

A SYNTHESIS OF
6-n-PROPYL-7-METHYLTETRALIN-5-C¹⁴

by

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Dedicated to my wife, Dorothy,
whose patience and help made
this work possible.

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A SYNTHESIS OF
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I. INTRODUCTION

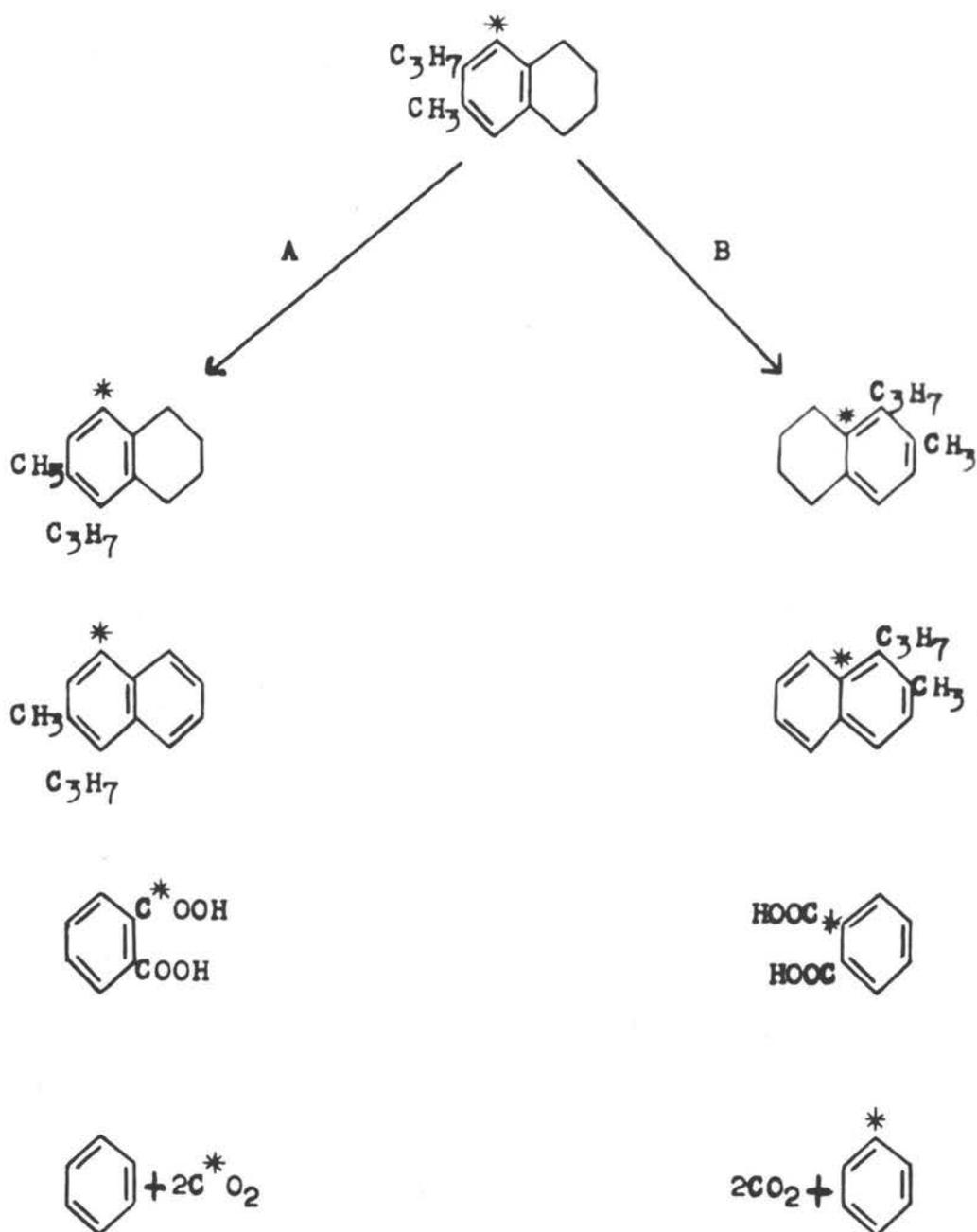
With the objective of testing the nature of the Jacobsen rearrangement suggested by Arnold and Barnes (3, pp.960-62) in 1944, Smith and Lo (40, pp.2209-15) prepared and rearranged several 6,7-dialkyltetralins. When 6,7-dimethyltetralin was heated with sulfuric acid followed by steam distillation, 5,6-dimethyltetralin was isolated. Since both alkyl groups were identical, it was impossible to prove whether the methyl group or the cyclic chain had migrated. Accordingly, 6-methyl-7-n-propyltetralin was tested and it was found that the rearranged product was 5-n-propyl-6-methyltetralin. To account for this product, one must either assume that the tetramethylene chain was cleaved and closed ortho to the propyl group or that the propyl group migrated per se. The migration of a n-propyl carbonium ion in the presence of excess sulfuric acid is unlikely since the isopropyl carbonium ion is much more stable and many instances are known in which isomerization occurs under acid conditions.

Migration of the chain appeared to be a valid assumption which could be unequivocally confirmed or disproved by labeling the tetralin with carbon-14. Rearrangement and subsequent degradation of the product would indicate which mechanism was correct as shown by the

reaction sequence in Figure I. If rearrangement occurred by path A, i.e., by migration of the propyl group, the isotopic carbon would appear in position eight. Degradation would produce phthalic acid labeled in one carboxyl group. Decarboxylation would then produce radioactive carbon dioxide and unlabeled benzene. Should the rearrangement proceed through route B, the end products would be radioactive benzene and "cold" carbon dioxide.

It was therefore the purpose of this work to synthesize the required radioactive compound which would be rearranged and degraded by other investigators to provide knowledge of the mechanism of the Jacobsen rearrangement of 6-methyl-7-n-propyltetralin and other 6,7-dialkyltetralins.

FIGURE 1.

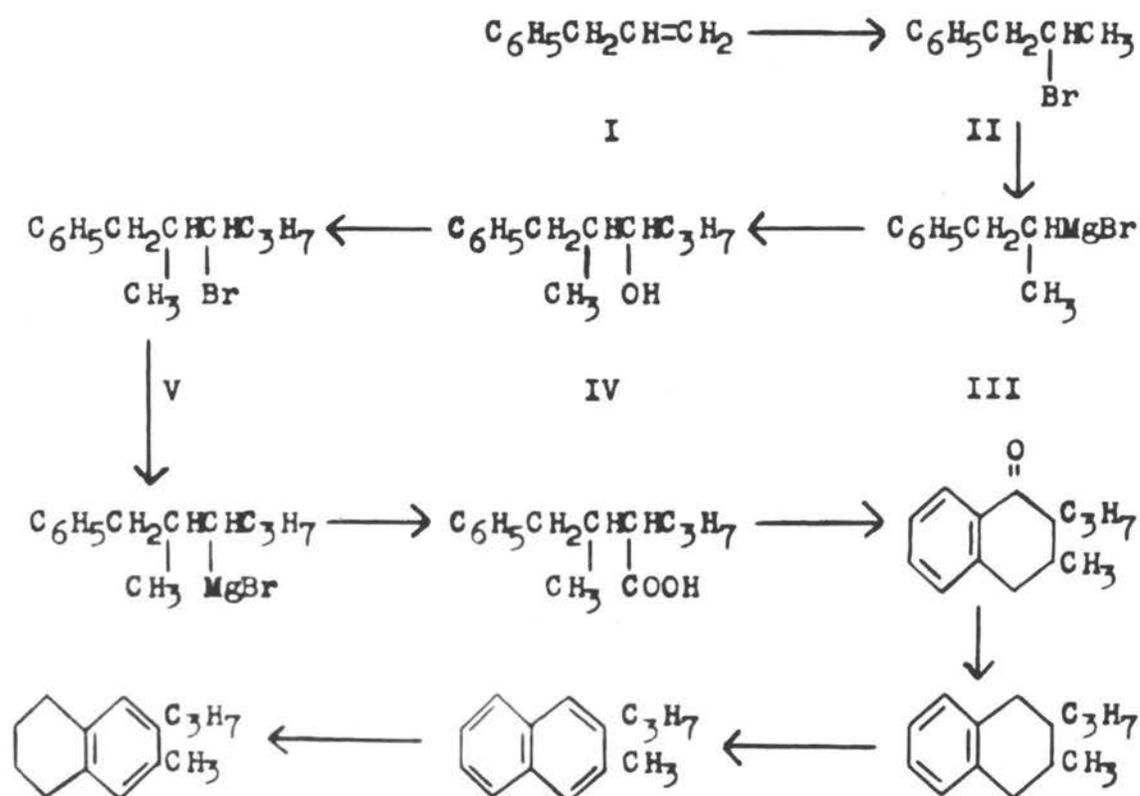


II. DISCUSSION OF RESULTS

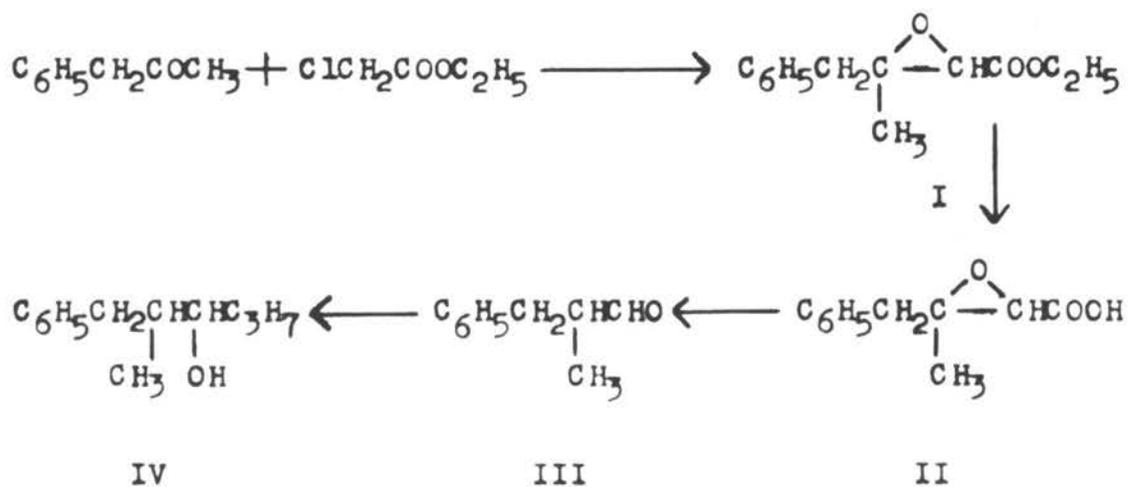
Two unsuccessful attempts were made to synthesize the desired compound before a third proved successful. Figure 2 shows the first reaction sequence that was tried. By altering conditions of time and temperature, good yields of 1-phenyl-2-methyl-hexanol-3 (IV) were finally obtained. This compound has not previously been reported in the literature. The 3,5-dinitrobenzoate of the alcohol was prepared but due to the difficulty of obtaining this derivative in a pure, crystalline form at first, an alternate synthesis of the alcohol was undertaken as a further proof of structure. This reaction scheme is also shown in Figure 2.

In attempts to prepare 1-phenyl-2-methyl-3-bromohexane (V), reactions were carried out using 48% HBr (34,p.1078), PBr_3 in petroleum ether (18,p.2621), PBr_3 in benzene and PBr_3 without solvent (27,p.762) to determine which method would result in highest yields and give most easily purified materials. In all cases, distillation of the product resulted in incomplete separation as evidenced by the gradual boiling point increase. Also, all fractions gave immediate precipitates when treated with cold, aqueous silver nitrate. Attempted separations by chromatographic methods gave the same results. Formation of a

FIGURE 2.



Alternate Synthesis:



bromide was also shown by the precipitation of sodium bromide when a distilled fraction was treated with sodium iodide in acetone.

It was noticed that upon distillation, hydrogen bromide was fairly readily given off. The ease of hydrogen bromide loss and the reactivity with aqueous silver nitrate suggested a possible rearrangement whereby a tertiary bromide was formed instead of the expected secondary product. Further investigation of the literature indicated that this was probably the case since Whitmore and Johnston (42,p.2265) were able to show that in all cases where a bromide was prepared from a secondary alcohol, rearrangement to the tertiary bromide occurred when the hydroxyl was adjacent to a "forked" or "iso" branch. On the basis of this evidence, the synthesis through the alcohol intermediate was discontinued.

The second mode of attack is shown in Figure 3. Compounds III to XI were unreported in the literature. This synthesis had the advantage of introducing the carbon-14 immediately prior to cyclization and would involve a minimum number of steps to the desired tetralin after the isotope had been introduced into the synthesis.

The reaction solvents used in the Reformatsky reaction to produce III were those used by Natelson and Gottfried (32,pp.970-71). These authors also suggested

using thin zinc strips that had been cleaned by sandpapering the surface. This was tried but it was found necessary to wash the zinc with dilute hydrochloric acid before the reaction would take place. In later experiments, it was noted that the use of forty-mesh zinc, activated by the hydrochloric acid washing, led to easier initiation of the reaction and higher yields.

Several methods of dehydrating III were tried without success. Neither refluxing with a few crystals of iodine (20, pp. 1748-53) in the original solvents nor refluxing with ninety per cent formic acid (37, p. 68) completely dehydrated the material and only low yields of IV were obtained. Even less dehydration occurred by passing dry hydrogen chloride gas through the crude product at 100°C. (32, pp. 970-71). Complete dehydration in good yields was finally accomplished by the use of phosphorous pentoxide (24, p. 2462).

It should be mentioned that there was no evidence for complete α, β -unsaturation. However, with similar compounds in the literature (9, p. 1159; 37, p. 68), the double bond was found in conjugation with the ester group.

The unsaturated acid (V) was easily and quantitatively hydrogenated over Adams' catalyst to yield VI. The saturated acid (VI) was obtained in good yields but the only solid derivative which could be formed from it was

the silver salt. Tars resulted when anilides and amides were attempted and no crystalline material could be obtained from other acid derivatives.

Silver, α -n-propyl- β -methyl- γ -phenylbutyrate (VII) was prepared from the potassium salt (13,p.33) by the procedure given in the experimental section, Synthesis B. It was also found that it could be easily made in slightly lower yields by dissolving the acid in dilute ammonium hydroxide and precipitating the desired salt with silver nitrate after first boiling off the excess ammonia (35,p.371). Regardless of the method used, it was impossible to keep the precipitate pure white. It changed to a light tan-gray even when dried and stored in the dark as much as possible.

Attempts were made to decarboxylate VII by adding the salt to a bromine-carbon tetrachloride solution at -25°C . (13,pp.33-34), adding the salt to a bromine-petroleum ether solution at -10°C . (43,p.5371), adding bromine to a suspension of the silver salt in carbon tetrachloride at room temperature (1,pp.52-53) and by adding bromine to the silver salt in boiling carbon tetrachloride (8,p.701). All methods tried gave very low yields of VIII and some of the original acid was always recovered as evidenced by the boiling point and refractive index.

Qualitative tests with sodium iodide in acetone and silver nitrate in alcohol indicated a secondary bromide and carbon-hydrogen data agreed with the calculated values.

The Grignard reagent (IX) could be obtained only in yields of 15-20%. Carbonation of the Grignard with carbon dioxide at room temperature, zero degrees centigrade and dry ice temperatures in diethyl ether or with di-n-butyl ether at 140°C. gave two fractions upon distillation. One was identified by boiling point and refractive index as the original bromide. A lower boiling fraction with a refractive index at 19°C. of 1.4900 was found to decolorize bromine in carbon tetrachloride without evolution of hydrogen bromide. It gave negative tests with ceric nitrate and ferric chloride but slowly decolorized cold, dilute potassium permanganate. It was insoluble in eighty-five per cent phosphoric acid but readily dissolved in cold, concentrated sulfuric acid. The above qualitative tests indicated an unsaturated molecule containing more than nine carbon atoms. Carbon-hydrogen data also indicated unsaturation:

	Calculated	Observed
$\begin{array}{c} \text{C}_6\text{H}_5\text{CH}_2\text{C}=\text{CHC}_3\text{H}_7 \\ \\ \text{CH}_3 \end{array}$	C - 88.56	C - 88.22
or	H - 11.44	H - 10.97
$\begin{array}{c} \text{C}_6\text{H}_5\text{CH}_2\text{CHCH}=\text{CHC}_2\text{H}_5 \\ \\ \text{CH}_3 \end{array}$		

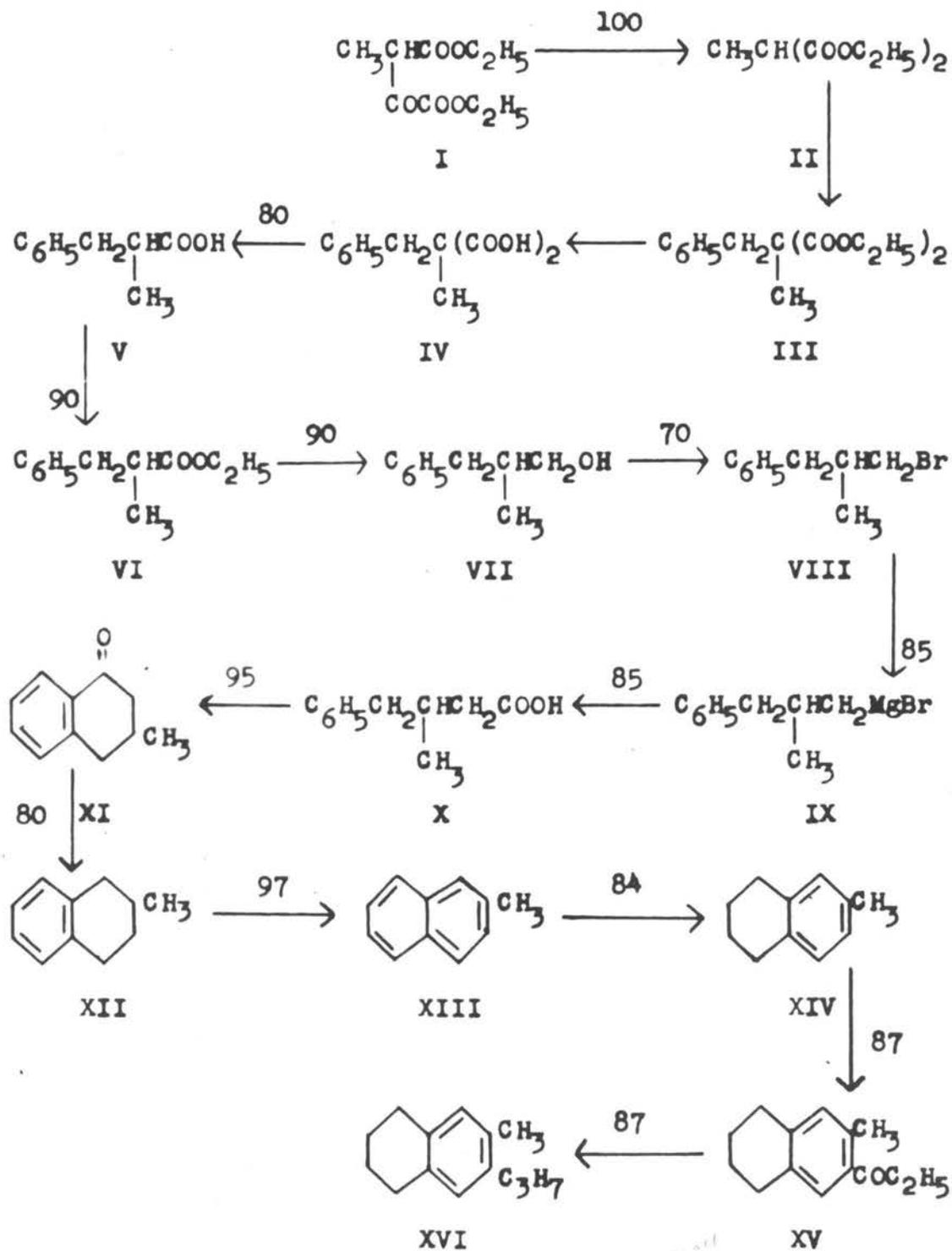
The reducing action of certain hindered Grignard reagents has long been known and Kharasch and Weinhouse (22, pp. 209-230) have related the complexity of the alkyl group to the reducing power of the Grignard based on reaction with benzophenone. It is possible that some similar effect is operative here although it seems very unlikely that reduction should take place with carbon dioxide.

Whatever the cause of this anomalous reaction, it was evident that the reaction procedure was no longer adequate and work on this scheme was discontinued.

The third and successful synthetic method is shown in Figure 4. It has the singular disadvantage with respect to the other methods that two additional reactions are necessary after the radioisotope has been introduced into the reaction. The main advantage lies in the fact that all of the compounds are reported in the literature. It was therefore necessary to alter reaction conditions for maximum yields, develop techniques for the manipulation of the radioactive materials and develop a procedure for the micro synthesis of 3-methyl-4-phenylbutyric acid-1-C¹⁴.

Most of the reactions were straightforward and went in fairly good yields. Better yields of VII were obtained through the use of a lithium aluminum hydride reduction of VI than reported by Levene and Marker (28, pp. 302-3) using sodium and alcohol.

FIGURE 4.



The syntheses of VIII and IX were accomplished without difficulty and the Grignard reagent was carbonated (28, pp.302-3) in 65-70% yields. In order to obtain larger amounts of X for use as starting material for the remainder of the synthesis, an alternate procedure, shown in Figure 5, was followed (12, pp.622-28). This product was used in the "cold runs" and as the diluent for the final radioactive preparation.

X was cyclized in 90-98% yields with polyphosphoric acid (25, pp.1893-94). This reagent had advantages over others because the reaction was run under extremely mild conditions, the yields were higher than most other methods, no side products were formed and decomposition of the mixture with water did not give a highly exothermic reaction as in the case of sulfuric acid. Thus, water could be safely added to the acid and the reaction carried out in one container.

2-Methyltetralin was obtained from XI by the usual Clemmensen reduction method. The yields were remarkably consistent, varying only from 76% to 81% for five reductions. No tests for ketones could be obtained with 2,4-dinitrophenylhydrazine from either the distillate or the residue.

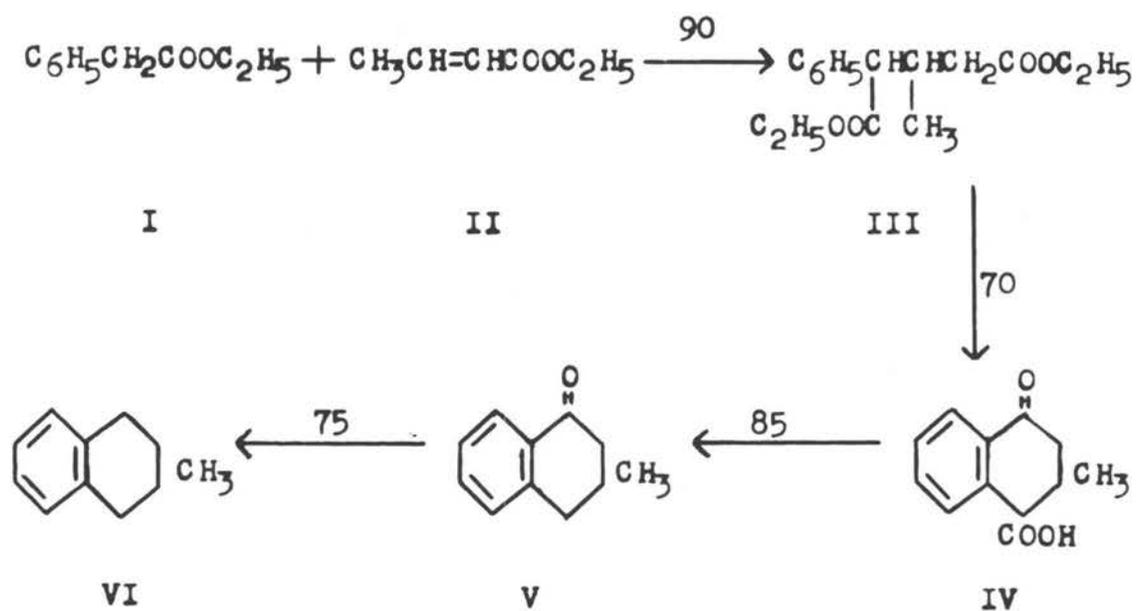
While determining the various procedures and conditions to be used, all of X except that needed for a final

cold run and for the radioactive procedure was exhausted. An alternate procedure, shown in Figure 6, was employed to prepare XI and XII on a larger scale in order to have enough material to work out the remainder of the reactions without repeating the tedious synthesis necessary to obtain X (V, Figure 5). After ten attempts, the procedure developed for the dehydrogenation of XII (prepared by the alternate synthesis), gave quantitative yields of 2-methylnaphthalene. It was found however, that on the final cold run, XII (prepared by cyclization from X) was incompletely dehydrogenated.

In order to ascertain that nothing in the reagents was causing this difference in results, a portion of 3-methyltetralone-1 (prepared by the alternate scheme) was treated with polyphosphoric acid and isolated in exactly the same manner as before. 2-Methyltetralin was obtained from this ketone under the same conditions used formerly, yet it still gave a quantitative yield of 2-methylnaphthalene. Below are the constants obtained for these compounds by the cyclization and alternate methods:

<u>Compound</u>	<u>Cyclization</u>	<u>Alternate</u>
XI	B.P. 131-133°C./9mm. \underline{n}^{20}_D , 1.5529	B.P. 134-137°C./ 10mm. \underline{n}^{20}_D , 1.5528
XII	B.P. 90-92°C./9mm. \underline{n}^{20}_D , 1.5281	B.P. 88-90°C./8mm. \underline{n}^{20}_D , 1.5278

FIGURE 6.



Whatever caused the dehydrogenation to fail with the tetralin from cyclization while proceeding with the tetralin from the alternate procedure is not readily explainable.

Because XII and XIII could not be separated by distillation, purification was accomplished by means of the picrate derivative. XII would not form such a derivative. Notably lower yields in this step were obtained due to the extra purification needed.

2-Methylnaphthalene (XIII) obtained from the picrate readily underwent reduction over Raney nickel. Lower temperatures were used than suggested by Fieser and Jones (17,p.1942) to prevent further reduction to 2-methyl-decalin. deRuiter and Jungers (36,pp.233-34) reported that naphthalene was reduced to tetralin over nickel at 100-125°C. and that no decalin was produced until the temperature reached 175-205°C. The radioactive 2-methylnaphthalene was reduced in a hundred milliliter stainless steel bomb insert which was placed in the usual five hundred milliliter high pressure bomb supplied by the Parr Instrument Company for catalytic high pressure hydrogenations. A sintered glass plate covered the opening to prevent any splashing and yet permit hydrogen to pass through. It was held in place by the pressure of the bomb head on a strip of metal placed on the glass plate. A

teflon gasket held the insert snugly in place while the bomb was shaking.

6-Methyl-7-propionyltetralin (XV) was prepared both by the method of Newman and Zahm (33,p.1098) with propionyl chloride in benzene and by the method of Smith and Lo (40,p.2213) using propionic anhydride and nitrobenzene. Higher yields were obtained by the former method, but both gave a 2,4-dinitrophenylhydrazone derivative whose melting point and mixed melting points were identical.

3-Methyl-4-phenylbutyric acid-1-C¹⁴ was prepared by the carbonation of IX with C¹⁴O₂ in the apparatus described by Van Bruggen (41,pp.45-47) for the synthesis of labeled acetic acid. A complete and exact description of the procedure involved in the carbonation of the Grignard with this apparatus has been previously reported by this author (29,pp.135-36). The yields were determined by potentiometric titration and averaged 85% for six attempts. Melting points and mixed melting points of the anilides derived from IX and X were identical.

The radioactive synthesis was carried out as described for the cold run except that 2-methyltetralin (XII) was distilled through a small column. This lowered the yield somewhat from that obtained in the cold runs. It was hoped that the additional purification would result

in a quantitative yield of 2-methylnaphthalene upon dehydrogenation. The reaction still did not go to completion and the picrate was used to isolate pure, crystalline XIII.

III. EXPERIMENTAL

Synthesis A

General equations are given in Figure 2.

1-Phenyl-2-bromopropane (II)

Allylbenzene (I) was prepared by the method of Carter (12, pp. 622-23) in 87% yield by allowing phenylmagnesium bromide to react with allyl bromide. Carter also prepared the bromo compound (II) by adding hydrogen bromide to I in glacial acetic acid. In a typical run, 180g. of HBr were dissolved in 240g. of ice cold glacial acetic acid. To this solution in a 500ml. bottle were added 120g. of allylbenzene. The bottle was tightly stoppered and allowed to sit at room temperature for thirty-six hours with occasional shaking. At the end of this time, the contents were poured over ice and the layers separated. The organic residue was taken up in ether, washed with sodium carbonate, water, and dried over sodium sulfate. The solvent was removed and the bromide distilled through a twelve inch Vigreux column under reduced pressure. There resulted an 80-85% yield of a colorless liquid boiling at 110-112°C. at 15mm.

1-Phenyl-2-methylhexanol-3 (IV)

To a Grignard reagent (III) prepared from 102g. (0.51mole) of 1-phenyl-2-bromopropane and 14.4g. (0.60

mole) of magnesium in 250ml. of anhydrous ether was added dropwise a freshly distilled solution of 28.8g. (0.40 mole) of n-butyraldehyde in 75ml. of ether to cause reflux. The solution was allowed to stand for twenty-four hours at room temperature and then refluxed for one hour. The material was cooled, decomposed with saturated ammonium chloride, ether extracted and dried over sodium sulfate. After removal of the solvent, fractionation of the residue resulted in a colorless, moderately viscous liquid of agreeable odor. Yield 70%; b.p. 107-110°C./0.90mm.; n_D^{19} , 1.5080.

Anal. Calcd. for $C_{13}H_{20}O$: C, 81.24; H, 10.49

Found: C, 81.40; H, 10.33

3,5-Dinitrobenzoate derivative

The 3,5-dinitrobenzoate was prepared by warming 3,5-dinitrobenzoyl chloride and the alcohol in anhydrous pyridine and recrystallizing the precipitate from an isopropyl alcohol-water mixture, m.p. 60-62°C.

Anal. Calcd. for $C_{20}H_{22}N_2O_6$: C, 62.16; H, 5.74

Found: C, 61.26; H, 5.63

Alternate synthesis of 1-phenyl-2-methylhexanol-3 (III)

General equations are shown in Figure 2. The synthesis of ethyl, 2-methyl-2-benzylglycidate (I) and 2-benzylpropionaldehyde (III) followed Darzens (16,

pp.1215-16). The aldehyde was condensed with n-propyl-magnesium bromide under the same conditions given above. Fractionation of the product gave a colorless liquid, b.p. 90-92°C./0.40mm.; n_D^{16} , 1.5089. 3,5-Dinitrobenzoate m.p. 60-61°C. Mixed m.p. with derivative prepared above, 60-62°C.

Synthesis B

General equations are given in Figure 3.

Ethyl, α -propyl- β -hydroxy- β -methyl- γ -phenylbutyrate (III)

α -Bromo-n-valeric acid (I) was prepared from n-valeric acid in 85% yield in a similar manner to the procedure reported by Marvel and Schriner (19, pp.115-16) for the synthesis of α -bromo-n-caproic acid. Ethyl, α -bromo-n-valerate (II) was prepared in 89% yield by refluxing the acid with a three-fold excess of absolute ethyl alcohol with a few grams of sulfosalicylic acid as catalyst. The reaction was carried out in the presence of dry carbon tetrachloride with a gravity separator to remove the water formed as suggested by Adams and Voorhees (19, p.421).

Twenty-one grams (0.321 mole) of c.p. 40 mesh zinc which had been briefly activated with 3N HCl, washed with distilled water and dried were placed in the bottom of a one liter three-necked flask equipped with condenser,

stirrer and dropping funnel. To the zinc were added a crystal of iodine and 20ml. of a mixture of 43g. (0.321 mole) of phenylacetone and 63g. (0.30 mole) of ethyl, α -bromo-n-valerate dissolved in 120ml. of benzene and 105ml. of toluene. The flask was heated on a steam bath and the remainder of the solution was added to provide reflux after the reaction had started. Heating was continued for two hours after the addition had been completed. The solution was cooled and the complex decomposed with dilute sulfuric acid. The layers were separated and the organic material was dried over sodium sulfate. After removal of the solvents under slightly reduced pressure, the residue was fractionated and the fraction boiling at 110-113°C. at 0.10mm. was collected. The yield of colorless, semi-viscous liquid was 60%; n_D^{22} , 1.4970.

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15

Found: C, 72.62; H, 9.13

Ethyl, α -propyl- β -methyl- γ -phenylcrotonate (IV)

57.4g. (0.217 mole) of the above hydroxy ester dissolved in 200 ml. of anhydrous benzene were dehydrated by refluxing for four hours with 40.0g. (0.282 mole) of P_2O_5 . The mixture was cooled, decomposed with ice cold water and extracted with ether. The organic layer was washed twice with water and dried over sodium sulfate.

Removal of the solvents left a clear yellow colored residue. Fractionation of this residue produced 45.0g. of a colorless liquid. Yield 84%; b.p. 93-94°C./0.10mm.; n_D^{27} , 1.5043.

Anal. Calcd. for $C_{16}H_{22}O_2$: C, 78.01; H, 9.00
 Found: C, 78.36; H, 9.04

α -Propyl- β -methyl- γ -phenylcrotonic acid (V)

To 27.0g. (0.1097 mole) of the above unsaturated ester were added 18.4g. (0.328 mole) of KOH dissolved in 100ml. of 30% ethyl alcohol. The heterogeneous mixture was refluxed until the upper layer disappeared (about twelve hours). The liquids were removed under reduced pressure to yield a nearly white, solid residue which was dissolved in a minimum of cold water, acidified with dilute hydrochloric acid and extracted with ether. The solvent was removed and the residue fractionally distilled to give 16.6g. of a colorless oil. Yield 69.4%; b.p. 130-131°C./0.10mm.; n_D^{28} , 1.5286.

Anal. Calcd. for $C_{14}H_{18}O_2$: C, 77.00; H, 8.32
 Found: C, 77.29; H, 8.41
 Calcd. for neut. eq.: 218.14
 Found: 217.0

α -Propyl- β -methyl- γ -phenylbutyric acid (VI)

In a typical run, 16.5g. (0.0756 mole) of V were dissolved in 50 ml. of glacial acetic acid and catalytically hydrogenated over 100mg. of platinum oxide at room temperature and two to three atmospheres. The catalyst was filtered from the solution and the acetic acid removed under reduced pressure. Fifteen grams of colorless product were obtained upon distillation. Yield 90%; b.p. 125-130°C./0.10-0.15mm.; n_D^{20} , 1.5088.

Anal. Calcd. for $C_{14}H_{20}O_2$: C, 76.31; H, 9.15

Found: C, 76.28; H, 8.96

Calcd. for neut. eq.: 220.30

Found: 222.4

Silver, α -propyl- β -methyl- γ -phenylbutyrate (VII)

Ten grams (0.0454 mole) of VI were dissolved in a solution of 2.55g. (0.0454 mole) of c.p. KOH in 120ml. of distilled water. A solution of 7.72g. (0.0454 mole) of $AgNO_3$ in 60ml. of distilled water was slowly added to the vigorously stirred solution of the potassium salt. The voluminous white precipitate that formed was filtered, washed with cold water, methanol and dried in a vacuum oven at 60°C. for five to six hours. Yield 38.6g. (85%).

Anal. Calcd. for $C_{14}H_{19}O_2Ag$: C, 51.39; H, 5.85

Found: C, 51.29; H, 5.97

1-Phenyl-2-methyl-3-bromohexane (VIII)

The silver salt described above was re-dried in a vacuum oven at 80°C. until dry enough to be powdered and passed through a thirty-five mesh screen (usually three to four days). In a flask provided with a dropping funnel, stirrer and condenser were placed 35g. (0.107 mole) of the silver salt, 150ml. of anhydrous carbon tetrachloride (dried by distillation and stored over P₂O₅). 17.4g. (0.1086 mole) of dry bromine were added to the vigorously stirred suspension as rapidly as gas evolution would permit (two to three minutes). When the addition had been completed, the contents were refluxed for one hour on a steam bath. The flask was cooled to room temperature and the silver bromide precipitate was filtered. The filtrate was washed with sodium bicarbonate, sodium bisulfite, water and dried over calcium chloride. After removal of the solvent, fractionation gave 4.92g. of a colorless liquid. Yield 18%; b.p. 84-85°C./0.10mm.; n_D^{20} , 1.5240.

Anal. Calcd. for C₁₃H₁₉Br: C, 61.18; H, 7.50

Found: C, 61.30; H, 7.47

Attempted carbonation of 1-(α -benzylethyl)-n-butylmagnesium bromide (IX)

The Grignard reagent was prepared in the ordinary manner from 2.55g. (0.01 mole) of the above bromide and

0.365g. (0.015 mole) of magnesium in 40ml. of anhydrous ether. The solution was freed of unreacted magnesium particles by filtering through a loose cotton plug. Yield, calculated from titration, 20%. The filtrate was cooled to about -70°C . in dry ice and a rapid stream of dry carbon dioxide was bubbled through. After one hour, the mixture was allowed to come to room temperature and decomposed with ice cold, dilute hydrochloric acid. The layers were separated and the aqueous layer further extracted with ether. The ethereal portions were combined and extracted three times with 10ml. of 5% NaOH. The basic solution was acidified with cold, dilute hydrochloric acid and extracted with ether. No product was obtained upon removal of the solvent. Evaporation of the solvent from the base-extracted ethereal fraction yielded a small amount of a light yellow liquid. The crude material was insoluble in base and had n_D^{21} , 1.5071. Distillation separated it into two components:

	B.P./0.05mm.	n_D^{19}
1.	45-46 $^{\circ}\text{C}$.	1.4900
2.	70-72 $^{\circ}\text{C}$.	1.5243

The constants on fraction 2 agree closely with the original bromide and it was further found to give a precipitate with silver nitrate upon warming. Fraction 1 gave positive tests for unsaturation with bromine and potassium permanganate. This fraction was probably 1-phenyl-2-

methylhexene-2 or 1-phenyl-2-methylhexene-3 or a mixture of both.

Anal. Calcd. for $C_{13}H_{18}$: C, 88.56; H, 11.44

Found: C, 88.22; H, 10.97

2-Propyl-3-methyl-1-tetralone (XI)

Twenty grams (0.0908 mole) of VI and 150g. of polyphosphoric acid¹ were heated at 70°C. for forty-five minutes with occasional stirring. During this time solution occurred and the material became orange in color. The flask was cooled and the contents poured over ice. The organic materials were extracted with ether, washed with 10% $NaHCO_3$, water and dried over sodium sulfate. The ether was removed on a water bath and the residue fractionally distilled to give 13.0g. of a colorless liquid. Yield 71%; b.p. 90-96°C./0.15-0.20mm.; n_D^{19} , 1.5349; 2,4-dinitrophenylhydrazone m.p., 162-164°C.

Anal. Calcd. for $C_{14}H_{18}O$: C, 83.12; H, 8.97

Found: C, 83.26; H, 8.77

Calcd. for $C_{20}H_{22}O_4N_4$: C, 62.81; H, 5.80

Found: C, 62.80; H, 5.73

¹ Sample kindly supplied by the Victor Chemical Company, Chicago, Illinois.

Synthesis C

General equations are given with yields obtained in Figure 4.

Methylbenzylacetic acid (V)

Pure diethylmethylmalonate (II) was obtained by decarbonylation (5,p.279) of ethylethoxylpropionate² (I). II was treated with benzyl chloride in the presence of sodium ethoxide to form diethyl, benzylmethylmalonate (III) under the usual alkylating conditions as given for similar compounds (5,pp.279-280). Refluxing III and a 50% excess of KOH in twice its volume of 20% ethyl alcohol for ten hours easily converted it to benzylmethylmalonic acid (IV). Decarboxylation (15,p.178) of IV was accomplished by heating at 180-200°C. until no more gas was evolved. The overall yield of methylbenzylacetic acid for the four steps was 80%. B.P. 164-167°C./15mm.; reported (23,p.1006) 160°C./12mm. The physical constants of the intermediates agreed closely with those in the literature.

2-Methyl-3-phenylpropanol-1 (VII)

Ethyl, benzylmethylacetate (VI) was prepared according to Levene and Marker (28,pp.302-303) in 90%

² The author wishes to express his appreciation to Dr. B. E. Christensen of Oregon State College for kindly supplying a quantity of this material.

yields. In a typical run 48.5g. (0.25 mole) of ethyl, benzylmethylacetate were dissolved in 200ml. of anhydrous ether in a flask equipped with stirrer, condenser and dropping funnel. A slurry of 9.5g. (0.25 mole) of LiAlH_4 in 300ml. of anhydrous ether was added to not exceed the reflux capacity of the system. When the addition had been completed, the mixture was stirred for an additional two hours. 26.4g. (0.30 mole) of ethyl acetate were added to decompose the excess lithium aluminum hydride and 18ml. of water were added to decompose the complex. The solid which formed was filtered and washed with ether. The ethereal portions were combined, the solvent removed on a water bath and the residue distilled. There was obtained 34g. of colorless liquid. Yield 92%; b.p. $129^\circ\text{C}/15\text{mm.}$; reported (6,p.1278) $128-9^\circ\text{C}/16\text{mm.}$

3-Methyl-4-phenylbutyric acid (X)

1-Bromo-2-methyl-3-phenylpropane (VIII) and 2-methyl-3-phenylpropylmagnesium bromide (IX) were obtained following Levene and Marker (28,pp.302-303) except that the halide was extracted with petroleum ether and the solution washed several times with concentrated sulfuric acid before distillation. The Grignard reagent was carbonated at -70°C. with dry carbon dioxide to form 3-methyl-4-phenylbutyric acid (X). B.P. $153-155^\circ\text{C}/6\text{mm.}$; reported (12,p.629) $168-170^\circ\text{C}/13\text{mm.}$ Anilide, m.p.

99.5-100°C.; reported (2,p.305) 100-101°C. Amide, m.p. 83-85°C.; reported (26,p.283) 83°C. Neutralization equivalent calculated, 178.0; observed, 178.6.

Alternate synthesis of 3-methyl-4-phenylbutyric acid (V)

General equations are given with yields obtained in Figure 5.

The following compounds were synthesized using the method of Carter (12,pp.622-28). Allylbenzene (I) and 1-phenyl-2-bromopropane (II) were made as previously described in Synthesis A. The above bromide was condensed with diethylmalonate in the presence of sodium ethoxide catalyst to form ethyl, α -carbethoxy- β -benzylbutyrate (III). The diester was hydrolyzed with alcoholic potassium hydroxide to yield α -carboxy- β -benzylbutyric acid (IV) which decarboxylated upon heating to give V. Overall yield based on II was 37.6%.

The product was distilled, dissolved in dilute potassium hydroxide solution and re-extracted with ether. The basic solution was acidified with dilute hydrochloric acid, the organic acid was ether extracted, washed with water and dried over sodium sulfate. Removal of the solvent and fractionation of the residue gave a colorless liquid. B.P. 119-121°C./0.20mm. Anilide, m.p. observed 99-100°C.; reported (2,p.305) 100-101°C. A mixed melting point with X in Figure 4 did not depress the melting point.

3-Methyltetralone-1 (XI)

In a typical procedure 20g. (0.1124 mole) of 3-methyl-4-phenylbutyric acid, prepared by the malonic ester synthesis, were added to 150g. of polyphosphoric acid in a 500ml. round bottom flask equipped with a mercury sealed stirrer. The flask was heated at 70-75°C. for sixty minutes with occasional stirring. It was then cooled in ice and approximately 300ml. of ice cold water were added forming white, milky droplets. The contents of the flask were extracted in a liquid-liquid extractor (designed to fit any standard taper flask) with petroleum ether for twenty-four hours. The solvent was removed under slightly reduced pressure and 240ml. of 5% Na₂CO₃ solution were added and mixed well. Extraction of the basic mixture was carried out with ethyl ether for fourteen hours. Removal of the solvent left a light yellow residue which was distilled through a simple take-off arm. Weight 17.0g.: yield 94.6%; b.p. 132-134°C./10mm.; reported (21,p.1857) 138°C./11mm.: n_D^{20} , 1.5529; reported (7,p.1729) 1.5590. 2,4-Dinitrophenylhydrazone (bright red crystals from ethyl acetate); m.p. 242°C., reported (12,p.1857) 242°C.

2-Methyltetralin (XII)

Seventy grams of c.p. mossy zinc were amalgamated (30,p.1440) in a 500ml. flask by shaking with a solution

of 7.0g. of mercuric chloride, 3.5ml. of concentrated hydrochloric acid and 85ml. of distilled water for five minutes. The liquid was decanted and the amalgam was covered with 80ml. of distilled water. 17.0g. (0.1063 mole) of 3-methyltetralone-1 were transferred to the flask, washing in any remaining material with 7.0ml. of purified, anhydrous toluene in small portions. A reflux condenser was attached, 70ml. of concentrated hydrochloric acid were added and the materials vigorously refluxed for forty-four hours adding 20ml. of concentrated hydrochloric acid every four hours. At the end of this time the flask was allowed to cool and the contents of the condenser were washed into the flask with a small amount of ethyl alcohol. Extraction of the mixture with petroleum ether for thirteen hours and removal of the solvent under slightly reduced pressure yielded a yellow colored liquid residue. To this residue were added 250ml. of 5% NaOH, the materials were well mixed and the tetralin re-extracted for ten and a half hours with petroleum ether. The solvent was removed and the residue distilled to give 12.4g. of 2-methyltetralin (XII). Yield 80%: b.p. 90-92°C./10mm.; reported (38, p.1431) 228-230°C./760mm.: n_D^{18} , 1.5293.

2-Methylnaphthalene (XIII)

In a typical run, the 2-methyltetralin was distilled directly into a 100ml. flask provided with a side arm for

the introduction of carbon dioxide. Ten grams (0.0685 mole) of 2-methyltetralin were mixed with 3.0g. of 10% Pd-C and a cold finger condenser inserted in the opening of the flask. The system was set up so that carbon dioxide from a tank could be dried through calcium chloride and sulfuric acid, passed through the reaction vessel and an ice-salt trap into an azotometer filled with 50% KOH. After flushing the system with carbon dioxide until only micro bubbles were obtained, the temperature of the flask was slowly raised from 210°C. to 250°C. until no more hydrogen was evolved (about ten hours). The cooled residue was taken up in ether and the catalyst removed by filtration. Removal of the solvent and distillation gave shiny white crystals in nearly quantitative yields. B.P. 107-110°C./10mm.: m.p. 35°C.; reported (39,p.259) 33-35°C. Picrate m.p. and mixed m.p. 114-116°C.; reported (39, p.259) 115-116°C. A mixed m.p. with picric acid lowered the original m.p. by 30°C.

Purification of 2-methylnaphthalene by picrate

Seven grams (0.0493 mole) of 2-methylnaphthalene and 30ml. of commercial tetralin were washed into a 500ml. three-necked flask with 10ml. of absolute ethyl alcohol. 17.9g. (0.0735 mole) of 90% picric acid were added and the mixture refluxed for five minutes. The melt was cooled and 25ml. of petroleum ether was added. The solvent was

filtered from the residue through a sintered glass plate inserted in one of the necks of the flask. This process was repeated twice. The picrate was decomposed with 3.2g. (0.08 mole) of NaOH dissolved in 250ml. of water and the hydrocarbon was steam distilled. The distillate was extracted for ten hours with petroleum ether. Removal of the solvent and distillation of the product produced 6.3g. of a white crystalline material. Yield 90%: b.p. 107-110°C./10mm.: m.p. 33-35°C.

6-Methyltetralin (XIV)

Eight grams (0.0564 mole) of 2-methylnaphthalene (XIII) were transferred to a special 100ml. stainless steel bomb insert with 3.0ml. of absolute ethyl alcohol and approximately 3ml. of a Raney nickel slurry were added. The reduction was carried out at 110°C. and an initial pressure of 1600 psi. The temperature was briefly raised to 125-130°C. to initiate the reaction and reduction was continued until the pressure remained constant (usually forty minutes). After the bomb was cooled and opened, the mixture was taken up in petroleum ether, the catalyst was removed by filtration and washed with more solvent. Distillation resulted in 6.9g. of 6-methyltetralin. Yield 84%: b.p. 95-99°C./10mm.; reported (40,p.2212) 99-103°C./12mm.: n_D^{25} , 1.5310; reported (40,p.2212) n_D^{20} , 1.5328.

Ten drops were oxidized (11,p.427) to trimellitic acid with 3ml. of 1:2 HNO_3 in sealed tube at 195-200°C. for twenty hours. The clear yellow solution was evaporated and the residue recrystallized from an ether-ligroin mixture. M.P. 212-215°C.; reported (31,p.50) 216°C.

6-Methyl-7-propionyltetralin (XV)

Ten grams (0.0685 mole) of 6-methyltetralin (XIV) and 6.4g. (0.0692 mole) of propionyl chloride were dissolved in 50ml. of anhydrous, thiophene-free benzene in a flask equipped with a condenser connection having a side arm for adding solids. The flask was cooled in an ice bath and stirred with a magnetic stirrer. Over a period of one hour, 9.24g. (0.0692 mole) of anhydrous AlCl_3 powder were added in small portions. When the addition had been completed, stirring was continued for two hours. The complex was decomposed by rapidly pouring 150ml. of 12% HCl down the condenser. The organic materials were extracted with ethyl ether for twenty-four hours in the extractor apparatus. Distillation produced 12.0g. of a pale yellow casted liquid. Yield 86.7%: n_D^{23} , 1.5462; reported (40,p.2213) n_D^{20} , 1.5479; 2,4-dinitrophenyl-hydrazone m.p. 169-172°C. Smith and Lo (40,p.2213) reported a melting point of 153-154°C.

Anal. Calcd. for $\text{C}_{20}\text{H}_{22}\text{N}_4\text{O}_4$: C, 62.81; H, 5.80
Found: C, 63.06; H, 5.92

6-Methyl-7-n-propyltetralin (XVI)

Fifty grams of zinc were amalgamated as previously described and covered with 50ml. of distilled water. 7.4g. (0.0366 mole) of 6-methyl-7-propionyltetralin (XV) were washed into the flask with 7.0ml. of purified, anhydrous toluene. A mixture of 100ml. of concentrated HCl and 65ml. of glacial acetic acid was added through the top of the condenser and the mixture was refluxed for forty-eight hours adding 10ml. of concentrated HCl every four hours. When the flask had cooled, the contents of the condenser were washed into the flask with a small amount of alcohol and the organic materials extracted for ten hours with petroleum ether. The solvent was removed under reduced pressure and the residue distilled giving 6.0g. of colorless 6-methyl-7-n-propyltetralin (XVI). Yield 87%: b.p. 135-138°C./8mm.; reported (40,p.2213) 130-135°C./11mm.: n_D^{19} , 1.5250; reported (40,p.2213) n_D^{19} , 1.5250.

Oxidation of the hydrocarbon with dilute nitric acid as previously described gave pyromellitic acid. M.P. 263-267°C.; reported (31,p.51) 264°C.

Alternate synthesis of 3-methyltetralone-1 (V) and 2-methyltetralin (VI)

General equations are given with yields obtained in Figure 6. Ethyl, phenylacetate (I) and ethyl crotonate (II) were prepared in the usual manner from the respective

acids by refluxing with ethyl alcohol in the presence of a few milliliters of concentrated sulfuric acid. Using the procedure of Connor and McCellan (14, pp. 576-577) diethyl, α -phenyl- β -methyl glutarate (III) was prepared by condensing I and II in the presence of sodium ethoxide in alcohol. The diester was cyclized and hydrolyzed in one step by heating with 80% H_2SO_4 to give 4-carboxy-3-methyltetralone-1 (IV). Decarboxylation was effected by heating a mixture of IV with quinoline and a small amount of copper oxide to form 3-methyltetralone-1 (V) following Baker and Carlson (4, p. 2260). B.P. 131-133°C./9mm.: n_D^{20} , 1.5528; 2,4-dinitrophenylhydrazone m.p. 241-242°C.; reported (12, p. 1887) 242°C. A mixed m.p. with XI from Figure 4 did not depress the original. 2-Methyltetralin (VI) was prepared from the above ketone as previously described for XII in Figure 4. B.P. 90-91°C.: n_D^{20} , 1.5278.

Total Synthesis of 6-n-propyl-7-methyltetralin-5-C¹⁴

General equations are given in Figure 4.

The introduction of carbon-14 into the molecule to form 3-methyl-4-phenylbutyric acid-1-C¹⁴ (X) will be described. The other compounds (XI to XVI) in the synthesis were obtained by following the exact conditions already given for their preparation except that 2-methyltetralin-4-C¹⁴ was distilled through a small column before

the dehydrogenation was attempted. Only the amounts of reagents, boiling points and yields obtained are listed for each compound.

3-Methyl-4-phenylbutyric acid-1-C¹⁴ (X)

The apparatus used for the carboxylation of the Grignard reagent (IX) was that described by Van Bruggen *et al.* (41, pp.45-47) and is shown in Plate I. A complete, detailed description of the procedure used has been previously reported by Logan and Odell (29, pp.135-36). The reaction was carried out at liquid nitrogen temperatures in a closed system at approximately ten millimeters pressure. Radioactive barium carbonate³ was decomposed with perchloric acid in the small bulb and was used to carbonate the Grignard reagent (IX) which was introduced into the larger reaction vessel in several small portions. The complex formed was decomposed with dilute hydrochloric acid and the organic materials were extracted with ether. 105.1mg. (0.5324 millimole, specific activity 0.0818mc./mg.) of BaC¹⁴O₃ were used to carbonate 5.0ml. of 1M 2-methyl-3-phenylpropylmagnesium bromide (IX). The acid-decomposed complex was extracted with ether for four hours and the solvent was removed in a current of air over 5.0ml. of 10% Na₂CO₃. The residues were mixed well

³ BaC¹⁴O₃ obtained from A.E.C., Oak Ridge, Tennessee.

and extracted twice with 5ml. of ether by pipette. The basic solution was acidified carefully with 6.0ml. of 10% HCl and re-extracted with ether for four hours. The ethereal solution was transferred to a five hundred milliliter flask, 20.0573g. of "cold" X was added and the solvent removed under slight vacuum. This residue was used directly for the cyclization step. Yield expected, based on titration of six cold runs, 85%.

3-Methyl-1-tetralone-1-C¹⁴ (XI)

20.1378g. (0.1132 mole) of X
150g. of polyphosphoric acid
B.P. 134°C./10mm.
Yield 90% (16.3g.)

2-Methyltetralin-4-C¹⁴ (XII)

16.3g. (0.1019 mole) of XI
70g. of amalgamated zinc
B.P. 90-92°C./10mm.
Yield 67.2% (10.0g.)

2-Methylnaphthalene-4-C¹⁴ (XIII) (Purified by picrate)

10.0g. (0.0685 mole) of XII
3.5g. of 10% Pd-C
B.P. 108-110°C./10mm.
Yield 66.8% (6.5g.)

7-Methyltetralin-5-C¹⁴ (XIV)

6.5g. (0.0458 mole) of XIII
3ml. of Raney nickel slurry
3.0ml. of absolute ethyl alcohol
B.P. 95-99°C./10mm.
Yield 89.3% (6.0g.)

6-Propionyl-7-methyltetralin-5-C¹⁴ (XV)

6.0g. (0.0411 mole) of XIV
5.60g. (0.042 mole) of AlCl₃
3.89g. (0.042 mole) of propionyl chloride
B.P. 170-174°C./12mm.
Yield 80.8% (6.7g.)

6-n-Propyl-7-methyltetralin-5-C¹⁴ (XVI)

6.7g. (0.0332 mole) of XV
50g. of amalgamated zinc
B.P. 137-140°C./13mm.
Yield 95.2% (5.9400g.)

IV. ANALYSIS

The radioactivity was determined by oxidizing 6.000mg. of the labeled material and 14.1mg. of the "cold" tetralin by the Van Slyke-Folch wet combustion method (10, pp.92-93). The barium carbonate formed was collected on a sintered glass filter (M), washed three times with distilled water, once with 95% ethyl alcohol and dried overnight at 100-110°C. This was further diluted for counting by mixing known amounts of labeled and unlabeled barium carbonate together, decomposing with acid and reprecipitating the barium carbonate.

A small amount of the reprecipitated barium carbonate was removed from the filter and made into a slurry by grinding it with 3ml. of a 25% ether - 75% alcohol solution in an agate mortar. The slurry was then added dropwise to a copper planchet (one inch in diameter) contained in a brass cup and the solvent was evaporated under an infrared lamp. The barium carbonate disc was counted using a Tracerlab end window counter (1.7mg./cm² mica) and corrected for self absorption from an empirically prepared curve. The specific activity observed was 7.44x 10⁴c./min./mg. The radioactive recovery was 23.8% based on the original BaC¹⁴O₃ used. The overall chemical yield based on X was 26.6%.

V. SUMMARY

Radioactive 6-n-propyl-7-methyltetralin has been prepared in an overall chemical yield of 26.6%. The radioactive recovery was 23.8%. The specific activity of the final product was 7.44×10^4 c./min./mg.

Nine other compounds unreported in the literature have been synthesized and characterized. Physical constants and carbon-hydrogen data were given.

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APPENDIX

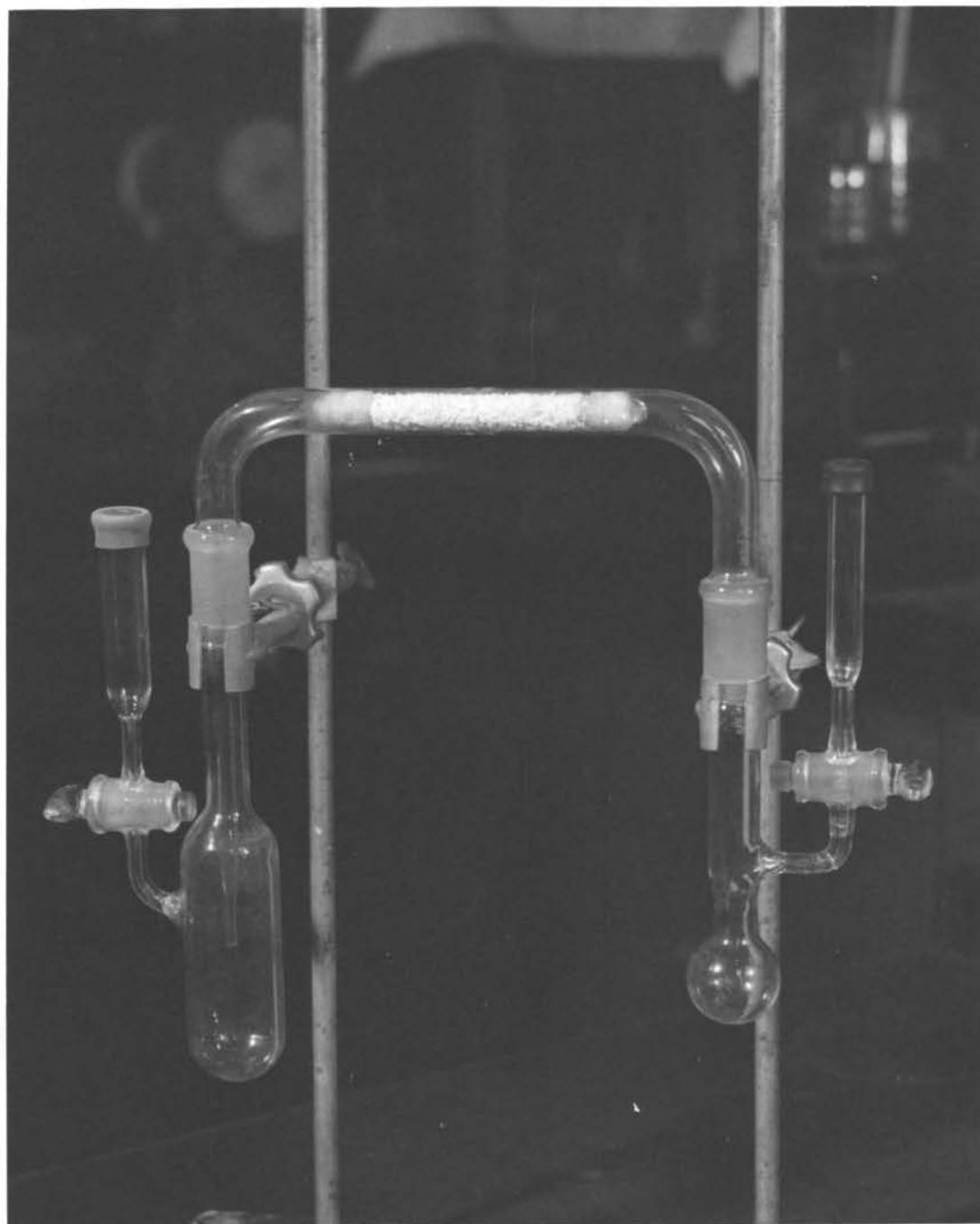


PLATE I

CARBONATION APPARATUS