Synthesis of Some Pyrimidine 2′-Amino-2′-deoxynucleosides

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The reaction of 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil with lithium azide in hexamethylphosphoramide at 150° gives 2′-azido-2′-deoxyuridine in 50% yield. Catalytic reduction of the latter compound gives 2′-amino-2′-deoxyuridine (**3**), the first such pyrimidine nucleoside to be described. The dichloroacetyl derivative of the 2′-amino group was prepared by conventional methods. Acetylation of **3** followed by reaction with phosphorus pentasulfide and amination of the resulting 4-thiouracil derivative gave 2′-amino-2′-deoxycytidine (**8**). The latter compound was also obtained directly by reaction of 3′,5′-di-*O*-acetyl-2′-azido-2′-deoxyuridine (**9**) with phosphorus pentasulfide in pyridine followed by treatment with methanolic ammonia. Reaction of **9** with *N*-iodosuccinimide gave the 5-iodo derivative and subsequent reduction of the azido group with sodium borohydride gave 2′-amino-2′-deoxy-5-iodouridine.

Spurred largely through the presence of the 3′-amino-3′-deoxy-β-D-ribofuranose moiety in the antibiotic puromycin,[1] considerable effort has been devoted to the synthesis of other amino sugar nucleosides. Thus, synthetic routes leading to purine ribofuranosyl nucleoside analogs containing 5′-amino-5′-deoxy-,[2] 2′-amino-2′-deoxy-,[3] and 3′-amino-3′-deoxy[4]-β-D-ribofuranosyl moieties have been described. Also syntheses leading to 5′-amino-5′-deoxy-,[5] 3′-amino-3′-deoxy-,[5a] 3′-amino-2′,-3′-dideoxy-,[6] and 3′-amino-2′,3′-dideoxy-2′-thio[7]-β-D-ribofuranosylpyrimidines have been described. The methods of synthesis have involved both transformations of preformed nucleosides[2,5b,6,7] and condensations of derivatives of suitable amino sugars with the purine or pyrimidine bases.[3,4,5a]

The notably missing member in the above series is the pyrimidine 2′-amino-2′-deoxyribonucleosides and in this paper we describe the synthesis of two such compounds, namely 1-(2-amino-2-deoxy-β-D-ribofuranosyl)-uracil (**3**) and 1-(2-amino-2-deoxy-β-D-ribofuranosyl)-cytosine (**8**).

While it has previously been shown that the anhydro bridge of 2,3′-anhydro-1-(2-deoxy-β-D-threopentofuranosyl)thymine can be opened by nucleophiles such as phthalimide anion,[6a] it has been stated by both Brown, *et al.*,[8] and by Horwitz, *et al.*,[5b] that 2,2′-anhydro-1-(β-D-arabinofuranosyl)uracil (**1a**) was resistant to reaction with azide ion in acetonitrile or dimethylformamide. In both cases, the attempted displacement reaction was actually done upon 5′-*O*-acetyl-2′-*O*-tosyluridine and the reaction led only to the formation of the anhydronucleosides (**1a** and **1b**) which resisted further attack. A comparable reaction between **1b** and iodide ion led, however, to 5′-*O*-acetyl-2′-deoxy-2′-iodouridine.[8] It thus seemed to be of interest to investigate the opening of such anhydronucleosides in other aprotic dipolar solvents known to favor nucleophilic attack.

The preparation of **1a** was done essentially according to Hampton[9] with the exception that the reaction of uridine with diphenyl carbonate was carried out in hexamethylphosphoramide (HMPT) rather than in dimethylformamide (DMF). This modification somewhat reduced the reaction time and substantially increased the yield of crystalline product to 88%. It is interesting to note that tlc of the crude product from this reaction in either DMF or HMPT showed the presence of two products with the characteristic ultraviolet spectrum of **1**. During work-up of the reaction, the more polar of these disappeared with exclusive formation of **1a**. It is possible that this very polar product is the unstable 3′-hemicarbonate of **1a** arising directly from opening of uridine 2′,3′-carbonate by the C_2-carbonyl of the uracil ring.[10]

In our initial efforts to react **1a** with lithium azide we used dimethyl sulfoxide (DMSO) as the solvent. Since nucleophilic opening of anhydronucleosides is known to be acid catalyzed,[11] trial experiments were carried out at 100° in the presence of benzoic acid, methanesulfonic acid, or ammonium chloride and in the absence of added acid. In no case was there any significant reaction during 2 hr at 100,° but at 150° all reactions rapidly turned dark and tlc showed the presence of a less polar compound with a uridine spectrum. The reactions containing acid appeared to be less colored and somewhat cleaner and subsequent studies were done using benzoic acid. The desired reaction product 2′-azido-2′-deoxyuridine (**2**) proved to be water soluble and work-up necessitated evaporation of the DMSO to dryness prior to chromatography. Nevertheless, **2** was isolated in modest yield from such a reaction. A notable improvement was achieved by conducting the reaction in HMPT rather than in DMSO.[12] At 150° in this solvent the reaction of **1a** with lithium azide was much more rapid than in DMSO and was essentially complete within 15 min. A second advantage of the use of HMPT lies in the selective extraction of this otherwise very polar solvent into chloroform *via* complex formation.[12] Subsequent chromatography of the reaction mixture on silicic acid led to the isolation of **2** as a chromatographically and analytically pure syrup in 50% yield. Subsequent reduction of **2** in the presence of a palladium catalyst rapidly gave 2′-amino-2′-deoxyuridine (**3**) that was obtained in crystalline form in 98% yield. Titration of **3** indicated pK_a values of 9.2 and 6.2 which

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(5) (a) H. M. Kissman and M. J. Weiss, *J. Amer. Chem. Soc.*, **80**, 2575 (1958); (b) J. P. Horwitz, J. A. Tomson, J. A. Urbanski, and J. Chua, *J. Org. Chem.*, **27**, 3045 (1962).

(6) (a) N. Miller and J. J. Fox, *ibid.*, **29**, 1772 (1964); (b) J. P. Horwitz, J. Chua, and M. Noel, *ibid.*, **29**, 2076 (1964).

(7) T. Sekiya and T. Ukita, *Chem. Pharm. Bull.*, **15**, 1503 (1967).

(8) D. M. Brown, D. B. Parihar, and Sir A. Todd, *J. Chem. Soc.*, 4242 (1958).

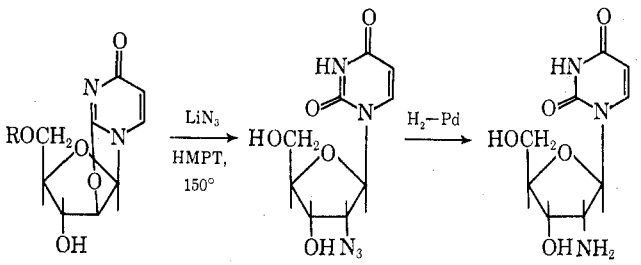
(9) A. Hampton and A. W. Nichol, *Biochemistry*, **5**, 2076 (1966).

(10) K. K. Ogilvie and D. Iwacha, *Can. J. Chem.*, **47**, 495 (1969).

(11) J. J. Fox and N. C. Miller, *J. Org. Chem.*, **28**, 936 (1963).

(12) See H. Normant, *Bull. Soc. Chim. Fr.*, 791 (1968), for a review on the utilities of HMPT.

are in good agreement with those of uridine (pK_a = 9.2)[13] and of various 2′-amino-2′-deoxy sugars (pK's = 6.1–7.7).[14]



1a, R = H
b, R = Ac

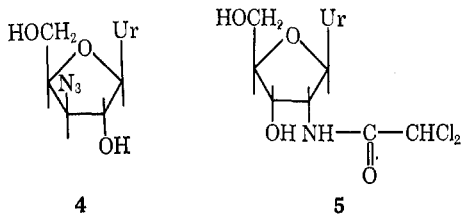
2

3

Brown, *et al.*,[15] have shown that the reaction of **1a** with sodium ethyl sulfide gives 1-(3-deoxy-3-ethylthio-β-D-xylofuranosyl)uracil rather than the desired 2′-2′-deoxy-2′-ethylthiouridine, this result presumably arising from intervention of the 2′,3′-*ribo*-epoxide. Accordingly, it was of importance to prove that the introduction of azide led to the desired compound **2** rather than to the 3′-azide-3′-deoxyxylo epimer (**4**). Confirmation of the proposed structures was provided by nmr spectroscopy. Thus, the acyl derivatives of **2** (**9**) showed extensive deshielding of C_3′H relative to that of C_2′H. The spectrum of the 5′-*O*-trityl derivative of **2** (to be described as part of a separate study) in DMSO-d_6 was even more convincing since C_3′H (4.44 ppm, q, 1, $J_{2',3'} = J_{3',4'} = J_{H,OH}$ = 6 Hz) could be readily shown to be spin coupled to the 3′-hydroxyl group (5.97 ppm, d, 1, $J_{H,OH}$ = 6 Hz). The assignments of sugar proton resonances were confirmed by spin decoupling experiments. These results are compatible only with the presence of a free 3′-hydroxyl group in **2** and exclude the alternative structure **4**.

The amino alcohols **3** and **8** were also found to be rapidly oxidized by periodate, 0.8 equiv of oxidant being consumed within 7 sec at pH 6.4. While some uncertainty attends the definitive assignment of configuration to cyclic amino alcohols by periodate oxidation,[16] this very rapid oxidation also supports the cis configuration for **3** and **8**. Under similar conditions, the periodate oxidation of 9-(3-amino-3-deoxy-β-D-arabinofuranosyl)adenine, a nucleoside containing a 2′,3′-*trans*-amino alcohol moiety kindly provided by Dr. Elmer Reist and the Cancer Chemotheraphy National Service Center, was slower, consumption of 0.65 and 0.9 equiv of oxidant requiring 10 and 100 min, respectively. This, once again, strongly supports our assigned configuration.

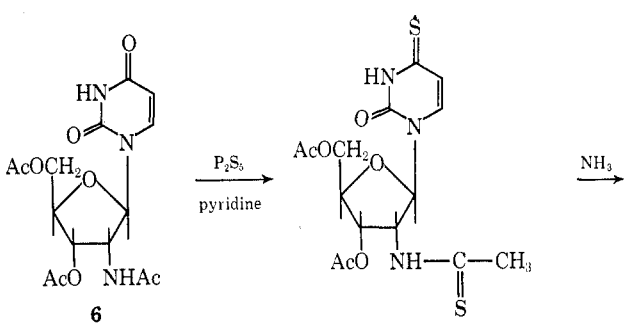
The availability of this amino alcohol **3** made it attractive to attempt to combine several of the structural features of the antibiotics puromycin and chloramphenicol by preparation of 2′-dichloroacetamideo-2′-deoxyuridine (**5**). The latter compounds was readily formed and isolated in 74% yield by heating a solution of **3** and excess methyl dichloroacetate in ethanol.



4

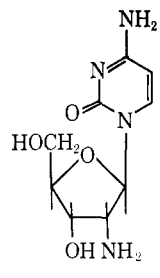
5

Conversion of **3** into the related 2′-amino-2′-deoxycytidine (**8**) was accomplished by the general thiation–amination procedure of Fox, *et al.*[17] Thus, acetylation of **3** gave the crystalline triacetate **6** in 90% yield. Subsequent reaction with phosphorus pentasulfide in refluxing anhydrous pyridine led to thiation of both the uracil ring and of the 2′-acetamido function. This reaction, or the following chromatography, was, however, accompanied by partial loss of one of the *O*-acetyl groups as shown by tlc and infrared spectroscopy. This crude material was satisfactory for subsequent steps but in order to characterize the dithio compound **7** the mixture was reacetylated, giving **7** as a chromatographically homogeneous and analytically pure, amorphous, yellow solid. It is interesting to note that the presence of a 2′-acylamido function has a rather striking effect upon the conformation of the furanose sugar ring. Thus, while the nmr spectra of most simple uridine derivatives show values of $J_{1',2'}$ ranging from 0 to 6 Hz the 2′-acetamido compound **6**, the 2′-dichloroacetamido compound **4**, and the 2′-thioacetamido **7** show $J_{1',2'}$ values of 8.5, 8, and 9 Hz, respectively. We have previously noted[18] that the 1′,2′ coupling constants of certain 2′- and 3′-*O*-trityluridines are also as large as 8 Hz but we are not aware of values as large as 9 Hz as in **7**. Treatment of crude **7** with methanolic ammonia at 120° both converted the thiouracil ring to a cytosine derivative and cleaved the *O*-acetyl and the 2′-thioacetamide groups with formation of the desired 2′-amino-2′-deoxycytidine (**8**). A similar cleavage of a thioacetamide has previously been described by Watanabe, *et al.*, in the case of a 3′-thioacetamido-β-D-glucopy-



6

7



8

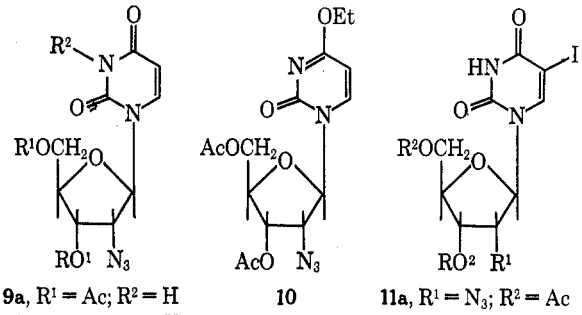
(13) P. A. Levene and H. S. Simms, *J. Biol. Chem.*, **65**, 519 (1925).
(14) (a) C. B. Barlow, R. D. Guthrie, and A. M. Prior, *Carbohyd. Res.*, **10**, 481 (1969); (b) S. Inouye, *Chem. Pharm. Bull.*, **16**, 1134 (1968).
(15) D. M. Brown, D. B. Parihar, Sir A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 3028 (1958).
(16) G. E. McCasland and D. A. Smith, *J. Amer. Chem. Soc.*, **73**, 5164 (1951).
(17) J. J. Fox, D. Van Praag, I. Wempen, I. L. Doerr, L. Cheong, J. E. Knoll, M. L. Eidinoff, A. Bendich, and G. B. Brown, *ibid.*, **81**, 178 (1959).
(18) A. F. Cook and J. G. Moffatt, *ibid.*, **89**, 2697 (1967).

ranosyl nucleoside.[19] In this way, crystalline **8** was obtained in 24% overall yield from **6** and was characterized by elemental analysis and spectral properties.

As a possible alternative route to **8** and to 2′-azido-2′-deoxycytidine we have also reacted 3′,5′-di-*O*-acetyl-2′-azido-2′-deoxyuridine (**9a**) with thionyl chloride and a catalytic amount of DMF in chloroform according to the general method of Žemlicka and Sŏrm.[20] While the starting material disappeared with formation of the intermediate 4-*O*-chlorodimethylaminomethyl adduct as judged by its tlc behavior and ultraviolet spectrum,[20] the desired 4-chloro-1,2-dihydro-2-pyrimidinone nucleoside was isolated. The only crystalline compound isolated in low yield was 4-ethoxy-1-(3,5-di-*O*-acetyl-2-azido-2-deoxy-β-D-ribofuranosyl)-2(1*H*)-pyrimidinone (**10**) which must have arisen from the presence of traces of ethanol used as stabilizer in the chloroform. Further treatment of the crude product with ethanol raised the yield of **10** to 19%. While aminolysis of **10** would doubtless lead to the desired 2′-azido-2′-deoxycytidine we have not explored this route further.

The reaction of **9a** with phosphorus pentasulfide and pyridine led not only to thiation of the uracil ring but also to reduction of the azido function, probably due to the presence of hydrogen sulfide which is known to effect such reduction.[21] Subsequent amination of the crude thiation product led directly to 2′-amino-2′-deoxycytidine (**8**) in an overall yield of 39% from **9a**. This, thus, becomes the most direct route to **8**.

Reaction of **2** with benzoyl chloride did not give the desired 2′,3′-di-*O*-benzoyl derivative **9b** but rather a tribenzoyl derivative, presumably **9c** that would not be suitable for further transformation to the cytosine series. It did, however, prove possible to selectively remove the *N*-benzoyl group by brief treatment with hot pyridine containing 2% water giving the desired **9b**. This simple procedure may well prove to be useful during benzoylation of other uridine derivatives.



9a, R^1 = Ac; R^2 = H
b, R^1 = Bz; R^2 = H
c, R^1 = R^2 = Bz

10

11a, R^1 = N_3; R^2 = Ac
b, R^1 = NH_2; R^2 = H

Since it was of interest to introduce various substituents into the 5 position of the pyrimidine ring of **3**, we wished to prepare, as a common intermediate, a 2′-amino-2′-deoxy-5-halouridine. Direct halogenation of **3** appeared to be difficult due to side reactions of the amino group and so we preferred to attempt halogenation of the azidonucleoside **9a**. Preliminary experiments on the reaction of **9a** in chloroform with *N*-bromosuccinimide in the presence of benzoyl peroxide[22] indeed gave a mixture of two 5-bromonucleosides in 35% yield as shown by nmr and ultraviolet spectra. Since this mixture could be completely reduced to a mixture of **3** and its 5-bromo derivative with sodium borohydride (see below) one of the products was presumably the consequence of some side reaction with the azido function. Iodination of **9a** using *N*-iodosuccinimide in the presence of a catalytic amount of di-*n*-butyl disulfide,[23] however, was more effective and the pure 5-iodonucleoside **11a** was obtained in 51% yield. Selective catalytic reduction of the azido group of **11a** did not seem possible due to concomitant hydrogenolysis of the iodo group and attempted reduction of **2** with diborane, which has been used successfully with aliphatic α-iodoazides[24] led only to a product showing end absorption in its ultraviolet spectrum. Reduction of **2** using sodium borohydride in hot isopropyl alcohol[25] did, however, give crystalline **3** in 42% yield and encouraged us to apply the same reaction to **11a**. Here the reaction was less effective and even after prolonged reaction unreacted azido compounds remained and considerable loss of the 5-iodo function occurred. The desired crystalline 2′-amino-2′-deoxy-5-iodouridine (**11b**) was obtained in only 18% yield.

Further transformations of this compound await the development of a more efficient and selective method for reduction of the azido group. The preparation and some biological properties of further compounds derived from 2′-amino-2′-deoxy pyrimidine nucleosides will be described at a later date.

Experimental Section

General Methods.—Thin layer chromatography (tlc) was carried out on 0.25-mm layers of Merck silica gel GF and products were visualized by ultraviolet absorption or by spraying with a 5% solution of ammonium molybdate in 10% sulfuric acid followed by heating at 150°. Preparative tlc was done on 20 × 100 cm glass plates coated with a 1.3-mm layer of Merck silica gel HF and column chromatography on Merck silica with 0.05–0.20-mm particles. Nuclear magnetic resonance (nmr) spectra were determined using a Varian HA-100 spectrometer and are reported in parts per million downfield from an internal standard of TMS. The assignments of sugar proton resonances were confirmed by spin-decoupling experiments. Mass spectra were obtained using an Atlas CH-4 spectrometer with a direct inlet system. Optical rotatory dispersion spectra were obtained with a Jasco ORD/UV-5 instrument. Instrumental analyses are by the staff of the Analytical Laboratory of Syntex Research. We are particularly grateful to Dr. M. L. Maddox and Miss J. Tremble and to Dr. L. Tokes for their cooperation with nmr and mass spectrometry, respectively. Periodate oxidations were followed spectrophotometrically at 310 mμ.[26] Elemental analyses were obtained from Dr. A. Bernhardt, Mülheim, Germany, and from the Analytical Laboratories of the University of California, Berkeley. Melting points are corrected.

2,2′-Anhydro-1-(β-D-arabinofuranosyl)uracil[1] (1a).—Uridine (38 g) and diphenyl carbonate (44.4 g) were dissolved in hexamethylphosphoramide (150 ml) and, after addition of sodium bicarbonate (1.0 g), the mixture was heated at 150° for 20 min. Tlc (ethyl acetate–methanol, 1:1) then showed essentially only **1a** and a slightly slower spot with a uv spectrum similar to **1a's**. The mixture was cooled, added to water (1.2 l.), and extracted

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(24) F. W. Fowler, A. Hassner, and L. A. Levy, *J. Amer. Chem. Soc.*, **89**, 2077 (1967).
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(26) J. S. Dixon and D. Lipkin, *Anal. Chem.*, **26**, 1092 (1954).

three times with chloroform. The aqueous phase was evaporated to dryness and the residue crystallized from methanol giving 31.0 g (88%) of pure **1a** with mp 238–240° and spectral properties identical with that of an authentic sample.[9]

2'-Azido-2'-deoxyuridine (2).—A suspension of **1a** (2.26 g, 10 mmol) and lithium azide (3.50 g, 71 mmol) in anhydrous hexamethylphosphoramide (40 ml) was rapidly stirred in a 150° oil bath until most of the solid dissolved. Benzoic acid (1.22 g, 10 mmol) was then added and heating was continued for 15 min during which time the solution became very dark. The mixture was rapidly cooled, diluted with water (80 ml), and extracted with chloroform (200 ml). The chloroform extracts were back-extracted twice with water (80 ml each) and the combined aqueous solutions were extracted three times with chloroform and then evaporated to dryness leaving 8.0 g of a dark oil. This was dissolved in a mixture of acetone (80 ml) and methanol (30 ml), filtered, and applied to a 12.5 × 12.5 cm column of silicic acid. Elution with acetone followed by charcoal treatment gave 1.34 g (50%) of **2** as a colorless, tlc homogeneous (ethyl acetate–acetone, 1:1) syrup that has not been obtained crystalline: λ_{max}^{MeOH} 260 mμ (ε 9500); ν_{max}^{KBr} 2120 cm^{-1}; nmr (DMSO-d_6) 3.62 (m, 2, $C_{5'}H_2$), 3.89 (m, 1, $C_{4'}H$), 4.03 (t, 1, $J_{1',2'} = J_{2',3'} =$ 5.5 Hz, $C_{2'}H$), 4.31 (t, 1, $J_{2',3'} = J_{3',4'} =$ 5.5 Hz, $C_{3'}H$), 5.67 (d, 1, $J_{5,6} =$ 8 Hz, C_5H), 5.90 (d, 1, $J_{1',2'} =$ 5.5 Hz, $C_{1'}H$), 7.90 ppm (d, 1, $J_{5,6} =$ 8 Hz, C_6H).

Anal. Calcd for $C_9H_{11}N_5O_5$: C, 40.15; H, 4.12; N, 26.01. Found: C, 39.97; H, 4.41; N, 26.15.

2'-Amino-2'-deoxyuridine (3).—A solution of **2** (1.34 g, 5 mmol) in methanol was vigorously stirred in a hydrogen atmosphere with 10% palladium-on-carbon catalyst (700 mg) for 40 min. The mixture was filtered and evaporated leaving 1.18 g (98%) of crystalline **3** with mp 192–193°. A sample recrystallized twice from ethanol had mp 197–198°: $\lambda_{max}^{H_2O}$ 261 mμ (ε 9500); ORD (H_2O) positive Cotton effect with a peak at 275 mμ (Φ −2000°), and a trough at 242 (Φ −8600°); nmr (DMSO-d_6) 3.62 (m, 2, $C_{5'}H_2$), 3.90 (br q, 1, $J_{4',5'} \simeq$ 4 Hz, $J_{3',4'} =$ 5 Hz, $C_{4'}H$), 4.03 (t, 1, $J_{1',2'} = J_{2',3'} =$ 5.5 Hz, $C_{2'}H$), 4.31 (br t, 1, $J_{2',3'} =$ 5.5 Hz, $J_{3',4'} =$ 5 Hz, $C_{3'}H$), 5.67 (d, 1, $J_{5,6} =$ 8 Hz, C_5H), 5.90 (*d*, 1, $J_{1',2'} =$ 5.5 Hz, $C_{1'}H$), 7.90 ppm (d, 1, $J_{5,6} =$ 8 Hz, C_6H).

Anal. Calcd for $C_9H_{13}N_3O_5$: C, 44.44; H, 5.39; N, 17.28. Found: C, 44.33; H, 5.44; N, 17.44.

2'-Dichloroacetamido-2'-deoxyuridine (5).—A solution of **3** (243 mg, 1 mmol) and methyl dichloroacetate (1 ml) in methanol (10 ml) was heated under reflux for 6 hr. Upon cooling, crystalline **5** was obtained and after recrystallization from ethanol the yield was 260 mg (74%) with mp 246–247°: $\lambda_{max}^{H_2O}$ 262 mμ (ε 9300); ORD (H_2O) positive Cotton effect with a peak at 277 mμ (Φ +14,700°), crossover at 258 mμ, and a trough at 240 mμ (Φ −16,400°); nmr (pyridine-d_5) 3.97 (q, 1, $J_{gem} =$ 12 Hz, $J_{4',5'a} =$ 3 Hz, $C_{5'a}H$), 4.12 (q, 1, $J_{gem} =$ 12 Hz, $J_{4',5'b} =$ 3 Hz, $C_{5'b}H$), 4.50 (br s, 1, $C_{4'}H$), 4.86 (br d, 1, $J_{2',3'} =$ 5.5 Hz, $J_{3',4'} \simeq$ 1 Hz, $C_{3'}H$), 5.32 (br h, 1, $J_{1',2'} = J_{2',NH} =$ 8 Hz, $J_{2',3'} =$ 5.5 Hz, $C_{2'}H$), 5.73 (d, 1, $J_{5,6} =$ 8 Hz, C_5H), 6.83 (d, 1, $J_{1',2'} =$ 8 Hz, $C_{1'}H$), 6.83 (s, 1, $COCHCl_2$), 8.37 (d, 1, $J_{5,6} =$ 8 Hz, C_6H), 9.60 ppm (br d, 1, $J_{2'NH} =$ 8 Hz, $NHCOCHCl_2$).

Anal. Calcd for $C_{11}H_{13}N_3O_6Cl_2$: C, 37.30; H, 3.70; N, 11.86; Cl, 20.03. Found: C, 37.40; H, 3.91; N, 11.61; Cl, 19.41.

2'-Acetamido-3',5'-di-*O*-acetyl-2'-deoxyuridine (6).—A solution of **3** (850 mg, 3.5 mmol), acetic anhydride (4 ml), and pyridine (2 ml) in anhydrous dimethylformamide (20 ml) was stored overnight at room temperature. After addition of methanol the solution was evaporated to dryness and the residue was reevaporated with methanol giving a crystalline residue that was recrystallized from methanol giving 1.16 g (90%) of **6** with mp 199–200°: λ_{max}^{MeOH} 259 mμ (ε 9600); ν_{max}^{KBr} 1755, 1710, 1685 cm^{-1}; nmr (DMSO-d_6) 1.81 (s, 3, NAc), 2.06 and 2.12 (s, 3, OAc), 4.26 (s, 3, $C_{4'}H$ and $C_{5'}H_2$), 4.73 (q, 1, $J_{1',2'} =$ 8.5 Hz, $J_{2',3'} =$ 6 Hz, $C_{2'}H$), 5.12 (br d, 1, $J_{2',3'} =$ 6 Hz, $J_{3',4'} =$ 1 Hz, $C_{3'}H$), 5.74 (d, 1, $J_{5,6} =$ 8 Hz, C_5H), 5.90 (d, 1, $J_{1',2'} =$ 8.5 Hz, $C_{1'}H$), 7.70 (d, 1, $J_{5,6} =$ 8 Hz, C_6H), 9.18 (br d, 1, $J_{2',NH} =$ 9 Hz, NHAc), 11.37 ppm (br s, 1, N^3H).

Anal. Calcd for $C_{15}H_{19}N_3O_8$: C, 48.78; H, 5.18; N, 11.37. Found: C, 48.88; H, 5.31; N, 11.48.

3',5'-Di-*O*-acetyl-2'-deoxy-2'-thioacetamido-4-thiouridine (7).—Phosphorus pentasulfide (440 mg, 2 mmol) and **6** (370 mg, 1 mmol) were dissolved in anhydrous pyridine and heated under reflux for 80 min. After cooling, the red solution was decanted from some insoluble material and evaporated to dryness. The residue was dissolved in chloroform and washed with water, 0.2 *N* sulfuric acid, and sodium bicarbonate prior to preparative tlc using ethyl acetate. Elution of the major fast-moving band gave 300 mg (~80%) of a yellow foam that was shown by tlc to have partially lost one of the *O*-acetyl groups. Reacetylation with acetic anhydride in pyridine for 1 hr gave homogeneous **7** as a noncrystalline yellow solid: λ_{max}^{MeOH} 268 mμ (ε 12,400), 330 (17,500); ν_{max}^{KBr} 1750, 1715, 1625 cm^{-1}; nmr ($CDCl_3$) 2.19 and 2.21 (s, 3, OAc), 2.54 (s, 3, CH_3CSNH), 4.40 (m, 3, $C_{4'}H$ and $C_{5'}H_2$), 5.55 (m, 1, $C_{2'}H$), 6.45 (d, 1, $J_{1',2'} =$ 9 Hz, $C_{1'}H$), 6.49 (d, 1, $J_{5,6} =$ 8 Hz, C_5H), 7.40 (d, 1, $J_{5,6} =$ 8 Hz, C_6H), 8.23 (br d, 1, $J_{2',NH} =$ 8 Hz, $NHCSCH_3$), 8.65 ppm (br s, 1, N^3H).

Anal. Calcd for $C_{15}H_{19}N_3O_6S_2$: C, 44.87; H, 4.76; N, 10.46; S, 15.97. Found: C, 44.61; H, 4.94; N, 9.82; S, 15.58.

2'-Amino-2'-deoxycytidine (8). A.—Thiation of **6** (1.11 g, 3 mmol) was carried out exactly as above and the crude, washed chloroform solution was evaporated to dryness. The residue was dissolved in saturated methanolic ammonia and heated in a stainless steel bomb at 120° for 40 hr. After filtration and evaporation of the solvent, the residue was dissolved in water (50 ml), stirred with Dowex AG-1 (OH^-) resin (15 ml), and filtered. Evaporation of the filtrate left a colorless syrup that crystallized giving 200 mg (24% from **6**) of **8**. After recrystallization from ethanol the melting point was 196–197°: $\lambda_{max}^{pH\ 2}$ 276 mμ (ε 11,900); $\lambda_{max}^{pH\ 12}$ 270 mμ (8200), 230 (7600); ORD (0.01 *N* HCl) positive Cotton effect with a peak at 290 mμ (Φ +6200°), crossover at 274 mμ, and a trough at 225 mμ (Φ −7400°); nmr (DMSO-d_6) 3.23 (q, 1, $J_{1',2'} =$ 7 Hz, $J_{2',3'} =$ 5 Hz, $C_{2'}H$), 3.55 (br s, 2, $C_{5'}H_2$), 3.85 (m, 2, $C_{3'}H$ and $C_{4'}H$), 5.67 (d, 1, $J_{1',2'} =$ 7 Hz, $C_{1'}H$), 5.71 (d, 1, $J_{5,6} =$ 7.5 Hz, C_5H), 7.12 (br s, 2, NH_2), 7.76 ppm (d, 1, $J_{5,6} =$ 7.5 Hz, C_6H).

Anal. Calcd for $C_9H_{14}N_4O_4$: C, 44.44; H, 6.21; N, 23.00. Found: C, 44.65; H, 6.01; N, 22.90.

B.—A solution of **9a** (0.45 mmol) and phosphorus pentasulfide (120 mg) in pyridine (20 ml) was heated under reflux for 3 hr. The mixture was evaporated, dissolved in ethyl acetate, washed with water, and evaporated to dryness. The residue was treated in a steel bomb with saturated methanolic ammonia at 120° for 2 days and worked up as in A giving 42 mg (39%) of **8**.

3',5'-Di-*O*-acetyl-2'-azido-2'-deoxyuridine (9a).—A solution of **2** (135 mg, 0.5 mmol) in dimethylformamide (5 ml) was treated overnight with acetic anhydride (1 ml) and pyridine (0.5 ml). The solvent was evaporated and a solution of the residue in chloroform was washed with water, dried, and purified by preparative tlc using ethyl acetate–ether (1:1). Elution of the main band gave 130 mg (73%) of **9a** as a white foam: λ_{max}^{MeOH} 259 mμ (ε 9200); ORD (MeOH) positive Cotton effect with a peak at 280 mμ (Φ +4200°), crossover at 268 mμ, and a trough at 245 mμ (Φ −9400°); nmr ($CDCl_3$) 2.11 and 2.18 (s, 3, OAc), 4.37 (m, 4, $C_{2'}H$, $C_{4'}H$ and $C_{5'}H_2$), 5.21 (m, 1, $C_{3'}H$), 5.78 (d, 1, $J_{5,6} =$ 8 Hz, C_5H), 5.88 (d, 1, $J_{1',2'} =$ 4.5 Hz, $C_{1'}H$), 7.48 ppm (d, 1, $J_{5,6} =$ 8 Hz, C_6H).

Anal. Calcd for $C_{13}H_{15}N_5O_7$: C, 44.19; H, 4.28; N, 19.82. Found: C, 44.06; H, 4.16; N, 19.63.

4-Ethoxy-1-(3,5-di-*O*-acetyl-2-azido-2-deoxy-β-D-ribofuranosyl)-2(1*H*)-pyrimidinone (10).—A solution of **9a** (354 mg, 1 mmol) in a mixture of chloroform (unpurified, 5 ml), dimethylformamide (0.05 ml), and thionyl chloride (0.8 ml) was heated under reflux for 6 hr at which point tlc (ethyl acetate–ether, 1:1) showed disappearance of the starting material and formation of a main, fast-moving product. Preparative tlc of the evaporated mixture using the above solvent gave a syrup (110 mg) that was crystallized from chloroform–hexane giving 25 mg (7%) of **10** with mp 109–110°. The mother liquors were then heated under reflux with ethanol for 7 hr, evaporated, and purified by tlc as above giving a further 45 mg (12%) of crystalline **10**: λ_{max}^{MeOH} 275 mμ; nmr ($CDCl_3$) 1.36 (t, 3, $J =$ 6.5 Hz, OCH_2CH_3), 2.10 and 2.16 (s, 3, OAc), 4.40 (m, 6, $C_{2'}H$, $C_{4'}H$, $C_{5'}H_2$, and OCH_2CH_3), 5.88 (d, 1, $J_{5,6} =$ 7.5 Hz, C_5H), 5.89 (d, 1, $J_{1',2'} =$ 3 Hz, $C_{1'}H$), 7.78 ppm (d, 1, $J_{5,6} =$ 7.5 Hz, C_6H).

Anal. Calcd for $C_{15}H_{19}N_5O_7$: C, 47.24; H, 5.02; N, 18.36. Found: C, 46.95; H, 4.83; N, 18.02.

3',5'-Di-*O*-acetyl-2'-azido-2'-deoxy-5-iodouridine (11a).—A solution of **9a** (700 mg, 2 mmol) in DMSO (20 ml) containing di-*n*-butyl disulfide (0.1 ml) was added slowly to a solution of *N*-iodosuccinimide (1.8 g, 8 mmol) in DMSO (20 ml) and kept at 20° for 24 hr. Tlc (chloroform–acetone, 4:1) showed incomplete reaction, and, after 24 and 48 hr, further portions of *N*-iodosuccinimide (1.8 g) and di-*n*-butyl disulfide (0.1 ml) were added. After dilution with ethyl acetate the solution was extracted with saturated aqueous sodium chloride, sodium bicarbonate, and

sodium thiosulfate. Preparative tlc using the above solvent gave 490 mg (51%) of **11** as a homogeneous syrup: λ_{max}^{MeOH} 282 mμ (ε 7500), 215 (9700); ν_{max}^{KBr} 2120 cm^{-1} (N_3); nmr ($CDCl_3$) 2.21 and 2.25 (s, 3, OAc), 4.33 (q, 1, $J_{1',2'}$ = 4 Hz, $J_{2',3'}$ = 6 Hz, $C_{2'}H$), 4.41 (m, 3, $C_{4'}H$ and $C_{5'}H_2$), 5.23 (m, 1, $C_{3'}H$), 5.93 (d, 1, $J_{1',2'}$ = 4 Hz, $C_{1'}H$), 7.97 ppm (s, 1, C_6H); mass spectrum (70 eV) *m/e* 479 (M^+), 451 (M − N_2), 409 (M − N_2 − C_2H_2O), 391 (M − AcOH), 242 (M − base), 238 (base + H), 214 (sugar − N_2), 172 (sugar − N_2 − C_2H_2O).

Anal. Calcd for $C_{13}H_{14}N_5O_7I$: C, 32.58; H, 2.94. Found: C, 32.95; H, 3.11.

2'-Amino-2'-deoxy-5-iodouridine (11b).—A solution of **11a** (420 mg, 0.87 mmol) and sodium borohydride (300 mg) in 2-propanol (60 ml) was heated under reflux for 3 days. After evaporation of the solvent the residue was dissolved in water, brought to pH 6 with acetic acid, evaporated, and repeatedly coevaporated with methanol. The final residue was dissolved in water and passed through a column containing Dowex 50 (H^+) resin (60 ml). The eluate and washings contained 2250 optical density units (262 mμ) of 2'-azidonucleosides. Elution with 1 *N* ammonium hydroxide gave 2000 optical density units (273 mμ) of 2'-aminonucleosides. After evaporation to dryness, this material (200 mg) was purified by preparative tlc using acetone giving two main bands. The slower band (70 mg) consisted of 2'-amino-2'-deoxyuridine, while the faster band contained 60 mg (18%) of **12** which was crystallized from methanol with mp 204.5–205.5°: $\lambda_{max}^{H_2O}$ 287 mμ (ε 7200), 216 (11,900); $\lambda_{max}^{pH\ 13}$ 277 mμ (ε 5500); ORD (H_2O) multiple Cotton effect with a peak at 280 mμ (Φ +3700°) a trough at 250 mμ (Φ +3200°), a peak at 217 mμ (Φ 14,400°), and crossover at 205 mμ; nmr (pyridine-d_5) 4.01 (q, 1, $J_{1',2'}$ = 6.5 Hz, $J_{2',3'}$ = 5 Hz, $C_{2'}H$), 4.07 (AB of ABM, 2, J_{gem} = 14 Hz, $C_{5'}H_2$), 4.62 (br q, 1, $J_{4',5'a}$ = $J_{4',5'b}$ = $J_{3',4'}$ = 3 Hz, $C_{4'}H$), 4.77 (q, 1, $J_{2',3'}$ = 5 Hz, $J_{3',4'}$ = 5 Hz, $J_{3',4'}$ = 3 Hz, $C_{3'}H$), 6.52 (d, 1, $J_{1',2'}$ = 6.5 Hz, $C_{1'}H$), 9.10 ppm (s, 1, C_6H).

Anal. Calcd for $C_9H_{12}N_3O_5I$: C, 29.28; H, 3.28; N, 11.38. Found: C, 28.86; H, 3.33; N, 11.29.

2'-Azido-3',5'-di-*O*-benzoyl-2'-deoxyuridine (9b).—A solution of **2** (950 mg, 3.5 mmol) and benzoyl chloride (1.4 g, 10 mmol) in pyridine (10 ml) was kept for 16 hr at 23°. After addition of water, the solution was diluted with ethyl acetate, extracted with sodium bicarbonate, dried, and evaporated leaving a brown syrup. Purification by preparative tlc using benzene–ethyl acetate (9:1) gave 1.22 g (60%) of the *N*^{2},3'-*O*,5'-*O*-tribenzoate (**9b**) as a homogeneous foam with λ_{max} 250 mμ (sh), 232, and unchanged in alkali: nmr ($CDCl_3$) 4.4–4.8 (m, 4, $C_{2'}$, $C_{3'}$, and $C_{5'}H$'s), 5.60 (t, 1, $J_{2',3'}$ = $J_{3',4'}$ = 5.5 Hz, $C_{3'}H$), 5.66 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 5.97 (d, 1, $J_{1',2'}$ = 4 Hz, $C_{1'}H$), 7.4–7.7 and 7.9–8.2 ppm (m, 16, aromatic and C_6H).

This compound (1.2 g) was dissolved in pyridine (10 ml) containing 2% water and heated under reflux for 1 hr. Evaporation to dryness, preparative tlc using ether–hexane (85:15) and crystallization from chloroform–hexane gave 735 mg (75%) of **9b** with mp 153–154°: λ_{max}^{MeOH} 256 mμ (ε 11,900), 231 (28,800); nmr ($CDCl_3$) 4.49 (q, 1, $J_{1',2'}$ = 4 Hz, $J_{2',3'}$ = 6 Hz, $C_{2'}H$), 4.6–4.8 (m, 3, $C_{4'}H$ and $C_{5'}H_2$), 5.63 (t, 1, $J_{2',3'}$ = $J_{3',4'}$ = 6 Hz, $C_{3'}H$), 5.64 (d, 1, $J_{5,6}$ = 8 Hz, C_5H), 6.04 (d, 1, $J_{1',2'}$ = 4 Hz, $C_{1'}H$), 7.4–7.7 and 8.0–8.2 ppm (m, 11, aromatic and C_6H).

Anal. Calcd for $C_{23}H_{19}N_5O_7$: C, 57.86; H, 4.01; N, 14.66. Found: C, 57.77; H, 4.06; N, 14.80.

Registry No. —**2**, 26929-65-7; **3**, 26889-39-4; **5**, 26889-40-7; **6**, 26889-41-8; **7**, 26929-67-9; **8**, 26889-42-9; **9a**, 26889-43-0; **9b**, 26889-44-1; **10**, 26889-45-2; **11a**, 26889-46-3; **11b**, 26889-47-4.

Macrocyclic Polyether Sulfides

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Macrocyclic polyether sulfides have been synthesized and some of their properties have been determined. These compounds contain two to four oxygen atoms and two to four sulfur atoms in the polyether–polysulfide ring. Formation of complexes of the macrocyclic polyether sulfides with alkali, alkaline earth, and silver cations is reported.

The preparation and properties of a number of macrocyclic polyethers derived from aromatic vicinal diols have been previously reported.[1] It was shown that certain of these compounds, particularly those containing five to ten oxygen atoms in the polyether ring, form stable complexes with cations including those of the alkali and alkaline earth metals and silver. In a continuation of this work, some macrocyclic polyethers in which two to four –O– linkages are replaced by –S– linkages were synthesized in order to determine the effects of this change on the complexing of cations. Differences were to be expected because oxygen is a smaller atom than sulfur, the C–O–C bond angle is greater than the C–S–C bond angle, and the electronegativity of oxygen is higher than that of sulfur which makes the C–S bond less ionic than the C–O bond. It is the purpose of this paper to report on the preparation of the macrocyclic polyether sulfides and to give a brief description of some of their properties.

4,7,10-Trioxa-1-thiacyclododecane, 4,10-dioxa-1,7-dithiacyclododecane, 4,7,13,16-tetraoxa-1,10-dithiacyclooctadecane, and 4,7,10,16,19,22-hexaoxa-1,13-dithiacyclotetracosane,[2] 1,3,5,7,9-oxatetrathiacyclodecane, and 1,3,5,7,9,11-oxapentathiacyclododecane[3] have been previously described, but their tendency to form complexes with cations is not mentioned.

The code letters and the structural formulas of the compounds described in this paper are shown in Figure 1. The digits within the diagrams indicate the total number of atoms in the polyether ring. The full names of the compounds and their preparation are given in the Experimental Section.

Results and Discussion

In general, the compounds were prepared by refluxing in 1-butanol under nitrogen cyclic vicinal mercaptophenol or dithiols with equivalent proportions of terminally substituted ether dichlorides and sodium hydroxide. The yields, melting points, and analytical data are shown in Table I. No attempt was made to maximize the yields or develop methods of recovery.

The infrared spectra of the compounds showed the

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