ium chloride in dimethylformamide. In the region examined, 3000–1650 cm.$^{-1}$, the only significant changes in spectrum during polymerization were the gradual disappearance of NCA carbonyl absorption (1850 and 1780 cm.$^{-1}$) and the appearance of absorption at 2330 cm.$^{-1}$ due to dissolved carbon dioxide. Polymerization proceeded at a negligible rate at −78°. When 0.2 equivalent of sodium methoxide was used as initiator at −78° there was an initial reaction (complete in 10 minutes) which destroyed NCA without producing the absorption expected for a carboxylic ester. After this reaction no further decrease in NCA absorption occurred so long as the reaction mixture was held at −78°. At about 0° polymerization proceeded at an appreciable rate.

CHICAGO, ILLINOIS

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, UNIVERSITY OF KANSAS, AND THE WELLCOME RESEARCH LABORATORIES]

Oxygen Glycosides from the Hilbert–Johnson Pyrimidine Nucleoside Synthesis[1]

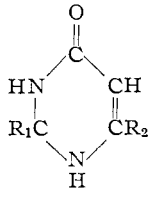
BY PHILIP NEWMARK AND IRVING GOODMAN

RECEIVED MARCH 28, 1957

Synthesis of the nucleosides of 6-methyluracil (I), 6-methyl-2-thiouracil (II), 2-thiouracil (III) and barbituric acid (IV) was attempted by means of the Hilbert and Johnson pyrimidine nucleoside synthesis. No nucleosides were obtained. Both α- and β-isomers of the oxygen glucosides were isolated for I and II, and as one of the by-products, 4-ethoxy-6-methyl-2(1)-pyrimidone, all previously unreported. No condensation products were obtained for III or IV.

The classic reaction of Hilbert and Johnson,[2] involving the condensation of 2,4-dialkoxypyrimidines with acetylglycosyl bromides, was employed successfully by Hilbert and co-workers[3–5] and by others[6,7] for the preparation of uracil and cytosine nucleosides. Visser, Goodman and Dittmer[8] and Fox and Goodman[7] showed further that nucleosides of thymine and 5-methylcytosine could be obtained from the reaction of acetylglycosyl halides with 2,4-diethoxy-5-methylpyrimidines.

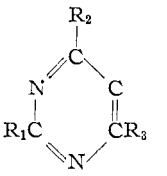
The work reported here concerns attempts by means of the Hilbert–Johnson reaction to synthesize nucleosides of several pyrimidines of biological interest which are not natural constituents of nucleic acids. We hoped in this way to prepare analogs of the naturally occurring nucleosides which might serve as metabolite antagonists for the normal nucleic acid derivatives. The pyrimidines selected were 6-methyluracil (I), 6-methyl-2-thiouracil (II), 2-thiouracil (III) and barbituric acid



	R_1	R_2
I	O	CH_3
II	S	CH_3
III	S	H
IV	O	OH

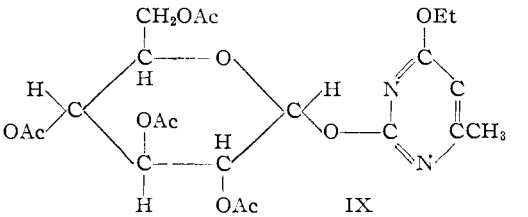
(IV). This study revealed some practical limitations of the reaction with respect to the structure of the pyrimidine moiety.

Condensation of tetra-O-acetyl-α-D-glucopyranosyl bromide with the ethoxy derivatives of 6-methyluracil and 6-methyl-2-thiouracil, V and VI respectively, yielded in each case both α- and β-

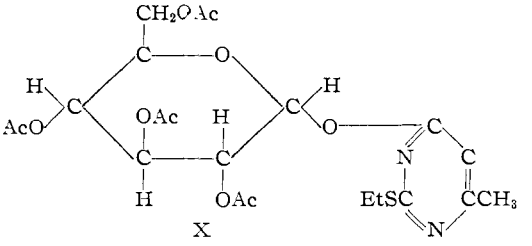


	R_1	R_2	R_3
V	OC_2H_5	OC_2H_5	CH_3
VI	SC_2H_5	OC_2H_5	CH_3
VII	SC_2H_5	OC_2H_5	H
VIII	OC_2H_5	OC_2H_5	OC_2H_5

isomers of the glucosides IX and X but no N-glucosylamines (nucleosides). Isolation of the α-form of IX from the same reaction was reported recently by Rabinowitz and Gurin.[9] Neither glucosides nor N-glucosylamines were obtained when the ethoxy derivatives of 2-thiouracil and barbituric acid, VII and VIII respectively, were allowed to react with tetra-O-acetyl-α-D-glucopyranosyl bromide. Although the use of the acetylglycosyl chlorides rather than the corresponding bromides increased the yields of the uracil and thymine nucleosides,[7] we obtained neither N-glycosylamines nor glycosides when we treated acetylglycosyl chlorides with the ethoxypyrimidines V,



IX



X

(1) This paper, which was presented in part at the 122nd Meeting of the American Chemical Society in Atlantic City, N. J., September, 1952, was the result of work initiated by the authors at the University of Colorado, with the aid of a fellowship (P.N.) and of a grant-in-aid (I.G.) from the U. S. Public Health Service. Nomenclature used in this article is in accord with the Rules of Carbohydrate Nomenclature, *Chem. Eng. News*, **31**, 1775 (1953).

(2) G. E. Hilbert and T. B. Johnson, THIS JOURNAL, **52**, 4489 (1930).

(3) G. E. Hilbert and E. F. Jansen, *ibid.*, **58**, 60 (1936).

(4) G. E. Hilbert, *ibid.*, **59**, 330 (1937).

(5) G. E. Hilbert and C. E. Rist, *J. Biol. Chem.*, **117**, 371 (1937).

(6) G. A. Howard, B. Lythgoe and A. R. Todd, *J. Chem. Soc.*, 1052 (1947).

(7) J. J. Fox and I. Goodman, THIS JOURNAL, **73**, 3256 (1951).

(8) D. W. Visser, I. Goodman and K. Dittmer, *ibid.*, **70**, 1926 (1948).

(9) J. L. Rabinowitz and S. Gurin, *ibid.*, **75**, 5758 (1953).

TABLE I

ULTRAVIOLET MOLAR ABSORPTIVITIES OF PYRIMIDINES AND PYRIMIDINE GLUCOSIDES

Compound	Solvent	Maxima λ, mμ	Maxima ε × 10⁻³	Minima λ, mμ	Minima ε × 10⁻³
4-Ethoxy-6-methyl-2(1)-pyrimidone	95% ethanol	273	8.4	235	1.2
	Water	271	6.8	237	1.1
	0.1 *N* KOH	276	7.4	215	1.3
2-Ethoxy-6-methyl-4(3)-pyrimidone	95% ethanol	262	6.9	235	3.9
	Water	255	7.1	235	4.3
	0.1 *N* KOH	263	8.4	242	3.9
	0.1 *N* H_2SO_4	256	7.3	233	3.3
1-Ethyl-6-methyl-2,4(1,3)-pyrimidonedione	95% ethanol	267	11.8	234	2.0
	Water	268	10.3	235	1.7
	0.1 *N* KOH	266	8.8	242	3.3
	0.1 *N* H_2SO_4	269	10.0	235	1.7
2,4-Diethoxy-6-methylpyrimidine	95% ethanol	259	7.8	235	2.3
2-Tetra-O-acetyl-D-glucopyranosyloxy-4-ethoxy-6-methylpyrimidine					
α-isomer	95% ethanol	255	6.6	234	2.1
β-isomer	95% ethanol	255	6.5	234	2.2
2-Ethylthio-6-methyl-4(3)-pyrimidone	95% ethanol	285	7.5	258	5.1
		230	10.3		
	Water	232	14.5	>320	<0.18
	0.1 *N* NaOH	277	7.4	263	5.9
	in 50% EtOH	247	9.3	240	8.5
2-Ethylthio-4-ethoxy-6-methylpyrimidine	95% ethanol	252	14.3	227	4.0
2-Ethylthio-4-tetra-O-acetyl-D-glucopyranosyloxy-6-methylpyrimidine					
α-isomer	95% ethanol	252	12.5	225	1.5
β-isomer	95% ethanol	252	11.6	225	1.0

VI and VII. Earlier, Hilbert[10] reported failure to isolate nucleosides when the acetylglycosyl bromides were allowed to react with 2-methoxy-4-aminopyrimidine. More recently, Michelson, Drell and Mitchell[11] noted that the ethoxy derivatives of orotic acid (6-carboxyuracil) and of its esters also failed to condense with the bromoacetyl sugars.

The complex character of this condensation has been demonstrated by Hilbert and co-workers.[5,12] From the interaction of 2,4-diethoxypyrimidine and tri-O-acetyl-D-ribopyranosyl bromide, they obtained 1-ethyluracil and 4-ethoxy-2(1)-pyrimidone as well as both the nucleoside and riboside. With the exception of the nucleoside, the products we isolated from the interaction of 2,4-diethoxy-6-methylpyrimidine (V) and tetra-O-acetyl-α-D-glucopyranosyl bromide were comparable, *viz.*, 1-ethyl-6-methyluracil, 4-ethoxy-6-methyl-2(1)-pyrimidone (previously unreported) and 2-tetra-O-acetyl-D-glucopyranosyloxy-4-ethoxy-6-methylpyrimidine.

For practical purposes the structural variation of 2,4-dioxopyrimidines for which nucleosides may be synthesized by means of the Hilbert–Johnson reaction would appear to be limited to the 5-position. However, the method for synthesis of pyrimidine nucleosides newly reported by Fox and co-workers[13] in which the chloromercuri derivatives of the pyrimidines are treated with acetylhalogeno sugars may be successful with some pyrimidines for which the Hilbert–Johnson reaction is impractical. Also one of us has shown recently[14] that 6-aminouracil nucleosides can be obtained by a Traube reaction between acetylglycosylureas and cyanoacetic acid.

Structure of Glucosides.—Identification of the condensation products isolated as the glucosides IX and X was based upon correct elemental analyses, ultraviolet absorption spectra and an examination of the acid and alkali labilities.

a. Ultraviolet Absorption Spectra.—There are marked similarities in the ultraviolet absorption spectra between the glucosides IX and X and the corresponding ethoxypyrimidines V and VI,[15] as shown in Table I, which should be expected from similarly substituted pyrimidines.

b. Acid Lability.—When IX and X were treated with dry hydrogen chloride gas dissolved in absolute methanol, only 6-methyluracil (I) and 6-methyl-2-thiouracil (II), respectively, were recovered. The hydrolysis residues in each case reduced Fehling solution. In this respect IX and X are unlike the acetylated N-glycosylamines (nucleosides) obtained from the reactions of 2,4-diethoxypyrimidine and 2,4-diethoxy-5-methylpyrimidine with acetylglycosyl halides but rather are like the acid-labile 2-tri-O-acetyl-D-ribopyranosyloxy-4-ethoxypyrimidine reported by Hilbert and Rist.[5]

(10) G. E. Hilbert, THIS JOURNAL, **56**, 190 (1934).

(11) A. M. Michelson, W. Drell and H. K. Mitchell, *Proc. Nat. Acad. Sci.*, **37**, 396 (1951).

(12) G. E. Hilbert, E. F. Jansen and S. B. Hendricks, THIS JOURNAL, **57**, 552 (1935).

(13) J. J. Fox, N. Yung, J. Davoll and G. D. Brown, *ibid.*, **78**, 2117 (1956); J. J. Fox, N. Yung, I. Wempen and I. L. Doerr, *ibid.*, **79**, 5060 (1957).

(14) I. Goodman, *Federation Proc.*, **15**, 264 (1956).

(15) A determination of the structure of such compounds based upon absorption spectrophotometry is discussed in detail by D. Shugar and J. J. Fox, *Biochim. et Biophys. Acta*, **9**, 199 (1952), and by G. H. Beaven, E. R. Holiday and E. A. Johnson, in "The Nucleic Acids," E. Chargaff and J. N. Davidson (eds.), Academic Press, Inc., New York, N. Y., 1955.

c. Alkali Lability.—The fact that IX and X reduced Fehling solution suggested that they were alkali labile. When they were heated with 0.1 N sodium hydroxide in 90% ethanol, IX yielded 4-ethoxy-6-methyl-2(1)-pyrimidone; X gave 2-ethylthio-6-methyl-4(3)-pyrimidone. At room temperature in 0.03 *N* sodium hydroxide–50% ethanol, the reactions proceeded slowly enough to be followed conveniently in the ultraviolet absorption spectrophotometer. The data are summarized in Figs. 1 through 3. The alkali lability of glycosides possessing an allylic or aromatic aglycone is well documented.[16]

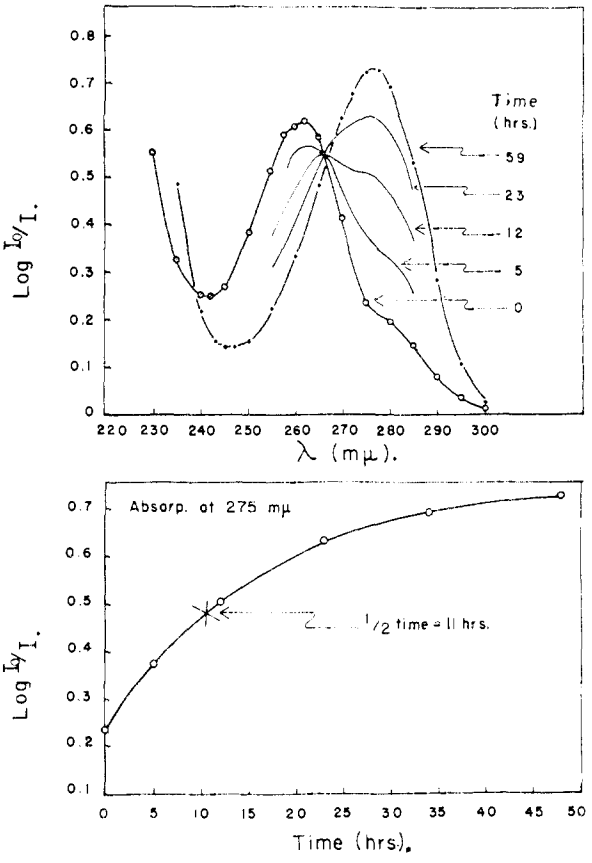


Fig. 1.—Change in ultraviolet absorption spectrum of 2-tetra-O-acetyl-α-D-glucopyranosyloxy-4-ethoxy-6-methylpyrimidine in 0.1 *N* sodium hydroxide/50% ethanol at room temperature.

The isomers of IX and X were identified as α–β- pairs on the basis of: identical elemental analyses; very similar ultraviolet absorption spectra; differences in melting points; lability of all of the compounds to alkali, but greater lability of the β-isomers (Figs. 1, 2 and 3); differences in optical rotation such that the molecular rotation values for each pair when calculated according to Hudson's second rule of isorotation agree with values for other α–β–pairs of tetra-O-acetylglucosides (see Table II).

Glycosides may be considered to be formed in the Hilbert–Johnson reaction by means of a reaction analogous to the Koenigs–Knorr condensation,[17] with the elimination of a volatile alkyl halide rather than an insoluble silver halide. Accordingly, the β-isomer may be assumed to form first. Under conditions of prolonged heating in the presence of small amounts of halide ions, mutarotation of glycosides was observed to occur by

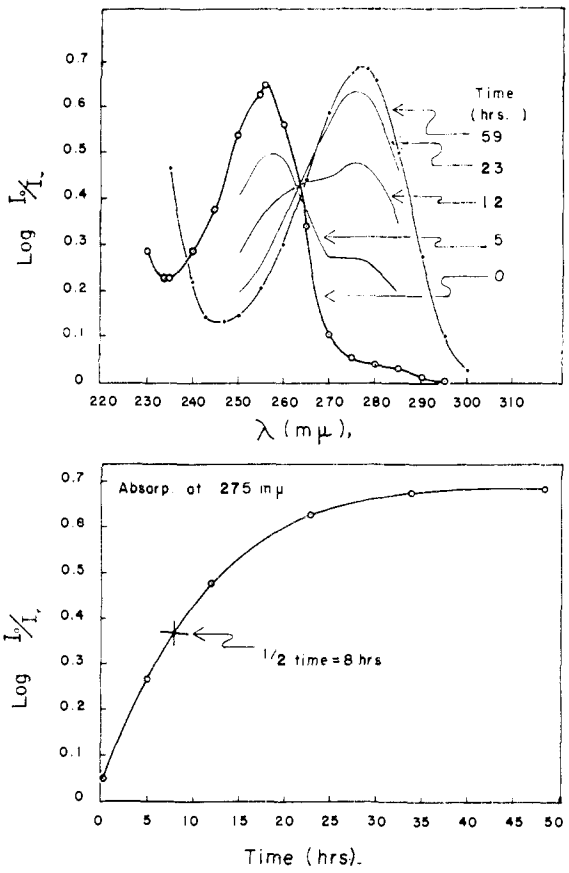


Fig. 2.—Change in ultraviolet absorption spectrum of 2-tetra-O-acetyl-β-D-glucopyranosyloxy-4-ethoxy-6-methylpyrimidine in 0.1 *N* sodium hydroxide/50% ethanol at room temperature.

TABLE II

MOLECULAR ROTATIONS OF SOME α- AND β-DERIVATIVES 2,3,4,6-TETRA-O-ACETYL-D-GLUCOSE

1-Substituent	M_α	M_β	$2B = M_\alpha + M_\beta$
None[a]	+48,400	+ 770	+49,170
Acetyl[a]	+39,700	+ 1,480	+41,180
Chloro[a]	+60,900	− 4,770	+56,130
Methyl[a]	+47,280	− 6,590	+40,690
Isopropyl[b]	+55,800	− 9,500	+46,300
t-Butyl[b]	+52,100	− 4,700	+47,400
Cyclohexyl[c]	+52,300	−10,200	+42,100
Phenyl[d]	+70,000	−12,600	+57,400
1-Naphthyl[d]	+81,000	−31,100	+49,900
Glucosides IX	+59,200	− 2,000	+57,200
Glucosides X	+51,200	− 1,500	+49,700

[a] F. J. Bates and Associates, Polarimetry, Saccharimetry and the Sugars, U. S. Govt. Printing Office, Washington, D. C., 1942. [b] B. Lindberg, *Acta Chem. Scand.*, **3**, 156 (1949). [c] E. Pacsu, THIS JOURNAL, **52**, 2568 (1930). [d] H. Vogel and A. Georg, "Tabellen der Zucker und ihrer Derivate," Julius Springer, Verlag, Berlin, Germany, 1931.

(16) C. E. Ballou, *Adv. in Carbohydrate Chem.*, **9**, 59 (1954).

(17) W. Koenigs and E. Knorr, *Ber.*, **34**, 957 (1901).

Fischer.[18] Predominance of the α-isomer in equilibrium mixtures of both α- and β-methyl glucosides was demonstrated by Levene, Raymond and Dillon.[19] Thus, mutarotation with the equilibrium shifted toward the α-form may explain the observed proportions of isomers isolated from our reaction mixtures.

Experimental[20]

Acetylglycosyl Halides.—Tetra-O-acetyl-α-D-glucopyranosyl bromide was prepared by a simplified one-step procedure[21] without isolating tetra-O-acetyl-β-D-glucose as an intermediate. The method of Skraup and Kremann[22] was used for tetra-O-acetyl-α-D-galactopyranosyl chloride. Brauns'[23] directions were followed for tri-O-acetyl-α-D-arabinopyranosyl chloride and tri-O-acetyl-α-D-xylopyranosyl chloride.

Ethoxypyrimidines.—Compounds V, VI, VII and VIII were all synthesized from the corresponding pyrimidones I, II, III and IV, respectively. The pyrimidones were treated with phosphorus oxychloride alone,[24] or with the oxychloride plus dimethylaniline[25] to yield the chloropyrimidines. These in turn were treated with sodium ethoxide in absolute ethanol to give the ethoxypyrimidines, using the modifications of Sprague and Johnson[26] and Hilbert and Jansen.[3]

2-Ethylthio-6-methyl-4(3)-pyrimidone.—The methylation procedures of Wheeler and MacFarland[27] and of Barrett, Goodman and Dittmer[28] were utilized for the reaction of 6-methyl-2-thiouracil with ethyl iodide. This method gave higher yields and a purer product than was obtained from the condensation of ethyl acetoacetate with pseudoethylthiourea hydrobromide.[29]

2-Ethylthio-4(3)-pyrimidone.—Treatment of 2-thiouracil with ethyl iodide according to the directions of Barrett, Goodman and Dittmer[28] for 2-methylthio-4(3)-pyrimidone gave better yields and an initially purer product than were achieved by the procedure of Wheeler and Liddle.[30]

2,4,6-Triethoxypyrimidine.—The mild conditions we employed[26,3] in treating 2,4,6-trichloropyrimidine[25] with sodium ethoxide gave a much higher yield (95%, m.p. 8–9°, $n^{20}D$ 1.4863) than was achieved originally by Winkelman.[31]

Anal. Calcd. for $C_{10}H_{16}N_2O_3$: N, 13.20. Found: N, 13.16.

Condensation Reactions.—Hilbert's[4] procedure was followed. Equal weights of the ethoxypyrimidines and acetylglycosyl bromides were allowed to react in an oven at 80°, with care taken to exclude moisture and at the same time to permit evaporation of the volatile by-product ethyl bromide by venting the reaction flask through a drying tube outside of the oven. Reaction temperatures of about 100° were employed when the sugars were in the form of the acetylglucosyl chlorides.

2-Tetra-O-acetyl-α-D-glucopyranosyloxy-4-ethoxy-6-methylpyrimidine.—To 15 g. of 2,4-diethoxy-6-methylpyrimidine[9,32] in a 50-ml. erlenmeyer flask were added 15 g. of tetra-O-acetyl-α-D-glucopyranosyl bromide. The flask was fitted with rubber stopper and outlet tube and kept in an oven at 80° for 70 hr. An equal volume of ether was added after the reaction mixture had cooled and 0.3 g. of 6-methyluracil was filtered off. The residue was placed in a refrigerator overnight resulting in the precipitation of the α-glucoside, which after washing with ether and drying weighed 6.3 g. and melted at 164°. Decolorization with Darco G-60 and recrystallization from 95% ethanol raised the melting point to 166–167° and optical rotation to $[\alpha]^{30}D$ +122.5° (*c* 0.5 in chloroform). Fehling solution was reduced after 5 minutes heating. An additional 0.3 g. of product was recovered after the original reaction mixture was heated further at 80° for 40 hr. and then placed in a refrigerator for 3 weeks. The final yield was 6.6 g. (37% based on the acetylglucosyl halide).

Anal. Calcd. for $C_{21}H_{28}N_2O_{11}$: N, 5.78. Found: N, 5.82.

2-Tetra-O-acetyl-β-D-glucopyranosyloxy-4-ethoxy-6-methylpyrimidine.—The reaction mixture was returned to a refrigerator after filtering off the second crop of α-glucoside. Three weeks later an additional 0.5 g. of crystalline product was filtered off, washed with ether and dried. This material melted at 117–120°. Decolorization with Darco G-60 and recrystallization from ethanol raised the melting point to 120–121° and optical rotation to $[\alpha]^{30}D$ −4.2 (*c* 0.5 in chloroform). Analyses and ultraviolet absorption spectrum (Table I) checked with the values for the α-glucoside, but 15 minutes heating in a water-bath was required for reduction of Fehling solution.

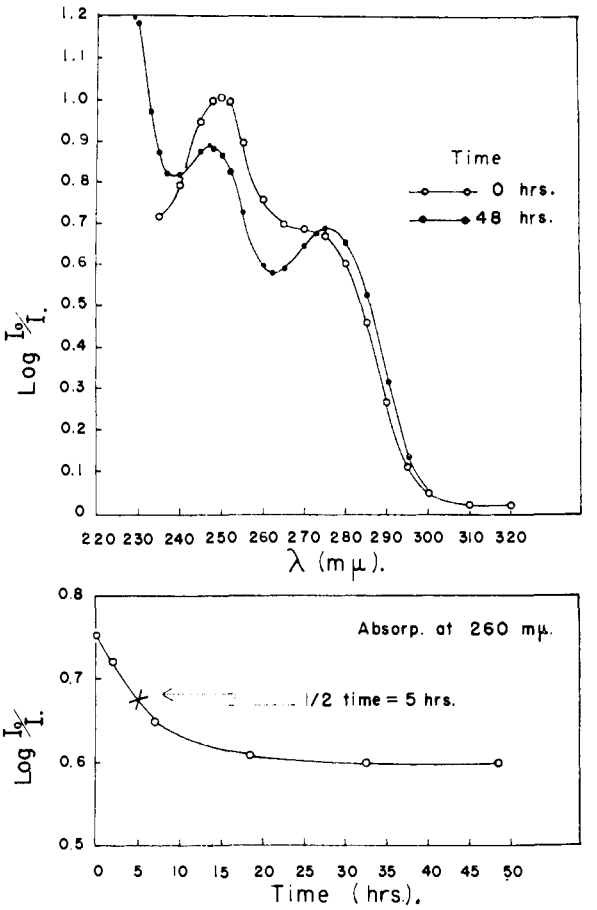


Fig. 3.—Change in ultraviolet absorption spectrum of 2-ethylthio-4-tetra-O-acetyl-α-D-glucopyranosyloxy-6-methylpyrimidine in 0.1 *N* sodium hydroxide/50% ethanol at room temperature. With the *beta* isomer hydrolysis was complete in less than 30 minutes, by the time the first readings were taken.

(18) E. Fischer, *Ber.*, **28**, 1145 (1895).

(19) P. A. Levene, A. L. Raymond and R. T. Dillon, *J. Biol. Chem.*, **95**, 696 (1932).

(20) All melting points are corrected. Ultraviolet absorption spectra were measured in a Beckman model DU spectrophotometer.

(21) J. J. Fox, Ph.D. Thesis, Univ. of Colorado, 1950.

(22) H. Skraup and R. Kremann, *Monatsh.*, **22**, 379 (1901).

(23) D. H. Brauns, THIS JOURNAL, **46**, 1484 (1924); **47**, 1280 (1925).

(24) S. Gabriel and J. Colman, *Ber.*, **32**, 1525 (1899).

(25) J. Baddiley and A. Topham, *J. Chem. Soc.*, 678 (1944).

(26) J. M. Sprague and T. B. Johnson, THIS JOURNAL, **57**, 2252 (1935).

(27) H. L. Wheeler and D. F. MacFarland, *Am. Chem. J.*, **42**, 101 (1909).

(28) H. W. Barrett, I. Goodman and K. Dittmer, THIS JOURNAL, **70**, 1753 (1948).

(29) C. O. Johns, *Am. Chem. J.*, **40**, 348 (1908).

(30) H. L. Wheeler and L. M. Liddle, *ibid.*, **40**, 547 (1908).

(31) W. Winkelman, *J. prakt. Chem.*, **115**, 292 (1927).

(32) B.p. 121–122° (11 mm.), $n^{20}D$ 1.4876. *Anal.* Calcd. for $C_9H_{14}O_2N_2$: N, 15.37. Found: N, 15.21. Compound prepared before appearance of reports by R. Andrisano, *Boll. sci. Faculta chim. ind. univ .Bologna*, **5**, 52 (1944); **5**, 56 (1947); and by Rabinowitz and Gurin.[9]

Anal. Calcd. for $C_{21}H_{28}N_2O_{11}$: C, 52.06; H, 5.82; N, 5.78. Found: C, 52.43; H, 6.00; N, 5.97.

1-Ethyl-6-methyl-2(1),4(3)-pyrimidonedione.—Following isolation of the acetyl glucosides the sirupy residue was subjected to methanolysis with an excess of dry hydrogen chloride for three days at room temperature. Evaporation of the excess methanol, addition of water and cooling resulted in the precipitation of 2.5 g. of impure 6-methyluracil. Evaporation of the solvent a second time and the addition of ethanol brought down another 1.5 g. of 6-methyluracil. When the residual solution was cooled 0.4 g. of a compound was deposited which after treatment with Darco G-60 and recrystallization from ethanol melted at 197–198° and analyzed correctly for an ethyl-substituted 6-methyluracil. An additional 0.3 g. of this compound was extracted with chloroform from the impure 6-methyluracil. The melting point of the compound agreed with the literature value for 1-ethyl-6-methyluracil.[33] A sample of 1-ethyl-6-methyluracil prepared by treating V with ethyl iodide had the same ultraviolet absorption spectrum (Table I) and melting point, and the mixed melting point with the compound we isolated showed no depression.

Anal. Calcd. for $C_7H_{10}N_2O_2$: N, 18.17. Found: N, 18.09.

4-Ethoxy-6-methyl-2(1)-pyrimidone.—One gram of the α-form of IX was refluxed for 19 hr. in 40 ml. of 90% ethanolic 0.3 *N* sodium hydroxide. Excess solvent was evaporated and the residue was decolorized with Darco G-60 in ethanol. Evaporation of the solvent a second time and the addition of a few ml. of water resulted in a white crystalline precipitate (0.23 g.). After two recrystallizations the compound sintered at 190° and melted at 196°. It contained no sugar. Analysis confirmed the presence of an ethoxyl group. Hydrolysis of the compound in dilute hydrochloric acid yielded 6-methyluracil. Depression of mixed melting points with authentic samples of 2-ethoxy-6-methyl-4(3)-pyrimidone[34] and of 1-ethyl-6-methyl-2,4(1,3)-pyrimidonedione and comparisons of the ultraviolet absorption spectra of the three isomers (Table I) confirmed the assignment of structure.

With the exception of 6-methyluracil this compound was the only product isolated from the reaction of V with the tetra-O-acetyl-α-D-glycopyranosyl chlorides of galactose, arabinose and xylose.

(33) O. Hoebel, *Ann.*, **353**, 242 (1907).

(34) W. M. Bruce, THIS JOURNAL, **26**, 449 (1904).

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17; ethoxyl, 29.14. Found: C, 54.07; H, 6.54; N, 18.05; ethoxyl, 34.55.

4-Tetra-O-acetyl-α-D-glucopyranosyloxy-2-ethylthio-6-methylpyrimidine.—Fifteen grams of VI and 15 g. of tetra-O-acetyl-α-D-glucopyranosyl bromide were heated at 80° for 26 hr. Upon the addition of ether there were precipitated 0.25 g. of 6-methyluracil and 0.9 g. of crude 2-ethylthio-6-methyl-4(3)-pyrimidone. After two more days of heating the remaining reaction mixture at 80°, the addition of ether resulted in the precipitation of 3.7 g. of a compound which melted at 118°. Decolorization with Norite and two recrystallizations from ethanol gave a product which melted at 125–126° and had an optical rotation $[\alpha]^{30}D$ +102.3 (*c* 0.5 in chloroform). Fehling solution was reduced after 5 minutes heating in a boiling water-bath. Recovery of an additional 0.3 g. of the α-isomer following the isolation of the β-isomer (see below) raised the yield to 4.0 g. (22%).

Anal. Calcd. for $C_{21}H_{28}N_2O_{10}S$: N, 5.59. Found: N, 5.44.

4-Tetra-O-acetyl-β-D-glucopyranosyloxy-2-ethylthio-6-methylpyrimidine.—The reaction mixture remaining after the α-glucoside had precipitated was heated at 80° for an additional two days. Addition of ether brought down a precipitate which was freed of traces of I by dissolving it in chloroform in which I is insoluble. Evaporation of the chloroform left a residue which when dissolved in ethanol, decolorized with Darco G-60 and placed in a refrigerator yielded 0.4 g. of the β-glucoside, m.p. 170°. After recrystallization the melting point was 176–177° and the optical rotation $[\alpha]^{30}D$ −3.0° (*c* 0.5 in chloroform). Both analysis and ultraviolet absorption spectrum (Table I) were like the α-isomer, but the reduction of Fehling solution required 15 minutes heating on a water-bath.

Anal. Calcd. for $C_{21}H_{28}N_2O_{10}S$: N, 5.59. Found: N, 5.53.

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The Isomerization of C^{14}-Labeled Sugars to Saccharinic Acids[1]

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D-Galactose-1-C^{14}, lactose-1-C^{14} and D-mannose-1-C^{14} have been isomerized by treatment with lime water, respectively to "α"-D-galactometasaccharinic acid, "α"-D-isosaccharinic acid and "α"-D-glucosaccharinic acid. The observed distribution of label in the former two products is in agreement with the Nef–Isbell intramolecular mechanism for their formation. The pattern and relative distribution of the label found in the "α"-D-glucosaccharinic acid indicate that fragment recombination is a predominant feature in its formation from the monosaccharide.

Two general mechanisms have been proposed for the formation of saccharinic acids by the action of alkali on reducing sugars.[2] These are (1) recombination of appropriate fragments directly to the saccharinic acids[3,4] and (2) intramolecular isomerization involving, as the final step, the benzilic acid type of rearrangement of α-dicarbonyl intermediates to the saccharinic acids.[5–7] Obviously a mechanism involving fragment recombination followed by isomerization is also possible. Recent extensive studies[2] by Kenner and his associates on saccharinic acid formation from substituted monosaccharides (including oligo- and polysaccharides) have provided strong experimental support for the Isbell intramolecular isomerization mechanism.[7] The present study, in which certain aldose sugars labeled in C-1 with carbon-14 were isomerized to

(1) For a preliminary communication concerning part of this work, see J. C. Sowden and D. J. Kuenne, THIS JOURNAL, **75**, 2788 (1953).

(2) For a general review of the saccharinic acids, including theories of the mechanism of their formation, see J. C. Sowden, "Adv. in Carbohydrate Chem.," **12**, 35 (1957).

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