# [CONTRIBUTION FROM THE LOS ALAMOS SCIENTIFIC LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

# A CONTRIBUTION TO THE TOTAL SYNTHESIS OF ALIZARIN<sup>1</sup>. SYNTHESIS OF 1,2-DIHYDROXY-9,10-ANTHRAQUINONE-9-C<sup>14</sup>

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Several possible syntheses of alizarin (1,2-dihydroxyanthraquinone) appear readily adaptable to the labeling of this compound with isotopic carbon. All of those considered involve a carboxyl-labeled intermediate acid obtainable *via* either the Grignard or the halogen-metal interconversion reaction.

Preparation of carboxyl-labeled phthalic acid from *o*-bromotoluene offers two possibilities: condensation with chlorobenzene to give 2-chlorobenzoylbenzoic acid followed by ring closure to give 2-chloroanthraquinone, or condensation with benzene followed by ring closure to give anthraquinone and sulfonation at the 2-position. Either of these 2-substituted anthraquinones may be converted to alizarin by heating under pressure with sodium hydroxide and an oxidizing agent, *e.g.*, potassium chlorate.

Another approach, similar to the above, is the formation of carboxyl-labeled 2-benzylbenzoic acid from 2-bromodiphenylmethane *via* the Grignard reaction. Ring closure of this acid readily gives anthrone, and the desired product is obtained by oxidation to anthraquinone, and subsequent sulfonation.

All three of the above sequences entail one or more low-yield reactions in which labeled intermediates are involved. This is especially true in the case of the sulfonation of anthraquinone since only partial conversion may be effected with a minimum of polysubstitution. Repeated treatment of the unconverted quinone would be required.

In view of the undesirable features of the foregoing approaches to the problem, a new total synthesis of alizarin was developed which gives excellent yields in all of the steps in which isotopically labeled intermediates are involved. The reaction sequence is given in Figure 1.

Phenyl 2-bromobenzoate (III) was prepared in good yield by the conventional Schotten-Baumann reaction from 2-bromobenzoyl chloride (II) and phenol. The Fries rearrangement of III gave a quantitative yield of 2-bromo-4'-hydroxybenzophenone (IV) using the procedure of Rosenmund and Schnurr (1) who prepared 4-hydroxybenzophenone. Montagne (2) first prepared coumpond JV by another method.

The hitherto unreported 2-bromo-4'-hydroxydiphenylmethane (V) was prepared by the Clemmensen reduction (3) of IV.

Since the isotopic carbon was to be introduced in this synthesis of alizarin via the carbonation of either the magnesium or lithium organo-compound derived from V, it was desirable to inactivate the 4'-hydroxyl group. Parham and Anderson (4) have described an excellent method of protecting the hydroxyl

<sup>1</sup> Work performed under the auspices of the Atomic Energy Commission.

group in reactions which are carried out in basic media; namely, formation of a cyclic acetal with dihydropyran. The new compound 4-(2-bromobenzyl)phenyl-2-tetrahydropyranyl ether (VI) was prepared by their general procedure in nearly quantitative yield.



A study was made to determine the optimum conditions for the preparation of 2-(4-hydroxybenzyl)benzoic acid (VII) from compound VI by the halogenmetal interconversion reaction with butyllithium. A constant ratio of 4 millimoles of aryl halide to 3 millimoles of butyllithium was maintained. The interconversion reactions were carried out under an atmosphere of dry nitrogen at  $-25^{\circ}$ . Approximately 10 minutes was allowed for the dropwise addition of the aryl halide, dissolved in 10 cc. of dry ether, to the stirred butyllithium solution. Following this addition, the time allowed for the halogen-metal interconversion was varied from 20 to 60 minutes. The resulting organo-lithium compound in each experiment was then carbonated at  $-60^{\circ}$  with 2 millimoles of carbon dioxide.

The results indicated that in this instance the halogen-metal interconversion reaction is relatively slow. A 45% yield of crude acid (based on barium carbonate) was obtained with a total reaction time of 30 minutes. The highest yields, 90 to 95%, were obtained with a total reaction time of about 50 minutes. Longer reaction periods than this gave yields of 83 to 84%. However, comparison of the melting points of the crude acid indicated that the actual maximum yield was about 83 to 84%. The product of highest yield melted at 132–134°; whereas, in several experiments in which the yields were 83 to 84% the products melted at 148–149°. Melting points for this compound, prepared by other methods, recorded in the literature are  $153-154^{\circ}$  (5) and  $145-146^{\circ}$  (6).

Bistrzycki and Yssel de Schepper (6) prepared 2-hydroxy-9-anthrone (VIII) by effecting a ring closure of 2-(4-hydroxybenzyl)benzoic acid with concentrated sulfuric acid. Blicke and Weinkauf (5) also prepared this compound using the same procedure. Neither of the above references gives yield data. Several experiments were made using sulfuric acid as the condensing agent. Dissolution of the phenolic acid in concentrated sulfuric acid was always attended by rapid color changes, orange to brown. Apparently the ring closure was accompanied by a considerable amount of sulfonation in the phenolic ring as a portion of each product was water soluble. Yields of crude products, after washes with sodium bicarbonate solution and water, with subsequent drying, ranged from 50 to 75%. These products melted over a range from 210 to 218°. The purified compound melts at  $221^{\circ}$  (6).

Since Fieser and co-workers (7, 8) have prepared anthrone and several homologues in good yield using liquid hydrogen fluoride to effect the ring closure, this reagent was also tried. When anhydrous conditions and a platinum container were used, fairly pure nearly colorless products were obtained in 88 to 100% yields.

2-Hydroxy-9-anthrone (VIII) was oxidized to 2-hydroxyanthraquinone (IX) essentially by the procedure of Blicke and Weinkauf (5), using sodium dichromate and acetic acid. Practically quantitative yields of the quinone (96 to 100%) were obtained (m.p. 298° to  $306^{\circ}$ ). Blicke and Weinkauf give  $303-304^{\circ}$  as the melting point of their crude product.

1,2-Dihydroxyanthroquinone (X) is usually prepared by fusing either anthraquinone-2-sulfonic acid or 2-haloanthraquinones with potassium hydroxide, or by heating these compounds under pressure  $(170-210^{\circ})$  with concentrated aqueous base and an oxidizing agent such as potassium chlorate. It was considered quite likely that oxidation at the 1-position, when the 2-hydroxy group was already present, would not require conditions as drastic as are necessary when the hydrolytic cleavage of a 2-chloro or 2-sulfonic substituent is involved. This did not prove to be the case. A solution of 2-hydroxyanthraquinone and a molar equivalent of potassium chlorate in 12 N sodium hydroxide heated under reflux for as long as 47 hours gave a mixture of alizarin and starting material. The treatment of 2-hydroxyanthraquinone in a Parr bomb under experimental conditions (9) which give 90% yields of alizarin from anthroquinone-2-sulfonic acid also gave a mixture of alizarin and starting material. It was found, however, that either re-treatment of the sublimed mixture under the same conditions or doubling the reaction time with an excess of potassium chlorate gave practically complete conversion to alizarin.

#### EXPERIMENTAL

2-Bromobenzoyl chloride. Dry 2-bromobenzoic acid, 50 g., was treated with an excess of thionyl chloride. The mixture was refluxed on the water-bath until the evolution of gas ceased. Excess thionyl chloride was distilled off, and the acyl chloride was vacuum-distilled, yield 54 g., b.p.  $91-93^{\circ}$  (1 mm.).

Phenyl 2-bromobenzoate. To 109.5 g. of 2-bromobenzoyl chloride was added a solution of 51.6 g. of phenol and 44 g. of sodium hydroxide in 400 cc. of water. The mixture was shaken vigorously for 25 minutes. The oily organic layer was separated and the aqueous layer was extracted three times with 50-cc. portions of ether. The combined ether extracts were added to the oily fraction, and this solution was washed three times with water and was then dried over magnesium sulfate. The dried ethereal solution was filtered and the ether was removed by distillation on the water-bath and then under a vacuum. The crude, ether-free ester weighed 118.8 g. (86%), and was used directly in the Fries rearrangement.

2-Bromo-4'-hydroxybenzophenone. Freshly sublimed anhydrous aluminum chloride, 69 g., was added to 118.8 g. of phenyl 2-bromobenzoate. The mixture was then heated in an oil-bath at 140° for 15 minutes. The solid light-brown mass was cooled and then decomposed with ice-water. The water was decanted and the product, upon being warmed with dilute hydrochloric acid, changed to a viscous white oil which solidified to a white, granular mass upon cooling. The yield of crude product, m.p. 90–92°, was quantitative. The crude material crystallized from a mixture of benzene and heptane melted at 100–103°. Montagne (2) prepared this compound in another manner and reported a melting point of 100–105°, or 114° when the sample was heated rapidly.

2-Bromo-4'-hydroxydiphenylmethane. This new compound was prepared by the Clemmensen reduction (3) of 2-bromo-4'-hydroxybenzophenone. Zinc amalgam was prepared from 200 g. of mossy zinc by the method of Martin (10). To the freshly prepared zinc amalgam was added 75 cc. of water, 200 cc. of concentrated hydrochloric acid, and 118 g. of 2bromo-4'-hydroxybenzophenone. The mixture was refluxed for  $14\frac{1}{2}$  hours. Additions of 50 cc. of concentrated hydrochloric acid were made approximately every 3 hours. When the mixture was cooled, the aqueous phase deposited white needles which melted at 83-84°. The major part of the product did not crystallize but remained a viscous oil which was dissolved in 500 cc. of ether. The ether solution was washed with water, dried over "Drierite" and filtered. The ether was distilled on the water-bath, the last traces being removed under a vacuum. At 0.5 mm., 65.6 g. (57.5%) of material, b.p. 157-161°, was collected. The distillate, which solidified rapidly, was crystallized from chloroform-hexane solvent to give a product of m.p. 83-84°. This material recrystallized from *n*-hexane in long colorless needles, m.p. 85-85.5°.

2-Bromo-4'-hydroxydiphenylmethane is very soluble in benzene, chloroform, acetone, ethanol, methanol, and ethyl ether, and only slightly soluble in hot *n*-hexane and *n*-heptane.

Anal. Calc'd for C13H11BrO: C, 59.33; H, 4.21.

Found: C, 59.33; H, 4.34.

4-(2-Bromobenzyl) phenyl 2-tetrahydropyranyl ether. 2-Bromo-4'-hydroxydiphenylmethane (11.3 g.) was mixed with 14.5 g. of dihydropyran in which it partially dissolved. One drop of concentrated hydrochloric acid was added to the cooled mixture. During the initial spontaneous warming, the mixture was intermittently agitated and cooled in an ice-water bath. All of the phenolic compound dissolved. After 15 hours at room temperature, the colorless solution was diluted with 100 cc. of ether, washed 3 times with 50-cc. portions of 10% sodium hydroxide, and finally with water. Acidification of the combined basic washes precipitated only a very small amount of unreacted phenolic compound. The ethereal solution was dried over magnesium sulfate, filtered, and the ether was removed on the water-bath. Excess dihydropyran was distilled off at 1 mm. and a final oil-bath temp. of 110°. Even under these conditions the crude product weighed 1.6 g. in excess of the theoretical yield and retained the odor of dihydropyran.

In a preceding experiment it was found that this acetal could not be vacuum distilled (1 mm.) without extensive decomposition (47.5%) of the starting phenol was recovered), and that the acetal could be crystallized from methanol or ethanol. If essentially all of the excess dihydropyran was removed under a vacuum, the crude acetal crystallized after standing several days at 0°.



FIG. 2. APPARATUS FOR ISOTOPIC SYNTHESIS

Accordingly, the crude acetal was warmed under a vacuum (0.5 mm.) for several hours and then dissolved in the minimum of boiling dry methanol (about 60 cc.). Sufficient solvent was used so that the acetal did not separate as an oil upon cooling the solution to 0°. After 5 days at 0°, the colorless crystalline mass was filtered and washed with a small amount of cold methanol. The product, after drying under a vacuum, weighed 12.67 g. (85%), m.p. 43-44°. This acetal is soluble in cold hexane, ethyl acetate, chloroform, benzene, carbon tetrachloride and ether; quite soluble in hot and moderately soluble in cold methanol and ethanol.

Anal. Calc'd for C18H18BrO2: C, 62.43; H, 5.24.

Found: C, 62.63; H, 5.13.

2-(4-Hydroxybenzyl)benzenecarboxylic-9- $C^{14}$  acid. The isotopically-labeled acid was synthesized in the apparatus shown in Figure 2, which was also used in the preliminary experiments. Five millicuries, 406.5 mg. (2.06 millimoles), of C<sup>14</sup> barium carbonate was weighed into flask C of the carbon dioxide generator. The entire system was then assembled and evacuated for two hours through N. Reaction vessel A and addition buret B were flushed with a stream of dry nitrogen and, with nitrogen flowing through A, B was removed. With a pipet, 5.5 cc. of 0.56 N ethereal butyllithium solution (3.09 millimoles) was transferred into A. B was quickly replaced and stopcocks J and K were opened to permit flow of nitrogen. K was removed and 1.425 g. (4.12 millimoles) of 4-(2-bromobenzyl)phenyl 2-tetrahy-

dropyranyl ether dissolved in 10 cc. of dry ether was run into B. K was replaced and G was closed leaving a nitrogen atmosphere in the system. Reaction vessel A was immersed in a Dry Ice-acetone bath at  $-25^{\circ}$  and the magnetically-driven glass stirrer was started. The aryl bromide solution was added dropwise to the butyllithium during 15 minutes. Stirring was continued for 50 minutes while the bath was maintained at  $-25^{\circ}$ .

During the stirring period, the  $C^{14}$  carbon dioxide was generated with sulfuric acid and collected in reservoir *P* cooled with liquid nitrogen. The trap *D* was cooled to  $-77^{\circ}$  with a Dry Ice-acetone bath in order to remove any sulfur dioxide, sulfur trioxide, and moisture from the carbon dioxide.

With the pale yellow aryllithium solution in A frozen with liquid nitrogen, the reaction chamber was evacuated, warmed to  $-55^{\circ}$ , cooled with liquid nitrogen and again evacuated. The C<sup>14</sup> carbon dioxide was then allowed to vaporize and react with the rapidly stirred aryllithium solution cooled to  $-60^{\circ}$  (bath temperature). The last of the carbon dioxide was condensed in A with liquid nitrogen and the solution was again stirred at  $-60^{\circ}$  for 3 minutes. The lithium salt of the acid and the acetal were then hydrolyzed with 4 ml. of 15% hydrochloric acid introduced through B. Stirring was continued for an additional 15 minutes and the mixture was allowed to stand several hours at room temperature.

The reaction mixture was transferred into a continuous liquid-liquid extractor for isolation of the C<sup>14</sup>-labeled acid. The aqueous phase in the extractor was made basic by the careful addition of saturated sodium bicarbonate solution. The ether layer was evaporated under an infrared lamp leaving a residual oily layer which was thoroughly mixed with the aqueous phase. The basic solution was extracted with ether for 24 hours to remove excess 2-bromo-4'-hydroxydiphenylmethane and 2,3-dihydropyran. After acidification of the solution with 6 N hydrochloric acid, extraction with ether was continued for 46 hours to isolate the labeled acid. The ether solution of product was dried over magnesium sulfate, filtered, and the ether was distilled off on a water-bath. The oily residue soon crystallized and traces of ether and a small amount of radioactive liquid (probably valeric acid) were removed under a vacuum and collected in a cold trap until the residue came to constant weight. The slightly pink crystalline product weighed 438 mg. (93.3%).

2-Hydroxy-9-anthrone-9- $C^{14}$ . The crude acid was dissolved in dry ether, transferred into a 100-cc. platinum beaker (in 1-ml. portions) and evaporated to dryness. Ring closure to the desired anthrone was effected with liquid hydrogen fluoride. The platinum crucible was placed inside a  $2\frac{3}{4} \times 3$  inch stainless steel cylinder fitted with a transparent "Bakelite" cover. The cover was equipped with a stainless steel inlet tube, which was an extension of the condenser coil and a similar outlet tube connected to a "Bakelite" guard tube filled with anhydrous potassium fluoride.

The steel cylinder was cooled with a bath at  $-10^{\circ}$  and hydrogen fluoride was condensed in the coil, cooled with Dry Ice, until about 5 cc. had collected in the crucible. During this time (7 minutes) the bath temperature was kept at  $-10^{\circ}$ ; then during the next 30 minutes the bath temperature rose to 20°. The inlet tube was removed and the hydrogen fluoride was evaporated with a stream of nitrogen.

The solid residue was broken up with a stirring rod and triturated with 5% sodium bicarbonate solution. The product was then washed with water into a sintered glass funnel. The air-dried product and a small amount of residue in the beaker were dissolved in warm acetone which was filtered into a 100-cc. 3-necked flask. Evaporation of the solvent under a vacuum gave a quantitative yield, 407.8 mg., of a pale-yellow crude product.

2-Hydroxyanthroquinone-9- $C^{14}$ . The flask containing the crude hydroxyanthrone was equipped with a glass stirrer and the crushed material was suspended in 12 cc. of acetic acid. One molar equivalent of sodium dichromate dihydrate (578 mg.), dissolved in 1 cc. of hot water, was added to the stirred suspension. The flask was then immersed in a waterbath at 55°; the temperature was raised to 82° during 20 minutes and was maintained there for 10 minutes. As the acetic acid solution cooled to room temperature, the yellow 2-hydroxyanthraquinone crystallized. Dilution of the acetic acid with 30 cc. of water resulted in precipitation of additional product. About 90% of the acetic acid was neutralized by the addition of 14.3 g. of powdered sodium bicarbonate to the stirred solution. The quinone was collected in a sintered glass funnel, washed three times with water, and air-dried. The combined mother liquors were extracted for 50 hours with ether to obtain a small additional amount of product. The total crude product was dissolved in hot acetone, filtered, and evaporated to dryness. The crude 2-hydroxyanthraquinone-9-C<sup>14</sup> weighed 434.2 mg. (99.7%).

1,2-Dihydroxy-9, 10-anthraquinone-9-C<sup>14</sup> (Alizarin). The crude 2-hydroxyanthraquinone-9-C<sup>14</sup> was broken up with a spatula and transferred into an 8-cc. Parr bomb. The dry hydroxyquinone was broken up with a stirring rod and sufficient powdered sodium hydroxide (0.1 gram) was added to form the sodium salt. Then 3 cc. of water and 286 mg. of KClO<sub>3</sub> (1.2 molar equivalents) were added and the reagents were thoroughly mixed. After washing the stirring rod with 1 cc. of water, 4 g. of powdered sodium hydroxide was added to the red solution. The sealed bomb was then heated in an oil-bath at 165–175° for 43 hours.

The resulting dark blue mass of alizarin salt and sodium hydroxide was dissolved in hot water (150 cc.), warmed to  $60^{\circ}$ , acidified with 6 N hydrochloric acid, and allowed to cool. The orange precipitate was collected in a sintered glass funnel and washed several times with cold water. The combined mother liquor and wash water was extracted continuously for 48 hours with ether to obtain an additional small amount of product.

The crude alizarin was transferred to the vacuum sublimator with acetone and the acetone was removed by evaporation. During six 6-12 hour periods of sublimation at 0.1-0.2 mm. and 125°, the total yield of sublimed C<sup>14</sup> alizarin was 314.2 mg. (65.4% based on BaC<sup>14</sup>O<sub>3</sub>), melting at 287-288°.

The product possessed a specific activity of one millicurie per 90 milligrams. The radioactivity was determined from a sample which was burned in a combustion apparatus. The carbon dioxide was precipitated as barium carbonate, and an aliquot was plated for countng with an end-window Geiger counter.

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