SYNTHESIS OF $^{14}$C LABELED 1,1-dichloro 2,2-bis(p-ethylphenyl)ethane (PERTHANE) AND RELATED DEGRADATION PRODUCTS

by

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STATEMENT BY AUTHOR

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BIOGRAPHICAL

Steven C Halladay was born in Provo, Utah on May 22, 1947. He attended grammar school in Provo, Utah and was graduated from Provo High School in 1964.

He obtained his undergraduate education at Southern Utah State College, Cedar City, Utah, where he received the Bachelor of Science degree in 1969. His undergraduate major was zoology; his minor was botany.

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He is married to the former Lara Lynn Barron of Cedar City, Utah.
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ABSTRACT

This reports the synthesis and verification of $^{14}$C Perthane® and three closely related compounds.

The first study was the synthesis and verification of $^{14}$C Perthane®. Synthesis was accomplished by condensing dichloracetaldehyde diethyl acetal with $^{14}$C ethylbenzene. Pilot reactions with a theoretical yield of 3.97 grams were run until a consistent 90 percent of the theoretical yield was obtained. The methods used during the pilot reactions were then applied to the synthesis of the $^{14}$C Perthane®. Verification of the $^{14}$C Perthane® utilized electron capture gas chromatography (ECGC), nuclear magnetic resonance spectrometry (NMR), mass spectrometry, infrared spectrometry (IR), and melting point determination. The specific activity of the compound was also calculated from liquid scintillation counting.

The second study was the synthesis and verification of 1-chloro 2,2-bis(p-ethylphenyl)ethylene. The synthesis involved the dehydrohalogenation of the purified p,p' isomer of Perthane®, by refluxing with alcoholic alkali. Verification was accomplished using ECGC, NMR, mass spectrometry, and IR.

The third study was the synthesis and verification of di(p-ethylphenyl) acetic acid. Only one of the several methods investigated gave a quantitative yield, reacting glyoxylic acid with ethylbenzene
using concentrated sulfuric acid as the catalyst. Verification was by ECGC, mass spectrometry, IR, and melting point determination.

The fourth study was the synthesis and verification of 4,4'-diethylbenzophenone. This synthesis involved the oxidation of 1-chloro 2,2-bis(p-ethylphenyl)ethylene using CrO₃. Verification was by ECGC, NMR, mass spectrometry, and IR.
INTRODUCTION

Perthane® or Q-137 are common names for the chlorinated organic insecticide 1,1-dichloro 2,2-bis(p-ethylphenyl)ethane. Perthane was introduced as an experimental insecticide by Rohm and Haas Company in 1950 (Spencer, 1968). Commercial use of Perthane on alfalfa and other forage crops has been effective against: six-spotted leaf-hopper (*Macrosteles fasciorms* (Stal)), cabbage looper (*Trichoplusia ni* (Hubner)), beet leaf hopper (*Circulifer tenellus* (Baker)), apple maggot (*Rhagoletis pomonella* (Walsh)), and red-banded leaf roller (*Argyrotaenia velutinana* (Walker)) (Negherbon, 1959). Promising results were reported in control of the cotton leaf perforator (*Bucculatrix thurberiella* Busck) (Moore, 1971), clover weevil (*Hypera punctata* (Fabricius)), *Lygus* spp., alfalfa caterpillar (*Colias eurytheme* Boisduval), orange tortrix of citrus (*Argyrotaenia citrana* (Fernold)), various leaf eating insects of cole crops, and household, livestock, fruit, and garden insects (Negherbon, 1959).

Perthane is related to 1,1,1-trichloro 2,2-bis(p-chlorophenyl)ethane (DDT) but may be more specifically considered an analogue of 1,1-dichloro 2,2-bis(p-chlorophenyl)ethane (DDD or TDE). Perthane's toxicity to warm blooded animals is relatively low as compared to other chlorinated hydrocarbon insecticides, yet it retains high toxicity for many insects (Negherbon, 1959). In a study made by
Gordon (1964) the acute oral LD$_{50}$ of Perthane to the white rat was established at 8170 mg/Kg as compared to 113 mg/Kg for DDT reported by Spencer (1968).

From studies made by Finnegan et al., (1955), Taliaferro and Leone (1957), and Bleiberg (1961), it was shown that Perthane, like DDD (Woodard, Davidow, and Lehman, 1948), can produce adrenal cortical atrophy in mammals. Finnegan et al., (1955), suggested that Perthane may cause some functional effects on the adrenal cortex of rats, predominately in males, that tend to depress growth without any adverse effect on survival.

Technical grade Perthane has the appearance of brownish, oily, crystalline mass made up of para, para' (p,p') and ortho, para' (o,p') isomers with a melting point between 60-61°C. Both isomers are found in the oil and in the crystalline mass. The o,p' isomer, due to its lower melting point, is found in greater abundance in the oil whereas the p,p' isomer is found mostly in the crystalline mass. The purified white crystals are essentially the p,p' isomer which melt between 56-57°C. The melting point of the purified o,p' isomer is 49-50°C (Nichols, 1960). The composition of the technical Perthane was calculated by Bleiberg (1961) from the weights of the products obtained after completing successive stages of separation. It was found to be: crystalline p,p' isomer 69%, o,p' isomer (oil) 8%, and unidentified material 23%. Perthane is very soluble in all common organic solvents while practically insoluble in water (Gordon, 1964).

Assumptions concerning the degradation of Perthane in this study are based on previous degradative studies made with DDT and
other commercially important DDT analogs. The DDT analogs referred to are: DDD, 1,1-bis(4-chlorophenyl) 2,2,2-trichloroethanol (Kelthane), and 2,2-bis(p-methoxyphenyl) 1,1,1-trichloroethane (Methoxychlor).

From mammals fed or exposed to DDT, the metabolites DDD, di (p-chlorophenyl) acetic acid (DDA), 1,1-dichloro 2,2-bis(p-chlorophenyl)ethylene (DDE), and 4,4'-dichlorobenzophenone (DCB) have been isolated and identified (Stohlman and Smith, 1945; White and Sweeney, 1945; Carter et al., 1949; Mattson et al., 1953; Cueto, Barnes, and Mattson, 1956; Hayes, Durham, and Cueto, 1956; Rothe et al., 1957). A pathway for the metabolism of DDT in rats has been proposed on the basis of studies with DDT and related compounds (Finley and Pillmore, 1963; Datta, Laug, and Klein, 1964; Klein et al., 1964; Peterson and Robison, 1964). These studies indicated that the degradation of DDT to DDA proceeded through the pathway using DDD as an intermediate product and not through DDE as postulated by White and Sweeney (1945).

DDD has also been identified by McKinley and Grice (1960) as a DDT metabolite in the body fat of rats. Other studies suggested that the major fecal products in rats consisted of DDA conjugated with cholic acid or amino acids (Jensen et al., 1957). After administration of p,p'-DDT in oil and p,p'-DDA in water to rats via a stomach tube, a conjugate of p,p'-DDA was isolated from feces and urine. This conjugate contained one molecule each of serine and aspartic acid together with eight molecules of water per molecule of p,p'-DDA. The presence of four other metabolites was also indicated, possibly identical with 1) p,p' dichlorobenzhydrol, 2) p,p'-dichlorodiphenylmethane, 3) DCB, 4) DDE (Pinto, Camien, and Dunn, 1965).
Still another pathway was indicated by studies with the Rhesus monkey (Durham, Ortega, and Hayes, 1963). When fed DDT, the monkeys did not store detectable DDE. However, when DDE was fed, the monkeys accumulated DDE. It was noted, particularly in view of the monkeys' apparent inability to convert DDT to DDE, that DDA was both a urinary and fecal excretory product. These findings suggest that the metabolic pathway between DDT and DDA does not proceed through DDE as an intermediate product. This was in agreement to the situation found in the human after ingesting DDT (Morgan and Roan 1971; Roan, Morgan and Paschal 1971).

The toxicity of Kelthane was studied by Smith et al., (1959) and McKinley and Grice (1960). These workers obtained evidence suggesting that DDE was a metabolite of Kelthane. This finding was later verified by the work of Brown, Hughes and Viriyakonndha (1969). They also presented evidence concerning the storage and distribution of Kelthane in the rat. The major metabolites found were DCB and DDE.

The metabolism of methoxychlor in the mouse was studied by Kapoor et al., (1970). The major metabolites found were 2-(p-methoxyphenyl) 2(p-hydroxyphenyl) 1,1,1-trichloroethane, 2,2-bis(p-hydroxyphenyl) 1,1,1-trichloroethane, 2,2-bis(p-methoxyphenyl)ethylene, 2,2-bis(p-hydroxyphenyl) 1,1-dichloroethylene, 4,4-dihydroxybenzo-phenone.

No information is available in the literature concerning the metabolic fate of Perthane in mammals, nor are the suspected Perthane metabolites available to undertake such a metabolic study. Therefore,
the objective of this study was to synthesis $^{14}$C Perthane, 1-chloro 2,2-bis(p-ethylphenyl)ethylene, di(p-ethylphenyl) acetic acid, and 4,4'-diethylbenzophenone. These compounds could then be used in later studies dealing with the metabolic fate of Perthane in mammals. The structures of these compounds are found in Figure 1.
Figure 1. Structures of $^{14}$C Perthane and potential Perthane metabolites. The * indicates the $^{14}$C label.
Synthesis of $^{14}$C Perthane

Modifications of a method suggested by Lyman (1969), for the laboratory preparation of Perthane were used. This involved reacting ethylbenzene with dichloroacetaldehyde diethyl acetal catalyzed by concentrated $\text{H}_2\text{SO}_4$ (Figure 2).

The $^{14}$C labeled ethylbenzene (ethyl-1-$^{14}$C) used in this reaction was obtained from the Mallinckrodt Nuclear Laboratory in St. Louis. The specific activity of the $^{14}$C ethylbenzene was 0.96 mCi/mM with a total volume of 0.128 ml (0.001 mole). The materials was received and stored in a flame-sealed ampoule at 0°C.

The ampoule was opened by snapping off the top at the pre-scratched constricted neck. The contents of the ampoule were then poured into a 50 ml erlenmeyer flask. Rinsing of the ampoule was accomplished by using a glass 1cc tuberculin syringe equipped with a 22 gauge, one inch hypodermic needle. The top and bottom of the ampoule were rinsed three times, each rinse consisting of 0.5 ml ethylbenzene, which was added to the flask. The rinses plus the $^{14}$C ethylbenzene totaled 3.128 ml (0.0255 mole). The addition of 2.1 ml (0.0127 mole) of dichloroacetaldehyde diethyl acetal was accomplished by using a 1cc tuberculin syringe equipped with a 22 gauge needle. This addition was used to rinse down the sides of the erlenmeyer flask.
Figure 2. Reaction involved in the laboratory preparation of $^{14}$C Perthane. The * indicates the $^{14}$C label.
The contents of the flask were mixed by swirling for several minutes. After mixing, 6.6 ml (0.1234 mole) of concentrated H$_2$SO$_4$ were added as the catalyst. The acid was added dropwise from a calibrated burette fitted with a teflon stopcock over a twenty minute period, to avoid an increase in the reaction temperature. The flask was continuously swirled during and for an additional fifteen minutes after the addition of the acid. The flask was then allowed to stand with occasional swirling every 3-5 minutes for thirty minutes. The total reaction time was one hour and five minutes.

From a calibrated burette, fitted with a teflon stopcock, 15 ml of distilled water was added dropwise to the flask while swirling to stop the reaction, and to maintain a constant temperature warm to the touch. With the addition of the water complete and the mixture cooled to room temperature, the contents of the flask were decanted into a 60 ml separatory funnel. The flask was then rinsed three times using 5 ml portions of redistilled pentane. The rinses were added to the separatory funnel. The contents of the separatory were extracted twice using a total of 50 ml of redistilled pentane. During each extraction the separatory was shaken vigorously for one minute then allowed to stand until a complete separation of the phases was observed. The aqueous phase was extracted a second time and discarded.

After each 25 ml extraction the pentane layer was washed three times with 30 ml portions of distilled water. The separatory was again shaken vigorously for one minute after each addition of distilled water and allowed to stand until separation of the two phases was
observed. The aqueous phase was then discarded. After discarding the third wash the pentane layer was filtered through anhydrous sodium sulfate to eliminate traces of water.

The two pentane extracts containing the $^{14}$C Perthane were combined in a 350 ml beaker. The pentane was then evaporated using a stream of dry air. After evaporating the pentane the beaker was placed in an ice bath and vibrated to crystallize the $^{14}$C Perthane.

$^{14}$C Perthane Analysis

Electron Capture Gas Chromatography

The composition of the $^{14}$C Perthane was obtained by electron capture gas chromatography (ECGC) using a Micro-Tek Model DSS-171 Type-DPT gas chromatograph with a tritium source electron capture detector and Sargent recorder, Model TR. Analyses were made using 2% SE 52 on 60-80 mesh, DMCS treated, acid washed firebrick in an 8 foot, 1/4 inch O.D. glass column. The nitrogen carrier gas was passed through a molecular sieve and maintained at a flow rate of 90 ml/minute. Temperatures of the inlet, column and detector were maintained at or near 210°C. A standard solution of 1.0Ng/λ was prepared and 6.0λ injected into the chromatograph. The area beneath each peak was calculated and compared to obtain percentages of the components which made up the synthesized $^{14}$C Perthane.

Purification of the $^{14}$C Perthane

Purification of the $^{14}$C Perthane was accomplished by dissolving 1.72 grams of the labeled material in the least amount of hot
absolute ethanol as possible. When the $^{14}$C Perthane was completely dissolved the beaker containing this solution was placed in the deep freeze. As the solution cooled the $p,p'$ isomer crystallized.

Two recrystallizations were required to obtain the purified $p,p'$ isomer which was then analyzed by ECGC to determine its purity.

**Specific Activities of the Technical and Purified $^{14}$C Perhanes**

The specific activities of the technical and purified $p,p'$ isomer of the $^{14}$C Perthane were obtained by liquid scintillation. Two standard solutions, one of the $^{14}$C Perthane and one of the purified $p,p'$ isomer, were prepared for analysis by dissolving 20 mg of material in 10 ml of toluene. From these standard solutions the samples to be analyzed were prepared in triplicate by mixing 1.0 ml of a 1:100 dilution of the standard solution with 9.0 ml of fluor. The fluor was prepared by mixing 0.06 grams of 1,4-bis[2-(5-phenyl-oxazolyl)]benzene (POPOP) and 5.0 grams of 2,5-diphenyloxazole (PPO) in one liter of toluene. The sample used for counting background activity was prepared by adding 1.0 ml of toluene to 9.0 of the fluor. A standard $^{14}$C sample from Nuclear Chicago, having 259,000 disintegrations per minute, was used to determine the counting efficiency of the scintillation system.

The $^{14}$C standard, background counting sample and the samples containing the $^{14}$C Perthane and $p,p'$ isomer were placed in the scintillation spectrometer. These were allowed to stand for ten minutes in the dark to equilibrate before counting. Each sample was counted for four minutes to obtain a 99% confidence level with 1.7 percent
error. These counts were then used in calculating specific activities.

Nuclear Magnetic Resonance Spectrometry

The p,p' isomer of the $^{14}$C Perthane was prepared for nuclear magnetic resonance spectrometry (NMR) by dissolving 0.1 grams of labeled material in 0.5 ml of carbon tetrachloride. Using a disposable glass pipet the solution was added to the glass NMR tube. Tetramethylsilane (TMS) was then added to the solution in the NMR tube to serve as the internal reference standard. The tube containing the solution was then placed in a Varian HA-100 spectrometer at 100 MHz and the spectrum determined.

Mass Spectrometry

The preparation for mass spectrometry consisted of filling the glass dipper with the purified p,p' isomer. This was accomplished by applying pressure on the p,p' isomer crystals with the end of the glass dipper containing the small cup. The p,p' isomer crystals being between the glass dipper and the table top were forced into the small cup. The glass dipper was then placed inside a Hitachi-Perkin-Elmer RMU-6E Double Focusing Mass Spectrometer and the spectrum determined.

Infrared Spectrometry

Infrared spectral data were obtained on a Doublebeam Perkin-Elmer Model 337 Grating Infrared Spectrophotometer using a NaCl Sealed Cell 0.20 mm space for liquid samples.
The technical $^{14}C$ Perthane and p,p' isomer were prepared for IR spectrometry by dissolving 0.1 grams of the labeled material in 0.25 ml of carbon tetrachloride. The sampling cell was then filled with this solution by using a 1cc glass syringe. The reference cell was filled with carbon tetrachloride alone. Both cells were placed in the infrared spectrometer and the spectrum of the purified p,p' isomer of the $^{14}C$ Perthane was determined.

**Melting Point Determination**

The melting point determinations were made using a Fisher-Johns Melting Point Apparatus. The $^{14}C$ p,p' isomer was prepared for melting point analysis by pulverizing to a fine powder using a small mortar and pestle. Approximately 5 mg of the powder was placed between two clean glass covers. The two glass covers were pressed gently but firmly together and placed in the Fisher-Johns melting point apparatus and the melting point determined.

**Synthesis of 1-chloro 2,2-bis(p-ethylphenyl)ethylene**

In a 500 ml erlenmeyer flask fitted with a refluxing condenser, 25 grams (0.0813 mole) of purified, unlabeled p,p' isomer of Perthane was placed. To this was added 150 ml of a 5% KOH in 95% ethanol. Once the crystals were dissolved the solution was gently refluxed for three hours. The addition of a few boiling stones prevented any loss due to bumping.

At the end of three hours 100 ml of cold distilled water was added to the mixture. This cooled solution was then decanted into a
500 ml separatory funnel. The 500 ml flask was rinsed three times using 10 ml portions of redistilled hexane, with the rinses added to the separatory. The contents of the separatory were extracted twice using 150 ml of redistilled hexane each time. During each extraction the contents of the separatory were shaken vigorously for one minute then allowed to stand until a complete separation of the phases were observed.

After each extraction the hexane layer was washed three times with 100 ml portions of distilled water. The separatory was shaken vigorously for one minute with each wash and allowed to stand until separation was observed. After discarding the third wash the hexane layer was filtered through anhydrous sodium sulfate to eliminate traces of water.

The two hexane extractions were combined and placed in a 600 ml beaker. The solvent was evaporated under a stream of dry air with low heat, leaving a clear, colorless oil, 1-chloro 2,2-bis(p-ethylphenyl)ethylene. The reaction involved can be seen in Figure 3.

**Analysis of 1-chloro 2,2-bis(p-ethylphenyl)ethylene**

**ECGC, NMR, Infrared, and Mass Spectrometry**

The 1-chloro 2,2-bis(p-ethylphenyl)ethylene compound was prepared for ECGC, NMR and infrared spectrometry. The procedures used for these preparations were the same as previously described for the ECGC, NMR and infrared spectrometry of the purified $^{14}$C Perthane with one exception. ECGC of this compound was accomplished by injecting 1± of the 1Ng/λ standard into the chromatograph instead of 6±.
Figure 3. Reaction involved in the synthesis of 1-chloro 2,2-bis(p-ethylphenyl)ethylene.
The preparation of this compound for mass spectrometry was accomplished by placing a small amount of the oil inside the L and S sample bottle, which was in turn placed inside the mass spectrometer and the spectrum determined.

**Synthesis of Di(p-ethylphenyl) Acetic Acid**

Three grams (0.0325 mole) of purified glyoxylic acid monohydrate was placed in a 200 ml round bottom flask fitted with a magnetic stirrer bar and a thermometer. To the flask 75 ml (0.6124 mole) of ethylbenzene was added serving as one of the reactants and the reaction medium. The mixture was cooled in an ice bath to 10°C. While vigorously stirring this cooled solution, 15 ml (0.2804 mole) of concentrated $\text{H}_2\text{SO}_4$ was added dropwise from a calibrated burette fitted with a teflon stopcock. The acid was added at a rate as to maintain the temperature of the solution below 20°C. After addition of the acid, 1.5 ml (0.280 mole) of fuming sulfuric acid was added dropwise from a calibrated burette fitted with a teflon stopcock, again maintaining the temperature below 20°C. When this was completed the solution was allowed to react for an additional one hour making the total reaction time two hours. The mixture was poured into a 600 ml beaker containing 100 grams of crushed ice and then diluted with five volumes of distilled water. This mixture was then decanted into a 500 ml separatory funnel to be extracted. The flask and beaker were rinsed three times each with 10 ml portions of redistilled diethyl ether, with rinses added to the separatory. The contents of the separatory were extracted twice with 200 ml portions of redistilled
diethyl ether. The separatory was shaken vigorously for one minute and allowed to stand until a complete separation of the two phases was observed. The aqueous phase was reextracted and discarded. The diethyl ether extracts were washed three times with a total of 225 ml of distilled water. The separatory was again shaken for one minute after each addition of the distilled water and allowed to stand until the two phases separated. After the third wash the diethyl ether extracts were each extracted twice with 100 ml volumes of a 5% aqueous potassium hydroxide solution. The separatory was shaken one minute after each addition of the potassium hydroxide and allowed to stand until the phases separated. The potassium hydroxide extracts were combined in a 350 ml beaker. The beaker was placed in an ice bath cooling the extracts to 10°C. While stirring, the potassium hydroxide extracts were acidified slowly to a pH of 4.0-5.0 using concentrated hydrochloric acid, which precipitated the di(p-ethylphenyl) acetic acid. The reaction involved in this synthesis can be seen in Figure 4.

Analysis of Di(p-ethylphenyl) Acetic Acid

ECGC

Di(p-ethylphenyl) acetic acid presented a special problem when analyzing it by ECGC, since it is relatively insensitive to this type of analysis. To increase the sensitivity of the compound to ECGC a methylester of the compound was prepared.

In a 12 ml centrifuge tube fitted with a glass stopper was placed 10 mg of the di(p-ethylphenyl) acetic acid. To the centrifuge
Figure 4. Reaction involved in the synthesis of di(p-ethylphenyl) acetic acid.
tube 2.0 ml of redistilled benzene was then added and the tube shaken until the di(p-ethylphenyl) acetic acid was dissolved. To this solution 4.0 ml of diazomethane was added and the glass stopper secured firmly. The contents of the tube were mixed thoroughly by shaking and allowed to stand for two hours while methylation took place.

Caution must be taken when working with diazomethane. This compound though an excellent methylating agent is quite volatile and could be fatal if the vapors are inhaled. Steps involving the use of this compound should only be followed while working under a well ventilated hood in the laboratory.

A good indication that the methylation reaction was taking place was the production of nitrogen gas in the solution. After nitrogen evolution ceased the tube was opened and the contents placed under a stream of dry air to remove excess diazomethane not involved in the reaction. The loss of the yellow color leaving a clear solution indicated the complete removal of excess diazomethane.

A 2.0Ng/λ standard solution containing the methylester of di(p-ethylphenyl) acetic acid was prepared and 6.0λ injected into the chromatograph. Another standard containing 20.0Ng/λ of the unmethylated di(p-ethylphenyl) acetic acid was prepared and 6.0λ was injected into the chromatograph. The retention times of this and the methylated standard were compared.

Mass Spectrometry, Infrared Spectrometry, and Melting Point Determination

The di(p-ethylphenyl) acetic acid was prepared for mass spectrometry, IR, and melting point determination. The procedures used
for these preparations were those previously described for the mass spectrometry, IR, and melting point determination of the purified $^{14}$C Perthane. There was only one change in the preparation procedure used for IR spectrometry. Because of the solubility factor involved chloroform was used as the solvent instead of carbon tetrachloride.

**Synthesis of 4,4'-Diethylbenzophenone**

In a 500 ml erlenmeyer flask, fitted with a magnetic stirrer bar and a reflux condenser, was added 170 ml of glacial acetic acid. To the erlenmeyer flask 10 grams (0.0369 mole) of the 1-chloro 2,2-bis(p-ethylphenyl)ethylene prepared earlier was dissolved in the acid. This mixture was then heated to reflux. To this refluxing solution 9.0 grams (0.0899 mole) of chromium trioxide was added in very small amounts over a two hour period by dropping the chromium trioxide through the reflux condenser. Care was taken while adding this material because of the violent reaction which takes place upon contact with the solution. After completion of the addition the solution was refluxed for an additional 1.5 hours. At the end of the reaction time the solution was allowed to cool to room temperature and decanted into a 500 ml separatory funnel for extraction. The flask was rinsed three times with 10 ml portions of redistilled hexane, which was added to the separatory funnel. The contents of the separatory were also extracted twice with 100 ml portions of hexane. The separatory funnel was shaken vigorously for one minute and allowed to stand until a separation of the phases was observed. The aqueous phase was reextracted and discarded.
After each extraction the hexane was washed three times with 75 ml portions of distilled water. The separatory was again shaken for one minute and allowed to stand until the two phases separate. After discarding the third washing the hexane layer was filtered through anhydrous sodium sulfate.

The hexane extracts, containing the 4,4'-diethylbenzophenone, were combined in a 600 ml beaker. The hexane was evaporated under a stream of dry air with low heat. Evaporation of the hexane left a yellow oil, the 4,4'-diethylbenzophenone. The reaction involved in this synthesis can be seen in Figure 5.

Analysis of 4,4'-Diethylbenzophenone

ECGC, NMR, and Infrared Spectrometry

The preparation and procedures used for these analyses were those previously described for the ECGC, NMR, and IR spectrometry of the purified 14C Perthane.

Mass Spectrometry

The 4,4'-diethylbenzophenone compound was prepared for mass spectrometry using the same procedure as for the mass spectrometry of 1-chloro 2,2-bis(p-ethylphenyl)ethylene.
Figure 5. Reaction involved in the synthesis of 4,4'-diethylbenzophenone.
RESULTS AND DISCUSSION

Synthesis of $^{14}$C Perthane

The synthesis of the $^{14}$C Perthane by condensing dichloro-acetaldehyde diethyl acetal with ethylbenzene gave a quantitative yield. The theoretical yield was 3.90 grams while the actual yield was 3.46 grams, or 88.71% of the theoretical.

The method of synthesis suggested by Lyman (1969) was a scaled-down version of that used for the preparation of Perthane on a commercial basis. Lyman suggested the method for the laboratory preparation of $^{14}$C Perthane with a theoretical yield of 307 grams. With this mass yield and only 0.128 ml of $^{14}$C ethylbenzene to add to the reaction the specific activity of the $^{14}$C Perthane would be too low to be useful in metabolic studies. Each stop of the suggested method was then modified to give the highest possible yield for small scale preparation of Perthane. As the theoretical yield of the pilot reactions were reduced from 307 grams to 50 grams and eventually to 3.97 grams, the need to cool the reaction mixture in an ice bath prior to and during the addition of the concentrated H$_2$SO$_4$ was unnecessary. To avoid loss of reactants and degradation of the already formed Perthane it was important to add the acid at a rate slow enough to prevent excessive heat build up.

The addition of water to stop the reaction presented another problem with temperature. The exothermic reaction of adding water
to concentrated sulfuric acid was controlled by placing the flask in a water bath during the addition of water.

It was found convenient to eliminate several steps suggested by Lyman for the cleanup and extraction of the Perthane. These methods involved unnecessary usage of glassware and excessive manipulation of the reaction mixture which served as a source of contamination and material loss. These suggested methods were replaced with simple, and less time consuming extraction procedures.

**Analysis of 14C Perthane**

The 14C Perthane was analyzed by ECGC to determine its composition. This analysis indicated the 14C Perthane contained 73.75% p,p'-isomer, 12.39% o,p'-isomer and 13.86% other impurities. For comparison technical grade Perthane supplied by the Rohm and Haas Chemical Company was also analyzed. It contained 69% p,p'-isomer, 8% o,p'-isomer and 23% other impurities. The retention times of the p,p'-isomer and the o,p'-isomer of the 14C Perthane were found to be 70mm and 84mm respectively in reference to the solvent peak (Figure 6).

The purification of the 14C Perthane was accomplished using two recrystallizations from hot ethanol. A total weight of 0.706 grams of the white crystalline precipitate representing the p,p'-isomer of the 14C Perthane was collected.

Analysis by ECGC to determine the purity showed that this crystalline material contained 94.87% p,p'-isomer, 3.34% o,p'-isomer and 1.79% other molecules.
Figure 6. Gas chromatogram showing the o,p' isomer and p,p' isomer of the $^{14}$C Perthane. The retention times of the o,p' and p,p' isomers are 70mm and 84mm respectively in reference to the solvent peak.
This purification was a standard method used by many authors. Haller et al., (1945) studying the chemical composition of technical DDT and Cristol and Haller (1948) studying technical DDD used this separation and purification. Bleiberg (1961) and Gordon (1964) also used it to purify technical grade Perthane.

By using the described method of analysis the specific activity of the $^{14}$C Perthane was calculated to be 9.3$\mu$Ci/mM, while the purified p,p' isomer was 9.57$\mu$Ci/mM.

Based on the assumption that there was 100% incorporation of the $^{14}$C ethylbenzene in the synthesis of the $^{14}$C Perthane the theoretical activity of the $^{14}$C Perthane was calculated to be 0.96 mCi/3.971 grams of material. The actual activity of the $^{14}$C Perthane was 0.904 mCi/3.461 grams of material. The percent yield for the reaction was thus calculated to be 94.2% of the theoretical.

The NMR spectrum of the purified p,p' isomer of $^{14}$C Perthane (Figure 7) consisted of five groups of signals: a downfield multiplet ($\tau$ 2.83, 2.89) integrating to eight protons, a doublet ($\tau$ 3.72) integrating to one proton, a doublet ($\tau$ 5.55) integrating to one proton, an upfield quartet ($\tau$ 7.4) integrating to four protons, and a triplet ($\tau$ 8.8) integrating to six protons. The chemical shift and coupling constant assignments for the purified p,p' isomer of $^{14}$C Perthane are given in Figure 8.

Mass spectrometry of $^{14}$C Perthane presented an unusual situation. There was the possibility that the $^{14}$C Perthane molecule would not contain a $^{14}$C label and the possibility it was labeled with one
Figure 7. NMR spectrum for purified p,p' isomer of $^{14}$C Perthane.
Figure 8. NMR parameters for purified p,p' isomer of $^{14}$C Perthane.

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<tr>
<td>He 2.83, 2.89</td>
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or even two $^{14}$C atoms. Taking this into account it was decided to report the major fragments for the unlabeled Perthane. The mass spectrum indicated the parent peak to be at m/e 307. Fragmentation of this molecule gave major peaks at m/e 15, 29, 83, 105, and 202. The mass spectrum of the $^{14}$C Perthane and major identified fragments can be seen in Figure 9.

The IR spectrums of $^{14}$C Perthane and the purified $^{14}$C Perthane were compared to reference spectrums reported by Bleiberg (1961). These comparisons showed the same absorption characteristics as the reference spectrums. The characteristic absorption at 690-750, 1090-1250, 1400-1550 and 2800-3100 cm$^{-1}$ gave evidence that the compound synthesized was $^{14}$C Perthane. The IR spectrums for $^{14}$C Perthane and the purified $^{14}$C Perthane can be seen in Figure 10.

The melting point of the purified p,p' isomer of $^{14}$C Perthane was found to be 57-58°C. The melting point of authentic purified p,p' isomer of Perthane supplied by the Rohm and Haas Company was 56-57°C. An examination was made of the melting point behavior of a mechanical mixture of purified $^{14}$C Perthane and purified Perthane supplied by the Rohm and Haas Company. Both compounds melted at 56-57°C. This characteristic testing for the identity of a solid from a reference solid gave very good evidence that the purified $^{14}$C Perthane was indeed purified $^{14}$C Perthane.

_Synthesis of 1-chloro 2,2-bis(p-ethylphenyl)ethylene_

The dehydrohalogenation of the purified p,p' isomer of Perthane to form 1-chloro 2,2-bis(p-ethylphenyl)ethylene was readily
Figure 9. Mass spectrum of $^{14}C$ Perthane and major identified fragments. The * indicates the $^{14}C$ label.
Figure 10. Infrared spectra for $^{14}$C Perhanes.

a) Technical $^{14}$C Perthane

b) Purified $^{14}$C Perthane
brought about by refluxing with alcoholic alkali. The theoretical yield was calculated to be 21.95 grams, while 21.3 grams was actually obtained. The yield was calculated to be 97% of the theoretical.

**Analysis of 1-chloro 2,2-bis(p-ethylphenyl)ethylene**

The EGC analysis of 1-chloro 2,2-bis(p-ethylphenyl)ethylene indicated the compound to be 96% pure. The retention time for this compound was found to be 54mm in reference to the solvent peak (Figure 11).

The NMR spectrum of 1-chloro 2,2-bis(p-ethylphenyl)ethylene (Figure 12) consisted of four groups of signals: two downfield singlets (τ 2.815 and 2.935) integrating to eight protons, a singlet (τ 3.54) integrating to one proton, an upfield quartet (τ 7.36) integrating to four protons, and a triplet (τ 8.74) integrating to six protons. The singlet upfield (τ 7.975) was later found to be attributed to contamination of the solvent used. This singlet was in no way connected to the compound. The chemical shift and coupling constant assignment for the 1-chloro 2,2-bis(p-ethylphenyl)ethylene compound are given in Figure 13.

The mass spectrometry of 1-chloro 2,2-bis(p-ethylphenyl)ethylene indicated the parent peak to be at m/e 270. Fragmentation of this molecule gave major peaks at m/e 29, 105, and 165. The mass spectrum of 1-chloro 2,2-bis(p-ethylphenyl)ethylene and major identified fragments can be seen in Figure 14.

The IR spectrum of this compound indicated the same characteristic absorption peaks as reported by the Sadtler Standard Spectra
Figure 11. Gas chromatogram showing the 1-chloro 2,2-bis(p-ethyl-phenyl)ethylene peak with a retention time of 54mm in reference to the solvent peak.
Figure 12. NMR spectrum for 1-chloro 2,2-bis(p-ethylphenyl) ethylene.
Figure 13. NMR parameters for 1-chloro 2,2-bis(p-ethylphenyl)ethylene.

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<td>Hc 3.54</td>
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<tr>
<td>Hd 2.815, 2.935</td>
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Figure 14. Mass spectrum of 1-chloro 2,2-bis(p-ethylphenyl)ethylene and major identified fragments.
(1962). This analysis showed the presence of aromatic hydrogens absorbing to the left of \(3000 \text{ cm}^{-1}\) and aliphatic hydrogens absorbing to the right of \(3000 \text{ cm}^{-1}\). The most characteristic absorption at \(1580-1625 \text{ cm}^{-1}\) gives reference to the presence of a double bond between two carbon atoms. The absorption peak at \(650-760 \text{ cm}^{-1}\) was weak but could indicate the presence of one chlorine attached to an aliphatic carbon atom. By comparing areas of characteristic absorption to the absorption areas of the Sadtler reference spectrum the assumption could be made that the desired 1-chloro 2,2-bis(p-ethylphenyl)ethylene was synthesized. The infrared spectrum of this compound is presented in Figure 15.

**Synthesis of Di(p-ethylphenyl) Acetic Acid**

Modification of a method used by White and Sweeney (1945) for the synthesis of di(p-chlorophenyl) acetic acid gave the desired di(p-ethylphenyl) acetic acid compound. The theoretical yield of this reaction was calculated to be 8.71 grams, while the actual yield was 6.99 grams, or 80.25% of the theoretical.

Decomposition of the glyoxylic acid takes place at temperatures over 35°C, thus care must be taken to avoid high temperatures of the reaction. Other modifications of this method involved the lengthening of the reaction time and cooling the basic extracts in an ice bath prior to acidification. It was observed that if the basic extracts were not cooled prior to and during acidification a gas was given off. It was speculated that some decarboxylation was taking place during the acidification. Yields were also much lower for the reactions with suspected decarboxylation.
Figure 15. Infrared spectrum for 1-chloro 2,2-bis(p-ethylphenyl) ethylene.
Many methods were explored in an attempt to synthesize the di(p-ethylphenyl) acetic acid compound. A method used by Grummitt, Buck, and Stearns (1945) for the synthesis of di(p-chlorophenyl) acetic acid was investigated. This was a type of saponification of DDE. It involved mixing the DDE with potassium hydroxide and 95% ethanol and heating in a sealed Carius tube at 150-160°C for 24 hours. This method was then applied to the synthesis of di(p-ethylphenyl) acetic acid using 1-chloro 2,2-bis(p-ethylphenyl)ethylene as the material being saponified. No combination or modification of this method gave the desired product.

Another method of Grummitt, Buck and Egan (1945) for the synthesis of di(p-chlorophenyl) acetic acid was tried. This involved refluxing a mixture of diethylene glycol, potassium hydroxide, and DDT at a temperature of 134-137°C for 6 hours. This method was then used substituting Perthane for the DDT. Analysis of the material from this reaction showed 1-chloro 2,2-bis(p-ethylphenyl)ethylene to be the major material formed during the reaction with no di(p-ethylphenyl) acetic acid being formed.

A Friedel-Craft reaction was then investigated, involving the reaction of acetyl chloride with diphenyl acetic acid and using AlCl₃ as the catalyst. Separation of the synthesized material from the reaction mixture was difficult. Preliminary analysis of the separated material suggested that a complex was formed during the reaction. It was speculated that this complex could involve the formation of a long chain of aluminum-oxygen molecules forming a complex with the acid group of the diphenyl acetic acid. Another possibility was the
formation of an eight membered ring if the acetyl chloride attached to the ring in the ortho position. The aluminum from the catalyst could form a complex between the ketone group on the added ethyl groups and the acid group of the diphenyl acetic acid. The complex formation made this reaction impractical for the synthesis of di(p-ethylphenyl) acetic acid.

A reaction reported by Brault and Kerfanto (1964) for the preparation of diphenyl acetic acid was investigated. This reacted dichloroacetic acid with morpholine using extreme caution, due to the exothermic reaction. Ethylbenzene was then added to the reaction flask and mixed with newly synthesized material. To this mixture concentrated sulfuric acid was added to serve as the catalyst in the formation of di(p-ethylphenyl) acetic acid. Some di(p-ethylphenyl) acetic acid was produced but the method could not be modified enough to give quantitative yields. It was observed throughout the reaction that a gas was liberated. This could represent gas resulting from decarboxylation of the forming di(p-ethylphenyl) acetic acid. This decarboxylation could account for the poor yields obtained.

**Analysis of Di(p-ethylphenyl) Acetic Acid**

ECGC of the normal and methylated di(p-ethylphenyl) acetic acid indicated that it was an acid. The retention times for the o,p' isomer and p,p' isomer of the normal di(p-ethylphenyl) acetic acid were found to be 40mm and 54mm respectively in reference to the solvent peak. The retention times for the o,p' isomer and p,p' isomer of the methylated di(p-ethylphenyl) acetic acid were found to be
49.5mm and 59.5mm respectively in reference to the solvent peak. The relative insensitivity of the normal compound compared to the increased sensitivity due to methylation and their suspected retention times can be seen in Figure 16.

Mass spectrometry of $\text{di}(p$-ethylphenyl$)$ acetic acid indicated the parent peak to be at $m/e$ 268. Fragmentation of this molecule gave major peaks at $m/e$ 15, 29, 45, and 223. The mass spectrum of $\text{di}(p$-ethylphenyl$)$ acetic acid and major identified fragments is shown in Figure 17.

IR spectrum of $\text{di}(p$-ethylphenyl$)$ acetic acid showed very characteristic absorption peaks. The most characteristic peaks were at 1725 cm$^{-1}$, indicating the presence of carboxylic acid group, and between 2500-3500 cm$^{-1}$ indicating characteristic hydrogen bonding found for this type of compound. Comparing this spectrum to other carboxylic acid spectra it can be assumed the $\text{di}(p$-ethylphenyl$)$ acetic acid was synthesized. The IR spectrum of $\text{di}(p$-ethylphenyl$)$ acetic acid is shown in Figure 18.

The $\text{di}(p$-ethylphenyl$)$ acetic acid did not appear to have a sharp melting point. The melting point range was from 110-115°C.

**Synthesis of 4,4'-Diethylbenzophenone**

The oxidation of 1-chloro 2,2-bis(p-ethylphenyl)ethylene was conducted by the procedure of Cristol and Haller (1948). The theoretical yield was 8.78 grams, with 6.58 grams of the 4,4-diethylbenzophenone actually obtained, or 74.94% of the theoretical.
Figure 16. A comparison of retention times for normal and methylated di(p-ethylphenyl) acetic acid by ECGC.

a) The retention times for normal o,p' and p,p' isomers are 40mm and 54mm in reference to the solvent peak.

b) The retention times for methylated o,p' and p,p' isomers are 49.5mm and 59.5mm in reference to the solvent peak.
Figure 17. Mass spectrum of di(p-ethylphenyl) acetic acid and major identified fragments.
Figure 18. Infrared spectrum for di(p-ethylphenyl) acetic acid.
Analysis of 4,4'-Diethylbenzophenone

ECGC analysis of the synthesized 4,4'-diethylbenzophenone compound indicated that the isolated oil from the reaction contained two major compounds. One being the 4,4'-diethylbenzophenone and an unidentified compound. The retention time for the suspected peak of 4,4'-diethylbenzophenone was found to be 72 mm in reference to the solvent peak. The gas chromatogram showing the suspected peak and retention time can be seen in Figure 19.

The NMR spectrum of the 4,4'-diethylbenzophenone (Figure 20) consisted of four groups of signals: A downfield doubled (τ 2.34) integrating to four protons, a doublet (τ 2.78) integrating to four protons, an upfield quartet (τ 7.25) integrating to four protons, and a triplet (τ 8.74) integrating to six protons. The singlet upfield (τ 7.98) was investigated and found to be attributed to contamination of the solvent used. The singlet was in no way connected to the compound being analyzed. The chemical shift and coupling constant assignments for the 4,4'-diethylbenzophenone compound are given in Figure 21.

The mass spectrum of 4,4'-diethylbenzophenone indicated the parent peak to be at m/e 238. Fragmentation of this molecule gave major peaks at m/e 15, 28, 29, 105, and 133. The mass spectrum of 4,4'-diethylbenzophenone and major identified fragments is illustrated in Figure 22.

The infrared spectrum for 4,4'-diethylbenzophenone showed very characteristic absorption peaks. The most characteristic peaks were found at 1550-1750 cm⁻¹, indicating the presence of a ketone group,
Figure 19. Gas chromatogram showing the suspected peak of 4,4'-diethylbenzophenone. The retention time was found to be 72mm in reference to the solvent peak.
Figure 20. NMR spectrum for 4,4'-diethylbenzophenone
Figure 21. NMR parameters for 4,4'-diethylbenzophenone.

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<th>Coupling Constants (Hz)</th>
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Figure 22. Mass spectrum of 4,4'-diethylbenzophenone and major identified fragments.
and 2800-3100 cm$^{-1}$, representing aromatic hydrogens and aliphatic hydrogens. Comparing this spectrum to the benzophenone spectrum these characteristic absorption peaks strongly indicate that 4,4'-diethylbenzophenone was synthesized. The IR spectrum for 4,4'-diethylbenzophenone is shown in Figure 23.
Figure 23. Infrared spectrum for 4,4'-diethylbenzophenone.
SUMMARY

The method used for the synthesis of $^{14}$C Perthane gave a yield of 3.46 grams or 87.14% of the theoretical. The specific activities of the $^{14}$C Perthane and purified $^{14}$C p,p' isomer of Perthane was 9.3μ Ci/mM respectively. ECGC, NMR, mass spectrometry, IR and melting point determination all gave evidence that the material was $^{14}$C Perthane.

The method used for the synthesis of 1-chloro 2,2-bis(p-ethylphenyl)ethylene gave a yield of 21.3 grams or 96.8% of the theoretical. ECGC, NMR, mass and IR spectrometry of this compound gave evidence that the material was 1-chloro 2,2-bis(p-ethylphenyl)ethylene.

The method used for the synthesis of di(p-ethylphenyl) acetic acid gave a yield of 6.99 grams which was 80% of theoretical. ECGC, mass spectrometry, IR, and melting point determination of this compound gave evidence that the material was di(p-ethylphenyl) acetic acid.

The method used for the synthesis of 4,4'-diethylbenzophenone gave a yield of 6.58 grams which was 76.8% of theoretical. ECGC, NMR, mass, and IR spectrometry of this compound gave evidence that the material synthesized was 4,4'-diethylbenzophenone.
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