luted with 50 ml. of water, cooled at 0° and after neutralization with 2 *N* hydrochloric acid, precipitated by addition of 12 ml. of concentrated hydrochloric acid. After twelve hours, a resinous product had separated, which was freed from the supernatant liquid by decantation and heated on the steam-bath for 45 minutes with 120 ml. of 20% hydrochloric acid and for further two hours with 60 ml. of concentrated hydrochloric acid. The filtered solution was evaporated *in vacuo* to dryness and the residue taken up in 40 ml. of 50% alcohol. When pyridine was added to the solution, well-shaped needles separated which were recrystallized from water; m.p. 240° (dec.); yield 2.8 g. (21.4%, calculated on β-butylthioethyl chloride).

Anal. Calcd. for $C_8H_{17}NO_2S$: C, 50.3; H, 8.9; N, 7.3. Found: C, 50.4; H, 8.8; N, 7.1.[6]

Also **β-ethylthio-ethanol** can be produced by the above method more easily than by condensation of ethylene chlorohydrin with ethyl mercaptan[7]: to a solution of 82 g. of β-thioethanol and 4 g. of sodium hydroxide in 200 ml. of water, 154 g. of diethyl sulfate was added with stirring at 50°. The mixture was heated for six hours at 100° and extracted with ether; b.p. 99° (28 mm.); yield 71.5 g. (64%).

Anal. Calcd. for $C_4H_{10}OS$: S, 30.2. Found: S, 30.5.

(6) The amino-acid has been obtained by a different method, by E. Borek and H. Waelsch, *J. Biol. Chem.*, **147**, 135 (1949); *cf.* M. D. Armstrong and J. D. Lewis, *J. Org. Chem.*, **16**, 749 (1950).

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Some Heterocyclic Secondary Amines[1]

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Four unsymmetrically substituted heterocyclic secondary amines which involve the 2-pyridyl, 2-pyrimidyl and 2-thiazolyl radicals have been prepared as part of a program on the synthesis of basically substituted heterocyclic compounds containing the amidine structure. These compounds were prepared by the reaction of the sodium salt of a primary amine with an "active" heterocyclic halide. The sodium salt of the amine was employed since it has been established[3] that the ring nitrogen of 2-aminopyridine, for example, is capable of substitution *via* the imino form of the amine. The necessity of employing the sodium salt of the amine has been demonstrated during the course of this investigation.[4]

Although the method of synthesis employed appears to be straightforward, the actual preparation of pure samples of these amines has involved considerable difficulty. It has been impossible to develop one set of conditions which would satisfactorily lead to all the desired products. Thus the sodium salt of 2-aminopyridine reacted with 2-chlorothiazole in refluxing benzene to produce a 40% yield of 2-pyridyl-2′-thiazolylamine. Similarly, the sodium salt of aniline reacted with 2-chloropyrimidine to give a 22% yield of 2-anilinopyrimidine.[5] In contrast, the reaction of the sodium salt of 2-aminopyrimidine with 2-chlorothiazole in benzene led to no reaction; the same reactants in *p*-cymene produced an insoluble and infusible substance which probably arose from ring rupture. This latter reaction was successfully carried out in 9.5% yield by the direct reaction of the sodium salt of the amine with the heterocyclic halide. Correspondingly, the sodium salts of 2-aminopyrimidine and 2-aminopyridine did not produce 2-pyridyl-2′-pyrimidylamine when refluxed in benzene with 2-bromopyridine and 2-chloropyrimidine, respectively; however, the direct reaction of the sodium salt of 2-aminopyrimidine with 2-bromopyridine produced a 27% yield of 2-pyridyl-2′-pyrimidylamine.

Experimental[6]

Sodium Salts of 2-Aminopyrimidine and 2-Aminopyridine.—2-Aminopyrimidine (19.02 g., 0.2 mole) was added over a 10-minute period to a solution of sodium amide[7] (0.2 mole) in approximately 200 ml. of anhydrous liquid ammonia. After 2 additional hours of stirring, the solvent was evaporated, the gray-white sodium salt pulverized, extracted with two 100-ml. portions of anhydrous benzene and dried under vacuum over phosphorus pentoxide; yield 19 g. (85%).

The sodium salt of 2-aminopyridine was prepared in an analogous manner except for the extraction process which was omitted; this salt was dark blue in color.

2-Pyridyl-2′-thiazolylamine.—The sodium salt of 2-aminopyridine (35.9 g., 0.3 mole) was refluxed in 50 ml. of anhydrous benzene with stirring for one-half hour in order to ensure complete reaction. 2-Chlorothiazole[8] (30 g., 0.25 mole) in 40 ml. of anhydrous benzene was added over a 10-minute period to the warm suspension of the sodium salt while the reaction flask was being cooled in a cold water-bath. The reaction mixture was then stirred and heated at gentle reflux for 10 hours. The dark brown mixture was cooled and extracted with 250 ml. of a 1:1 mixture of concentrated hydrochloric acid and water. The acidic extract was cooled and adjusted to a *p*H 10 with 48% sodium hydroxide. The tan colored precipitate was filtered, washed with four 50-ml. portions of cold water and dried at 100°; yield 22 g., m.p. 191.8–193°. Recrystallization from 95% ethanol after treatment with charcoal gave 17.9 g. (40.3%) of light tan colored needles, m.p. 195.8–196.6°, sublimation at 15 mm. pressure and recrystallization from ethanol gave colorless needles which had essentially the same melting point as the discolored crystals. *Anal.* Calcd. for $C_8H_7N_3S$: C, 54.22; H, 3.98; N, 23.72; S, 18.09. Found: C, 54.32; H, 4.18; N, 23.75; S, 17.95.

2-Pyridyl-2′-pyrimidylamine.—The sodium salt of 2-aminopyrimidine (22.65 g., 0.193 mole) and 2-bromopyridine[9] (30.6 g., 0.193 mole) were heated in an oil-bath at 150–170° for 45 minutes. The cooled reaction mixture was thoroughly extracted by shaking with several portions of cold water; the addition of a cold 1:1 mixture of ethanol and ether converted the sticky mixture into a light cream colored powder which was filtered, washed with ether and dried under vacuum over phosphorus pentoxide; yield 9.1 g. (27.2%), m.p. 149.6–151.7°. Recrystallization from ethanol gave light cream colored hexagonal plates, m.p. 149.3–152.1°; vacuum sublimation under 2 mm. pressure produced

(1) Abstracted, in part, from a thesis presented by W. K. Detweiler to the Graduate Faculty of Lehigh University in partial fulfillment of the requirements for the Ph.D. degree, June, 1951.

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(3) A. E. Tschitschibabin, R. A. Konowalowa and A. A. Konowalowa, *Ber.*, **54**, 814 (1921).

(4) The direct fusion of 2-chloropyrimidine with 2-aminopyridine for 42 hours at approximately 100° gave an ionic halogen compound which upon treatment with base liberated a substance which melted at 182–184°; in contrast, the reaction of the sodium salt of the amine with the same halide gave 2-pyridyl-2′-pyrimidylamine which melted at approximately 150–152°. The higher melting material was not investigated further but may have been an isomeric material formed by reaction of a ring nitrogen.

(5) This reaction was run in order to determine the stability of 2-chloropyrimidine in the presence of a sodium salt of an active primary amine.

(6) All melting points have been corrected for thermometer stem-emergence.

(7) Prepared according to T. H. Vaughn, R. R. Vogt and J. A. Nieuwland, THIS JOURNAL, **56**, 2120 (1934).

(8) K. Ganapathi and A. Venkataraman, *Proc. Indian Acad. Sci.*, **22A**, 343–358 (1945); *C. A.*, **40**, 4095.

(9) C. F. H. Allen and J. R. Thirtle, *Org. Syntheses*, **26**, 16 (1946).

colorless crystals, m.p. 150.2–152.1°. *Anal.* Calcd. for $C_9H_9N_4$: C, 62.78; H, 4.68; N, 32.54. Found: C, 62.82; H, 4.68; N, 32.47.

2-Pyrimidyl-2′-thiazolylamine.—The sodium salt of 2-aminopyrimidine (22.18 g., 0.189 mole) and 2-chlorothiazole (22.58 g., 0.189 mole) were heated in an oil-bath at 95° for 2.75 hours when it became necessary to cool the reaction mixture in order to moderate an exothermic reaction which had developed; the reaction mixture was then heated for an additional 6 hours at 95°, cooled, suspended in 50 ml. of water and steam distilled (6 g. of 2-chlorothiazole was recovered). The residue from the steam distillation was filtered, washed with cold water and dried at 100°; yield 3.1 g. (9.5%), m.p. 209–211.8°. Cream colored crystals were obtained upon recrystallization from ethanol, m.p. 211–212.1°. Vacuum sublimation under 6 mm. pressure and recrystallization from ethanol gave colorless crystals, m.p. 212.1–212.6°. *Anal.* Calcd. for $C_7H_6N_4S$: C, 47.18; H, 3.39; N, 31.44; S, 17.99. Found: C, 47.22; H, 3.44; N, 31.44; S, 17.89.

2-Anilinopyrimidine.[10]—A mixture of aniline (3.26 g., 0.035 mole) and sodium amide (1.37 g., 0.035 mole) in 35 ml. of dry benzene was heated and stirred for 3.25 hours in an oil-bath at 92° under an atmosphere of nitrogen. 2-Chloropyrimidine (4 g., 0.035 mole) in 20 ml. of anhydrous benzene was added to the cooled reaction mixture. After the addition, this mixture was heated and stirred at gentle reflux for 4.5 hours, cooled and then steam distilled. The distillate was acidified with concentrated hydrochloric acid and shaken to extract the amine from the benzene portion of the distillate. A brown colored solid was precipitated from the acidic solution upon adjusting it to a *p*H 10; yield 2.7 g. Solution of this substance in boiling water and filtration from insoluble impurities produce 1.3 g. (22%) of colorless needles, m.p. 114.3–115.2°.

Acknowledgment—We are grateful to the Wm. S. Merrell Company for the funds that made this research possible and for many helpful discussions in connection with this investigation.

(10) T. B. Johnson and F. W. Heyl, *Am. Chem. J.*, **38**, 244 (1907), prepared this compound by the reduction of 4-chloro-2-anilinopyrimidine, m.p. 116°.

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The Hydrolysis of Glucose-4-phosphate[1]

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The mechanism by which galactose may be derived from glucose in biological systems is one which holds considerable interest. Robinson[3] suggested that D-glucose-4-phosphate, if present in nature, might be hydrolyzed at the C–O– bond at carbon number four with a resultant Walden inversion. This mechanism is referred to repeatedly, but it has never been tested directly. Cohn[4] has shown, using O^{18}, that hydrolysis of glucose-1-phosphate may occur at the C–O– bond or the –O–P bond depending on the catalyst used.

Experimental

The disodium and barium salts of D-glucose-4-phosphoric acid were prepared in this Laboratory.[5]

Acid Hydrolysis.—To 28 mg. of barium D-glucose-4-phosphate was added excess (2 ml. of 0.1 *N*) sulfuric acid. After barium sulfate was removed by centrifugation, the solution was maintained at 100° for 30 hours. The hydrolysis mixture was concentrated, extracted with pyridine[6] and chromatographed[7] (descending) on Whatman No. 1 paper, using *s*-collidine–water as a solvent. The spray used was that recommended by Trevelyan.[8] Well defined glucose spots were obtained, but no galactose spot was discernible. There was no difficulty in differentiating the spots due to the glucose and galactose standards.

Hydrolysis at *p*H 7.—A solution of 21.4 mg. of the disodium salt of glucose-4-phosphoric acid in 2.0 ml. of water was found to be at *p*H 7.2. After 42 hours heating at 100° in a stoppered tube 50% of the compound was hydrolyzed as evidenced by analysis for inorganic phosphate.[9] The solution was chromatographed as above and identical results were obtained.

Acid Phosphatase Action.—The enzyme used was obtained by ammonium sulfate precipitation of potato press juice.[10] A sample of 20.6 mg. of disodium glucose-4-phosphate was dissolved in 2.0 ml. of water. To each volume of this solution used was added an equal volume of molar acetate buffer, *p*H 5.2, and an equal volume of purified phosphatase solution. Liberation of inorganic phosphate indicated 90% hydrolysis after 12 hours incubation at 37°. A chromatogram of the solution showed only a glucose spot.

Alkaline Phosphatase Action.—Essentially identical experiments were performed using Armour intestinal phosphatase as a catalyst at a *p*H of 8.0. Neither chromatography nor the colorimetric method of Dische,[11] *et al.*, indicated the presence of galactose in the hydrolysis mixtures.

Conclusion.—The above results do not suggest the idea that Walden inversion occurs during the hydrolysis of sugar phosphates and in this they agree with the work of Cohn.[4] The mechanism of cleavage will be further investigated with O^{18}.

(1) Work performed under Contract N6onr-218, Office of Naval Research.

(2) To whom inquiries concerning this article should be addressed.

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DEPARTMENT OF CHEMISTRY
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The Reaction between Diazonium Fluoborates and Antimony Trichloride in Organic Solvents

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The present paper describes the reaction between antimony trichloride and diazonium fluoborates and is a continuation of our study of the reaction between the halides of certain elements and diazonium fluoborates in organic solvents. Under conditions similar to those employed with arsenic trichloride,[1] a mixture of arylstibonic and diarylstibinic acids was obtained. A number of attempts were made to separate the mixture of primary and secondary acids. Fractional crystallization of various derivatives of these acids was used, and it was found possible to obtain the pure secondary acids in low yields. However, analyses of the primary acids and m.ps. of the corresponding pyridinium chloroantimonates[2] indicated that the primary acids were invariably contaminated with small amounts of secondary acids.

The total yield as well as the ratio between the yields of the two acids varied with both the solvent

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(2) *Cf.* G. O. Doak and H. G. Steinman, *ibid.*, **68** 1987 (1946).