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Registry No.—1, 56782-26-4; 3, 6023-73-0; 7, 20802-15-7; 10 HCl, 56744-06-0; 11, 34990-33-5; 12, 56744-07-1; 13, 56744-08-2; 14, 56744-09-3; 15, 56744-10-6; 16, 56744-11-7; (3,4-dimethoxyphenyl)acetonitrile, 93-17-4; 1,2-dichloroethane, 107-06-2.

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(2) Fellow of the National Research Council, Canada, 1973–present.
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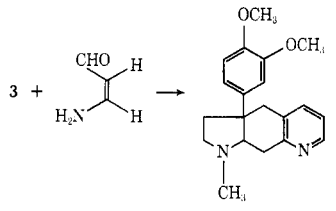

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A Convenient Synthesis of 2,3′-Imino-1-(β-D-lyxofuranosyl)uracil and Its Derivatives Using Azide Ion

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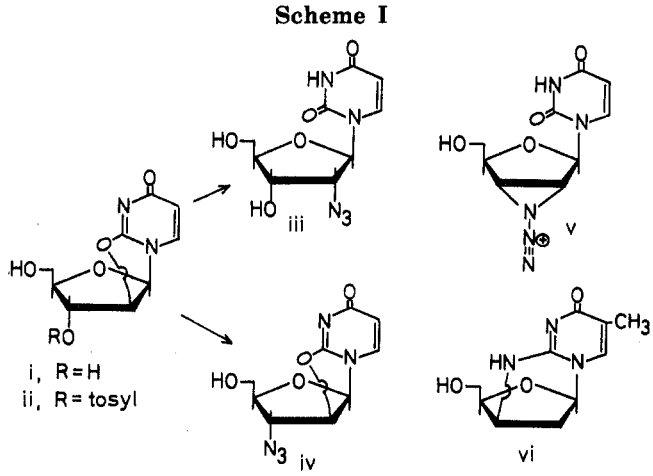
To exploit azide chemistry in the nucleoside area, a variety of derivatives of 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil were synthesized as substrates for the reaction of azide ion. These contain 2,2′-anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)-5-bromouracil (**1b**), 2,2′-anhydro-1-(5′-*O*-benzoyl-3′-*O*-tosyl-β-D-arabinofuranosyl)uracil (**1c**) and its 5′-chloro-5′-deoxy analog (**1e**), and analogous 2,2′-anhydro nucleoside with 5′-*O*-trityl and 3′-*O*-mesyl substituents (**1d**). These anhydro nucleosides as well as the known 2,2′-anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)uracil (**1a**) with in situ generated ammonium azide gave 2,3′-imino-1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (**3a**), its 5-bromo (**3b**) and 5′-*O*-trityl analog (**3c**). An analogous anhydro nucleoside with the 5′-azido group (**3e**) was obtained from 5′-chloro-5′-deoxy-2′,3′-di-*O*-tosyluridine (**4**). **3a** and **3c** were deprotected to 2,3′-imino-1-(β-D-lyxofuranosyl)uracil (**3d**). **3a** was derived to its 2′-*O*-acetyl (**5**) and 4-thioxo analogs (**6**). In contrast, 2,2′-anhydro-1-(5′-*O*-trityl-β-D-arabinofuranosyl)uracil (**7**) with the same reagent afforded 1-(2′-azido-2′-deoxy-5′-*O*-trityl-β-D-ribofuranosyl)uracil (**9**), which was converted to the 3′-*O*-mesyl derivative (**10**) for the NMR measurement.

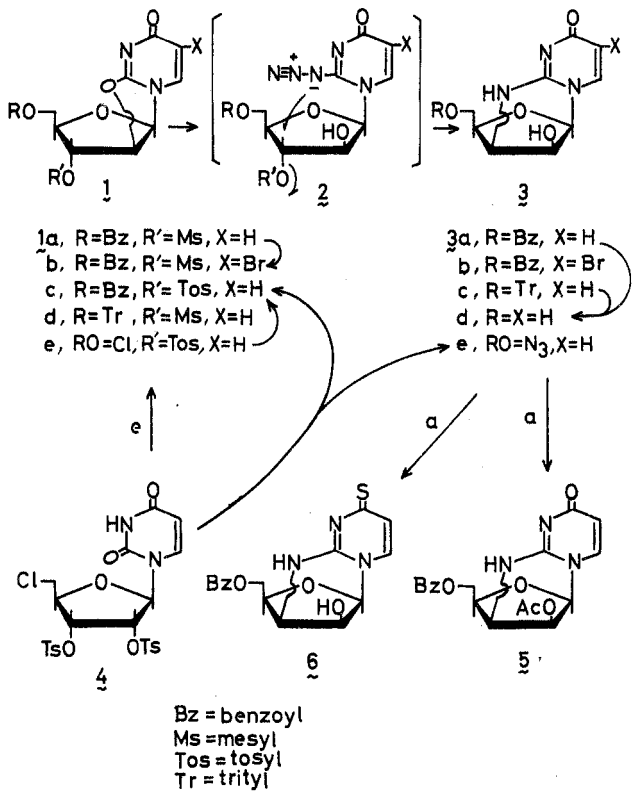
Introduction of an azide group followed by reductive cleavage has long been one of the standard methods for the syntheses of amino sugars and amino sugar nucleosides, while the use of other aspects of an azide reaction for the alterations of nucleosides is notably missing; an azide is known to have multiple reactivity leading to a nitrene, imine, and/or triazole depending upon reaction conditions and the character of a substrate.[1] Hence, our recent concern has been turned to exploitation of intramolecular nucleophilic reactions by an azide group in the nucleoside field, which would occur with or without decomposition of the introduced nitrogen chain. This paper describes a facile, selective, one-step synthesis of the derivatives of 2,3′-imino-1-(β-D-lyxofuranosyl)uracil (**3d**, Scheme II) from readily available 2,2′-anhydrouracil arabinosides.

Moffatt et al.[2] have shown that the reaction of 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil (i) with lithium azide gives 2′-azido-2′-deoxyuridine (iii), while Hirata[3] obtained 2,2′-anhydro-1-(3′-azido-3′-deoxy-β-D-arabinofuranosyl)-uracil (iv) from 2,2′-anhydro-1-(3′-*O*-tosyl-β-D-arabinofuranosyl)uracil (ii) and sodium azide (Scheme I). For the latter reaction an azidonium intermediate (v) has been proposed by Fox and coworkers[4] without any direct evidence. The proposed intermediate (v) was, however, interesting to us, since it suggested eventual synthesis of a compound with a "down" 2′,3′-imino function under appropriate conditions.

Scheme I



Scheme II



In a trial experiment using 2,2′-anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)uracil (**1a**)[5] and in situ generated ammonium azide,[6] a highly crystalline compound of mp 250–252° (**3a**, Scheme II) was obtained as a single product, no other products being detected by TLC using silica gel and 20% ethanol in benzene, 10% methanol in chloroform, and a couple of other solvent systems. This product did indicate the incorporation of one nitrogen atom with loss of the leaving group, no azide absorption in the infrared spectrum, and ultraviolet absorptions at 217 and 261 nm, the latter band being a low-intensity shoulder (see Table I). This characteristically weak second absorption was also observed in the spectrum of the debenzoylated compound (**3d**) and hence was no uridine absorption. This absorption pattern is quite similar to that of 2,3′-imino-1-(2-deoxy-β-D-*threo*-pentofuranosyl)thymine (vi),[7] which absorbs at 213 and 257–269 nm with ε 22700 and 4000 (sh), respectively. The structure of this product was thus assigned as 2,3′-imino-1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (**3a**). The NMR signals of **3a** with some structural significance were the one-proton triplet at 3.84 ppm ($H_{4'}$) and the doublet at 5.35 ppm ($H_{1'}$) (see Experimental Section). The coupling constant, $J_{1',2'}$ = 4.0 Hz, was reasonably predicted from a model study, on the basis of which the dihedral angle between $H_{1'}$ and $H_{2'}$ is expected to be approximately 40°, while for a xylo configuration it reaches as large a value as 70°. The signals of $H_{2'}$, $H_{3'}$, and 5′-methylene overlapped each other as a complex multiplet. Accordingly, **3a** was acetylated to 2,3′-imino-1-(2′-*O*-acetyl-5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (**5**), in the spectrum of which the signal of $H_{2'}$ appeared at 5.38 ppm ($J_{1',2'}$ = 4.0 Hz), clearly separated from the others. In this acetylation reaction, formation of two products was indicated by TLC but the faster moving one, most probably *N,O*-diacetate, was unstable and easily collapsed to **5** on attempted separation by silica gel chromatography or on treatment with aqueous acetic acid.

Table I
Ultraviolet Absorption Maxima of 2,3′-Imino Cyclonucleosides, 3a–e, 5, and 6, in Methanol

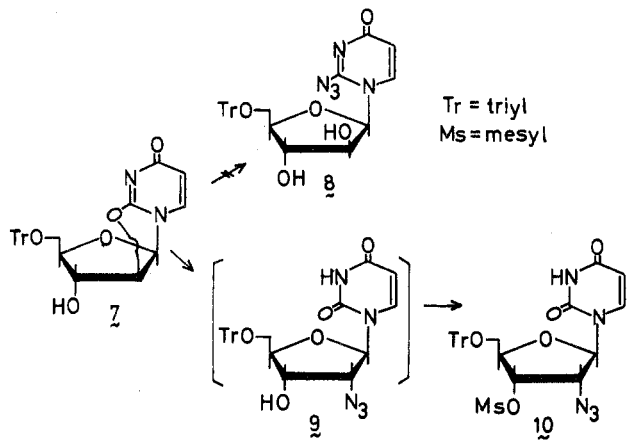
Compd	λ_{max}, nm	ε
3a	217, 261	33300, 4000 sh
3b	220, 267	29400, 5700 sh
3c	258	5200 sh
3d	215, 260	31100, 3700 sh
3e	212, 263	36600, 4080 sh
5	216, 261	39400, 4400 sh
6	228, 324	27600, 19400

Spurred by the finding of the new synthesis of an imino-bridged nucleoside, **3a**, specificity of this reaction was examined using a variety of substituted analogs of 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil (i). Thus, 2,2′-anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)-5-bromouracil (**1b**) was obtained from **1a** and *N*-bromoacetamide. The brominated position was confirmed by the ultraviolet absorption at 227 and 256 nm, and by the appearance of the NMR signal of H_6 as a singlet at 8.51 ppm which was compatible with the signal at 8.59 ppm shown by that of 2,2′-anhydro-1-(5′-*O*-acetyl-3′-*O*-benzoyl-β-D-arabinofuranosyl)-5-bromouracil.[8] The 3′-*O*-tosyl analog (**1c**) was synthesized from 2,2′-anhydro-1-(5′-chloro-5′-deoxy-3′-*O*-tosyl-β-D-arabinofuranosyl)uracil (**1e**) or directly from 5′-chloro-5′-deoxy-2′,3′-di-*O*-tosyluridine (**4**)[9] by treatment with sodium benzoate, the former (**1e**) being obtained in an excellent yield by treating the latter (**4**) with potassium carbonate. The 5′-*O*-trityl analog (**1d**) was also prepared by the standard method as described in the Experimental Section. Compounds **1c–e** showed uv absorptions at around 225 and 248 nm characteristic for a 2,2′-anhydro structure.

Reaction of excess ammonium azide with **1c**, **1b**, and **1d** gave the above obtained **3a**, 2,3′-imino-1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)-5-bromouracil (**3b**), and 2,3′-imino-1-(5′-*O*-trityl-β-D-lyxofuranosyl)uracil (**3c**), respectively, but no other by-products discernible by TLC. Acidic treatment of **3c** gave 2,3′-imino-1-(β-D-lyxofuranosyl)uracil (**3d**) above obtained from **3a** with methanolic ammonia. Compound **3d** resisted attempted hydrolytic cleavage of the imino bridge by 2 *N* hydrochloric acid or 3 *N* potassium hydroxide, and this stability coincides with the previous observations with the thymine analog (vi) and its *N*-methyl derivative.[7] Treatment of **1e** with a large excess of ammonium azide gave 2,3′-imino-1-(5′-azido-5′-deoxy-β-D-lyxofuranosyl)-uracil (**3e**), which was, however, always contaminated with unseparable halogen-containing compounds. It was eventually found that **3e** was obtainable in pure form directly from **4** as exemplified in the Experimental Section. The structures of all these 2,3′-imino nucleosides were established in terms of uv (see Table I), ir, and NMR spectra. Thiation of compound **3a** afforded 2,3′-imino-1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)-4-thiouracil (**6**).

The formation of **3a–e** from **1a–e** is rationalized by the initial attack of azide ion at C-2 followed by intramolecular nucleophilic displacement at C-3′ with release of a nitrogen molecule as visualized in formula **2**. Such an introduction of an azide group into pyrimidine bases through O^2-anhydro nucleosides is unprecedented and seemed to be directed by the presence of a leaving group at C-3′. Hence, a few trial experiments were done using known 2,2′-anhydro-1-(5′-*O*-trityl-β-D-arabinofuranosyl)uracil (**7**)[10] to ascertain the former observation with compound i.[2] Reaction between **7** and excess ammonium azide was rather sluggish even at a higher temperature (110°) but gave a reasonable yield (59%) of 1-(2′-azido-2′-deoxy-5′-*O*-trityl-β-D-ribofuranosyl)uracil (**9**) (Scheme III) and the starting material

Scheme III



(33%). Compound **9**[11] showed a uridine absorption at 257 nm but failed to give a clear-cut NMR spectrum at 60 MHz principally owing to the overlapping of $H_{2'}$ and $H_{3'}$ signals. A more convincing spectrum was obtained with the mesylated derivative, 1-(2′-azido-2′-deoxy-3′-*O*-mesyl-5′-*O*-trityl-β-D-ribofuranosyl)uracil (**10**), $H_{3'}$ being extensively deshielded relative to $H_{2'}$. Thus, **10** showed a separate triplet for $H_{3'}$ at 5.31 ppm with $J_{2',3'}$ (= $J_{3',4'}$) = 5.2 Hz and a doublet for $H_{1'}$ at 5.96 ppm with $J_{1',2'}$ = 4.3 Hz. While some uncertainty attended the assignments of the signals for $H_{2'}$ and $H_{4'}$, the ill-resolved signal envelope at 4.33 ppm contained splittings of 4.3 and 5.2 Hz. Although a reasonable analysis value was not obtained for this foamy compound and its further derivatization was abandoned owing to the material shortage, the above NMR data are sufficient to assign the structure. Thus, nucleophilic attack by azide ion on **7** occurred exclusively at C-2′, no side product corresponding to **8** being detected. It seems that the leaving group at C-3′ exerts, irrespective of 5′ substituent, a striking "through bond" electronegative influence to C-2, whereas the contrasted behavior of ii (Scheme I) is rather surprising.[12]

Experimental Section

All the melting points are uncorrected. The electronic spectra were measured on a Jasco Model ORD/UV-5 spectrophotometer. The nuclear magnetic resonance spectra were determined using a JNM C-60 HL spectrometer and tetramethylsilane as an internal standard,[13] while a few of the 100-MHz spectra were recorded with a Varian HA-100 spectrometer in the laboratory of the Takeda Chemical Industries Co., Ltd., for which we are grateful. Elemental analyses were carried out by Miss Y. Kawai using a Perkin-Elmer 240 elemental analyzer in this laboratory. Wakogel B-5 silica gel and Mallinkrodt silicic acid (100 mesh) were used for thin layer and column chromatography, respectively.

2,2′-Anhydro-1-(5′-*O*-benzoyl-3′-*O*-mesyl-β-D-arabinofuranosyl)-5-bromouracil (1b). *N*-Bromoacetamide (300 mg, 2.15 mmol) was added to a solution of **1a**[5] (500 mg, 1.22 mmol) in *N,N*-dimethylformamide (DMF) (20 ml) and the mixture was stirred at room temperature for 2 days. The yellow solution was evaporated in vacuo below 40° to a solid residue, which was digested with ice-water (15 ml) to give a pale-yellow precipitate. An aliquot of the collected solid was examined by TLC using 20% ethanol in benzene to show a single product. Crystallization from methanol gave 270 mg (62%) of colorless needles (**1b**): mp 252.5–254°; λ_{max} (MeOH) 227 nm (ε 27600) and 256 (12400); NMR (Me_2SO-d_6) δ 3.39 (3 H, s, mesyl), 5.56–5.80 (4 H, m, 5′-CH_2, $H_{4'}$ and $H_{3'}$ or $H_{2'}$), 5.37–5.51 (2 H, m, $H_{1'}$ and $H_{2'}$ or $H_{3'}$), 7.47–8.03 (5 H, m, benzoyl), and 8.51 (1 H, s, H_6).

Anal. Calcd for $C_{17}H_{15}N_2O_8SBr$: C, 41.90; H, 3.10; N, 5.75. Found: C, 41.81; H, 3.17; N, 5.77.

2,2′-Anhydro-1-(5′-*O*-benzoyl-3′-*O*-tosyl-β-D-arabinofuranosyl)uracil (1c). Method A. A mixture of **1e** (1.90 g, 4.74 mmol) and sodium benzoate (2.05 g, 14.22 mmol) in DMF (30 ml) was stirred at 90° for 7 hr and cooled. The mixture was evaporated in vacuo and the residue thoroughly triturated with ice–water (80 ml). The insoluble solid was collected by suction, air dried, and recrystallized from methanol to give 1.47 g (64%) of **1c** as colorless needles: mp 199–201°; λ_{max} (MeOH) 224 nm (ε 12700) and 249 (8600, shoulder).

Anal. Calcd for $C_{23}H_{20}N_2O_8S$: C, 57.02; H, 4.16; N, 5.78. Found: 57.13; H, 4.33; N, 5.87.

Method B. A mixture of **4**[9] (2.30 g, 4.03 mmol) and sodium benzoate (2.30 g, 16.0 mmol) in DMF (30 ml) was stirred at 95–100° for 6 hr. The solvent was evaporated off and the residue was extracted with ethyl acetate (3 × 100 ml) in the presence of water (80 ml). The ethyl acetate solution was dried over sodium sulfate and evaporated to give a paste, which was purified by preparative TLC using a silica gel plate (20 × 20 cm, 2 mm thick) and 5% methanol in chloroform. Elution of the main band with acetone and crystallization of the obtained solid from methanol gave 620 mg (32%) of crystals, mp 199–200°, identical with the product in method A in terms of infrared and ultraviolet spectroscopy.

2,2′-Anhydro-1-(5′-*O*-trityl-3′-*O*-mesyl-β-D-arabinofuranosyl)uracil (1d). To a solution of 5′-*O*-trityluridine (1.23 g, 2.53 mmol) in dry pyridine (20 ml) at −20° was added dropwise methanesulfonyl chloride (0.44 ml, 5.67 mmol) under stirring. After standing at 0° overnight, the mixture was treated with methanol (5 ml) at room temperature for 30 min and evaporated to a syrup, which was dissolved in methanol (10 ml) and precipitated into ice-water (150 ml). The precipitate was collected by suction, washed with water (50 ml), and air dried (1.6 g, 95%). TLC of an aliquot of the product revealed a single product with a slight amount of trityl alcohol.

A mixture of the above obtained crude 5′-*O*-trityl-2′,3′-di-*O*-mesyluridine (1.60 g, 2.49 mmol) and anhydrous potassium carbonate (0.35 g, 2.54 mmol) in dry acetone (10 ml) was heated to reflux for 2 hr. After cooling, the insolubles were filtered off and the filtrate evaporated in vacuo to a syrup, which was extracted with chloroform (3 × 100 ml) in the presence of water (80 ml). The chloroform solution was dried over sodium sulfate, concentrated, and applied on a silica gel column (3 × 15 cm). Elution with chloroform–methanol (95:5 v/v) gave 0.75 g (55%) of a practically homogeneous foam. The analytical sample was purified by TLC over silica gel ($CHCl_3$–EtOAc, 2:1): λ_{max} (MeOH) 248 nm (ε 14300, shoulder).

Anal. Calcd for $C_{29}H_{26}N_2O_7S$: C, 63.72; H, 4.80; N, 5.12. Found: C, 63.43; H, 5.06; N, 4.97.

2,2′-Anhydro-1-(5′-chloro-5′-deoxy-3′-*O*-tosyl-β-D-arabinofuranosyl)uracil (1e). A mixture of **4**[9] (0.7 g, 1.23 mmol) and anhydrous potassium carbonate (415 mg, 3 mmol) in acetonitrile (12 ml) was heated to reflux for 2 hr. After cooling, the insolubles were filtered off, and the filtrate was treated with Norit and concentrated in vacuo to give 0.43 g (ca. 90%) of crystals homogeneous by TLC (mp 227–229°), which were recrystallized from methanol as colorless needles: mp 232–234°; λ_{max} (MeOH) 226 nm (ε 22100) and 248 (8300).

Anal. Calcd for $C_{16}H_{15}N_2O_6SCl$: C, 48.16; H, 3.79; N, 7.03. Found: C, 47.91; H, 3.79; N, 6.86.

2,3′-Imino-1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (3a). Method A. To a solution of **1a** (1.02 g, 2.5 mmol) in DMF (20 ml) was added sodium azide (980 mg, 15 mmol) and ammonium chloride (810 mg, 15 mmol), and the mixture was stirred at 90° for 10 hr. After cooling, the insoluble materials were filtered off and the filtrate was evaporated in vacuo below 40° to a solid residue, which was thoroughly digested with ice-water (10 ml). The insoluble part was collected by suction and the aqueous filtrate was extracted with chloroform (2 × 100 ml) after adding ca. 20 ml of water. The extract was combined with the above obtained solid and recrystallized from methanol to give 570 mg (70%) of **3a** as colorless needles: mp 250–252°; NMR (Me_2SO-d_6) δ 3.84 (1 H, t, $H_{4'}$), 4.26–4.58 (4 H, m, $H_{2'}$, $H_{3'}$, and 5′-methylene), 5.35 (1 H, d, $J_{1',2'}$ = 4.0 Hz, $H_{1'}$), 5.46 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_5), 6.18 (1 H, br s, 2′-OH), 7.32–7.98 (6 H, m, H_6 and benzoyl), and 8.45 (1 H, br s, NH).

Anal. Calcd for $C_{16}H_{15}N_3O_5$: C, 58.36; H, 4.59; N, 12.76. Found: C, 58.10; H, 4.67; N, 12.70.

Method B. A mixture of **1c** (500 mg, 1.03 mmol), sodium azide (335 mg, 5.15 mmol), and ammonium chloride (290 mg, 5.15 mmol) in DMF (10 ml) was stirred at 90° for 17 hr. The reaction mixture was worked up as in method A to give 190 mg (56%) of **3a** after recrystallization from methanol. Its identity with the above obtained product was confirmed by mixture melting point and infrared spectra.

2,3′-Imino-1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)-5-bromouracil (3b). A mixture of **1b** (1.25 g, 2.5 mmol), sodium azide

(1.0 g, 1.54 mmol), and ammonium chloride (810 mg, 1.53 mmol) in DMF (20 ml) was stirred at 90° for 37 hr and cooled. TLC of an aliquot of the mixture using 20% ethanol in benzene showed the persistence of a small amount of the starting material and another product which moved slightly slower than the former. The inorganic materials were filtered off and the filtrate evaporated in vacuo below 40° to a solid residue, which was collected after digestion with ice–water (15 ml). Extraction of the filtrate with chloroform (2 × 50 ml) gave an additional crop. The total product was repeatedly recrystallized from methanol to give 390 mg (38%) of colorless needles of mp 260–261°: NMR (Me_2SO-d_6) δ 3.87 (1 H, m, $H_{4'}$), 4.24–4.61 (4 H, m, $H_{2'}$, $H_{3'}$, and 5′-methylene), 5.42 (1 H, d, $J_{1',2'}$ = 4.0 Hz, $H_{1'}$), 6.19 (1 H, d, 2′-OH), 7.36–8.01 (6 H, m, H_6 and benzoyl), and 8.45 (1 H, br s, NH).

Anal. Calcd for $C_{16}H_{14}N_3O_5Br$: C, 47.06; H, 3.47; N, 10.28. Found: C, 46.92; H, 3.55; N, 10.27.

2,3′-Imino-1-(5′-*O*-trityl-β-D-lyxofuranosyl)uracil (3c). A mixture of **1d** (550 mg, 1 mmol), sodium azide (400 mg, 6.15 mmol), and ammonium chloride (330 mg, 6.17 mmol) in DMF (10 ml) was stirred at 90° for 23 hr, and the reaction mixture was worked up similarly as for **3a** and **3b**. TLC of the crude product showed a small amount of the starting material and another slower moving product (10% methanol in chloroform). Crystallization from methanol gave 260 mg (55%) of **3c** as colorless needles: mp 270–271°; NMR (Me_2SO-d_6) δ 3.67 (2 H, m, 5′-methylene), 4.17–4.56 (3 H, m, $H_{2'}$, $H_{3'}$, and $H_{4'}$), 5.23–5.61 (2 H, m, $H_{1'}$ and H_5), 6.13 (1 H, br s, OH), 7.08–7.66 (16 H, m, trityl and H_6), and 7.76 (1 H, br s, NH).

Anal. Calcd for $C_{28}H_{25}N_3O_4$: C, 71.93; H, 5.39; N, 8.99. Found: C, 72.02; H, 5.48; N, 8.98.

2,3′-Imino-1-(β-D-lyxofuranosyl)uracil (3d). Method A. A suspension of powdered **3a** (200 mg, 0.61 mmol) in a mixture of concentrated ammonium hydroxide and methanol (1:3 v/v) (25 ml) was stirred at room temperature for 4 hr. The resulting solution was evaporated in vacuo at room temperature and the residue was triturated with a small amount of ether to give a crystalline solid, which was filtered and recrystallized from methanol to give needles (**3d**) which became slightly brown colored at above 282° but did not melt even at 290°: yield 137 mg (73%); NMR (Me_2SO-d_6) δ 3.54 (2 H, t, 5′-methylene), 3.76 (1 H, t, $H_{4'}$), 4.17 (1 H, m, $H_{2'}$), 4.49 (1 H, t, $H_{3'}$), 4.98 (1 H, br s, 5′-OH), 5.33 (1 H, d, $J_{1',2'}$ = 3.5 Hz, $H_{1'}$), 5.51 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_5), 6.16 (1 H, br s, 2′-OH), 7.42 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_6), and 9.42 (1 H, br s, NH).

Anal. Calcd for $C_9H_{11}N_3O_4$: C, 48.00; H, 4.92; N, 18.66. Found: C, 48.01; H, 4.94; N, 18.40.

Method B. A suspension of **3c** (146 mg, 0.31 mmol) in a mixture of ether (5 ml), chloroform (5 ml), and saturated hydrogen chloride solution in dioxane (1 ml) was stirred at room temperature for 30 min. The resulting solution was evaporated in vacuo at room temperature and the residue triturated with ether (10 ml) to give a crystalline solid. The collected solid was dissolved in ethanol and neutralized with saturated ethanolic ammonia and the solvent was evaporated off to give a solid residue, which was digested with water (1 ml) and the insoluble part was collected. Recrystallization from methanol gave 45 mg (64%) of needles (**3d**), identical with the product obtained by method B in terms of infrared and ultraviolet spectra.

2,3′-Imino-1-(5′-azido-5′-deoxy-β-D-lyxofuranosyl)uracil (3e). A mixture of compound **4** (1.75 g, 3.08 mmol), sodium azide (1.18 g, 18.4 mmol), and ammonium chloride (990 mg, 18.4 mmol) in DMF (20 ml) was stirred at 90–95° for 8 hr. The mixture was evaporated in vacuo and the residue digested with ice–water (7 ml). The sparingly soluble part was collected by suction (0.33 g) and repeatedly crystallized from hot water to give 0.29 g (37%) of **3e** as needles, which decomposed at around 275° under black coloration, ir (KBr) νN_3 2130 cm^{-1}.

Anal. Calcd for $C_9H_{10}N_6O_3 \cdot \frac{1}{2}H_2O$: C, 41.70; H, 4.25; N, 32.42. Found: C, 41.98; H, 4.11; N, 32.15.

2,3′-Imino-1-(2′-*O*-acetyl-5′-*O*-benzoyl-β-D-lyxofuranosyl)uracil (5). A mixture of **3a** (200 mg, 0.61 mmol) and acetic anhydride (0.33 ml, ca. 3.3 mmol) in dry pyridine (6 ml) was warmed at 50° for a while to effect a solution. The solution was left at room temperature overnight and evaporated in vacuo to a paste, which was repeatedly coevaporated with ethanol. TLC at this stage using a silica gel plate and 20% ethanol in benzene as a developer showed two spots in approximately equal amounts. The syrupy mixture was then warmed with 20% acetic acid at 90° for 10 min. An aliquot was taken, thoroughly evaporated, and examined by TLC using the same solvent system to show only one spot, the faster moving one having now disappeared. The mixture was again evaporated to a gum, which was repeatedly coevaporated with ethanol to give a crystalline residue. Recrystallization of the collected solid from a mixture of methanol and ethanol gave 195 mg (86%) of prisms of mp 263–266° dec: NMR (Me_2SO-d_6) δ 4.20 (1 H, t, $H_{4'}$), 4.38 (2 H, m, 5′-methylene), 4.61 (1 H, m, $H_{3'}$), 5.38 (1 H, t, $J_{1',2'}$ = 4.0 Hz, $H_{2'}$), 5.51 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_5), 5.72 (1 H, d, $J_{1',2'}$ = 4.0 Hz, $H_{1'}$), 7.34–7.99 (6 H, m, H_6 and 5′-benzoyl), and 8.72 (1 H, br s, NH).

Anal. Calcd for $C_{18}H_{17}N_3O_6$: C, 58.22; H, 4.61; N, 11.32. Found: C, 58.22; H, 4.84; N, 11.47.

2,3′-Imino-1-(5′-*O*-benzoyl-β-D-lyxofuranosyl)-4-thiouracil (6). Phosphorus pentasulfide (112 mg, 0.5 mmol) in dry pyridine (5 ml) was stirred at 95° for 30 min, and to this was added **3a** (110 mg, 0.33 mmol). After stirring at this temperature for 3 hr, the mixture was cooled and evaporated to a syrup, which was digested with water (3 ml) and the separated solids were collected. TLC of an aliquot of the solids indicated one main product with a couple of minor by-products. Purification by preparative TLC over silica gel (10 × 20 cm, 2 mm thick, benzene–EtOH, 8:2) gave, after elution of the main band with acetone, needles which were recrystallized from methanol to give 35 mg (30%) of **6** as methanolate: mp 181–183°; NMR (Me_2SO-d_6) δ 3.19 (3 H, s, methanol), 4.22 (1 H, m, $H_{4'}$), 4.32–4.84 (4 H, m, $H_{2'}$, $H_{3'}$, and 5′-methylene), 5.52 (1 H, d, $J_{1',2'}$ = 4.0 Hz, $H_{1'}$), 6.39 (1 H, br s, 2′-OH), 6.43 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_5), 7.23–8.17 (6 H, m, benzoyl and H_6), and 9.22 (1 H, br s, NH).

Anal. Calcd for $C_{16}H_{15}N_3O_4S \cdot CH_3OH$: C, 54.10; H, 5.07; N, 11.13. Found: C, 54.30; H, 5.03; N, 11.17.

1-(2′-Azido-2′-deoxy-5′-*O*-trityl-β-D-ribofuranosyl)uracil (9). A mixture of **7**[10] (500 mg, 1.08 mmol), sodium azide (350 mg, 5.38 mmol), and ammonium chloride (300 mg, 5.60 mmol) in DMF (15 ml) was stirred at 110° for 20 hr. After cooling, the mixture was filtered and the filtrate evaporated in vacuo to a syrup, which was digested with ice–water (10 ml). The separated precipitate was filtered by suction, dried by pressing on a porous plate, and taken into chloroform (10 ml). The sparingly soluble solid collected by suction proved to be practically homogeneous starting material (167 mg, 33%). The filtrate was concentrated and submitted to preparative TLC using a silica gel plate (20 × 20 cm, 2 mm thick) and 10% methanol in chloroform. Elution of the faster moving main band with acetone gave 320 mg (59%) of a homogeneous foam (**9**) which resisted crystallization and hence was directly used for the next step: ir (KBr) νN_3 2120 cm^{-1}; λ_{max} (MeOH) 257 nm (ε 9400).

1-(2′-Azido-2′-deoxy-3′-*O*-mesyl-5′-*O*-trityl-β-D-ribofuranosyl)uracil (10). Methanesulfonyl chloride (0.06 ml, 0.77 mmol) was added to a precooled solution (at −20°) of **9** (320 mg, 0.63 mmol) in pyridine (4 ml) under stirring and the mixture was left at −20° overnight, treated with methanol (1 ml) at room temperature for 1 hr, and then evaporated in vacuo. The residue was extracted with chloroform (3 × 50 ml) in the presence of water (20 ml) and the chloroform extract applied on a silica gel column (2 × 17 cm). Elution with chloroform–ethyl acetate (5:1 v/v) gave 300 mg (80%) of a practically homogeneous foam (**10**), a portion of which was further purified by TLC over silica gel (10% MeOH in $CHCl_3$) for the elemental analysis and spectral measurements: ir (KBr) νN_3 2120 cm^{-1}; λ_{max} (MeOH) 257 nm (ε 10100); NMR ($CDCl_3$) δ 3.05 (3 H, s, mesyl), 3.56 (2 H, br s, 5′-methylene), 4.33 (2 H, triplet-like q, J = 4.3 and 5.2 Hz, $H_{2'}$ and $H_{4'}$), 5.31 (1 H, t, $J_{2',3'}$ = 5.2 Hz, $H_{3'}$), 5.49 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_5), 5.96 (1 H, d, $J_{1',2'}$ = 4.3 Hz, $H_{1'}$), 7.33 (15 H, s, trityl), 7.76 (1 H, d, $J_{5,6}$ = 8.0 Hz, H_6) and 9.10 (1 H, br s, NH).

Registry No.—**1a,** 56687-59-3; **1b,** 56615-01-1; **1c,** 56615-02-2; **1d,** 56615-03-3; **1e,** 56615-04-4; **3a,** 56615-05-5; **3b,** 56615-06-6; **3c,** 56615-07-7; **3d,** 56615-08-8; **3e,** 56615-09-9; **4,** 56615-10-2; **5,** 56615-11-3; **6,** 56615-13-5; **7,** 3249-94-3; **9,** 34407-66-4; **10,** 56615-14-6; *N*-bromoacetamide, 79-15-2; sodium benzoate, 532-32-1; 5′-*O*-trityluridine, 6554-10-5; methanesulfonyl chloride, 124-63-0; sodium azide, 26628-22-8.

References and Notes

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(3) M. Hirata, *Chem. Pharm. Bull.*, **16,** 291 (1968).
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(6) Less basic ammonium azide was considered preferable to sodium azide so as not to injure the 5'-ester portions and some other sensitive parts of products and also of the starting material (**1a**). According to our experiences, the former reagent seems to be more soluble in DMF than the latter, and the aqueous washings of the reaction mixtures after evaporation of the reaction solvent usually indicated a practically neutral pH, when equimolar amounts of ammonium chloride and sodium azide were used. The uses of some other soluble azide salts have been described: W. G. Finnegan, R. A. Henry, and R. Lofquist, *J. Am. Chem. Soc.*, **80**, 3908 (1958).
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(10) J. F. Codington, I. L. Doerr, and J. J. Fox, *J. Org. Chem.*, **29**, 558 (1964).
(11) This compound has previously been obtained via another route and fully characterized by 100-MHz NMR spectroscopy [D. Wagner, J. P. H. Verheyden, and J. G. Moffatt, *J. Org. Chem.*, **37**, 1876 (1972)]. The shortage of our sample has hampered repeating the measurement at 100 MHz for comparison. The authors are indebted to one of the referees for the information of the above publication.
(12) It must be added that in a trial experiment with **1b** and sodium azide in DMF **3b** was isolated in a low yield from a rather complex mixture.
(13) Measurements after D_2O exchange were also carried out for all the compounds containing labile protons.

Photochemical Formation of Spiro and Bicyclo 1-Acylaminoazetidin-2-ones. Models for the Syntheses of Penicillin-like Systems. II[1]

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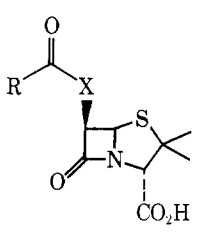
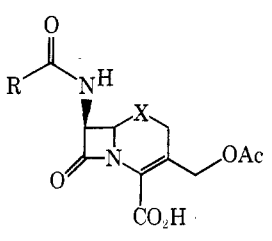
The syntheses and photochemistry of spiro 2-acetylpyrazolidin-3-ones **1d, 2d,** and **13d,** spiro 1-acetylpyrazolidin-3-one **8,** and N-unsubstituted spiro pyrazolidin-3-one **1a** were studied. Upon irradiation these systems were shown to give 1-acetamidoazetidin-2-ones **6, 5, 15, 6,** and 1-aminoazetidin-2-one **7,** respectively, in good yields. A cis-fused bicyclo pyrazolidin-3-one **33a** was also synthesized and irradiated to give bicyclo β-lactam **34a** in 45% isolated yield. β-Lactam **34a** was also synthesized by a second route which involved amination of β-lactam **35a** obtained from the reaction of chlorosulfonyl isocyanate and cyclohexene. The stereochemistry and some reactions of these systems are discussed.

There has been considerable interest in the syntheses of molecules related to the penicillin and cephalosporin antibiotics over the last several decades.[2] During this time many "established" structure–activity relationships concerning these antibiotics have evolved including, among others, the necessity of having the 6-amido group in penicillin (Ia) or the ring sulfur in cephalosporin (IIa) in order to maintain activity. Recent reports on the syntheses of fundamentally different active "penicillin-like" (Ib–d)[3] and "cephalosporin-like" (IIb,c)[4] systems indicate, however, the tentative nature of some of these "established" relationships and the need for continuing studies of different structural analogs of these antibiotics.

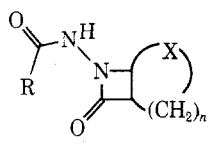


Ia, X = NH, penicillin
b, X = O
c, X = CH_2
d, X = NHNH

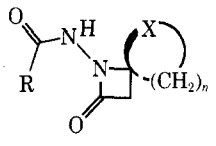


IIa, X = S, cephalosporin
b, X = O
c, X = CH_2

Our interests in this area include approaches to the syntheses of 6-azapenicillins (III, n = 2), 7-azacephalosporins (III, n = 3), and related spiro systems (IV).[5]



III, X = S, CH_2
n = 2, 3



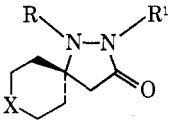
IV, X = S, CH_2
n = 3, 4

Toward these goals we have been examining methods applicable to the synthesis of the *N*-acylaminoazetidin-2-one moiety, which is the dominant feature of both III and IV. Previously we reported on the photochemical rearrangement of monocyclic 2-acyl 5,5-dimethylpyrazolidin-3-ones to give *N*-acylaminoazetidin-2-ones in isolated yields as high as 65%.[1,6] We have now examined the effects of several structural features on this photochemical ring contraction reaction as well as the presence of a remote sulfur atom. This report includes our findings on the syntheses and photochemical reactions of an assortment of 5- and 6-spiro pyrazolidin-3-ones and a 6-fused bicyclo pyrazolidin-3-one as well as the preparation of an *N*-acylaminoazetidin-2-one related to III (X = CH_2) using a procedure which involves amination and acylation of an azetidin-2-one.

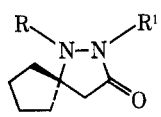
Carbon Spiro Systems. Starting with the known α,β-unsaturated esters, ethyl cyclohexylideneacetate[7] and ethyl cyclopentylideneacetate,[8] carbon spiro systems **1a** and **2a** were prepared by condensation of the respective esters with hydrazine.

While **1a** was obtained in quite good yield, the yield of **2a,** the 5-spiro system, was generally 15–20% lower, presumably because of the increased strain involved in the ring closure step. Both of these acyl hydrazides were solids and were significantly more stable to air oxidation than 5,5-dimethylpyrazolidin-3-one which we had prepared previously.[1] Condensation of either **1a** or **2a** with 2,2,2-trichloroethoxycarbonyl chloride (TrOCCl)[9] under Schotten–Baumann conditions gave 1,2-diacylhydrazides **1b** and **2b,** respectively, in good yields.

Acylation of **1b** or **2b** with acetyl chloride and triethylamine in tetrahydrofuran solvent gave *O*-acyl derivatives **3** and **4,** which were easily rearranged to their corresponding



1, X = CH_2; 13, X = S



2

a, R = R¹ = H; b, R = TrOC, R¹ = H;
c, R = TrOC, R¹ = CH_3CO; d, R = H, R¹ = CH_3CO