$H_2S^{35}O_4$[5] and then converting to sulfanilic acid using a small scale modification of the baking method of Huber.[6] The yields were about 95% for 50 mg. and 60 to 70% for 2 to 5 mg. batches. The product contained less than 0.2% of ortho or meta isomers and two recrystallizations from carrier sulfate reduced the free $S^{35}O_4^{=}$ to less than 0.2% of the total S^{35}. Not more than 0.6% of the sulfanilic acid sulfur exchanged with free sulfate in acid, basic, or neutral solution in 55 days at 80°.

Full experimental details of this preparation are available on microfilm.[7]

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(5) Obtained from the Isotopes Division of the U. S. Atomic Energy Commission, Oak Ridge, Tennessee.

(6) W. Huber, *Helv. Chim. Acta*, **15**, 1372 (1932).

(7) For full experimental details of this preparation order Document 3489 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.

DEPARTMENT OF BACTERIOLOGY AND PARASITOLOGY
UNIVERSITY OF CHICAGO
CHICAGO 37, ILLINOIS
RECEIVED DECEMBER 15, 1951

Small Scale Synthesis of Several Carbon-14 Labeled α-Hydroxy Acids[1]

BY D. M. HUGHES, R. OSTWALD[2] AND B. M. TOLBERT

For a series of biological studies the preparation of the two singly labeled glycolates and the three singly labeled lactates was undertaken as follows[3–5]

$$RCO_2Na + HCl\,(g) \longrightarrow RCO_2H\,(anhyd.) + NaCl$$

$$CH_3CO_2H + Cl_2 \xrightarrow[CH_3COCl]{P_4,\ I_2} CH_2ClCO_2H + HCl$$

$$CH_2ClCO_2H + CaCO_3 \longrightarrow (CH_2OHCO_2)_2Ca + CaCl_2 + CO_2$$

$$CH_3CH_2CO_2H + Br_2 \xrightarrow[CH_3CH_2COCl]{P_4,\ I_2} CH_3CH_2BrCO_2H + HBr$$

$$2CH_3CH_2BrCO_2H + 4OH^- + Zn^{++} \longrightarrow (CH_3CH_2OHCO_2)_2Zn + 2Br^-$$

The purity of the calcium glycolate was checked by three methods. In the first, the salt was recrystallized from water and the specific activity remeasured. It was found that the activity did not change, thus confirming the gross purity of the product. A C and H analysis of the product agreed well with the calculated values, although it was noted that sometimes the dihydrated salt crystallized out and sometimes the anhydrous calcium glycolate was obtained. A two-dimensional paper chromatographic separation (butanol–propionic acid–water in the first direction; phenol–water in the second) and radioautographs of the resulting paper showed only one radioactive spot, thus confirming the radioactive purity of the salt.[6]

The purity of the zinc lactate was similarly checked by elementary analysis and paper chromatography. Attempts to recrystallize the crude zinc lactate from distilled water failed to give pure products because of partial hydrolysis of the zinc lactate. This was corrected by crystallizing the product from a 0.1 *M* zinc chloride solution.

In order to produce a stable zinc lactate of uniform hydration, the product was first dried *in vacuo* and then hydrated in the laboratory (relative humidity $\sim$ 50%). Evidence for exactly three waters of hydration was obtained not only from the analytical work (C, H, ash) but also from the weight ratio of the anhydrous to the hydrated material.

For biological experiments these salts can be easily and quantitatively converted to an aqueous solution of the free acid by mixing a solution of the salt with excess Dowex-50 ion exchange resin in the acid form. When the resin is filtered off, a zinc or calcium-free solution of the organic acid is left.

Yields, specific activities and scale of the several reactions are summarized in Table I.

TABLE I

Compound	Scale of reaction, mmoles	Sp. act. of prod., μc/mg.	Yield based on fatty acid, %
Calcium glycolate-1-C^{14}	13.3	0.24	65.0
Calcium glycolate-2-C^{14}	13.7	0.30	60.5
Zinc lactate-1-C^{14}	6.3	3.85	81.8
Zinc lactate-2-C^{14}	13.5	6.90	84.0
Zinc lactate-3-C^{14}	12.7	3.09	76.3

Acknowledgment.—The authors would like to thank Prof. M. Calvin for his continued help and encouragement in this work.

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(1) Details of the chemical procedure are available on microfilm. Order Document 3567 from the American Documentation Institute, 1719 N Street, N. W., Washington 16, D. C., remitting $1.00 for microfilm or $1.20 for photocopies readable without optical aid.

(2) Supported by a grant to Prof. D. M. Greenberg, University of California, from the American Cancer Society, Committee on Growth of the National Research Council. The work described in this paper was sponsored by the U. S. Atomic Energy Commission.

(3) A. Hölzer, *Ber.*, **16**, 2955 (1883).

(4) A. Kekulé, *Ann.*, **130**, 18 (1864).

(5) E. Fischer and G. Zemplén, *Ber.*, **42**, 4891 (1909).

(6) A. A. Benson, *et al.*, THIS JOURNAL, **72**, 1710 (1950).

RADIATION LABORATORY AND
DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIFORNIA
RECEIVED JANUARY 31, 1952

The Synthesis of Bis-(2-hydroxy-3,5,6,-trichlorophenyl)-methane-C^{14} (Hexachlorophene)[1]

BY HERBERT M. ISIKOW AND WILLIAM S. GUMP

RECEIVED JANUARY 31, 1952

In the course of a study of the uptake of bis-(2-hydroxy-3,5,6-trichlorophenyl)-methane[2] (hexachlorophene) from soap solutions by the skin of experimental animals, it was necessary to prepare this compound labeled with carbon-14. Its preparation was readily effected by condensing 2,4,5-trichlorophenol with formaldehyde-C^{14} in the presence of sulfuric acid. Carbon-14 was thus incorporated into the methylene bridge of hexachlorophene as shown by the equation

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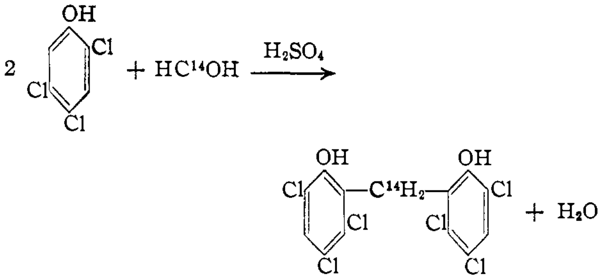
(1) For detailed paper order Document 3568 from American Documentation Institute, 1719 N Street, N. W., Washington 6, D. C., remitting $1.00 for microfilm (images 1 inch high on standard 35-mm. motion picture film) or $1.00 for photocopies (6 × 8 inches) readable without optical aid.

(2) W. S. Gump, U. S. Patent 2,250,480 (July 29, 1941).



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 (±4.6%) cts./min./mM.[3]; specific activity of starting formaldehyde-C^{14}: 3.52×10^8 (±4.4%) cts./min./mM.[4]; radiochemical yield: 60.6 ± 3.9%.

(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.

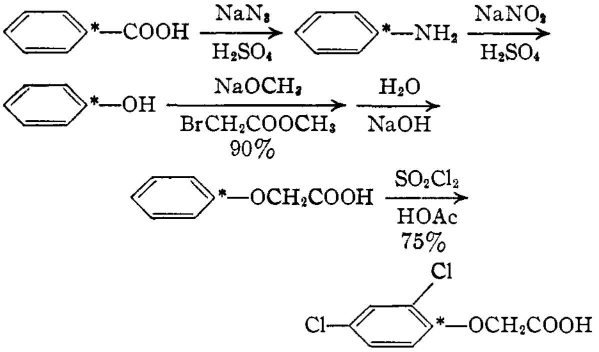
Synthesis of 2,4-Dichlorophenoxyacetic Acid Labeled with Isotopic Carbon[1]

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)	Yield, % Benzoic acid recovered	Yield, % 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.

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