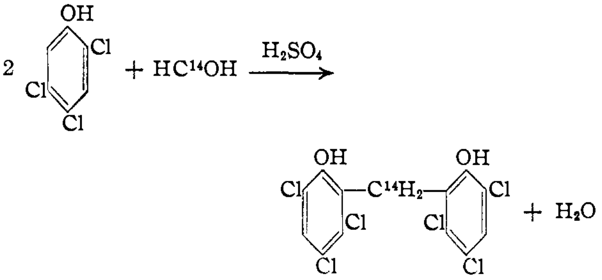

Hexachlorophene-C^{14} (m.p. 166–167°, cor.) was isolated in a 59.6% over-all chemical yield as two crops, in the second of which 12.5% was recovered with carrier; specific activity (of undiluted product): 3.58×10^8 ($\pm 4.6\%$) cts./min./mM.[3]; specific activity of starting formaldehyde-C^{14}: 3.52×10^8 ($\pm 4.4\%$) cts./min./mM.[4]; radiochemical yield: $60.6 \pm 3.9\%$.

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(3) Counted as a film (<0.01 mg./cm.²) in a proportional flow counter. A geometry of ~55% was estimated for this counter from the data of W. E. Graf, *et al.*, *Nucleonics*, **9**, No. 4, 22 (1951). The per cent. error shown includes errors of counting and pipetting.

(4) Counted as a film (<0.01 mg./cm.²) of the dimedone derivative.

RADIOISOTOPE LABORATORY
U. S. TESTING COMPANY, INC.
HOBOKEN, N. J., AND THE
RESEARCH LABORATORIES OF THE
GIVAUDAN CORPORATION
DELAWANNA, N. J.

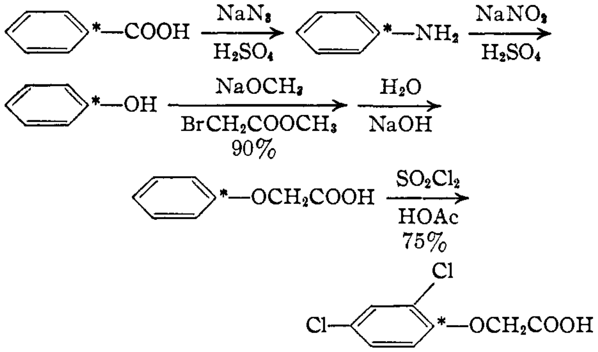
Synthesis of 2,4-Dichlorophenoxyacetic Acid Labeled with Isotopic Carbon[1]

BY MELVIN FIELDS, SEYMOUR ROTHCHILD AND MORRIS A. LEAFFER

Investigation of the synthesis of carbon-14 labeled 2,4-dichlorophenoxyacetic acid, 2,4-D, was undertaken with the purposes of preparing samples of this plant growth regulator labeled at each of the carbon atoms of the acetic acid chain and in the aromatic ring, and of developing procedures suited to the ultimate preparation of material with high specific activity. After our work had been completed there was reported the synthesis of carboxyl labeled 2,4-D from potassium acetate in yields of 36–72%.[2] By the procedure described in this communication the conversion of sodium acetate to side chain-labeled 2,4-D was achieved in yields of 75–80% and the transformation of ring labeled benzoic acid to 2,4-D was accomplished in yields of 25–45%.

The conversion of 1 millimole of tagged sodium acetate to carboxyl or methylene labeled 2,4-D was achieved by bromination of the acetate with a mixture of red phosphorus and bromine containing 0.1 millimole of freshly distilled acetyl chloride and 1 millimole of anhydrous hydrogen chloride, followed by treatment of the bromoacid with an excess of 2,4-dichlorophenol in alkaline solution.

The preparation of 2,4-dichlorophenoxy-1-C^{14} acetic acid from benzoic acid-1-C^{14}[3] was accomplished by the following sequence of reactions



The concentration of the sulfuric acid employed in the Schmidt reaction with benzoic acid plays a significant role in determining the yield of aniline. In Table I are summarized the results observed with 96–100% sulfuric acid; under comparable conditions with 75% sulfuric acid, the yield of aniline is reported to be only 15%.[4]

TABLE I

EFFECT OF CONCENTRATION OF SULFURIC ACID IN SCHMIDT REACTION

Concn. sulfuric acid	Yield, % Aniline hydrochloride (uncorrected)	Benzoic acid recovered	Aniline hydrochloride (corrected)
96	60–65	20–25	75–87
98	71	13	89
100	91	0	91

An increase in the amount of sodium azide or of the quantity of 96% sulfuric acid used appeared to have no appreciable effect on the extent of the conversion. Although 100% sulfuric acid has been employed in the Schmidt reaction with hindered aromatic acids,[5] the advantage of its use with unhindered acids does not appear previously to have been noted.

Several procedures for the chlorination of phenoxyacetic acid were investigated. With excess sulfuryl chloride in glacial acetic acid solution at 75°, 2,4-D was obtained in 74% yield. With this reagent in the absence of a solvent, phenoxyacetic acid was converted to the *p*-chloro derivative while in boiling carbon tetrachloride no reaction was observed. As reported by Haskelberg[6] reaction with chlorine gas in acetic acid solution afforded 2,4-D in 75% yield; on a small scale, however, regulation of the quantity of chlorine is troublesome, and an excess of the reagent leads to formation of the 2,4,6-trichloro derivative.[6] Chlorination of phenoxyacetic acid with alkaline hypochlorite gave 2,4-D in at best 59% yield as compared with a reported yield of 75%.[7]

The specific activities of the 2,4-dichlorophenoxyacetic acid-1-C^{14} and -2-C^{14} were 1.1×10^4 and

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(1) This paper is based upon work done for the Biological Department, Chemical Corps, Camp Detrick, Frederick, Maryland, under Contract No. DA-18-064-CML-10 with Tracerlab, Inc.

(2) H. R. Mahler, R. J. Speer and A. Roberts, *Science*, **110**, 562 (1949).

(3) M. Fields, M. A. Leaffer and J. Rohan, *ibid.*, **109**, 35 (1949).

(4) L. H. Briggs, G. C. DeAth and S. R. Ellis, *J. Chem. Soc.*, 61 (1942).

(5) M. S. Newman and H. C. Gildenhorn, THIS JOURNAL, **70**, 317 (1948).

(6) L. Haskelberg, *J. Org. Chem.*, **12**, 426 (1947).

(7) C. Y. Hopkins and M. J. Chisholm, *Can. J. Research*, **24**, 208 (1946).

1.2×10^4 c./sec./mg., respectively; that of the ring-labeled compound was 235 c./sec./mg.[8]

Experimental

2,4-Dichlorophenoxyacetic Acid from Bromoacetic Acid.—From the reaction of 139 mg. of bromoacetic acid with a fifteen-fold excess of 2,4-dichlorophenol in sodium hydroxide solution, 210 mg. (95%) of 2,4-D, m.p. 138.5–139.5°, was isolated.

Conversion of Sodium Acetate to 2,4-D.—Thirty-seven and one-half milligrams (1 millimole) of anhydrous hydrogen chloride, 7.9 mg. (0.1 mM.) of freshly distilled acetyl chloride and 192 mg. (1.2 mM.) of bromine were distilled under high vacuum into a 25-ml. r.b. flask chilled in liquid nitrogen containing 82 mg. of sodium acetate and 1.5 mg. of red phosphorus. The flask, sealed in vacuum, was immersed in a boiling water-bath until the bromine color had nearly disappeared (1 to 5 hours). The product was dissolved in 1 cc. of water and converted to 2,4-D as already described. Consistent yields of 75–80% from sodium acetate were obtained. Omission of the hydrogen chloride and acetyl chloride from the bromination mixture lowered the over-all yield to 40–63%.

Aniline.—Ten grams of sodium azide was added over a period of 50 minutes to a rapidly stirred mixture of 12.2 g. of benzoic acid, 80 ml. of chloroform and 40 ml. of 100% sulfuric acid maintained at 40°. When the evolution of nitrogen had ceased, the reaction mixture was diluted with water and made alkaline; extraction with ether and treatment with hydrogen chloride afforded 11.8 (91%) of aniline hydrochloride; m.p. 194.5°.

Phenol.—Diazotization of 13.00 g. of aniline hydrochloride followed by hydrolysis of the diazonium salt gave 7.04 g. (75%) phenol, b.p. 95° (25 mm.).

Phenoxyacetic Acid.—Methyl phenoxyacetate, prepared from sodium phenoxide and methyl bromoacetate, was hydrolyzed in dilute sodium hydroxide solution, which on acidification yielded phenoxyacetic acid, m.p. 97–98°[9] in 90% yield.

2,4-Dichlorophenoxyacetic Acid.—The temperature of a mixture of 1.74 g. of phenoxyacetic acid, 0.39 g. of sulfuryl chloride and 7 ml. of glacial acetic acid was slowly raised from 0 to 75° and then maintained at the latter temperature until gas evolution ceased. Dilution of the reaction mixture with water and crystallization of the precipitate from benzene afforded 1.87 g. (74%) 2,4-D, m.p. 137–138°.

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[8] All samples were converted to barium carbonate and counted using the upper shelf of a Tracerlab lead pig and a Tracerlab TGC-2 Geiger–Müller tube with a 1.0 mg./cm.^{2} mica window.

[9] R. Fusco and F. Mazzucchi, *Gazz. chim. ital.*, **71**, 406 (1941); *C. A.*, **37**, 121 (1943).

BOSTON 10, MASS. RECEIVED JULY 18, 1951

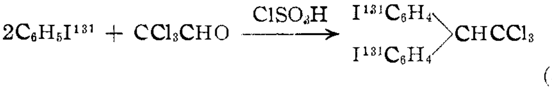
Synthesis of Radioactive Iodine[131] Analog of DDT[1]

BY JENS A. JENSEN AND GEORGE W. PEARCE

The iodine^{131} analog, 1,1,1-trichloro-2,2-bis-(*p*-iodo^{131}-phenyl)-ethane, of DDT has been prepared by the steps

$$C_6H_5NH_2 + HNO_2 \xrightarrow[NaNO_2]{HCl} C_6H_5N_2Cl \qquad (1)$$

$$C_6H_5N_2Cl + NaI^{131} \longrightarrow C_6H_5I^{131} \qquad (2)$$



$$2C_6H_5I^{131} + CCl_3CHO \xrightarrow{ClSO_3H} \begin{matrix} I^{131}C_6H_4 \\ I^{131}C_6H_4 \end{matrix}\!\!>\!CHCCl_3 \qquad (3)$$

The method of Lucas and Kennedy[2] was used for the first two steps. Twenty-two millimoles of aniline was converted to 15 millimoles of iodobenzene, using 22 millimoles of NaI in which 25 millicuries of NaI^{131} was incorporated. The steam distilled product plus 6 millimoles of inactive iodobenzene was condensed with 8 millimoles of chloral using chlorosulfonic acid as condensing agent. Recrystallization of the crude product from 1 to 1 acetone–alcohol gave 1.42 g. (2.6 millimoles) of DI*DT, m.p. 173–174°, 25% yield based on iodobenzene. Activity recovery was 22.4% corrected for decay, but not for inactive iodobenzene added. Specific activity was 2.5 microcuries per milligram. The synthesis can be completed in 2–3 days.[3]

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[1] From the Technical Development Branch, Communicable Disease Center, U. S. Public Health Service, Federal Security Agency, Savannah, Georgia.

[2] "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1946, p. 351.

[3] For a detailed description order Document 3488 from American Documentation Institute, 1719 N Street, N. W., Washington 6, D. C., remitting $1.00 for microfilm (images 1 inch high on standard 35-mm. motion picture film) or $1.20 for photocopies (6 × 8 inches) readable without optical aid.

TECHNICAL DEVELOPMENT BRANCH
SAVANNAH, GEORGIA RECEIVED AUGUST 16, 1951

A Preparation of C[14] Labeled Isopropyl N-Phenylcarbamate[1,2]

BY ALBERT V. LOGAN AND JOSEPH MURRAY[2]

The preparation of C^{14} labeled isopropyl N-phenylcarbamate (IPC) was undertaken as the initial phase of a plan to study the mode of action of the compound upon many weedy annual grasses. The experimental procedures described here were adopted as the most economical and best suited for the preparation of the IPC. Plant studies are underway at the present time utilizing the radioactive compound.[3]

Experimental

Acetic acid labeled with C^{14} in the carbonyl group was prepared by a modification of the Grignard method used by Van Bruggen.[4] The yields on two separate runs were 69.1 and 77.3% based on the BaC^{14}O$_3$ used. The radioactive barium acetate (254 mg., 0.995 millimole) obtained from the neutralization of the acetic acid was placed in a combustion tube backed by an equal amount of inactive barium acetate in a separate boat. Pyrolysis was carried out under vacuum at 500°.[5] The resulting carbonyl labeled acetone was collected in a liquid nitrogen cooled trap. The acetone was redistilled and reduced by the action of lithium aluminum hydride[6] in ether solution. The labeled isopropyl alcohol was dried over recalcined calcium oxide and vacuum transferred to a dry reaction vessel.

The IPC was prepared by heating 0.3 ml. of phenyl isocyanate with the isopropyl alcohol at 80° for three hours. The product was crystallized from boiling heptane; 160 mg. of IPC, m.p. 84–85°, was obtained. A second crop of crystals 164 mg., m.p. 79–80°, was obtained from the mother liquor. The yield of pure compound was 38% based upon BaC^{14}O$_3$ used and barium acetate added. The over-all

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[1] Published with the approval of the Monograph Publications Committee, Oregon State College, as Research Paper No. 191, School of Science, Department of Chemistry.

[2] This note is based on a thesis submitted by Joseph Murray in partial fulfillment of the requirements for the degree of Master of Science at Oregon State College, June, 1950.

[3] For detailed experimental description order Document 3564 from American Documentation Institute, 1719 N Street, N. W., Washington 6, D. C., remitting $1.00 for microfilm (images 1 inch high on standard 35-mm. motion picture film) or $1.00 for photocopies (6 × 8 inches) readable without optical aid.

[4] J. T. Van Bruggen, C. K. Claycomb and T. T. Hutchens, *Nucleonics*, **7**, 45 (1950).

[5] A. V. Grosse and S. Weinhouse, *Science*, **104**, 402 (1946).

[6] R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 1197 (1947).