ratio of near unity would be expected if some SN2 attack by methanol on the bicyclic cation (7) to produce α-pyranoside (14) offsets a slight decrease in rate of formation of this isomer because of blocking of attack upon one side of the monocyclic carboxonium ion (13) by the C_2 hydroxyl group.

Registry No.—D-Galactose, 59-23-4; methyl α-D-galactofuranoside, 3795-67-3; methyl β-D-galactofuranoside, 1824-93-7; methyl α-D-galactopyranoside, 3396-99-4; methyl β-D-galactopyranoside, 1824-94-8; D-glucose, 50-99-7; methyl-α-D-glucofuranoside, 1824-88-0; methyl β-D-glucofuranoside, 1824-89-1; methyl α-D-glucopyranoside, 97-30-3; methyl β-D-glucopyranoside, 709-50-2.

The Synthesis of 4-β-D-Ribofuranosyl-*as*-triazin-3(4*H*)-one 1-Oxide, a Potential Uridine Antagonist[1]

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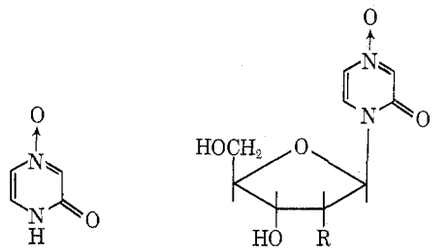
4-β-D-Ribofuranosyl-*as*-triazin-3(4*H*)-one 1-oxide (**8**), a structural analog of uridine, has been prepared by the reaction of 3-methoxy-*as*-triazine 1-oxide (**3**) with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**5**) followed by debenzoylation with $NaOCH_3$. Both proton and carbon-13 nmr were used to assign the site of nitrogen ribosylation, the first such reported application to a six-membered heterocyclic system. An unusual deoxygenation of the *N*-oxide function of 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*as*-triazin-3(4*H*)-one 1-oxide (**6**) with ethanolic ammonia resulted in the formation of 4-β-D-ribofuranosyl-*as*-triazin-3(4*H*)-one (**10**). Reduction of the *as*-triazine ring of **6** was found to occur to yield 2,5-dihydro-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*as*-triazin-3(4*H*)-one (**11**). Small coupling constants for the anomeric protons of **6** and **8** were found to change to larger values on reduction of the aglycon portion of the molecule. pK_a measurements on *as*-triazin-3(4*H*)-one 1-oxide (**7**) and on the reduced product 2,5-dihydro-*as*-triazin-3(4*H*)-one (**15**) point out the unusual character of the *as*-triazin-3(4*H*)-one 1-oxide ring system.

Emimycin, an antibiotic isolated[2] from Streptomyces No. 2020-I, has been shown to be 2(1*H*)-pyrazinone 4-oxide (**1**).[3] The antibacterial activity of **1** is reversed by uracil, uridine, and 2′-deoxyuridine.[4] The syntheses of 1-β-D-ribofuranosylemimycin (**2**) and 1-β-D-2′-deoxyribofuranosylemimycin (**2a**) have recently been



1

2, R = OH
2a, R = H

reported.[5,6] The increased potency of **2a** over that of emimycin as a bacteriocidal agent illustrates the desirability of studying related nucleoside derivatives.

The present work describes the syntheses of *as*-triazin-3(4*H*)-one 1-oxide (**7**) (3-azaemimycin) and of the corresponding uridine analog 4-β-D-ribofuranosyl-*as*-triazin-3(4*H*)-one 1-oxide (**8**) (Scheme I). The synthesis of 3-methoxy-*as*-triazine 1-oxide (**3**) by oxidation of 3-methoxy-*as*-triazine (**4**) with perbenzoic acid has been reported in 15% yield.[7] Utilizing *m*-chloroperbenzoic acid[8] in refluxing benzene, the yield of **3** was increased to 30%. Treatment of **3** with 2,3,5-tri-*O*-benzoyl-D-ribofuranosyl bromide (**5**) in acetonitrile yielded a single nucleoside product, 4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*as*-triazin-3(4*H*)-one 1-oxide (**6**) plus small amounts of another product which was identified as *as*-triazin-3(4*H*)-one 1-oxide (**7**) on the basis of pmr, mass spectra, and elemental analysis. The formation of **7** can be explained by the hydrolysis of 3-methoxy-*as*-triazine 1-oxide (**3**) by residual HBr and/or acetic acid, which are difficult to remove completely in the preparation of halogenose **5**. Addition of dilute methanolic HCl to an acetonitrile solution of **3** resulted in the formation of **7**.

Treatment of **6** with sodium methoxide removed the benzoyl blocking groups to give the desired uridine analog 4-β-D-ribofuranosyl-*as*-triazin-3(4*H*)-one 1-oxide (**8**). The assignment of the β-glycosidic configuration of **6** and **8** was based on the very small coupling constant of the anomeric proton observed in the pmr spectrum of **8** (*vide infra*).

Reductive removal of the *N*-oxide function was accomplished by hydrogenation of **8** in the presence of a 5% palladium-on-charcoal catalyst, but simultaneous reduction of the triazine ring was also observed. Unexpectedly, the formation of the nucleoside 4-β-D-ribofuranosyl-*as*-triazin-3(4*H*)-one (**10**) was found to occur upon treatment of the blocked nucleoside **6** with alcoholic ammonia. This deoxygenation of the *N*-oxide function of **6** with ethanolic ammonia at room temperature was indeed surprising, since only one analogous reaction could be found in the literature,[9] and in this example more vigorous conditions, heating in liquid NH_3 at 150°, resulted in the formation of 4,4′-dichloro-3,3′-dipicolyl from the corresponding di-*N*-oxide. Nevertheless, because both **6** and **8** were found to be completely stable even in refluxing EtOH, it

(1) This work was presented in part before the Division of Medicinal Chemistry at the 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 1972.

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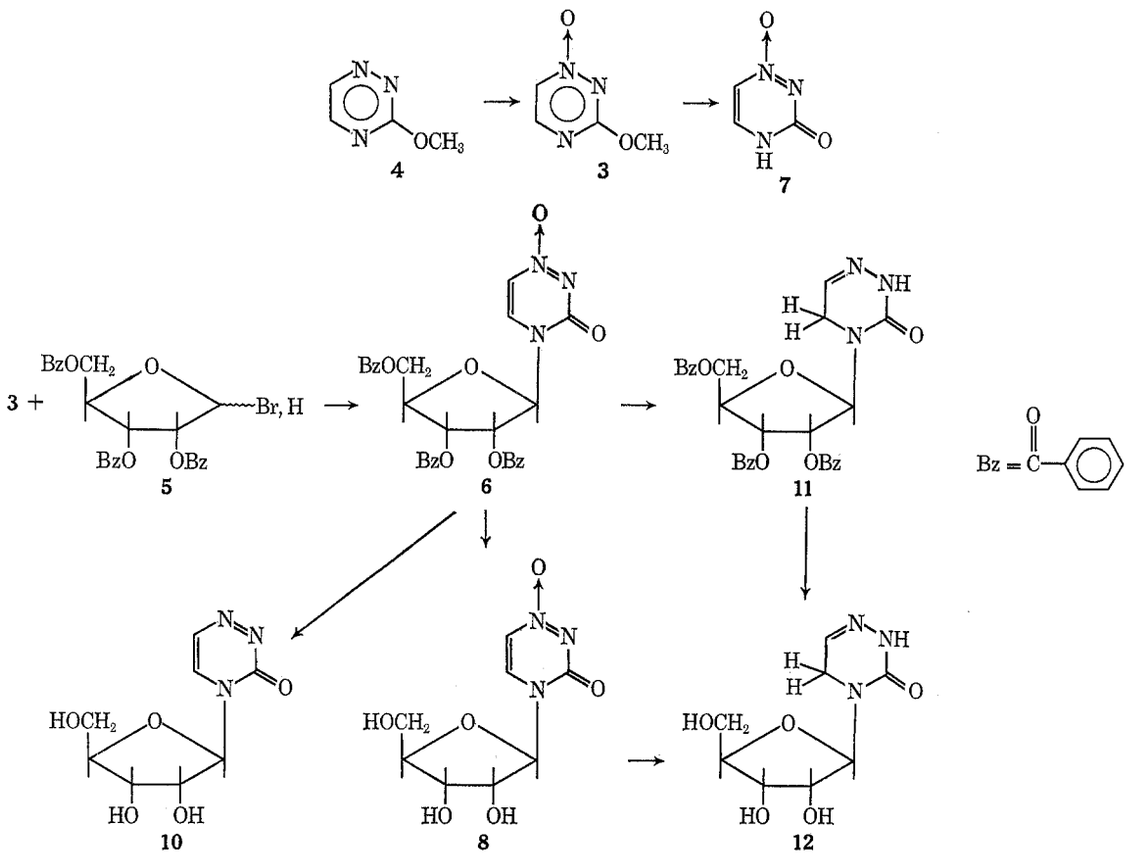
SCHEME I



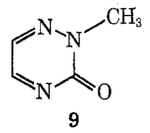
was established without doubt that this unusual deoxygenation was due to the effect of NH_3 rather than to the solvent EtOH applied in the above reaction.

TABLE I

UV SPECTRA OF 9 AND 10

	9	10
EtOH	λ_{max} 243 (ϵ 2608)	λ_{max} 225–226 (ϵ 6981)
	λ_{max} 309 (ϵ 655)	λ_{sh} 255 (ϵ 4936)
		λ_{sh} 346 (ϵ 2400)
pH 1	λ_{max} 243 (ϵ 3304)	λ_{max} 226–227 (ϵ 6487)
	λ_{max} 310 (ϵ 604)	λ_{sh} 225 (ϵ 4795)
		λ_{sh} 346 (ϵ 2120)
pH 11	λ_{max} 243 (ϵ 3022)	λ_{max} 234 (ϵ 6008)
	λ_{max} 310 (ϵ 353)	λ_{max} 347 (ϵ 2891)

The uv spectra of **10** (Table I) at various pH values were found to be substantially different from the uv spectra recorded for 2-methyl-*as*-triazin-3(2*H*)-one (**9**).[10] This eliminated position 2 as a site of glycosylation.



9

The first use of both proton and carbon-13 nmr to establish the glycosylation site has been reported by our laboratories in the case of 1-β-D-ribofuranosyl-1,2,4-triazoles.[11] The assignment was based on the use of the previously reported α and β substitution shifts observed in other heterocyclic systems when the neutral species is compared with the anionic form.[12–14] The use of both proton and carbon-13 nmr to confirm the site of ribosylation of the nucleosides **6** and **8** is the first reported instance of such a study for a six-membered heterocyclic ring system.

The nmr data are summarized in Table II. The proton assignments in the *as*-triazine 1-oxides were made assuming the same relative ordering of the H_5 and H_6 protons reported by Paudler and Chen[7] for 3-methoxy-*as*-triazine 1-oxide (**3**). The H_6 resonance was observed to occur at 1.54 ppm upfield from the H_5 resonance. Upon introduction of the ribose group the

TABLE II

^1H AND ^{13}C CHEMICAL SHIFTS OF *as*-TRIAZINE 1-OXIDES

	Pmr[a]		Cmr[b]			
Compd	H_5	H_6	C_3	C_5	C_6	CH_3
4	9.24	8.78	165.6	152.0	145.6	55.4
3	9.37	7.83	167.3	156.4	125.6	55.7
7	8.22	7.70	151.8	142.4	120.9	
8	8.78	7.80	153.4	138.6	120.9	
Anion of **7**	8.18	7.52	164.9	152.2	118.9	

[a] Pmr spectra of 10% Me_2SO solutions were obtained on a 60-MHz Hitachi Perkin-Elmer R20A nmr spectrometer with a probe temperature of 34°. Chemical shifts are reported in parts per million downfield from internal DSS. [b] Cmr spectra of 40% Me_2SO solutions were obtained on a Bruker HX-90 nmr spectrometer operating at 22.62 MHz in the Fourier Transform Mode at a probe temperature of 35°. Chemical shifts are reported in parts per million downfield from internal TMS.

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H_6 resonance shifts downfield by 0.1 ppm, whereas the H_5 resonance exhibits a greater downfield shift of 0.56 ppm compared with **7**. This implies that the ribose is attached to the N-4, since otherwise the ribose group would exert a greater effect on H_6. Similar ribosylation effects on shifts of α hydrogens have been reported.[11,15]

The carbon-13 chemical shifts of 3-methoxy-*as*-triazine 1-oxide (**3**) and *as*-triazin-3(4*H*)-one 1-oxide (**7**) are also presented in Table II along with the values of the anion of **7** and 3-methoxy-*as*-triazine (**4**). The carbon-13 methyl resonance and the carbonyl resonance are readily identified, since they appear at high field and at low field, respectively, compared to the remainder of the resonance positions. However, the C_5 and C_6 resonances cannot be readily distinguished. A comparison of the chemical shift changes of the corresponding carbon-13 resonances in 3-methoxy-*as*-triazine (**4**) and their counterparts in the *N*-oxide **3** revealed that the resonance at 145.6 ppm from TMS exhibits an upfield shift of 20 ppm when the *N*-oxide is introduced in the 1 position and was therefore assigned to the C_6 resonance. Similar upfield shifts were observed for carbons adjacent to N-1 in adenosine 1-oxide *vs.* adenosine.[16] The remaining resonance at 152.0 ppm must be due to the C_5 resonance. The carbon-13 spectra of compounds **7** and **8** are assigned accordingly with the C_6 resonance appearing upfield from the C_5 resonance. Ribosylation of compound **7** therefore results in an upfield shift of 3.8 ppm for the C_5 resonance while the chemical shifts of the C_6 resonance both before and after ribosylation are identical. The glycosylation site in compound **8** must be the N-4 position and not N-2 because of this large effect at C_5.

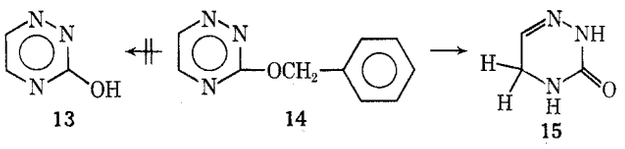
The assignment of this structure for compound **8** is confirmed by examining the α and β substitution shifts when compared with the *as*-triazin-3-one 1-oxide anion. This anion was formed by neutralization of compound **7** by LiOH in Me_2SO. Large upfield shifts of 13.6 and 11.5 ppm were observed for the adjacent C_5 resonance and the carbonyl resonance of the nucleoside **8** as compared to the triazine anion, while the C_6 resonance exhibited a downfield shift of 2.0 ppm. These shift changes are of the same order of magnitude and direction as α and β substitution shifts reported for other heteroaromatic systems,[13,14] that is, large upfield α values and small negative β shifts.

The ease of reduction of the triazine ring of the nucleosides **6** and **8** to yield 2,5-dihydro-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*as*-triazin-3(4*H*)-one (**11**) and the analogous deblocked nucleoside **12** is of interest, since the reduction of the structurally related 6-azauridine is much more difficult.[17,18] Attempts to prepare 3-hydroxy-*as*-triazine (**13**)[10] by hydrogenation of 3-benzyloxy-*as*-triazine (**14**) furnished only the reduced product 2,5-dihydro-*as*-triazin-3(4*H*)-one (**15**), the parent heterocycle of nucleosides **11** and **12** (Scheme II).

As noted previously, the anomeric proton in 4-β-D-ribofuranosyl-*as*-triazin-3(4*H*)-one 1-oxide (**8**) displayed an unusually small coupling constant in the pmr spectrum (broad singlet in DMSO, J = 2 Hz in D_2O). Reduction of the aglycon, however, produced a nucleoside **12** which displayed a more "normal" coupling constant ($J_{1',2'}$ = 5.5 Hz in D_2O) for the anomeric proton. It was thus apparent that the *as*-triazin-3-one 1-oxide ring was strongly affecting the anomeric proton. Such an effect on the $H_{1',2'}$ coupling constant could be due to an altered conformation of the pentofuranose ring and thus to an altered $H_{1',2'}$ dihedral angle, a phenomenon described as a "steric effect." Alternatively, the aglycon could influence the $H_{1',2'}$ coupling constant *via* an electronic effect without significantly changing the conformation of the pentofuranose ring of **8** as compared to **12**, or a combination of both effects could be operative. That the vicinal coupling constant on saturated carbons is dependent on the electronegativity of the substituents on those carbons, in addition to the dependency on the dihedral angle as described by the familiar Karplus relationship,[19] has been well documented.[20-22] While an unusual steric effect of the aglycon on the pentofuranose ring in compound **8** cannot be ruled out, it is certainly not indicated by inspection of molecular models. Furthermore, such a steric effect would be unlikely to operate in **8** but not in the reduced nucleoside **12**. On the other hand, pK_a measurements of the corresponding aglycons **7** and **15** clearly show the very large difference in the electronic character of the two ring systems. The acidic pK_a of **7** was found to be 4.60, an extremely low pK_a value in comparison with the pK_a values of most purine and pyrimidine bases, while the pK_a of the reduced ring, 2,5-dihydro-*as*-triazin-3(4*H*)-one (**15**), was found to be greater than 11. The possibility of a correlation between the acidity of the aglycon and the $H_{1',2'}$ coupling constant is supported by the recently published data of Nesnow, *et al.*[23] These authors reported a broadened singlet for the anomeric proton of 4-hydroxy-5-fluoro-1-β-D-ribofuranosyl-2-pyridone (5-fluoro-3-deazauridine) while the anomeric proton of 3-deazauridine[24] appears as a doublet, J = 2.5 Hz. In this example too, it is hard to envision a steric effect between the aglycon and the sugar, while the electronic character of the aglycons is quite different as reflected by the difference in the acidic pK_a of these two nucleosides. pK_a values of 6.5 and 4.5 are reported for 3-deazauridine[24] and 5-fluoro-3-deazauridine,[23] respectively.

The interesting antitumor properties of 4-β-D-ribofuranosyl-*as*-triazin-3(4*H*)-one 1-oxide (**8**) have been communicated separately elsewhere.[25]

SCHEME II



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Experimental Section

General.—Nmr spectra were recorded on a Hitachi Perkin-Elmer R-20A spectrometer in $CDCl_3$ (TMS), deuterated DMSO (DSS), or D_2O (DSS) with the appropriate internal standards. Uv spectra were determined on a Cary 15 ultraviolet spectrophotometer, and mass spectra were recorded on a Perkin-Elmer 270 mass spectrometer. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Melting points were determined on a Thomas-Hoover Unimelt capillary melting point apparatus, and are uncorrected. Evaporations were performed under reduced pressure on a rotary evaporator. Thin layer chromatography was performed on Analtech precoated (250 μ) silica gel GF plates, and the spots were visualized by irradiation with a Mineralight uv lamp. Column chromatography was carried out utilizing the method of Loev and Goodman[26] in plastic tubes (purchased from J. T. Baker) transparent to uv light. The tubes were packed with silica gel powder (Baker catalog #3405) containing 1% zinc silicate fluorescent indicator (Baker catalog #2101). The compounds were applied to the column preabsorbed on silica gel. This was accomplished by adding silica gel to a solution of the compounds followed by evaporation to dryness. The columns were then eluted with the appropriate solvent. The position of the bands on the column was visualized by irradiation with Mineralight uv lamp. These columns are referred to in the text as "dry columns." pK_a values were measured by alkalometric titration with 0.005 N NaOH performed on a Radiometer Autoburette ABU 12 coupled to Radiometer Titrator 11 and Radiometer Titrigraph. Elemental analyses were performed by Heterocyclic Chemical Corp., Harrisonville, Mo. 64701.

3-Methoxy-*as*-triazine 1-Oxide (3).—To a solution of **4** (7.5 g, 0.0675 mol) in C_6H_6 (520 ml) was added *m*-chloroperbenzoic acid (purchased from K & K Laboratories Inc., 37.0 g, 0.182 mol active ingredient) and the resulting mixture was refluxed for 24 hr. C_6H_6 was then evaporated, the residue was dissolved in $CHCl_3$, and the $CHCl_3$ solution was extracted three times with saturated Na_2CO_3 solution. After drying (Na_2SO_4) the mixture was applied to a dry column of silica gel and eluted with $CHCl_3$–EtOAc (9:1). The main uv-absorbing component was vacuum sublimed (65°, 0.2 mm) to give **3** (2.576 g, 30.0%). Resublimation raised the melting point to 70–72°, identical with that reported by Paudler and Chen.[7]

4-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-*as*-triazin-3(4*H*)-one 1-Oxide (6) and *as*-Triazin-3(4*H*)-one 1-Oxide (7).—To a solution of halogenose **5** [freshly prepared from 10.08 g (20 mmol) of 2,3,5-tri-*O*-benzoyl-1-*O*-acetyl-D-ribofuranose][27] in CH_3CN (100 ml) was added **3** (2.04 g, 16 mmol). The resulting clear solution was allowed to stand without stirring. After 1 week the mixture of crystals deposited from this solution was filtered off and the filter cake was treated with hot $CHCl_3$ (1 l.). The $CHCl_3$-insoluble crystals of **7** were removed by filtration and recrystallized from H_2O to give 0.195 g (10.8%), mp 228–230° dec. Recrystallization from H_2O furnished a sample for analysis: mp 234° dec; uv $\lambda_{max}^{H_2O}$ 256, 337 nm (ε 6780, 5880); $\lambda_{max}^{pH\ 1}$ 264, 337 nm (ε 7000, 5320), $\lambda_{max}^{pH\ 11}$ 252, 335 nm (ε 7240, 6350); nmr (deuterated DMSO) 8.22 (d, J = 5 Hz), 7.70 ppm (d, J = 5 Hz); mass spectrum molecular ion at m/e 113 and characteristic peak at m/e 97 owing to loss of oxygen from the NO function.

Anal. Calcd. for $C_3H_3N_3O_2$: C, 31.87; H, 2.67; N, 37.16. Found: C, 31.75; H, 2.67; N, 36.92.

The hot $CHCl_3$ solution obtained above was concentrated, EtOH was added, and after standing at 25° for 12 hr white fluffy crystals of **6** were collected and recrystallized from $CHCl_3$–EtOH to give pure **6** (3.40 g, 42.5%), mp 236–238°, $[\alpha]^{22}D$ +31° (c 1.0, $CHCl_3$). The yield of **7** varied in different batches between 0 and 30%, but the yield of **6** based on **3** not converted to **7** was consistently 40–45%.

Anal. Calcd for $C_{29}H_{23}N_3O_9$: C, 62.47; H, 4.15; N, 7.53. Found: C, 62.49; H, 4.25; N, 7.34.

4-β-D-Ribofuranosyl-*as*-triazin-3(4*H*)-one 1-Oxide (8).—To a suspension of **6** (1.70 g, 3.05 mmol) in anhydrous MeOH (60 ml) was added a solution of $NaOCH_3$ (0.486 g, 9.0 mmol) in anhydrous MeOH (50 ml) and the mixture was stirred for 5 hr. Dowex 50 WX8 ion exchange resin (H^+ form, 18 ml wet volume in MeOH) was added to the clear solution and stirring was continued for 10 min. The ion exchange resin was removed by filtration, the MeOH solution was concentrated to a few milliliters, and Et_2O (150 ml) was added. After standing overnight, crystalline **8** (0.576 g, 77%) was collected by filtration and washed with large amounts of Et_2O, mp 172–173° dec. Two recrystallizations from MeOH furnished a sample for analysis: mp 174–176° dec; uv $\lambda_{max}^{H_2O\text{ and }pH\ 1}$ 207, 267, 343 nm (ε 16,750, 8510, 7640); $\lambda_{max}^{pH\ 11}$ 232, 273, 340 nm (ε 9380, 6640, 740); nmr (deuterated DMSO) 8.78 (d, J = 5.5 Hz), 7.80 (d, J = 5.5 Hz), 5.78 (broad singlet), 4.10 ppm (multiplet); $[\alpha]^{22}D$ +229° (c 1.0, H_2O). Characteristic peaks in the mass spectrum were those at m/e 133 and 113 (cleavage of the glycosidic bond) and at m/e 97 (loss of oxygen from the NO function).

Anal. Calcd for $C_8H_{11}N_3O_6$: C, 39.18; H, 4.52; N, 17.13. Found: C, 39.33; H, 4.50; N, 17.20.

2,5-Dihydro-4-(2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)-*as*-triazin-3(4*H*)-one (11).—Into a suspension of **6** (0.800 g, 1.435 mmol) and 5% Pd-on-charcoal catalyst (0.080 g) in $CHCl_3$ (200 ml) was bubbled H_2 for 90 min. The catalyst was then removed by filtration, and the clear solution was concentrated to dryness. The residual oil was applied to a dry column of silica gel and eluted with $CHCl_3$–EtOAc (9:1) to give **11** (0.684 g, 87.5%). Rechromatography furnished a sample for analysis, mass spectrum molecular ion at m/e 543.

Anal. Calcd for $C_{29}H_{25}N_3O_8$: C, 64.08; H, 4.63; N, 7.73. Found: C, 64.05; H, 5.14; N, 7.46.

2,5-Dihydro-4-β-D-ribofuranosyl-*as*-triazin-3(4*H*)-one (12). Method A.—Syrupy **11** (0.360 g, 0.663 mmol) was dissolved in 25 ml of ethanolic NH_3 (saturated at 0°). After standing in a pressure bottle at 25° for 3 days the solvent was evaporated and the residue was dissolved in H_2O and $CHCl_3$. The aqueous layer was extracted with $CHCl_3$ and concentrated to dryness and the residue was dried by coevaporation with EtOH *in vacuo*. The residual oil was applied to a dry column of silica gel and eluted with the upper phase of EtOAc–*n*-PrOH–H_2O (4:1:2) to give **12** as an oil (0.115 g, 75%), one spot on silica plates with the above mentioned solvent system (R_f 0.27): λ_{max}^{MeOH} 215 and 245 nm; nmr olefinic proton at 7.10 (pseudotriplet), anomeric at 5.85 (d, J = 5.5 Hz), CH_2 protons of the heterocycle at 3.74 ppm (pseudodoublet). On irradiation of the latter, the signal at 7.10 ppm collapsed to a sharp singlet. The mass spectrum showed a molecular ion at m/e 231.

Anal. Calcd for $C_8H_{13}N_3O_5$: C, 41.55; H, 5.66; N, 18.17. Found: C, 41.51; H, 5.87; N, 17.89.

Method B.—To a solution of **8** (0.245 g, 1 mmol) in 50 ml of EtOH was added 5% Pd on charcoal (0.025 g) and H_2 gas was bubbled into the rapidly stirred mixture. After 1 hr the catalyst was removed by filtration, and the EtOH was evaporated to give a syrup which was chromatographed on a dry column of silica gel as described for the preparation of **12** from **11**. The product (0.195 g, 84.5%) was identical in every respect with that of method A.

4-β-D-Ribofuranosyl-*as*-triazin-3(4*H*)-one (10).—Blocked nucleoside **6** (0.900 g, 1.62 mmol) was treated with 120 ml of ethanolic ammonia (saturated at 0°) in a pressure bottle at 25° for 5 days. After evaporation of the solvent the brown residue was dissolved in H_2O (100 ml) and was extracted three times with $CHCl_3$ (80 ml each). The aqueous phase was evaporated to dryness, and the residue was dissolved in H_2O (25 ml) and filtered from insoluble material. The solution was evaporated to dryness again and the brown residue was crystallized from EtOH to give **10** (0.160 g, 43.2%). Two recrystallizations furnished a sample (yellow powder) for analysis, for uv see Table I. This compound appeared to be unstable on prolonged standing, and the signals in the nmr spectrum were unusually broadened, indicating possible decomposition in the solvent, deuterated DMSO.

Anal. Calcd for $C_8H_{11}N_3O_5$: C, 41.92; H, 4.83; N, 18.33. Found: C, 41.97; H, 4.86; N, 18.41.

***as*-Triazin-3(4*H*)-one 1-Oxide (7) by Acid Hydrolysis of 3.**—To a solution of **3** (0.100 g, 0.788 mmol) in CH_3CN (5 ml) was added dilute methanolic HCl (0.5 N, 0.125 ml) and the solution was allowed to stand for several days. The crystalline material deposited from this solution was recrystallized from H_2O to give **7** (0.004 g, 4.5%); melting point and uv were identical with those of the analytically pure sample of **7** described above.

3-Benzyloxy-*as*-triazine (14).—Sodium metal (1.1 g, 48 mmol) was dissolved in benzyl alcohol (100 ml), and 3-methylthio-

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as-triazine[28] (5.08 g, 40 mmol) was added. After 24 hr stirring at 25° Dry Ice was added, and the solution containing some precipitate was concentrated *in vacuo* to 40 ml. After dilution with C_6H_6 the precipitate was removed by filtration and the solution was concentrated to dryness. The residue was vacuum distilled [bp 120° (0.3 mm)] to give pure **14** as crystals (1.58 g, 21%), mp 69–70°.

Anal. Calcd for $C_{10}H_9N_3O$: C, 64.15; H, 4.84; N, 22.44. Found: C, 64.13; H, 4.82; N, 22.31.

2,5-Dihydro-*as*-triazin-3(4*H*)-one (15).—To a solution of **14** (0.561 g, 3 mmol) in DMF (40 ml) was added 5% Pd on charcoal (50 mg), and H_2 was bubbled into the solution for 90 min. The catalyst was then removed by filtration and the solvent was evaporated. The residual white powder was crystallized from EtOH to give **15** (0.18 g, 60.5%), mp 135–136°. Concentration of the EtOH mother liquor yielded an additional 0.065 g (combined yield 82%). An analytically pure sample was obtained by recrystallization from EtOH: mp 136–137°; λ_{max}^{MeOH} 243 nm (ϵ 2440); nmr (D_2O) 7.01 (t, J = 3 Hz), 4.02 (d, J = 3 Hz); mass spectrum molecular ion at m/e 99.

Anal. Calcd for $C_3H_5N_3O$: C, 36.36; H, 5.08; N, 42.40. Found: C, 36.39; H, 5.04; N, 42.30.

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Registry No.—**3**, 27531-67-5; **4**, 28735-22-0; **5**, 22860-91-9; **6**, 40919-31-1; **7**, 40919-32-2; **8**, 40919-33-3; **10**, 40919-34-4; **11**, 40919-35-5; **12**, 40919-36-6; **14**, 40919-37-7; **15**, 40919-38-8.

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Peripheral Synthesis of Secondary Medium-Ring Nitrogen Heterocycles[1]

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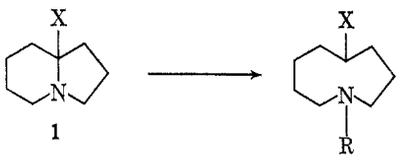
Three methods for preparing secondary azacyclononanes from 9-substituted indolizidines were investigated. The first method utilized previously developed ring-opening reactions to give *N*-benzylazacyclononanes, which were debenzylated by cleavage with alkyl chloroformates. *N*-Benzyl-5-ethylideneazacyclononane (**8**) was converted to **11** in this way *via* either the ethyl or the 2,2,2-trichloroethyl carbamate. The former group was removed with methyllithium and the latter with zinc dust. Only this latter sequence was successful for debenzylating *N*-benzyl-5-(2′-phenylethylidene)azacyclononane (**12**) to **17**. The second method involved direct cleavage of 9-vinylindolizidine (**3**) and 9-benzylindolizidine (**22**) with ethyl or phenyl chloroformate. Catalytic reduction and hydrolysis of the carbamate from **3** gave **19**. Hydrolysis of the carbamate from **22** caused transannular cyclization back to the starting material. In the final method, **3** was treated with $LiAlH_4$ and $NiCl_2$ to give 9-ethylindolizidine (**20**) and 5-ethyl- (**19**), 5-vinyl- (**10**), and 5-ethylideneazacyclononane (**11**) in varying proportions depending on the reaction conditions. All the secondary amines prepared in this study were converted to the known *N*-methyl homologs.

The peripheral synthesis of medium-ring azacycles as developed in our laboratory[3–5] leads exclusively to compounds in which the ring nitrogen is tertiary (eq 1, R = CH_3). While such compounds are of interest because of their relation to certain alkaloids[6,7] as well as their ability to undergo transannular reactions,[8,9] the availability of the corresponding secondary amines would provide additional possibilities for studies in these areas. At the time this project was initiated the preparation of secondary medium-ring azacycles was limited to two general methods: the ring expansion of cycloalkanones,[10] and the electrolysis of β-keto-1-azabicycloalkanes.[11] Although both of these syntheses are somewhat limited in scope by the availability of starting materials or the reaction conditions, a potentially general route has been described[12] more recently which nicely complements those to be discussed in this paper.

As before[3–5] our method involves the selective cleavage of the central carbon–nitrogen bond of bridgehead-substituted 1-azabicycloalkanes (eq 1), which in the



1 (1)

present study were restricted to the readily available[4,5,13] 9-substituted indolizidines (**1**). Selectivity was assured by the nature of the 9 substituent and the cleavage was facilitated by quaternization of the nitrogen atom. The three methods to be described can be classified according to the character and fate of this quaternary stage: (1) the quaternary compound gives a tertiary amine which is subsequently dealkylated; (2) the quaternary intermediate yields a derivative which can be converted to the secondary amine; or (3) the quaternary intermediate decomposes directly to the secondary amine.

The first method is based on the previously described[3–5] successful synthesis of *tertiary* medium-ring azacycles and requires the selective dealkylation of these compounds to the desired secondary amine. The reaction chosen for this purpose, the chloroformate ester cleav-

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(13) An improved preparation of one of the precursors of these starting materials, 9-cyanoindolizidine (**2**), is described in the Experimental Section.