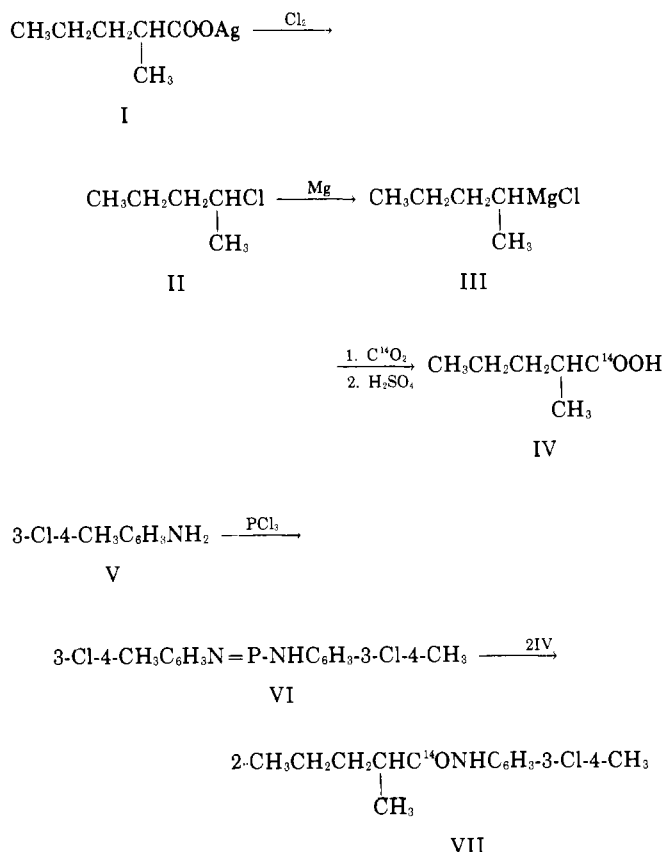


# Synthesis of *N*-(3'-Chloro-4'-methylphenyl)-2-methylpentanamide-1-C<sup>14</sup>

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*N*-(3'-Chloro-4'-methylphenyl)-2-methylpentanamide-1-C<sup>14</sup>, a radiotagged form of the selective herbicide solan, was prepared for use in fundamental biological studies. To achieve the synthesis, isomerically pure 2-chloropentane, which was prepared by the reaction of silver 2-methylpentanoate with chlorine, was converted to the Grignard reagent which was reacted with carbon-14 dioxide. The resulting acid reacted with *N,N'*-bis-(3-chloro-4-methylphenyl)-phosphenimidous amide, which was obtained from the reaction of 3-chloro-4-methylaniline with phosphorus trichloride, and the desired compound was obtained with an overall radioyield of 62%.

*N*-(3'-Chloro-4'-methylphenyl)-2-methylpentanamide is the selective herbicide solan, which is used commercially primarily in tomato culture. A sample radiotagged in the 1-position was required for fundamental biological studies and the following scheme was used for the preparation:



Although 2-methylpentanoic-1-C<sup>14</sup> acid (IV) has been prepared previously in very small quantities and with very low activities as part of inseparable mixtures by irradiation of pentane and C<sup>14</sup>O<sub>2</sub> with x-rays, (1), or with β-rays (7), these methods were not suitable for the synthesis of larger quantities of pure materials.

2-Bromopentane, which might conceivably have replaced 2-chloropentane (II) in the synthesis, was available commercially, but was unsuitable for our purposes because gas phase chromatography (GPC.) showed that the commercial

sample was a mixture of 2- and 3-bromopentane. Also, preliminary experiments showed that this bromide gave poor yields of Grignard reagent.

Prior workers have shown that secondary alkyl halides frequently consist of mixtures of isomers unless special methods of preparation are used (2-4, 8, 10, 11). The next lower homolog of 2-chloropentane, namely 2-chlorobutane, had been prepared by reaction of the silver salt of 2-methylbutyric acid with chlorine (5), although in this case only one secondary butyl chloride is possible. The silver salt of 2-methylpentanoic acid has reacted with bromine to give 2-bromopentane (3).

The above considerations led us to choose to prepare 2-chloropentane as outlined in the scheme above, with expectation that a satisfactory yield of pure isomer would be obtained from the same acid which serves as the starting point for the preparation of commercial solan. We also expected that the Grignard reagent from the chloride would be obtained in better yield than the analogous reagent from the bromide. This approach resulted in a product, which was shown to be pure 2-chloropentane by its GPC and its infrared spectrum (I.R.). Other acids had been prepared by carbonation of a Grignard reagent with C<sup>14</sup>O<sub>2</sub> (6). A preliminary run with C<sup>12</sup>O<sub>2</sub> proved that pure 2-methylpentanoic acid could be obtained, as indicated by GPC and I.R. The subsequent run with C<sup>14</sup>O<sub>2</sub> gave a 77% chemical yield of IV.

The use of *N,N'*-bis-(3-chloro-4-methylphenyl)-phosphenimidous amide (VI) for the preparation of VII was based on its successful use in a nonradioactive synthesis (9). Preliminary work indicated that the product from this reagent was more easily purified than the product obtained from the reaction of the acyl chloride and the amine, while the yields by both methods were the same. The chemical yield for the final step of the radio synthesis was 84%, and the radioyield for the entire synthesis was 62%. There was obtained 1.3 grams of *N*-(3'-chloro-4'-methylphenyl)-2-methylpentanamide-1-C<sup>14</sup> (VII) with an activity of 3.55 μc./mg. which was shown to be pure by GPC and I.R. Some less pure material with lower activity was also obtained.

## EXPERIMENTAL

**2-Chloropentane (II).** 2-Methylpentanoic acid (Matheson, Coleman and Bell, P8065) after purification by rectification had b.p. 102-3° (20 mm. of Hg), *n*<sub>D</sub><sup>20</sup> 1.4123, had only one peak in its GPC and gave a satisfactory I.R. spectrum. The acid was neutralized with aqueous potassium hydroxide solution and then converted at 80° with aqueous silver nitrate to the silver salt (I) in 81% yield.

A solution of 0.22 mole of chlorine in 120 ml. of nitrobenzene was added with stirring during 0.5 hr. to 0.2 mole of I suspended in 100 ml. of nitrobenzene maintained at 15° C. Rapid evolution of carbon dioxide occurred after the addition was complete. The filtrate from the reaction mixture was distilled through a Vigreux column until the pot temperature reached 98° (20 mm. of Hg), the boiling point of nitrobenzene. The crude product, which had been condensed with a dry ice condenser, was washed with dilute sodium thiosulfate solution to remove chlorine and was dried with magnesium sulfate. The 2-chloropentane distilled at 94–5° (760 mm. of Hg), had an  $n_D^{25}$  1.4052, and was obtained in 43% yield. The absence of impurities was shown by the I.R. spectrum and GPC. Previous workers (8) reported the following constants: b.p. 94.8–95.3°,  $n_D^{20}$  1.4068.

**2-Methylpentanoic-1-C<sup>14</sup> Acid(IV).** Grignard reagent was prepared from 0.0105 gram atoms of magnesium, 0.010 mole of 2-chloropentane, and 20 ml. of ethyl ether with the aid of a crystal of iodine under a nitrogen blanket. Carbon-14 dioxide was generated into an evacuated apparatus from 0.0432 grams ( $2.19 \times 10^{-4}$  mole) of BaC<sup>14</sup>O<sub>3</sub>, containing 10.07 mc. of activity, and 5 ml. of water by addition of 5 ml. of 2N HCl. The gas was dried by passage over CaCl<sub>2</sub> and was condensed in a trap with liquid nitrogen. The Grignard reagent was chilled in a liquid nitrogen bath, and the C<sup>14</sup>O<sub>2</sub> was transferred to the evacuated reaction flask by allowing the C<sup>14</sup>O<sub>2</sub> trap to warm to room temperature. The reaction flask was allowed to warm up to –20° C. and C<sup>12</sup>O<sub>2</sub> was swept through the apparatus into the stirred Grignard flask held at about 0° C. until no further absorption of C<sup>12</sup>O<sub>2</sub> occurred, as evidenced by the fact that a mercury filled capillary manometer no longer indicated any fall in pressure. The reaction apparatus was vented, was warmed to room temperature, and 10 ml. of 25% sulfuric acid was added to the Grignard flask. After the solids dissolved, the liquid layers were separated and the lower aqueous layer was extracted with ether. The combined ether layers containing the 2-methylpentanoic-1-C<sup>14</sup> acid were extracted with standard NaOH, and titration with H<sub>2</sub>SO<sub>4</sub> indicated that the chemical yield of IV was 77%. After acidification,

**N - (3' - Chloro - 4' - methylphenyl) - 2 - methylpentanamide-1-C<sup>14</sup>(VII).** 3-Chloro-4-methylaniline(V) (0.00835 mole) and 5 ml. of toluene were stirred while 0.0033 mole of phosphorus trichloride was added slowly. The reaction mixture consisting of crude N,N'-bis-(3-chloro-4-methylphenyl)-phosphonimidous amide(VI) was then heated with an oil bath at 80° while the toluene solution containing 0.0076 mole of IV was added during five minutes. The mixture first was heated for one hour with the bath at 105° and then was refluxed for 2.5 hours with the bath at 125°. The aqueous solution was extracted with ether. This ether extract containing the IV was mixed with 5 ml. of toluene and was distilled through a small packed column, to remove the ethyl ether. The distillation was stopped when the vapor reached 109° (760 mm. of Hg) and the pot temperature was 114°. The toluene solution remaining in the pot contained the IV.

A similar run was carried out entirely with C<sup>12</sup>O<sub>2</sub> to verify the purity of the product. The 2-methylpentanoic acid obtained by evaporation of the final ether extracts (instead of distillation with toluene) was pure, as indicated by GPC and I.R. spectroscopy.

After the reaction mixture had cooled, it was extracted with 5% sodium hydroxide solution, which dissolved the complex phosphorous acid, and then with water. Extractions with 10% hydrochloric acid removed the unreacted amine, and these washes were followed by water washes. The same 10 ml. portion of toluene was used to extract each of the aqueous extracts in the order in which they were used. The toluene wash was combined with the washed

reaction solution, and the solvent was removed by vacuum distillation up to a bath temperature 100°. The crude N-(3'-chloro-4'-methylphenyl)-2-pentanamide-1-C<sup>14</sup>, 1.60 grams, left in the pot represented a chemical yield of 84% for the last step or 65% for the two radio steps. The crude product was recrystallized 5 times from isooctane, and 1.03023 grams of VII obtained, m.p. 79–82°, 3.55 $\mu$ c./mg. activity, which gave a satisfactory I.R. spectrum and a satisfactory GPC. The radio count was done on a combusted sample by the New England Nuclear Laboratories. Nonradioactive VII had m.p. 83–4°.

Nonradioactive VII, 0.416 grams, was added to the first mother liquor from radio-VII, and recrystallized. These crystals were then recrystallized from each succeeding mother liquor until the final crystals which were obtained weighed 0.5730 grams with m.p. 74–81° and 2.25 $\mu$ c./mg. activity. A second portion of nonradioactive VII, 0.1932 grams, was recrystallized from the combined mother liquors to give 0.2166 grams of crystals with m.p. 68–80° and 1.61 $\mu$ c./mg. activity. Thus, a total of 6.29 $\mu$ c. of radio VII was obtained, which corresponds to an isolated radioyield of 62%.

#### INFRARED SPECTRA

Infrared spectra were determined with a Baird Model 4-55 apparatus. Solid samples were determined in a potassium bromide pellet while liquid samples were determined in 0.028 mm. cell with sodium chloride windows.

#### GAS PHASE CHROMATOGRAPHY

The liquids were chromatographed in a 20 ft. stainless steel tube, ¼ inch o.d., packed with 30-60 mesh Fluoropak 80 coated with 10% Apiezon Grease L liquid phase. An F&M model 500 apparatus was used, and the carrier gas was helium. For 2-chloropentane, the column temperature was 90°; for 2-methylpentanoic acid, 175°.

VII was chromatographed at 220° C. in a 12 ft. column, 4 mm. i.d., packed with 60-80 inch glass beads coated with 0.1% by weight Hochvacuum Fett R. An F&M model 500 apparatus was used with helium carrier gas.

#### ACKNOWLEDGMENT

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