SHORT COMMUNICATIONS

THE SYNTHESIS OF 4-CHLORO-2-[^{14}C]METHYLPHENOXYACETIC ACID (" METHOXONE ")*

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In recent years 4-chloro-2-methylphenoxyacetic acid (" Methoxone ") has become an accepted selective herbicide. As part of a study of the translocation and metabolism of this compound in plants a sample labelled in the methyl group with ^{14}C was required by our colleague, Mr. C. G. Greenham.§ The synthesis from barium [^{14}C]carbonate is described here. " Methoxone " does not appear to have been labelled with ^{14}C previously, but Sorensen (1951) labelled the compound with ^{36}Cl for use in isotope dilution analysis.

Some of the 4-chloro-2-[^{14}C]methylphenoxyacetic acid has been tested on bean plants. Although a small amount of the radioactive carbon (less than 1 per cent.) is converted to carbon dioxide, the labelled compound is suitable for a number of investigations. The work is continuing (Greenham, personal communication).

[^{14}C]Carbon dioxide was converted to [*carboxy*-^{14}C]salicylic acid by the Kolbe reaction using a procedure similar to that of Mandel and Smith (1950). The salicylic acid was reduced by lithium aluminium hydride to *o*-hydroxy-[*alcoholic*-^{14}C]benzyl alcohol which was further reduced by Raney alloy to yield [*Me*-^{14}C]*o*-cresol (Papa, Schwenk, and Whitman 1942). Neither of these intermediates was isolated. The *o*-cresol was converted directly to *o*-[^{14}C]methylphenoxyacetic acid by reaction with chloroacetic acid. Chlorination of this compound in glacial acetic acid at 100 °C (Sorensen 1951) gave the crude product which was purified by paper chromatography. The overall yield of the pure " Methoxone " from barium carbonate was about 10 per cent. However, as only one radioactive run was performed this yield could probably be improved. Although the chlorination reaction produced only 36 per cent. of the product, the unchlorinated acid was recovered and could be used again.

Experimental

The radiochemical yield at each stage was determined by carrier dilution analysis. All samples were counted at infinite thickness in polythene disks (Popják and Beeckmans 1950) with a thin end-window Geiger-Mueller tube. Melting points are uncorrected.

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[Carboxy-^{14}C]*salicylic Acid.*—Freshly cut sodium (73·7 mg) was dissolved in dry ethanol (2 ml) in a glass tube (about 20 by 1·3 cm) with a constriction near the open end. A solution of phenol (314 mg) in ethanol (1 ml) was then added and the solution evaporated to dryness in a stream of nitrogen. The tube was attached to a vacuum manifold (Calvin *et al.* 1949) and evacuated to less than 10^{-3} mm Hg for several hours to remove the last traces of ethanol. Carbon dioxide (1 mMole; 790 μc; generated from $Ba^{14}CO_3$ obtained from the Radiochemical Centre, Amersham, England) was then condensed into the tube by means of liquid oxygen and the tube sealed off *in vacuo*. The tube was allowed to warm to room temperature and was then heated at 140 °C for 20 hr inside a steel container. After cooling to room temperature, the contents of the tube were dissolved in water, acidified, and extracted with ether. The ethereal solution was extracted with aqueous sodium bicarbonate. Acidification of the aqueous extract yielded crude [*carboxy*-^{14}C]salicylic acid (yield 135·6 mg, 98 per cent. based on $BaCO_3$; 785 μc/mMole), m.p. 150–156 °C. Paper chromatography of this material in *n*-butanol-5N ammonium hydroxide indicated that the salicylic acid was contaminated with approximately 1·5 per cent. *p*-hydroxybenzoic acid. The crude salicylic acid was recrystallized from water (121 mg), m.p. 158–159 °C (lit. 159 °C). [*Carboxy*-^{14}C]salicylic acid was prepared in this way several times in connection with other work, the yield of the recrystallized product never being less than 70 per cent. A portion of this high specific activity material was diluted with carrier for the subsequent reactions.

2-[^{14}*C*]*Methylphenoxyacetic Acid.*—An ethereal solution of [*carboxy*-^{14}C]-salicylic acid (181 mg; 161 μc; 123 μc/mMole) was treated with lithium aluminium hydride (Brown 1951) to yield *o*-hydroxy[*alcoholic*-^{14}C]benzyl alcohol as an extract in 10 per cent. aqueous sodium hydroxide. This extract was treated with Raney alloy according to the method of Papa, Schwenk, and Whitman (1942). The resulting alkaline solution of [*Me*-^{14}C]*o*-cresol (radiochemical yield 70·0 μc, 44 per cent.) was converted directly to 2-[^{14}C]methylphenoxyacetic acid (62 mg, 28 per cent. based on $BaCO_3$; 118 μc/mMole), m.p. 152 °C (lit. 152 °C) by reaction with chloroacetic acid.

4-Chloro-2-[^{14}*C*]*methylphenoxyacetic Acid.*—Chlorine (5 per cent. in excess of the theoretical amount) was generated by the method of Brown, Gillies, and Stevens (1953) and carried in a stream of N_2 into a solution of 2-[^{14}C]methylphenoxyacetic acid (62 mg) in glacial acetic acid (25 ml). The crude product was chromatographed on four sheets (20 by 45 cm) of Whatman No. 3 MM paper, using *iso*amyl alcohol-5N ammonium hydroxide as the solvent. Autoradiography (with "Kodirex" film) of the developed chromatograms revealed the presence of two radioactive bands, one (R_F 0·33) corresponding to unchanged starting material and the other (R_F 0·57) to the product. The "Methoxone" bands were eluted with water and the aqueous solution decolorized with charcoal, filtered, and finally freeze-dried to yield "Methoxone" as the ammonium salt (yield 29·4 mg, 10·3 per cent. based on $BaCO_3$; 120 μc/mMole). The product was found to be at least 99 per cent. radiochemically pure when examined by chromatographic techniques and by carrier dilution analysis.

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