

NUCLEIC ACIDS COMPONENTS AND THEIR ANALOGUES. LI.*
SYNTHESIS OF 1-GLYCOSYL DERIVATIVES OF 5-AZAUACIL
AND 5-AZACYTOSINE

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For the preparation of 1-glycosyl derivatives of 5-azauracil and 5-azacytosine a method is described starting from peracetylglycosyl isocyanates. Addition of 2-methylisourea affords 1-peracetylglycosyl-4-methylisobiurets which are condensed with ethyl orthoformate to form 1-peracetylglycosyl-4-methoxy-2-oxo-1,2-dihydro-1,3,5-triazines. Deacetylation and demethylation of the latter compounds affords 1-glycosyl-5-azauracils whereas deacetylation followed by amination yields 1-glycosyl-5-azacytosines. By this procedure, glucopyranosyl, ribopyranosyl and ribofuranosyl derivatives of 5-azauracil as well as of 5-azacytosine have been prepared.

In the course of biochemical studies about cultivation of *Escherichia coli* in the presence of a subbacteriostatic concentration of 5-azauracil (2,4-dioxo-1,2,3,4-tetrahydro-1,3,5-triazine), ribosylbiuret¹ forming by decomposition of the unstable ribosyl-5-azauracil has been found in the medium. A detailed study of 5-azauracil anabolites has shown that cleavage of ribosyl-5-azauracil to ribosylbiuret proceeds in the culture of *E. coli* via N-formylribosylbiuret², i.e., analogously to the cleavage of 5-azauracil to biuret³. Moreover, it has been demonstrated with the use of a cell-free extract of *E. coli* that 5-azauracil is a suitable substrate for microbial phosphorylases as well as pyrophosphorylases which makes possible the synthesis of ribosyl-5-azauracil and ribosyl-5-azauracil 5'-phosphate⁴, resp. We have expected that ribosyl derivatives of 5-azauracil or 5-azacytosine (4-amino-2-oxo-1,2-dihydro-1,3,5-triazine) could exhibit marked biological effects similar to those of the corresponding 6-azaanalogues. In fact, preliminary experiments seem to support this assumption⁵⁻⁷.

In this paper, we have studied the possibility of a chemical preparation of 1-glycosyl derivatives of 5-azauracil and 5-azacytosine which would represent the hitherto undescribed analogues of the appropriate pyrimidine nucleosides. Our attention has been focussed on the glucopyranosyl, ribopyranosyl and ribofuranosyl derivatives. The ribosyl derivatives were proposed for correlation with the above products of enzymic reactions.

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In a recent paper⁸, we have described a general method for the preparation of 1-substituted 5-azauracils as well as 5-azacytosines which consists in the condensation of isobiurets with orthoesters followed by treatment with hydrogen chloride or ammonia. Since this method represents, according to our experience, the most suitable procedure for the preparation of this type of compounds, we have tried to synthesize also the required glycosyl derivatives in this manner. We have started from tetra-acetylglucopyranosyl isocyanate which was prepared by Fischer⁹ in a 22% yield on treatment of 1-bromo-2,3,4,6-tetra-O-acetyl- α -D-glucopyranose (*I*) with silver cyanate. Later on, Johnson and Bergmann¹⁰ described formation of a second, lower-melting modification. In several experiments, we isolated merely the higher-melting form. Furthermore, we were able to increase the yield (70%) by a suitable arrangement of the reaction conditions. Treatment with ammonia results in a product⁹ to which the structure of 1- β -D-glucopyranosylurea was ascribed^{11,12}. Consequently, the product of the treatment with silver cyanate may be considered as 2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl isocyanate (*II*).

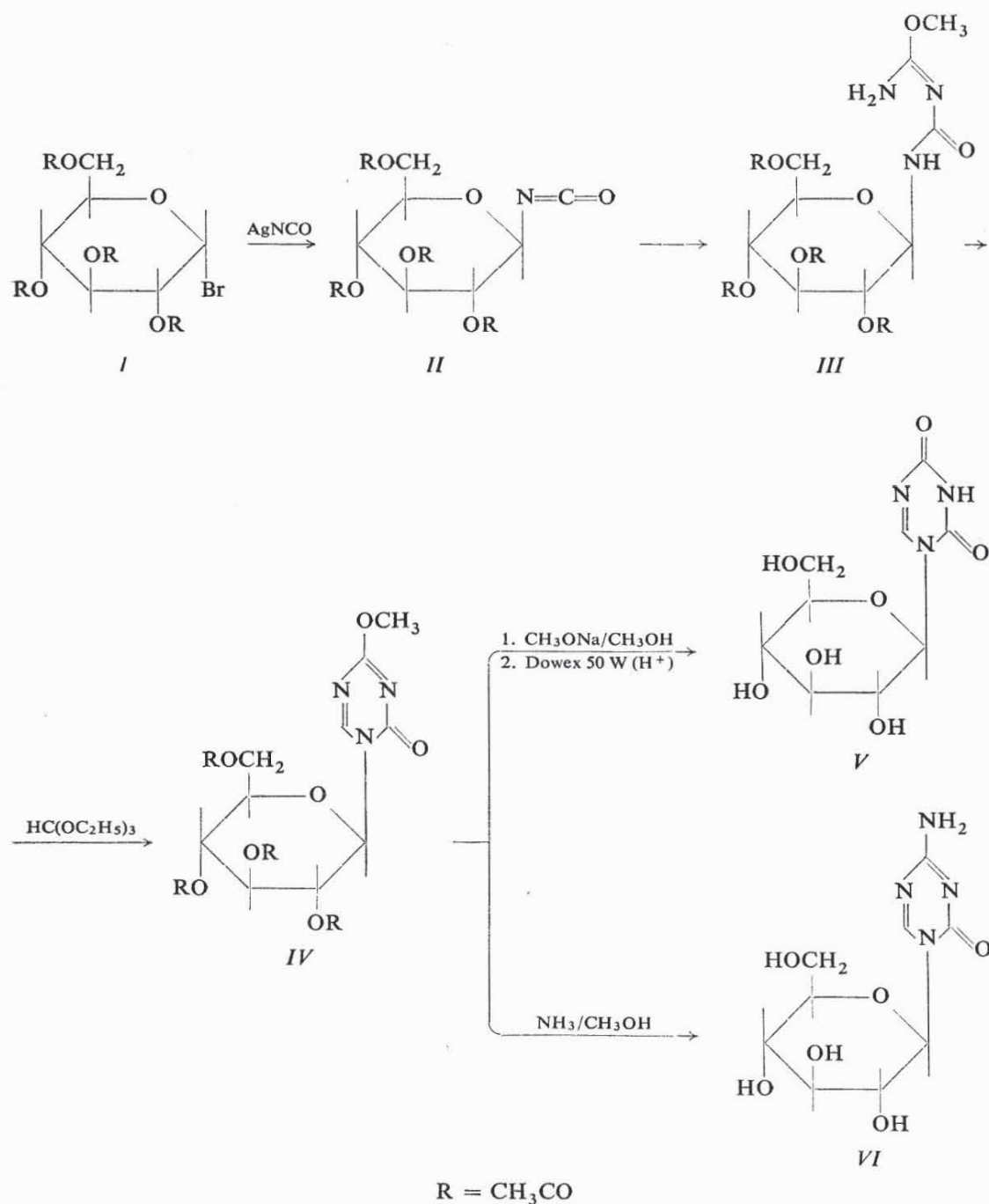
Addition of 2-methylisourea afforded a high yield of a chromatographically homogeneous amorphous product analyzing in agreement with the expected 1-(2,3,4,6-

Table I
Ultraviolet Spectra

Compounds	Solvent	$\lambda_{\max}$ m μ	log ϵ
1,4-Dimethylisobiuret	96% ethanol	221	4.18
<i>III</i>	96% ethanol	221	4.26
<i>X</i>	96% ethanol	221	4.28
<i>XVI</i>	96% ethanol	221	4.27
1-Methyl-4-methoxy-2-oxo-1,2-dihydro-1,3,5-triazine	acetonitril	254	3.34
<i>IV</i>	acetonitril	254	3.40
<i>XI</i>	acetonitril	253	3.39
<i>XVII</i>	acetonitril	253	3.36
1-Methyl-5-azauracil	96% ethanol	245	3.20
<i>V</i> ^a	96% ethanol	240	3.25
<i>XII</i> ^a	96% ethanol	240	3.24
1-Methyl-5-azacytosine	water, pH 5.0	247	3.74
<i>VI</i> ^a	water, pH 5.0	243	3.81
<i>XIII</i> ^a	water, pH 5.0	243	3.80
<i>XXII</i> ^a	water, pH 5.0	246	3.78

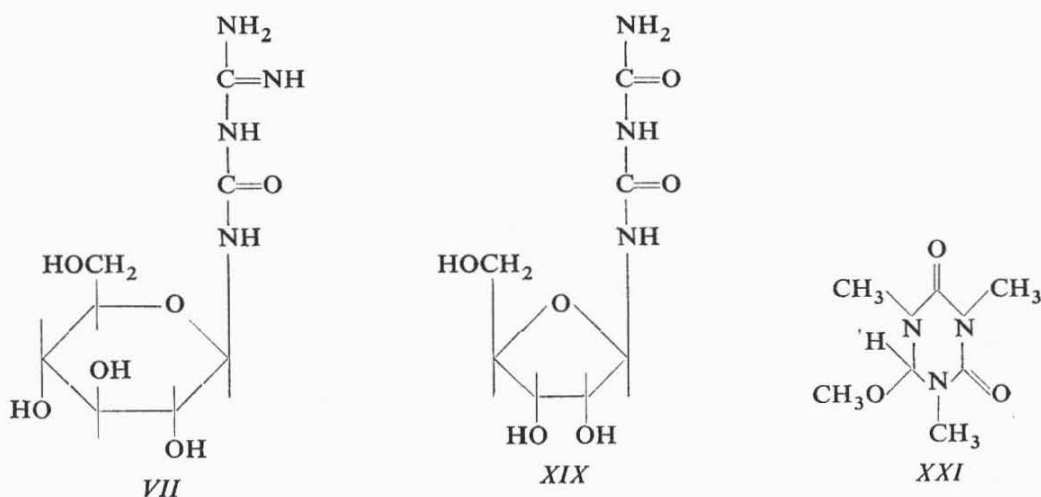
^a Spectra of the 5-azauracil and 5-azacytosine glycosyl derivatives were measured immediately after dissolution because of the time-dependence of their extinction coefficient^{13,25}.

tetra-O-acetyl- β -D-glucopyranosyl)-4-methylisobiuret (*III*). Its ultraviolet spectrum is practically identical with that of the analogous 1,4-dimethylisobiuret (see Table I). The above product was condensed at 135°C with ethyl orthoformate in the stream of dry nitrogen to yield crystalline 1-(2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl)-4-methoxy-2-oxo-1,2-dihydro-1,3,5-triazine (*IV*). Its structure was established on comparison of the ultraviolet spectrum with that of the analogous 1-methyl-4-methoxy-2-oxo-1,2-dihydro-1,3,5-triazine (Table I).



Transformation of the glucoside *IV* into the required 1- β -D-glucopyranosyl-5-azauracil (*V*) was accomplished with methanolic hydrogen chloride or Dowex 50 W(H⁺) ion exchange resin in methanol or sodium methoxide followed by Dowex 50 W(H⁺) resin. When crystallised from aqueous ethanol, the substances formed a solvate with ethanol and water. Water may be removed by heating *in vacuo* at 130°C for 1 hour whereas removal of ethanol requires 10 hours at the same temperature. Its structure was verified on a comparison of the ultraviolet spectrum with that of the analogous 1-methyl-5-azauracil¹³, and, furthermore, by an acidic hydrolysis yielding 5-azauracil and glucose. Moreover, the formation of a stable adduct with ethanol in the case of the glucoside *V* closely resembles the behaviour of 1-methyl-5-azauracil¹⁴. The structure of both these adducts will be discussed in detail in a subsequent paper of this Series¹⁵.

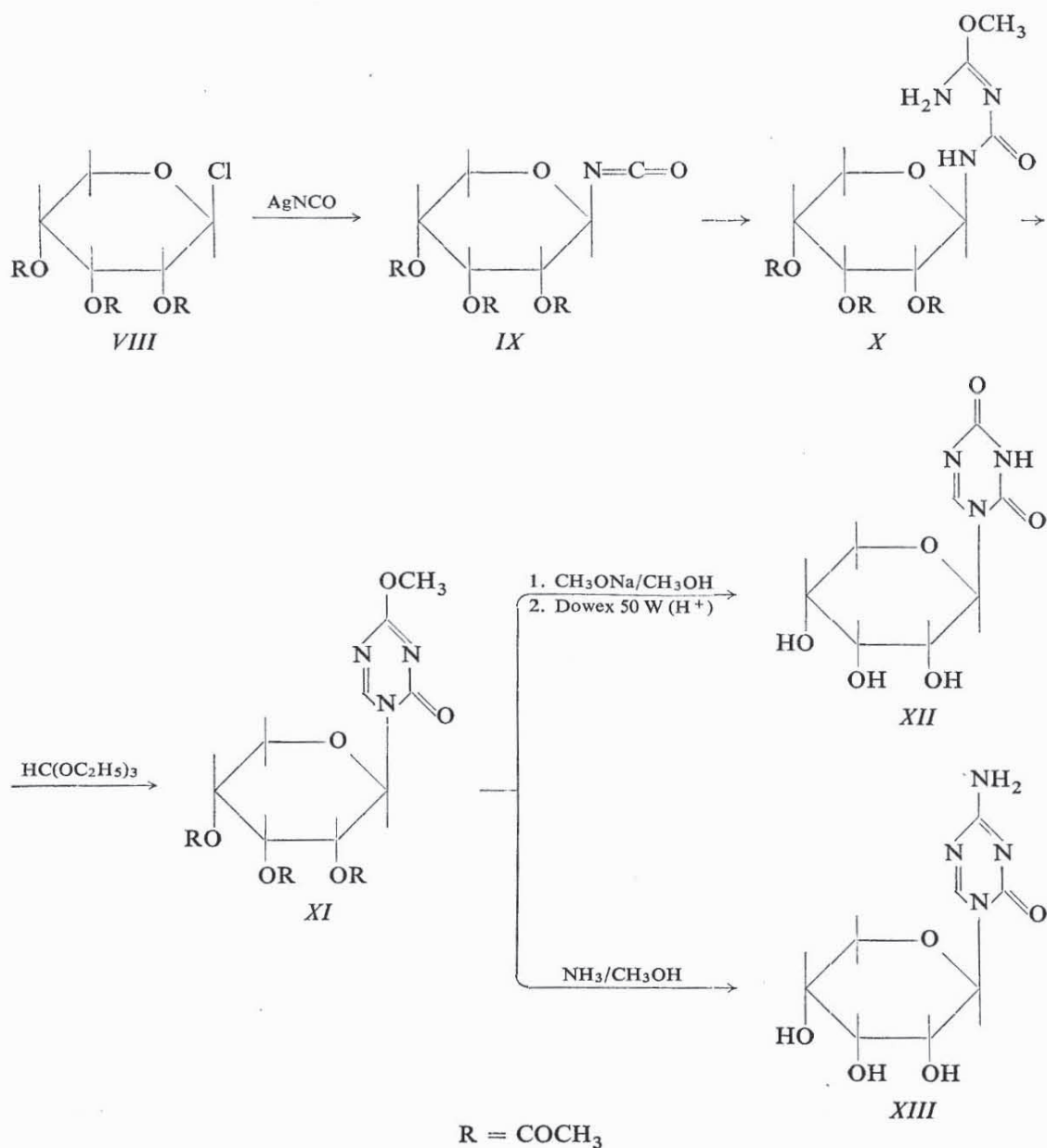
A short action of a methanolic solution of ammonia at room temperature on the glucoside *IV* afforded crystalline 1- β -D-glucopyranosyl-5-azacytosine (*VI*) in a good yield. Its structure was confirmed on comparison of the ultraviolet spectrum with that of the analogous 1-methyl-5-azacytosine (see Table I) and by acidic hydrolysis yielding 5-azacytosine and glucose. The prolonged action of the methanolic solution of ammonia led to a second product, namely, 1- β -D-glucopyranosyl-3-guanyljurea (*VII*). This compound is obviously formed by cleavage of the triazine ring of the glucosyl derivative *VI*.



The above procedure was used also for the synthesis of 5-azauracil and 5-azacytosine ribopyranosyl derivatives. The starting 1-chloro-2,3,4-tri-O-acetyl- β -D-ribose (*VIII*) was reacted with silver cyanate under similar conditions as in the preceding case. 2,3,4-Tri-O-acetyl- β -D-ribose isocyanate (*IX*) was obtained as amorphous solid but its analysis as well as infrared spectrum, $\nu(\text{N}=\text{C}=\text{O})$, 2252 cm^{-1} , closely resembling that of peracetylglucosyl isocyanate *II*, $\nu(\text{N}=\text{C}=\text{O})$, 2253 cm^{-1} , both speak in favour of the supposed structure. Since in the reactions of halogenoses with silver cyanate the same steric course can be assumed as in the reactions with the

silver or mercury salts of pyrimidine and purine bases, we have used the rule of Baker¹⁶ for allotment of the configuration at the glycosidic centre of the molecule. Treatment of the isocyanate *IX* with 2-methylisourea afforded a high yield of crystalline 1-(2,3,4-tri-O-acetyl- β -D-ribofuranosyl)-4-methylisobiuret (*X*) the structure of which was confirmed by the ultraviolet spectrum (see Table I). Condensation of this compound with ethyl orthoformate at 135°C resulted in crystalline 1-(2,3,4-tri-O-acetyl- β -D-ribofuranosyl)-4-methoxy-2-oxo-1,2-dihydro-1,3,5-triazine (*XI*) the ultraviolet spectrum of which corresponded to the proposed structure (Table I).

Successive treatment of the ribosyl derivative *XI* with sodium methoxide and Dowex 50 W (H^+) ion exchange resin yielded a product to which the structure of



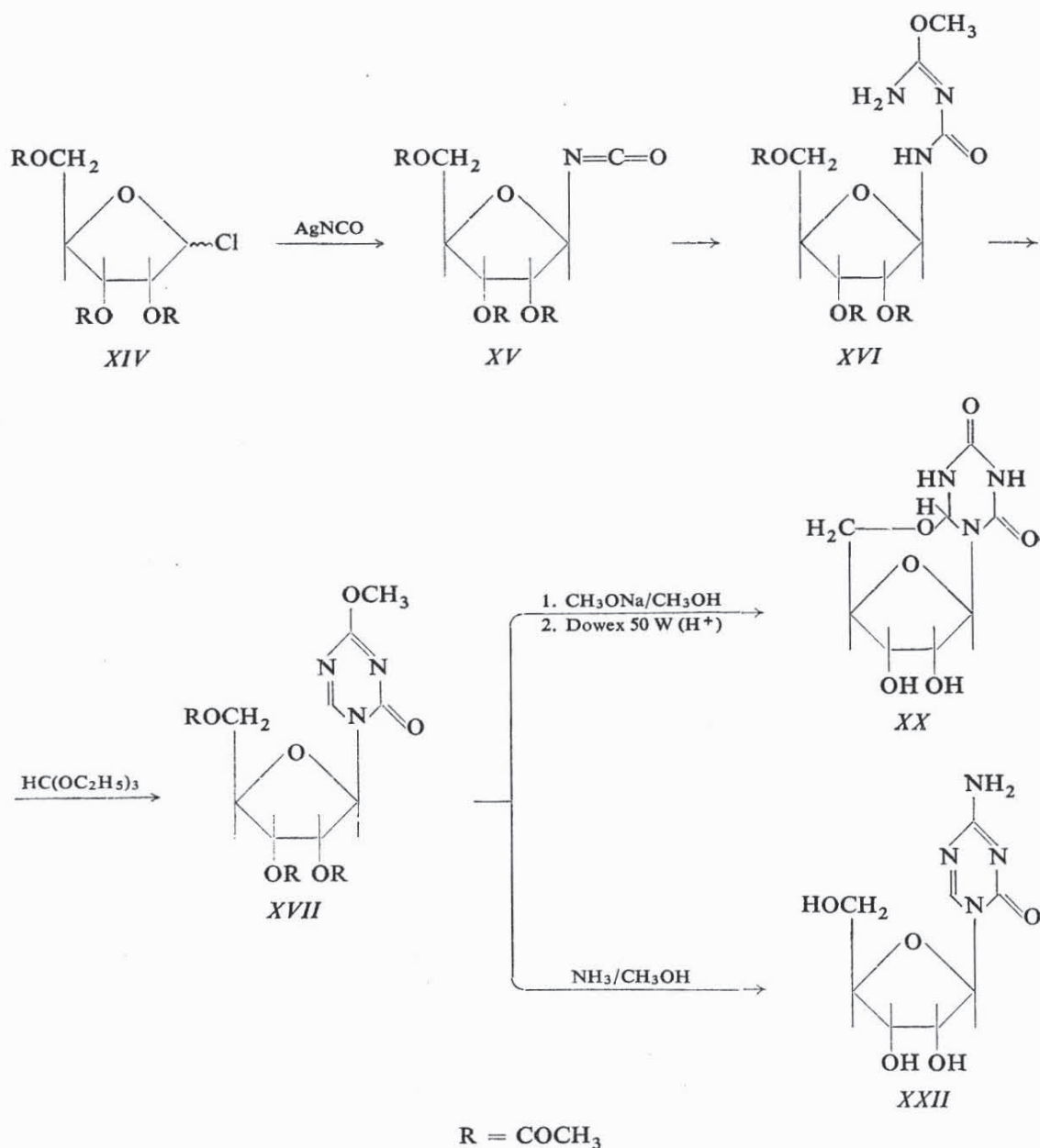
1- β -D-ribose-5-azauracil (*XII*) was ascribed on the basis of the ultraviolet spectrum (see Table I). This compound was cleaved by the action of hydrochloric acid with the formation of ribose and 5-azauracil, and, furthermore, formed a solvate with ethanol.

Treatment of the compound *XI* with a methanolic solution of ammonia afforded the expected 1- β -D-ribose-5-azacytosine (*XIII*) as crystals. The proposed structure was again confirmed by the ultraviolet spectrum (Table I) and acidic hydrolysis yielding ribose and 5-azacytosine.

Finally, the above method was applied also for the preparation of 5-azauracil and 5-azacytosine ribofuranosyl derivatives. The reaction of 1-chloro-2,3,5-tri-O-acetyl-D-ribofuranose (*XIV*) with silver cyanate was performed under similar conditions as in the preceding examples. 2,3,5-Tri-O-acetyl- β -D-ribofuranosyl isocyanate (*XV*) was obtained as sirup and was characterised by the infrared spectrum, $\nu(\text{N}=\text{C}=\text{O})$, 2252 cm^{-1} . The β -configuration at the glycosidic centre of the molecule was ascribed on the basis of Baker's rule¹⁶. The proof of validity of this assumption follows also from the structure of ribofuranosyl-5-azauracil (*XX*) (*vide infra*). Treatment of the isocyanate *XV* with 2-methylisourea afforded crystalline 1-(2,3,5-tri-O-acetyl- β -D-ribofuranosyl)-4-methylisobiuret (*XVI*) the spectrum of which was similar to spectra of the preceding isobiurets (Table I). Condensation of this product with ethyl orthoformate at 135°C resulted in glassy 1-(2,3,5-tri-O-acetyl- β -D-ribofuranosyl)-4-methoxy-2-oxo-1,2-dihydro-1,3,5-triazine (*XVII*) possessing the expected ultraviolet spectrum (Table I).

Deacetylation and demethylation of the ribofuranosyl derivative *XVII* was expected, in analogy to the treatment of the compounds *IV* and *XI*, to yield 1- β -D-ribofuranosyl-5-azauracil (5-azauridine; *XVIII*). The reaction was again performed by the successive treatment with sodium methoxide and Dowex 50 W (H^{+}) ion exchange resin. A crystalline product was obtained the elementary analysis of which corresponded to 5-azauridine. The substance, however, did not form any adduct with ethanol (in contrast to the analogous products *V* and *XII*) and, in a neutral medium, did not exhibit any maximum in the near ultraviolet region. At pH 5.0, the expected maximum ($\lambda_{\text{max}} 241\text{ m}\mu$) was registered but the molar extinction coefficient was considerably lower ($\log \epsilon 2.68$) in comparison with other 1-substituted 5-azauracils. Moreover, the absorption disappeared rather quickly (no maximum could be registered after one hour). The infrared spectrum (in dimethyl sulfoxide) showed a broad band at approx. 1535 cm^{-1} (the triazine ring) and two carbonyl maxima at 1670 and 1715 cm^{-1} . No maximum at 1630 cm^{-1} (characteristic for the azomethine linkage¹³) could be found (also in nujol suspension). Oxidation with potassium periodate at pH 7.0 and room temperature consumed 1.5 mole of periodic acid per 1 mole of the ribosyl derivative in the course of 24 hours as determined polarographically¹⁷ (the theory requires 1 mole of periodic acid). The higher value is obviously due to a subsequent oxidation. During the paper electrophoresis in a borate buffer (pH 7.0) the substance migrated to the anode similar to uridine. The

substance was readily cleaved with hydrochloric acid even at room temperature with the formation of ribose and 5-azauracil, and with dilute aqueous ammonia afforded 1- β -D-ribofuranosylbiuret (XIX). Spectral data showed that in neutral solutions and in the solid state the substance possessed no double bond in the position 5,6 of the azauracil moiety. This fact can be explained by the addition of a hydroxylic function to the azomethine linkage. Principally, any of the three hydroxylic functions in positions 2', 3' or 5' can be involved intra- or intermolecularly. The possibility of a intermolecular addition can be precluded on the basis of the fact that both glucopyranosyl derivative *V* and ribopyranosyl derivative *XII* of 5-azauracil do not undergo such a reaction. Results of the oxidation with potassium periodate and the

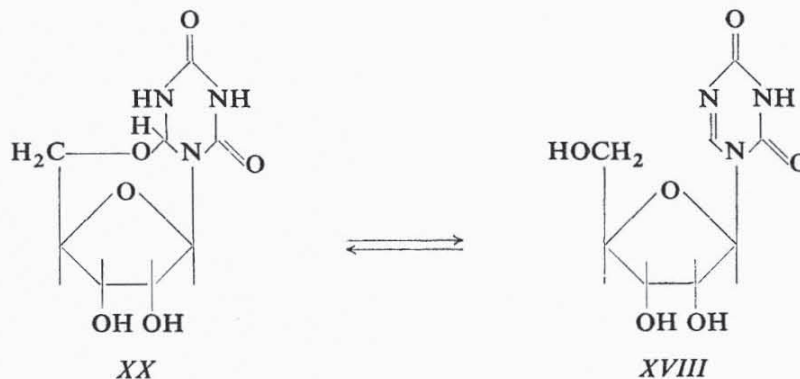


electrophoretic behaviour are in agreement with a free *cis*-diol arrangement on the carbon atoms 2' and 3'. The intramolecular addition to the azomethine linkage is, therefore, accomplished with the primary alcoholic function and the substance may be formulated as 5',6-anhydro-6-hydroxy-5,6-dihydro-5-azauridine (XX). The infrared spectrum of the substance is similar to that of the related 1,3,5-trimethyl-6-methoxy-2,4-dioxohexahydro-1,3,5-triazine¹⁸ (XXI) measured in dimethyl sulfoxide (a broad band at 1520, 1680 and 1720 cm^{-1}); this fact is a further support of the proposed structure.

The spontaneous intramolecular addition of the primary hydroxylic function to the azomethine linkage represents simultaneously a proof of the β -configuration on the glycosidic centre of the molecule. Since glucosyl-5-azauracil V which also possesses a free primary alcoholic function does not undergo this reaction, it may be assumed that the addition will be probably limited to furanosyl derivatives with β -configuration and a free hydroxylic function in the position 5'.

Both 5',6-anhydro-6-hydroxy-5,6-dihydro-5-azauridine (XX) and ribosylbiuret XIX were identical with products forming in the medium in the course of cultivation of *E. coli* in the presence of 5-azauracil¹. The identification was carried out by means of paper chromatography.

From the ultraviolet spectrum of the ribosyl derivative XX in a weakly acidic medium it could be assumed that the compound is partly transformed into 5-azauridine (XVIII) and that some equilibrium exists depending on the pH of the solution. This problem will be discussed in full detail elsewhere¹⁵.



Treatment of the ribofuranosyl derivative XVII with a methanolic solution of ammonia afforded readily crystalline 1- β -D-ribofuranosyl-5-azacytosine (5-azacytidine XXII). Structure of this compound was confirmed on comparison of ultraviolet (see Table I) and infrared (Fig. 1) spectra with those of the analogous 1-methyl-5-azacytosine. By means of hydrochloric acid, the product was cleaved into ribose and 5-azacytosine.

In summary it may be noted that the 5-azaanalogues of pyrimidine nucleosides differ in their properties very markedly from the pyrimidine as well as 6-azapyrimidine nucleosides, especially by the ease of cleavage of the N-glycosidic bond by the action

of mineral acids and by the instability of the triazine moiety in alkaline media. As quite exceptional may be regarded also the behaviour of the 5-azauracil ribofuranosyl derivative where an intramolecular addition of the primary alcoholic function occurs to the azomethine linkage.

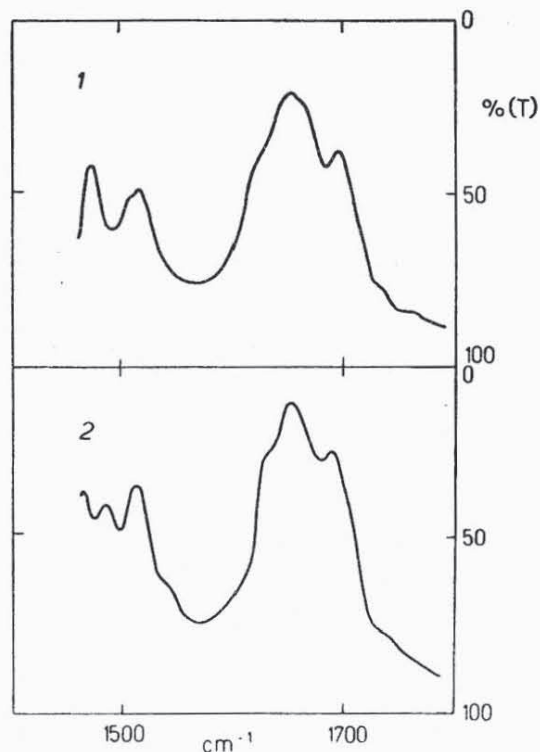


Fig. 1
Infrared Spectra of 1-Methyl-5-azacytosine (1) and 5-Azacytidine (2)
(Measured in Nujol Suspension)

Experimental

Melting points were determined on a heated microscope stage and are corrected. Unless otherwise stated, the analytical samples were dried at 0.3 mm Hg and room temperature for ten hours. Paper chromatography was performed on paper Whatman No 1 by the descending technique (without previous saturations) in solvent systems (S_1) 1-butanol-acetic acid-water (4 : 1 : 1) and (S_2) 1-butanol-ethanol-water (40 : 11 : 19). Detection was carried out by viewing in ultraviolet light or according to Reindel and Hoppe¹⁹. The vicinal *cis*-diol arrangement of the ribosyl derivatives was detected with potassium periodate and benzidine²⁰.

2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl isocyanate (II)

α -Acetobromoglucose (4.11 g; 0.01 mole) was heated in dry xylene (20 ml) with thoroughly dried silver cyanate²¹ (4.5 g; 0.03 mole) under efficient stirring and with exclusion of atmospheric moisture. The bath temperature was gradually increased to 100°C in the course of 30 minutes and the mixture was kept at this temperature for further 30 minutes. Additional two portions of silver cyanate (1.5 g; 0.01 mole) were then added in intervals of 30 minutes, the mixture was heated for 30 minutes, filtered off while still hot and the precipitate washed twice with 10-ml portions of hot xylene. The combined filtrates were cooled and precipitated with light petroleum (40 ml).

The supernatant was decanted (the residual precipitate was discarded), treated with additional 20 ml of light petroleum and a little active charcoal and the mixture was quickly filtered through a French filter. The clear filtrate deposited almost instantaneously the crystalline isocyanate. The next day, the product was collected, yield 2.3 g; m.p. 119–120°C (literature records¹⁰ m.p. 120°C and 125°C (see⁹). Concentration of the mother liquors followed by crystallisation from the ethyl acetate–light petroleum solvent mixture afforded additional 0.37 g of the product. Total yield 2.55 g (70%). Infrared spectrum (chloroform): $\nu(\text{N}=\text{C}=\text{O})$, 2253 cm^{-1} .

1-(2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl)-4-methylisobiuret (*III*)

A stirred solution of 2,3,4,6-tetra-O-acetyl- β -D-glucopyranosyl isocyanate (3.73 g; 0.01 mole) in dry chloroform (50 ml) was slowly treated at -15°C under exclusion of atmospheric moisture with a solution of freshly prepared 2-methylisourea²² (0.7 g; 9.5 millimoles) in chloroform (10 ml). The resulting solution was allowed to stand at room temperature for one hour and the chloroform was evaporated under diminished pressure (bath temperature 30°C). The residual sirup was dissolved in benzene (10 ml) and the solution treated with light petroleum (50 ml). The supernatant was decanted and discarded. The glassy residue was dissolved in hot benzene (10 ml), the solution allowed to cool and treated with light petroleum (50 ml). The resulting solid precipitate was repeatedly triturated under light petroleum and decanted. Yield 4.01 g (94%, based on 2-methylisourea), m.p. 90–100°C. Attempts to crystallise this product from various solvents failed. The R_F value 0.84 (the solvent system S_1), detected according to Reindel and Hoppe¹⁹. The ultraviolet spectrum is given in Table I. For $\text{C}_{17}\text{H}_{25}\text{N}_3\text{O}_{11}$ (447.3) calculated: 45.65% C, 5.64% H, 9.39% N; found: 45.48% C, 5.88% H, 9.06% N.

1-(2,3,4,6-Tetra-O-acetyl- β -D-glucopyranosyl)-4-methoxy-2-oxo-1,2-dihydro-1,3,5-triazine (*IV*)

A solution of the isobiuret derivative *III* (4.47 g; 0.01 mole) in ethyl orthoformate (40 ml) was heated (bath temperature, 135°C) in distillation apparatus in a stream of pure dry nitrogen under exclusion of atmospheric moisture (potassium hydroxide tube) for eight hours. After five hours of heating, the crystalline condensation product began to deposit and clog the nitrogen inlet tube. For the remaining period of heating nitrogen was introduced to the surface of the mixture. After standing at -15°C overnight, the crystals were collected and washed with a small amount of ether. Yield 2.28 g (50%); m. p. 235–237°C. The melting point did not change on recrystallisation of the product from absolute ethanol. The ultraviolet spectrum is shown in Table I. For $\text{C}_{18}\text{H}_{23}\text{N}_3\text{O}_{11}$ (457.3) calculated: 47.27% C, 5.07% H, 9.19% N; found: 47.40% C, 5.09% H, 9.12% N.

1- β -D-Glucopyranosyl-5-azauracil (*V*)

A suspension of the methoxytriazine *IV* (4.57 g; 0.01 mole) in absolute methanol (300 ml) was allowed to stand at room temperature in a stoppered vessel with 50 ml of 0.5N sodium methoxide in methanol for 30 minutes. The resulting solution was treated with moist Dowex 50 W (H^+) ion exchange resin (100 g) previously washed with water and methanol. The mixture was kept at room temperature under occasional stirring for two hours, filtered off and the resin washed thoroughly with methanol. The combined filtrates were evaporated under diminished pressure (bath temperature 30°C) and the glassy residue was dissolved without any heating in 1000 ml of the ethanol. The resulting solution was concentrated under diminished pressure (bath temperature 30°C) to a small volume (30 ml). A solid was deposited in the course of the evaporation. The mixture was allowed to stand for three days at room temperature and for one day at $+3^{\circ}\text{C}$. The crystalline product was collected and washed with a small amount of ethanol. Yield 2.41 g

(71%) of a chromatographically homogeneous product; the detection was performed by viewing in ultraviolet light and according to Reindel and Hoppe¹⁹ (treatment of the paper with chlorine was prolonged for 30 minutes); the R_F value 0.11 (the solvent system S_1) and 0.08 (the solvent system S_2). The substance melted at 175–180°C (softening from 165°C). The analysis showed that glucosyl-5-azauracil *V* was solvated with ethanol and water. For $C_9H_{13}N_3O_7 \cdot C_2H_6O \cdot H_2O$ (339.3) calculated: 38.94% C, 6.24% H, 12.39% N; found: 39.05% C, 6.20% H, 12.65% N. — When dried over P_2O_5 for 1 hour at 130°C/0.05 mm Hg, the substance loses the water. For $C_9H_{13}N_3O_7 \cdot C_2H_6O$ (321.3) calculated: 41.12% C, 5.96% H, 13.08% N; found: 41.30% C, 5.94% H, 13.28% N. Ethanol was removed by drying over phosphorus pentoxide at 130°C/0.05 mm Hg for ten hours. For $C_9H_{13}N_3O_7$ (275.2) calculated: 39.27% C, 4.76% H, 15.27% N; found: 38.94% C, 5.01% H, 15.03% N. The substance is sparingly soluble in ethanol and readily soluble in water. The recrystallisation was performed by dissolving the substance in a minimum amount of water without any heating, addition of a tenfold volume of ethanol, inoculation and standing at +3°C overnight. The substance separated in the form of colorless fine needles solvated with ethanol and water; m.p. 183–185°C. The ultraviolet spectrum is shown in Table I.

The preparation of glucosyl-5-azauracil *V* from the methoxytriazine *IV* was accomplished also by the action of moist Dowex 50 W (H^+) ion exchange resin for 4 hours (without the previous removal of the protecting acetyl groups with sodium methoxide) or by treatment with an 1% solution of dry hydrogen chloride in absolute methanol for 4 hours (the hydrogen chloride was removed with silver carbonate). In both these procedures, the yield was lower than in the preparation described in the preceding paragraph. The action of methanolic hydrogen chloride was accompanied by the formation of 5-azauracil (R_F value 0.31) as shown by paper chromatography in the solvent system S_1 .

Hydrolysis. Glucosyl-5-azauracil *V* (275 mg; 1 millimole) was heated in a steam bath with 1 ml of 6N-HCl for five minutes. The mixture was evaporated under diminished pressure, the residue was treated with ethanol (10 ml) and evaporated again. The residue was refluxed shortly with ethanol (2 ml) and the solution allowed to stand at +3°C overnight. The crystalline solvate of 5-azauracil with ethanol was collected and washed with ethanol. Drying over phosphorus pentoxide at 130°C/0.05 mm Hg for ten hours afforded 92 mg (81%) of 5-azauracil, m.p. 284–285°C (decomposition; sealed capillary) undepressed on admixture with an authentic specimen. The identification was further performed by comparison of the ultraviolet spectra (λ_{max} 237 m μ , $\log \epsilon$ 3.5) and by paper chromatography. In the mother liquors, glucose was detected by means of paper chromatography. The cleavage with hydrochloric acid was found to proceed even at room temperature, though very slowly.

1- β -D-Glucopyranosyl-5-azacytosine (*VI*)

The methoxytriazine *IV* (4.57 g; 0.01 mole) was kept at room temperature for 90 minutes in a sealed tube with 50 ml of absolute methanol previously saturated at 0°C with dry ammonia gas. The mixture was shaken occasionally. In the course of 40 minutes, a clear solution was obtained. The solution was concentrated under diminished pressure (bath temperature 25°C) to a small volume (the amorphous product partly separated). The residue was triturated with absolute ether (300 ml) and the resulting powder was repeatedly decanted with additional crops of absolute ether (three 100-ml portions). The amorphous product was then collected, washed with ether and triturated with 80 ml abs. methanol. The substance gradually dissolved and separated again in the form of crystals. The mixture was allowed to stand at room temperature overnight and then filtered off. The product was washed with methanol and dried under diminished pressure. Yield 1.65 g (60%) of glucosyl-5-azacytosine *VI*, m.p. 258–260°C (decomposition). The ultraviolet spectrum is shown in Table I. The substance was chromatographically homogeneous and was detected in ultraviolet light or according to Reindel and Hoppe¹⁹; the R_F values 0.07 (the

solvent system S_1) and 0.05 (the solvent system S_2). The recrystallisation was performed by dissolving in a minimum amount of water (without heating), addition of a tenfold volume of methanol, inoculation and standing at $+3^\circ\text{C}$ overnight. The recrystallised substance melted at 260 to 262°C (decomposition). For $\text{C}_9\text{H}_{14}\text{N}_4\text{O}_6$ (274.2) calculated: 39.42% C, 5.15% H, 20.43% N; found: 39.33% C, 5.19% H, 20.15% N.

Hydrolysis. Glucosyl-5-azacytosine *VI* (274 mg; 1 millimole) was heated in a steam bath with 1 ml of 6N-HCl for five minutes. The mixture was allowed to cool, diluted with acetone (2 ml) and kept at room temperature overnight. The crystalline material was collected, washed with acetone and dried under diminished pressure to give 104 mg (70%) of 5-azacytosine hydrochloride. The identification was performed by comparison of the ultraviolet spectra (in 4N-HCl, λ_{max} 250 m μ , $\log \epsilon$ 2.95) and by paper chromatography. The cleavage proceeds readily even at room temperature. Glucose was detected in the mother liquors.

1- β -D-Glucopyranosyl-3-guanylurea (*VII*)

The methoxytriazine *IV* (0.457 g; 1 mmole) was kept at room temperature with 5 ml of methanolic ammonia for 48 hours (*cf.* the preceding preparation). The solution was evaporated under diminished pressure (bath temperature 30°C), the residue was dissolved in methanol (50 ml) and the resulting solution evaporated again. The residue was triturated with methanol (4 ml) and allowed to stand overnight. The obtained crystals were collected, washed with methanol and dried under diminished pressure to give 0.12 g (41%) of the solvate of glucosylguanylurea *VII* with methanol as indicated by analysis; m.p. $201-203^\circ\text{C}$ (decomposition). For $\text{C}_8\text{H}_{16}\text{N}_4\text{O}_6 \cdot \text{CH}_4\text{O}$ (296.2) calculated: 36.49% C, 6.81% H, 18.92% N; found: 36.33% C, 6.60% H, 18.94% N. The recrystallisation was performed by dissolving the substance in a minimum amount of water and treating the solution with a tenfold volume of hot ethanol. The resulting crystals melted at $207-209^\circ\text{C}$ (decomposition) and represented the hydrate of glucosylguanylurea *VII*. For $\text{C}_8\text{H}_{16}\text{N}_4\text{O}_6 \cdot \text{H}_2\text{O}$ (282.2) calculated: 34.03% C, 6.42% H, 19.85% N; found: 34.04% C, 6.13% H, 20.00% N. The solvated water was removed on heating over phosphorus pentoxide at $100^\circ\text{C}/0.05$ mm Hg for 8 hours. For $\text{C}_8\text{H}_{16}\text{N}_4\text{O}_6$ (264.2) calculated: 36.36% C, 6.11% H, 21.20% N; found: 36.48% C, 6.35% H, 20.90% N. The substance exhibited no absorption in the near ultraviolet region. The paper chromatograms were detected according to Reindel and Hoppe¹⁹. The R_F values: 0.14 (the solvent system S_1) and 0.11 (the solvent system S_2). Some glucosyl-5-azacytosine *VI* was detected in the mother liquors by means of paper chromatography.

2,3,4-Tri-O-acetyl- β -D-ribofuranosyl isocyanate (*IX*)

Dry hydrogen chloride was introduced with cooling and under exclusion of atmospheric moisture into a suspension of finely ground 1,2,3,4-tetra-O-acetyl- β -D-ribofuranose (6.36 g; 0.02 mole) in absolute ether (100 ml) and acetyl chloride (1 ml) for two hours. The stoppered flask was allowed to stand at $+3^\circ\text{C}$ for five days. The solution was evaporated under diminished pressure (bath temperature 20°C) to the consistence of a thick sirup. The residual hydrogen chloride and acetic acid were removed by repeated codistillations (*in vacuo*) with five 40-ml portions of dry toluene (bath temperature 30°C). The colorless sirup was diluted with absolute ether (10 ml) to deposit immediately the crystalline 1-chloro-2,3,4-tri-O-acetyl- β -D-ribofuranosyl chloride (*VIII*). The mixture was allowed to stand at -15°C overnight, filtered off, the product washed with a small amount of absolute ether and dried in a desiccator over potassium hydroxide. Yield 4.9 g (83%); m.p. $93-95^\circ\text{C}$ (the literature records²³ m.p. 95°C).

The above halogenose *VIII* (2.95 g; 0.01 mole) was heated with the thoroughly dried silver cyanate²¹ (4.5 g; 0.03 mole) in 20 ml of dry xylene under similar conditions as in the case of glucosyl isocyanate *II*. When the reaction was finished, the silver salts were removed by filtration and washed with two 10-ml portions of hot xylene. The combined filtrates were cooled and

precipitated with dry light petroleum (80 ml). The mixture was allowed to stand in a stoppered vessel at $+3^{\circ}\text{C}$ overnight. The clear colorless supernatant was decanted (the residual glassy precipitate was discarded) and evaporated under diminished pressure (bath temperature 45°C) to the consistence of a thick colorless sirup which was dried at 0.3 mm Hg for ten hours. Yield 2.4 g (80%) of the glassy isocyanate *IX*. The analytical sample was dissolved in ether, reprecipitated with a fivefold volume of light petroleum and dried under diminished pressure. The infrared spectrum (chloroform): $\nu(\text{N}=\text{C}=\text{O})$, 2252 cm^{-1} . For $\text{C}_{12}\text{H}_{15}\text{NO}_8$ (301.8) calculated: 47.87% C, 5.02% H, 4.65% N; found: 48.30% C, 5.10% H, 4.75% N.

1-(2,3,4-Tri-O-acetyl- β -D-ribosepyranosyl)-4-methylisobiuret (*X*)

A solution of the crude ribopyranosyl isocyanate *IX* (3.01 g; 0.01 mole) in chloroform (50 ml) was gradually treated at -15°C with a solution of the freshly prepared 2-methylisourea (0.67 g; 9 mmole) in chloroform (10 ml). The solution was allowed to stand at room temperature for one hour and evaporated under diminished pressure (bath temperature 30°C). On addition of hot benzene (10 ml) to the residue the crystallisation occurred. The mixture was allowed to stand at room temperature overnight, the crystals were collected and washed with a small amount of benzene. Yield 3.1 g (92%, based on 2-methylisourea) of the isobiuret derivative *X*, m.p. $191-195^{\circ}\text{C}$. Recrystallisation of a concentrated solution from ethanol raised the m.p. to $194-196^{\circ}\text{C}$. The ultraviolet spectrum is shown in Table I. The R_F value in the solvent system S_1 , 0.81 (detected according to Reindel and Hoppe¹⁹). For $\text{C}_{14}\text{H}_{21}\text{N}_3\text{O}_9$ (375.3) calculated: 44.80% C, 5.64% H, 11.20% N; found: 44.88% C, 5.59% H, 10.94% N.

1-(2,3,4-Tri-O-acetyl- β -D-ribosepyranosyl)-4-methoxy-2-oxo-1,2-dihydro-1,3,5-triazine (*XI*)

The isobiuret derivative *X* (3.75 g; 0.01 mole) was dissolved in hot ethyl orthoformate (30 ml) and the solution worked up similarly as in the case of the substance *IV*. After 8 hours, the colorless solution was cooled, precipitated with light petroleum (80 ml) and the semisolid precipitate treated with hot benzene (20 ml). The crystalline slurry was allowed to stand at room temperature overnight. The next day, the product was collected and washed with a small amount of benzene. Yield 2.14 g (55%) of the ribosyltriazine *XI*, m.p. $194-198^{\circ}\text{C}$. Recrystallisation from absolute ethanol raised the m.p. to $195-198^{\circ}\text{C}$. The ultraviolet spectrum is shown in Table I. For $\text{C}_{15}\text{H}_{19}\text{N}_3\text{O}_9$ (385.3) calculated: 46.75% C, 4.97% H, 10.91% N; found: 47.00% C, 4.86% H, 10.77% N.

1- β -D-Ribopyranosyl-5-azauracil (*XII*)

The methoxytriazine *XI* (3.85 g; 0.01 mole) in absolute methanol (300 ml) was deacetylated and demethylated similarly as in the case of glucosyl-5-azauracil *V*. The ion exchange resin was removed by filtration and the filtrate was evaporated under diminished pressure (bath temperature 30°C). The residue was dissolved (without heating) in ethanol (600 ml) and the solution concentrated under diminished pressure to a small volume (bath temperature 30°C). A small amount of an amorphous precipitate separated. The residue was triturated with ether (300 ml), the powder repeatedly decanted with three 100-ml portions of ether, collected, washed with ether and dried under diminished pressure. Yield 1.60 g (55%) of a white powder, m.p. $145-150^{\circ}\text{C}$, analyzing as solvate of ribopyranosyl-5-azauracil with ethanol. For $\text{C}_8\text{H}_{11}\text{N}_3\text{O}_6 \cdot \text{C}_2\text{H}_6\text{O}$ (291.3) calculated 41.23% C, 5.88% H, 14.43% N; found: 41.26% C, 6.05% H, 14.15% N. Removal of the ethanol was accomplished by heating the substance at $130^{\circ}\text{C}/0.05\text{ mm Hg}$ for ten hours. For $\text{C}_8\text{H}_{11}\text{N}_3\text{O}_5$ (245.2) calculated: 39.19% C, 4.52% H, 17.14% N; found: 38.95% C, 4.65% H, 16.90% N. The product was chromatographically homogeneous and was detected by viewing in ultraviolet light, according to Reindel and Hoppe¹⁹ (the treatment with chlorine was prolonged for 30 minutes),

and, finally, with potassium periodate²⁰; the R_F values, 0.18 (the solvent system S_1) and 0.12 (the solvent system S_2). The ultraviolet spectrum see in Table I.

Hydrolysis. Ribopyranosyl-5-azauracil *XII* (245 mg; 1 mmole) was hydrolysed with 6N-HCl in the same manner as glucosyl-5-azauracil *V*. Yield 85 mg (75%) of 5-azauracil. By means of paper chromatography, ribose was detected in the mother liquors. The cleavage with hydrochloric acid takes place also at room temperature, but very slowly.

1- β -D-Ribopyranosyl-5-azacytosine (*XIII*)

The methoxytriazine *XI* (3.85 g; 0.01 mole) was kept at room temperature in a sealed vessel for 90 minutes with 50 ml of absolute methanol previously saturated (at 0°C) with dry ammonia. The resulting solution was evaporated under diminished pressure (bath temperature 25°C) and the residue was triturated with absolute ether (200 ml). The amorphous powder was repeatedly decanted with absolute ether (three 100-ml portions) and dissolved in absolute methanol (50 ml). The solution which was allowed to stand at room temperature overnight, deposited crystalline ribopyranosyl-5-azacytosine *XIII*. The crystals were collected, washed with a small amount of methanol and dried under diminished pressure to give 1.44 g (59%) of the product, m.p. 248 to 250°C (decomposition). The ultraviolet spectrum is shown in Table I. The substance was chromatographically homogeneous and was detected by viewing in ultraviolet light, by the method of Reindel and Hoppe¹⁹ and with potassium periodate²⁰; the R_F values, 0.10 (the solvent system S_1) and 0.07 (the solvent system S_2). The recrystallisation was performed by dissolving the substance in a minimum amount of water (without heating), addition of a tenfold volume of methanol, inoculation and standing at +3°C overnight. The recrystallised product melted at 250–252°C (decomposition). For $C_8H_{12}N_4O_5$ (244.2) calculated: 39.34% C, 4.95% H, 22.94% N; found: 39.08% C, 5.09% H, 22.84% N.

Hydrolysis. Ribopyranosyl-5-azacytosine *XIII* (244 mg; 1 mmole) was hydrolysed with 6N-HCl in analogy with the hydrolysis of the glucosyl derivative *VI*. Yield 97 mg (65%) of 5-azacytosine hydrochloride. By paper chromatography, ribose was detected in the mother liquors. The cleavage proceeds readily even at room temperature.

2,3,5-Tri-O-acetyl- β -D-ribofuranosyl Isocyanate (*XV*)

Dry hydrogen chloride was introduced with cooling for 4 hours into a suspension of finely ground 1,2,3,5-tetra-O-acetyl- β -D-ribofuranose²⁴ (31.8 g; 0.1 mole), absolute ether (500 ml) and acetic anhydride (2 ml). The mixture was allowed to stand in a stoppered vessel at +3°C for five days. The resulting solution was evaporated under diminished pressure at 20°C (bath temperature) and the residual sirup was repeatedly coevaporated (bath temperature 30°C) with five 100-ml portions of dry toluene. Finally, the yellowish sirup was dissolved in dry xylene (300 ml) and the resulting solution was treated with silver cyanate²¹ (45.0 g; 0.3 mole) similarly as in the case of the glucosyl isocyanate *II*. The silver salts were removed by filtration and washed with two 50-ml portions of dry xylene. The combined filtrates were cooled and treated with dry light petroleum (1000 ml); a small amount of a glassy precipitate separated. The mixture was allowed to stand at +3°C in a stoppered flask overnight. The clear supernatant was decanted and evaporated under diminished pressure (bath temperature 45°C). The yellowish sirup was dried at room temperature and 0.3 mm Hg for ten hours to give 19.2 g of the product contaminated with a small amount of 1,2,3,5-tetra-O-acetyl- β -D-ribofuranose (see the preparation of the isobiuret derivative *XVI*). Infrared spectrum (chloroform): $\nu(N=C=O)$, 2252 cm^{-1} .

1-(2,3,5-Tri-O-acetyl- β -D-ribofuranosyl)-4-methylisobiuret (*XVI*)

A stirred solution of the crude ribofuranosyl isocyanate *XV* (15.0 g) in chloroform (200 ml) was treated at –15°C under exclusion of atmospheric moisture with a thin stream of the freshly

prepared 2-methylisourea (2.95 g; 0.04 mole) in chloroform (50 ml). The solution was allowed to stand at room temperature for one hour and evaporated under diminished pressure (bath temperature 30°C). The residue was dissolved in dry benzene (50 ml) and reprecipitated with dry light petroleum (200 ml). After decantation, the yellowish sirup was dissolved in additional 50 ml of benzene and reprecipitated with light petroleum (200 ml). The residual solvents were removed under diminished pressure at room temperature (8 hours). The resulting faintly yellowish foam (14.3 g, *i.e.* 95% based on 2-methylisourea) was dissolved in 30 ml of hot dry benzene and the solution was allowed to stand at room temperature for six days. The crystalline product (10.2 g; 68%) was collected and washed with a small amount of benzene; m.p. 70–76°C. The recrystallisation from absolute ethanol raised the m.p. to 72–78°C. Further crystallisation did not change this m.p. The ultraviolet spectrum is shown in Table I. The R_F value in the solvent system S_1 , 0.79 (detected according to Reindel and Hoppe¹⁹). For $C_{14}H_{21}N_3O_9$ (375.3) calculated: 44.80% C, 5.64% H, 11.20% N; found: 44.59% C, 5.67% H, 11.21% N. For the next synthetic step, the crude reprecipitated product may be used (without any crystallisation).

The supernatants after precipitation of the crude isobiuret derivative *XVI* were combined and concentrated to a volume of 10 ml. On standing at room temperatures for four days in a open vessel, the sirup deposited developed crystals of 1,2,3,5-tetra-O-acetyl- β -D-ribofuranose (1.2 g) melting at 81–82°C without depression on admixture with an authentic specimen.

1-(2,3,5-Tri-O-acetyl- β -D-ribofuranosyl)-4-methoxy-2-oxo-1,2-dihydro-1,3,5-triazine (*XVIII*)

A solution of the isobiuret derivative *XVI* (15.0 g; 0.04 mole) in ethyl orthoformate (100 ml) was heated under same conditions as in the case of the glucosyl derivative *IV*. After 8 hours, the colorless solution (when crude isobiuret was used, the solution was faintly yellow) was cooled and precipitated with 500 ml of dry light petroleum. The glassy precipitate was dissolved in hot absolute benzene (50 ml) and the solution was precipitated with light petroleum (200 ml). The precipitation was repeated once more and the product was dried *in vacuo*. Yield 9.7 g (63%) of a solid foam. The ultraviolet spectrum is shown in Table I. The analytical sample was dissolved in ethyl acetate and precipitated with light petroleum. For $C_{15}H_{19}N_3O_9$ (385.3) calculated: 46.75% C, 4.97% H, 10.91% N; found: 47.10% C, 4.99% H, 10.50% N.

5',6-Anhydro-6-hydroxy-5,6-dihydro-5-azauridine (*XX*)

The methoxytriazine *XVII* (3.85 g; 0.01 mole) was deacetylated and demethylated in 300 ml of absolute methanol by the procedure described for the case of glucosyl-5-azauracil *V*. The treatment with the ion exchange resin was prolonged for 3 hours. The resin was removed by filtration, washed with methanol and the combined filtrates were evaporated under diminished pressure (bath temperature 25°C). The residual sirup was dissolved in acetone (50 ml). The resulting solution began to deposit the crystalline product almost immediately. After standing at +3°C overnight, the crystals were collected and washed with acetone and methanol. Yield 0.7 g (28%), m.p. 206–208°C (decomposition). The substance is insoluble in organic solvents and sparingly soluble in cold water. When heated with water, the substance is destroyed. The recrystallisation may be performed with a great loss from dilute acetic acid. The recrystallised substance melted at 210–211°C (decomposition). In the oxidation with potassium periodate¹⁷, the substance consumed 1.5 mole of periodic acid in the course of 24 hours. The infrared spectrum (dimethyl sulfoxide): a broad band at 1535 cm^{-1} (the triazine ring); $\nu(\text{CO})$, 1670 cm^{-1} , 1715 cm^{-1} . Paper electrophoresis (a borate buffer, pH 7.0, 30 min, 200 V/cm, Whatman paper No 1): 1.2 cm. In paper chromatography, the substance (a 5% solution of the substance in 50% acetic acid was applied) remained homogeneous; the R_F values, 0.26 (the solvent system S_1) and 0.23 (the solvent system S_2). Detections were performed with potassium periodate and benzidine²⁰, according to Reindel and Hoppe¹⁹ (the action of chlorine was prolonged for 30 minutes) and, finally by viewing

in ultraviolet light (the spots absorbed only weakly). For $C_8H_{11}N_3O_6$ (245.2) calculated: 39.19% C, 4.52% H, 17.14% N; found: 39.12% C, 4.50% H, 17.08% N.

Hydrolysis. The ribosyl derivative *XX* (123 mg; 0.5 mmole) was hydrolysed with 6*N*-HCl by the same procedure as in the case of glucosyl-5-azauracil *V*. Yield 40 mg (71%) of 5-azauracil. By paper chromatography, ribose was detected in the mother liquors. The cleavage proceeds readily even at room temperature.

1-β-D-Ribofuranosylbiuret (*XIX*)

A solution of the ribosyl derivative *XX* (245 mg; 1 mmole) in 2% ammonia in 50% aqueous methanol (30 ml) was allowed to stand at room temperature overnight. The solvents were evaporated under diminished pressure (bath temperature 30°C) and the residual sirup was dissolved in a minimum amount of 96% ethanol. The solution was allowed to stand at -15°C for three days. The crystals were collected, washed with ethanol and dried. Yield 96 mg (41%), m.p. 176–179°C. The product was chromatographically homogeneous; detection was performed with potassium periodate and benzidine²⁰ and according to Reindel and Hoppe¹⁹; the R_F values, 0.22 (the solvent system S_1) and 0.19 (the solvent system S_2). The recrystallised sample melted at 180–181°C (water). For $C_7H_{13}N_3O_6$ (235.2) calculated: 35.74% C, 5.57% H, 17.88% N; found: 35.58% C, 5.71% H, 17.63% N.

5-Azacytidine (*XXII*)

The methoxytriazine *XVII* (3.85 g; 0.01 mole) was kept at room temperature in a sealed vessel for 90 minutes with 30 ml of absolute methanol previously saturated (at 0°C) with dry ammonia. The substance dissolved almost immediately and, in the course of 25 minutes, the crystalline 5-azacytidine began to separate. The mixture was allowed to stand at -15°C overnight. The next day, the crystals were collected, washed with methanol, triturated with methanol, collected again, washed and dried over sulfuric acid and potassium hydroxide in a vacuum desiccator. Yield 1.4 g, m.p. 228–230°C (decomposition). A further crop (0.15 g) of the product was obtained on evaporation of the mother liquors under diminished pressure and crystallisation of the residue from 2 ml of absolute methanol. Total yield, 1.55 g (64%). The ultraviolet spectrum is shown in Table I. The infrared spectrum may be seen on Fig. 1. The substance was chromatographically homogeneous. Detection was performed by viewing in ultraviolet light or according to Reindel and Hoppe¹⁹ or with potassium periodate-benzidine²⁰. The R_F values, 0.14 (the solvent system S_1) and 0.11 (the solvent system S_2). For $C_8H_{12}N_4O_5$ (244.2) calculated: 39.34% C, 4.95% H, 22.94% N; found: 39.45% C, 5.02% H, 23.11% N. The substance was recrystallised by dissolving in water on a steam bath (5 ml of water per 1 g), addition of hot methanol (30 ml of methanol per 1 g) and standing at +3°C overnight; m.p. 230–231°C (decomposition).

Hydrolysis. 5-Azacytidine (112 mg; 0.5 mmole) was hydrolysed with 6*N*-HCl by the procedure as in the case of glucosyl-5-azacytosine *VI*. The time of heating was prolonged for 15 minutes (after 5 minutes, some starting compound was detected in the mixture in addition to 5-azacytosine, as shown by paper chromatography). In the mother liquors, ribose was detected by means of paper chromatography.

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Резюме

А. Писка́ла и В. Шо́рм: *Составляющие нуклеиновых кислот и их аналоги. LI. Синтез 1-гликозильных производных 5-азаурацила и 5-азацитозина*. Описан метод получения 1-гликозильных производных 5-азаурацила и 5-азацитозина, исходящий из перацетилгликозил-изоцианатов. Присоединением 2-метилизомочевины полученные 1-перацетилгликозил-4-метилизобиуреты конденсируются с ортомуравьиноэтиловым эфиром с образованием 1-перацетилгликозил-4-метокси-2-оксо-1,2-дигидро-1,3,5-триазинов, которые затем дезацетилированием и деметилированием превращаются в 1-гликозил-5-азаурацилы или дезацетилированием и аминированием в 1-гликозил-5-азацитозины. Таким образом были получены глюкопиранозильное, рибопиранозильное и рибофуранозильное производные 5-азаурацила и глюкопиранозильное, рибопиранозильное и рибофуранозильное производные 5-азацитозина