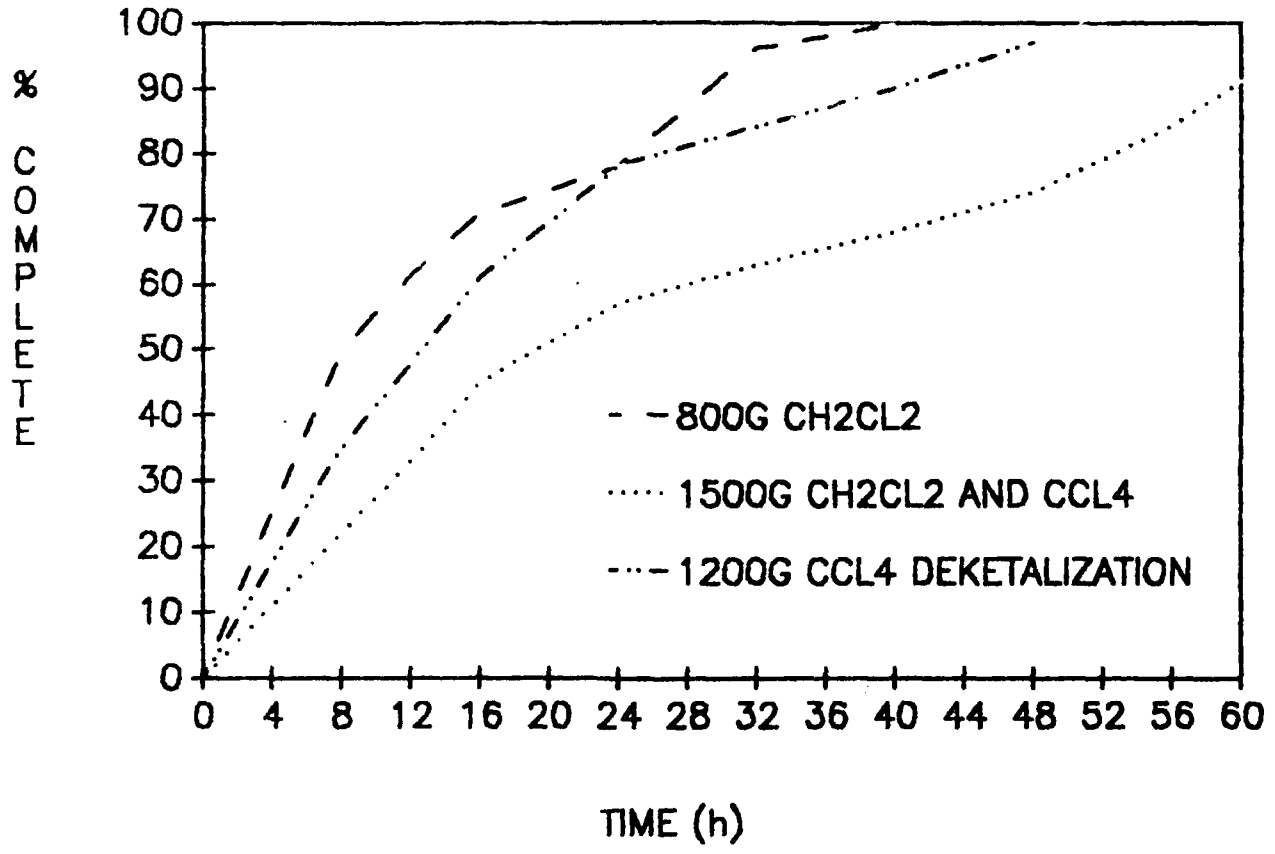
not improve the color. The use of the monoketal recrystallized from carbon tetrachloride eliminated this problem.

To avoid possible quenching by oxygen most reactions were conducted under nitrogen. The use of photosensitizers such as acetone, acetophenone or xanthone did not improve the rate of reaction.

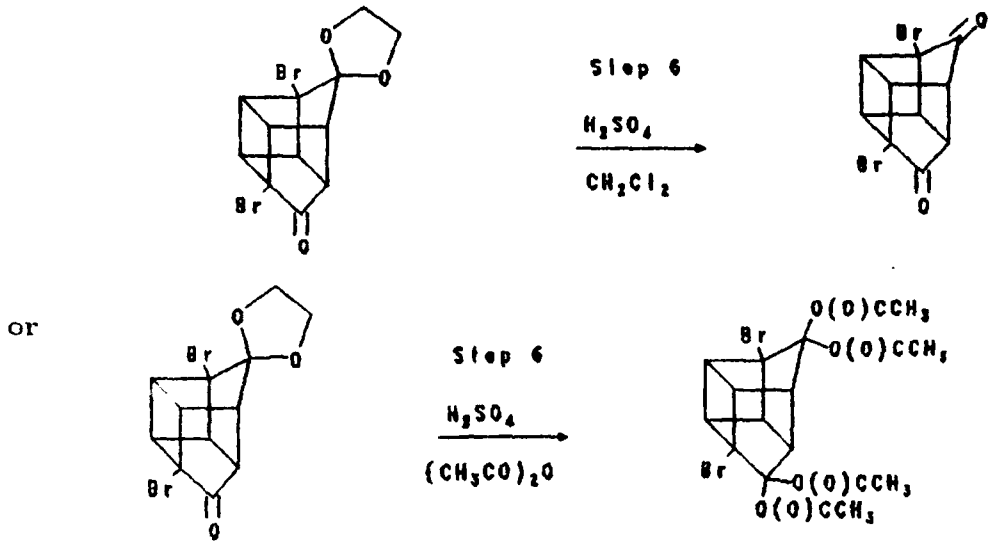
The size of the light used in the photolysis was important as the scale was increased above 1 kilogram. The 450 watt Hanovia lamps generally required times of 1 week or more. The use of a 1200 watt Hanovia lamp decreased the reaction time to 2-4 days and resulted in less color formation.

The shape of the photolysis reactor was found to be important. When modified spherical 22 L flasks were used, the runs proceeded slowly. Subsequently, a reactor was constructed with a water-cooled immersion well in a long slender flask, allowing most of the solution to be within 5-10 cm of the light source. Because of the formation of algae in the cooling water and solids on the surface of the cold finger containing the light source, it was necessary to remove and clean the cold finger after every reaction. The wires to the bulb became hot enough to sublime metal oxides onto the inner surface of the cold finger. This surface was cleaned with dilute hydrochloric acid.

The photolysis was monitored by glc analysis. When the conversion reached 90% the reaction was stopped and the material was used without isolation in the next step.


% COMPLETE
100
90
80
70
60
50
40
30
20
10
0
0 4 8 12 16 20 24 28 32 36 40 44 48 52 56 60
TIME (h)
800G CH2CL2
1500G CH2CL2 AND CCL4
1200G CCL4 DEKETALIZATION

Deketalization to Cage Dione or Cage Tetraacetate.



The hydrolysis of the cage ketal to 5,9-dibromopentacyclo-[5.3.0.0.^{2,5}0.^{3,9}.0^{4,8}]deca-6,10-dione (cage dione) required strong acid catalysis. The cage dione was highly water soluble which precluded the practical use of aqueous acids. A method was developed for hydrolyzing the cage ketal in concentrated sulfuric acid and then isolating the dione by extraction with methylene chloride. The hydrolysis was found to take several hours at room temperature and although the reaction was faster at elevated temperatures, the yield diminished. The product partitioned between the sulfuric acid and the methylene chloride. On a small scale, approximately 60-70% of the product could be removed by 10 extractions with methylene chloride, but product remained in the sulfuric acid (Table XI) As the scale increased, the extraction, separation and handling of large amounts of concentrate sulfuric acid presented a safety hazard.

The use of continuous extraction in large liquid-liquid extractors provided a satisfactory method of isolating the cage dione from the

sulfuric acid. However, in reactions above the kilogram scale, the extraction times were longer than one week and significant hydrolysis of the methylene chloride occurred. The cage dione has poor solubility in methylene chloride and crystallized out of the hot solutions and charred. Charring was avoided by replacing the methylene chloride with fresh solvent every three days. The cage dione produced in these extractions contained some residual sulfuric acid and removal of the solvent gave a thick paste from which the residual methylene chloride was difficult to remove. Cage dione prepared in this manner was not purified further and was used directly in the Favorskii step. This hydrolysis was labor intensive.

Table XI. Isolation Cage Dione from H_2SO_4 by Multiple Extractions.[a]

Cage ketal g	Cage Dione g	H_2SO_4 mL	CH_2Cl_2 mL	yield %
5.0	2.7	20 (b)	20	62
5.0	3.3	20	20	75
670	340	2000	2000	58
900	400	2500	2500	52
2000	1.100	8000	9000	63

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a. 10 extractions for each entry.
b. Sodium sulfate (10 g) was added to sulfuric acid mixture.

Alternative methods for hydrolyzing the cage ketal were studied. Stirring the ketal in acetone with acid catalysts gave 10% hydrolysis after 24 hours, but then no further hydrolysis occurred. The use of suspended silica gel or Nafion in various solvents failed to remove the ketal. Anhydrous copper sulfate in acetone also failed to promote hydrolysis.

Table XII. Multiple Extractions of Cage Dione from H_2SO_4.

Extraction #	g Isolated	%
1	60	15.5
2	74	19.2
3	58.5	15.1
4	58	15.0
5	33.5	8.6
6	21	5.4
7	19.5	5.0
8	20.5	5.2
9	30	7.7
10	12	3.1
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Total	387	100.0

Table XIII. Isolation of Cage Dione by Continuous Extraction.

Cage Ketal kg (mol)	H_2SO_4 kg (mol)	CH_2Cl_2 L	Time h	Yield kg (%)
0.004 (0.011)	0.036 (.36)	0.1	37	0.0023 (67)
1.5 (4.14)	7.2 (72)	8	432	1.02 (77)
1.2 (3.3)	7.2 (72)	8	288	0.83 (81)
2.0 (5.5)	7.2 (72)	8	288	1.64 (82)
2.0 (5.5)	7.2 (72)	8	216	1.2 (68)
2.0 (5.5)	7.2 (72)	8	252	1.4 (80)
1.7 (4.7)	7.2 (72)	8	120	1.2 (80)
1.9 (5.3)	7.2 (72)	8	240	1.6 (77)
0.725 (2.0)	7.2 (72)	8	264	0.4 (61)
1.7 (4.7)	7.2 (72)	8	192	1.3 (58)
1.4 (9.0)	7.2 (72)	8	240	0.85 (67)
1.5 (4.14)	7.2 (72)	8	240	0.573 (44) (a)
1.6 (2.5)	7.2 (72)	8	216	0.91 (64)

---

a. Solids Crystallized and Charred.

The ring strain of the cage structure due to the presence of a sp^2 hybride carbon at the carbonyl may explain the stability of the ketal. To take advantage of this strain effect, the cage ketal was reacted with acetic anhydride to form the tetraacetate. The ketal was dissolved in acetic anhydride, cooled, and sulfuric acid added slowly. The reaction,

which required a mole of sulfuric acid, was exothermic and required external cooling as the acid was added. Reaction temperatures over 40°C resulted in decomposition. When the acid addition was complete the mixture was stirred for 1 hour and quenched by pouring slowly onto ice. Excessively rapid quenching resulted in hydrolysis of the tetraacetate to the dione which could not be isolated from the water solution. The solid tetraacetate was filtered, washed with water, 10% aqueous potassium carbonate, and air dried. This procedure resulted in yields of 70-90% of the tetraacetate, a white crystalline material with a melting point of 190°C, which could be purified by recrystallization from ethyl acetate. With the exception of water and residual acetic acid, the crude tetraacetate was more than 99% pure and usually suitable for the Favorskii reaction without recrystallization.

Table XIV. Cage Tetraacetate.

Cage Ketal g (mol)	Acetic Anhydride L (mol)	H_2SO_4 g (mol)	Yield g (%)
100 (0.28)	0.8 (7.8)	27 (0.28)	110 (77)
390 (1.1)	1.1 (10)	320 (3.2)	373 (72)
530 (1.5)	1.2 (11)	200 (2.0)	335 (45)
600 (1.65)	1.2 (11)	200 (2.0)	0 (0) (a)
770 (2.13)	2.0 (21)	300 (3.0)	675 (61) (b)
1755 (4.85)	3.2 (49)	800 (8.2)	2160 (90)
3600 (9.94)	10.0 (95)	1900 (19.4)	4000 (77)
1800 (4.9)	8.0 (78)	1500 (16)	2200 (85)

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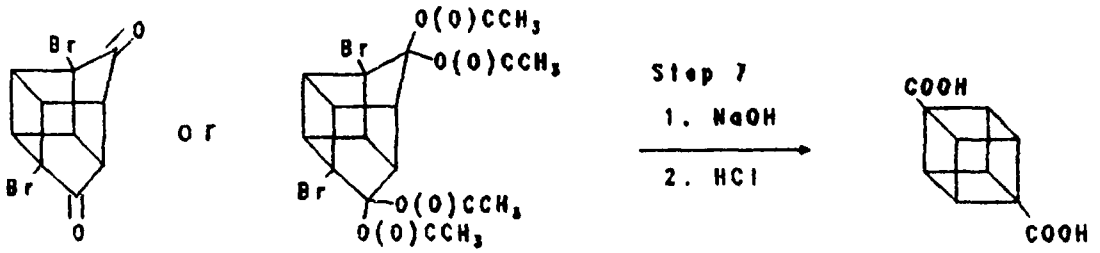
a. Water quench at 20°C.
b. Broken flask

Favorskii Contraction to Cubane-1,4-diacid.



The base-catalyzed double Favorskii ring contraction of the cage dione has been studied in several laboratories[8,14] and has been reported to give varying results with yields below 20%.[9] During Phase I, when the reaction scale was below 100 g of cage dione, cubane dione was consistently obtained in 50% yield. However, during this program, on a kilogram scale, poor results were obtained with yields as low as 15%. Initially it appeared that the difficulty was caused by the long reaction times. The Favorskii reaction was conducted in a 10 molar excess of 25-30% aqueous sodium hydroxide. The base was then neutralized with 37% aqueous hydrochloride acid at a rate such that the reaction temperature did not exceed 0°C. At the kilogram scale, the acidification required over 8 hours with external cooling. It was reasoned that the partially protonated salt was unstable during the long acidification. However, a reverse acidification procedure in which the alkaline mixture was added to excess acid, immediately protonating both carboxylic acids, failed to give better yields.

The Favorskii reaction of the cage dione was found by ^1H NMR in D_2O (see appendix) to proceed in two steps. The first contraction gave a homocubane acid which reacted further to the cubane diacid. The homocubane intermediate was formed in high yield even at caustic concen-

trations as low at 10% and temperatures as low as 50°C. The conversion of the homocubane to the diacid required a reaction temperature of 110°C for 4 hours at base concentrations of 20-40%. At 10% base concentration, the homocubane was only 80% converted after 24 hours at 110°C.

During the second step the formation of impurities, possibly by ring opening reactions, was observed in the region of δ 3.0-3.5 in the ^{1}H NMR. In some reactions, aromatic signals at δ 7-7.5 were also noted. The aromatic material was identified as isophthalic acid, indicating a cataclismic decomposition of either cubane or the homocubane intermediate. Prolonged heating of the reaction mixture increased the amount isophthalic acid, but this by-product was not formed from the reaction of base and cubane diacid in control reactions.

An increase in reaction scale increased the formation of impurities. In parallel runs, 2 g and 20 g of dione were converted to cubane diacid. The small run led to only to cubane diacid, whereas the larger run showed significant side-products. No differences in yield were observed between reactions using distilled water or tap water, argon or oxygen atmosphere, or purified NaOH or commercial 50% caustic. Similarly, radical scavengers such as hydroquinone or chelating agents such as EDTA made no difference in yields. After 10 hours at 55°C and 20% caustic, 97% of the cage dione was converted to the homocubane. The reaction was then heated to 110°C for 4 hours. The result was identical to a control reaction which had been heated directly to 110°C for 4 hours.

When the cage dione was added to caustic solution, some black tar was formed. Reactions in which the cage dione was dissolved in water to form a homogenous solution before addition of the base gave higher yields

(54%) than identical reactions in which the dione was dissolved in caustic (39%). This method had the further advantage that the small amount (usually 5-10%) of unphotolyzed open dione present in the cage dione did not dissolve and could be removed by filtration and recycled.

Effects of other counter ions in the Favorski reaction was also investigated. Sodium hydroxide was found to give better results than either lithium or potassium hydroxide (Table XV).

Table XV. Effect of Counter Ions on Favorski

Caustic[a]	Yield (%)[b]
LiOH	20
NaOH	50
KOH	31

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a. 25% Aqueous Solutions
b. Isolated as Diester

Reaction time was identified as a contributing factor leading to diminished yields. Although pure disalt was indefinitely stable in basic water solutions, in the basic Favorskii reaction mixture it does not appear to be as stable. Thus, when identical reactions were acidified after 30 minutes, 24 hours and 48 hours, cubane diacid was isolated in 49%, 42% and 40% yields, respectively.

An alcohol-contaminated sample of monoketal was recrystallized from CH_2Cl_2 to remove all traces of alcohol, and then photolyzed and reacted with sulfuric acid to produce the cage dione. Although the NMR indicated this material was the same purity as alcohol contaminated material prepared previously, it was lighter in color. When 400 g of this cage dione was

reacted under Favorskii conditions, cubane-1,4-diacid was obtained in 50% yield. This trace of alcohol appears to be the source of the low yields in the Favorskii reaction observed on scale up. This problem was overcome by conducting the hydrolysis of the bisketal in carbon tetrachloride, eliminating alcohol incorporation. Also, purification of the cage dione was effected by conversion to the tetraacetate derivative which was easily purified by recrystallization.

Table XVI. Favorskii Reaction of Cage Dione

Cage Dione g (mol)	50% NaOH kg (mol)	Acidification time h	Yield (a) g (%)
1 (0.003)	0.008 (0.01)	0.5	- (19)(b)
50 (0.16)	0.20 (2.6)	1	- (30)(b)
50 (0.16)	0.36 (4.5)	1	- (43)(b)
50 (0.16)	0.45 (5.7)	1	- (52)(b)
250 (0.79)	2.25 (28)	5	- (23)(b)
500 (1.57)	4.3 (56)		- (41)(b)
1000 (3.14)	8.6 (107)		- (25)(b)
1000 (3.14)	8.6 (107)		- (41)(b)
500 (1.57)	4.3 (56)		- (26)(b)
500 (1.57)	4.3 (56)		- (26)(b)
500 (1.57)	4.3 (56)		- (42)(b)
1000 (3.14)	8.6 (107)		- (21)(b)
500 (1.57)	4.3 (56)		- (31)(b)
500 (1.57)	4.3 (56)		- (31)(b)
500 (1.57)	4.3 (56)		- (31)(b)
850 (2.7)	5.4 (68)		200 (40)
1300 (4.1)	10.5 (131)		210 (42)
1300 (4.1)	10.5 (131)		170 (34)
1480 (4.7)	12.0 (150)		165 (15)

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a. Isolated yield, Pure by NMR and TGA analysis
b. Isolated as Dimethyl Ester.

Table XVII. Favorskii Reaction of Cage Tetraacetate

Tetraacetate g (mol)	50% NaOH kg (mol)	Acidification time h	Yield (a) g (%)
8 (0.015)	0.040 (0.5)	0.1	1.6 (53) (b)
200 (0.36)	1.5 (1.8)	0.5	47 (67) (b)
141 (0.25)	1.0 (12.5)	0.5	26.5 (53) (b)
670 (1.28)			115 (47) (c)
1755 (3.36)			285 (47) (c)
3600 (6.9)			800 (60) (b)
2200 (4.21)			430 (52) (d)

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a. Isolated yield pure by NMR and TGA analysis
b. Reverse acid quench at 0-10°C
c. acid quench at 25°C
d. Reverse acid quench at -5-+5°C

The Favorskii reaction of the cage tetraacetate was investigated. The tetraacetate was insoluble at room temperature in water or alkaline solutions but dissolved readily in 25% sodium hydroxide solution at 100°C to give a dark brown solution characteristic of Favorskii reactions. This solution was heated for 2 hours, acidified and the cubane diacid was isolated. Reactions of 200 g gave 52 and 65% yields. Larger scale reactions of 1.7 kg and 3.6 kg gave 47 and 60% yields. In all cases, the cubane diacid was filtered readily from the reaction mixture and was light tan in color and free from tarry by-products found in the reactions using the cage dione. The samples of diacid were washed with cold acetone and were found to be pure by nmr and DSC analysis. TGA analysis showed the presence of 2-5% inorganic salt.

Temperature control in the acidification of the tetraacetate Favorskii reaction mixture was not critical. Parallel runs acidified at -5°C and 25°C gave 49% and 47% yields, respectively. Similar results were obtained by

addition of acid to the reaction mixture (reverse quench) or addition of the reaction mixture to acid. A carefully acidified reaction mixture was monitored by NMR at pH 14, 12, 7, 4, and 1 and no additional side-products were formed. The solubility of cubane diacid is 2.5 mg/ml (0.25%) at pH 7 and essentially zero at pH 1. Dilution of the basic Favorskii reaction mixtures by 50% with water prior to acidification had no effect on yields, but further dilution appeared to lower the yield.

The diacid obtained from low yield Favorskii reactions was difficult to purify because of the presence of large amounts of a complex black material. Prior to this study, cubane-1,4-dicarboxylic acid was purified by conversion to the dimethyl ester. The crude diacid contaminated with salt and tarry by-products was dissolved in methanol containing catalytic sulfuric acid and stirred for 10-24 hours at room temperature gave crude diester. Purification of the crude diester by bulb-to-bulb distillation at 100-125°C at 0.5 mm gave dimethyl ester of 98% purity. The temperature must be carefully controlled as in one case at 140°C, an explosion occurred. This method of purification was too slow to be practical on a large scale. Steam distillation of crude cubane-1,4-dicarboxylate was also used on a small scale run but the ester was water soluble and methylene chloride extraction was needed. On scale up the diester was hydrolyzed during this process.

Recrystallization of the crude diester from a variety of solvents was investigated. The black tarry impurities were not removed by recrystallization from alcohols, acetone or chlorinated solvents. The best results were obtained by recrystallization of the diester from hexane in which the impurities were insoluble. Since the solubility of the diester in hexane

was less than 1%, large volumes were required. The use of higher boiling heptane and octane did not improve the solubility of the diester. The solubility problem was overcome by continuous Soxhlet extraction of the diester with hexane or heptane. The use of 500 mL thimbles allowed the purification of 500 g of cubane diester per week. The diester purified by hexane extraction was light yellow and contained a small amount of dimethyl isophthalate. This aromatic impurity was insoluble in acetone and was removed by acetone extraction followed by low temperature recrystallization from methylene chloride.

Methods of isolating the diacid directly from the Favorskii reaction mixture were studied. Addition of excess diethyl sulfate to the basic solution gave a 50% yield of monoethyl ester. Reaction of this material with acidic ethanol gave the diethyl ester. Addition of tetra-n-butylammonium salts followed by continuous extraction with toluene or methylene chloride gave trace amounts of cubane diacid disalt. The dimethyl ester was prepared in low yield by addition of diazomethane to the basic solution.

After the diester was purified by recrystallization, it was hydrolyzed with base to regenerate the diacid. Since both the esterification and the hydrolysis steps gave yields of 60 to 80%, this transformation resulted in substantial losses. A method was sought to isolate the pure diacid from its crude preparation mixture without esterification. The solubility of cubane-1,4-dicarboxylic acid in common solvents was investigated and is shown in Table XVIII.

Table XVIII. Solubility of Cubane-1,4-dicarboxylic Acid

Solvent	Solubility g/L	Comments
THF	>14	a
Acetone	4	a
Ethyl Acetate	1.3	a
Acetonitrile	0.95	a
Diethyl Ether	0.90	b
Dichloromethane	0.30	c

Solubility at 25°C of a Saturated Solution
a. Dissolves impurities
b. Partially dissolves impurities
c. Does not dissolve impurities

When the crude diacid was prepared from the tetraacetate rather than the cage dione, it contained only small amounts of tarry by-products and could be purified by washing with cold acetone or ethyl acetate. Cubane-1,4-diacid has a low solubility in these solvents, but the organic impurities were extracted readily leaving essentially pure diacid. In some cases, the crude reaction product contained sodium bromide or sodium chloride. These inorganic salts were removed by dissolving the diacid in aqueous base, filtering, and reprecipitating with hydrochloric acid.

Improvements were made in the quality control procedures for each step of the cubane synthesis. Purified samples of each of the six intermediates in the process were prepared and a quantitative glc procedure developed using an internal reference. The purity of the diacid was established by titration with standard base and by DSC and TGA analysis. The DSC of the diacid in a sealed container over the range of 20°C to 300°C at 10°C/min showed a minor exotherm at 220°C (10.75 J/g), a major

decomposition at 246°C (1656 J/g) and a minor exotherm at 276°C (141 J/g). TGA analysis of the diacid in air showed no significant weight loss up to 200°C, 3.4% loss to 226°C and catastrophic decomposition above 245°C (50% weight loss at 248°C). A 4% carbon ash residue remained at 275°C which disappeared by 600°C.

Table XIX. Relative GC Retention Times for Cubane Intermediates.

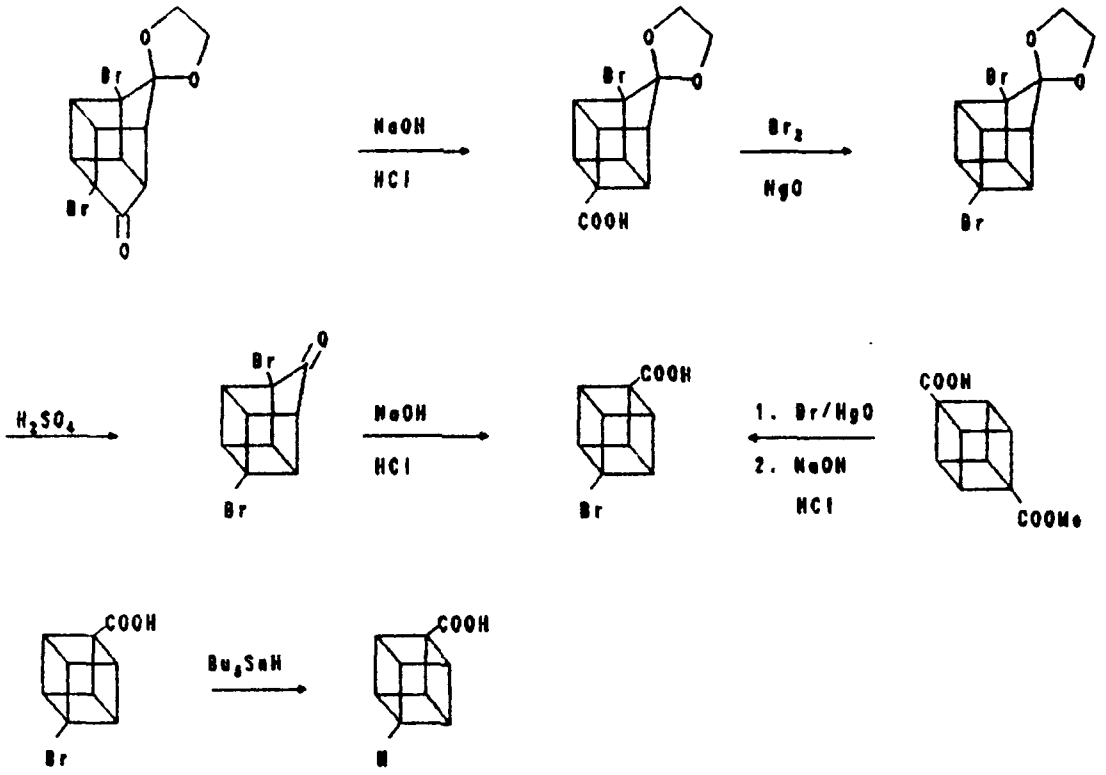
Compound	Time	Method
Toluene	0.625	a
Cyclopentanone	1.1	a
Cyclopentanone Ketal	2.9	a
Monobromo Ketal	1.9	b
Dibromo Ketal	2.8	b
Tribromo Ketal	3.5	b
Bisketal	7.5	b
Monoketal	6.8	b
Dione ketal	6.0	b

Using Perkin-Elmer 3900 gas chromatograph and 6' 3% OV-17 on Chrom-Q column
a. 50°C to 180°C at 16°C/min
b. 170°C to 280°C at 16°C/min

B. Synthesis of Cubanecarboxylic Acid.

The monofunctional cubane derivatives have possible applications as pendant groups in energetic polymers. An example of this concept has been demonstrated by Manser[12] at Aerojet in polymers of cubyl ether derivatives of oxetanes. Therefore, efficient methods of preparing this cubanecarboxylic acid were investigated (Scheme 2).

The cage monoketal was available from the synthesis of cubane diacid. Reaction of this intermediate with base prior to deketalization results in a mono-Favorskii reaction to form a homocubane acid.[9] This reaction was found to give yields above 80% at the 1 kilogram scale. The homocubane



Scheme 2

acid was decarboxylated with bromine and mercuric oxide[13] to give 1,4-dibromopentacyclo[4.3.0.0.^{2,5}0.^{3,8}0.^{4,7}]nonan-9-one ethylene ketal in 65-70% yield. Deketalization of this intermediate gave poor yields on scale-up. The resulting dibromo ketone was insoluble in methylene chloride and was isolated from sulfuric acid by ether extraction. On a 50 g scale the hydrolysis was complete in 48 hours, but on a 250 g scale, 5 days was required. The yield of the ketone at these levels was 50% and 30%, respectively. The reaction of sodium hydroxide and the dibromo ketone gave 4-bromocubanecarboxylic acid in 40% yield on a 10 g scale, but only 10-15% on the 250 g scale. This second Favorskii step required reflux times of ten hours at 40% base concentrations. Because of the poor yields of this step, an alternate route to the synthesis of 4-bromocubanecar-

boxylic acid was chosen.

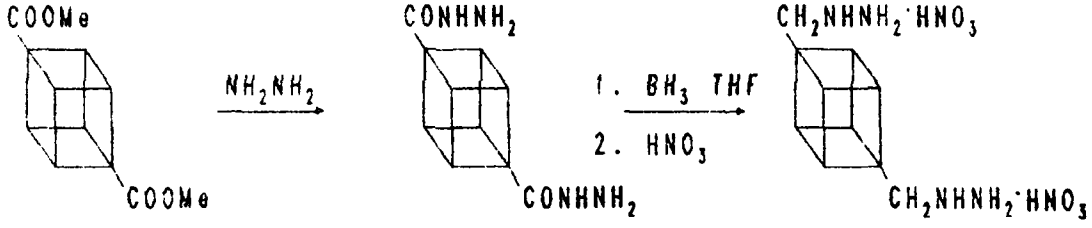
Dimethyl cubane-1,4-dicarboxylate was converted to the monoacid-monoester by selective hydrolysis using a procedure of Eaton.[5] Hydrolysis with molar amounts of sodium hydroxide, precipitation of the mono salt with ether, and acidification gave 80% yields of the monoacid monoester. Reaction of the monoacid with bromine and mercuric oxide gave 4-bromocubanecarboxylic acid in 90% yield and 250 g of the acid was produced by this method. This method gave reliable results on scale-up.

The bromo acid was reduced with tri-n-butyltin hydride[14] to give cubanecarboxylic acid. This reaction gave nearly quantitative yields on a 5 g scale but poor yields on a 100 g scale. AIBN and benzoyl peroxide were used as initiators and ultraviolet light was found to catalyze the reaction, but also destroy the tin hydride. On a small scale, the tin hydride was used in molar amounts for the reduction, but at 100 g scale, a 3:1 molar ratio was required to effect complete reduction. The product was isolated by dissolving it in aqueous base, removing the tin by-products by ether extraction and reprecipitating with acid. The course of the reduction was followed by ^{1}H NMR. Glc gave unreliable results because of decomposition of 4-bromocubane carboxylic acid on the column.

The direct synthesis of cubanecarboxylic acid by the thermal decomposition of the peroxy-*t*-butyl methyl ester[8] was investigated. This reaction was found to give the desired monoacid contaminated with a substantial amount of a cubane derivative containing a *t*-butyl group, possibly the *t*-butyl ether. Only column chromatography was found to purify the contaminated monoacid. This method was not considered feasible for scale up.

C. Synthesis of Cubyl Hydrazines.

The reaction of dimethyl cubane-1,4-dicarboxylate with hydrazine hydrate gives a quantitative yield of the 1,4-dihydrazide. The reduction of the dihyrazide to cubane-1,4-dihydrazine was attempted following several literature procedures.[15,16] Lithium aluminum hydride or boro-hydrides gave no cubane-containing products under normal reaction conditions. However, when a 10 molar excess of BH_3 in THF was used, reduction of the hydrazide to the hydrazine occured. The dihydrazine was not stable as a free base and was highly soluble in water. Therefore the reduction mixture was quenched with methanolic solutions of acids and the hydrazines isolated as the corresponding salts.



The dihydrazine dioxalate was the most stable salt isolated, but the diacetate, ditriflate, disulfate and dinitrate were also prepared. The diperchlorate and dinitroformate salts decomposed after several hours at room temperature. All of the cubane di(methylene hydrazine) salts showed two peaks by ^1H NMR; a singlet at δ 4.0 (cubyl hydrogens) and a singlet at δ 3.7 (methylene hydrogens). The ^{13}C NMR of the sulfate salt showed three signals that were assigned after a gate decoupling experiment: a signal at δ 48.9 (decoupled gave a singlet which was assigned as quaternary carbons on the cubane ring), signal at δ 48.2 (decoupled gave a triplet, J_{C-H} = 143 Hz, which was assigned to the methylene carbons), and

a signal at δ 40 (decoupled gave a doublet, J_{C-H} = 158 Hz, which was assigned as the tertiary carbon on the cubane). The high value of the later ^{13}C C-H coupling constant was consistent with those found in highly strained cubane systems. Elemental analysis showed that the oxalate salt contained two oxalate groups and that each of the hydrazine groups was monoprotonated.

$$HC_2O_4^- \quad H_2NNH_2CH_2\text{-Cub-}CH_2NH_2NH_2^+ \quad C_2O_4H^-$$

Attempts were made to prepare a tetrasalt of the dihydrazine by the use of stronger acids. Nitric and sulfuric acid gave disalts. Quantitative analysis by ^1H NMR and ^{19}F NMR of the dihydrazine triflate salt prepared in excess triflic acid, showed that no higher salts were obtained. Cubane 1,4-di(methylenehydrazine) was observed as a free base in the ^1H NMR by neutralizing the oxalate salt. However, this material was unstable and decomposed on standing to unidentified tars.

Table XX. Cubane-1,4-di(methylenehydrazine) Salts.

Cubane 1,4-di(methylene hydrazine) salt	yield	stability in air
oxalate	83%	stable
sulfate	80%	stable
trifluoroacetate	52%	stable
triflate	47%	stable
nitrate	70%	slightly unstable
perchlorate	78%	unstable

Reaction of tetramethyl cubane-1,2,4,7-tetracarboxylate with hydrazine hydrate gave the tetrahydrazide in quantitative yield. Reduction of the tetrahydrazide with excess BH_3 in THF followed by acid quench with oxalic

acid gave the corresponding 1,2,4,7-tetra(hydrazinomethyl)cubane as the tetra oxalate salt in 89% yield. Attempts to prepare nitrate and perchlorate salts of this tetrahydrazine were not successful.

III. EXPERIMENTAL SECTION[17]

Cyclopentanone Ethylene Ketal. A mixture of toluenesulfonic acid (250 g, 1.32 mol), toluene (30 gal), cyclopentanone (17.5 gal, 747 mol), and ethylene glycol (17.5 gal, 1188 mol) was heated at reflux for 28 h while the water (5.5 gal) was removed by azeotropic distillation. Glc analysis indicated that the reaction was was 83% complete. The toluene layer was separated from the unreacted ethylene glycol, and was distilled in three 14 gal portions through a 5 foot bubble column using a reflux ratio of 3:1. Toluene and cyclopentanone were collected until a head temperature of 150°C was attained. The reflux was discontinued and cyclopentanone ethylene ketal was collected until a pot temperature of 165°C was reached. After the third portion was distilled, the pot residues were combined and distilled to a pot temperature of 175°C to afford a total of 84.8 kg (85%) of cyclopentanone ethylene ketal, a colorless, hygroscopic liquid, bp 152-155.

2,2,5-Tribromocyclopentanone Ethylene Ketal. Liquid bromine (460 g, 2.88 mol) was added, dropwise, over 15 min, to a stirred solution of CH_2Cl_2 (700 ml), p-dioxane (88 g, 1 mol) and cyclopentanone ethylene ketal (100 g, 0.78 mol) at 18°C. The mixture was warmed to 28°C over 1 h and the progress of the reaction was followed by glc. The mixture was cooled to 15°C, and water (500 ml) and saturated Na_2SO_3 solution (500 ml) were added. The mixture was stirred for 10 min, the layers separated, and the organic layer was washed with a mixture of saturated Na_2SO_3 solution (500

ml) and 17% NaOH solution (500 ml). The organic layer was dried ($MgSO_4$), and the solvent evaporated *in vacuo* at 40°C. The residual oil was crystallized at -40°C for 16 h. The precipitate was filtered, washed with cold CCl_4 and air dried for 1 h to give 120 g (54%) of 2,2,5-tribromocyclopentanone ethylene ketal, a white solid, mp (DSC) 71-73°C: NMR ($CDCl_3$) δ 2.1 (m, 1 H), 2.7 (m, 2 H), 3.0 (m, 1 H), 4.4 (m, 4 H), 4.84 (m, 1 H); ^{13}C NMR 30.1, 44.9, 47.3, 67.7, 68.0, 114.5.

***endo*-2,4-Dibromodicyclopentadiene-1,8-dione Bisethylene Ketal from 2,2,5-Tribromocyclopentanone Ethylene Ketal.** A solution of 2,2,5-tribromocyclopentanone ethylene ketal (120 g, 0.33 mol) in CH_2Cl_2 (100 ml) was added rapidly to a refluxing solution of NaOH (45 g, 1.12 mol) in ethanol (700 ml), and the mixture was refluxed for 3 h. The progress of the reaction was monitored by following the disappearance of 2,5-dibromocyclopentenone ethylene ketal by glc. The hot mixture was poured into water (10 l) and stirred for 2 h. The precipitate was filtered, washed with water (2 X 200 ml), and dried 16 h *in vacuo* to give 55 g (84%) of *endo*-2,4-dibromodicyclopentadiene-1,8-dione bisethylene ketal as a pale yellow solid, mp 178°C (DSC): ^1H NMR 2.8 (t, 1 H), 3.05 (d,d, 1 H), 3.5 (d,d, 1 H), 4.0 (m, 4 H), 4.2 (m, 4 H), 5.9 (d, 1 H), 6.05 (d, 1 H), 6.2 (d,d, 1 H); ^{13}C NMR 47.3, 49.6, 55.7, 65.2, 65.3, 66.2, 66.4, 67.8, 115.7, 126.1, 128.1, 132.5, 133.1, 124.5.

***endo*-2,4-Dibromodicyclopentadiene-1,8-dione Bisethylene Ketal from Cyclopentanone Ethylene Ketal.** Liquid bromine (27.2 kg, 170 mol) was added with a metering pump to a stirred solution of CH_2Cl_2 (30 l), p-dioxane (5.26 kg, 59.7 mol, freshly distilled from $LiAlH_4$)) and cyclopentanone ketal (6.59 kg, 51.4 mol) at such a rate that the temperature did

not exceed 20°C. Ice water cooling was required to control a significant exotherm during the addition of the first 9 kg of bromine. Subsequently, the reaction mixture spontaneously cooled to 12°C as a result of the evolution of hydrogen bromide gas. After the addition of bromine was complete, the mixture was stirred for 1 h at 12-15°C, warmed to 27°C over 1 h, and stirred 1 h. Glc analysis indicated that the bromination was complete.

The reaction mixture was cooled to 10°C and water (12 l), saturated Na_2SO_3 (12 l), and 15% aqueous NaOH (10 l) were added sequentially. This mixture was stirred for 10 min, and the organic layer was washed with saturated sodium sulfite solution (8 L). Methylene chloride (28 l) was removed by distillation. The residue was cooled to 30°C and added slowly to a refluxing solution of ethanol (105 l) and NaOH (7 kg, 175 mol). The mixture was refluxed for 3 h, during which time a mixture of CH_2Cl_2 and ethanol (20 l) was removed by distillation. The residue was added to water (250 gal), stirred for 8 h, and allowed to stand for 2 d. The precipitate was centrifuged, washed with water (2 X 20 l), and spun dry for 6 h to give 8.35 kg (80%) of *endo*-2,4-dibromodicyclopentadiene-1,8-dione bisethylene ketal, as a beige solid containing 5% water, mp 178°C (DSC): ^1H NMR 2.8 (t, 1 H), 3.05 (d,d, 1 H), 3.5 (d,d, 1 H), 4.0 (m, 4 H), 4.2 (m, 4 H), 5.9 (d, 1 H), 6.05 (d, 1 H), 6.2 (d,d, 1 H); ^{13}C NMR 47.3, 49.6, 55.7, 65.2, 65.3, 66.2, 66.4, 67.8, 115.7, 126.1, 128.1, 132.5, 133.1, 124.5.

***endo*-2,4-Dibromodicyclopentadiene-1,8-dione-8-ethylene Ketal.** A solution of *endo*-2,4-dibromodicyclopentadiene-1,8-dione bisethylene ketal (750 g, 1.85 mol) in carbon tetrachloride (10 l) was refluxed for 15 min and filtered while hot, as rapidly as possible through a pad of celite. Con-

centrated HCl (37%, 2 l) was added to the filtrate, and the mixture was refluxed for 2 h until the glc analysis indicated the conversion of the bisketal was complete. While the temperature was above 70°C, the layers were separated, and the organic layer was cooled to -20°C. The resulting precipitate was filtered to give 470 g (60%) of *endo*-2,4-Dibromodicyclopentadiene-1,8-dione-8-ethylene ketal, mp (DSC) 172-173°C (lit[9]. 172-174°C): ^{1}H NMR ($CDCl_3$) δ 3.04 (m, 1 H), 3.21 (d,d, 1 H), 3.65 (d,d, 1 H), 3.9-4.35 (m, 4 H), 5.95 (m, 2 H), 7.63 (d, 1 H); ^{13}C NMR 48.0, 48.6, 52.9, 66.4, 67.1, 67.7, 127.6, 131.0, 131.2, 135.4, 159.1, 199.5.

5,9-Dibromopentacyclo[5.3.0.0.^{2,5}0.^{3,9}0.^{4,8}]decane-6,10-dione-6-ethylene ketal. A solution of freshly recrystallized *endo*-2,4-dibromodicyclopentadiene-1,8-dione-8-ethylene ketal (800g, 2.2 mol) in CH_2Cl_2 (8 l) was photolyzed (1200 w Hanovia) for 24-100 h. The progress of the reaction was followed by glc. When the conversion was over 90% complete, the solvent was evaporated and the crude mixture was used in the subsequent step without further purification. Recrystallization gave a white solid, mp 141°C and 149°C (DSC): ^{1}H NMR 2.6 (1 H), 2.9 (1 H), 3.4 (m 4 H), 4.1 (m 4 H); ^{13}C NMR 41.1, 43.2, 43.9, 46.8, 46.9, 47.7, 54.2, 60, 65.8, 66.3, 120.9, 204.9.

5,9-Dibromopentacyclo[5.3.0.0.^{2,5}0.^{3,9}0.^{4,8}]decane-6,10-dione. 5,9-Dibromopentacyclo[5.3.0.0.^{2,5}0.^{3,9}0.^{4,8}]decane-6,10-dione-6-ethylene ketal (2 kg, 6.5 mol) was dissolved in concentrated H_2SO_4 (4 L). This solution was stirred at room temperature for 4 h and then extracted with CH_2Cl_2 (7 L) in a continuous liquid-liquid extractor for 3 d, and an additional 3 days with fresh CH_2Cl_2 (7 L). The combined organic layers were dried ($MgSO_4$) and filtered through a 2 inch pad of silica gel and the solvent was evaporated. The residue of 1.25 kg (70%) was 5,9-dibromo-

pentacyclo[5.3.0.0.^{2,5}0.^{3,9}0.^{4,8}]decane-6,10-dione, an amorphous beige solid, pure by ^{1}H NMR and glc analysis and was used without further purification: ^{1}H NMR 2.3 and 3.0.

5,9-Dibromopentacyclo[5.3.0.0.^{2,5}0.^{3,9}0.^{4,8}]decane-6,6,10,10-tetraacetate. A solution of 5,9-dibromopentacyclo[5.3.0.0.^{2,5}0.^{3,9}0.^{4,8}]decane-6,10-dione-6-ethylene ketal (1755 g, 4.85 mol) in acetic anhydride (5.2 L) was heated to 30°C and H_2SO_4 (1.5 L) was added portionwise at 30-35°C. The mixture was cooled to 10°C over 2 h and then added to a rapidly stirred mixture of ice/water (15 kg/ 20 L) over 20 min at a rate such that the reaction temperature stayed between -15 and -5°C. The precipitate was filtered and washed sequentially with water (20 L), 10% aqueous potassium carbonate (20 L), and water (20 L). It was then dried (35°C/1.0 mm) for 4 h to give 2160 g (90%) of 5,9-dibromopentacyclo- [5.3.0.0.^{2,5}0.^{3,9}0.^{4,8}]decane-6,6,10,10-tetraacetate, mp 185-190°C. An analytical sample was prepared by recrystallization from ethyl acetate/hexane, mp 190-192°C: IR (CH_2Cl_2) 3050, 1760, 1420, 1360, 1220, 1190, 1060, 1020 cm^{-1}; ^{1}H NMR δ 4.0 (m, 2 H), 3.3 (dd, J = 8.0, 5.0 Hz, 2 H), 3.2 (t, J = 5.3 Hz, 2 H), 2.1 (s, 6 H), 2.05 (s, 6 H); ^{13}C NMR δ 168.07, 167.45, 110.61, 60.82, 48.87, 47.01, 42.59, 21.43. Anal. Calcd for $C_{18}H_{18}BrO_6$: C, 41.40; H, 3.47. Found: C, 41.58; H, 3.59.

5,9-Dibromopentacyclo[5.3.0.0.^{2,5}0.^{3,9}0.^{4,8}]decane-6,10-dione Bisethylene Ketal. Unpurified 5,9-dibromopentacyclo[5.3.0.0.^{2,5}0.^{3,9}0.^{4,8}]decane-6,6,10,10-tetraacetate (21 g, 0.05 mol) containing ethylene glycol and acetic acid was heated with 10% aqueous Na_2CO_3 (100 mL) at 60°C for 3 h. The dark red mixture was filtered, and the precipitate was recrystallized from toluene to give 2.5 g (10%) of 5,5-dibromopentacyclo[5.3.0.0.^{2,5}0.^{3,9}0.^{4,8}]-decane-6,10-dione bisethylene ketal, as a white solid, mp 190-194°C. An

analytical sample was prepared by recrystallization from ethyl acetate-hexane, mp 195-197°C: IR (CH_2Cl_2) 3050, 2970, 1620, 1495, 1320, 1220, 1140, 1090, 1050, 1030, 1010, 960 cm^{-1}; ^1H NMR δ 4.2 (m, 4 H), 4.0 (m, 4 H), 3.25 (s, 4 H), 2.63 (m, 2 H); ^{13}C NMR δ 120.49, 66.3, 65.8, 61.6, 49.6, 45.8, 44.5. Anal. Calcd for $C_{14}H_{14}O_4Br_2$: C, 41.40, H, 3.47. Found: C, 40.98, H, 3.57.

Cubane-1,4-dicarboxylic acid from 5,9-Dibromopentacyclo-[5.3.0.0.^{2,5}0.^{3,9}0.^{4,8}] decane-6,6,10,10-tetraacetate. 5,9-Dibromopentacyclo[5.3.0.0.^{2,5}0.^{3,9}0.^{4,8}]decane-6,6,10,10-tetraacetate (3600 g, 6.9 mol) was added portionwise to a stirred, refluxing solution of NaOH (9 kg, 222 mol) in water (27 l) over 15 min. The mixture was refluxed for 2 h, cooled to room temperature and concentrated HCl (24 L) was added at a rate such that the reaction temperature did not exceed 0°C. After 1 h, the precipitate was filtered, washed with water, and air dried for 16 h. The residue was triturated with cold (-20°C) acetone (1 L), filtered and dried (30°C/ 1 mm Hg) to give 830 g (62%) cubane diacid as a beige solid, mp (DSC) 226-228°C, dec 230°C: NMR (D_2O/Acetone-d6) δ 4.18 (s, 6 H).

Cubane-1,4-dicarboxylic Acid from 5,9-Dibromopentacyclo-[5.3.0.0.^{2,5}0.^{3,9}0.^{4,8}]decane-6,10-dione. A solution of 5,9-dibromopentacyclo-[5.3.0.0.^{2,5} 0.$^{3.9}$.0$^{4.8}$]deca-6,10-dione (1000 g, 3.1 mol) and aqueous sodium hydroxide (30% 10.85 kg) in a 22 L 3 neck round bottom flask was refluxed for 5 h. The solution was cooled to 0 °C to 5 °C with a methanol ice-bath and acidified by dropwise addition of 37% HCl (6.5 L). The mixture was stirred at 0 °C for 30 min, filtered and air dried to give brown solid mixture (approximately 60:40) of cubane-1,4-dicarboxylic acid and sodium chloride 450 g, mp 231-235 °C; ^1H NMR acetone-d6) 4.1 (s, 6 H)

Purification of Cubane-1,4-dicarboxylic Acid from the Favorskii Mixture. A mixture of crude cubane-1,4-diacid and salt (800 g) (obtained from the filtration of an acidified Favorskii reaction mixture resulting from 1 kg of cage dione) was stirred with 10% aqueous NaOH (600 mL) for 0.5 h and filtered. The filtrate was acidified by dropwise addition of 37% HCl. The solid was filtered, and washed with cold water (3 x 50 mL) and cold acetone (3 x 50 mL), and dried at ambient temperature *in vacuo* (0.5 mm) to give 175 g (30% based on cage dione) of 95% pure cubane-1,4-dicarboxylic acid (by titration with standard NaOH) as a white powder, mp 225°C: ^{1}H NMR (DMSO-d6) δ 4.09 (s).

Dimethyl Cubane-1,4-dicarboxylate. Crude cubane-1,4-dicarboxylic acid-sodium chloride mixture (450 g) was dissolved in methanol (3.7 L) containing concentrating sulfuric acid (15 mL) and the solution was refluxed overnight. The reaction mixture was filtered hot and the solvent was evaporated to give a brown solid which was continuously extracted (Soxhlet) with hexane for 10 h. The hexane solution was cooled and filtered to give 120 g of dimethyl cubane-1,4-dicarboxylate as a light brown solid, mp 161-162 °C (lit[9] 161-162°C): ^{1}H NMR δ 3.55 (s, 6 H), 4.1 (s, 6 H).

1-Bromopentacyclonona-9-one Ethylene Ketal 4-Carboxylic Acid. A solution of 5,9-dibromopentacyclo[5.3.0.0.^{2,5}0.^{3,9}0.^{4,8}]decane-6,10-dione-6-ethylene ketal (350 g, 0.998 mol) and KOH (2.1 kg, 37 mol) in water (7.0 L) was stirred at room temperature for 20 min, and then refluxed for 2 h. The solution was cooled, acidified with concentrated HCl (3.0 L) and filtered. The precipitate was washed (ethanol) and dried to give 193 g (65%) of 1-bromopentacyclononan-9-one ethylene ketal 4-carboxylic acid,

as a light brown solid, mp 186-187 °C (lit[13] 187-189): ^{1}H NMR ($CDCl_3$) δ 2.98-3.21 (m, 1 H), 3.5-3.88 (m, 5 H), 3.88-4.32 (m, 4 H).

1,4-Dibromopentacyclononan-9-one Ethylene Ketal. A solution of bromine (400 g, 129 mL, 2.5 mol) in CH_2Br_2 (500 mL) was added dropwise to a solution of 1-bromopentacyclononan-9-one ethylene ketal 4-carboxylic acid (500 g, 1.66 mol) in boiling CH_2Br_2 (2.0 L) containing red HgO (402 g, 1.86 mol), and the mixture was refluxed for 3 h under nitrogen. The mixture was cooled to room temperature, filtered, and the solvent was evaporated to give a light brown solid. This residue was extracted with hexane (3 x 300 mL), and the combined extracts were evaporation to give 420 g (80%) of 1,4-dibromopentacyclononan-9-one ethylene ketal as a white solid, mp 140-142 (lit[13] 138 - 141°C): ^{1}H NMR ($CDCl_3$) δ 3.80 - 4.40 (m, 4 H), 3.60 - 3.85 (m, 5 H), 2.95 - 3.28 (m, 1 H).

1,4-Dibromopentacyclononan-9-one. 1,4-Dibromopentacyclononan-9-one ethylene ketal (250 g, 0.76 mol) was added to concentrated H_2SO_4 (2500 mL) and water (1200 mL) and was the mixture stirred at room temperature for 3 d. The solution was poured over crushed ice, and extracted with ether (4 x 500 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give 200 g (90%) of 1,4-dibromopentacyclononan-9-one, mp 140-142°C (lit[13] 132-134): IR (KBr) 3040, 1755 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.6 - 4.2 (mult. 5 H), 3.2 - 3.55 (m, 1 H).

4-Bromocubanecarboxylic Acid from 1,4-Dibromopentacyclononan-9-one. 1,4-Dibromopentacyclononan-9-one (200 g, 0.70 mol) was dissolved in aqueous 25% KOH (4.0 L) and the solution was refluxed for 4 h. The solution was cooled to room temperature, diluted with water (2 L) and extracted with ether. The water layer was acidified with 10% aqueous HCl

and was extracted with ether (4 x 500 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give 90 g (48%) of 4-bromocubanecarboxylic acid as a dark brown solid, mp 204°C: ^1H NMR (Acetone -d_6) δ 4.28 (m, 6 H). The acid was further purified by sublimation (100°C /0.5 mm), mp 206-209°C (lit[14] 210°C): ^1H NMR ($CDCl_3$) δ 4.28 (m 6 H).

4-Carbomethoxycubane Carboxylic Acid. A solution of NaOH (13.4 g, 0.33 mol) in methanol (350 mL) was added dropwise to a stirred solution of dimethyl cubane-1,4-dicarboxylate (70 g, 0.318 mol) in diethyl ether (1600 mL) and THF (700 mL) at room temperature under nitrogen. The milky suspension was stirred 15 h, and the solvent was evaporated *in vacuo*. The residue was dissolved in water (2.3 L), and extracted with chloroform (200 mL x 2). The organic layer was dried ($MgSO_4$), and evaporated to give unreacted dimethyl cubane-1,4-dicarboxylate (12 g, 17%). The aqueous layer was acidified with concentrated HCl to pH 3, and was extracted with chloroform (4 x 250 mL). The combined organic layers were dried ($MgSO_4$), and evaporated to give 60 g (90%) of 4-carbomethoxycubane carboxylic acid as a white solid, mp 180-182°C, ^1H NMR δ 3.7 (s, 3 H), 4.27 (m, 6 H).

4-Bromocubanecarboxylic Acid from 4-Carbomethoxycubanecarboxylic Acid. Bromine (155.8 g, 0.97 mol) was added dropwise to 4-carbomethoxycubanecarboxylic acid (118 g, 0.57 mol) and red mercuric oxide (121 g, 0.57 mol) in dibromomethane (2.0 L) at 75°C in a flask protected from light. The mixture was heated at 75°C for 2 h during which time all the mercuric oxide dissolved. The solvent was evaporated and the residue was extracted with hexane. The hexane was evaporated to give 140 g (90%) of methyl-4-bromocubanecarboxylate mp 110-113°C.

Methyl-4-bromocubanecarboxylate (53 g, 0.22 mol) was refluxed in 10% aqueous NaOH (830 mL) for 2 h. The resulting solution was extracted with chloroform and acidified with 6 N HCl. The aqueous solution was extracted with ether (4x 300 mL). The combined organic layers were washed with saturated NaCl, dried ($MgSO_4$), and evaporated to give 40 g (80%) of 4-bromocubanecarboxylic acid, mp 206-209°C; (lit[14] 210°C): ^1H NMR ($CDCl_3$) δ 4.28 (m, 6 H).

Cubanecarboxylic Acid. A solution of 4-bromocubanecarboxylic acid (38 g, 0.167 mol) and tri-n-butlytin hydride (65 g, 0.223 mol) in THF (2.3 L) was irradiated with a medium pressure mercury lamp for 4 h. The solvent was evaporated, and the residue was dissolved in ether (900 mL) and was extracted with 10% aqueous NaOH (200 mL). The aqueous solution was washed with ether (100 mL), the organic extracts were discarded. The aqueous layer was neutralized with 10% aqueous HCl, and extracted with ether (3 x 150 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated to give 21.5 g (93%) of cubanecarboxylic acid as a white solid, mp 123-125°C (lit[14] 125-126°C): ^1H NMR (Acetone-d_6) δ 3.9 (m, 4 H), 4.35 (m, 3 H).

Cubane-1,4-di(methylenehydrazine) Dioxalate. A solution of cubane 1,4-dihydrazide (0.5 g, 2.27 mmol) in 1 M BH_3.THF (23 mL, 23 mmole) was refluxed under N_2 for 20 hours. Excess BH_3.THF was removed by distillation and deoxygenated methanol (20 mL) was added to the residual white solid at room temperature. The solution was then refluxed for 30 minutes and cooled to room temperature. A solution of oxalic acid (1.0 g, 11 mmol) in methanol (10 mL) was then added and the solution stirred at room temperature for another 30 minutes. Ether (100 mL) was added to the

reaction mixture until no more solid precipitated. The solution was placed in the freezer for 5 h, then filtered to give a white solid: 0.7 g (83%), m.p. 224-225°C (dec.). Analytically pure sample was obtained by recrystallization from MeOH/Et_2O, mp 224-255°C (dec): IR (KBr) 3100, 1800, 1640, 1380, 1210 cm^{-1}; ^1H NMR (D_2O) 3.94 (s, 6 H), 3.41 (s, 4 H). Anal. Calcd for $C_{14}H_{20}N_4O_8$: C, 45.19; H, 5.37; N, 15.05. Found: C, 45.08; H, 5.86; N, 15.02.

Cubane-1,4-di(methylenehydrazine) Dinitrate. The dinitrate salt was prepared by the above procedure using HNO_3 to give a 70% yield of a white solid, m.p. 195-196°C (dec.): IR (KBr) 3100, 1550, 1250, 1190, 1040, ^1H NMR (D_2O) 3.93 (s, 6 H), 3.42 (s, 4 H); Anal. Calcd for $C_{14}H_{18}N_6O_6$: C, 37.76; H, 5.66; N, 26.41. Found: C, 36.80; H, 5.59; N, 24.72.

Cubane-1,4-di(methylenehydrazine) Disulfate. The disulfate salt was prepared by the above procedure using H_2SO_4 to give an 80% yield of a white solid, m.p. 168-169°C (dec.): ^1H NMR (D_2O) 3.93 (s, 6 H), 3.42 (s, 4 H); ^{13}C NMR (DMSO) 53.17, 53.09, 44.79.

Cubane-1,4-di(methylenehydrazine) Ditriflate. The ditriflate salt was prepared by the above procedure using triflic acid to give 47% of a white solid, m.p. 210-211°C (dec.): ^1H NMR (D_2O) 3.93 (s, 6 H), 3.42 (s, 4 H). ^{13}C NMR (DMSO) 44.06, 51.91, 53.74.

Cubane-1,4-di(methylenehydrazine) Ditrifluoroacetate. The ditrifluoroacetate salt was prepared by the above procedure using trifluoroacetic acid to give 52% of a white solid, m.p. 148-149°C (dec): IR (KBr) 3100, 1680, 1400, 1350, 1200 cm^{-1}; ^1H NMR (D_2O) 3.95 (s, 6 H), 3.43 (s, 4 H).

Cubane-1,4-di(methylenehydrazine) Diperchlorate. The diperchlorate

salt was prepared by the above procedure using perchloric acid to give 78% of a white solid which decomposed after several hours at room temperature: ^{1}H NMR (D_2O) 3.96 (s, 6 H), 3.42 (s, 4 H).

Cubane-1,2,4,7-tetracarboxylic Acid Tetrahydrazide. Tetramethyl cubane-1,2,4,7-tetracarboxylate (5.0 g, 14.9 mmol) was dissolved in anhydrous hydrazine (26 mL) and the solution was refluxed for 3 h. The solution was cooled, diluted with methanol (120 mL) and filtered. The precipitate was washed with methanol and ethyl acetate to give 4.9 g (82%) of cubane-1,2,4,7-tetracarboxylic acid tetrahydrazide as a white solid, mp 242°C (dec): IR (KBr) 3400, 1600, 1560, 1380, 1280, 960 cm^{-1}; ^{1}H NMR (D_2O) δ 4.73 (s), 4.45 (s). Anal. Calcd for $C_{12}H_{16}N_8O_4$: C, 42.87; H, 4.76; N, 33.33. Found: C, 42.41; H, 5.02; N, 33.14.

1,2,4,7-Tetra(hydrazinomethyl)cubane Tetraoxalate. A solution of cubane-1,2,4,7-tetracarboxylic acid hydrazide (0.30 g, 0.9 mmol) in 1 M BH_3-THF (40 mL) was refluxed under N_2 for 48 h. The solution was cooled and the solvent was removed *in vacuo*. The residue was dissolved in anhydrous methanol (30 mL) under nitrogen and a solution of anhydrous oxalic acid (0.7 g, 7.8 mmol) in anhydrous methanol (6 mL) was added. The mixture was stirred for 30 min and deoxygenated ether (100 mL) was added. The precipitate was filtered and dried to give 0.55 g (89%) of 1,2,4,7-tetra(hydrazinomethyl)cubane tetraoxalate a white solid, mp 150°C (dec): IR (KBr) 3600-2800, 1780, 1600, 1300 cm^{-1}; ^{1}H NMR δ 4.7 (s), 3.95 (s), 3.32 (s). Anal. Calcd for $C_{20}H_{40}N_8O_{16}$: C, 37.50; H, 5.0; N, 17.5. Found: C, 37.36; H, 6.24; N, 17.24.

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17. Elemental analyses were obtained from Galbraith Labs. Melting points are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained in $CDCl_3$ on a Brucker AC 200 spectrometer and chemical shifts are in parts per million from TMS. IR spectra were obtained in CH_2Cl_2 on a Perkin-Elmer 700 spectrometer. DSC and TGA analysis were performed on a Dupont 9900 Thermoanalyzer.

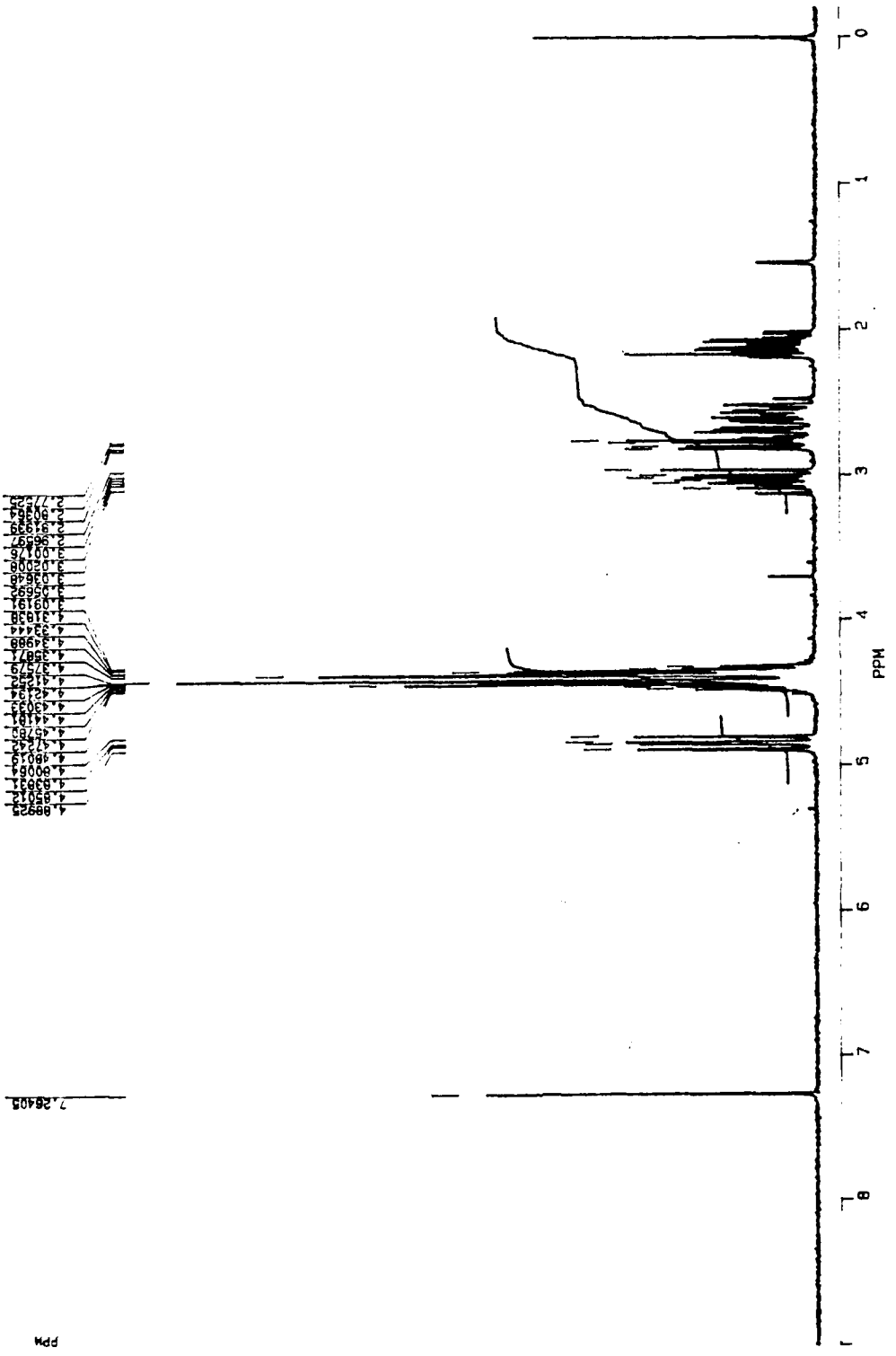

FIGURE 1. ^{1}H NMR OF 2,2,5-TRIBROMOCYCLOPENTANONE ETHYLENE KETAL

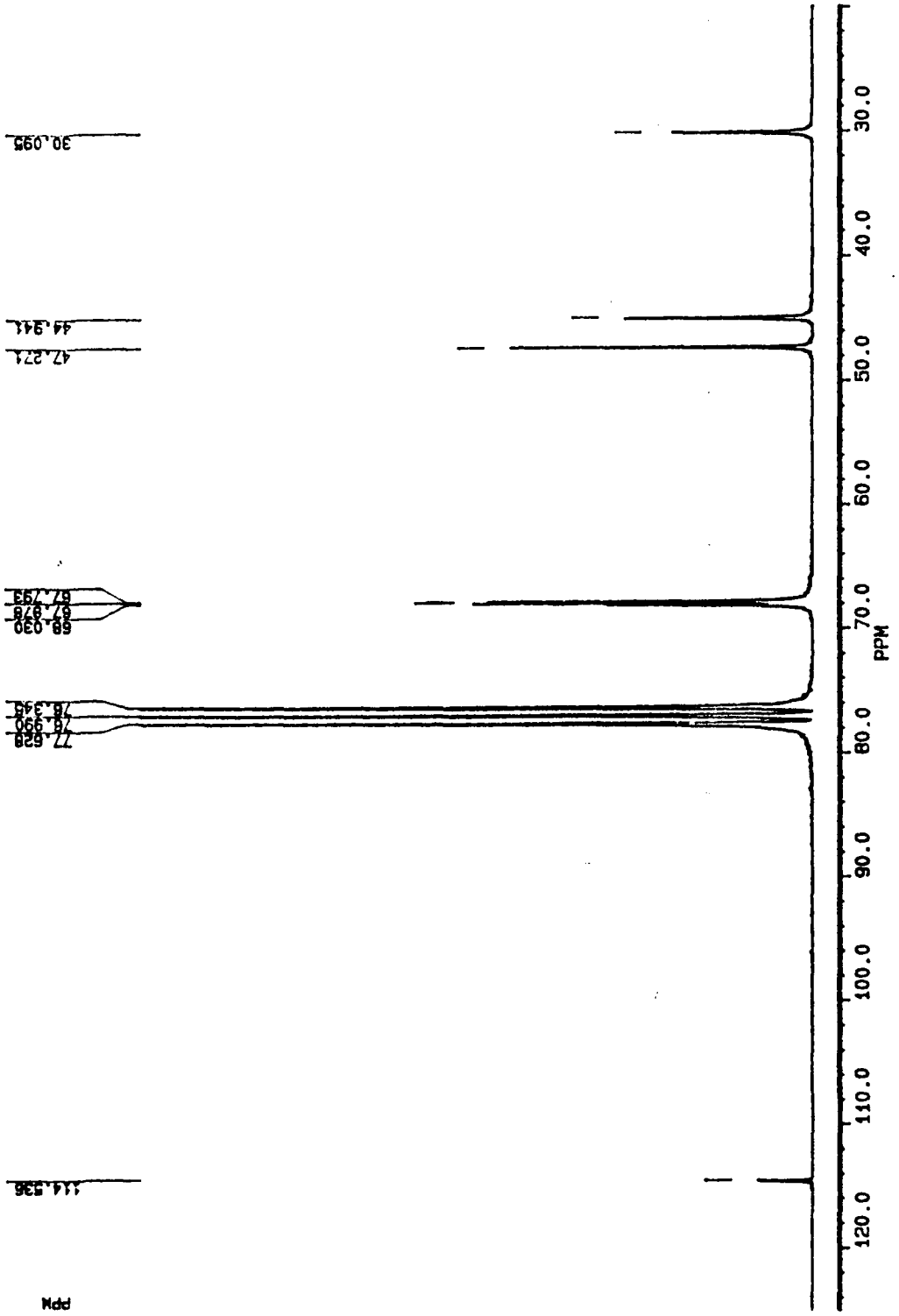

FIGURE 2. ^{13}C NMR OF 2,2,5-TRIBROMOCYCLOPENTANONE ETHYLENE KETAL

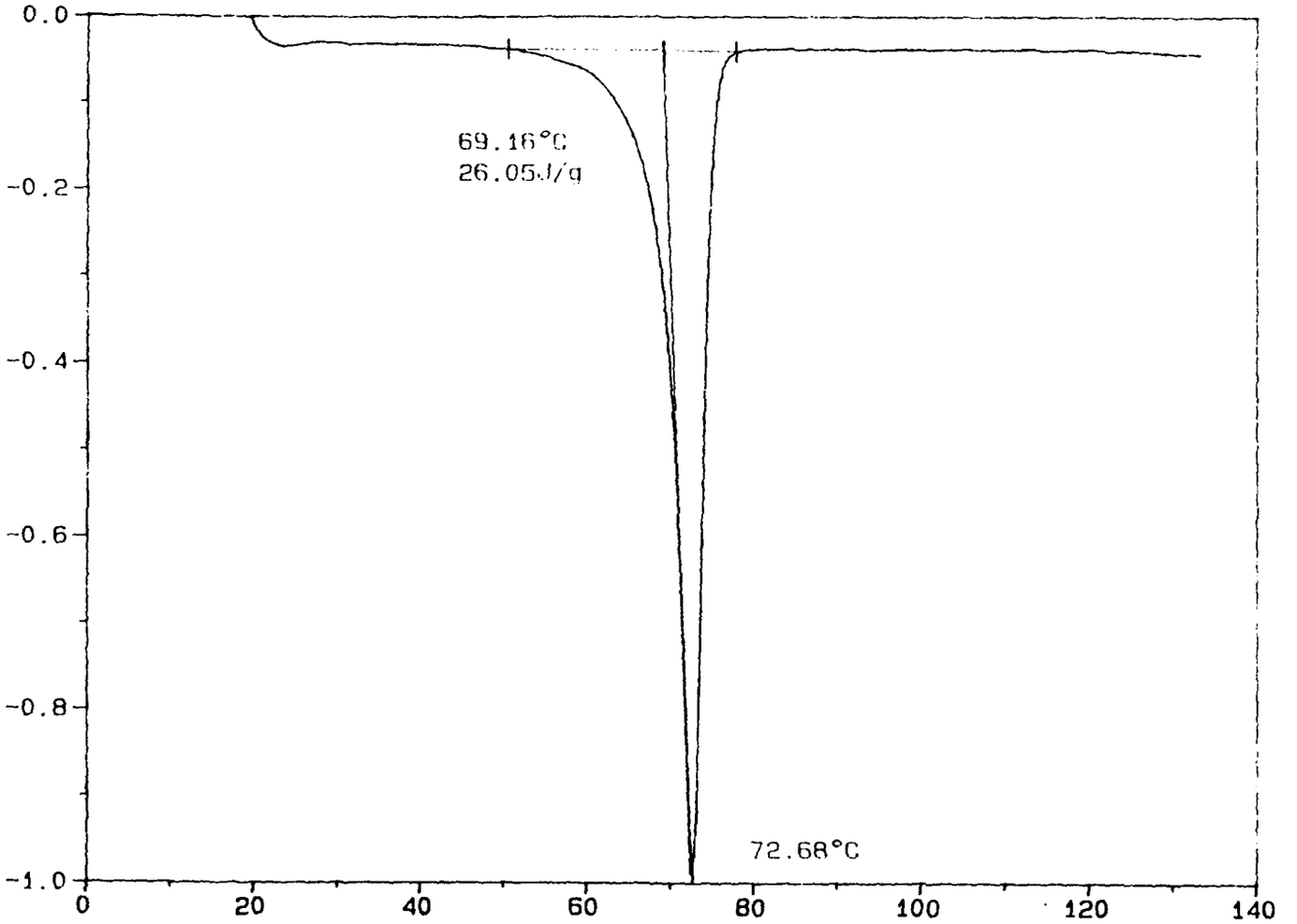

FIGURE 3. DSC OF 2,2,5-TRIBROMOCYCLOPENTANONE ETHYLENE KETAL

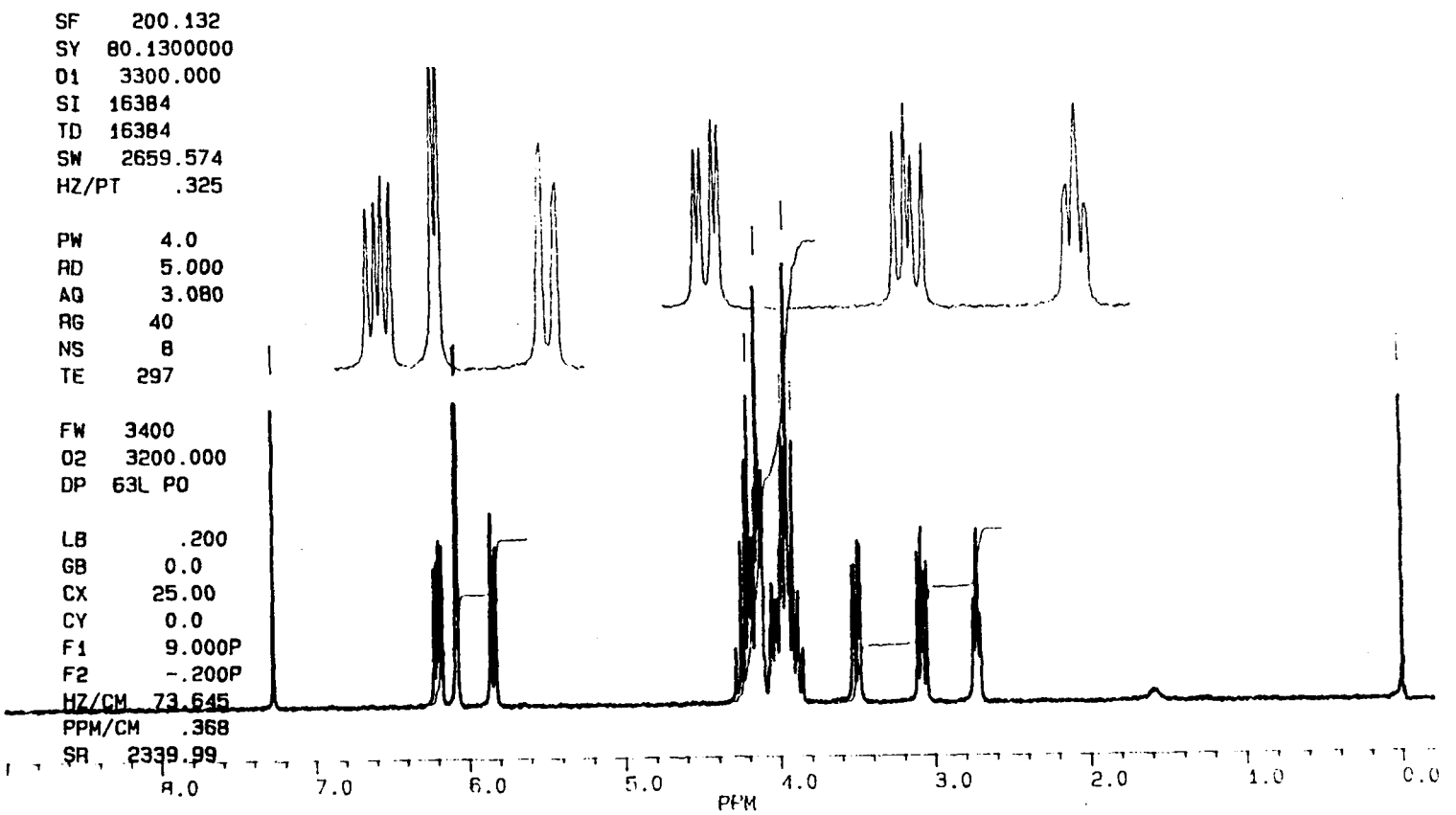

FIGURE 4. ^{1}H NMR OF BISKETAL

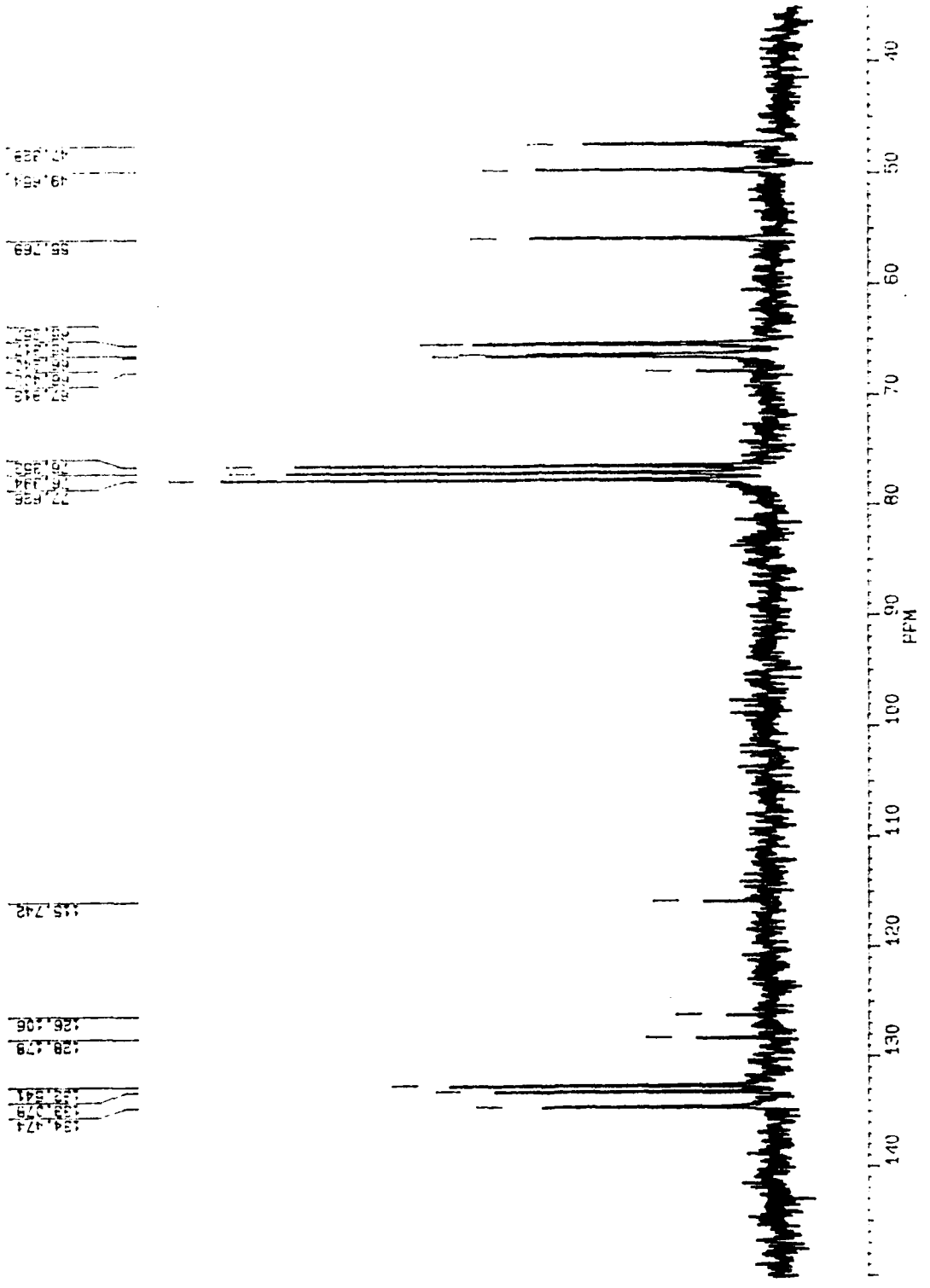

FIGURE 5. ^{13}C NMR OF BISKETAL

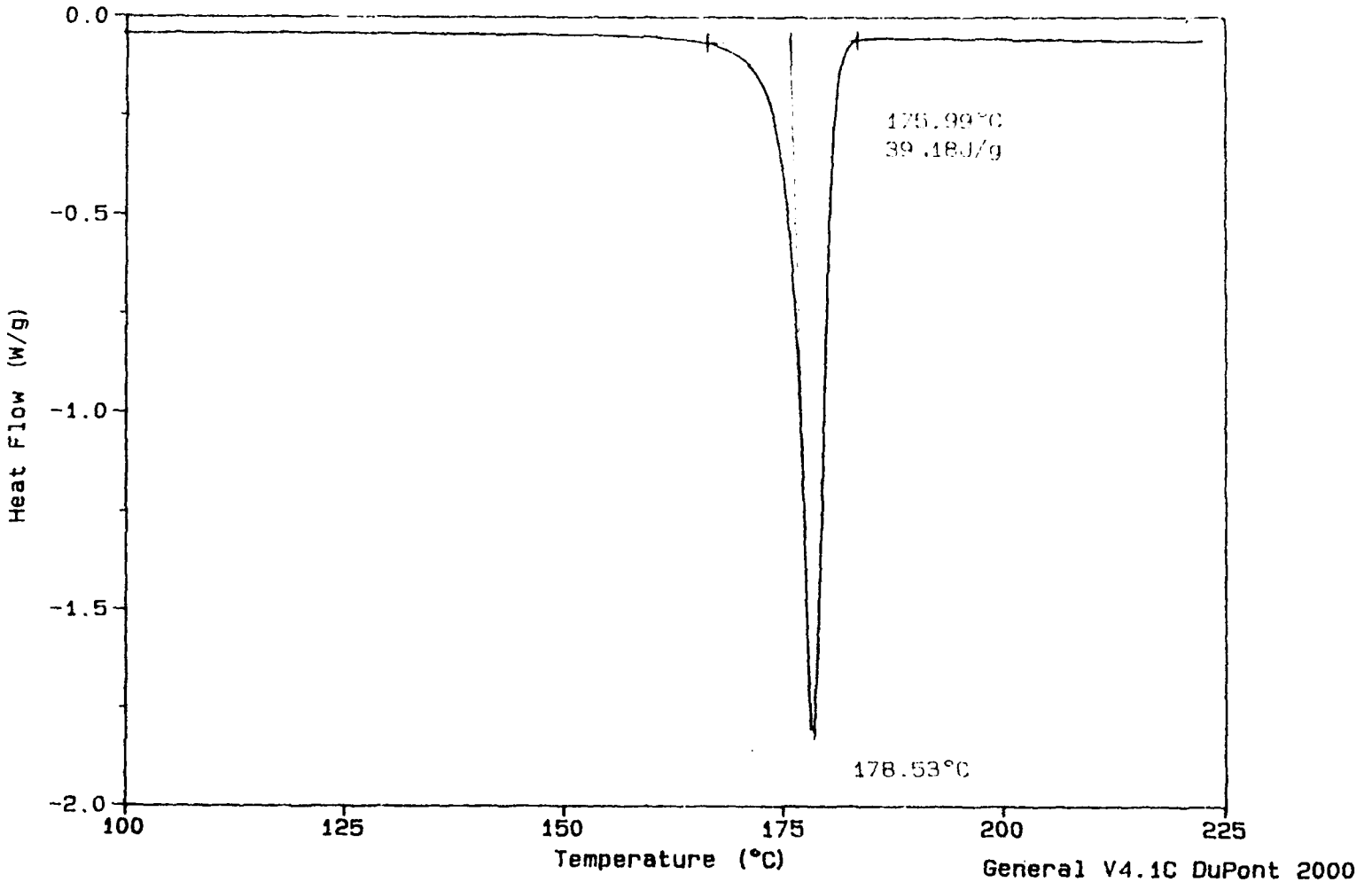

FIGURE 6. DSC OF BISKETAL

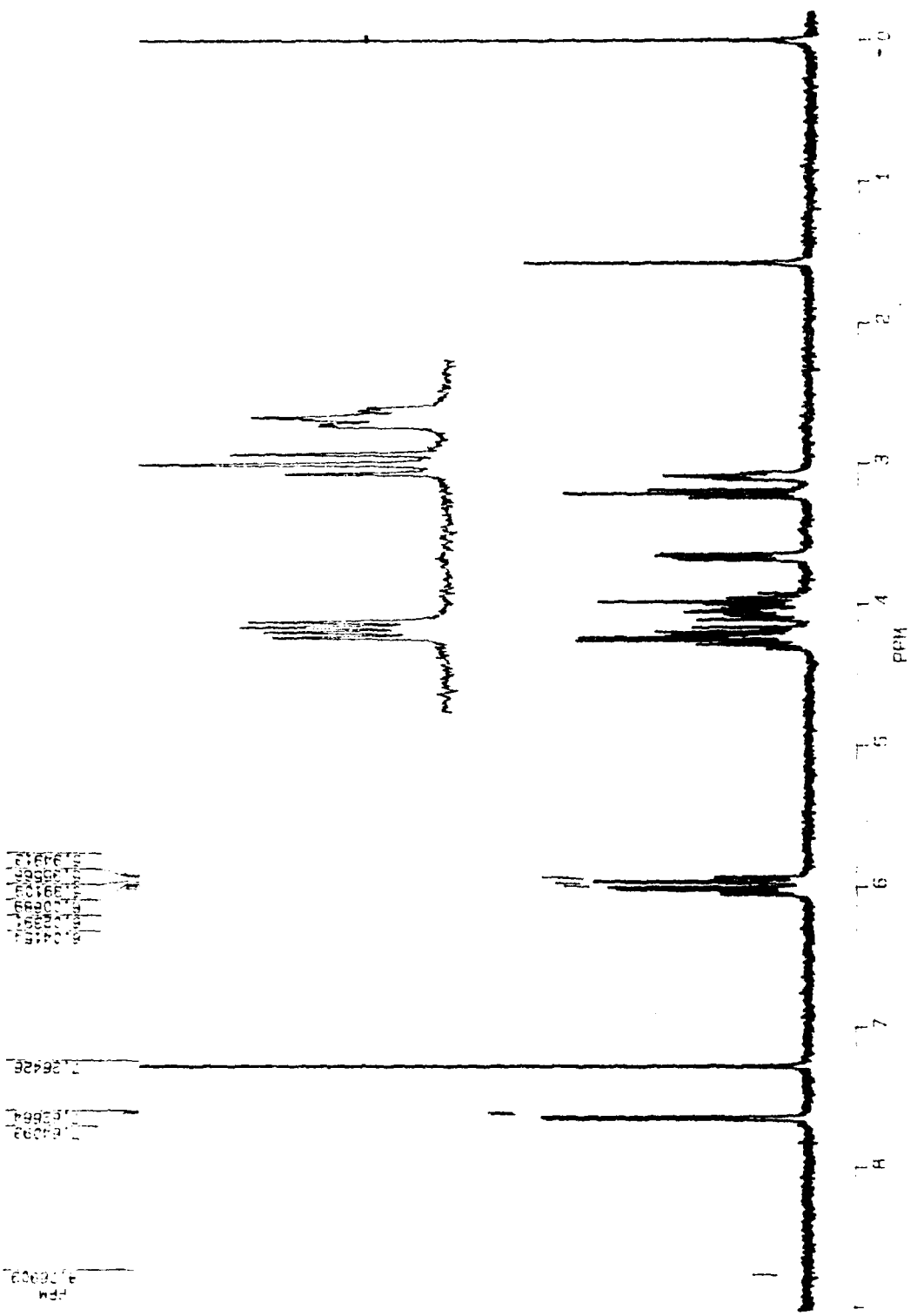

FIGURE 7. ^{1}H NMR OF MONOKETAL

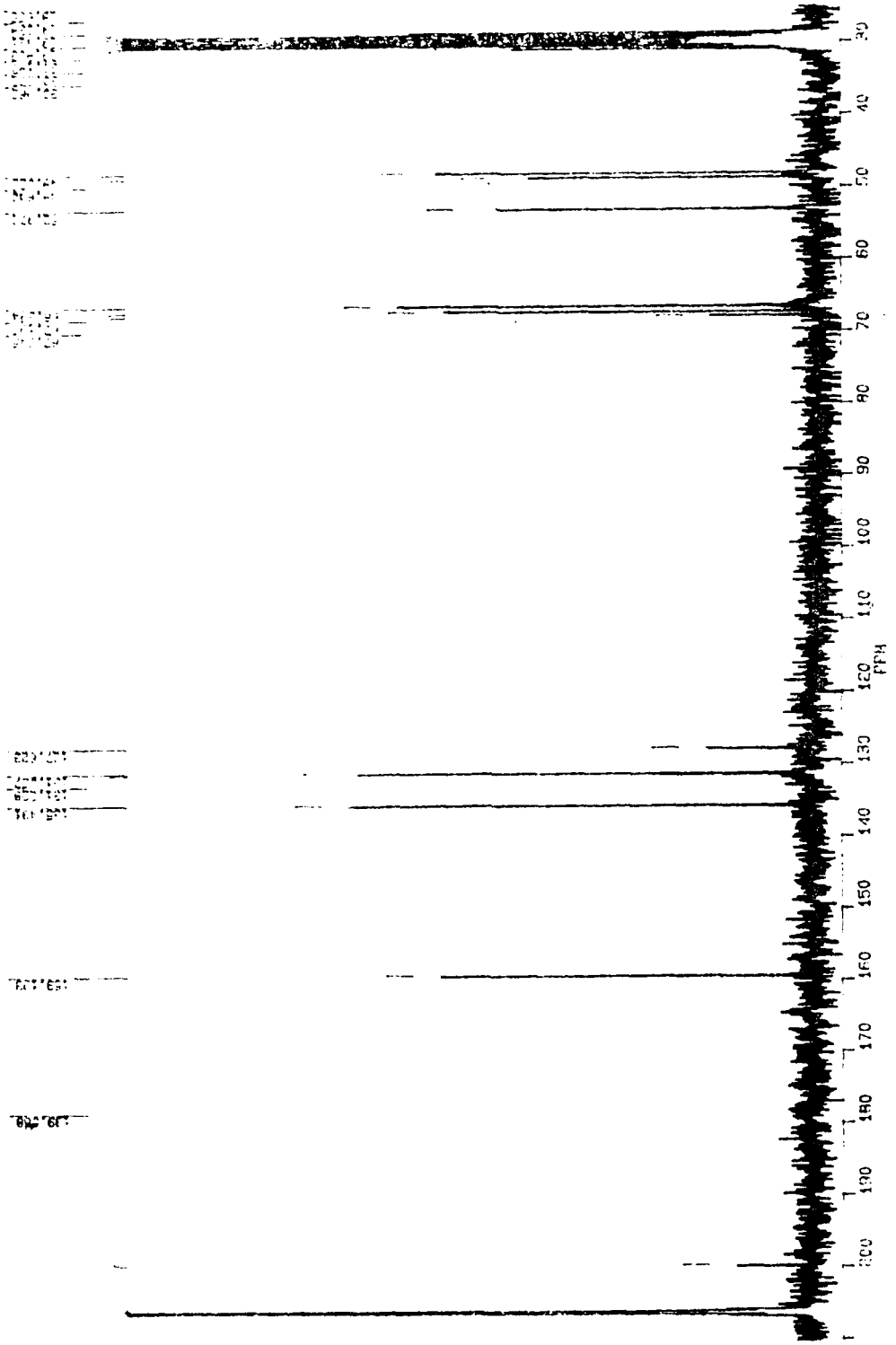

FIGURE 8. ^{13}C NMR OF MONOKETAL

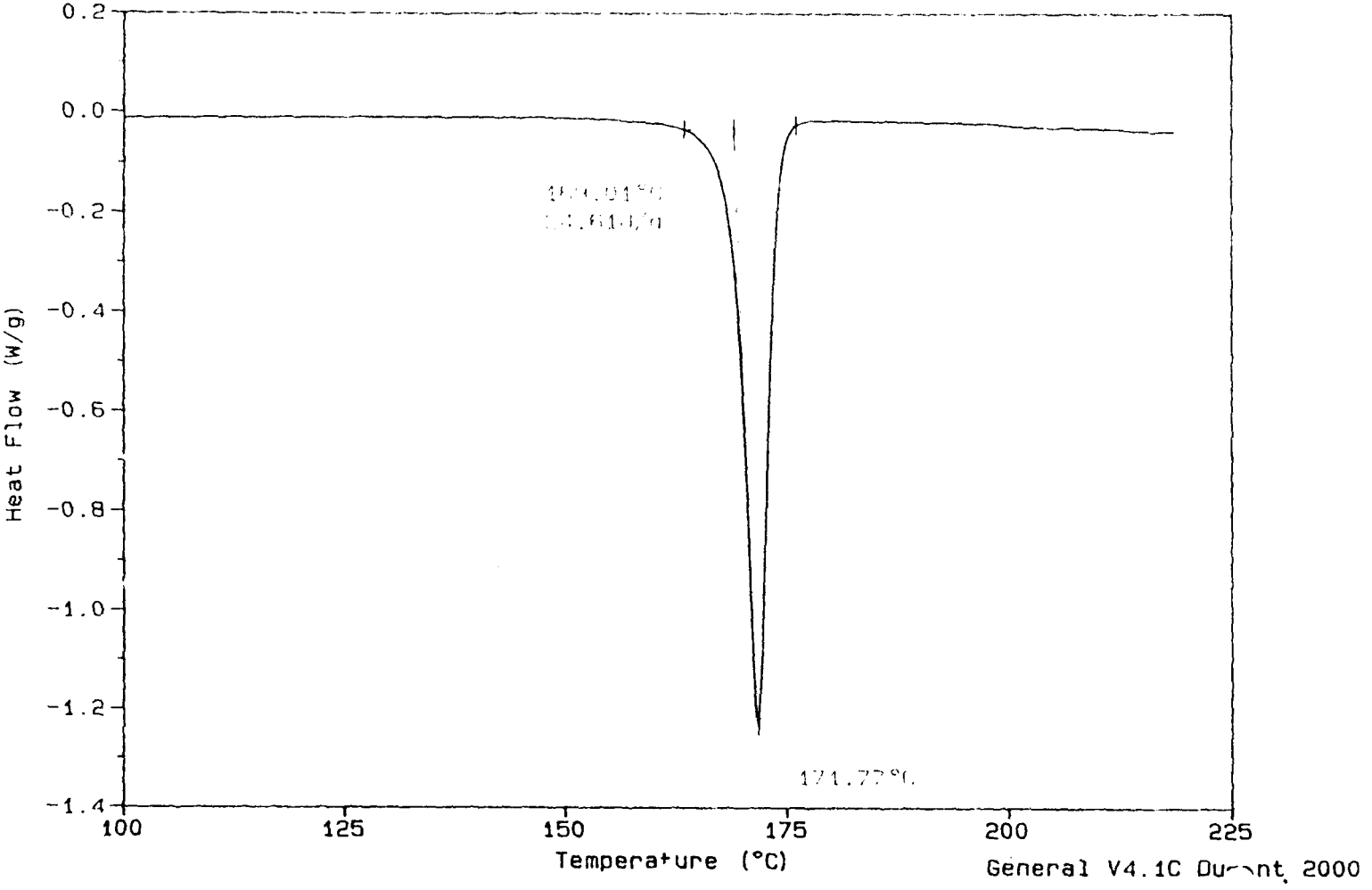

FIGURE 9. DSC OF MONOKETAL

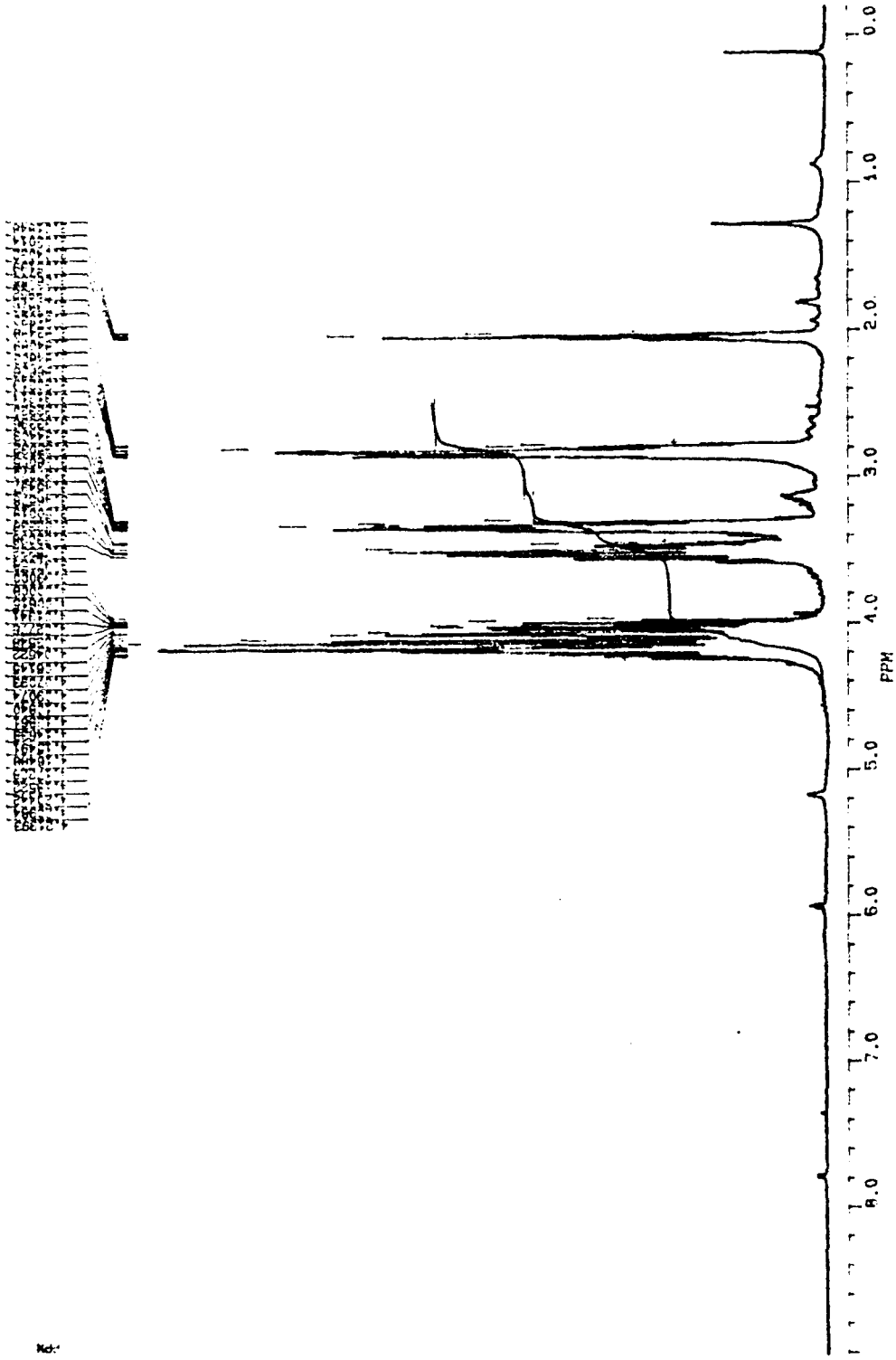

FIGURE 10. ^{1}H NMR OF CAGE KETAL

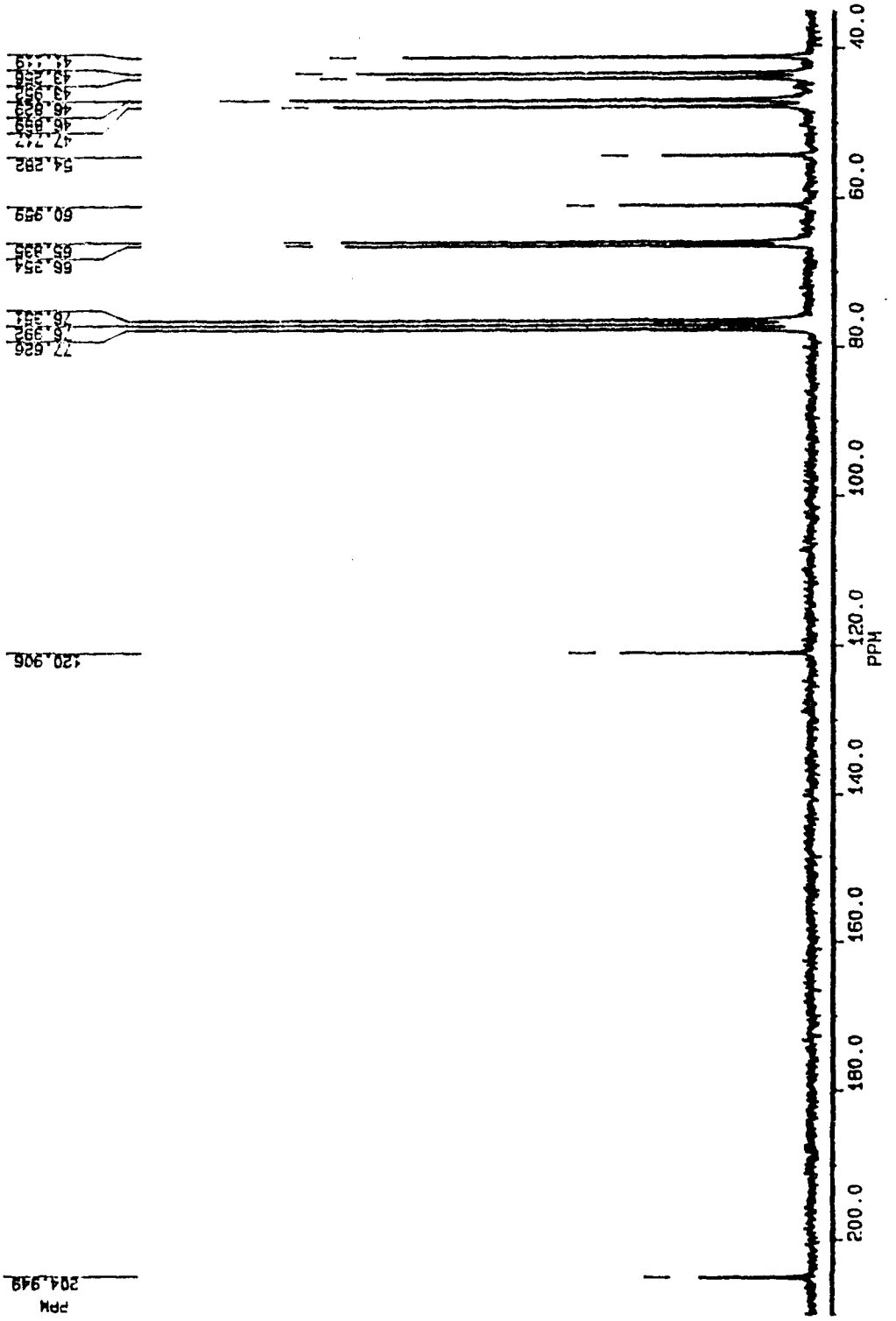

FIGURE 11. ^{13}C NMR OF CAGE KETAL

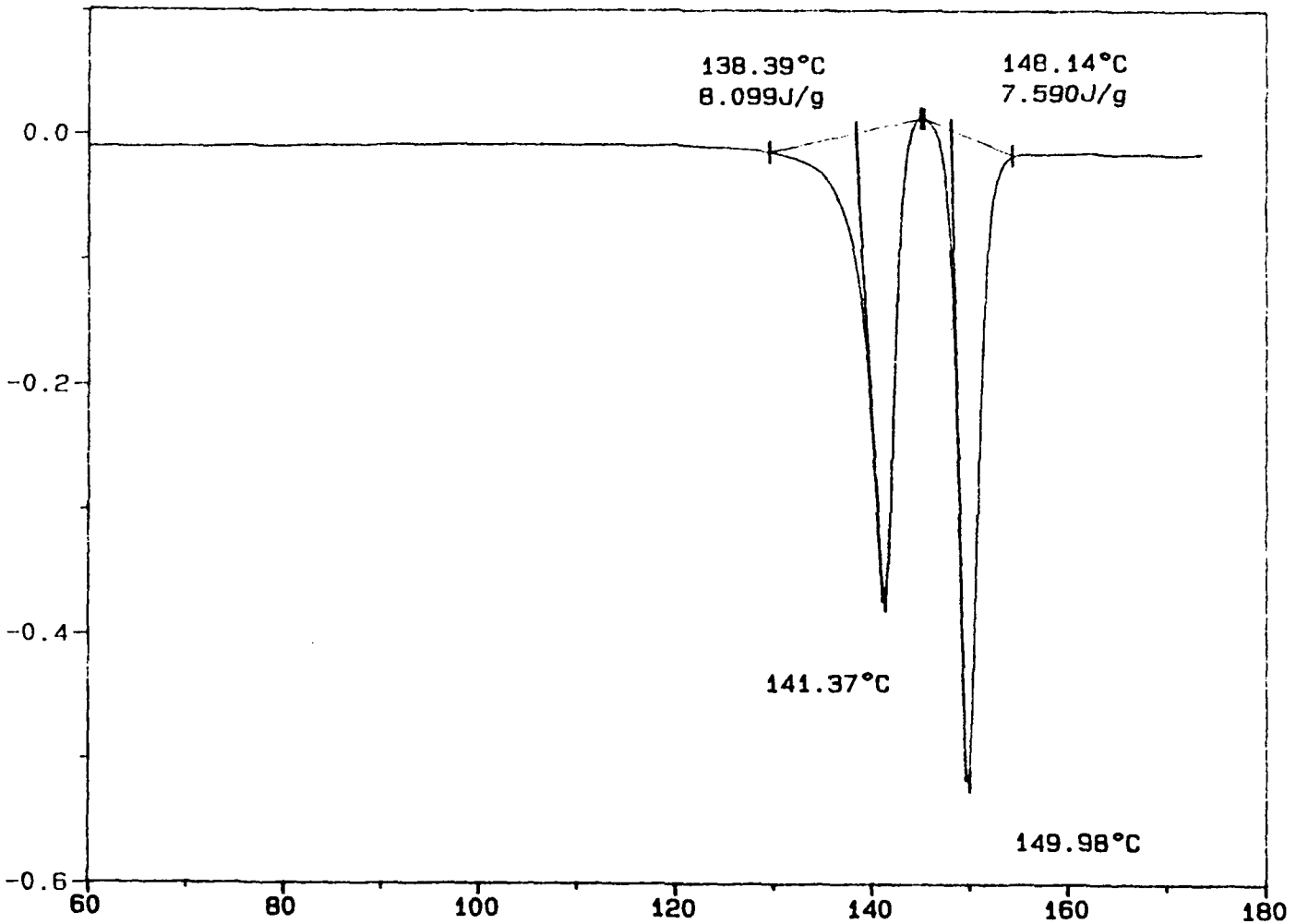

FIGURE 12. DSC OF CAGE KETAL

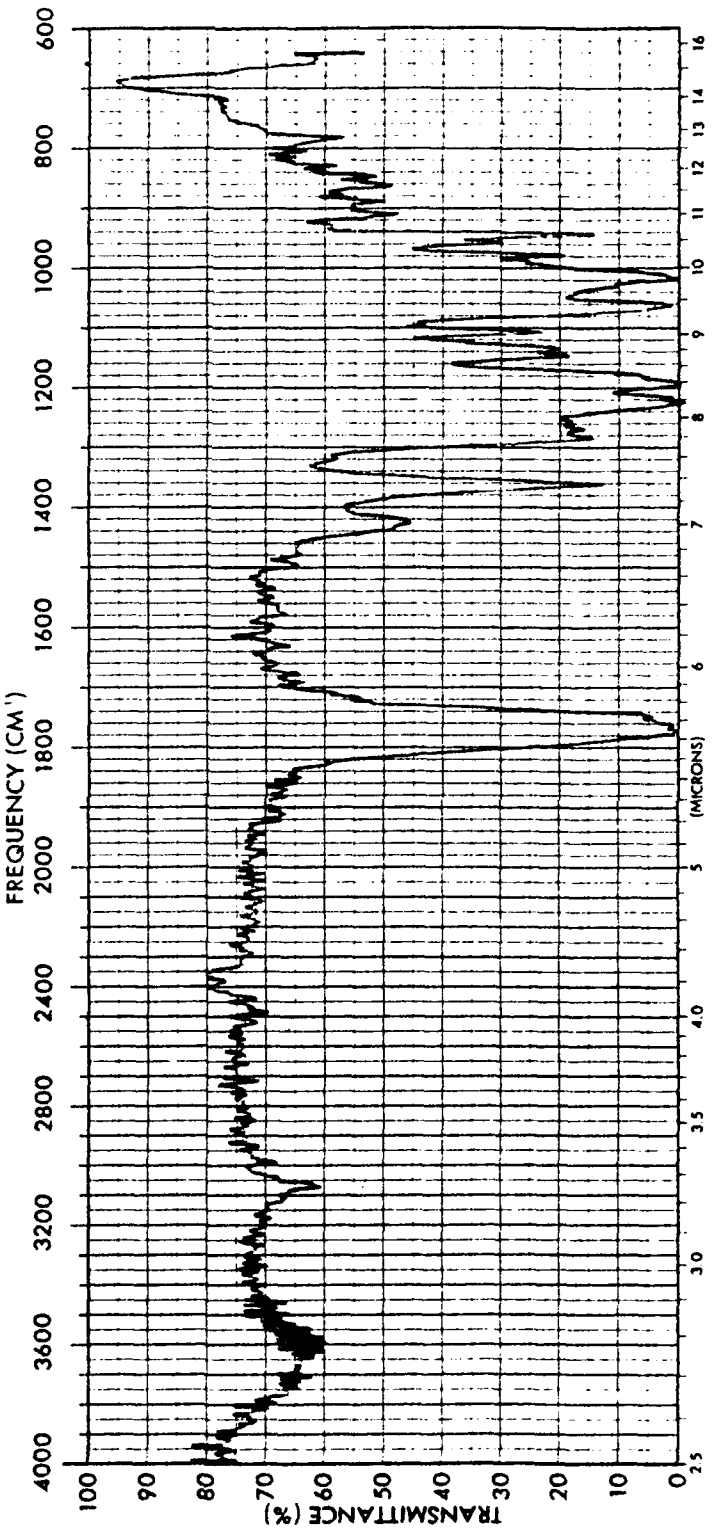

FIGURE 13. IR OF CAGE TETRAACETATE

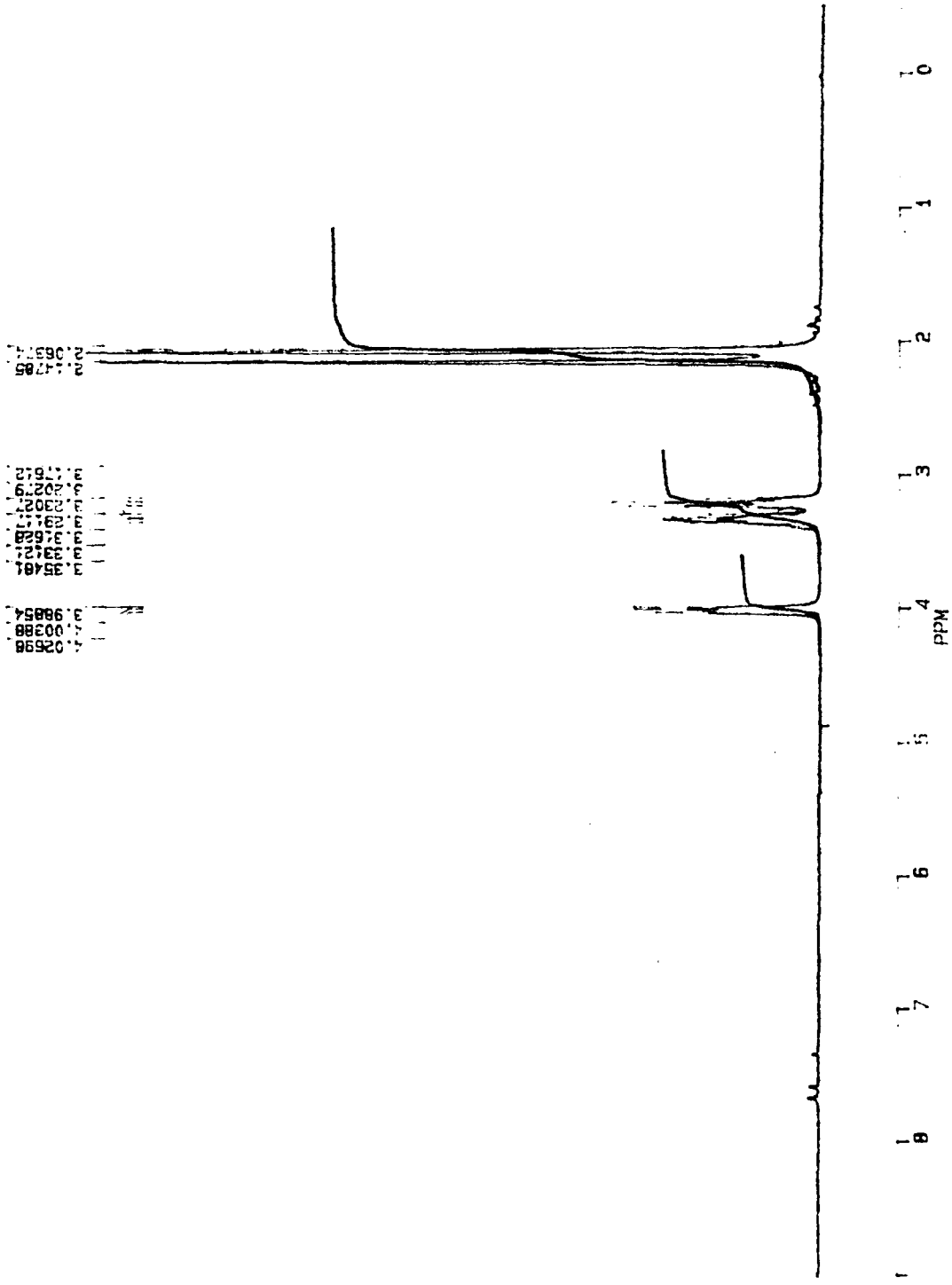

FIGURE 14. ^{1}H NMR OF CAGE TETRAACETATE

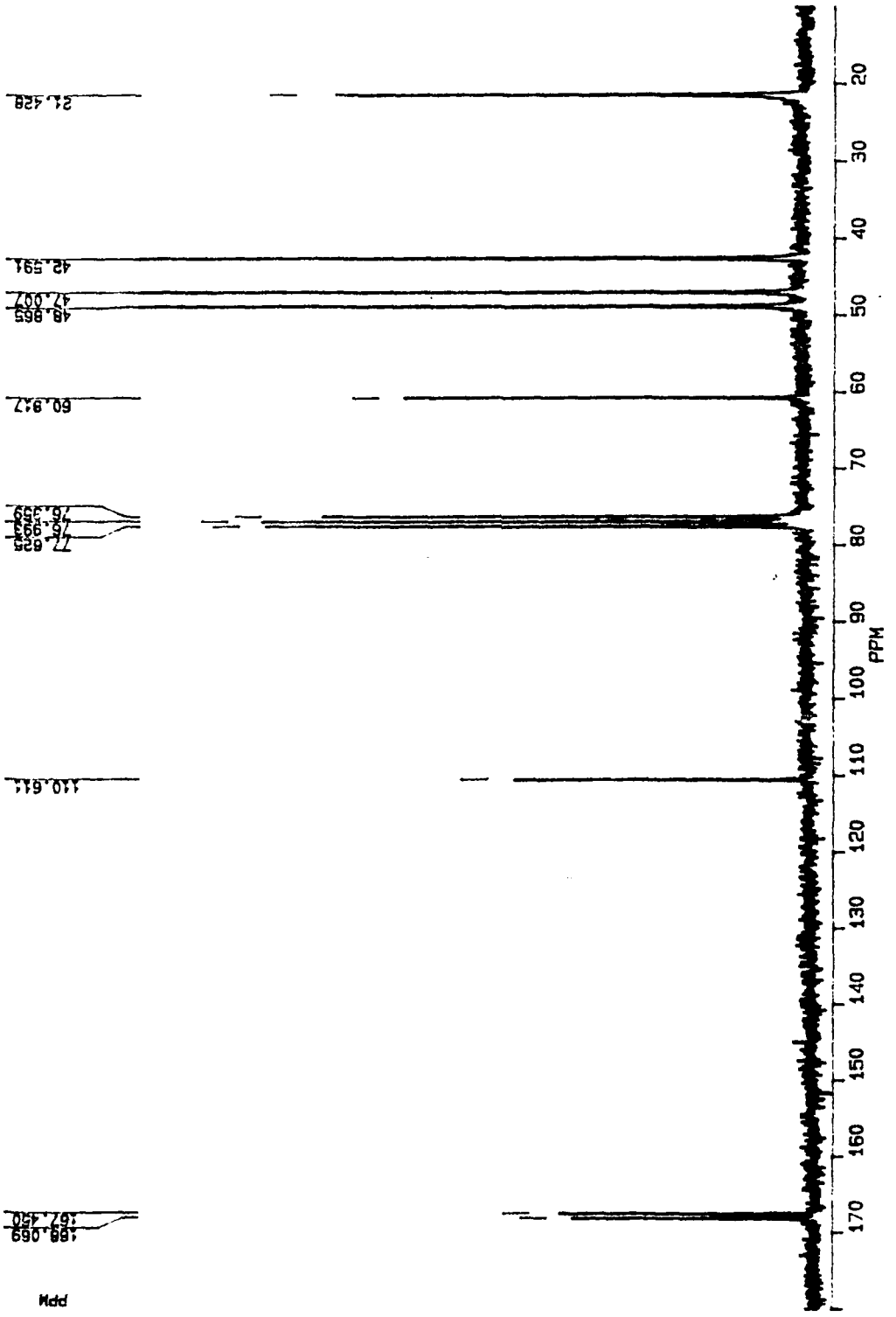

FIGURE 15. ^{13}C NMR OF CAGE TETRAACETATE

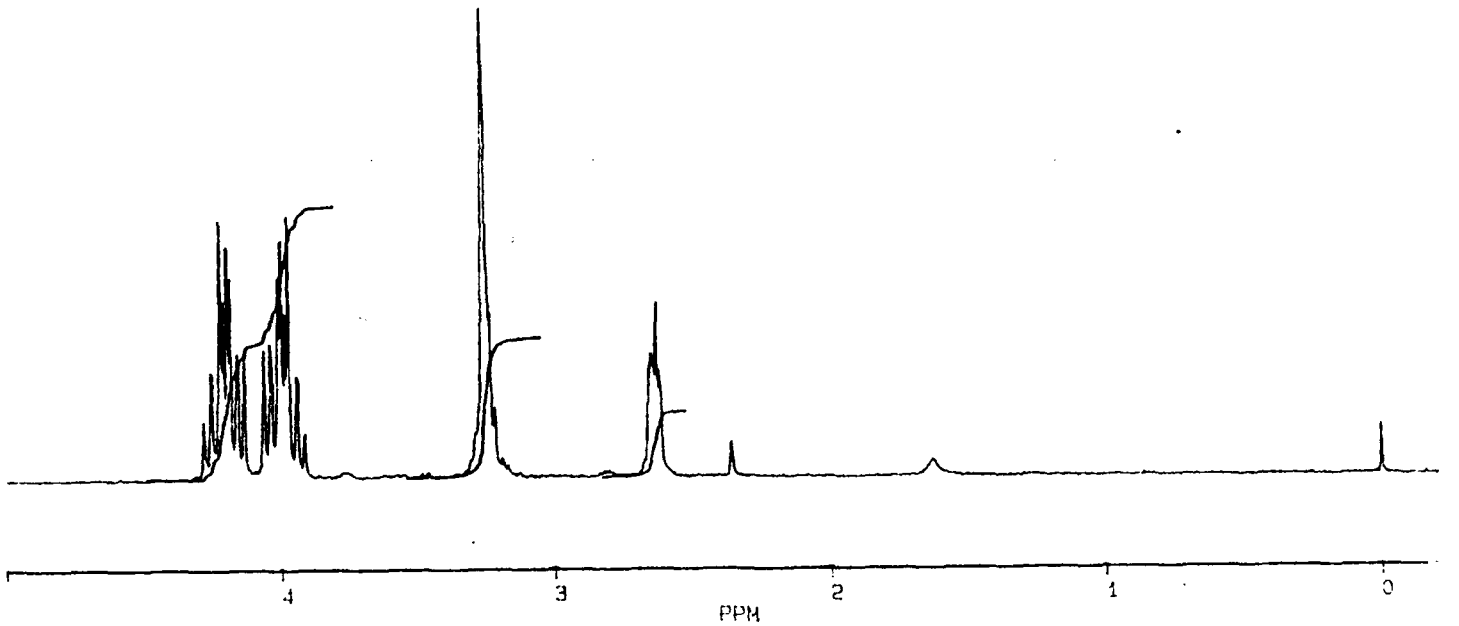

FIGURE 16. ^{1}H NMR OF CAGE BISKETAL

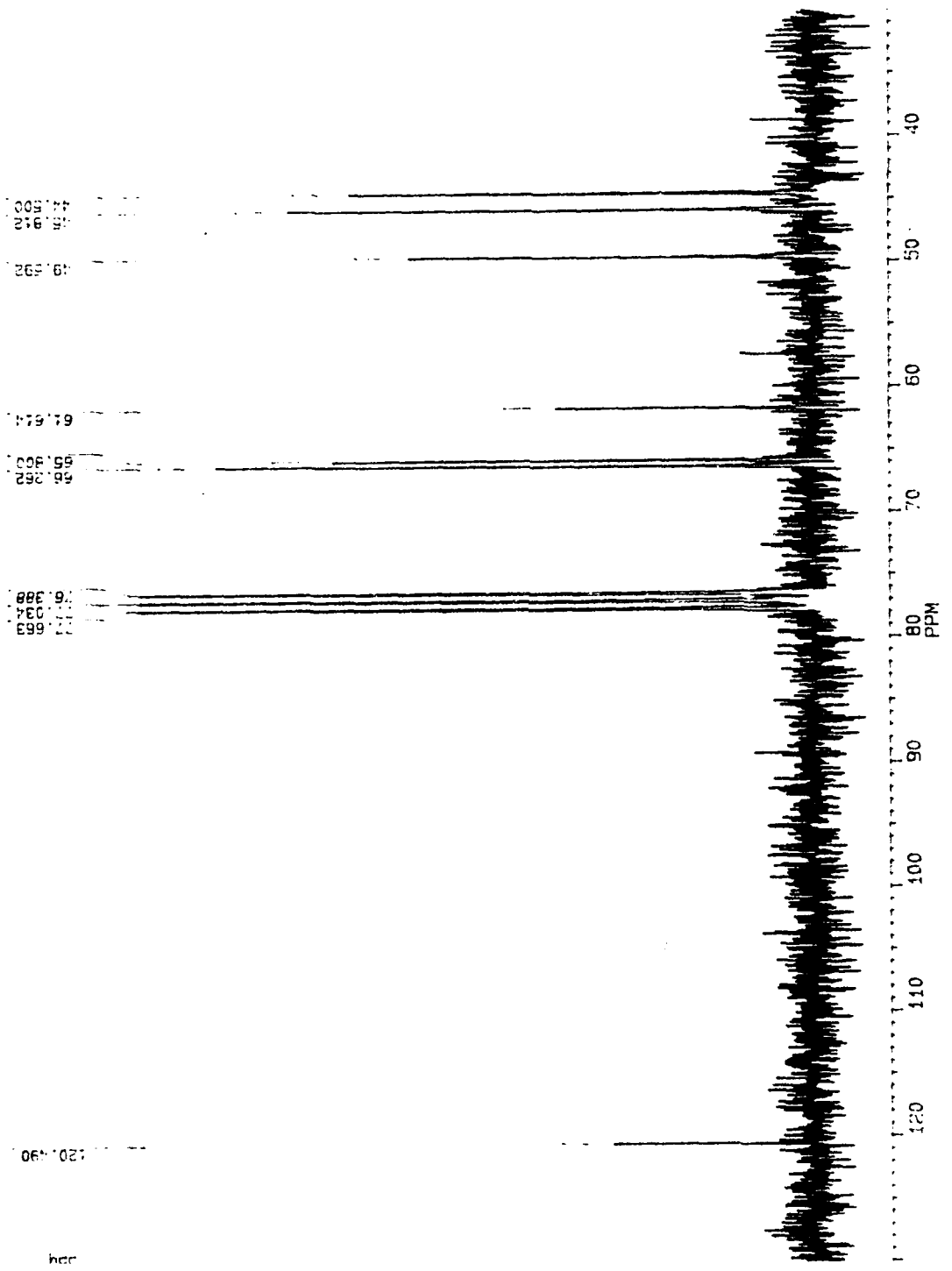

FIGURE 17. ^{13}C NMR OF CAGE BISKETAL

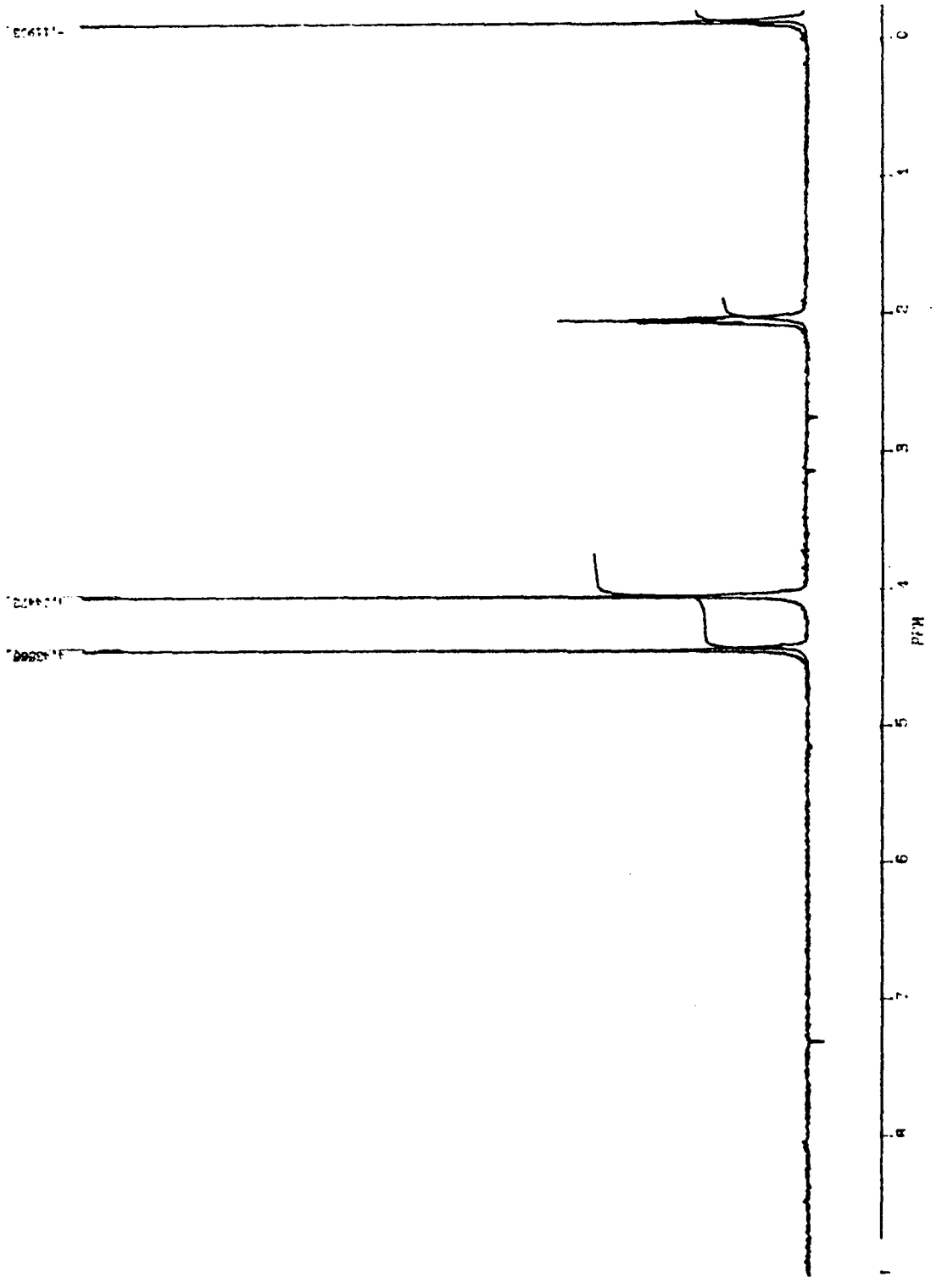

FIGURE 18. ^{1}H NMR OF CUBANE-1,4-DIACID

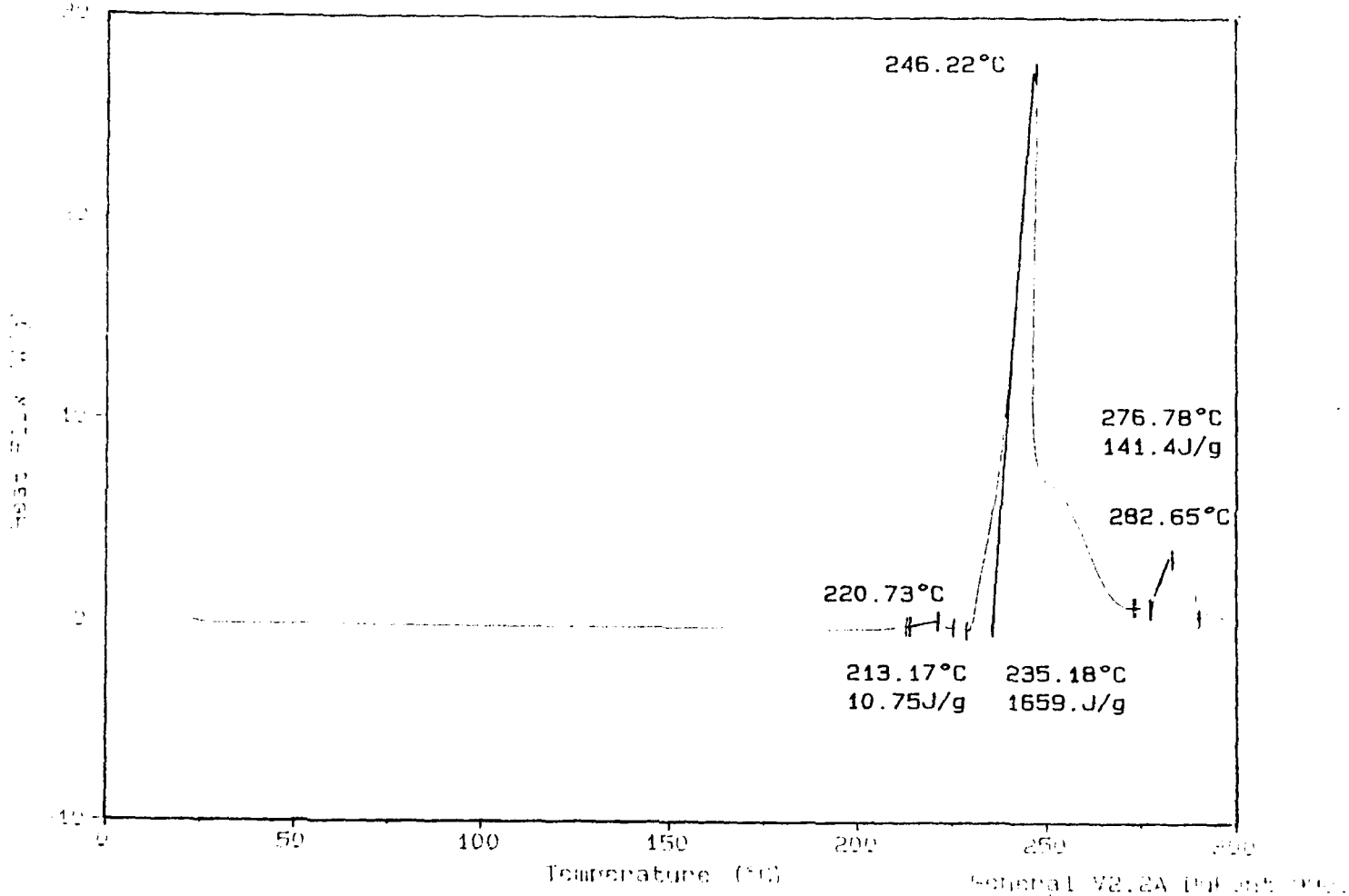

FIGURE 19. DSC OF CUBANE-1,4-DIACID

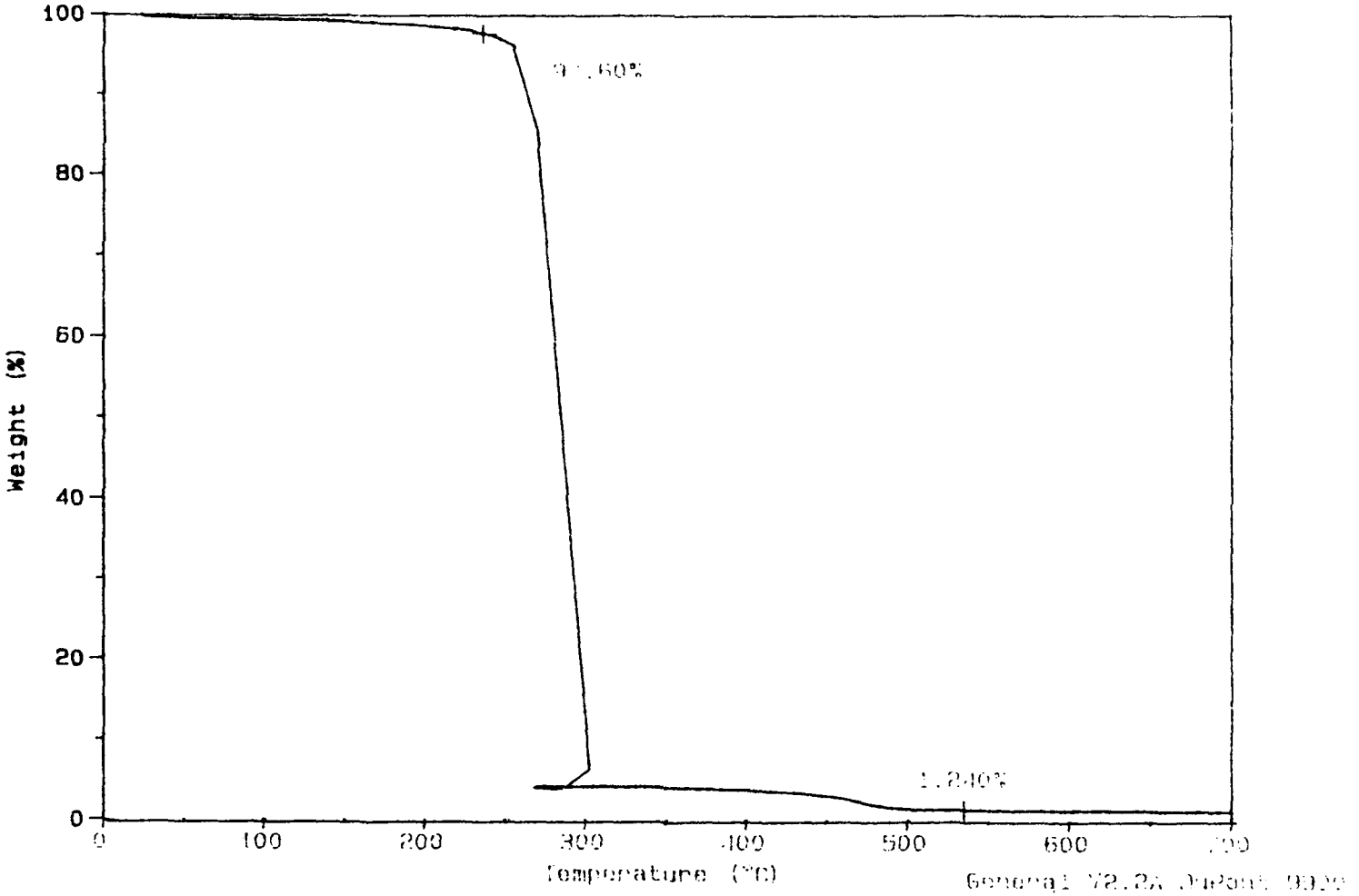

FIGURE 20. TGA OF CUBANE-1,4-DIACID

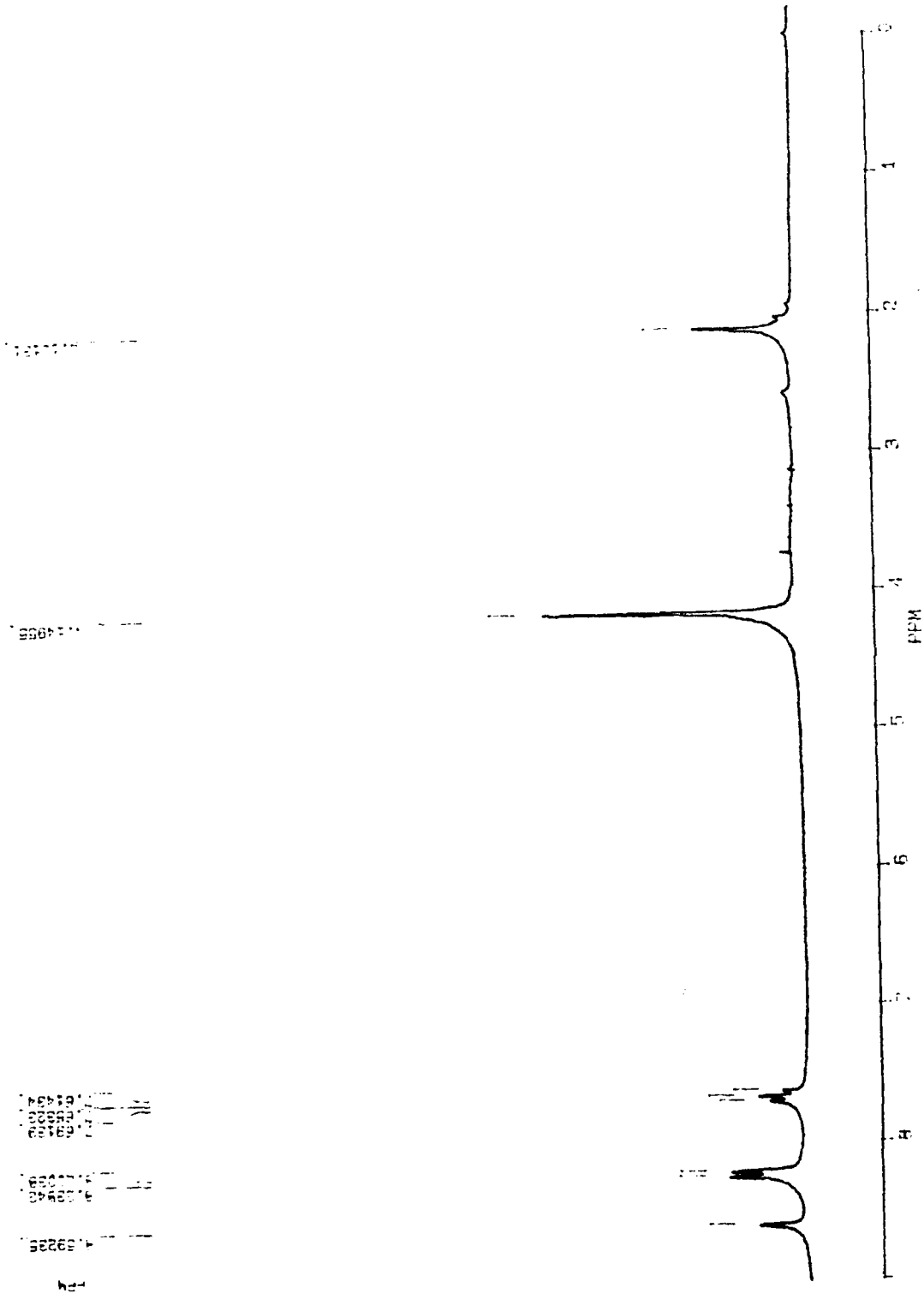

FIGURE 21. ^{1}H NMR OF ISOPHTHALIC ACID IN CUBANE-1,4-DIACID

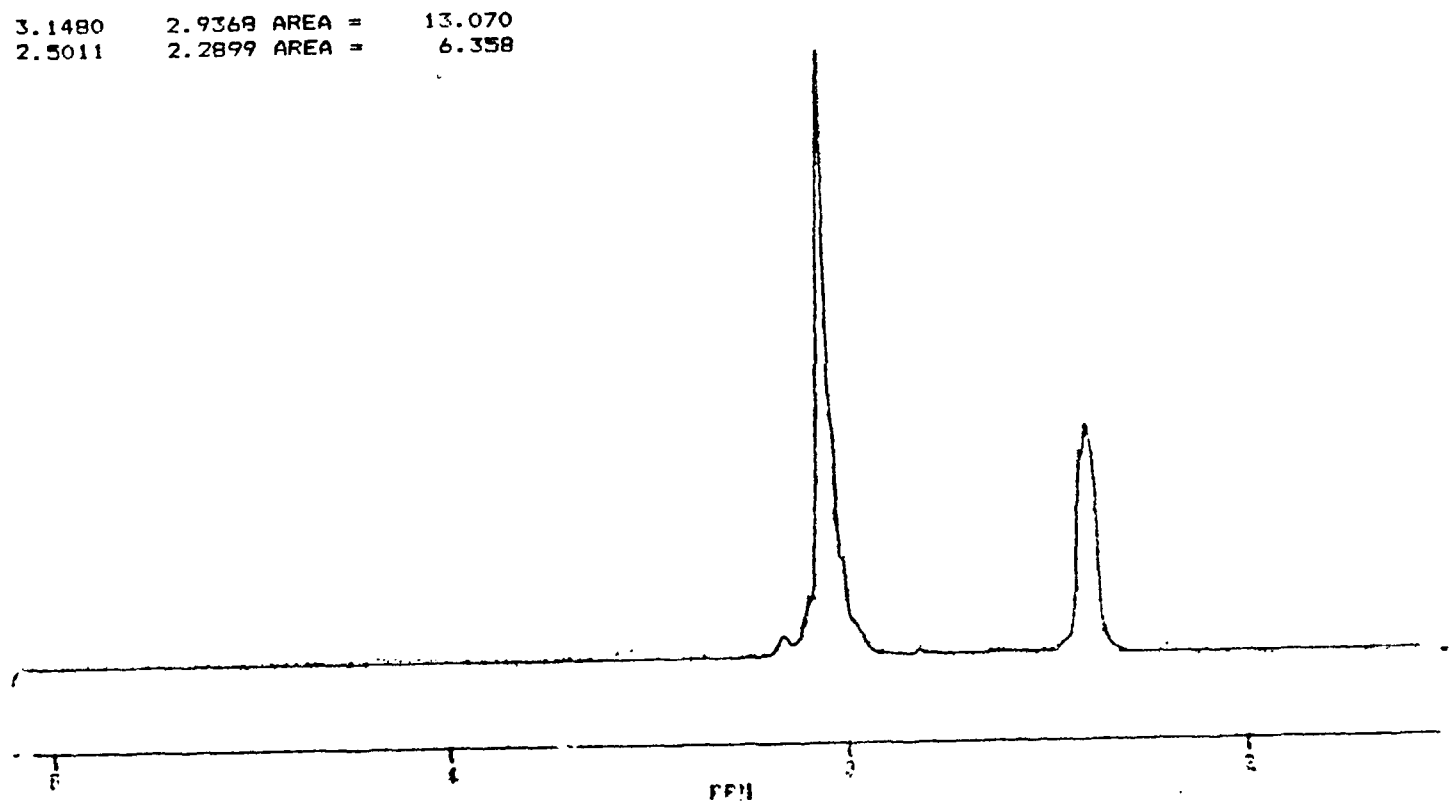

FIGURE 22. ^{1}H NMR OF CAGE DIONE IN D_2O AFTER 5 MIN AT 25°C

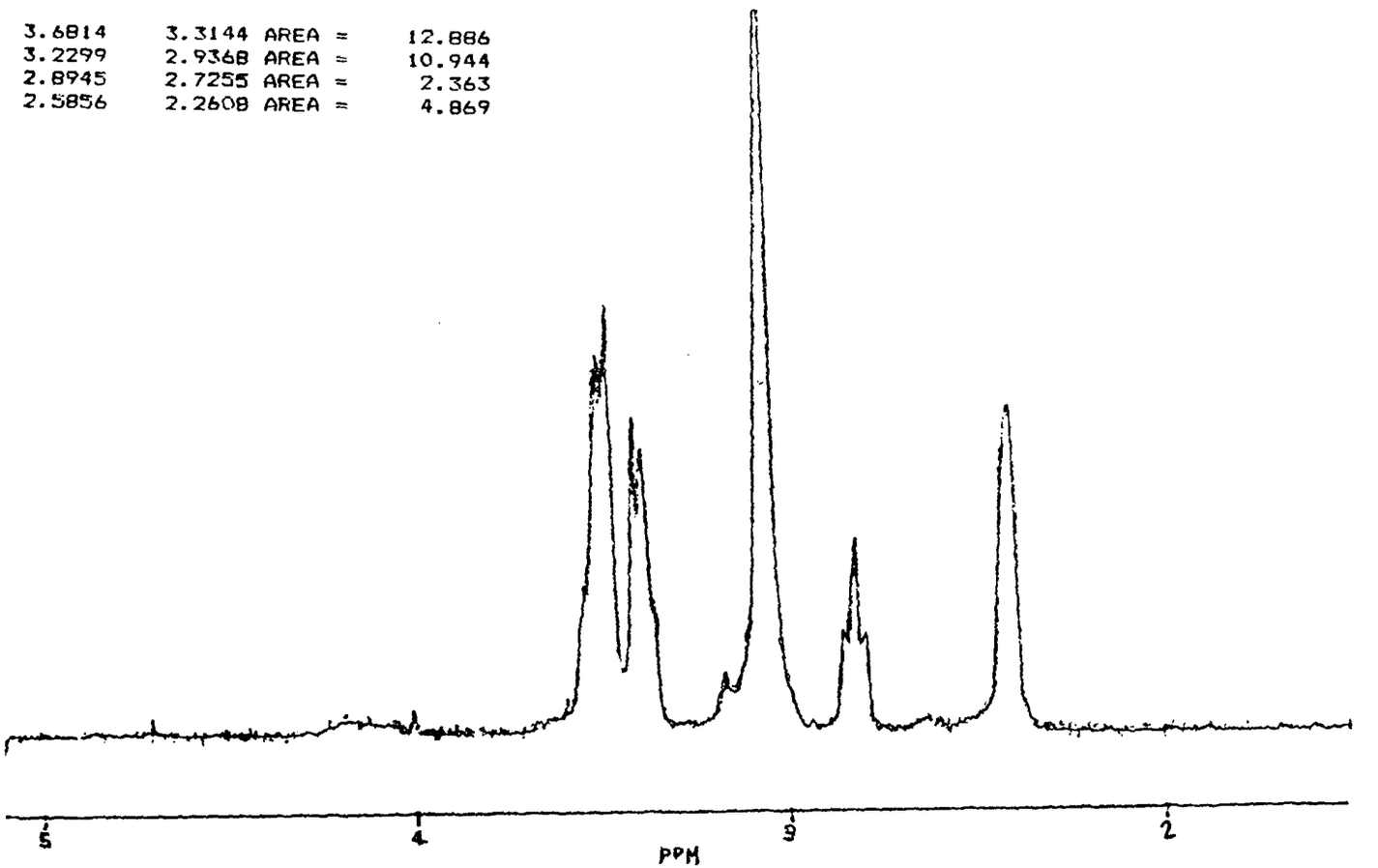

FIGURE 23. ^{1}H NMR OF CAGE DIONE AND HOMOACID IN D_2O AFTER 1 H AT 60°C

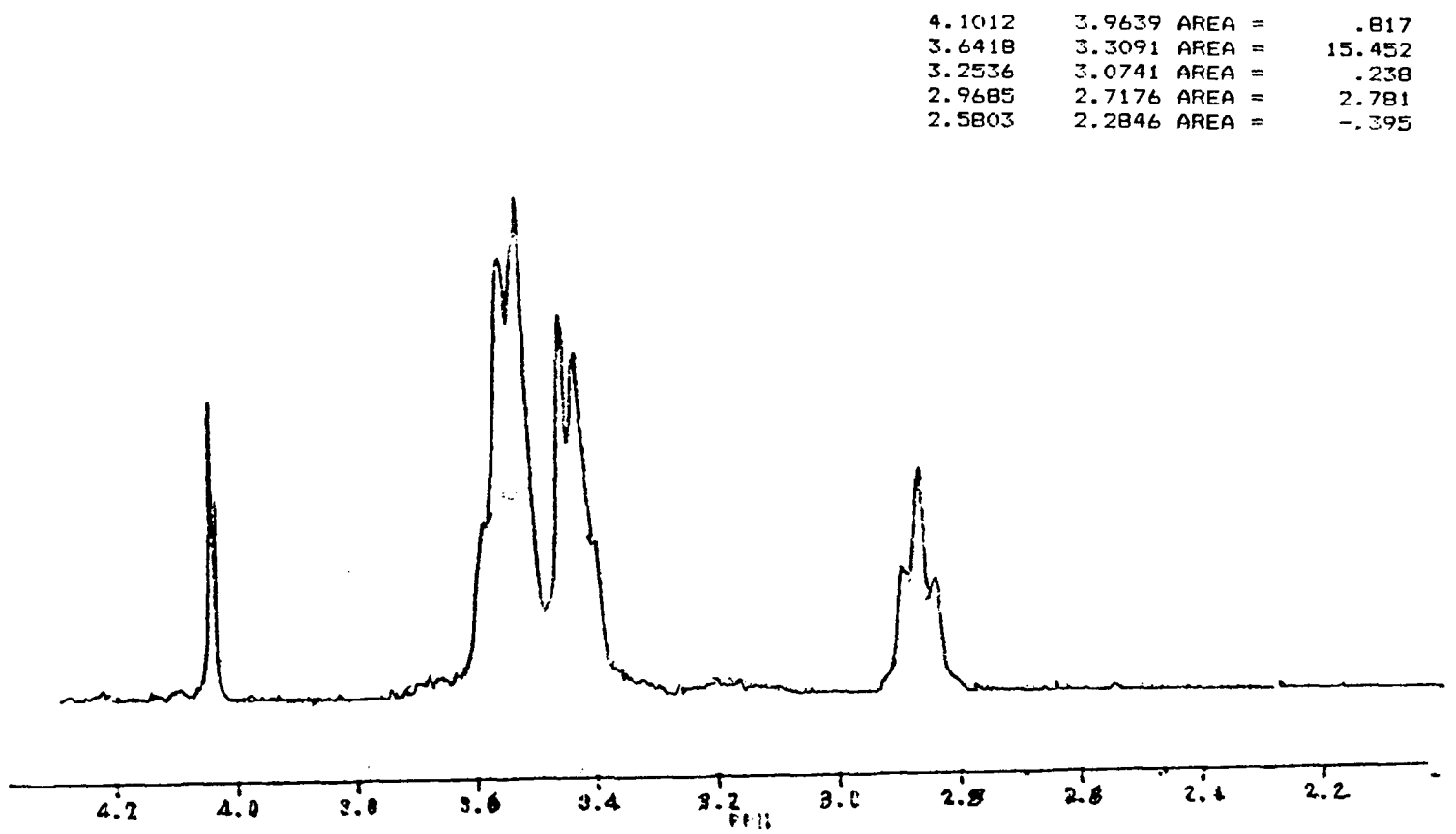

FIGURE 24. ^{1}H NMR OF HOMOACID AND CUBANE DIACID IN D_2O AFTER 3 H AT 60°C

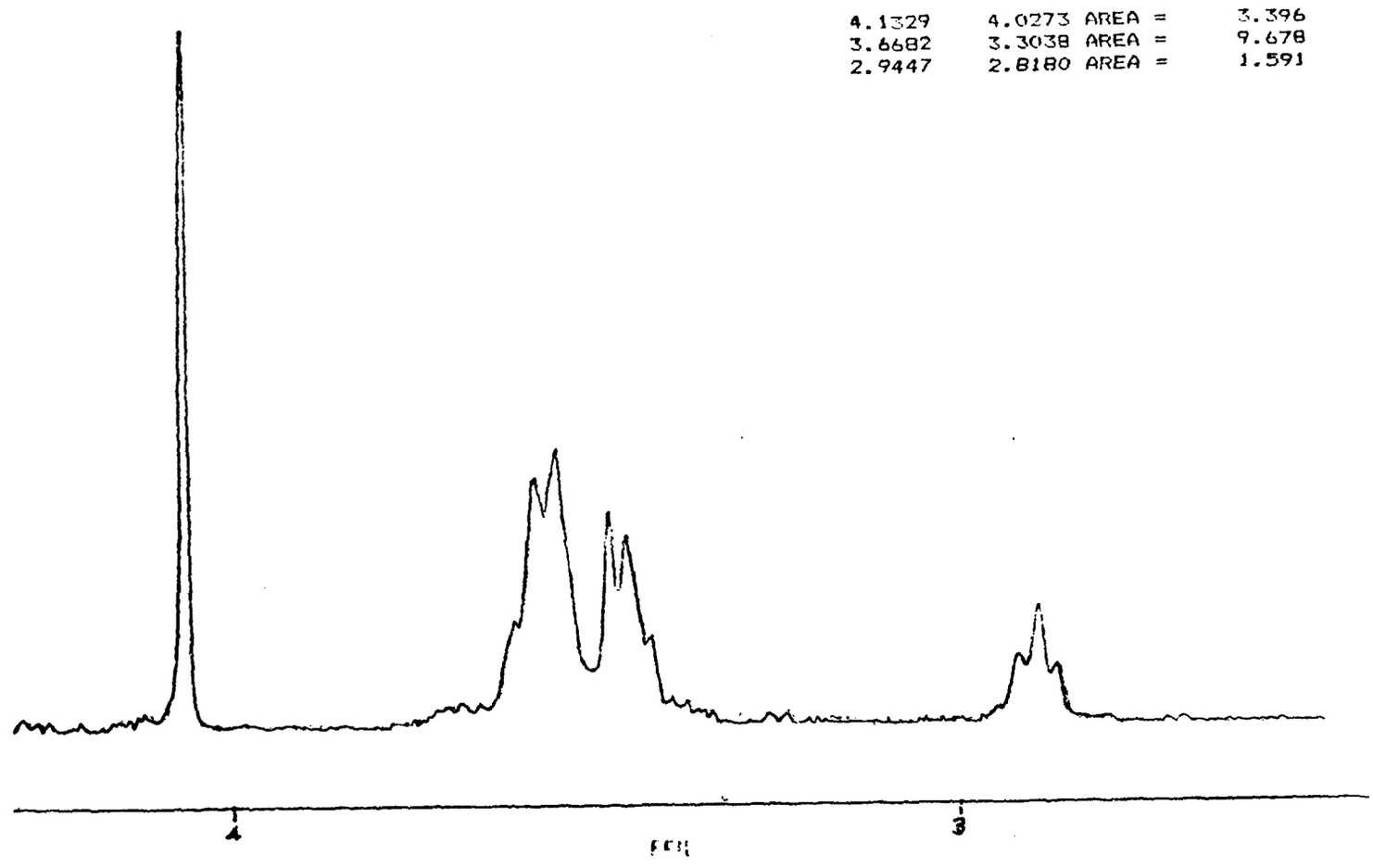

FIGURE 25. ^{1}H NMR OF HOMOACID AND CUBANE DIACID IN D_2O AFTER 20 H AT 60°C

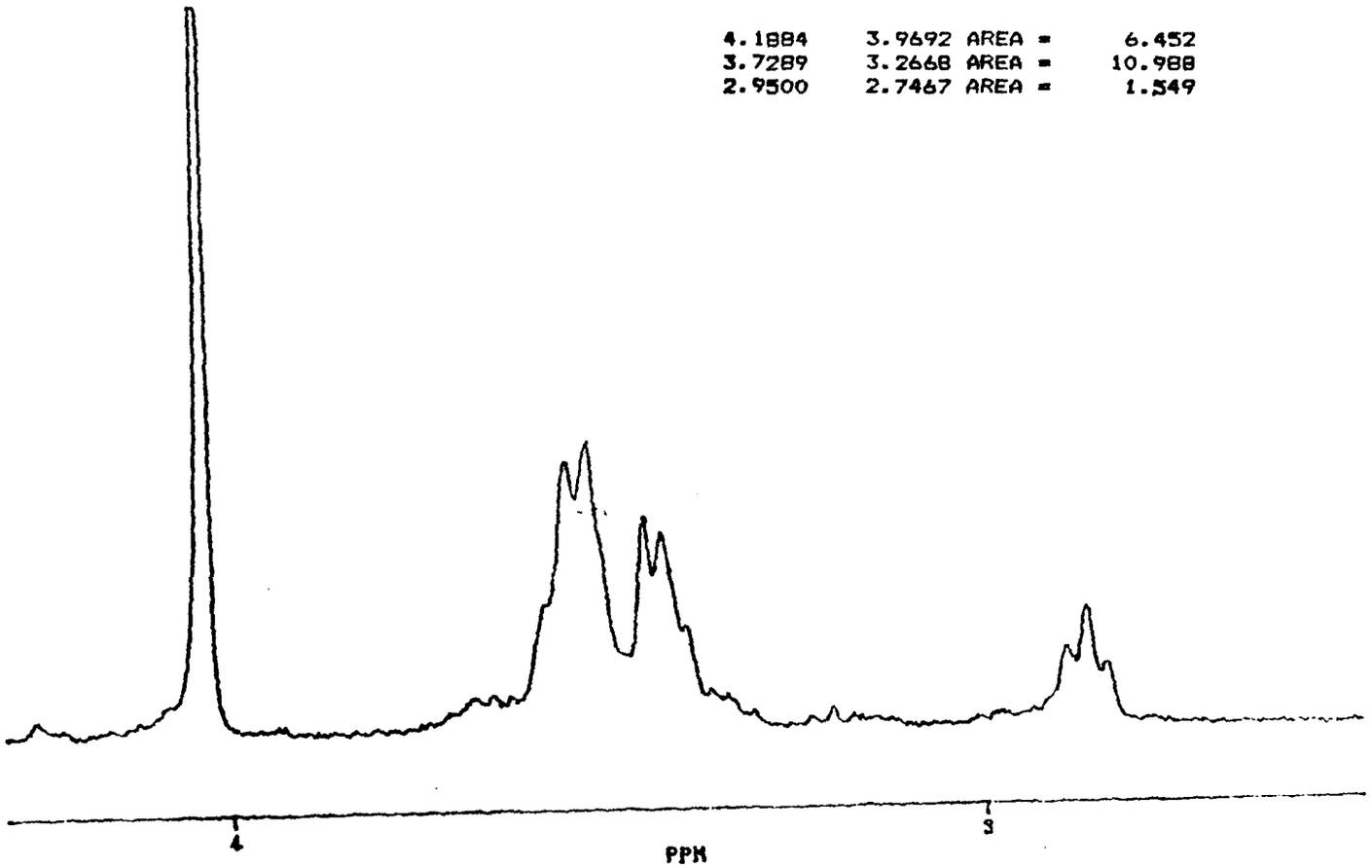

FIGURE 26. ^{1}H NMR OF HOMOACID AND CUBANE DIACID IN D_2O AFTER 20 H AT 60°C AND 1 H AT 110°C

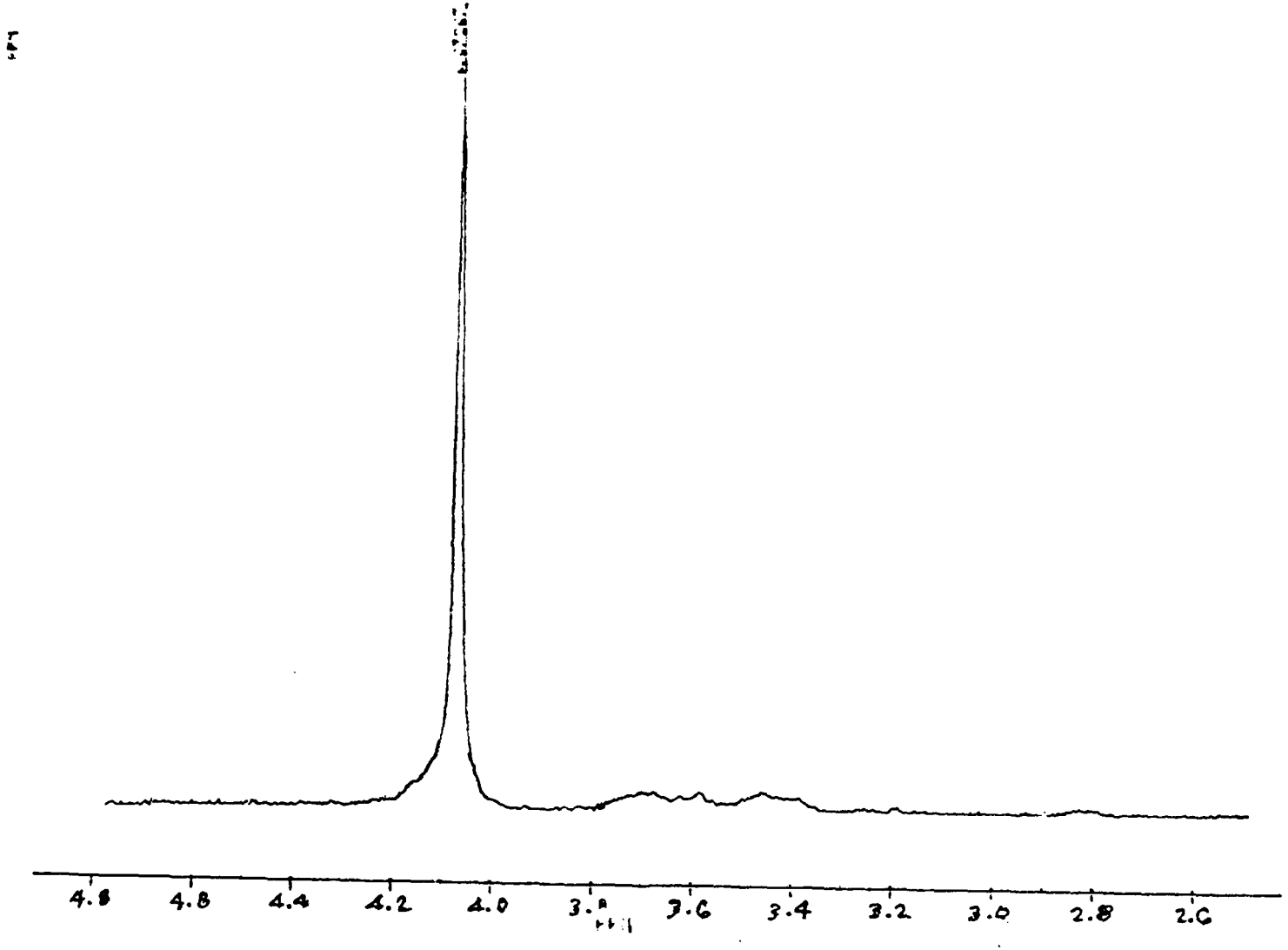

FIGURE 27. ^{1}H NMR OF HOMOACID AND CUBANE DIACID IN D_2O AFTER 20 H AT 60°C AND 4 H AT 110°C

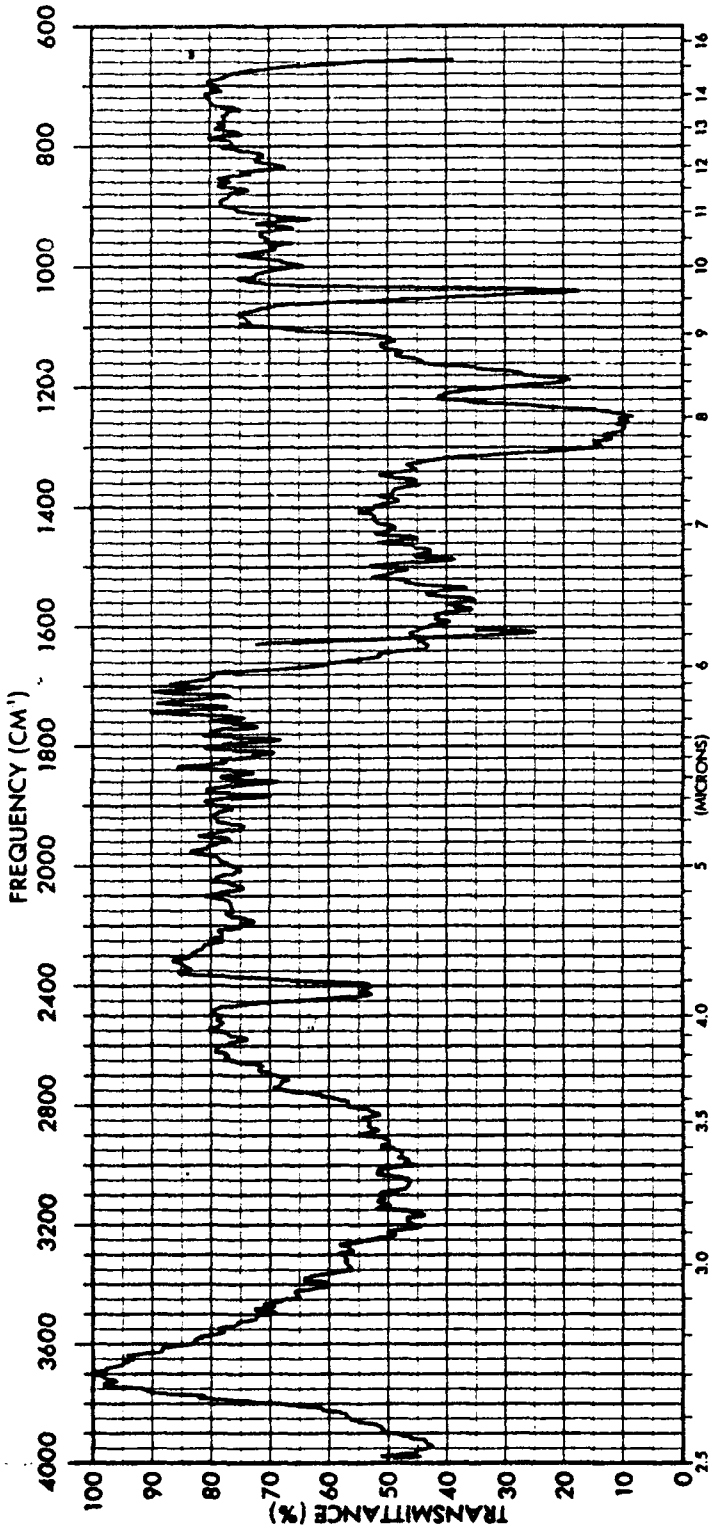

FIGURE 28. IR OF 1,4-DIHYDRAZOMETHYLCUBANE DINITRATE

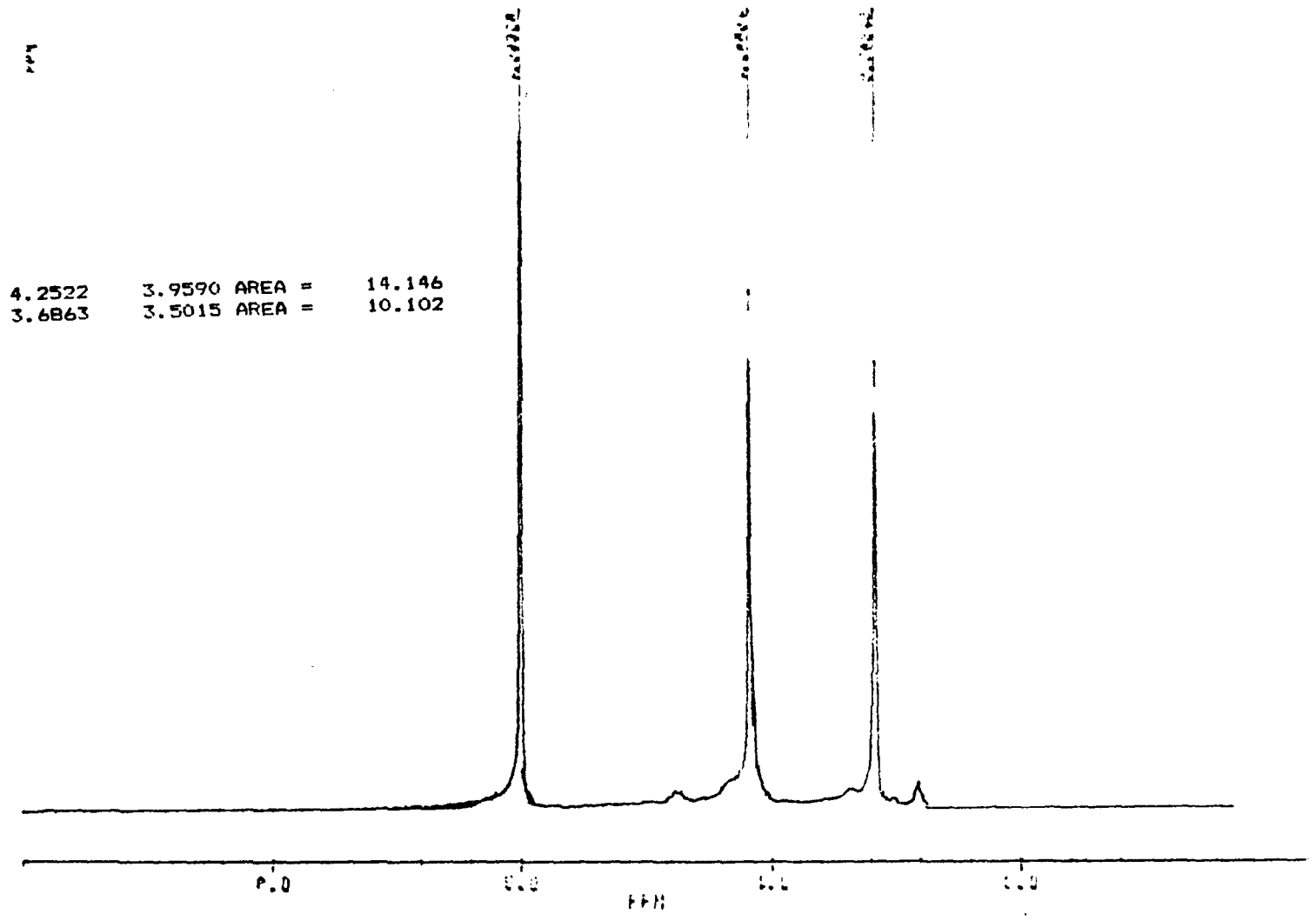

FIGURE 29. ^{1}H NMR OF 1,4-DIHYDRAZOMETHYLCUBANE DINITRATE

#	CURSOR	FREQUENCY	PPM	INTENSITY
1	6027	2704.590	53.7440	2.263
2	6154	2612.412	51.9123	4.160
3	6698	2217.691	44.0686	16.036
4	6899	2071.214	41.1579	-2.753
5	6928	2050.620	40.7487	7.179
6	6956	2029.730	40.3336	28.053
7	6985	2008.733	39.9163	61.933
8	7014	1987.737	39.4991	71.903
9	7043	1966.778	39.0826	62.018
10	7072	1945.814	38.6660	27.707
11	7100	1924.996	38.2524	7.371
12	7127	1905.356	37.8621	-2.555

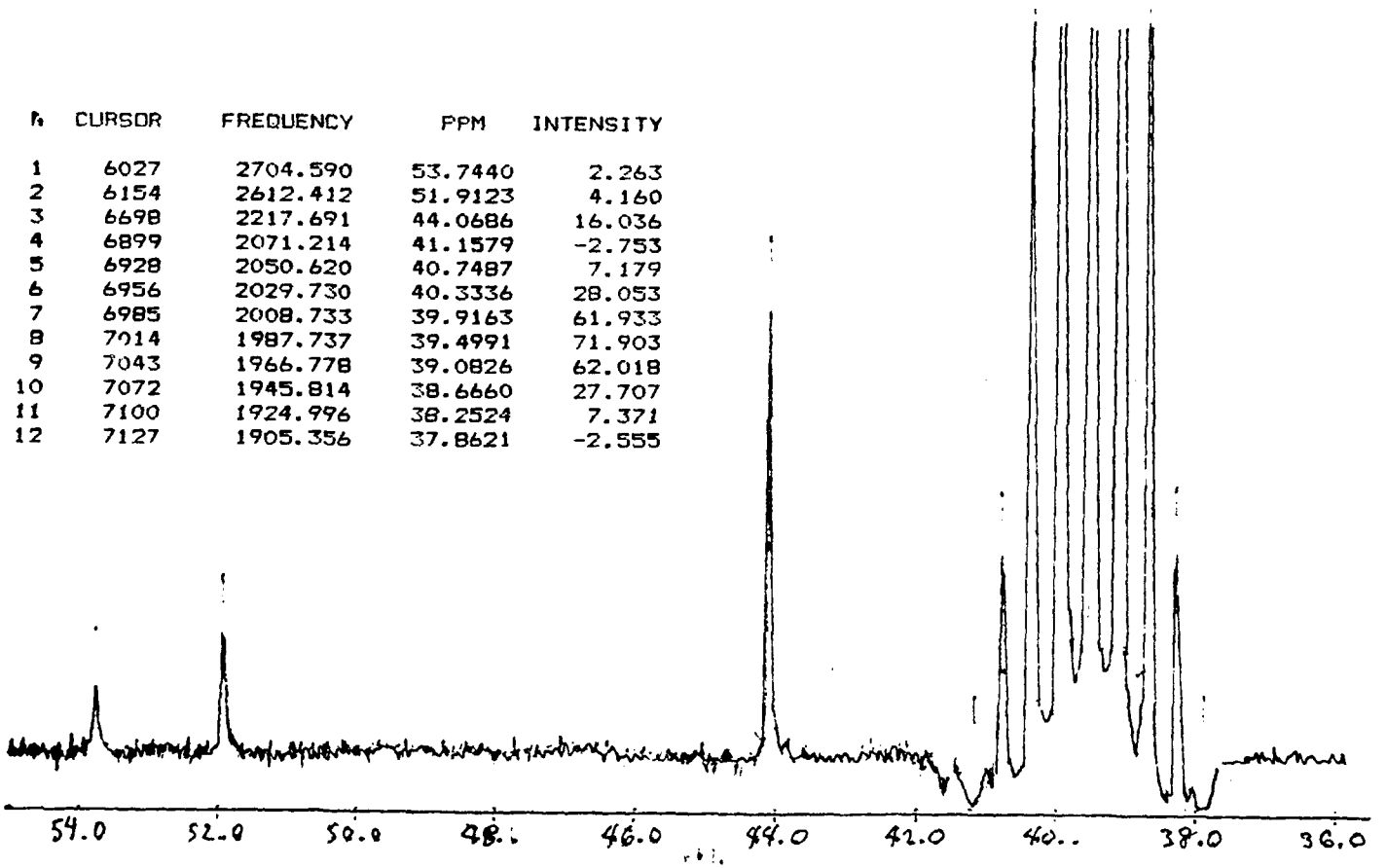

FIGURE 30. ^{13}C NMR OF 1,4-DIHYDRAZOMETHYLCUBANE DITRIFLATE

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