

danyl)-propionic acid have been under investigation. This acid had previously been prepared by v. Braun and co-workers¹ in a several step, side-chain building process starting with 1-indanone. It seemed desirable to develop a synthesis involving a readily prepared metallic derivative of the inexpensive indene. Although indenyllithium had been prepared previously² from indene using ethyllithium and diethylmercury, it seemed advisable to avoid this latter expensive and poisonous reagent.

Using a procedure similar to that employed in the synthesis of 9-fluorenyllithium and fluorene-9-carboxylic acid,³ we have obtained indenyllithium and indene-1-(or 3)-carboxylic acid in good yields from the reaction of butyllithium with indene, followed by treatment with solid carbon dioxide.

Indenyllithium was found to react with ethyl β -bromopropionate to give a low (14%) yield of ethyl β -[1(or 3)-indenyl]-propionate. The major reaction probably involved the loss of hydrogen bromide from the β -bromo ester. The ester product on hydrolysis gave β -[1(or 3)-indenyl]-propionic acid which was readily hydrogenated to the β -[1-indanyl]-propionic acid.

Experimental

Indenyllithium and Indene-1(or 3)-carboxylic Acid.—Approximately 0.2 mole of *n*-butyllithium was prepared in 150 ml. of dry ether by the procedure of Gilman, *et al.*⁴ To this solution 21.8 g. (0.188 mole) of indene (Eastman Kodak Co. Practical grade) was added over a period of 30 minutes with the evolution of butane. The rust colored mixture was refluxed for two hours and then poured in a thin stream onto solid carbon dioxide. One liter of water was cautiously added to the lithium-free ether mixture. The basic aqueous layer was acidified with hydrochloric acid to give 20.1 g. of indene-1(or 3)-carboxylic acid which was recrystallized from benzene, m.p. 159–160°; neut. equiv., calcd. 160.2, found 160 and 158.7.⁵

This experiment indicated that at least 67% of the indene had been converted into its lithium derivative.

β -[1(or 3)-Indenyl]-propionic Acid.—A solution of indenyllithium, prepared as in the previous experiment, was transferred through a glass wool filter into a nitrogen swept separatory funnel and added slowly in 30 minutes to a 160 ml. of dry ether solution of 34 g. (0.187 mole) of ethyl β -bromopropionate cooled to 3–5°. After the addition was complete the reaction mixture was allowed to stand at room temperature for 12 hours. The cooled solution was mixed with ice and ammonium chloride and the ether layer distilled to give 7.6 g. of the crude ethyl β -[1(or 3)-indenyl]-propionate, b.p. 155–163° (15 mm.). Hydrolysis of this ester with 20% sodium hydroxide produced 5.3 g. (14.7% yield based on the bromo ester) of β -[1(or 3)-indenyl]-propionic acid. Recrystallization from aqueous alcohol and then benzene gave colorless crystals, m.p. 129–130°. Aqueous alkaline solutions of this unsaturated acid decolorized potassium permanganate instantly while aqueous acetone solutions gave a slower decolorization at 25°.

(1) (a) J. v. Braun and J. Reutter, *Ber.*, **59B**, 1922 (1926); (b) J. v. Braun and E. Danzinger and Z. Koehler, *ibid.*, **50**, 56 (1917).

(2) (a) W. Schlenk and E. Bergmann, *Ann.*, **465**, 227 (1928); (b) O. Blum-Bergmann, *ibid.*, **484**, 28 (1931).

(3) R. R. Burtner and J. W. Cusic, *THIS JOURNAL*, **65**, 264 (1943).

(4) H. Gilman, *et al.*, *ibid.*, **71**, 1499 (1949).

(5) W. S. Knowles, J. A. Kuck and R. C. Elderfield, *J. Org. Chem.*, **7**, 377 (1942). No evidence seems to be available to establish the location of the carboxy group with respect to the five-ring double bond. It seems probable that the correct structure is indene-3-carboxylic acid with C=O conjugated with the C=C bond.

(6) Since completing our work we have noticed that G. R. Clemo *et al.*, *J. Chem. Soc.*, 863 (1951), have reported the preparation of β -[3-indenyl]-propionic acid, m.p. 120.5–121.5°, by four methods two of which start with indene and two starting with 1-indanone, all of which gave rather low yields. In spite of the difference in melting points we believe that our acid is essentially the same as that of Professor Clemo.

Anal. Calcd. for C₁₂H₁₂O₂: C, 76.57; H, 6.43; neut. equiv., 188.2. Found: C, 76.84; H, 6.38; neut. equiv., 188.5 and 190.2.

β -[1-Indanyl]-propionic Acid.—A sample of β -[1(or 3)-indenyl]-propionic acid (1.95 g.) in absolute alcohol was hydrogenated in the presence of palladinized charcoal under three atmospheres of hydrogen for seven hours. Isolation produced 1.45 g. of the crude acid, m.p. 45–48.5°. Recrystallization from petroleum ether gave a purer product, m.p. 49.5–51°.¹

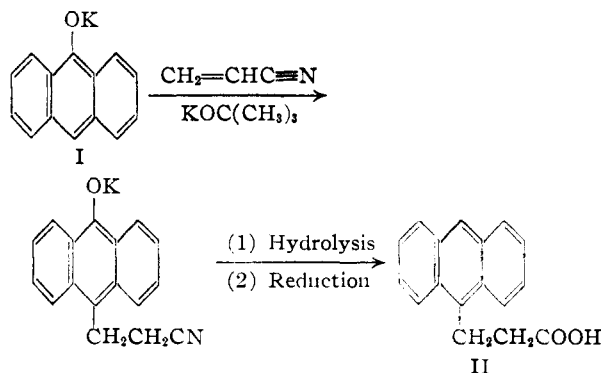
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The Monocyanoethylation of Anthrone. An Improved Synthesis of β -(9-Anthranyl)-propionic Acid and β -(9,10-Dihydro-9-anthranyl)-propionic Acid¹

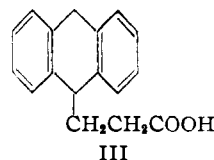
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The cyanoethylation of anthrone as previously carried out by Bruson² gave 9,9-di-(β -cyanoethyl)-anthrone in 88% yield. Since it has been shown that certain phenols can be monocyanoethylated in excellent yield on a ring carbon³ it was thought that anthrone as its potassium enolate salt could be monocyanoethylated in the 10-position. This has been carried out in excellent yield by allowing potassium anthranolate (I) to react with acrylonitrile in *t*-butyl alcohol using potassium *t*-butoxide as the condensing agent. The product was not isolated but was hydrolyzed and reduced with zinc dust in ammonium hydroxide to β -(9-anthranyl)-propionic acid (II) which was obtained in over-all yield of 90–95% from anthrone.



Reduction of the β -(9-anthranyl)-propionic acid (II) with sodium in *n*-amyl alcohol gave an 86% yield of β -(9,10-dihydro-9-anthranyl)-propionic acid (III). This synthesis of the dihydro acid (III) in 77.6% over-all yield from anthrone represents



considerable improvement over its three-step syn-

(1) This work was supported in part by a grant from the National Cancer Institute, U. S. Public Health Service.

(2) H. A. Bruson, *THIS JOURNAL*, **64**, 2457 (1942).

(3) H. A. Bruson, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 94.

thesis from 9-anthraldehyde described by Cook, Ludwiczak and Schoental.¹

Experimental⁵

β -(9-Anthranil)-propionic Acid (II).—A 1-l., three-necked flask with ground glass joints was fitted with a dropping funnel, condenser and mercury-sealed stirrer. The air in the system was replaced by dry nitrogen and 200 ml. of *t*-butyl alcohol⁶ was added. After 4.88 g. (0.125 mole) of potassium was dissolved in the alcohol, 19.4 g. (0.1 mole) of anthrone,⁷ m.p. 154–155°, was added with the aid of 10 ml. of *t*-butyl alcohol and the solution was stirred for one hour at room temperature. To this reddish-brown solution of potassium anthranilate was added dropwise over a period of one hour a solution of 7.3 ml. (0.11 mole) of acrylonitrile (Eastman Kodak Co.) in 40 ml. of anhydrous *t*-butyl alcohol. During the addition of the nitrile a bright red precipitate separated. The solution was refluxed for two hours and a clear deep red colored solution was obtained. After the addition of 11 ml. of concentrated hydrochloric acid (sp. gr. 1.18) in 225 ml. of water the *t*-butyl alcohol was removed by distillation during which time an additional 100 ml. of water was added. After the removal of 350 ml. of distillate the contents remaining in the flask were cooled and the aqueous layer was separated from a brown oil by decantation. The oily nitrile was refluxed for two hours with 100 ml. of concentrated hydrochloric acid during which time a solid acid separated. After cooling, the hydrochloric acid was removed with the aid of a sintered glass filter stick and the solid remaining in the flask was washed with 100 ml. of water. The solid acid was dissolved in 360 ml. of concentrated ammonium hydroxide and 240 ml. of water and the resulting solution was heated at 90–95° in an oil-bath for four hours with 60 g. of zinc dust (activated with copper sulfate). During the reduction the solution changed in color from reddish-orange to pale yellow. The cooled reaction mixture was filtered to remove excess zinc and the filtrate was extracted once with ether. The aqueous layer was acidified with hydrochloric acid and a tan oil separated which solidified on standing. The solid was filtered, washed with water and dried to give 22.5 g. (90% yield) of β -(9-anthranil)-propionic acid (II), m.p. 190–193° (reported⁴ m.p. 191–192°), as pale yellow crystals. Recrystallization of a small sample of the crude acid from glacial acetic acid gave pale yellow prisms, m.p. 194–195°.

In a larger run using 0.3 mole of anthrone and *t*-butyl alcohol (Eastman Kodak Co.) which had not been dried over sodium the yield of crude acid obtained was 71.3 g. (95% yield), m.p. 188–193°. When methyl acrylate was substituted for the nitrile in the condensation the yield of β -(9-anthranil)-propionic acid (II) was lowered to 60%.

β -(9,10-Dihydro-9-anthranil)-propionic Acid (III).—Twenty grams (0.08 mole) of crude β -(9-anthranil)-propionic acid (II), m.p. 190–193°, was dissolved in 500 ml. of *n*-amyl alcohol (Eastman Kodak Co., practical grade) in a 1-l. round-bottomed flask equipped with a reflux condenser. To this refluxing solution was added 16.6 g. (0.72 mole) of sodium in small pieces over a period of five hours. The *n*-amyl alcohol was removed by steam distillation and the aqueous solution remaining in the flask was filtered and allowed to cool. The sodium salt of the dihydro acid crystallized in glistening plates and was filtered, washed with water, and redissolved in hot water. The resulting solution was acidified with hydrochloric acid to give 15.07 g. (74.5% yield) of almost colorless β -(9,10-dihydro-9-anthranil)-propionic acid (III), m.p. 137–140° (reported⁴ m.p. 139–140°). Acidification of the mother liquor from the crystallization of the sodium salt gave 5.9 g. of a yellow solid, m.p. 120–130°, which upon recrystallization from benzene gave an additional 2.32 g. (11.5% yield) of almost colorless dihydro acid (III), m.p. 134–140°. Recrystallization of a sample of the acid from benzene gave colorless crystals, m.p. 139–140°.

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(4) J. W. Cook, R. S. Ludwiczak and R. Schoental, *J. Chem. Soc.*, 1112 (1950).

(5) All melting points are uncorrected.

(6) Dried by refluxing over and distilling from sodium.

(7) K. H. Meyer, "Organic Syntheses," Coll. Vol. 1, John Wiley & Sons, Inc., New York, N. Y., 1941, p. 60.

5-Ethoxyquinoxaline¹

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The recent synthesis of 5-hydroxyquinoxaline^{3,4} prompts us to report the synthesis of 5-ethoxyquinoxaline which had been prepared as an intermediate in this Laboratory. It was prepared from the known 2,3-dinitrophenetole⁵ by catalytic reduction to the intermediate 2,3-diaminophenetole, which was not isolated but condensed with sodium glyoxal bisulfite to form 5-ethoxyquinoxaline. Both 5-ethoxyquinoxaline and copper-5-quinoxalinate have been found to produce 100% inhibition of the standard organism, *Aspergillus niger*, in 250 parts per million concentrations. Further investigation of the fungistatic properties of these compounds is in progress.

Experimental

2,3-Dinitrophenetole.—The method of Blanksma⁵ as modified by Verkade and Witjens⁶ was not found satisfactory for preparing the desired quantity of product. However, the following procedure was employed to obtain the 2,3-dinitrophenetole in reasonable yield and in a good state of purity. Twenty grams (0.088 mole) of 1-ethoxy-2,3-dinitro-4-aminobenzene⁶ was dissolved in 200 ml. of concentrated sulfuric acid; 70 g. of water was added dropwise to the acid solution with mechanical stirring in an ice-bath. The suspension of the sulfate was diazotized at 0–5° with a solution of 6.07 g. (0.088 mole) of sodium nitrite in 25 g. of water, which was added dropwise in about 35 minutes. The diazonium solution was stirred for another hour at the same temperature and poured into a liter of boiling 95% ethanol. The mixture was boiled for 45 minutes, then diluted with enough water to give a final volume of about 4 liters. A dark brown precipitate formed during the dilution and was removed by filtration on a buchner funnel. The yield of the crude product was 13.6 g., m.p. 96–99°. The average yield from seven similar runs was 14.0 g. If further purification is desired, the product can be crystallized from 95% ethanol. For our use the product was not further purified.

5-Ethoxyquinoxaline.—Forty-eight grams (0.226 mole) of 2,3-dinitrophenetole was dissolved in 1800 ml. of 95% ethanol and reduced with hydrogen in the presence of 6 g. of 5% palladium-on-charcoal catalyst. During filtration from catalyst, the solution darkened considerably. To the filtrate was added 100 ml. of 2 *M* acetic acid and 50 ml. of 4 *M* sodium acetate solution. The resulting solution was heated to 60° and poured rapidly into a solution of 67.11 g. (0.226 mole) of sodium glyoxal bisulfite (Carbide and Carbon Chemicals Corp.) in 2 liters of water which had previously been heated to 60° and the mixture was stirred for one hour. It was then cooled in an ice-bath and made strongly alkaline by the addition of 120 g. of sodium hydroxide pellets and 500 g. of sodium carbonate. The mixture separated into two layers, a clear aqueous layer and a dark alcohol-water layer. The layers were separated, and the dark alcohol layer was reduced to less than half its volume at the water-pump. This dark mixture was then recombined with the clear layer, and a dark oil separated which was extracted with a pound of benzene. The benzene extract was dried over anhydrous calcium sulfate. The benzene was then removed at the water-pump, and the residual dark oil was vacuum distilled. The fraction that distilled from 106–117° at 0.5 to 2 mm. was collected. It was brownish-yellow in color and solidified in the receiving flask. Recrystallization from petroleum ether gave a white prod-

(1) Taken from the thesis submitted by William K. Easley in partial fulfillment of the requirements for the Ph.D. degree at The Division of Chemistry, Graduate School, Georgetown University, Washington, D. C.

(2) The Chemstrand Corporation, Marcus Hook, Pennsylvania.

(3) F. E. King, N. G. Clark and P. M. H. Davis, *J. Chem. Soc.*, 3012 (1949).

(4) S. K. Freeman and P. E. Spoerri, *J. Org. Chem.*, **16**, 438 (1951).

(5) J. J. Blanksma, *Rec. trav. chim.*, **27**, 49 (1908).

(6) P. E. Verkade and P. H. Witjens, *ibid.*, **65**, 361 (1946).