The acetone was evaporated and the residue was treated with water (150 cc.). The insoluble crystalline residue was filtered, washed thoroughly with water, and dried, giving white crystals (0.090 g., 0.000242 mole, 87%), m.p. 162–164°, having an infrared spectrum in Nujol identical with that of the analytical sample. Two recrystallizations from 95% ethanol yielded white needles (0.073 g., 70%), m.p. 164°; λ_{max} mμ (log ϵ) in 95% C_2H_5OH: 226 (4.65), 264 (4.22), 285 (3.95), 293 (3.95), 315 infl. (3.54); ν_{NH} none, $\nu_{C=C}$ 1606 cm.$^{-1}$ in Nujol. The infrared spectrum in Nujol was identical with the corresponding spectra of the samples described in parts A and B.

Anal. Calcd. for $C_{26}H_{32}N_2$ (372.53): C, 83.82; H, 8.66; N, 7.52. Found: C, 83.75; H, 8.69; N, 7.73.

The Dinitration of *m*-Toluic Acid

G. H. HARRIS, P. S. TRAYLOR,[1] B. C. FISCHBACK, AND A. W. BAKER

The Dow Chemical Co., Pittsburg, Calif.

Received December 12, 1961

The nitration of *m*-toluic acid with a mixture of fuming nitric and sulfuric acids was recently carried out by Blatt.[2] He separated the reaction products and isolated approximately equal proportions of 2,6-dinitro-*m*-toluic acid and 4,6-dinitro-*m*-toluic acid.

We have nitrated *m*-toluic acid using Blatt's procedure and have analyzed the reaction products by differential infrared analysis after quantitative conversion to their methyl esters *via* diazomethane. The mixture was found to contain 53 ± 0.5% 2,6-dinitro-*m*-toluic acid, 43 ± 1% 4,6-dinitro-*m*-toluic acid, 2.5 ± 0.5% 2,4-dinitro-*m*-toluic acid, and 1.5 ± 0.5% of the isomeric 5,*x*-dinitro-*m*-toluic acids.

The samples of pure 2,4-, 2,6-, and 4,6-dinitro-*m*-toluic acids, which were used as analytical standards after conversion to their methyl esters, were prepared in the following manner. 4,6-Dinitro-*m*-toluic acid was prepared by the method of Errera and Maltese.[3] 2,4-Dinitro-*m*-toluic acid was prepared by diazotizing 2,4-dinitro-*m*-toluidine,[4] converting this to the nitrile, and then hydrolyzing to 2,4-dinitro-*m*-toluic acid. The same scheme was used to prepare the 2,6-dinitro-*m*-tolunitrile, but hydrolysis of this nitrile could not be carried beyond the amide. Attempts made to convert the amide to its acid involved common methods such as diazotization,[5] the use of potassium hydroxide,[6] 100% phosphoric acid,[7] or aqueous hydrochloric acid[8] at 230°.

We then decided to nitrate 2-nitro-*m*-toluic acid[9] in sulfuric acid solvent and then separate the 2,6-dinitro-*m*-toluic acid from the 2,4-dinitro isomer by a selective esterification technique.[10] We found that this nitration product contained 96.2 ± 0.5% 2,6-dinitro-*m*-toluic acid and 3.8 ± 0.5% 2,4-dinitro-*m*-toluic acid and that the former precipitated during the reaction in nearly pure form. Conversion of this acid to its corresponding amide gave a product which was identical with 2,6-dinitro-*m*-toluamide made by hydrolysis of the nitrile.

Physical properties of the heretofore unreported 2,4- and 2,6-dinitro-*m*-toluyl chlorides, amides, and nitriles are described in the Experimental.

Experimental[11]

Analytical Equipment.—The infrared analyses were obtained with a Beckman double-beam IR-7 prism-grating spectrophotometer. The samples were run 5% (weight per volume) in chloroform in 0.1-mm. cells. Samples were compared differentially against carefully prepared standard mixtures of the three isomers and, for additional accuracy, pen-expansion techniques were employed. The presence of the three isomers was unequivocally verified and the accuracy of the determinations checked by repeated sampling.

Nitration of *m*-Toluic Acid.—The method of Blatt[2] was repeated exactly.

2-Nitro-*m*-toluic Acid.—*m*-Toluic acid was nitrated by the procedure of Müller.[9] Filtration of the precipitate from nitric acid (*d* 1.5) and subsequent recrystallization from xylene gave the compound in 41.4% yield (m.p. 222.5–223.5°).

2,6-Dinitro-*m*-toluic Acid.—Nitrating acid was prepared by adding 23.2 g. (0.332 mole) of fuming nitric acid (*d* 1.5) to 200 ml. of concd. sulfuric acid. Forty grams (0.221 mole) of 2-nitro-*m*-toluic acid was quickly added to the nitrating mixture. During the addition the temperature of the reaction mixture rose from 36° to 52°, solution took place, and a new solid precipitated from the solution. After stirring an additional hour at 52°, the mixture was cooled to 20° and the solid filtered off. The latter was washed with sulfuric acid and then ice water. Yield of product melting at 178.5–179.5° was 30.2 g. (60.4%). Recrystallization from toluene gave 95% recovery of 2,6-dinitro-*m*-toluic acid melting at 178.7–179.5°. Blatt[2] reports 182–183°.

Anal. Calcd. for $C_8H_6N_2O_6$: C, 42.48; H, 2.67; N, 12.40. Found: C, 42.52; H, 2.59; N, 12.37.

The filtrate from the nitration was diluted with ice water. This precipitated 11.6 g. (23.2%) of a second fraction which proved to be a mixture of 2,4, and 2,6-dinitro-*m*-toluic acids melting at 156–176°. A composite mixture of the two fractions was found to contain 96.2 ± 0.5% of 2,6-dinitro-*m*-toluic acid and 3.8 ± 0.5% 2,4-dinitro-*m*-toluic acid by infrared analysis.

2,6-Dinitro-*m*-toluyl chloride was prepared by refluxing 6.3 g. (0.0278 mole) of 2,6-dinitro-*m*-toluic acid in 30 ml. of thionyl chloride for 1 hr. After the excess thionyl chloride was removed by reduced pressure distillation, 6.8 g. (99.9%) the crude acid chloride soldified. A small portion was removed and recrystallized from a 3:1 hexane–toluene mixture. The purified product, obtained as long pale yellow needles, melted at 87.7–88.9°.

Anal. Calcd. for $C_8H_5ClN_2O_5$: C, 39.30; H, 2.06; Cl,

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14.50; N, 11.45. Found: C, 39.90; H, 3.35; Cl, 14.48; N, 11.24.

Methyl 2,6-dinitro-*m*-toluate, prepared from the acid chloride with methanol, was obtained as pale, yellow needles melting at 83.5–85°. Blatt[2] reports a m.p. of 83–84°. It was found that this ester did not form by treatment of 2,6-dinitro-*m*-toluic acid with methanol in the presence of dry hydrogen chloride.

2,6-Dinitro-*m*-toluamide was prepared by treating the acid chloride dissolved in toluene with cold aqueous ammonia. Yield was 99% and the crude product melted at 234.2–236.2°. One crystallization from glacial acetic acid gave a purified product melting at 235.5–236.5°.

Anal. Calcd. for $C_8H_7N_3O_5$: C, 42.67; H, 3.13; N, 18.66. Found: C, 43.01; H, 3.05; N, 18.67.

This amide was also prepared by the following sequence of reactions. 2,3-Dinitro-*p*-toluidine[12] was oxidized with peroxytrifluoroacetic acid[13] in chloroform to yield 2,3,4-trinitrotoluene in 87.0% yield (m.p. 110.3–111.3°). This was then heated with ethanolic ammonia to 100° for 5 hr. to give a 94.6% yield of 2,6-dinitro-*m*-toluidine melting at 93.5–94°. This was converted to the nitrile *via* the Sandmeyer reaction. The nitrile which melted at 84.5–85° was hydrolyzed to the desired amide in 57.5% yield by refluxing in equal volumes of sulfuric acid, acetic acid, and water for 18 hr. The amide thus prepared melted at 234.2–235.0° and was in every respect identical with the amide prepared from the acid chloride described above.

2,4-Dinitro-*m*-toluic acid was prepared by converting 2,4-dinitro-*m*-toluidine[4] to 2,4-dinitro-*m*-tolunitrile *via* the Sandmeyer reaction. This nitrile (m.p. 60.2–60.9°) was refluxed with equal volumes of sulfuric acid, acetic acid, and water for 12 hr. followed by cooling and dilution with more water. The precipitate was filtered, taken up in an excess of sodium bicarbonate solution, and refiltered. The filtrate, when treated with an excess of hydrochloric acid, precipitated 2,4-dinitro-*m*-toluic acid in 91.5% yield, m.p. 201.5–202.5°.

Anal. Calcd. for $C_8H_6N_2O_6$: C, 42.48; H, 2.67; N, 12.40. Found: C, 42.64; H, 2.39; N, 12.43.

2,4-Dinitro-*m*-toluyl chloride was prepared from the corresponding acid by refluxing in an excess of thionyl chloride for 2 hr. After removal of the excess of thionyl chloride by reduced pressure distillation, the crude solid residue was recrystallized from 2,2,4-trimethylpentane in 80% yield. The purified product melted at 98–99°.

Anal. Calcd. for $C_8H_5ClN_2O_5$: C, 39.30; H, 2.06; Cl, 14.50; N, 11.45. Found: C, 39.58; H, 2.19; Cl, 14.25; N, 11.58.

Methyl 2,4-dinitro-*m*-toluate was prepared from the acid chloride and methanol. Yield of product melting at 136.0–136.8° was 82%.

Anal. Calcd. for $C_9H_8N_2O_6$: C, 45.02; H, 3.36; N, 11.67. Found: C, 45.03; H, 3.37; N, 11.60.

Treatment of 2,4-dinitro-*m*-toluic acid with methanol in the presence of dry hydrogen chloride gave this ester in 83.4% yield.

2,4-Dinitro-*m*-toluamide was prepared by treating 3.24 g. (0.01325 mole) of 2,4-dinitro-*m*-toluyl chloride dissolved in toluene with 4.4 g. (0.032 mole) of concd. ammonium hydroxide dissolved in ice water. The solid which precipitated was filtered, washed with ice water, and dried. One recrystallization from toluene gave 2.9 g. (97% yield) of 2,4-dinitro-*m*-toluamide melting at 179–180°.

Anal. Calcd. for $C_8H_7N_3O_5$: C, 42.67; H, 3.13; N. 18.66. Found: C, 43.04; H, 3.07; N, 18.63.

Acknowledgment.—We are indebted to Mrs. Ethel Rightmire for her help with the infrared analyses.

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Synthesis of 5-Ethyluridine, a Model 5-Alkyl Substituted Pyrimidine Nucleoside[1]

JACOB SHAPIRA

Radioisotope Service, Consolidated Veterans Administration Hospital, Little Rock, Ark., and the Department of Biological Chemistry, University of Illinois College of Medicine, Chicago, Ill.

Received August 14, 1961

In recent years, a wide variety of analogs of the pyrimidines and their derivatives have been prepared and tested for their antimetabolic properties. However, the 5-alkyl derivatives have been relatively neglected. In connection with studies of the relative effects of pyrimidine analogs on the metabolism of bacteria and human leukocytes, it was decided to prepare the riboside of 5-ethyluracil as a model compound of this type.

The pyrimidine base itself has been synthesized previously by a variety of methods[2–4] and two were examined here. The first of these followed the sequence of reactions described by Merkats[4a] but involved several modifications. All of the steps in his method were examined with the aim of increasing the yields. The final over-all yield obtained here for the series of reactions was about 30%. More recently, Burckhalter and Scarborough[4b] synthesized 5-ethyluracil in 18% yield by a different method.

5-Ethyluracil riboside was prepared using a modification of the procedure described by Fox.[6] 1-*O*-Acetyl-2,3,5-tribenzoyl-β-D-ribose[7] was converted to the corresponding 1-chloro compound, condensed with di(5-ethyluracil)mercury which had been prepared by a procedure similar to that described[6] for thymine, and the benzoylated riboside hydrolyzed with ammonia saturated ethanol. The product was obtained in 20% over-all yield after chromatography on Dowex-1.

Experimental

5-Ethylbarbituric Acid.—It was found that sodium methoxide in dimethylformamide gave consistently good yields and obviated the need for specially dried glassware and anhydrous ethanol. To a suspension of 60 g. (1.1 moles, 10% excess) of sodium methoxide in 600 ml. of anhydrous dimethylformamide was added, in small portions with constant stirring, 188 g.(1.0 mole) of ethyldiethylmalonate and then 60 g. (1.0 mole) of solid urea. The temperature of the reaction mixture was slowly raised to 130° with

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