small sample of 4-phenylphenyl 5-bromo-2-furoate obtained by the bromination of 4-phenylphenyl 2-furoate was refluxed in 20% potassium hydroxide (water–ethanol, 1:1) solution for 20 hr. From the reaction mixture, 4-phenylphenol, m.p. 161–162° (which was converted to the benzoate, m.p. 146–147°[4]), and 5-bromo-2-furoic acid, m.p. 185.5–186.5°, were obtained.

(4) S. E. Hazlet, G. Alliger, and R. Tiede, *J. Am. Chem. Soc.*, **61**, 1447 (1939).

## A New Chemical Synthesis of 2-D-Ribofuranosyl-*as*-triazine-3,5(2*H*,4*H*)-dione (6-Azauridine)[1]

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A recent communication[2] describing a synthesis of 6-azauridine prompts us to report a new chemical route to this compound which offers added evidence that attachment of the ribose is at the 2- position of the *as*-triazine ring. An earlier synthesis,[3] resulting from the direct ribosidation of the mercury salt of 6-azauracil led to two isomers, neither of which was obtained crystalline.

This paper describes a method for the chemical synthesis of 6-azauridine based on the findings of E. Cattelain,[4] who demonstrated that alkylation of 6-benzyl-3-(methylthio)-*as*-triazin-5(2*H*)-one[5] occurred at the 2- position of the *as*-triazine ring.

Accordingly, we synthesized the desired intermediate, 3-(methylthio)-*as*-triazin-5 (4*H*)-one (III). Since this work was completed the preparation of III has been reported and assigned the (4*H*) structure, based on a series of $pK_a$ determinations.[6] The same authors report that similar to the experience of Cattelain,[4] methylation of III was found to occur exclusively in the 2- position of the *as*-triazine ring (1-position of the 6-azauracil system).

In this laboratory III was made *via* two routes: first by cyclization of glyoxylic acid, 3-methylisothiosemicarbazone (I), or more conveniently by methylation of glyoxylic acid, 3-thiosemicarbazone (II), with concurrent cyclization.

Condensation of IV (mercuribis salt of III) with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride by the method of Fox *et al.*[7] gave, after hydrolytic desulfurization, a product which proved to be 2′,3′,5′ - tri - *O* - benzoyl - 6 - azauridine (V). Debenzoylation in methanolic ammonia led to crystalline 6-azauridine (VI), identical in all respects to material produced by fermentation.

### Experimental[8]

**3-(Methylthio)*as*-triazin-5(4*H*)-one (III).**—A. A solution of 17.2 g. (0.074 mole) of 3-methylisothiosemicarbazide, hydroiodide in 90 ml. of water was added to a solution of 6.8 g. (0.074 mole) of glyoxylic acid, hemihydrate in 75 ml. of *N* sodium hydroxide at room temperature. After a short time, 11.2 g. of glyoxylic acid, 3-methylisothiosemicarbazone (I), m.p. 180–190° dec., separated.

*Anal.* Calcd. for $C_4H_7N_3O_2S$: C, 29.83; H, 4.38; N, 26.07; S, 19.89. Found: C, 29.60; H, 4.56; N, 25.76; S, 19.56.

After refluxing 11 g. of I in 700 ml. of 95% ethanol for 5 hr. 4.4 g. of unchanged material was filtered off and a total of 2.8 g. (29%) of III was obtained by concentration of the mother liquor.

B. To a solution of 107 g. (1.17 moles) of thiosemicarbazide in 3 l. of 80% ethanol at 70° was added 116.7 g. (1.27 moles) of glyoxylic acid, hemihydrate in 600 ml. of 80% ethanol. After 5 min., a solution of 52 g. (1.3 moles) of sodium hydroxide in 325 ml. of water was added, followed by 189 g. (1.33 moles) of methyliodide. The mixture was refluxed for 2.5 hr. and then concentrated to one third the original volume. After cooling, the crude product was filtered and recrystallized from ethyl acetate to yield 108 g. (64%) of 3-(methylthio)-*as*-triazin-5(4*H*)-one (III); m.p. 222–224°.

*Anal.* Calcd. for $C_4H_5N_3OS$: C, 33.55; H, 3.52; N, 29.35; S, 22.40. Found: C, 33.54; H, 3.44; N, 29.03; S, 22.56.

The intermediate glyoxylic acid, 3-thiosemicarbazone (II), has been isolated and recrystallized from water; m.p. 165° dec.

*Anal.* Calcd. for $C_3H_5N_3O_2S$: C, 24.49; H, 3.43; N, 28.56; S, 21.79. Found: C, 24.37; H, 3.41; N, 28.22; S, 21.33.

**2,2′-Mercuribis[3-(methylthio)-*as*-triazin-5(2*H*)-one] (IV).**—A warm solution of 6.38 g. (0.02 mole) of mercuric acetate in 50 ml. of methanol was added to a warm solution of 5.72 g. (0.04 mole) of III in 120 ml. of methanol. After cooling, the precipitate was filtered and washed successively with water, ethanol, and ether. The product (IV) weighed 8.6 g. (88%) and had a good analysis for a compound containing a ratio of 2 moles of triazine and one mole of mercury.

*Anal.* Calcd. for $C_8H_8N_6O_2S_2Hg$: N, 17.33; S, 13.22. Found: N, 16.77; S, 13.07.

**2′,3′,5′-Tri-*O*-benzoyl-6-azauridine (V).**—A suspension of 3.76 g. (0.0078 mole) of IV in 200 ml. of toluene was dried by azeotropic distillation of 100 ml. of the solvent. A dried solution of 15 g. (0.031 mole) of amorphous 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl chloride[9,10] in 100 ml. of benzene was added, and the mixture was distilled to remove benzene. The mixture was then refluxed for .75 hr., cooled, and filtered. The filtrate was concentrated to dryness

(1) Since 6-azauridine has become established in the literature as the name for the subject compound, we propose to use the familiar name throughout this paper.

(2) M. Prystaš, J. Gut, and F. Šorm, *Chem. Ind.*, No. **25**, 947 (June 24, 1961).

(3) R. E. Handschumacher, *J. Biol. Chem.*, **235**, 764 (1960).

(4) E. Cattelain, *Bull. Soc. Chim.*, **11**, 249 (1944).

(5) The structure given is the one assigned by E. Cattelain[4] for the product obtained by cyclization of phenylpyruvic acid, 3-methylisothiosemicarbazone.

(6) J. Gut, M. Prystaš, and J. Jonáš, *Collection Czech. Chem. Commun.*, **26**, 986 (1961).

(7) J. J. Fox, N. Yung, J. Davoll, and G. B. Brown, *J. Am. Chem. Soc.*, **78**, 2117 (1956).

(8) Analyses were carried out by the Analytical Division, Squibb Institute for Medical Research: microanalyses by Mr. J. Alicino and his associates; infrared and ultraviolet determinations by Dr. N. Coy and her colleagues. Melting points are uncorrected.

(9) E. F. Recondo and H. Rinderknecht, *Helv. Chim. Acta*, **42**, 1171 (1959).

(10) H. M. Kissman, C. Didaks, and B. R. Baker, *J. Am. Chem. Soc.*, **77**, 18 (1955).

and the residue extracted into chloroform. The extract was washed with dilute potassium iodide solution, then with water, and, after drying, it was concentrated to a sirupy residue. The residue was dissolved in 200 ml. of 95% ethanol, treated with 20 ml. of concd. hydrochloric acid, and refluxed for 1.5 hr., whereupon methyl mercaptan evolved. After the reflux period, the solution was concentrated slightly, causing precipitation of 2.6 g. (30%) of crude V. A sample for analysis, recrystallized from ethyl acetate, had a m.p. of 191–194°.

*Anal.* Calcd. for $C_{29}H_{23}N_3O_9$: C, 62.47; H, 4.16; N, 7.55. Found: C, 62.02; H, 4.11; N, 7.53.

**6-Azauridine (VI).**—A solution of 590 mg. (1.06 mmoles) of V in 200 ml. of methanol, saturated at 5° with ammonia, was held for 3 days at room temperature. After concentration to dryness, the residual sirup was dissolved in water and the solution was washed with ether. The aqueous solution was concentrated to dryness and the residue dissolved in absolute ethanol and reconcentrated. This operation was repeated several times to assure removal of water. Recrystallization of the residue from absolute ethanol afforded 160 mg. (62%) of 6-azauridine (VI); m.p. 157–159°, undepressed by biosynthetic material. The infrared spectrum was identical to that of authentic material as was the ultraviolet spectrum: $\lambda_{max}^{0.2\ N\ NaOH}$ 257 mμ (ε 6988).

*Anal.* Calcd. for $C_8H_{11}N_3O_6$: C, 39.19; H, 4.52; N, 17.14. Found: C, 39.79; H, 4.56; N, 17.34.

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## 2,4-Dinitrothiazole. The Boron Trifluoride–Nitrogen Tetroxide Nitration of 2-Nitrothiazole

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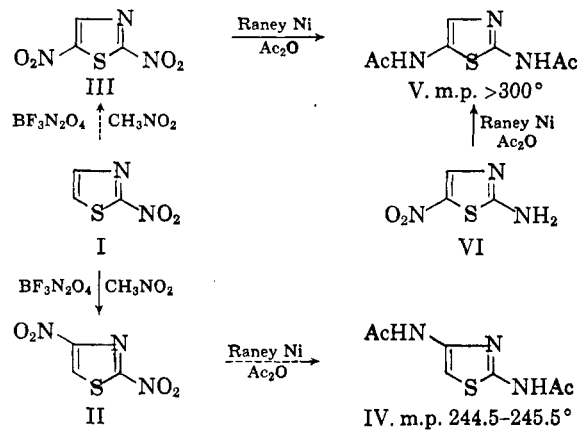
The only C-dinitrothiazoles that have been reported are 2,4-dinitro-5-acetamidothiazole,[1] and 2 - nitramino - 3,4,5 - trinitro - 2 - thiazoline.[2] Ganapathi,[3] however, has presented data that place the structure of the former compound in considerable doubt. In fact, his evidence indicates that this compound is indeed the mononitrothiazole (5-acetamido-4-nitrothiazole). In contrast to the work of Prijs,[4] we have found that 2-nitrothiazole (I) can be nitrated in excellent yield using a complex of boron trifluoride and nitrogen tetroxide.[5] It is curious to note however, that the nitration which is described below, does not proceed satisfactorily unless an excess of boron trifluoride is present in the nitration mixture.[6]

Two isomers are possible from the nitration of 2-nitrothiazole: 2,4-dinitro-(II) and 2,5-dinitrothiazole (III). Since the corresponding acetylated




diamines (IV and V) of the two possible products (II and III) were known,[7–9] the reduction of the dinitro compound seemed the best means of identification. Using 2-amino-5-nitrothiazole (VI) as a model compound, several chemical reductions were attempted in vain. Ultimately, reductive acetylation with Raney nickel catalyst was successful. Contrary to the experience of Ganapathi,[7] this reduction proceeded smoothly yielding the previously described[7] 2,5-diacetamidothiazole (V). When the nitration product (II) was subjected to this same procedure, 2,4-diacetamidothiazole (IV) resulted. This was identified by a mixed melting point determination and comparison of the infrared spectrum with that of an authentic sample prepared according to Davies.[9]

### Experimental

**2,4-Dinitrothiazole (II).**—A stirred solution of 10 ml. of nitrogen dioxide–nitrogen tetroxide (Matheson) in 25 ml. of nitromethane was cooled to 0°, and boron trifluoride gas was bubbled in until dense white fumes were evolved from the condenser. A solution of 2 g. of 2-nitrothiazole[4] (m.p. 74–75°) in 25 ml. of nitromethane was added portionwise with stirring, and the mixture was refluxed for 1 hr. The mixture was then filtered hot, the solids washed with 25 ml. of nitromethane, and the solvent removed by evaporation in a stream of air. The yield was 2.60 g. Crystallization from benzene afforded 2,4-dinitrothiazole (m.p. 145.5–146.5° corr.) in 80% yield.

*Anal.* Calcd. for $C_3HN_3O_4S$: C, 20.59; H, 0.57; N, 24.00. Found: C, 20.84; H, 0.59; N, 24.25.

**Reductive Acetylation of 2-Amino-5-nitrothiazole (VI).**—

(1) B. Prijs, W. Menigisen, S. Fallab, and H. Erlenmeyer, *Helv. Chim. Acta*, **35**, 187 (1952).

(2) S. J. Viron and A. Taurins, *Can. J. Chem.*, **31**, 885 (1953).

(3) K. Ganapathi and K. D. Kulkarni, *Proc. Indian Acad. Sci.*, **37A**, 758 (1953).

(4) B. Prijs, J. Ostertag, and H. Erlenmeyer, *Helv. Chim. Acta*, **30**, 1200 (1947).

(5) G. B. Bachman, H. Feuer, B. R. Bluestein, and C. M. Vogt, *J. Am. Chem. Soc.*, **77**, 6188 (1955).

(6) Bachman's nitration procedure involves filtering and pressing the solid complex on a porous plate, thus any excess boron trifluoride dissolved in the solvent is removed.

(7) K. Ganapathi and A. Venkataraman, *Proc. Indian Acad. Sci.*, **22A**, 343 (1945).

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