Experimental

The nitroaminoguanidine was prepared by the method of Phillips and Williams,[5] and was recrystallized repeatedly from water to a purity of 99.9 ± 0.1% as determined by a Jamieson hydrazine nitrogen analysis.[6] The melting point is an unsatisfactory criterion for ascertaining the purity of this compound.

The solubility was determined in three types of aqueous systems: (1) distilled water, (2) distilled water in which the *p*H had been adjusted with a 0.1 *N* solution of hydrochloric acid or sodium hydroxide, and (3) 0.25 molal sodium phosphate buffer solutions made by mixing suitable ratios of mono-, di- or tri-sodium orthophosphate. About 1 g. of nitroaminoguanidine was dissolved in 100 ml. of such a solution in a glass-stoppered flask, the whole cooled to the desired temperature and kept at that temperature by a thermostat constant to ±0.1°. After two hours of agitation (longer might cause hydrolysis) samples of 5 to 25 g. were removed by pressure filtration through a fine-pored, sintered Pyrex glass filter stick into stoppered and tared iodine flasks. The cooled samples were weighed and then titrated with potassium iodate by the Jamieson[6] method. For a given set of conditions, the reproducibility of the solubility determination was about five parts per 1000. Suitable corrections have been applied to the determinations in the buffered solutions for the weight of dissolved phosphate, and the results expressed in grams per 100 g. of water.

The *p*H was measured at 30° on filtered samples of solution after temperature and solution equilibrium had been established.

(5) Phillips and Williams, *ibid.*, **50**, 2465 (1928).

(6) Jamieson, *Am. J. Sci.*, **33**, 352-353 (1912); "Volumetric Iodate Methods," Chemical Catalog Co., Inc., New York, N. Y., 1926, p. 36. Also see Smith and Wheat, *Ind. Eng. Chem., Anal. Ed.*, **11**, 200 (1939).

INORGANIC CHEMISTRY SECTION
CHEMISTRY DIVISION
U. S. NAVAL ORDNANCE TEST STATION
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Acetic Propionic Anhydride

BY J. B. POLYA AND T. M. SPOTSWOOD

In the course of investigating acylating mechanisms by unsymmetrical acylating agents, acetic propionic anhydride was required. The only reference to this compound which we have been able to find is contained in a paper of Verkade[1] who has prepared it from propionyl chloride and potassium acetate and who has determined the hydrolytic constant. Verkade determined the molecular weight by saponification and concluded from this determination that his product was a pure compound. It is true that previous distillation of the product at a boiling point intermediate between those of acetic and propionic anydrides made the presence of an exactly equimolecular mixture of acetic and propionic anhydrides very unlikely, but it was felt that a more rigorous proof of purity would be desirable.

Anhydrous sodium acetate (20 g.) was made into a paste with dry ether (20 cc.); propionyl chloride (20 g.) was added gradually while the mixture was cooled with water. On completing the addition the mixture was refluxed on a water-bath for two hours. More ether (20 cc.) was added, the mixture was filtered, the ether removed and the residue fractionated under reduced pressure. The first fraction boiling between 55 and 61° under 29 mm. pressure was discarded. The next fraction distilled between 61 and 67° at the same pressure. The residue consisted of an oil which did not boil below 160° (29 mm.). The second fraction was redistilled at 70–75° (40 mm.) with very little loss. This fraction boiled at 153.5° at 760 mm. without decomposition and was shown to be pure acetic propionic anhydride. The yield was 15 g. or 60%.

The boiling point at 40 mm. pressure is identical with the one reported by Verkade. The average boiling points at three pressures fit well on a Clausius–Clapeyron line. Assuming absence of association, the molecular weight was found to be 116.5 by saponification. At 17° the specific gravity was 1.0367 and the refractive index n_D 1.4020. The molecular refractivity from these data is 27.26 against 26.96 required by theory.

Acetic propionic anhydride (5.00 g.) and absolute ethanol (1.98 g.) was refluxed for forty-five minutes. The mixture was chilled and diluted with ice-water. The mixed esters were isolated by separating the supernatant layer of esters, extracting the residue with ether and then washing and drying the ethereal solution of the esters before removing the solvent. A portion of the mixed esters was saponified by normal alcoholic alkali and titrated with 0.1 *N* hydrochloric acid. In this manner the mixture was found to contain 64.4% ethyl acetate and 35.6% ethyl propionate. Previous experiments of a similar nature with N-acetylpropionamide gave 62–66% ethyl acetate and 34–38% ethyl propionate.[2] When the experiment was repeated with the same quantities using an equimolecular mixture of acetic and propionic anhydrides the ester mixture was found to contain 50.7% ethyl acetate and 49.3% ethyl propionate.

(1) Verkade, *Rec. trav. chim.*, **35**, 299 (1916).

(2) Polya and Spotswood, *ibid.*, **67**, 927 (1948).

CHEMISTRY DEPARTMENT
UNIVERSITY OF TASMANIA
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The Preparation of 3-Iodoalizarin

BY MARGARET G. PRATT AND S. ARCHER

In the course of some biological studies, it became desirable to have at hand an alizarin derivative which was opaque to X-rays. Accordingly, we investigated the preparation of 3-iodoalizarin, a substance which seemed to fulfill the requirements.

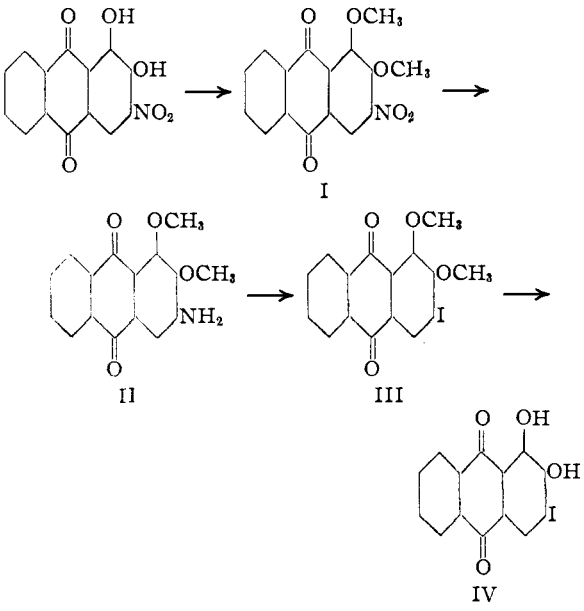
The compound has been prepared previously by Perkin and Story[1] who iodinated alizarin-1-methyl ether (1-methoxy-2-hydroxyanthraquinone) and then demethylated the product. Unfortunately the starting material is difficultly accessible and the synthesis does not appear to be adaptable to larger scale preparations.

The procedure we employed is outlined below. 3-Nitroalizarin[2] was methylated previously by Perkin[3] who employed the dipotassium salt and a large excess of sodium carbonate and methyl sulfate. We were able to duplicate their experiment only once and found subsequently that a minor variant in detail, namely, doubling the recommended amount of sodium carbonate, ensured the reproducibility of their preparation. The conversion of the nitro ether, I, to the amine, II and the iodo ether, III, was carried out according to more or less established procedures. De-

(1) Perkin and Story, *J. Chem. Soc.*, 2620 (1931).

(2) Schunk and Roemer, *Ber.*, **12**, 584 (1879).

(3) Perkin and Story, *J. Chem. Soc.*, 1416 (1929).



methylation of III gave the desired iodoalizarin which corresponded in properties to the compound prepared originally by Perkin.[1]

Experimental

1,2-Dimethoxy-3-nitroanthraquinone (II).—To a stirred suspension of 45 g. of 3-nitroalizarin in one liter of ethanol there was added a solution of 17.7 g. of potassium hydroxide in 400 ml. of ethanol. The dark precipitate was filtered off, washed with ethanol and dried. The salt was pulverized, leached with boiling ethanol and filtered. After drying at 100° the product weighed 57 g. It was suitable for the methylation step.

A suspension of 5.8 g. of the dry potassium salt and 32 g. of anhydrous sodium carbonate in 26 ml. of dimethyl sulfate was warmed to 140° in the course of forty-five minutes and held there for one-half hour. After cooling to room temperature the mixture was washed with water and the semi-solid residue taken up in boiling benzene. The extract was filtered from a small amount of insoluble material, concentrated and then treated with ligroin. On cooling, the ether separated. The crystals were removed by filtration and recrystallized from the same solvent pair to give 2.4 g. of yellow needles, m. p. 165–167° (lit. val. 168–171°). Runs five times the size gave comparable yields.

3-Amino-1,2-dimethoxyanthraquinone.—The reduction of the nitro compound was carried out according to the method of Perkin and Story.[3] From 10 g. of the nitro body we obtained 6.0 g. of the amine, m. p. 204°, after recrystallization from benzene.

1,2-Dimethoxy-3-iodoanthraquinone.—Six grams of the aminoanthraquinone was dissolved in 400 ml. of acetic acid with gentle warming. Then 27.6 ml. of 0.1 *N* hydrochloric acid and 140 ml. of water was added and the suspension cooled to 5°. Diazotization was carried out with the aid of 1.6 g. of sodium nitrite in 30 ml. of water. After two hours the solution was filtered and added to potassium iodide solution (8.5 g. in 100 ml. of water). The mixture was warmed to 60°, kept there for thirty minutes and filtered. After crystallization from ethanol the product melted at 165–167°; wt., 6.0 g.

Anal. Calcd. for $C_{16}H_{11}IO_4$: I, 32.2. Found: I, 31.3.

1,2-Dihydroxy-3-iodoanthraquinone (3-Iodoalizarin).—A quantity of 7.3 g. of the above ether was demethylated according to the method of Perkin and Story.[1] There was obtained 4.3 g. of pure 3-iodoalizarin which melted at 228.6–229.7° (cor.) after two crystallizations from xylene. Perkin[1] reported 227–229° as the melting point for the compound.

Anal. Calcd. for $C_{14}H_7IO_4$: I, 34.67. Found: I, 34.44.

STERLING-WINTHROP RESEARCH INSTITUTE
RENSSELAER, NEW YORK RECEIVED MARCH 14, 1949

Crystalline Naphthalene-β-sulfonates of Streptomycin and Dihydrostreptomycin

BY PETER P. REGNA AND R. A. CARBONI

Several crystalline derivatives of streptomycin have been reported, namely, the reineckate sulfate,[1] helianthate,[2] calcium chloride double salt,[3] and the trihydrochloride.[4] We have prepared crystalline naphthalene-β-sulfonates of streptomycin and dihydrostreptomycin which are sparingly soluble in water, but very soluble in methyl alcohol. Both salts crystallize from water in fine needles. Under similar conditions, the naphthalene α-sulfonate salt of streptomycin and dihydrostreptomycin showed no tendency to crystallize.

The streptomycin and dihydrostreptomycin naphthalene-β-sulfonates were prepared by dissolving 2.5 g. of the amorphous sulfate in 10 ml. of water. An equal amount of naphthalene-β-sulfonic acid was dissolved in 10 ml. of water. Both solutions were warmed to 40°, mixed, and the solution was neutralized to *p*H 6.5 with a saturated solution of barium hydroxide. The precipitate was filtered, and the filtrate was allowed to crystallize.

When the white streptomycin naphthalene-β-sulfonate was dried for three hours at 100° *in vacuo*, it gave the following analysis: Calcd. for $C_{21}H_{39}N_7O_{12}\cdot 3C_{10}H_7SO_3H$: C, 50.78; H, 5.26; N, 8.12; S, 7.97. Found: C, 50.69; H, 5.54; N, 8.45; S, 8.35. The anhydrous material gave $[\alpha]^{25}D$ −56.5° (*c*, 1% in water) and melted at 177–179°. Based on the Food and Drug Administration working standard, the crystalline salt should have a potency of 482 γ/mg. When assayed against *Escherichia coli* and *Bacillus subtilis* by methods of the Food and Drug Administration,[5] the material showed 475 γ/mg. and 505 γ/mg., respectively. In addition, chemical assays based on the maltol method[6] gave 490 γ/mg. and a modified guanidino assay[7] showed 490 γ/mg.

After drying the dihydrostreptomycin naphthalene-β-sulfonate for three hours at 100° *in vacuo*, the anhydrous salt had the following composition: *Anal.* Calcd. for $C_{21}H_{41}N_7O_{12}\cdot 3C_{10}H_7SO_3H$: C, 50.70; H, 5.42; N, 8.11; S, 7.96. Found: C, 50.95; H, 5.60; N, 8.33; S, 7.95. The anhydrous salt gave $[\alpha]^{25}D$ −52.1° (*c*, 1% in water); m. p. 184–186°. It produced a negative maltol test and assayed 530 γ/mg. by the streptidine analysis. Biological assays using *E. coli* gave 480 γ/mg. and using *B. subtilis* 505 γ/mg.

The acute mouse toxicity (LD_0) for the streptomycin salt is 4.5 mg. per 20 g. mouse (2100 γ) and for the dihydrostreptomycin salt 5.0 mg. per 20 g. mouse (2400 γ).

We wish to express our appreciation to Dr. B. Sobin

(1) Fried and Wintersteiner, *Science*, **104**, 273 (1946).
(2) Kuehl, Peck, Walti and Folkers, *ibid.*, **102**, 34 (1945).
(3) Peck, Brink, Kuehl, Flynn, Walti and Folkers, THIS JOURNAL, **67**, 1866 (1945).
(4) Heuser, Dolliver and Stiller, *ibid.*, **70**, 2833 (1948).
(5) Federal Register 12, 2224-2225 (April 4, 1947).
(6) Boxer, Jelinek and Leghorn, *J. Biol. Chem.*, **169**, 153 (1947).
(7) Monastero, unpublished results.