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.

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

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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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constant stirring. It was quite thick at first but thinned rapidly. After heating for 3 hr., approximately one-half of the dimethylformamide was removed using reduced pressure; the residual very viscous material was taken up in 1.5 l. of water heated to 60°, and then acidified with hydrochloric acid. There was a slight evolution of carbon dioxide. The solution was allowed to stand at 4° overnight. Filtration gave 105.2 g. of crystalline material, m.p. 208–211°. An additional 18.5 g. were obtained from the mother liquors. Total yield was 123.7 g. (79% yield). Recrystallization from 50% ethanol gave 80.0 g. of white product, m.p. 194–195° (lit.,[4a] m.p. 193–194°), λ_{max} 268 mμ (0.1 *N* sodium hydroxide).

5-Ethyl-2,4,6-trichloropyrimidine.—By following essentially the procedure of Merkats, but with the addition of an equimolar amount of dimethylanaline, there was obtained an 85% yield of pure product, m.p. 76–79° (lit.,[4a] m.p. 75–77°), λ_{max}[1] 268.5 mμ, λ_{max} 223.5 mμ (ethanol).

6-Chloro-5-ethyl-2,4-dimethoxypyrimidine.—Using anhydrous sodium methoxide and the procedure of Merkats, there was obtained a 92% yield of crude, low-melting product [λ_{max} 267 mμ (ethanol)] which was used without further purification. The literature[4a] gives the melting point of this product as 33–34°.

2,4-Dimethoxy-5-ethylpyrimidine.—Reduction of the previous product using zinc dust[4a] was not too successful and a method[5] for its catalytic reduction was adapted. A mixture was made of 20.3 g. (0.1 mole) of the previous product, 20 g. of magnesium oxide, 2 g. of 5% palladium-on-charcoal, and 200 ml. of 50% ethanol. This was hydrogenated at 15 p.s.i. at 60°. The uptake of hydrogen virtually ceased after 2 hr. at which time approximately 70% of the theoretical amount had been taken up. The hydrogenation bottle was centrifuged and the supernatant decanted. The residue was washed twice with 150-ml. portions of 95% ethanol. Removal of solvents gave a highly volatile, pale yellow oil [λ_{max} 260 mμ (ethanol)] which could not be crystallized and was not purified further.

5-Ethyluracil.—The combined product from a number of reductions, 15.6 g., was refluxed with concd. hydrochloric acid for 6 hr. Water was added to dissolve the white precipitate which formed and the solution was filtered and allowed to cool. The product was recrystallized several times from 70% ethanol which effectively removed a more alcohol soluble impurity. There was obtained 8.4 g. (76% yield) of pure white crystalline material, m.p. 302–303°, λ_{max} 264.5 mμ (0.1 *N* hydrochloric acid), λ_{max} 289 mμ (0.01 *N* sodium hydroxide). The melting point of this compound has been variously reported as 300–303°,[4b] 300°,[2] 300–303°,[3] and 300–303°.[4a]

2-Thio-5-ethyluracil.—This reaction was performed as described[4b] previously except that sodium hydride was used as the condensing agent rather than sodium. This permitted an appreciably shorter reaction time with no decrease in yield. To a 1-l., three-necked flask equipped with a stirrer, condenser, and dropping funnel was added successively 14.4 g. (0.6 mole) of sodium hydride, 250 ml. of anhydrous ether, and 58.1 g. (0.5 mole) of ethylbutyrate. There was then added over a 3-hr. period 55.6 g. (0.75 mole) of ethyl formate in 100 ml. of ether, and the mixture was then refluxed overnight. Subsequent steps were as originally described. There was produced 10.7 g. (17% yield) of product, m.p. 190–191° (lit.,[2] 191–193°), λ_{max} 277 mμ (0.1 *N* hydrochloric acid), λ_{max}[2] 259 mμ, λ_{max}[3] 309 mμ (0.001 *N* sodium hydroxide), and the mother liquors yielded an additional 3.6 g. of material, m.p. 165–180°.

5-Ethyluridine.—To a solution of 1.73 g. (0.016 mole) of 5-ethyluracil in 100 ml. of 20% aqueous ethanol containing 0.64 g. (0.016 mole) of sodium hydroxide was added 5 g. of Celite, and the mixture was stirred vigorously at 70°. There was then added slowly a hot solution of 2.16 g. (0.008 mole) of mercuric chloride in 30 ml. of ethanol and then 200 ml. of hot water. The solution was filtered, the product was washed with hot water, and dried *in vacuo*.

To 350 ml. of a solution of anhydrous ether saturated at 0° with gaseous hydrogen chloride wax added 7.9 g. (0.0156 mole) of dry 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose[7] and 1 ml. of acetyl chloride. The solution was allowed to stand at 3° for 3 days and was then evaporated to dryness *in vacuo*. The residue was evaporated to dryness with several portions of benzene, dissolved in 25 ml. of xylene, and added to a refluxing suspension of the previously prepared di(5-ethyluracil)mercury in 200 ml. of xylene. The mixture was stirred at reflux for 3 hr., filtered through Celite, and evaporated to dryness *in vacuo*. The residue was dissolved in a mixture of 200 ml. of chloroform and 30 ml. of 30% aqueous potassium iodide and the layers were separated. The organic phase was washed with an additional 20 ml. of 30% aqueous potassium iodide and then with water. After drying over sodium sulfate, the solution was evaporated to dryness, taken up in 150 ml. of anhydrous ethanol, and the solution was saturated at 0° with ammonia. After several days standing, the solution was evaporated to dryness *in vacuo*, dispersed in 150 ml. of water and extracted three times with 50 ml. portions of ether. The aqueous phase was decolorized with charcoal and evaporated to dryness *in vacuo*. Attempts to crystallize the product from ethyl acetate and from ethanol were not successful. The residual material after removal of solvents was dissolved in 1 *N* ammonium hydroxide and passed through a 2.5 × 30 cm. column of Dowex 1-X8 in the formate form which had been pretreated with 1 *N* ammonium hydroxide. The column was washed with 1 *N* ammonium hydroxide until no further ultraviolet absorbing material was eluted and the product was then eluted with 500 ml. of 1 *N* formic acid. The formic acid was removed *in vacuo* and the residue was crystallized from absolute ethanol several times to give 0.8 g. (20% yield) of white crystalline material, m.p. 184–186° (uncorr.), λ_{max} 266.5 mμ (0.1 *N* hydrochloric acid or 0.001 *N* sodium hydroxide).

Anal. Calcd. for $C_{11}H_{17}O_6N_2$: C, 48.3; H, 6.26; N, 10.2. Found: C, 48.3; H, 6.03; N, 10.3.

Paper chromatography with 65% v./v. isopropyl alcohol–2 *N* hydrochloric acid[8] gave an R_f of 0.77. This compared with 0.84 for the free base, 0.76 for thymine, and 0.78 for thymidine.

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A Convenient Synthesis of Benzothiazole from Dimethylformamide

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In 1880, Hofmann[1] reported the preparation of benzothiazole from 2-aminobenzenethiol and formamide. His synthesis required a high temperature and yielded only a small amount of benzothiazole. In this note, we wish to report a convenient synthesis using an amide which results in high yields of

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