N-Isopropylethylenediamine dipicrate: Calcd. for $C_5H_{14}N_2 \cdot 2C_6H_3N_3O_7$: C, 36.4; H, 3.6. Found: C, 36.7; H, 4.1.

N-Butylethylenediamine dipicrate: Calcd. for $C_6H_{16}N_2 \cdot 2C_6H_3N_3O_7$: C, 37.6; H, 3.8. Found: C, 37.3; H, 4.0.

Grateful acknowledgment is made to the Dow Chemical Co. which furnished a sample of 2-bromoethylamine hydrobromide, and to Sharples Chemicals, Inc., which furnished the *n*-propylamine.

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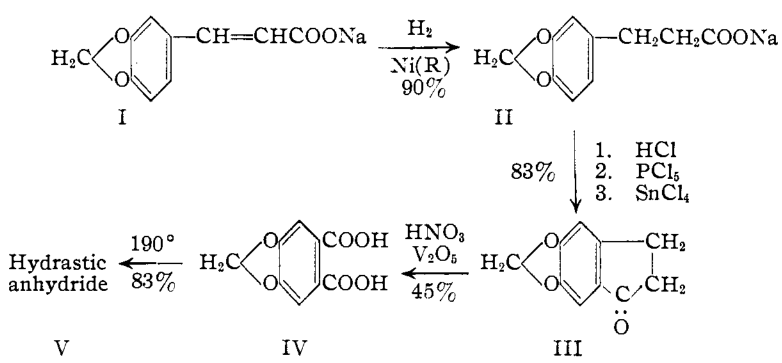
RECEIVED OCTOBER 6, 1950

The Synthesis of Hydrastic Acid

BY WILKINS REEVE AND HERBERT MYERS

Of the methods available for the preparation of hydrastic acid[1,2,3] (IV), the four step scheme of Perkin and Robinson appears to be the most promising even though the over-all yield from piperonal is only 2 to 3%. In the present work, these steps have been carried out by different means with the result that hydrastic acid can be obtained in an over-all yield of 25–27%, and hydrastic anhydride in an over-all yield of 20–23%. The greatest improvement has been realized in the oxidation step III → IV which was effected in 45% yield in contrast with less than 5% by the old method.



Melting points ranging from 172 to 188°[1,4] have been reported for hydrastic acid. We have found its melting point to be approximately 225° by a procedure which corrects for the lowering of the observed melting point occurring, due to decomposition, during the time the melting point sample is heated. The time necessary for the sample to melt when placed in a bath at a given temperature is plotted against the temperature as shown in Fig. 1. The straight line AB represents the time required for the heat to flow through the capillary tube and the sample; the temperature of immediate melting is where the lines meet. This procedure may prove useful with other thermally unstable materials.

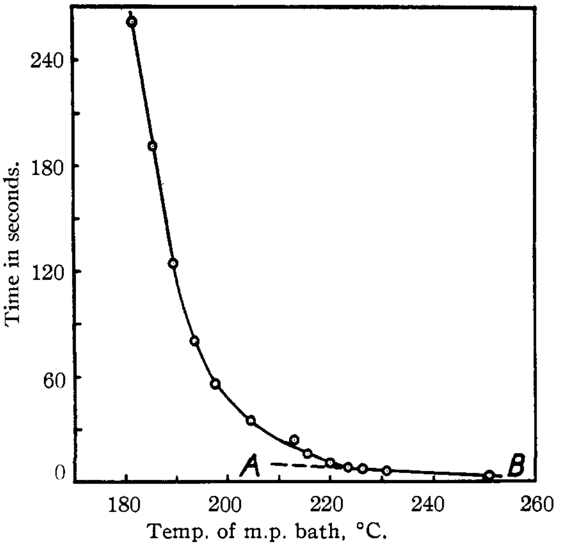


Fig. 1.—Relationship between m.p. of pure hydrastic acid and time sample is in the m.p. bath.

In view of the unsuitability of the melting point as a measure of purity, the solubility temperature[5] was determined, and found to be 86.5° at a 12:1 ratio of water to hydrastic acid. The solubility temperatures at other ratios were also determined over the temperature range of 34 to 87°, and from these data a solubility equation was calculated.

$$\log S = 0.2879 + 0.01384t + 5.82 \times 10^{-6} t^2$$

S = solubility in g./l. water; t = temp. in °C.

The maximum deviation between the observed and the calculated solubility data using the above equation is 2%. Some values for the calculated solubility are: at 20° (3.9 g./l.), 40° (8.6), 60° (21.3), 80° (57), 100° (180). By differentiation of the above equation, it can be calculated that the solubility temperature at a 12:1 ratio is lowered 0.18° for each per cent. of soluble impurity.

Experimental

All melting points are corrected. Analyses are by Mrs. Mary Aldridge and Mr. Byron Baer of this Laboratory.

3,4-Methylenedioxydihydrocinnamic acid was prepared by hydrogenating a slurry of the sodium salt of 3,4-methylenedioxycinnamic acid[6] (from 380 g. (1.98 moles) of the acid and 80 g. of sodium hydroxide) in 1300 ml. of distilled water under 3000 lb. (200 atm.) pressure at 110–130° over 50 g. of Raney nickel for 2 hours. The reaction mixture was filtered to remove the catalyst and acidified with concentrated hydrochloric acid to congo red. Water was added as necessary to thin the thick slurry of the insoluble acid which precipitated. After filtering and air drying, 345 g. (90%) was obtained, m.p. 83–84°; reported m.p. 87–88°.[1] This light tan colored material was satisfactory for the next step. A pure white product, m.p. 87–88°, was obtained after two recrystallizations from water, using 2 g. of acid and 0.4 g. of activated carbon (Darco G-60) per 100 ml. of water. The yield after two recrystallizations was 1.4 g.

5,6-Methylenedioxyhydrindone-1.—The acid chloride of the dihydrocinnamic acid was prepared by adding 208 g. (1 mole) of phosphorus pentachloride to a chilled solution of 194 g. (1 mole) of the crude 3,4-methylenedioxydihydrocinnamic acid, dissolved in 1500 ml. of dry, thiophene-free benzene, and stirring for 1.5 hours at room temperature. An excess of the phosphorus pentachloride attacks the methylenedioxy bridge and lowers the yield.

The cyclization was carried out by the dropwise addition

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[1] W. H. Perkin, Jr., and R. Robinson, *J. Chem. Soc.*, **91**, 1084 (1907).

[2] E. Oertly and A. Pictet, *Ber.*, **43**, 1336 (1910).

[3] T. S. Stevens and M. C. Robertson, *J. Chem. Soc.*, 2790 (1927).

[4] M. Freund, *Ann.*, **271**, 370, 381 (1892).

[5] W. Reeve and R. K. Adams, *Anal. Chem.*, **22**, 755 (1950).

[6] R. D. Haworth, W. H. Perkin, Jr., and J. Rankin, *J. Chem. Soc.*, **125**, 1693 (1924).

over a 3-hour period of the above benzene solution to a chilled and stirred solution of 521 g. (2 moles) of anhydrous stannic chloride dissolved in 300 ml. of benzene and stirring for 15 minutes. The solid tin complex was changed to a liquid complex by adding 300 ml. of ordinary ether. The reaction mixture was poured into a mixture of 4 l. of 6 *N* NaOH and 2 to 3 liters of chopped ice and stirred for 15 minutes. The benzene layer was separated, and the hydrindone suspended in the alkaline solution allowed to stand overnight. It was then filtered, washed with water, thoroughly air-dried, dissolved in 5 l. of boiling benzene to remove inorganic salts and filtered hot. The benzene solutions were combined and steam distilled to remove the benzene, and the resulting insoluble hydrindone filtered and washed with water. A light yellow material (148 g., 83% of theory) m.p. 159–164° was obtained which was pure enough for the next step. A pure white product was obtained by crystallizing 10 g. of the hydrindone from 150 ml. of a 2:1 ethanol–water mixture in the presence of 3.5 g. of activated carbon. There was obtained 8.2 g., m.p. 163–164°; reported m.p. 160°[1] and 161°.[7]

Hydrastic Acid.—A mixture of 100 g. (0.57 mole) of 5,6-methylenedioxyhydrindone-1, 6 g. (0.03 mole) of vanadium pentoxide, 1200 ml. of distilled water, and 300 ml. of concentrated nitric acid was heated in a 5-l. flask under reflux until the reaction started, and then for 1.5 hours, with occasional swirling, after the violent phase of the reaction had subsided. The hot reaction mixture was quickly filtered through asbestos to remove the vanadium pentoxide before some of the hydrastic acid crystallized. The filtrate was neutralized to litmus with 15% sodium hydroxide solution, acidified with glacial acetic acid to a congo red endpoint, and then heated to the boiling point. Lead acetate solution (500 ml., 10%) was added until the lead salt of hydrastic acid was completely precipitated, the mixture allowed to cool, filtered, and the yellowish-white precipitate washed with three 100-ml. portions of 3% acetic acid.

The lead salt was converted to crude hydrastic acid by making a slurry with 900 ml. of tap water, heating to boiling, and adding concentrated nitric acid (75 ml.) dropwise from a buret until solution was effected. The hot solution was filtered by gravity through a heated funnel, and the filtrate cooled slowly to ice-bath temperature, allowed to stand 0.5 hour, filtered, washed with two 75-ml. portions of ice-water, and air-dried (yield 66 g.). An additional 17 g. of crude hydrastic acid was obtained from the filtrate by neutralizing as before to precipitate the hydrastic acid as lead hydrastate, filtering, washing and converting this to the crude hydrastic acid as above. The material was often contaminated with small amounts of lead hydrastate.

The combined, crude fractions of hydrastic acid were purified by two precipitations as the lead salt and a recrystallization from water. This was done by dissolving the material in 800 ml. of boiling tap water (adding a little nitric acid if an appreciable amount of the insoluble lead hydrastate was present), and precipitating the lead hydrastate with 10% lead acetate solution (approximately 500 ml. was required). If nitric acid was added, an equivalent amount of sodium hydroxide was added at this point. The lead salt was filtered, dissolved again in dilute nitric acid, filtered, neutralized to litmus with sodium hydroxide solution and acidified to congo red with acetic acid as before, and the lead hydrastate then converted to hydrastic acid as before. The yield was 57 g., solubility temperature 86.1° at 12:1 (corresponding to a purity of 98%), with a neutralization equivalent of 104.7 (theory, 105.0). An additional 5 g. was recovered from the filtrate by precipitating the lead salt, etc., as previously described. The combined 62 g. of pale yellow hydrastic acid was recrystallized from 620 ml. of distilled water, using 6 g. of activated carbon (Darco G-60) to remove the color. An almost white product resulted (53 g., 44.5% of theory), solubility temperature 86.5° at 12:1. This material was used to prepare the anhydride.

A pure white product, having the same solubility temperature, was obtained after three more recrystallizations from water with activated carbon. *Anal.* Calcd. for $C_9H_6O_6$: C, 51.44; H, 2.88. Found: C, 51.42; H, 2.91. The following solubility temperatures were determined: 12:1, 86.5°; 25:1, 73.8°; 50:1, 58.7°; 100:1, 42.8°; 150:1, 33.9°.

Hydrastic Anhydride.—This was prepared by stirring and heating 50 g. of hydrastic acid for 5 minutes after melting in a 1000-ml. beaker immersed in an oil-bath maintained at 190°.[4] A light tan product (44 g., 96%), m.p. 178.5–181° was obtained. This was dissolved in 1000 ml. of hot benzene, 9 g. of activated carbon added, filtered hot through asbestos, cooled to 10°, and filtered. There was obtained 29 g. of a pure white product (64% of theory), m.p. 179–180° (determined in a sealed tube); reported m.p., 175°.[4] *Anal.* Calcd. for $C_9H_4O_5$: C, 56.59; H, 2.11. Found: C, 56.48; H, 2.30. An additional 9 g. of white material, m.p. 177.5–179.5°, was isolated by concentrating the filtrate (total yield, 83%).

Acknowledgment.—We wish to express our appreciation to the National Institutes of Health for a grant which made this work possible. Mr. Roy G. Weston of these laboratories worked out the conditions for the hydrogenation of the 3,4-methylenedioxycinnamic acid.

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RECEIVED OCTOBER 16, 1950

Quinazolines. XI. Synthesis of Several Aminoquinazolines and Their Sulfa Derivatives[1]

BY M. B. NAFF AND B. E. CHRISTENSEN

Although the search for new sulfa drugs has been most extensive very little attention has been given to the sulfaquinazolines. For this reason the work in this Laboratory was extended to include the synthesis of a number of such compounds.

The principal task in the execution of such a program is the synthesis of the various aminoquinazolines required for the coupling. In this study all the isomeric aminoquinazolines were prepared with the exception of the 2- and 4-aminoquinazolines. The 2-aminoquinazoline in contrast to the 4-amino isomer, had been previously successfully coupled with acetylsulfanilyl chloride by Dewar.[2] Macbeth and Rodda,[3] however, report the successful preparation of a sulfaquinazoline using 4-aminoquinazoline but failed to give any details or analytical data. Earlier work in this Laboratory had indicated that it would be difficult if not impossible to couple the 4-amino isomer due to its amide-like characteristics, thus confirming the experiments of Dewar.

5-Aminoquinazoline was synthesized from 5-nitro-4-quinazolone which had been prepared according to the directions of Bogert.[4] This nitroquinazolone was converted to the 4-chloro derivative. The reduction of 4-chloro-5-nitroquinazoline was extremely difficult; it was necessary to subject this material to prior purification using Raney nickel, remove the nickel and then proceed with the reduction using palladized calcium carbonate at 0° following essentially the directions of Elderfield.[5] This critical operation yields the dihydroderivative of 5-aminoquinazoline which was found to be very sensitive to air oxidation. For this reason it was necessary to remove the palladized

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[7] W. Borsche and W. Eberlein, *Ber.*, **47**, 1469 (1914).

[1] The work in this paper was made possible by a grant-in-aid from the Research Corporation. Published with the approval of the Monograph Publications Committee, Oregon State College, as Research Paper No. 169, School of Science, Department of Chemistry.

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