[Contribution from the B. F. Goodrich Research Center]

Beta-Propiolactone. XVII.[1] Preparation of Isotope Labeled *Beta*-Propiolactone and Hydracrylic Acid[2]

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A procedure and apparatus is described for the preparation of one gram quantities of isotope labeled β-propiolactone and hydracrylic acid. The sequence of reactions used is the following. 2-Bromoethanol → hydracrylonitrile → β-iodopropionic acid → β-propiolactone + polyhydracrylic acid. Polyhydracrylic acid → hydracrylic acid.

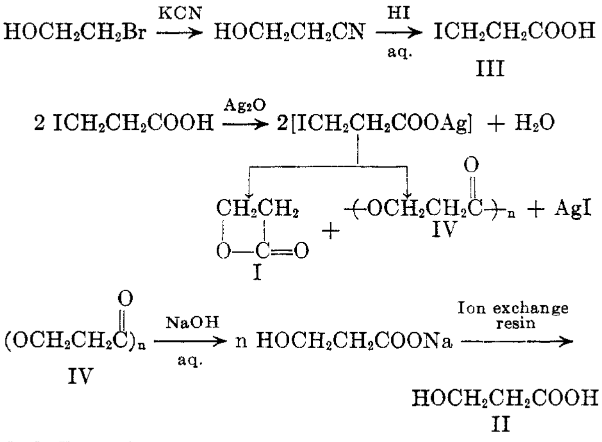
The virucidal activity of β-propiolactone (I) was first demonstrated by Mangun and co-workers.[3] Continuing work on the biological effects of I would be aided by the availability of isotope labeled I and its hydrolysis product, hydracrylic acid (II). This paper describes a procedure and apparatus for the preparation of one gram samples of I and II isotopically labeled at the 1-carbon atom, at the 2,3-carbon atoms, or at all three carbon atoms.

I was first prepared by Johannson[4] by mixing solutions of silver nitrate and sodium β-iodopropionate. The intermediate silver β-iodopropionate decomposed to form I which was extracted with ether to give a 9% yield. Subsequently I was prepared by the reaction of ketene and formaldehyde using a variety of catalysts.[5–9] The preparation of small amounts of I by the ketene-formaldehyde route poses many difficulties among which are the generation and measurement of small amounts of isotope labeled ketene and formaldehyde and the purification of small quantities of I. Because of the availability[10] of $BrC^{14}H_2C^{14}H_2OH$ and $KC^{14}N$, which are convertible to β-iodopropionic acid (III), the method of Johannson[4] was studied.

The reaction of 2-bromoethanol with potassium cyanide does not appear to be reported in the literature, but the reaction of sodium cyanide with 2-chloroethanol is well known.[11] The one step conversion of hydracrylonitrile to III was accomplished by refluxing with an excess of aqueous hydriodic acid. The corresponding reaction with hydrochloric and hydrobromic acids is reported to yield β-chloro- and β-bromo-propionic acids.[12] The over-all yields of III from 2-bromoethanol ranged from 64 to 72%. Since the conditions used by Johannson[4] for the preparation of I are now known to be unfavorable to the existence of I[13,14] the reaction of III was carried out with freshly prepared, dry silver oxide in inert solvents. When a mixture of silver oxide and III in dioxane was stirred at room temperature, a 52% yield of I was formed as shown by analysis.[15] Because of the difficulty in recovering I from dioxane solution, the reaction was repeated with anhydrous ether as the solvent. A 48% yield of I (by analysis) was obtained. After filtering off the silver iodide formed in the reaction and powdered silica gel which had been added to remove the water formed, the resulting ether solution was freed of ether to leave a mixture of I and polyhydracrylic acid (IV). I was separated from IV by evaporative distillation *in vacuo*. Yields of isolated, crude I of 41% were obtained. The purity of the crude I was 92% by analysis. Ether is the most probable impurity. Over-all yields of I of 27% based on 2-bromoethanol thus are possible.

An aqueous solution of II was prepared by refluxing IV with aqueous sodium hydroxide and passing the solution of sodium hydracrylate through a sul-

CHART I



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(1) For the previous paper in this series see *J. Am. Chem. Soc.*, **77**, 530 (1955).

(2) Part of this work was carried out under Department of the Army Contract with the Chemical Corps Biological Warfare Laboratories, Fort Detrick, Frederick, Maryland.

(3) Mangun, *et al.*, *Fed. Proc.*, **10**, 220 (1951).

(4) Johannson, *Lund University Annual*, New Series, Div. 2, Vol. 12, No. 8 (1915); *Chem. Abstr.*, **11**, 2576 (1917).

(5) Kung, U. S. Patent 2,356,459 (1944).

(6) Steadman and Breyfogle, U. S. Patent 2,424,590 (1947).

(7) Caldwell, U. S. Patents 2,450,116–118 (1948).

(8) Hagemeyer, U. S. Patents 2,450,131–134 (1948).

(9) Young and Fitzpatrick, U. S. Patent 2,580,714 (1952).

(10) Tracerlab Inc., Boston, Mass.

(11) *Org. Syntheses*, Coll. Vol. 1, 2nd ed., 256 (1941).

(12) Jacobs and Heidelberger, *J. Am. Chem. Soc.*, **39**, 1465 (1917).

(13) Gresham, *et al.*, *J. Am. Chem. Soc.*, **70**, 998 (1948).

(14) Gresham, *et al.*, *J. Am. Chem. Soc.*, **70**, 999 (1948).

(15) Tyler and Beesing, *Anal. Chem.*, **24**, 1511 (1952).

fonic acid ion exchange resin. The resulting dilute solution of II was concentrated to approximately 10% by freeze-drying. Titration with standard base indicated a 69.6% yield of II based on IV. The solution was shown to contain II by preparing the slightly soluble zinc-calcium double salt, ZnCa$(HOCH_2CH_2COO)_4$,[16] and comparing its x-ray powder diagram and infrared spectrum with those of an authentic sample of the double salt. Chart I summarizes the reactions reported in this paper.

Fig. 1

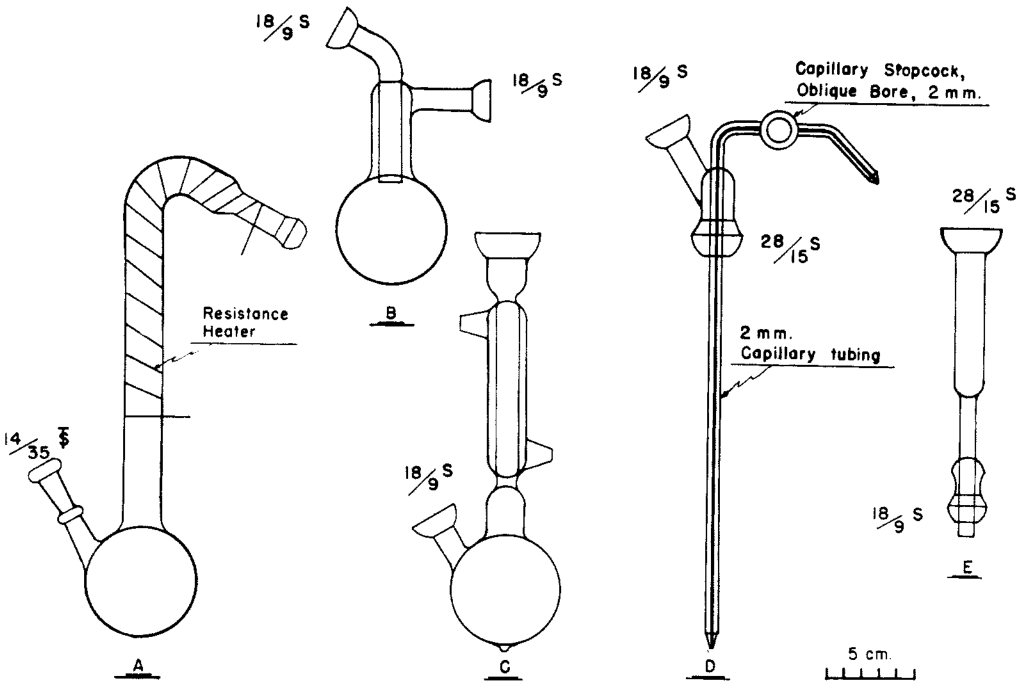
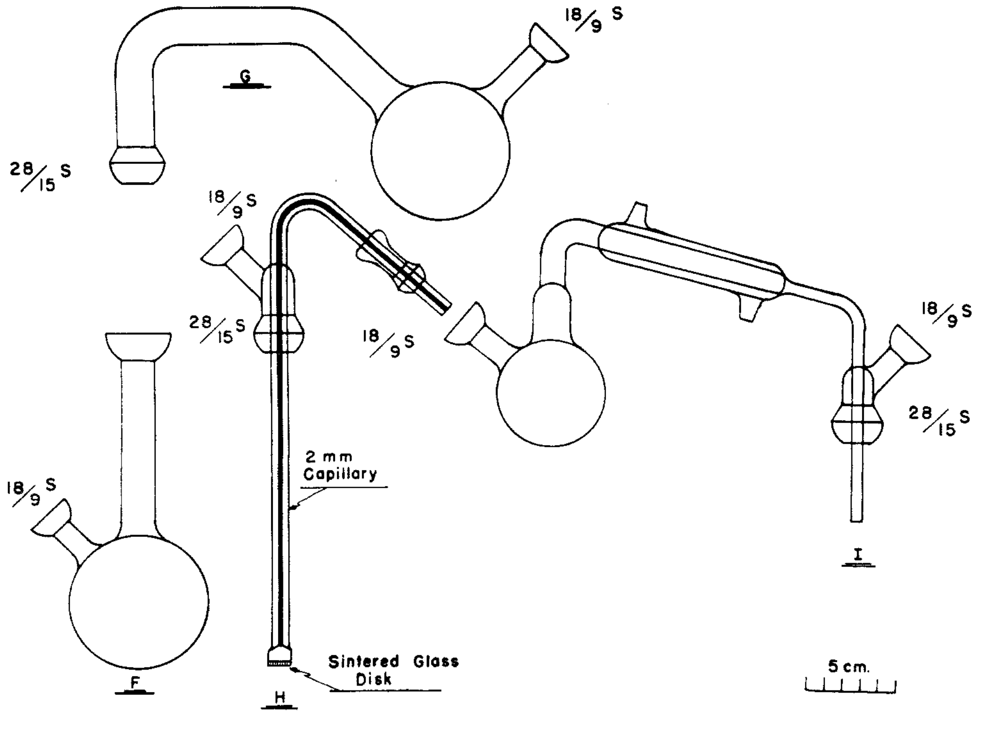


Fig. 2



EXPERIMENTAL

Apparatus.[17] The apparatus is shown in Figures 1 and 2. Spherical or standard taper caps were provided for all openings.

Preparation of $HOC^{14}H_2C^{14}H_2CN$. The $BrC^{14}H_2C^{14}H_2OH$ (1.0 millimole, 1.0 millicurie) was transferred from its breakseal tube to apparatus A (*via* the 14/35 standard taper joint) by means of a vacuum line of conventional design.[18] The inactive 2-bromoethanol (7.47 g., 59.8 millimoles) and 20 ml. of ethanol were added to apparatus A containing the radioactive 2-bromoethanol. With A mounted vertically and B attached and cooled in Dry Ice-acetone, the potassium cyanide solution (4.08 g. of 97% KCN, 60.8 millimoles, in 6.5 ml. of water) was poured into the magnetically stirred ethanol solution by means of a small funnel. The side arm was capped and the mixture was refluxed (heating mantle) with stirring for 6$^1/_2$ hours. Several jets of compressed air were directed on the vertical part of A to insure refluxing of the ethanol. After standing at room temperature overnight (capped), B was cooled in Dry Ice-acetone and connected to the vacuum system. With A rotated 30–45° from vertical to prevent splashing into B and with the mixture in A stirred magnetically, the pressure was slowly reduced to 3.0 mm. to distill the ethanol and most of the water into B. Flask A was warmed briefly with a water-bath at 40°. Air was admitted and B was removed and replaced by C (*via* the small joint). C was cooled in Dry Ice-acetone and with the vacuum system attached at the large joint of C, the product was distilled into C at 0.02 mm. A was heated in a water-bath at 60° and the resistance heater wrapped on A prevented condensation of hydracrylonitrile. The weight of nearly colorless hydracrylonitrile was 4.53 g. (105%).

Preparation of $IC^{14}H_2C^{14}H_2COOH$. With apparatus C mounted vertically and with water passing through the condenser, several carborundum boiling chips and 40 ml. of 56% hydriodic acid were added down the condenser. The solution was refluxed on a heating mantle for six hours, apparatus C was capped while hot, and the apparatus was allowed to stand at room temperature overnight. The water was removed from the condenser and apparatus D was inserted into apparatus C with the ground capillary in the identation in the bottom of C. Then 20 ml. of water and 10 ml. of redistilled chloroform were poured into the apparatus through the upper 18/9 spherical joint. With all of the openings capped and the stopcock closed, the entire apparatus was shaken with the upper part inclined slightly to minimize splashing upward. The apparatus was returned to the rack, the upper cap removed, and the stopcock opened. Application of gentle suction on the upper joint (by means of an adapter and medicine dropper bulb) caused a few air bubbles to clear the lower end of the capillary tube of aq. solution. Gentle air pressure applied at the upper joint forced the lower (chloroform extract) layer up the capillary and out at the tip. The flow was regulated by means of the stopcock. When the aqueous layer rose in the capillary the stopcock was closed, the air pressure released, and the stopcock opened thus returning the liquid in the capillary to flask C. The tip was washed with a few drops of chloroform. A further 10 ml. of chloroform was added through the upper 18/9 spherical joint and the extraction was repeated. The extractions were continued for a total of 15 times (150 ml. chloroform). The chloroform extract leaving the ground tip of D entered the top of E and was sucked through a layer of magnesium sulfate between two layers of glass wool. Apparatus E was attached to apparatus F *via* the 18/9 spherical joints and vacuum was applied *via* the upper joint. The chloroform extract thus was collected in F as a pale violet solution. Apparatus E was removed and the lower joint of F was capped. Apparatus G was attached to F and G was cooled in Dry Ice-acetone. Most of the chloroform was distilled from F to G at atmospheric pressure using a heating mantle and magnetic stirring. The last chloroform and a trace of iodine were removed by connecting the vacuum system at the 18/9 spherical joint of G and slowly reducing the pressure to 0.02 mm. Flask F was heated to 60° in a water-bath and the solid, nearly colorless iodo acid was broken up with the stirrer magnet. The weight of the β-iodopropionic acid was 8.54 g. (70.2% based on 2-bromoethanol). Flask F was capped and stored overnight in the refrigerator.

Preparation of β-propiolactone-2,3-C^{14}. The silver oxide was prepared by dissolving 8.81 g. of silver nitrate in 80 ml. of distilled water and adding aqueous 10% sodium hydroxide solution with stirring until the mixture was weakly basic. The aqueous solution was removed with a sintered glass filter stick. Distilled water was added and the mixture was stirred and filtered. In this way the silver oxide was washed with distilled water until neutral. The wet silver oxide was washed twice with anhydrous ethanol and twice with commercial anhydrous ether. The silver oxide was dried *in vacuo*. Apparatus F containing the β-iodopropionic acid was warmed to room temperature and the 28/15 spherical cap was removed. Then 40 ml. of commercial anhydrous ether, 4.94 g. of freshly prepared silver oxide, and 1.2 g. of Davison PA-100 silica gel[19] (powdered in a mortar) were added to the iodo acid. A small reflux condenser surmounted by a drying tube was attached to F. After stirring for four minutes the mixture was at the boiling point. For six minutes the reaction mixture boiled spontaneously and was cooled occasionally in a cold water-bath. After stirring for a total of 3 hours the stirrer was stopped, the condenser was removed, and apparatus H was inserted. Apparatus I containing a stirring magnet was attached to H by the 18/9 spherical joint and a flask was attached to the 28/15 spherical joint of I to act as a receiver. The remaining 18/9 joint of I was closed with an adapter and drying tube. Gentle air pressure applied to the 18/9 joint of apparatus H forced the ether solution of I and polymer through the sintered glass disk and into apparatus I. The solid remaining in F was washed twice with ether and the washings were transferred into I. Apparatus F–H was removed and I was capped. With the receiver cooled in Dry Ice and acetone and with water flowing in the condenser, most of the ether was distilled off at atmospheric pressure and a final water bath temperature of 55° (magnetic stirring). The drying tube was removed, the vacuum system was attached, and the water was removed from the condenser. With the magnetic stirrer operating, the pressure was slowly reduced to 10.0 mm. Flask I was heated with a water-bath until I began to condense on the upper cool part of the flask. Air was admitted, the receiver was removed, and apparatus I was attached to the vacuum line using the 18/9 joint on the flask. All other joints were capped and the I was separated from the polymer by distillation into the U-trap (cooled with liquid nitrogen) of the vacuum line with continuous pumping. The polymer was heated to 30° with a water-bath. The β-propiolactone-2,3-C^{14} was transferred to a break-seal tube and sealed off. The weight of product was 0.76 g. (24.7% from iodo acid). The polymer weighed 1.32 g.

Preparation of hydracrylic acid-2,3-C^{14}. To apparatus I, containing 1.28 g. of polyhydracrylic acid, was added 50 ml. of 0.5 *N* sodium hydroxide (through the 18/9 joint on the flask). Apparatus I was mounted at such an angle that the attached condenser acted as a reflux condenser and the mixture was refluxed for four hours with slow magnetic stirring. At the end of the refluxing period a small amount of water-insoluble liquid coated the inside of the flask. The cooled liquid was poured in the reservoir above a 12-mm.

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(16) Heintz, *Ann.*, **157**, 291 (1871).

(17) The apparatus was constructed by L. F. Dusek.

(18) Calvin, *et al.*, *Isotopic Carbon*, John Wiley and Sons, Inc., New York, 1948, p. 142.

(19) The Davison Chemical Corp., Baltimore, Md.

O.D., glass, ion exchange column packed with approximately 50 ml. (wet) of Dowex[20] 50-X8 in the acid form (40–80 mesh). The flow from the bottom of the column was regulated with a stopcock at 11–12 drops per minute. Apparatus I and the column were washed with five 10-ml. portions of distilled water. The last effluent collected had the *p*H of distilled water and gave only the background count. The total weight of effluent was 99.2 g. The oily film remaining in I and in the top of the ion exchange column was not radioactive. The oily material was probably "Silicone" stopcock grease. The effluent in a 200 ml. round-bottom flask was frozen as a coating on the interior of the flask by rotating the flask in a Dry Ice-acetone bath. The solid was freeze-dried by attaching the flask to the vacuum system through a Dry Ice-acetone cooled receiver. With the pressure at 0.02 mm. (measured after the cold receiver) about eight hours were required to reduce the weight of the solution to 7.4 g. The material remained frozen during the drying operation. The hydracrylic acid solution was transferred to a glass vial with a small amount of distilled water to give 10.72 g. of final solution. Assuming the yield of hydracrylic acid from polymer is the same as in the inactive preparation the solution contained 1.12 g. of hydracrylic acid.

The following latice spacings (Å) were calculated and the intensities of the lines were estimated from the powder x-ray diffraction pattern of $ZnCa(HOCH_2CH_2COO)_4$: 8.00 (I), 5.77 (MI), 5.16 (VW), 4.34 (VW), 4.04 (VW), 3.60 (I), 3.16 (W), 2.85 (W), 2.46 (W), 2.20 (VW), 2.093 (VW), 2.03 (VW), where I is intense, MI is moderately intense, W is weak, VW is very weak.

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[20] The Dow Chemical Co., Midland, Mich.