TECHNICAL NOTE

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A Clandestine Approach to the Synthesis of Phenyl-2-Propanone from Phenylpropenes

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ABSTRACT: A number of published syntheses for the manufacture of controlled substances appear to be impractical for the average clandestine laboratory. A closer inspection of these syntheses may reveal modifications which greatly simplify their application. An excellent example of this is the preparation of phenyl-2-propanone (P-2-P) from allylbenzene. In the prototype published method, oxygen is introduced into the reaction vessel by using a tank of compressed oxygen with a balloon for a gas reservoir. In our modification, oxidation is accomplished with a 30% hydrogen peroxide solution. P-2-P has been prepared by both methods and a comparison made of the reaction mixtures at various times during their synthesis. Additionally, propenylbenzene, a by-product of these reactions, can be converted to P-2-P by modification of a second synthesis. Gas chromatography and nuclear magnetic resonance spectral data are presented for each method.

KEYWORDS: toxicology, controlled substances, phenyl-2-propanone, amphetamine

Background

The investigation of clandestine drug manufacturing laboratories represents a combined effort between the criminal investigator and the forensic chemist. At an early point in an investigation the special agent will frequently request a list of the chemicals and synthesis methods used to produce a controlled substance. Providing these lists is often a very simple assignment for the forensic chemist. A general understanding of various chemicals reactions and techniques is a part of the forensic chemist's training, academic background, and experience. Additionally, numerous specific and detailed drug syntheses are also available to him from the open literature. The chemist may, none the less, encounter problems when reviewing published procedures. If the literature procedures do not explicitly illustrate the synthesis of the desired compound, the chemist may erroneously assume that it is not applicable to the clandestine laboratory. This conclusion may, in part, be due to the complicated nature of the procedure or to the apparent requirement for specialized equipment. It may also arise from the failure of the

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chemist to visualize an application of the literature to the synthesis of the clandestine drug. In this context, the synthesis methods are themselves clandestine; they are "hidden" within the literature. A determined study of literature procedures, however, often reveals that while they do not detail the synthesis of the drug in question, they can be modified to give useful or simple methods for its manufacture. Sometimes this requires only the substitution of appropriate chemicals or certain changes in reaction parameters or catalysts.

Examples of this conceptual approach can be shown by the synthesis of the nonpsychoactive controlled substance phenyl-2-propanone (P-2-P). Halting the clandestine manufacture of P-2-P is of particular interest to enforcement personnel since it serves as the primary precursor in a number of syntheses for amphetamine and methamphetamine. By substitution of the chemicals and through slight changes in procedure, two published syntheses have been modified for P-2-P manufacture. These simple changes are illustrated below and are of the type to be expected of a clandestine drug chemist. By procuring chemicals and using procedures not generally recognized for the production of the controlled substance, the clandestine chemist may improve his chances to escape detection. Each of the two procedures investigated give fair to excellent yields of P-2-P, and, by using the procedures consecutively, yields are greatly increased.

Experimental Procedure

Equipment

Gas liquid chromatography (GLC) employed a Hewlett Packard Model 5840A gas liquid Chromatograph, with a 1.8-m (6-ft) glass column and 10% OV-101 packing material. The temperature was maintained at 130°C. Infrared spectrophotometry (IR) was performed with a standard salt plate liquid sample holder or a potassium bromide matrix using a Perkin-Elmer 283 Spectrophotometer. Mass spectra (MS) were obtained using a Finnigan Model 4532 gas chromatograph/EI-CI mass spectrometer system. The optimum operating parameters for this unit required an analyzer temperature of 110°C and ionization voltage of 70 V. Nuclear magnetic resonance (NMR) spectra were recorded from 90 MHz Varian EM 390 spectrometer.

Allylbenzene Procedure

The following procedure, which Tsuji et al [*1*] used for the preparation of 1-decanone, required only the substitution of allylbenzene (1-phenyl-2-propene) for 1-decene. A three-neck round bottomed flask was fitted with a magnetic stirrer and a pressure-equalized dropping funnel containing allylbenzene.

The flask was charged with a mixture of palladium chloride, cuprous chloride, and aqueous *N,N*-dimethylformamide (DMF). With all outlets securely stoppered and wired down, an oxygen-filled balloon was placed over one neck and the flask contents stirred at room temperature to allow oxygen uptake. After a period of oxygenation, allylbenzene was added dropwise. The solution was continuously stirred under the pressurized balloon. During this period of addition, the color of the solution turned from green to black and gradually returned to green as the reaction approached completion. The mixture was poured into cold hydrochloric acid and extracted with methylene chloride (CH_2Cl_2). The extract was washed with saturated sodium bicarbonate and dried over anhydrous sodium sulfate. Through filtration and distillation, phenyl-2-propanone and *trans*-beta-methylstyrene (1-phenyl-1-propene) were recovered. The reaction is shown in Fig. 1. Yields approximate those listed in the "modified" procedure given below.

Modified Allylbenzene Procedure

The procedure employed was a simple modification of the preceding reaction. The equipment modification eliminates the oxygen filled balloon, which requires an outside source of ox-

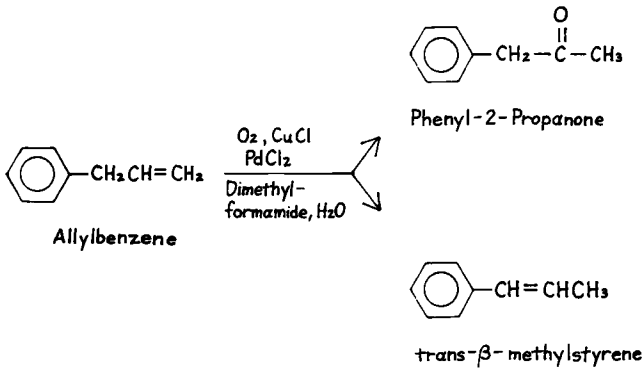


FIG. 1—*Synthetic procedure for phenyl-2-propanone—allylbenzene method.*

ygen, such as a compressed oxygen tank, and replaces it with a 30% hydrogen peroxide solution. The aqueous DMF solution is thus prepared by using 30% hydrogen peroxide in place of water. The quantity of palladium chloride catalyst was also decreased. This reaction is shown in Fig. 2. The synthesized P-2-P (49% yield) was separated from the reaction mixture by shaking with saturated aqueous sodium bisulfite solution and cooling the resultant mixture. Vacuum filtration of the mixture yielded crystalline P-2-P bisulfite addition product. Figure 3 shows an infrared spectrum of the compound. The two-phase filtrate was then separated and the organic layer containing the *trans*-beta-methylstyrene (45% yield) was recovered by extraction with CH_2Cl_2. The recovered *trans*-beta-methylstyrene still contained several grams of P-2-P and trace amounts of allylbenzene and *cis*-beta-methylstyrene.

Trans-*Beta-Methylstyrene Procedure*

By using a modification of Fujisawa and Deguchi's [*2*] synthesis of 3,4-methylenedioxybenzyl methyl ketone, the *trans*-beta-methylstyrene by-product of the previous reaction was also converted to P-2-P. This conversion was accomplished by dropping an acetone/*trans*-beta-methylstyrene solution into a stirred solution of hydrogen peroxide in formic acid [*2,3*]. The acidic solution was refluxed and, then, neutralized and extracted with CH_2Cl_2. After evaporating most of the CH_2Cl_2, the extracted mixture of glycol and glycol esters was stirred

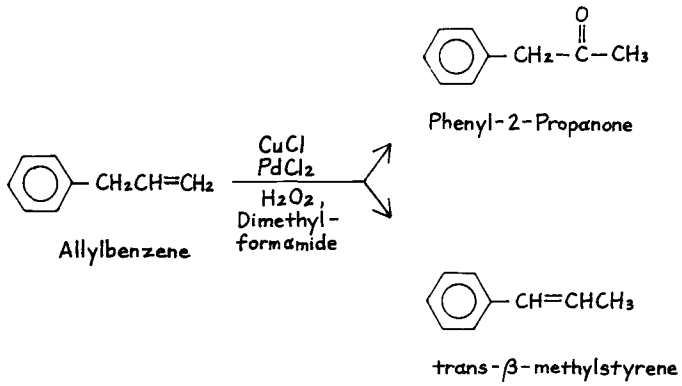


FIG. 2—*Synthetic procedure for phenyl-2-propanone—modified allylbenzene method.*

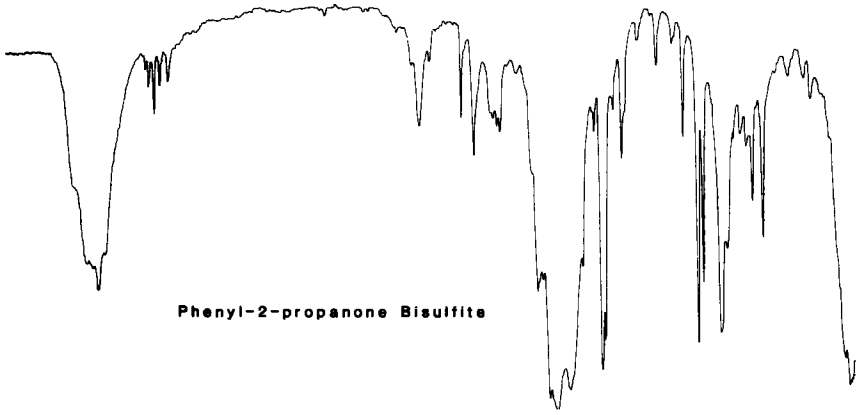


FIG. 3—*Infrared spectra for phenyl-2-propanone bisulfite addition product.*

and heated in a solution of methanol and dilute sulfuric acid. The resulting solution was neutralized with aqueous base and extracted with CH_2Cl_2 to yield phenyl-2-propanone (93%). The sequence shown in Fig. 4 was adapted from Fujisawa and Deguchi.

Discussion

The MS, IR, and NMR spectra of the initial starting material, allylbenzene; the major side product, *trans*-beta-methylstyrene; and the final product, P-2-P are shown in Figs. 5 through 7, 8 through 10, and 11 through 13, respectively. Figure 14 is the NMR spectrum of the original allylbenzene reaction after 1 h. After 19 h the NMR spectrum was unchanged. NMR spectra of the "modified" reaction mixture produced identical results. Failure of NMR to detect any difference between these time periods, or between the original and peroxide modified reactions, was primarily a result of the large amount of DMF relative to the components of interest. Using GLC, chromatograms were obtained for these same time periods for both of the reaction mixtures (Figs. 15 through 18). These figures do show the expected increase in P-2-P and formation of the predominant side product, beta-methylstyrene, as the reaction progressed. Each of the reaction mixtures was acidified and extracted with dichloromethane. The NMR spectra of the extracted reaction mixtures at 19 h (Figs. 19 and 20) confirmed that the two most abundant products are P-2-P and the trans *isomer* of beta-methylstyrene [*4*]. The gas chromatograms in Figs. 17 and 18 that show the reaction mixture of the peroxide modified allylbenzene procedure at 1 and 19 h, respectively, are essentially the same as Figs. 15 and 16. Although not labelled on these figures, the peak at 0.83 is due to the reaction solvent DMF.

The synthesis of P-2-P from *trans*-beta-methylstyrene was performed using the recovered impure side product from the allylbenzene (see the gas chromatogram, Fig. 21). Commercially

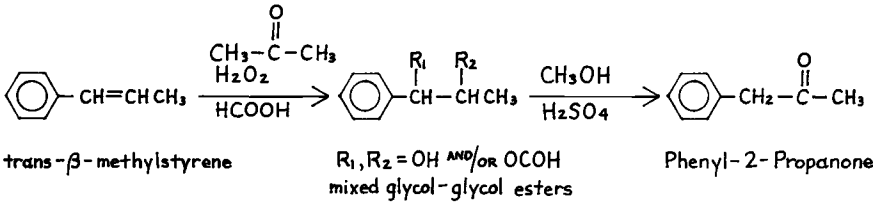


FIG. 4—*Synthetic procedure for pheynl-2-propanone*—trans-*beta-methylstyrene method.*

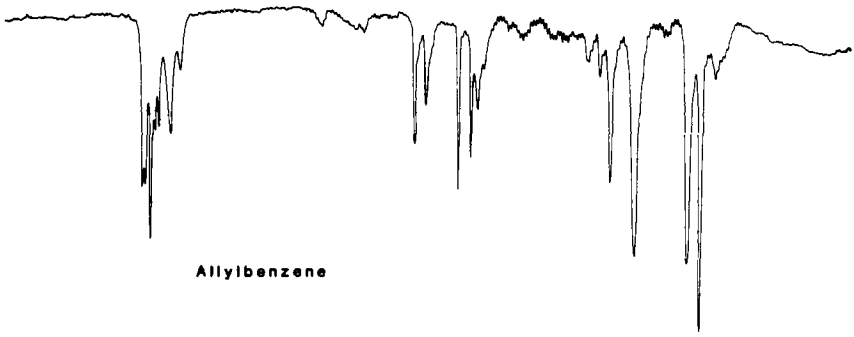


FIG. 5—*Infrared spectrum for allylbenzene.*

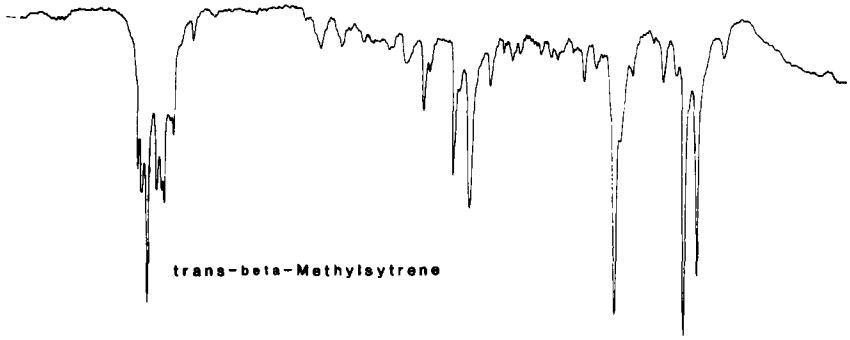


FIG. 6—*Infrared spectrum for* trans-*beta-methylstyrene.*

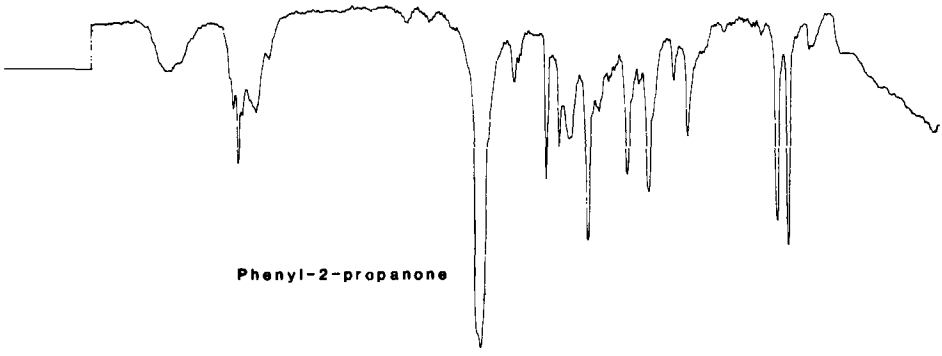


FIG. 7—*Infrared spectrum for phenyl-2-propanone.*

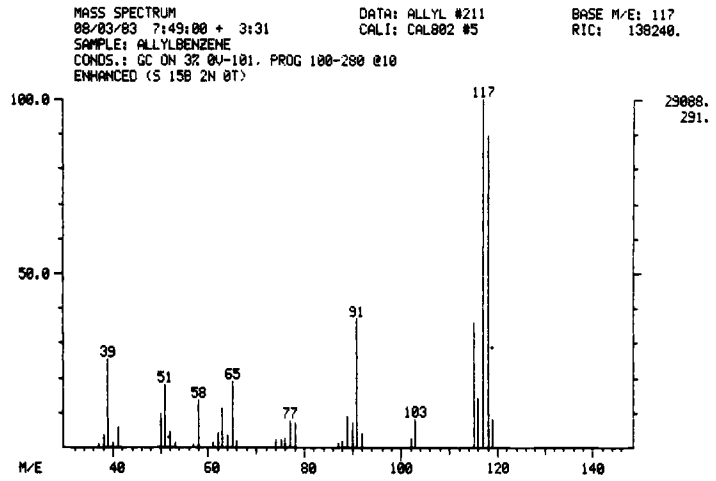


FIG. 8—*Mass spectrum for allylbenzene.*

obtained pure *trans*-beta-methylstyrene is also suitable; however, its current cost is approximately four times greater than allylbenzene. The NMR spectrum (Fig. 22) and the gas chromatogram (Fig. 23) show the reaction mixture near the end of the performic acid oxidation [5]. The multiplet in Fig. 22 centered at 1 ppm indicates that more than one form of this substance exists, while Fig. 23 suggests the formation of four new components. This type of oxidation primarily yields the glycol and glycol esters.

The mass spectrum of the major oxidation component indicates that it is phenyl-1-hydroxyl-2-formyl-propane (Fig. 24). Its isomer, phenyl-1-formyl-2-hydroxyl-propane (Fig. 25), is also formed. The difference in mass spectra between the two compounds occurs because of the loss of a hydroxyl group alpha to a phenyl ring (Fig. 24). This results in a difference in the intensities of masses 162 and 163. Beta cleavage here is the predominant reaction and is responsible for the 107 mass fragment [6]. The 77/79 masses are to be expected when the 107 AMU fragment is produced. The 135–136 AMU fragments are created by the loss of the formate ester. Figure 26 shows the mass spectrum of phenyl-1,2-diformyl-propane with beta cleavage and a rapidly occurring loss of the formate moiety. The peak at 6.82 min in Fig. 23 has not been fully confirmed by MS, but is indicative of the glycol, phenyl-1,2-dihydroxypropane. Hydrolyzing these oxidation products by refluxing with sulfuric acid and methanol produces P-2-P in high yield. The NMR spectrum of a hydrolysis sample removed after 2 h (Fig. 27) shows P-2-P to already be a major component. After 3½ h of hydrolysis, the NMR spectrum (Fig. 28) shows virtually the entire sample converted to P-2-P.

Conclusion

Although phenyl-2-propanone is not a sympathomimetic substance in and of itself, it is frequently synthesized in clandestine laboratories to produce the essential chemical for the manufacture of amphetamine or methamphetamine. By modification and coupling of available literature procedures, a sequence is presented for the manufacture of P-2-P. This sequence uses chemicals not normally associated with the clandestine synthesis of P-2-P. Evaluation of these syntheses underscores the diligence required of the forensic chemist to provide enforcement personnel with accurate information. The investigated reactions and procedures are easily performed and, when used consecutively, result in an approximate total yield for P-2-P of 79%.

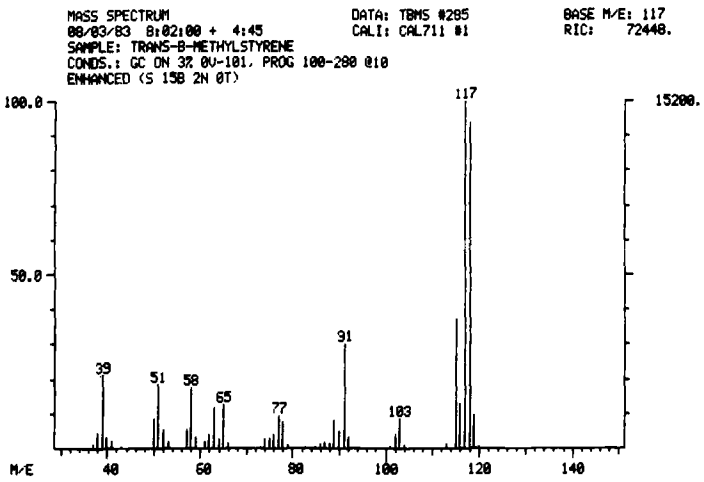


FIG. 9—*Mass spectrum for* trans-*beta-methylstyrene.*

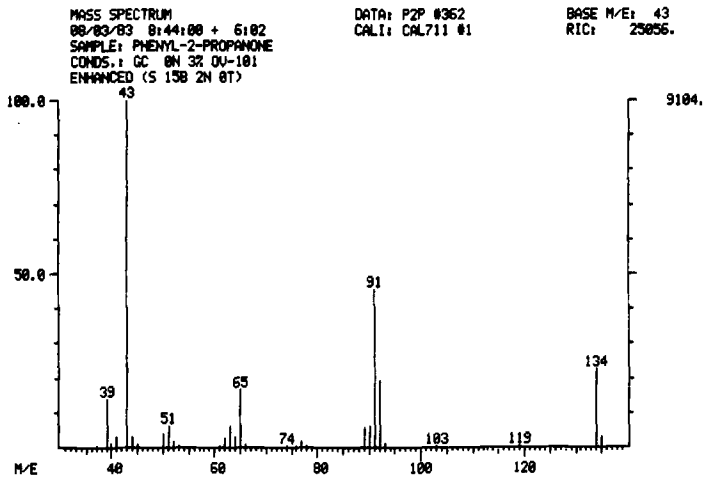


FIG. 10—*Mass spectrum for phenyl-2-propanone.*

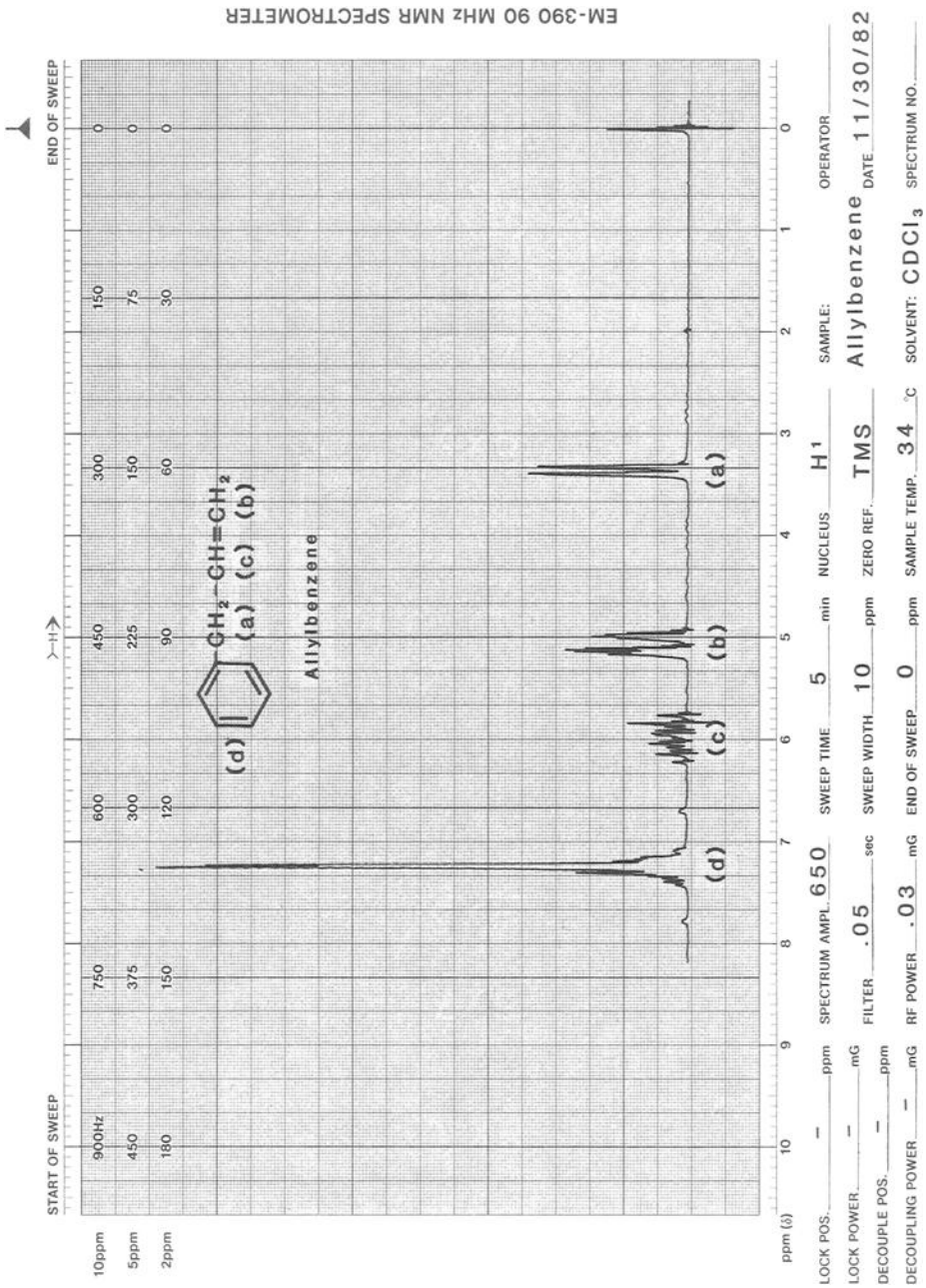


FIG. 11—*Nuclear magnetic resonance spectrum ($CDCl_3$) for allylbenzene.*

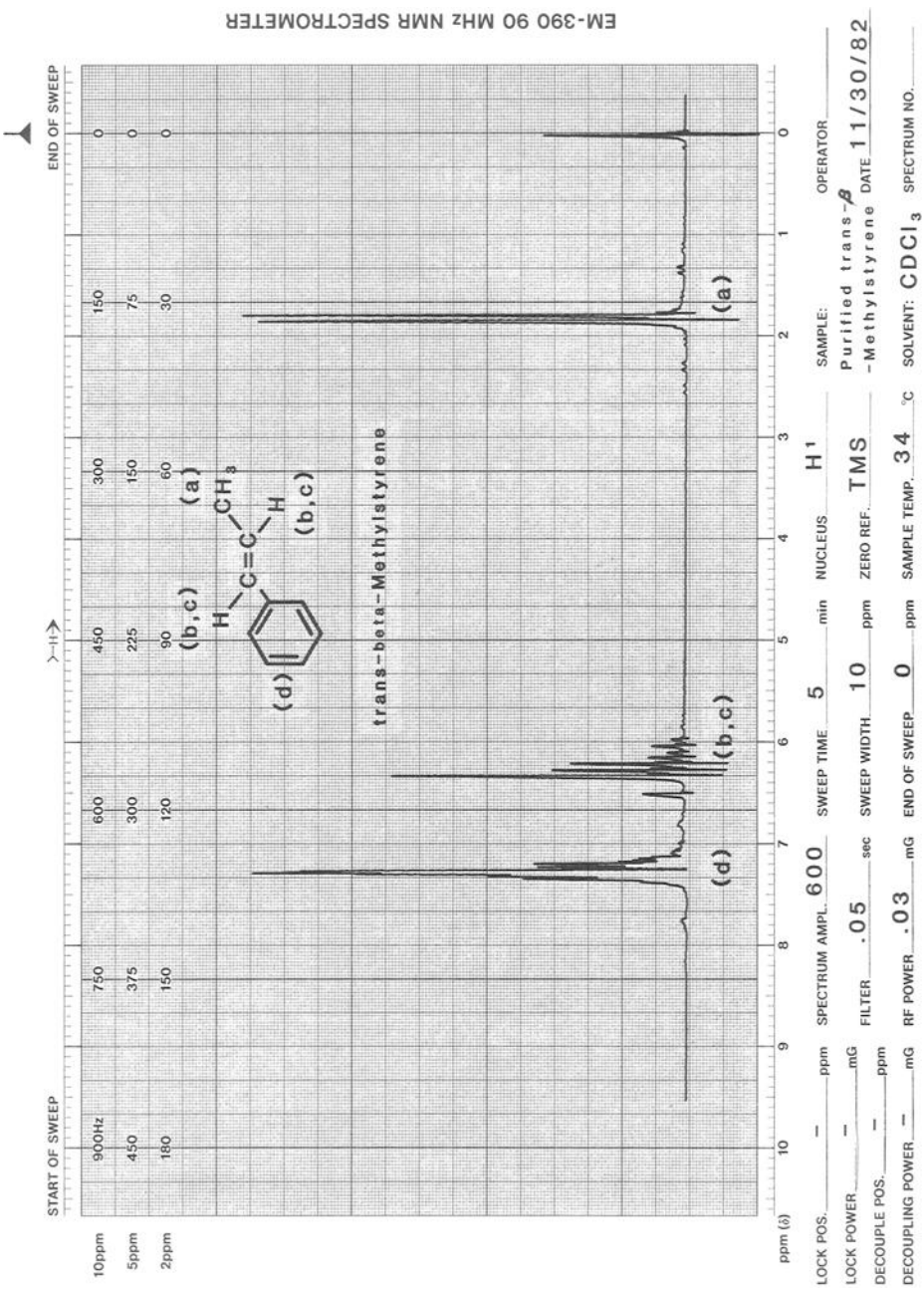


FIG. 12—Nuclear magnetic resonance spectrum ($CDCl_3$) for trans*-beta-methylstyrene.*

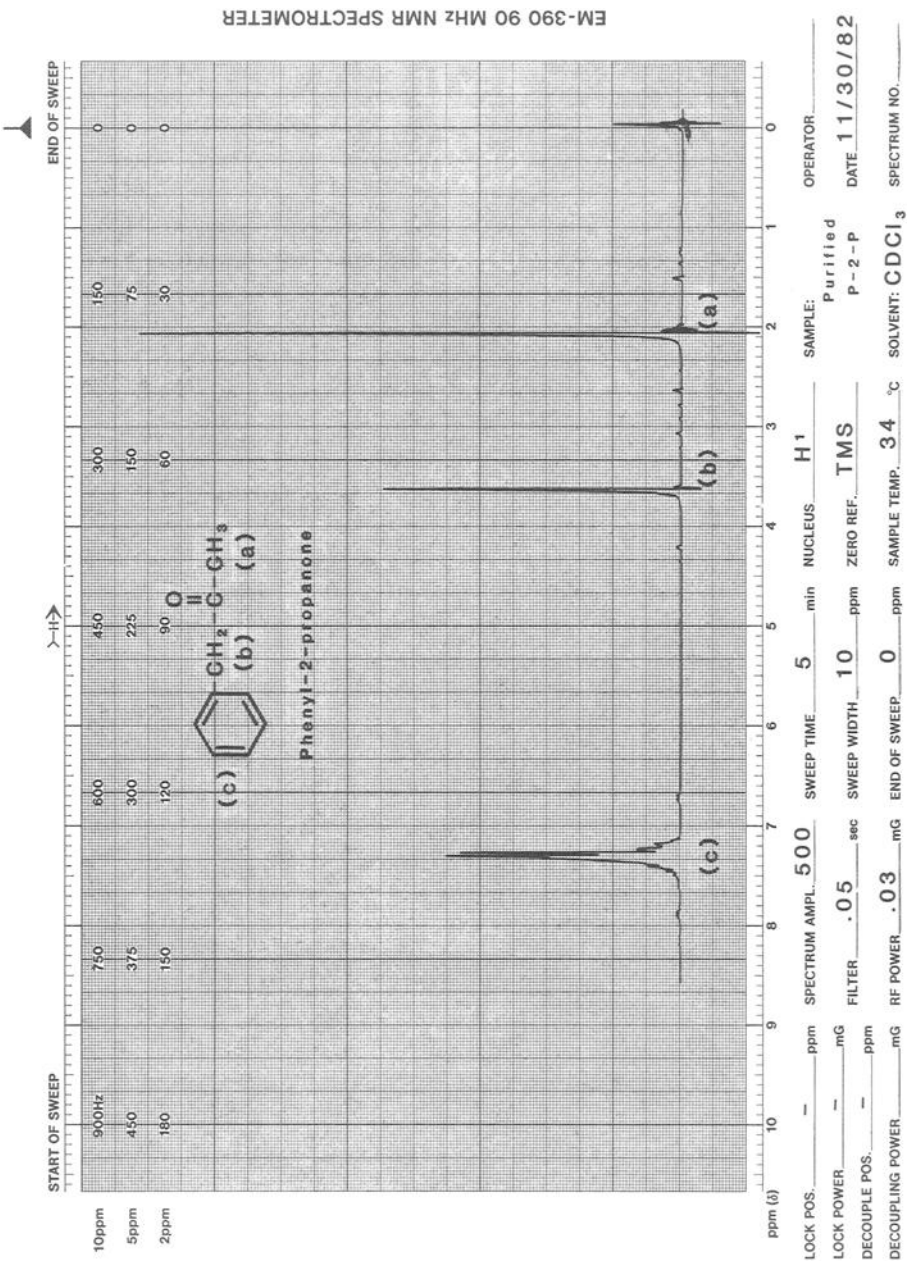


FIG. 13—*Nuclear magnetic resonance spectrum ($CDCl_3$) for phenyl-2-propanone.*

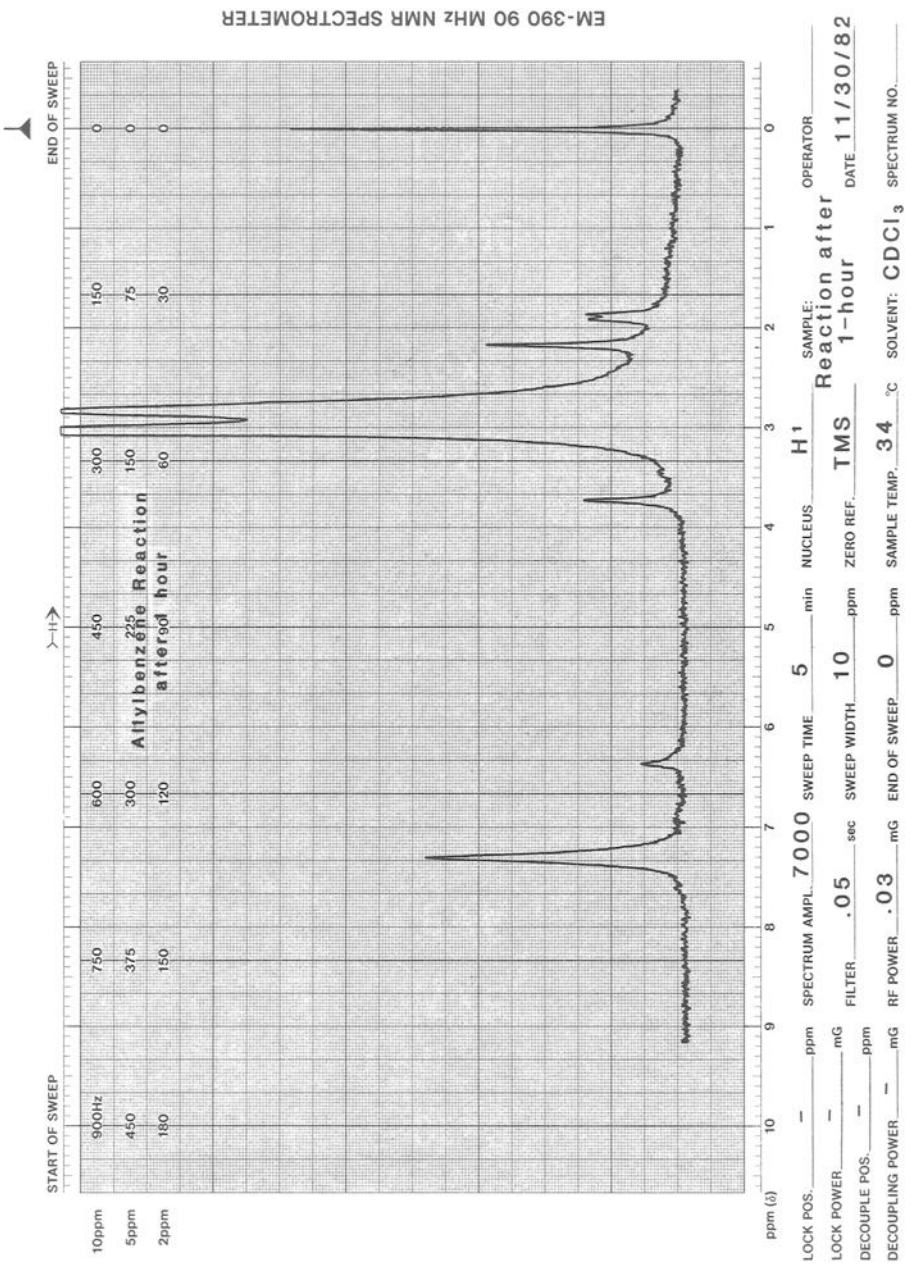


FIG. 14—*Nuclear magnetic resonance spectrum of allylbenzene reaction mixtures—literature procedure after 1 h.*

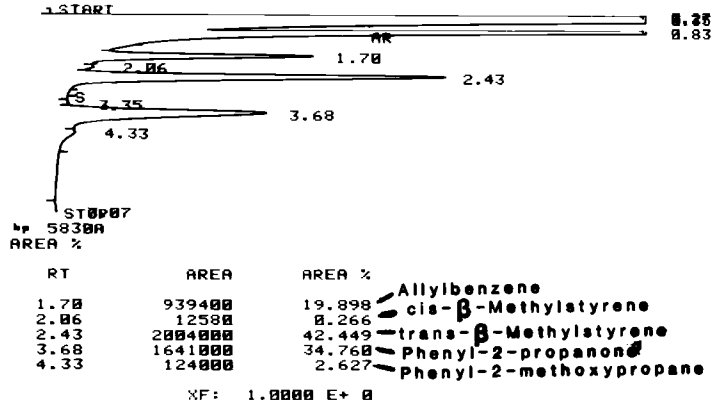


FIG. 15—*Gas chromatogram of the allylbenzene original procedure after 1 h.*

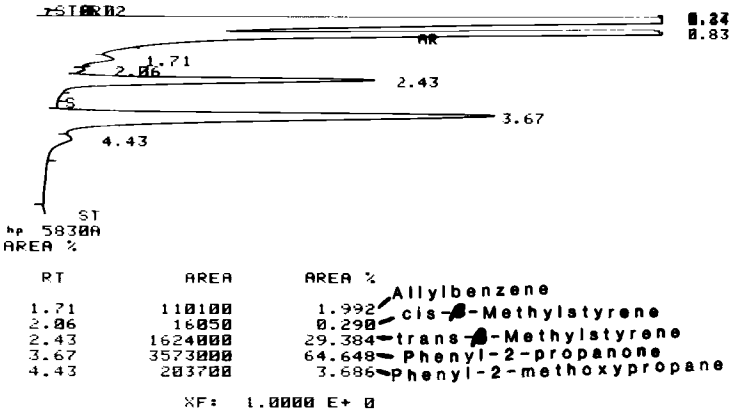


FIG. 16—*Gas chromatogram of the allylbenzene original procedure after 19 h.*

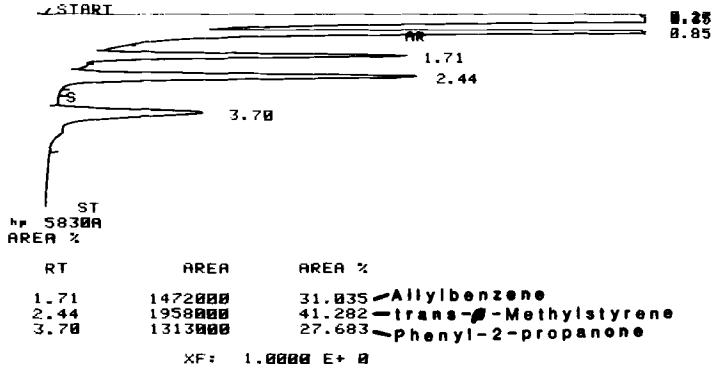


FIG. 17—*Gas chromatogram of the allylbenzene procedure modified after 1 h.*

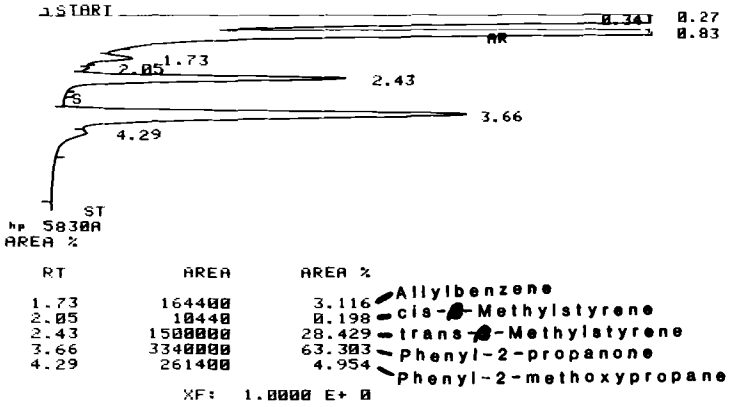


FIG. 18—*Gas chromatogram of the allylbenzene modified procedure after 19 h.*

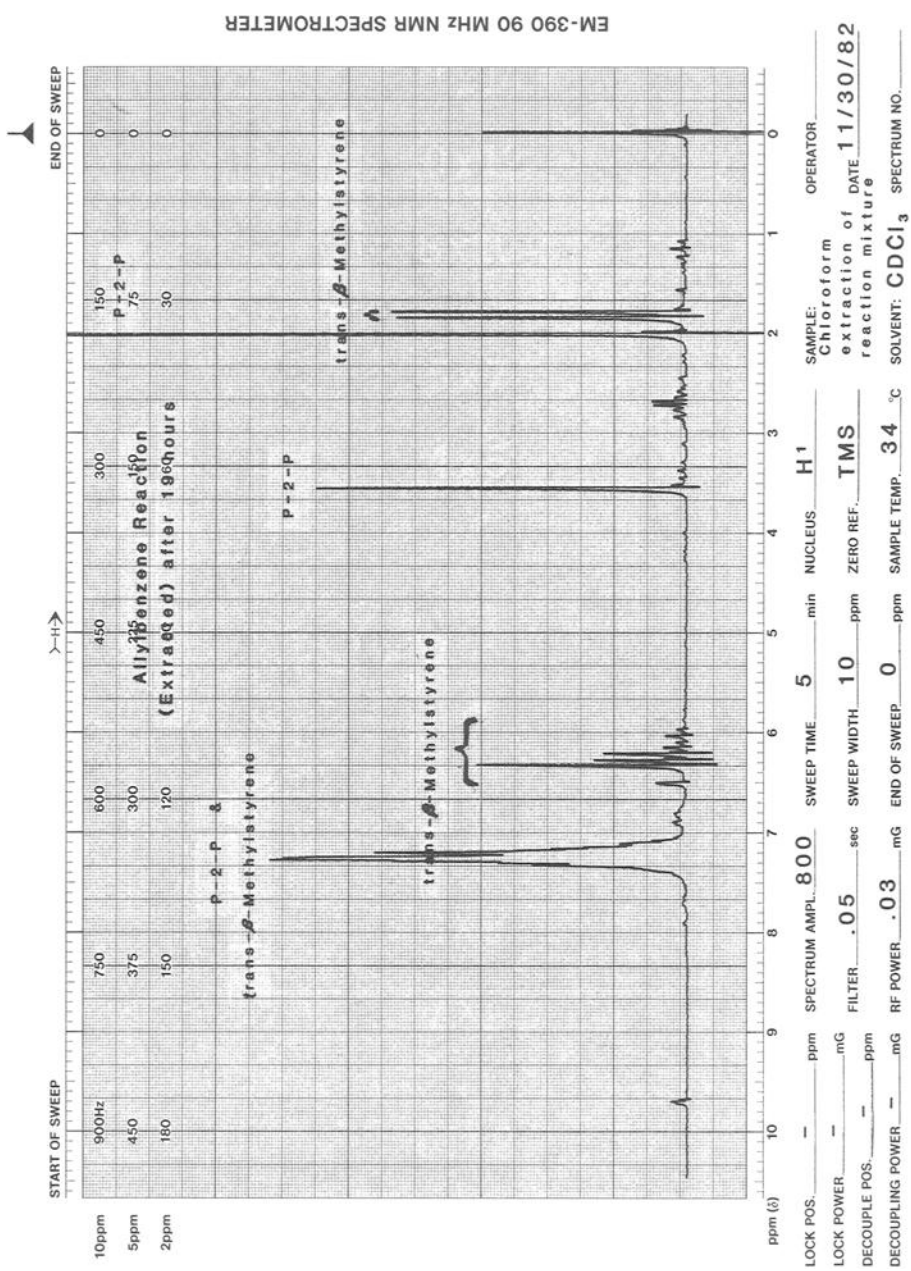


FIG. 19—*Nuclear magnetic resonance spectrum of allylbenzene reaction mixtures—literature procedure after 19 h (extracted).*

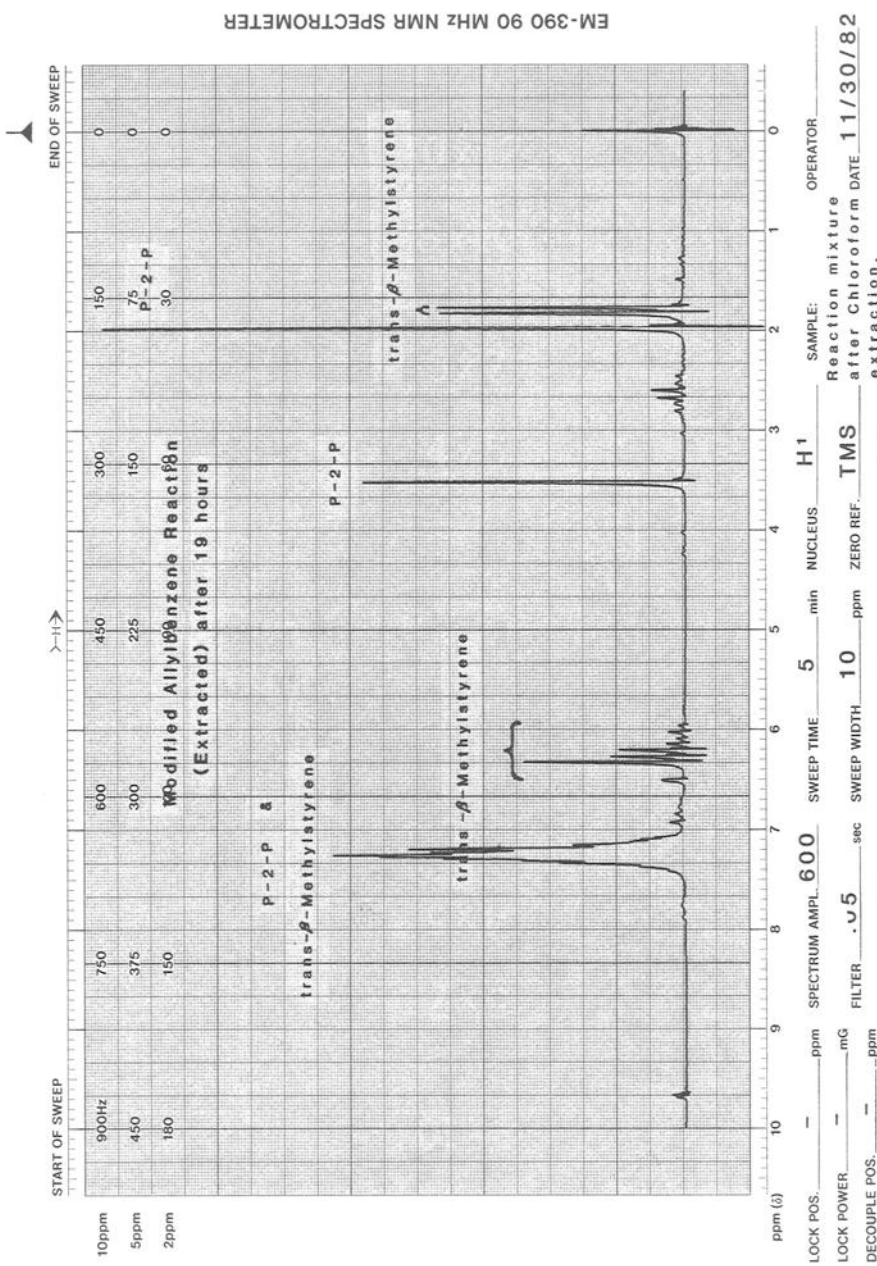
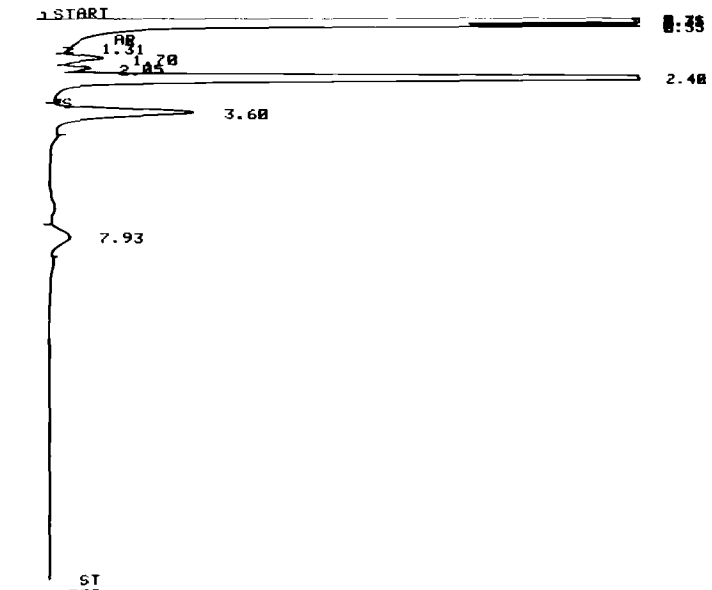


FIG. 20—*Nuclear magnetic resonance spectrum of allylbenzene reaction mixtures—modified procedure after 19 h (extracted).*



RT	AREA	AREA %	
1.70	223300	3.010	
2.05	138500	1.867	
2.40	5680000	76.554	-trans-β-Methylstyrene
3.60	1136000	15.311	-Phenyl-2-propanone
7.93	241800	3.259	

XF: 1.0000 E+ 0

FIG. 21—*Gas chromatogram of* trans-*beta-methylstyrene starting material.*

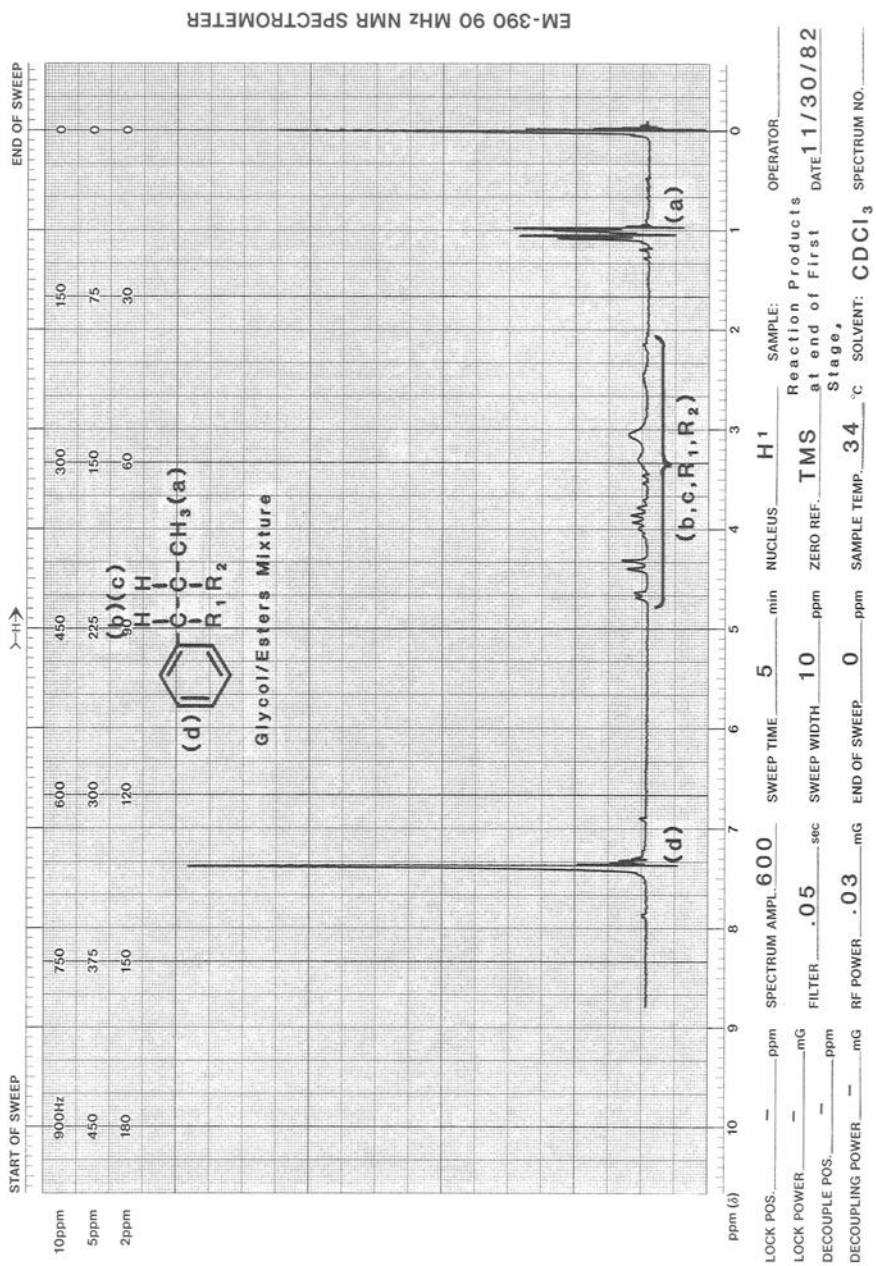
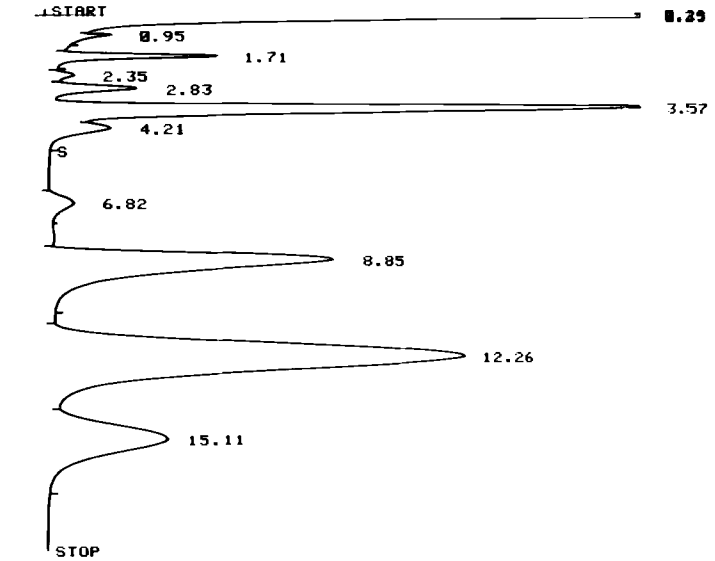


FIG. 22—*Nuclear magnetic resonance spectrum of the* trans*-beta-methylstyrene oxidation mixture.*



hp 5830A
AREA %

RT	AREA	AREA %	
1.71	737600	2.608	
2.35	96120	0.340	trans-β-Methylstyrene
2.83	533200	1.885	
3.57	5154000	18.220	1-Phenyl-2-Propanone
4.21	614500	2.172	
6.82	288100	1.018	1-Phenyl-1,2-Dihydroxypropane
8.85	5311000	18.775	1-Phenyl-1,2-Diformylpropane
12.26	11960000	42.280	1-Phenyl-1-Hydroxy-2-Formylpropane
15.11	3593000	12.702	1-Phenyl-1-Formyl-2-Hydroxypropane

XF: 1.0000 E+ 0

FIG. 23—*Gas chromatogram of the* trans-*beta-methylstyrene oxidation mixture.*

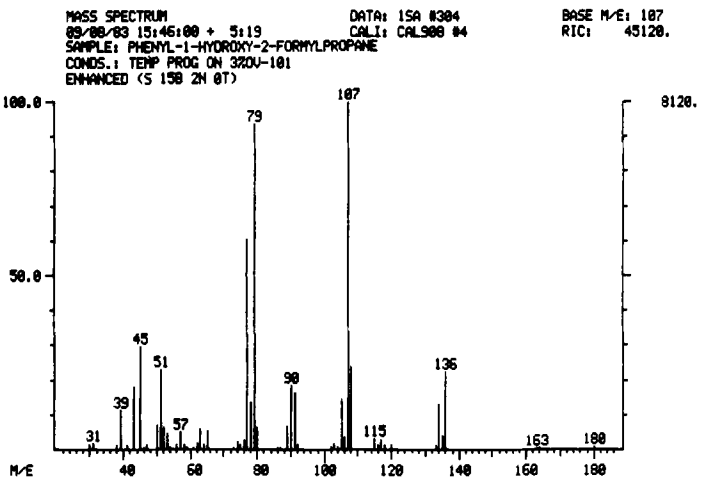


FIG. 24—*Mass spectrum of phenyl-1-hydroxy-2-formyl-propane.*

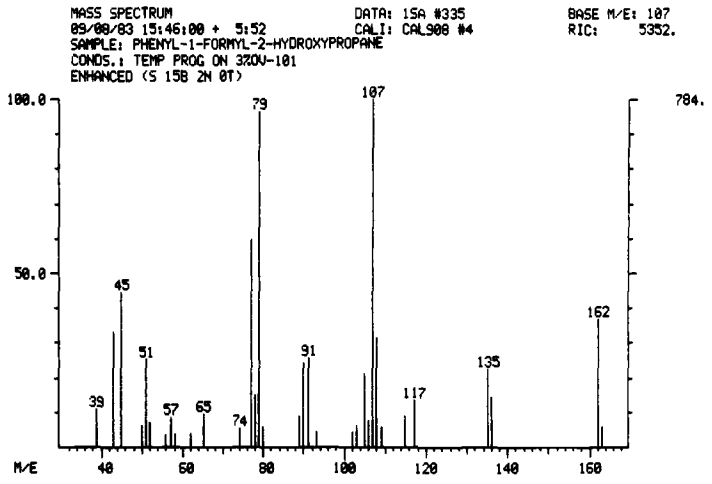


FIG. 25—*Mass spectrum of phenyl-1-formyl-2-hydroxy-propane.*

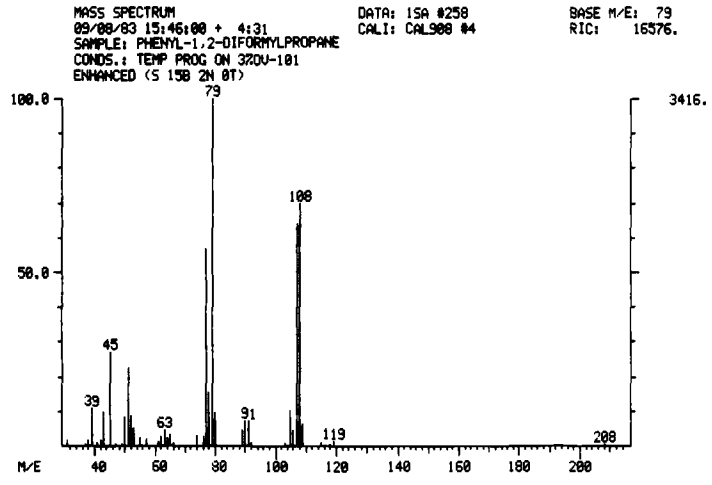


FIG. 26—*Mass spectrum of phenyl-1,2-diformyl propane.*

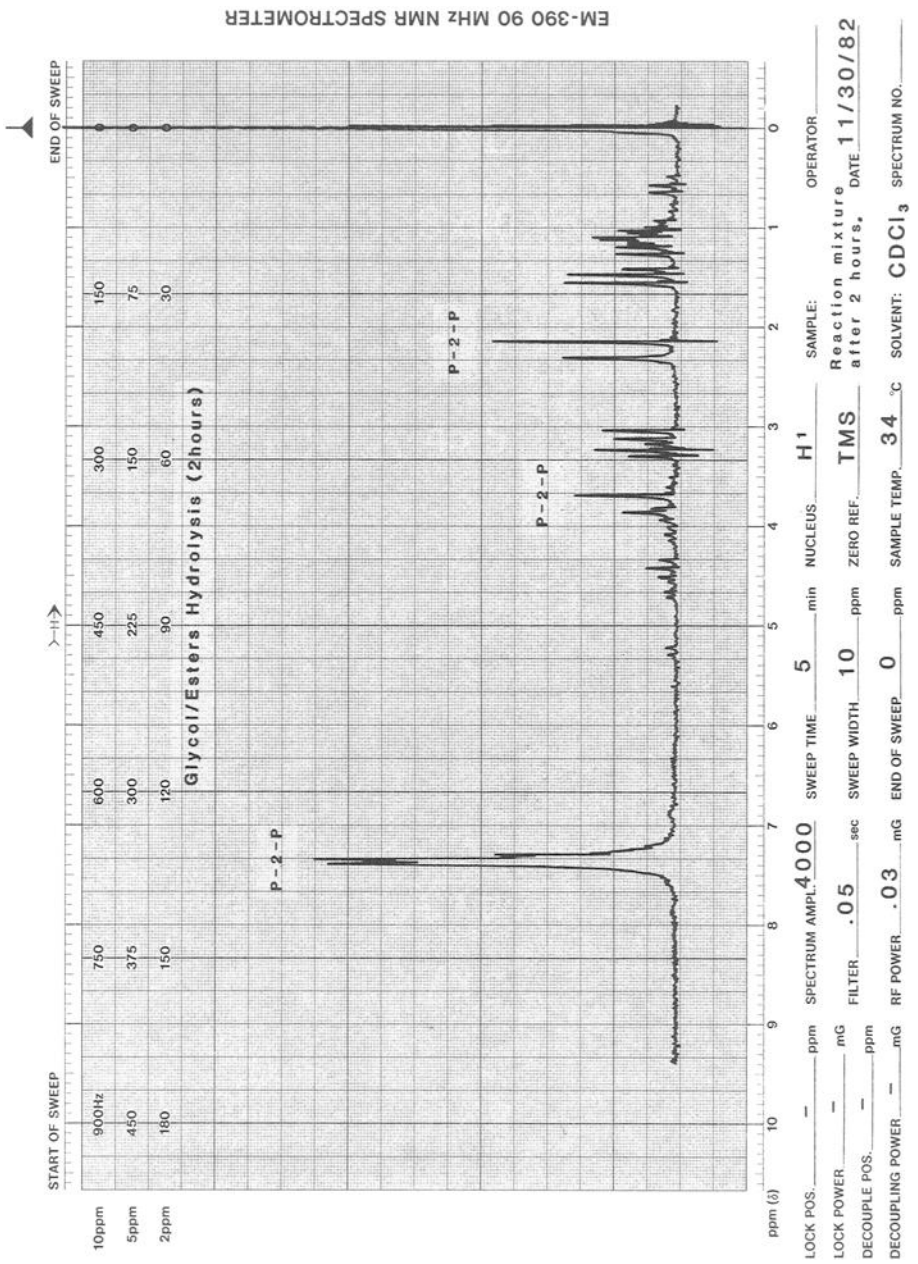


FIG. 27—*Nuclear magnetic resonance spectrum of* trans*-beta-methylstyrene hydrolysis after 2 h.*

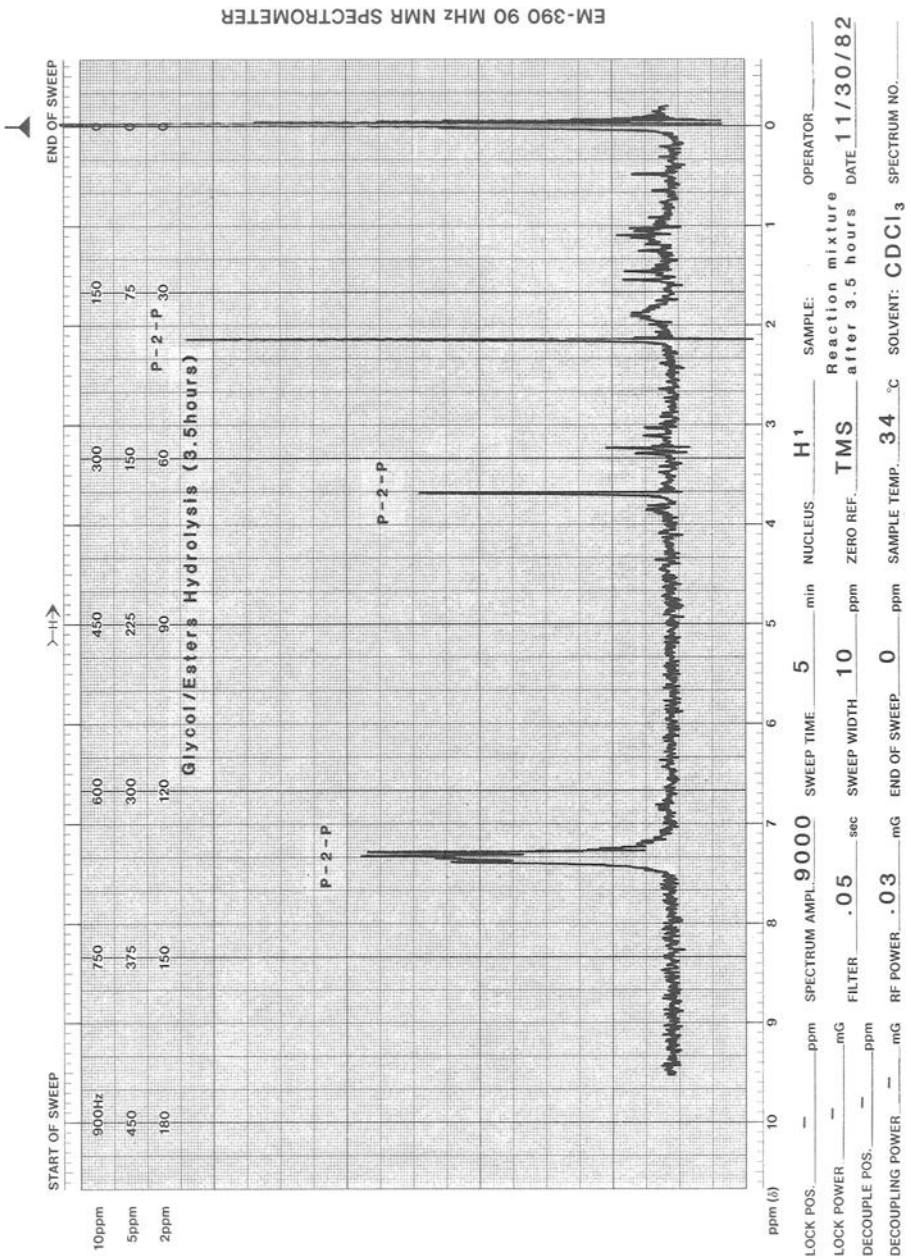


FIG. 28—*Nuclear magnetic resonance spectrum of* trans*-beta-methylstyrene hydrolysis after 3½ h.*

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