THE SYNTHESIS OF 1.2.3.4-TETRAHYDRO-(7-^{3}H)NAPHTHALENE AND (7-^{3}H)NAPHTHALENE LABELED WITH ^{14}C IN THE 1-OR 2-POSITION.

W. DEN HOLLANDER, P.J. VAN DER JAGT and B. VAN ZANTEN.

Chemical Laboratory of the Vrije Universiteit,
de Lairessestraat 174,
Amsterdam - THE NETHERLANDS.

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SUMMARY

Procedures are given for the preparation of (2-^{14}C), (7-^{3}H)naphthalene, (1-^{14}C), (7-^{3}H)naphthalene, 1.2.3.4-tetrahydro-(2-^{14}C), (7-^{3}H)naphthalene and 1.2.3.4-tetrahydro(1-^{14}C), (7-^{3}H)naphthalene. Starting with $^{14}CO_2$ the 1-^{14}C-labeled compounds were prepared in a 4- or 5-step synthesis in an overall yield of 56 or 44% respectively and the 2-^{14}C-labeled compounds in a 8- or 9-step synthesis in an overall yield of 52 or 39% respectively. The specificity of the ^{14}C-labeling was in all cases better than 97%.

Our investigations on the chemical effects of the β^--decay of carbon-14 are to ascertain whether or not particular molecular properties do have an influence on the retention. Manning and Monk[1] concluded from their experiments with chain-labeled ^{14}C-toluene and ^{14}C-ethylbenzene that the phenyl ring was capable to absorb part of the recoil energy produced by the decay $^{14}C \xrightarrow{\beta^-} {}^{14}N$.

These authors reported that after decay of ^{14}C in methyl labeled ^{14}C-toluene 100% retention of the nitrogen was found, and attributed this result to the presence of the attached aromatic system. On the other hand Skorobogatov and Nefedov[2] found that after decay of ^{14}C in multilabeled benzene, the retention was about 60%, independent of the storage conditions. This retention is comparable with that found by Wolfgang et al.[3] after decay of ^{14}C in ^{14}C-labeled ethane.

As a check on the above mentioned results and conclusions we decided to investigate the chemical effects of ^{14}C-decay in naphthalene, 1.2.3.4-tetrahydronaphthalene (tetralin) and decahydronaphthalene (decalin). Location of the ^{14}C-label in the 1- or 2-position of naphthalene and decalin or in the 1-, 2-, 5- or 6-position of tetralin simulates the type of labeled compounds investigated by forementioned authors and offers the opportunity to compare the amount of retention in chemical different carbon-positions of the forementioned compounds.

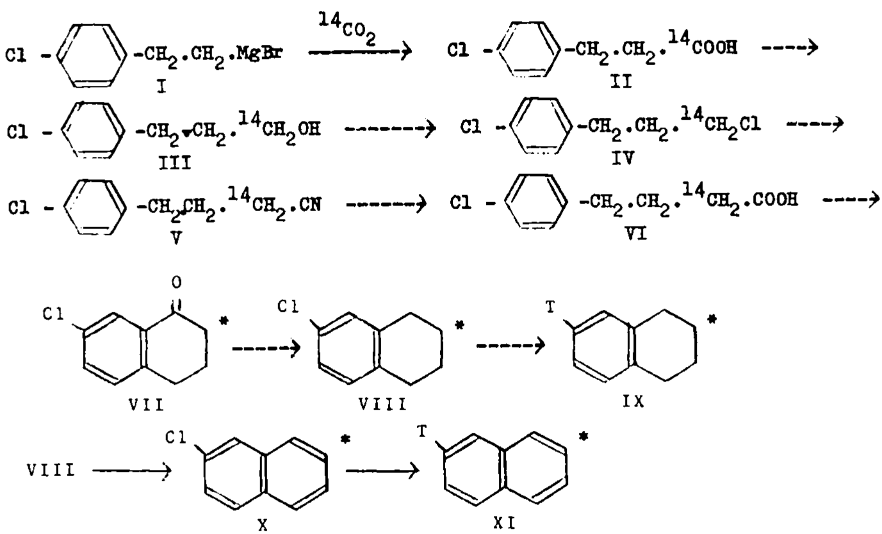
In this paper the synthesis is described of tritiated ^{14}C-labeled naphthalenes and tetralins, labeled with ^{14}C in the aliphatic ring. The synthesis of tritiated ^{14}C-labeled decalins and tetralins labeled with ^{14}C in the aromatic ring will be published soon.

As for the determination of the retention products a second label is necessary, we decided to use tritium bound to the molecule in a well-defined position. Although for our investigation proper high specific activities are required, the experiments described in this paper were carried out on a tracer level in order to establish unequivocally the positions of the labels. The following compounds were prepared: $(2-^{14}C),(7-^{3}H)$tetralin(IX), $(2-^{14}C),(7-^{3}H)$naphthalene(XI), $(1-^{14}C),(7-^{3}H)$tetralin (XVI) and $(1-^{14}C),(7-^{3}H)$naphthalene (XVIII). In the schemes I and II (see p. 5) the synthetic routes are indicated.

Almost the entire reaction series could be carried out in a multipurpose extraction device without intermediate purifications[4]. The first compounds which had to be purified by gaschromatography (GLC) were VIII, X, XV and XVII. After dehalogenation the position of the ^{14}C-label in VIII and XV was determined by oxidative degradation to phthalic acid and comparison of its specific activity with the specific activity of the original compound. The catalytic dehalogenation of chloronaphthalene and chlorotetralin with tritium gas and the purification of the obtained compounds are described elsewhere[5].

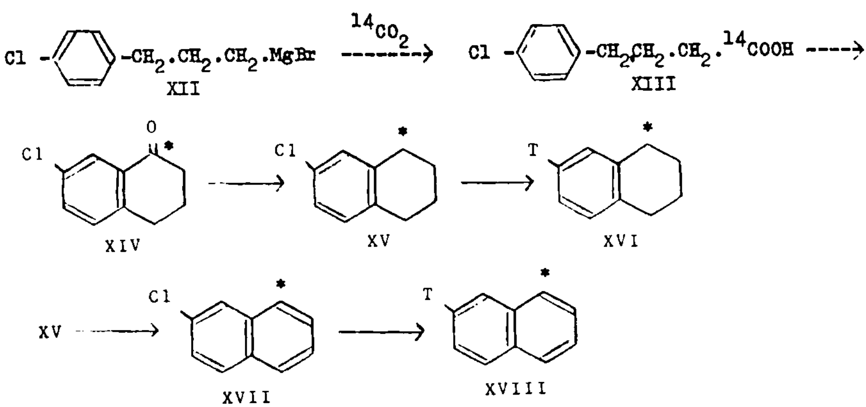
The overall yields of the compounds IX, XI, XVI and XVIII were 52%, 39%,56% and 44% respectively. The specific activity of the ^{14}C-label in these compounds proved to be the same as that of the starting $^{14}CO_2$ and the specificity of the ^{14}C-labeling was better than 97% in both the $1-^{14}C$- and the $2-^{14}C$-compounds.

Scheme I



Preparation of compounds IX and XI

Scheme II



Preparation of compounds XVI and XVIII

EXPERIMENTAL PART

3-(p-chloro phenyl)-(1-^{14}C)propionic acid (II)

To an all-glass system were sealed an ampoule containing 1.55 mmol of $^{14}CO_2$ (B), an ampoule containing 10 ml of 1.5N sulfuric acid (A) and an ampoule containing 1.40 mmol of the Grignard of 1-(p-chloro phenyl)-2-bromoethane (I) in 10 ml of diethyl ether (C), as shown in Fig. I.

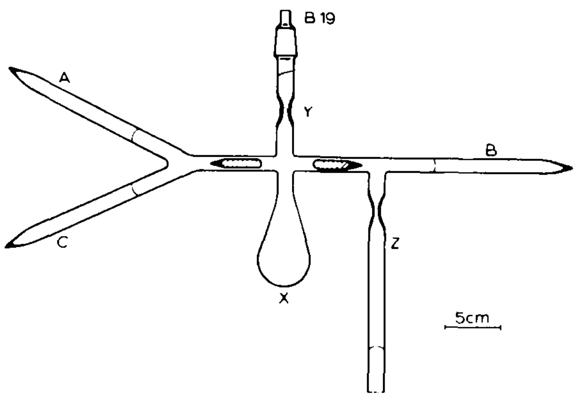


Fig. I.

Apparatus for the reaction of a Grignard with $^{14}CO_2$

The filled ampoules were prepared and evacuated beforehand and were equipped with breakseals.

The system was evacuated and sealed off at Y. After breaking the seal of C, the Grignard solution was transferred into vessel X and after cooling the vessel to about -40^{o}C, $^{14}CO_2$ was admitted. The content of X was kept at -30 to -40^{o}C for about 3 hours, followed by gradually warming up to 0^{o}C while intermittently vessel X was shaken. The reaction mixture was kept at 0^{o}C for 2 hours. After condensing the unused $^{14}CO_2$ and some diethyl ether in ampoule Z, this ampoule was sealed off. Then sulfuric acid from ampoule A was added and the system was opened by cutting off one of the side arms.

The content of vessel X was then transferred into a special device for continuous extraction[4] and II was purified and isolated by extraction with diethyl ether from alkaline and acidic medium. Based on an activity account for $^{14}CO_2$, the yield was 1.25 mmol = 90%.

1-hydroxy-3-(p-chloro phenyl)-(1-^{14}C)propane (III)

This reaction as well as all following reactions, was carried out in the extraction apparatus mentioned before[4].
The etherical solution of II was evaporated to dryness. After drying the residue by azeotropic distillation with benzene, the benzene was replaced by tetrahydrofuran and 1.0 mmol of solid $LiAlH_4$ was slowly added. The resulting reaction mixture was refluxed for 2 hours and the excess $LiAlH_4$ was decomposed by carefully adding 10 ml of water. The precipitate was dissolved by adding 2N sulfuric acid and III was isolated by continuous extraction with diethyl ether and subsequently freed from acid by extraction with alkali. After distilling off the solvent, III was dried by azeotropic distillation with benzene at reduced pressure. Yield[4] 1.19 mmol = 95%.

1-chloro-3-(p-chloro phenyl)-(1-^{14}C)propane (IV)

To the solution of 1.19 mmol III in 10 ml benzene was added 1 ml of $SOCl_2$ and a few drops of pyridine. The mixture was stirred for one hour at room temperature and half an hour at 80°C. After cooling to room temperature the excess of $SOCl_2$ was distilled off, 20 ml of an aqueous 5% sodium carbonate solution was added and IV was isolated by continuous extraction with diethyl ether. Yield 1.06 mmol = 90%.

1-cyano-3-(p-chloro phenyl)-(1-^{14}C)propane (V)

After distilling off the diethyl ether, IV was dissolved in 10 ml of dimethyl sulfoxide and 20 mmol of finely ground sodium cyanide were added. The reaction mixture was stirred and heated at 90°C for 20 minutes. Thereafter 100 ml of water were added and V was isolated by continuous extraction with petroleum ether b.p. 28-40°C. Yield 1.01 mmol = 95%.

4-(p-chloro phenyl)-(2-^{14}C)butyric acid (VI)

After distilling off the solvent, V was saponified by refluxing for 3 hours with 5 grams of NaOH and 5 grams of KOH in a mixture of 10 ml of water and 15 ml of glycol. The butyric acid VI was purified and isolated by continuous extraction with diethyl ethor from alkaline and acidic medium. Yield 0.99 mmol = 98%.

7-chloro-(2-^{14}C)tetralone-1 (VII)

Acid VI was freed from solvent and azeotropically dried with benzene. the benzene was then distilled off under reduced pressure and ring closure was carried out similar to the procedure described by House et al.[6]. To VI was added polyphosphoric acid, prepared from 6 ml of 85 % phosphoric acid and 10 grams of P_2O_5. The reaction mixture was stirred and heated for 1-2 hours at 110-120^{o}C, whereafter the vessel was cooled to 0^{o}C and crushed ice was added. Tetralone VII was isolated by continuous extraction with diethyl ether. Yield 0.94 mmol = 95%.

7-chloro-(2-^{14}C)tetralin (VIII)

The etherical solution of VII was distilled to dryness whereafter 10 ml of benzene and 10 ml of 6N hydrochloric acid were added. Tetralone VII was reduced to tetralin VIII by refluxing and vigorously stirring of this solution with about 4 grams of amalgated zinc for 12 hours. Product VIII was isolated by continuous extraction with petroleum ethor b.p. 40-60^{o}C and purified by chromatography on Al_2O_3. Yield 0.85 mmol = 90%.

Amalgated zinc was prepared in the following way. Zinc grains (40 mesh) were washed with 0.1N hydrochloric acid and with water. Then 10 ml of water and a few drops of a saturated mercurichloride solution were added, the mixture was shaken for a few minutes and the amalgated zinc was decanted and 3 times washed with water.

(2-^{14}C),(7-^{3}H)tetralin (IX)

The isolated chlorotetralin VIII was purified by temperature programmed GLC on 5% w/w Carbowax 20M + 5% w/w KOH on Chromosorb-W. The compound was trapped in a way described elswhere[7].

Catalytic dehalogenation with tritium gas and purification of the final product were carried out as published elswhere[5]. Yield 0.72 mmol = 85%.

2-chloro-(7-^{14}C)naphthalene (X)

From a solution of 1.2 mmol of VIII (not purified by GLC) in petroleum ether, the solvent was distilled off, replaced by benzene and azeotropically dried. In a nitrogen atmosphere 5 equivalents of 2.3-dichloro-

5.6-dicyano-quinone (DDQ) were added and the mixture was refluxed for 16 hours[8]. After the addition of 10 ml of water the mixture was refluxed for 30 minutes, cooled to room temperature and 10 ml of a 5% solution of NaOH in water were added. The reaction mixture was then vigorously stirred untill all solid compounds were dissolved. Chloronaphthalene X was isolated by continuous extraction with petroleum ether b.p. 28-40^{o}C. Yield 0.96 mmol = 80%.

<u>(2-^{14}C),(7-^{3}H)naphthalene (XI)</u>

Compound X was purified and trapped as described for compound VIII. The catalytic dehalogenation with tritium gas and the purification of the final product were carried out as published elswhere[5]. Yield 0.76 mmol = 80%.

<u>7-chloro-(1-^{14}C)tetralone-1 (XIV)</u>

This compound was prepared in the same way as 7-chloro-(2-^{14}C)tetralone-1 (VII), but this time from 4-(p-chloro phenyl)-(1-^{14}C)butyric acid (XIII). Butyric acid XIII was obtained by reaction of $^{14}CO_2$ with the Grignard of 1-bromo-3-(p-chloro phenyl)propane (XII) in the way described for compound II. Overall yield of XIV from $^{14}CO_2$ was 80%.

<u>(1-^{14}C),(7-^{3}H)tetralin (XVI)</u>

Synthetic route and purification were the same as for compound IX. Overall yield from XIV was 70%.

<u>(1-^{14}C),(7-^{3}H)naphthalene (XVIII)</u>

Synthetic route and purification were the same as for compound XI. Overall yield from XIV was 55%.

ACTIVITY ACCOUNT AND RADIOCHEMICAL PURITY.

Representative results of series of reactions starting from $^{14}CO_2$ and ending with 7-chloro-(2-^{14}C)tetralin (VIII) and 2-chloro-(7-^{14}C)naphthalene (X) are listed in Table I.

All compounds, except $^{14}CO_2$, were purified by GLC as described and subsequently dissolved in benzene. The concentration of this solution was determined by GLC by comparison with a series of standard solutions. The activity of the solution was determined by liquid

Table I.

compound	spec.act. (μC/mmol)	specificity	overall yield (%)
$^{14}CO_2$	11.60 ± 2%	--	--
VIII	11.57 ± 3%	≥ 97%	61
X	11.60 ± 3%	--	49
XV	11.62 ± 3%	≥ 97%	72
XVII	11.60 ± 3%	--	57

scintillation counting.*

In the same way the change in the specific activity was checked in a reaction series leading to 7-chloro-(1-^{14}C)tetralin (XV) and 2-chloro-(8-^{14}C)naphthalene (XVII). The results which indicate that no change in specific activity took place during the synthesis, are also summarized in Table I.

Location of the ^{14}C-label

In order to ascertain the radiochemical purity of the final compounds with respect to the location of the ^{14}C-label, some of the precursors were degraded.

a. degradation of 7-chloro-(1-^{14}C)tetralin (XV)

About 0.2 mmol of XV was converted into (1-^{14}C)tetralin by the procedure described for XVI. This tetralin was diluted with pure inactive tetralin to a specific activity of 2.60 μC/mmol. The oxidation of (1-^{14}C)tetralin to phthalic acid was carried out in the following way[9]. About 100 mg of the diluted (1-^{14}C)tetralin was refluxed with 10 ml of water and an equivalent amount of potassium permanganate was slowly added. After refluxing for about 16 hours a small amount of solid potassium permanganate was added again and the mixture was cooled to about 60°C. After acidifying with 20 ml of 10% sulfuric acid gas evolution took place and the mixture was heated for 30 minutes at 40-50°C. The

* Nuclear Chicago, Unilux I, Model 6850.

phthalic acid was isolated by continuous extraction with diethyl ether. After drying the etherical solution with sodium sulfate, an excess of an etherical solution of diazomethane was added. The dimethyl phthalate was recovered and purified by GLC on Reoplex 400. The specific activity of this ester, determined by gaschromatographic concentration determination and liquid scintillation counting, was 2.68 μC/mmol. Within the limits of the experimental error these results indicate a specificity of the labeling at the 1-position of ≥ 97%.

b. degradation of 7-chloro-(2-^{14}C)tetralin (VIII)

Compound VIII was converted into dimethyl phthalate in the same way as described above. The specific activity of the diluted tetralin of 1.18 μC/mmol was reduced to 0.015 μC/mmol for the dimethyl phthalate, indicating a specificity of the labeling at the 2-position of ≥ 97%.

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