Spring 5-1992

Senior Project

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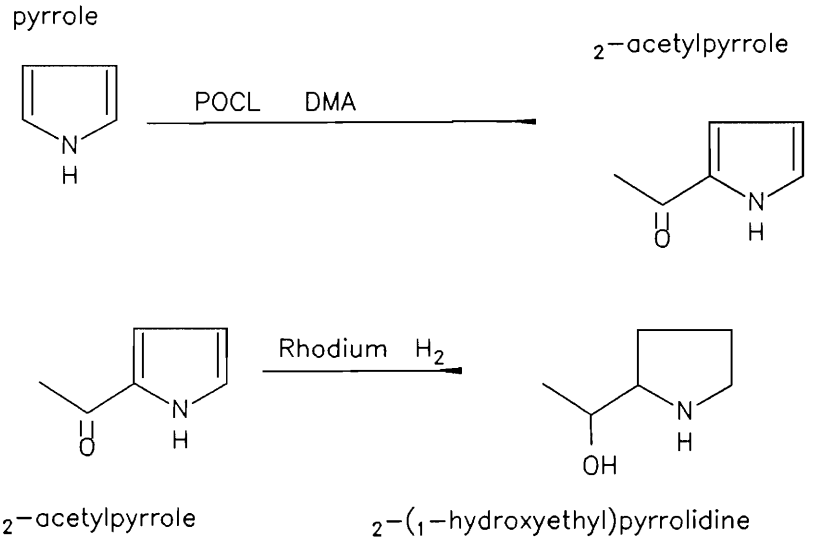
May 15, 1992

The goal of my past research was to synthesize the odorant 2-Acetyl-1-pyrroline, a compound that had been isolated from popcorn and rice. It was ultimately hoped that five grams of the substance could be prepared for analysis by the FDA.

The compound 2-acetyl-1-pyrroline is a heterogenous ring compound derived from pyrrole. The pyrrole molecule consists of four carbons, a nitrogen, and five hydrogens. The overall shape is that of a pentagon formed by the carbons and nitrogen with one hydrogen attached to each carbon or nitrogen. The compound is unsaturated with two carbon to carbon double bonds. The molecular system is conjugated with the pi electrons from the carbon bonds overlapping with the free pi orbital of the nitrogen.

The method selected to synthesize 2-acetyl-1-pyrroline involved the complete reduction/hydrogenation of 2-acetylpyrrole.

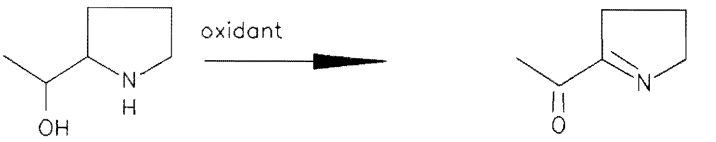


1 Proposed Method

This starting material is available commercially from a variety of chemistry supply houses, but the cost is prohibitive. It was decided that the syntheses should start at this compound. From readily available pyrrole and dimethylacetimide, 2-acetylpyrrole was synthesized using a POCl reaction found in Organic Syntheses (pp. 831-833); however, it was noted that the reaction was rather inefficient with approximately a 45% yield of crude product. Impurities in the crude compound seem to have consisted of various nitrogenous compounds as well as polymers of the desired product. Solubility in warm hexanes provided an useful method of removing some impurities, but the most effective method proved to be blotting with filter paper followed by a rinse of cold hexanes. The clean-up and purification alone seem to bear out the justification of the high commercial price. 2-acetylpyrrole was proven to be a crystalline, translucent solid, which impurities made yellowish. Its melting point is 89 - 90° Celsius. The NMR spectra 2-acetylpyrrole can be seen in d_6-DMSO (deuterated dimethylsulfoxide) on NMR #4 and in $CDCl_3$ on NMR #5.

Efforts at hydrogenating the 2-acetylpyrrole have generally met with limited success, which most references warned would be the case - citing nitrogen's tendency to poison catalysts. Two approaches were used to attempt hydrogenation. The first involved utilizing ethanol as the solvent. Ratios by mass of catalyst to 2-acetylpyrrole ranged from 1:1 to 1:3 with little apparent difference in effectiveness. Filtration of the catalyst through Celite followed by rotoevaporation of the ethanol left a brown, oily solid that was characterized by

a roasty odor. The development of the roasty odor seemed to be dependent on exposure to air which suggests the product requires oxidation after hydrogenation. NMR #1 is the spectrum of such a sample.



2-(1-hydroxyethyl)pyrrolidine 2-acetyl-1-pyrroline

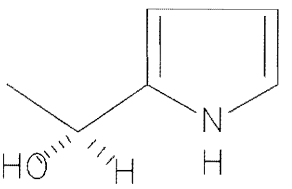
2 Oxidation

Spectra that identified the source of the odor was exceptionally hard to obtain, suggesting that there is little of the 2-acetyl-1-pyrroline formed through the method. This is born out by Peter Schieberle in his paper in the J. Agric. Food Chemistry (1991,39,1141-1144). He reports the odor threshold for 2-acetyl-pyrroline is 0.2 nanograms/liter. The best NMR obtained of the possible pyrroline compound is #1. The compound for the NMR was obtained from past hydrogenation attempts in ethanol that had been stored in a drawer for several weeks, which I use to site as proof for the need of oxidation. The spectrum clearly shows a large percentage of starting material, a pyrolline ring peak at 1 ppm, a singlet at 3.2 ppm, and a quartet at 3.5 ppm. The integrations do not clearly support the correct proportion of protons in the structure, but the existence of impurities render them imprecise. Further support for the hypothesis that the

compound is formed only after some oxidation comes from NMR #11 which is from a hydrogenation using ethanol as a solvent which was worked up immediately. The spectrum is that of 2-(1-hydroxyethyl)pyrrole. It is interesting to note that the ring proton's shifts have changed subtly from two multiplets near 7 ppm and one near 6 ppm to two multiplets near 6 ppm and one near 7 ppm.

The second method substituted acetic acid for ethanol as the solvent used during the hydrogenation. The rationale behind this was hoping the acid would help protonate the carbonyl and the nitrogen easing the addition of hydrogens to the double bonds. Upon neutralizing the acid with $NaHCO_3$, brown solids with the consistency of plastic apparently consumed most of the product. Only the NMR #7 which was performed on residues found in the water after neutralization of the acetic acid showed some sort of pyrroline structure at 1.2 ppm, but the different shifts prove hard to explain.

Finally, a test method using $NaBH_4$ in ethanol produced the 2-(1-hydroxyethyl)pyrrole at almost 100% yield. The NMR spectrum #3 provided the proof for this reaction. Ring protons show at 6.55 ppm, 6.05 ppm, and 6.00 ppm. The quartet at 4.65 ppm and doublet at 1.35 ppm result from the hydroxyethyl group.



3 2-(1-hydroxyethyl)pyrrole

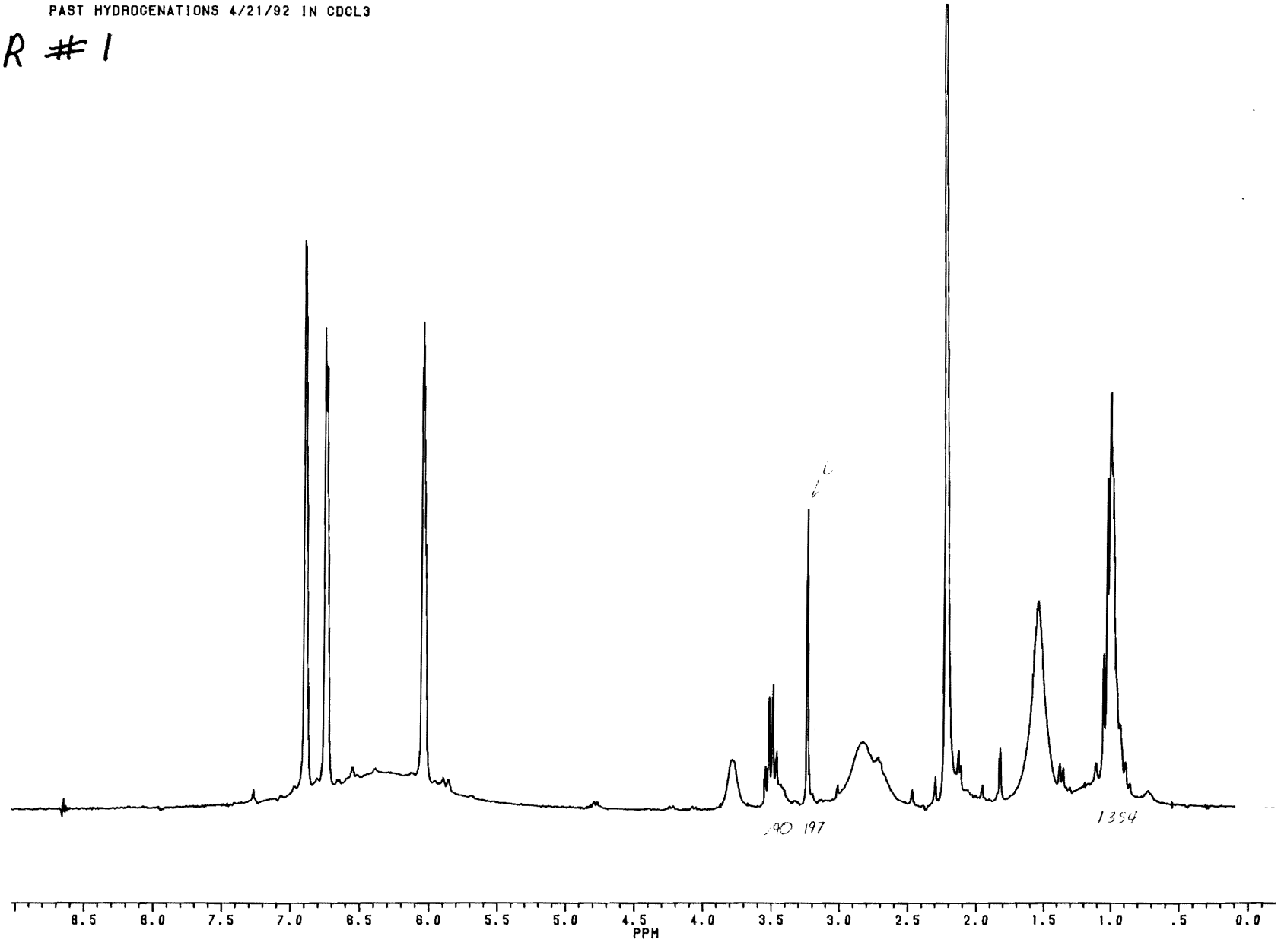
The best method for separation of the compounds was developed using TLC with a mobile phase of 1:1 ethyl acetate:hexanes. A silica gel column using this mixture resolved the 2-(hydroxyethyl)pyrrole in NMR #11 from starting material rather effectively.

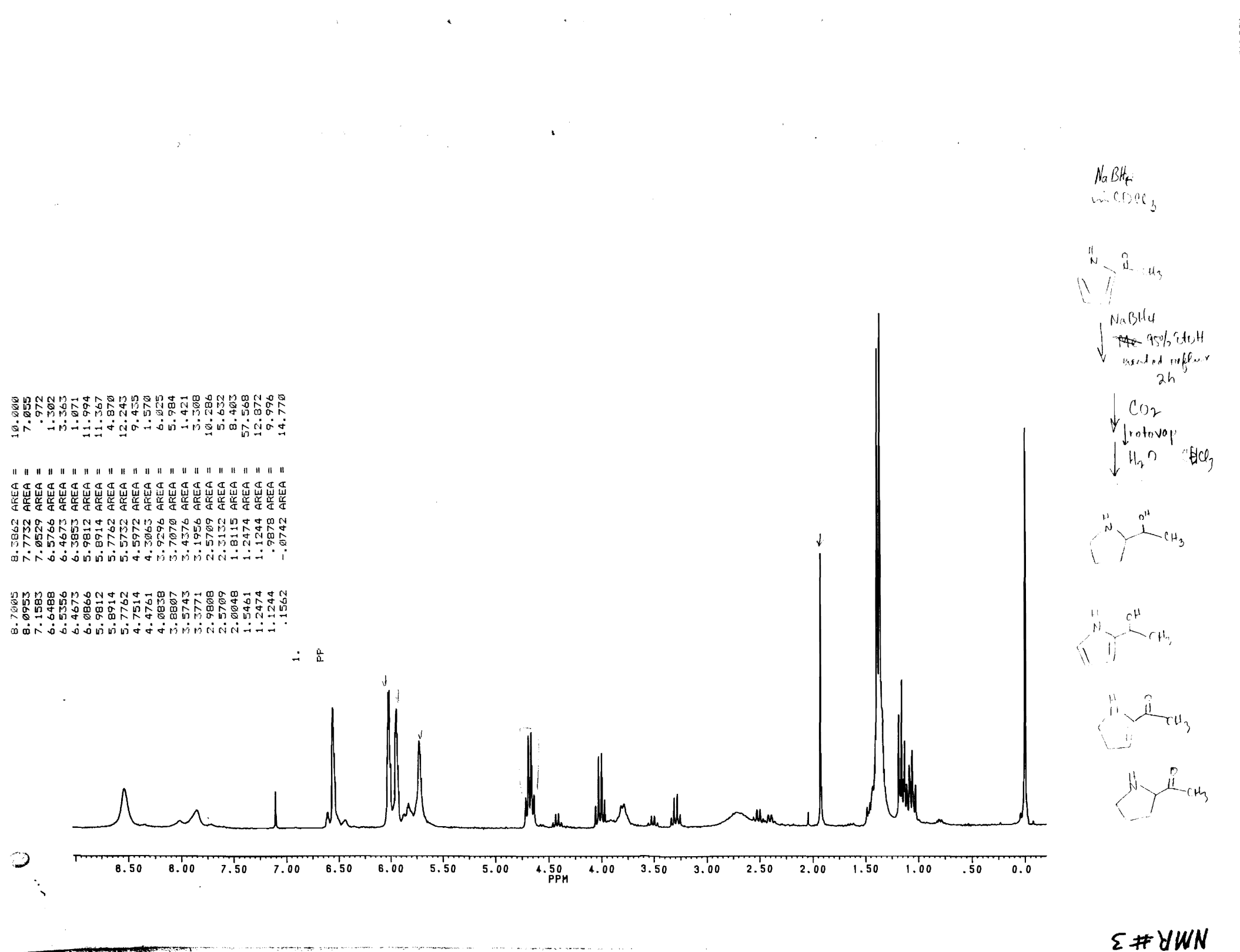
While TLC effectively separated the different compounds in various reactions, much time spent on using gas chromatography to determine the success of reactions was wasted. The rings apparently disintegrate in the injection block into random fragments, rendering the data useless.

In summation, the most successful method for hydrogenation was in ethanol. The indications are that the oxidation of a completely reduced 2-(1-hydroxyethyl)pyrrolidine is required to produce the 2-acetylpyrroline. The oxidation is very gently achieved as evidenced by the simple air oxidation that occurred when the hydrogenation was not stored under argon. The use of acetic acid as a solvent for hydrogenation was probably as successful as ethanol, but problems encountered with polymerization during the work-up diminish its usefulness. The use of $NaBH_4$ to synthesize the 2-(1-hydroxyethyl)pyrrole might be an interesting way to produce another starting material for the hydrogenation. Further work is needed on the separation and purification of the small amount of 2-acetylpyrroline to get a better proton and perhaps carbon-13 NMR profile.

PAST HYDROGENATIONS 4/21/92 IN CDCL3

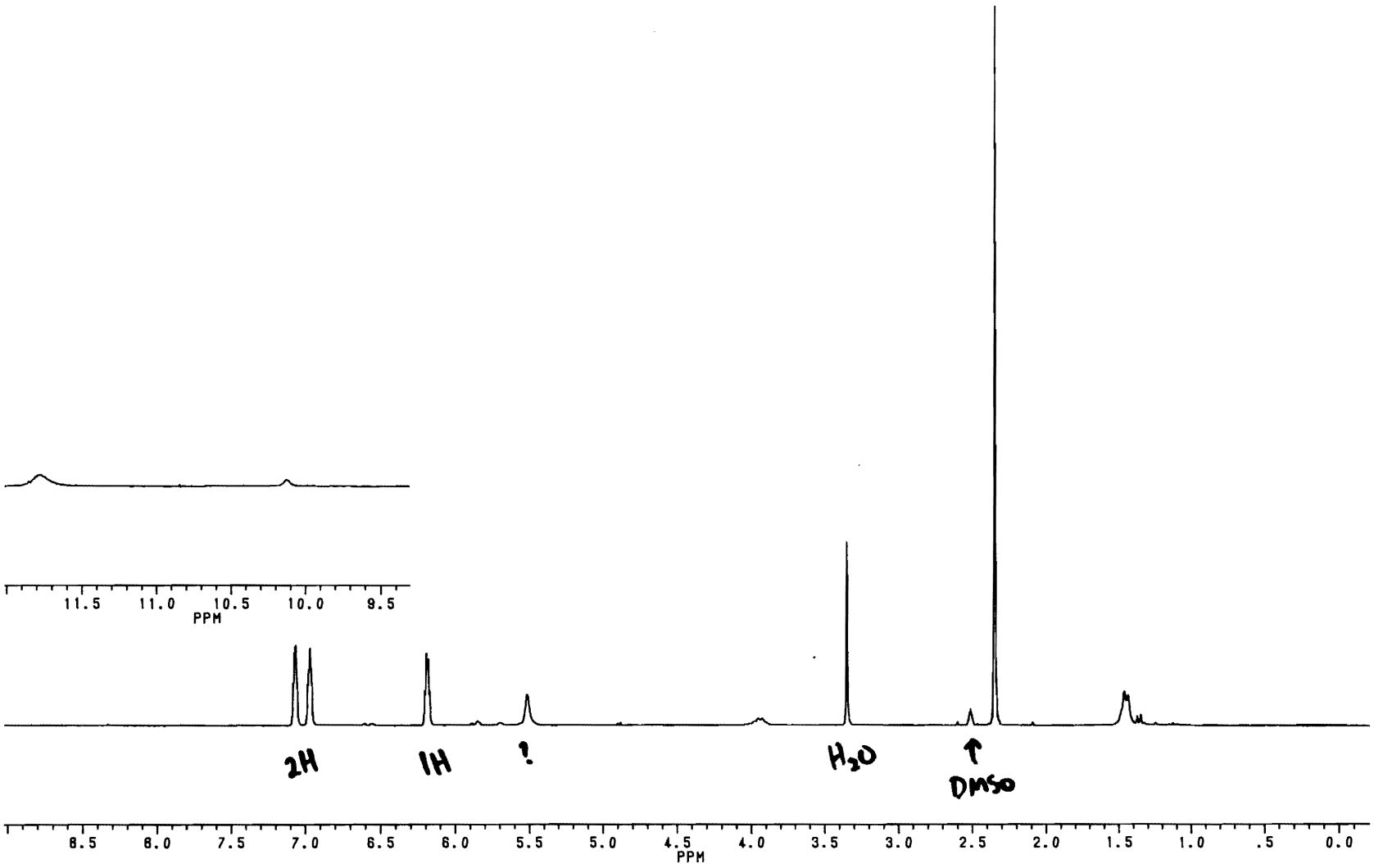
NMR #1




8.7005 8.3862 AREA = 10.000
8.0953 7.7732 AREA = 7.055
7.1583 7.0529 AREA = .972
6.6488 6.5766 AREA = 1.302
6.5356 6.4673 AREA = 3.363
6.4673 6.3853 AREA = 1.071
6.0866 5.9812 AREA = 11.994
5.9812 5.8914 AREA = 11.367
5.8914 5.7762 AREA = 4.870
5.7762 5.5732 AREA = 12.243
4.7514 4.5972 AREA = 9.435
4.4761 4.3063 AREA = 1.570
4.0838 3.9296 AREA = 6.025
3.8807 3.7070 AREA = 5.984
3.5743 3.4376 AREA = 1.421
3.3771 3.1956 AREA = 3.308
2.9808 2.5709 AREA = 10.286
2.5709 2.3132 AREA = 5.632
2.0048 1.8115 AREA = 8.403
1.5461 1.2474 AREA = 57.568
1.2474 1.1244 AREA = 12.872
1.1244 .9878 AREA = 9.996
.1562 -.0742 AREA = 14.770
1. PP
8.50 8.00 7.50 7.00 6.50 6.00 5.50 5.00 4.50 4.00 3.50 3.00 2.50 2.00 1.50 1.00 .50 0.0
PPM
NaBH4
in CDCl3
NaBH4
95% EtOH
heated reflux
2h
CO2
rotovap
H2O
HCl3

NMR #3

NMR #4



11.8683	11.7101 AREA =	5.411
10.2168	10.0587 AREA =	1.507
7.1247	7.0173 AREA =	9.280
7.0154	6.9119 AREA =	9.369
6.2326	6.1272 AREA =	9.216
2.4397	2.2836 AREA =	30.000

PP

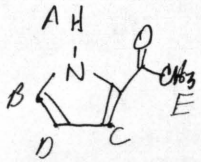
NMR #5

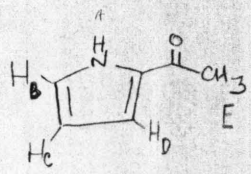
10.1918	9.4481	AREA =	.890
7.1115	7.0119	AREA =	1.000
6.9729	6.8928	AREA =	.957
6.3365	6.2272	AREA =	.950

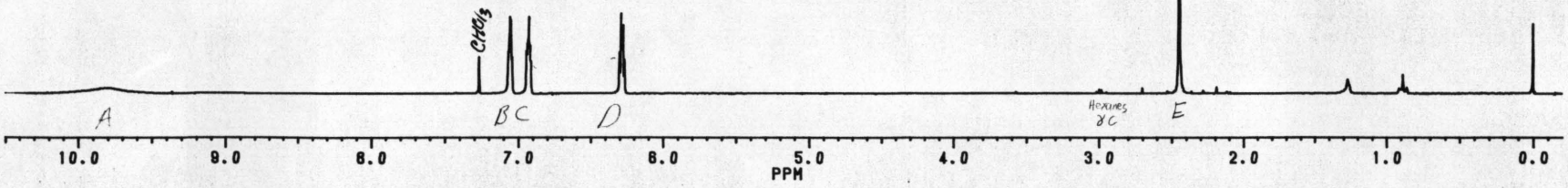
F1[PPM]= 10.500 F2[PPM]= 6.001 -.2P
HZ/CM= 76.47 PPM/CM= .3057

PROTON=D2
MIN. INTENSITY = .900 P MAXY = 18.00000 PP CONSTANT = 1.00000
INTENS. LEVEL = .900 NOISE = .01133 SENS. LEVEL = .04532
F1 = 2626.46 HZ = 10.5003 PPM F2 = -49.80 HZ = -.1991 PPM

#	CURSOR	FREQUENCY	PPM	INTENSITY	
1	3953	1816.506	7.2622	5.634	$CHCl_3$
2	4055	1766.476	7.0622	6.343	B
3	4060	1764.052	7.0525	11.500	B
4	4063	1762.895	7.0478	11.297	B
5	4068	1760.368	7.0377	5.550	B
6	4118	1735.687	6.9391	6.524	C
7	4121	1734.246	6.9333	7.594	C
8	4123	1733.355	6.9297	8.083	C
9	4126	1731.961	6.9242	11.435	C
10	4129	1730.480	6.9182	7.590	C
11	4131	1729.647	6.9149	7.329	C
12	4447	1575.221	6.2975	6.247	D
13	4452	1572.763	6.2877	12.002	D
14	4455	1571.350	6.2821	7.720	D
15	4457	1570.316	6.2779	8.104	D
16	4460	1568.976	6.2726	10.507	D
17	4465	1566.508	6.2627	5.182	D
18	6420	611.596	2.4451	146.242	E
19	6552	547.361	2.1883	.968	impurities
20	7023	317.195	1.2681	2.065	
21	7221	220.754	.8825	2.836	Hexanes
22	7673	-.031	-.0001	10.443	TMS

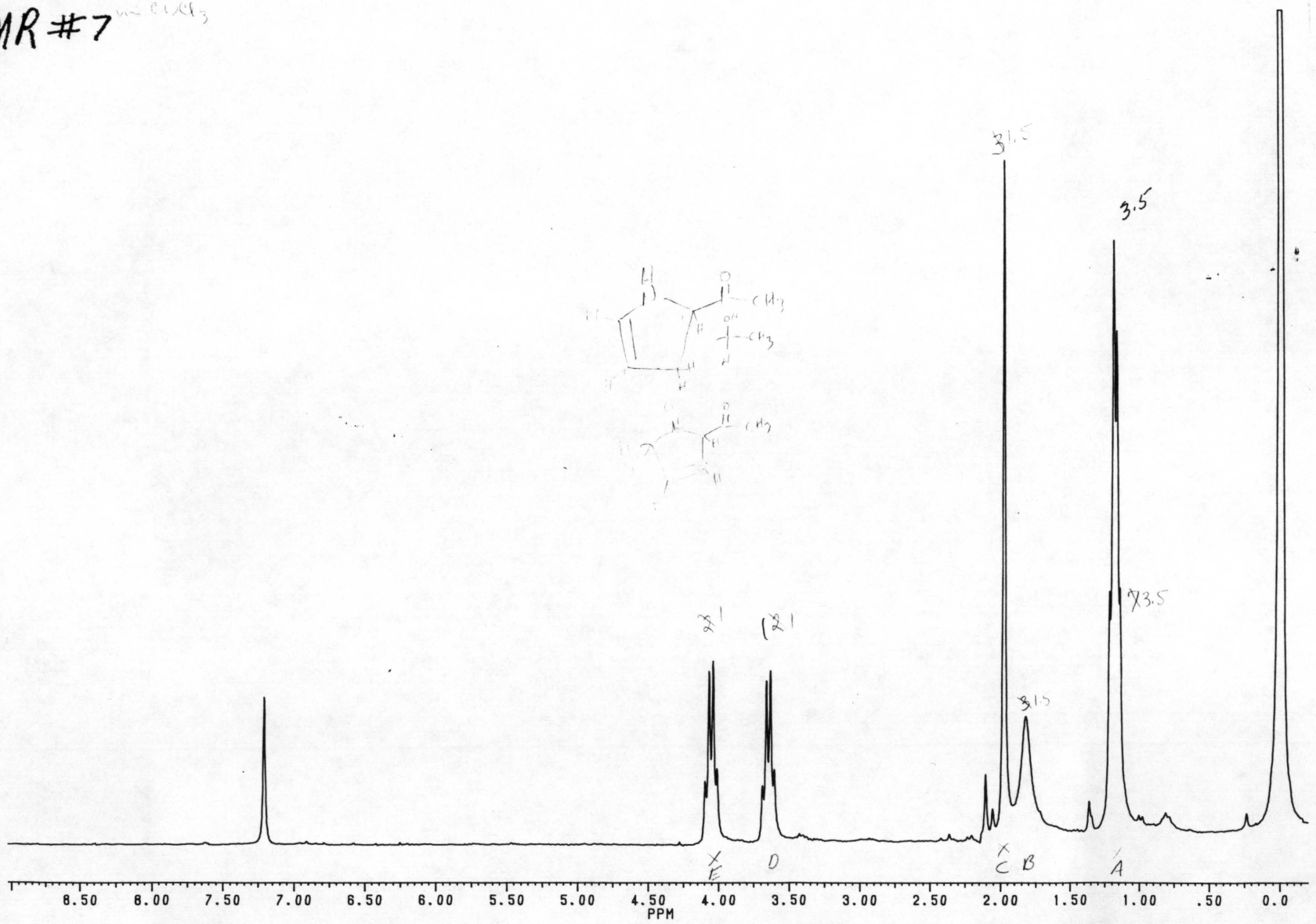






MK -- HYDROGENATION OF ACETYL PYRROLE IN GLACIAL ACOH

NMR #7



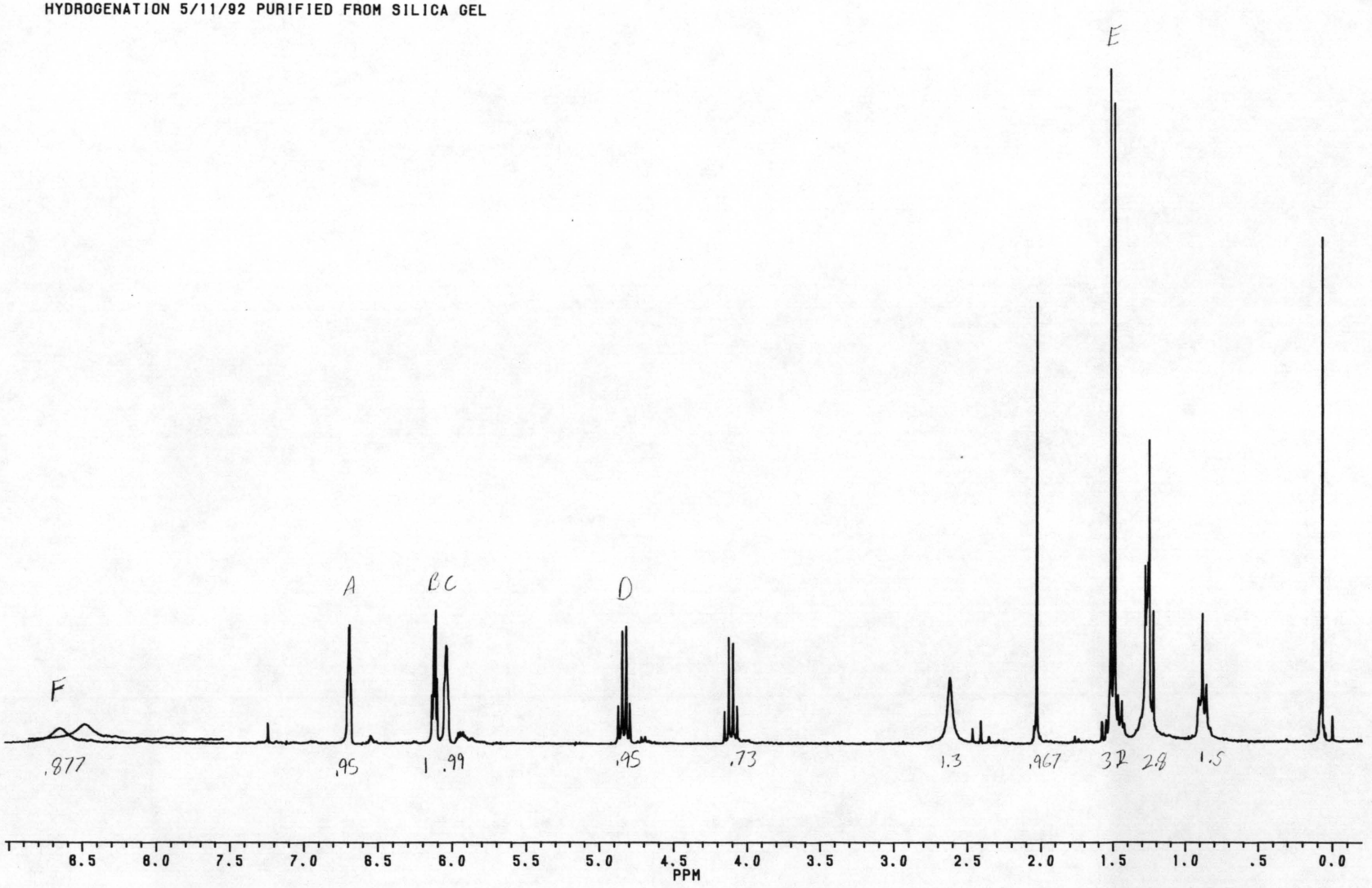
2.EP 22 7645 -.295 -.0012 84.479

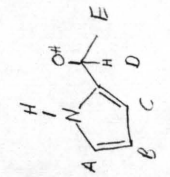
4.1540	3.9100 AREA =	20.000	2
3.7324	3.5294 AREA =	19.053	2
2.1473	2.0751 AREA =	3.478	
2.0751	2.0321 AREA =	1.922	
2.0321	1.9209 AREA =	30.716	3-2
1.8916	1.6729 AREA =	26.027	3
1.3938	1.3157 AREA =	3.587	
1.2728	1.0639 AREA =	72.092	7

11.5 E
11.5 D
1.5 C
2 B
46 A

NMR # 11

HYDROGENATION 5/11/92 PURIFIED FROM SILICA GEL





1.EP

8.8117	8.4779 AREA =	.877
6.7913	6.5981 AREA =	.946
6.1940	6.0788 AREA =	1.000
6.0788	5.9949 AREA =	.990
4.8880	4.7650 AREA =	.953
4.1697	4.0115 AREA =	.732
2.7290	2.5006 AREA =	1.299
2.0751	2.0067 AREA =	.967
1.5363	1.4719 AREA =	3.194
1.3626	1.2298 AREA =	2.879
1.2298	1.2083 AREA =	.372
.9702	.8121 AREA =	1.538