TABLE I
2-FUROATES OF 4-PHENYLPHENOL AND BROMO-4-PHENYLPHENOLS

Phenol Used[a]	Yield, %	M.P., °C.[b]	Formula	Bromine, % Calcd.	Bromine, % Found
4-Phenyl-	85.1	125–126	$C_{17}H_{12}O_3$	..	..
4-(4-Bromophenyl)-	88.9	153–154	$C_{17}H_{11}O_3Br$	23.3	23.7
2,6-Dibromo-4-phenyl-	85.5	152–153	$C_{17}H_{10}O_3Br_2$	37.9	37.9
2-Bromo-4-(4-bromophenyl)-	93.5	127–128	$C_{17}H_{10}O_3Br_2$	37.9	38.2
2,6-Dibromo-4-(4-bromophenyl)-	87.9	186.5–187.5	$C_{17}H_9O_3Br_3$	47.9	48.2

[a] The bromo-4-phenylphenols were prepared by recorded methods. [b] The esters were purified by crystallization from ethanol.

Further elution with methanol led to 25 mg. of an oil with an intense nitrile infrared absorption peak. It was acetylated by standard means and the product chromatographed on silica. This produced crystalline 4-ethoxysalicylonitrile acetate, m.p. 72.5–73.5°; spectra: ultraviolet (EtOH), λ_{max} 250 mμ (log ε 4.20) and 283 mμ (log ε 3.17), λ_{min} 226 mμ (log ε 3.74) and 280 mμ (log ε 3.09); infrared ($CHCl_3$), 4.48(s), 5.63(s), 6.20(s), and 6.35(m) μ.

Anal. Calcd. for $C_{11}H_{11}O_3N$: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.64; H, 5.53; N, 6.67.

A solution of 100 mg. of 4-ethoxysalicylaldoxime and 0.5 ml. of acetic anhydride was refluxed for 2 hr. and then poured onto 5 ml. of ice water. The resulting precipitate was filtered, crystallized from aqueous ethanol, and chromatographed on silica. Elution with 9:1 petroleum ether–ether led to a crystalline solid, m.p., m.m.p. 72–73.5°, identical in all respects with the above sample of 4-ethoxysalicylonitrile acetate.

The Bromination of 4-Phenylphenyl 2-Furoate

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A number of esters of the phenylphenols have been brominated previously, and the results of these studies have been reported.[1] In this investigation, an acyl group of different type than those involved in previous studies has been used, *viz.*, the furoyl group. The results are different. Bromination occurred in the acyl portion of the molecule rather than in the biphenyl group, and 4-phenylphenyl 5-bromo-2-furoate was formed. Such is in agreement with reports by Gilman[2] that the furan ring undergoes substitution reactions more readily than the benzene ring.

Reaction products were identified by mixed melting point procedures.

A number of related esters have been prepared.

(1) S. E. Hazlet and L. C. Hensley, *J. Am. Chem. Soc.*, **69**, 708 (1947) and earlier papers.

(2) See, for example: H. Gilman and E. B. Towne, *Rec. trav. chim.*, **51**, 1054 (1932); H. Gilman and N. O. Calloway, *J. Am. Chem. Soc.*, **55**, 4197 (1933); and H. Gilman and R. V. Young, *ibid.*, **56**, 464 (1934).

Experimental

2-Furoates of 4-Phenylphenol and Bromo-4-phenylphenols.—4-Phenylphenol (40 g., 0.235 mole) was dissolved in 30 ml. of pyridine and 60 ml. of *p*-dioxane; the solution was cooled to 5°, and 36.8 g. (0.282 mole) of 2-furoyl chloride was added in small portions. The mixture was heated at 70° for 1 hr. and then cooled; 400 ml. of water was added, and the solution was acidified with dilute hydrochloric acid. The crude product was obtained in nearly quantitative yield; purification was effected by crystallizations from ethanol, m.p. 125–126°.

Anal. Calcd. for $C_{17}H_{12}O_3$: C, 77.3; H, 4.55. Found: C, 77.4; H, 4.61.

Several 2-furoic acid esters of bromo-4-phenylphenols were prepared by similar procedures. The results are shown in Table I.

5-Bromo-2-furoic Acid.—Except that only a small excess of bromine was used, this compound was prepared in 64% yield by the method of Whittaker,[3] m.p. 187–187.5°.

5-Bromo-2-furoyl Chloride.—5-Bromo-2-furoic acid (3 g., 0.0157 mole) was treated with thionyl chloride (12 g., 0.101 mole) and a drop of pyridine. The mixture was refluxed on a steam bath for 6 hr., the excess thionyl chloride was removed by distillation, and the acid chloride—the residue—was used without purification.

4-Phenylphenyl 5-Bromo-2-furoate.—To the crude 5-bromo-2-furoyl chloride (*ca.* 0.0157 mole) were added 2 ml. of pyridine, 7 ml.of *p*-dioxane, and 2.67 g. (0.0157 mole) of 4-phenylphenol. The mixture was heated for 1 hr. on a steam bath, cooled, and diluted with 40 ml. of water; the odor of pyridine was discharged by the addition of dilute hydrochloric acid. The solid product was leached with hot water and then with 5% sodium carbonate solution and washed with hot water. Crystallizations from ethanol gave 2.2 g. (0.00641 mole, 40.8% yield) of 4-phenylphenyl 5-bromo-2-furoate, m.p. 152–153°.

Anal. Calcd. for $C_{17}H_{11}O_3Br$: Br, 23.3. Found: Br, 23.9.

Bromination of 4-Phenylphenyl 2-Furoate.—The ester (10 g., 0.0379 mole) was suspended in 30 ml. of glacial acetic acid, which had been heated to 115°. A trace of iron powder was introduced, and 6 g. (0.0375 mole) of bromine dissolved in 10 ml. of glacial acetic acid was added. The temperature of the mixture was maintained at 100° for 50 min.

The mixture was cooled to room temperature, and the precipitated solid (6 g.) was collected by filtration, m.p. 130–139°. Crystallizations from propanol gave 4.8 g. (0.014 mole, 37.3% yield) of 4-phenylphenyl 5-bromo-2-furoate, m.p. 149–150.5°.

The acidic solution was diluted with 250 ml. of water and neutralized with sodium carbonate solution; the precipitated solid (6.1 g.) was collected by filtration, m.p. 107–117°. Several crystallizations from ethanol gave 3.9 g. (0.0148 mole, 39.5% yield) of 4-phenylphenyl 2-furoate, m.p. 123–124°.

Hydrolysis of 4-Phenylphenyl 5-Bromo-2-furoate.—A

(3) R. M. Whittaker, *Rec. trav. chim.*, **52**, 352 (1933).

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).