chloride reaction b, above. Treatment of *trans* **8** in thionyl chloride with hydrogen chloride opened the oxazoline to give chloro compound *erythro* **12**.

Attempted Opening of *cis* 8 with Hydrogen Chloride.—A cold $CDCl_3$ solution of *cis* **8** in an nmr probe was saturated with hydrogen chloride. The only observable change was a downfield shift of the H_A and H_B doublets (J = 11 cps) as a result of protonation. The spectrum remained essentially unchanged after 24 hr at 37°.

Registry No.—**1** (*erythro*), 19185-82-1; **1** (*threo*), 19185-83-2; **2** (*erythro*), 19185-84-3; **2** (*threo*), 19185-85-4; **3** (*erythro*), 19185-86-5; **3** (*threo*), 19202-70-1; **4** (*erythro*), 19185-38-7; **4** (*threo*), 19185-39-8; **5**, 19185-44-5; **6**, 19185-45-6; **7** (*trans*), 19185-46-7, **8** (*cis*), 19185-47-8; **8** (*trans*), 19185-48-9; **9** (*cis*;) 19185-49-0; **9** (*trans*), 19185-50-3; **10** (*cis*), 19185-51-4; **10** (*trans*), 19185-52-5; **11** (*erythro*), 19185-40-1; **11** (*threo*), 19185-41-2; **12** (*erythro*), 19185-42-3; **12** (*threo*), 19185-43-4; **13** (*erythro*), 19191-01-6; **14** (*erythro*), 19191-02-7; *threo*-O-acetyl-β-phenylserine methyl ester hydrochloride, 19191-04-9; *erythro*-O-acetyl-β-(*p*-nitrophenyl)serine methyl ester hydrochloride, 19191-05-0; thionyl chloride, 7719-09-7.

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The Reaction of Arsenic Trihalides with Nucleosides. Halomethylene Dimethylammonium Halide. A New Halogenating Agent for Nucleosides[1]

RICHARD F. DODS[2] AND JAY S. ROTH[3]

University of Connecticut, Section of Biochemistry and Biophysics, Storrs, Connecticut 06268

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The reaction of 2′,3′-O-isopropylideneuridine (**1**) and uridine (**6**) with arsenic trichloride and arsenic tribromide gave good yields of 5′-deoxy-5′-chloro(bromo)-2′,3′-O-isopropylideneuridine (**3a** and **b**) and 5′-deoxy-5′-chloro(bromo)uridine (**7a** and **b**) when carried out in N,N-dimethylformamide (DMF). Arsenic triiodide gave poor results. Specificity for the 5′ position was found in the case of uridine. Two new nucleoside halogenating agents, chloromethylenedimethylammonium chloride (**2a**) and bromomethylenedimethylammonium bromide (**2b**), were found to be the actual halogenating agents. These agents gave excellent halogenation at the 5′ position of both **1** and **6**. Comparison was made of the facility by which these chloro and bromo derivatives cyclized to 5′-O²-cyclo nucleosides **4** and **8**. Attempts at the synthesis of nucleoside 5′-arsenate **5** indicated that these compounds may be too unstable to be isolated.

In attempts at the synthesis of arseno nucleosides we have studied the reactions of arsenic trihalides with nucleosides. In our study it was found that the reaction of 2′,3′-O-isopropylideneuridine (**1**) and uridine (**6**) with arsenic trichloride and arsenic tribromide in anhydrous N,N-dimethylformamide (DMF) gave good yields of 5′-deoxy-5′-chloro(bromo)-2′,3′-O-isopropylideneuridine (**3a** and **b**) and 5′-deoxy-5′-chloro(bromo)-uridine (**7a** and **b**) (Scheme I). Arsenic triiodide gave poor results. Surprisingly the reaction of uridine with the arsenic trihalides gave a high degree of specificity for the 5′ position. However when N,N-dimethylacetamide (DMA) was used as the solvent in the reaction of $AsCl_3$ with uridine, 3′-deoxy-3′-chlorouridine (**9**) was formed in addition to **7a**.

Arsenic trihalides have not been known to serve as halogenating agents for alcohols. Instead they have been reported[4,5] to react with alcohols to form dichloroarsenite derivatives. However, DMF has been reported[6-8] to react with inorganic acid halides ($COCl_2$, $POCl_3$, PCl_3, and $SOCl_2$) to form an active intermediate chloromethylenedimethylammonium chloride (**2a**). Initially **2a** found use as a formylating agent for aromatic, heterocyclic, and ethylenic compounds. Nonetheless compound **2a** and its bromide analog (**2b**) have been reported[9] to be highly effective in replacing hydroxyl and related groups with halogen. A mechanism for the formation of **2a** from $SOCl_2$ and DMF has been reported.[10] The applicability of this mechanism to the reaction of arsenic trihalides and DMF has been indicated by the report[11] of the chloromethylation of naphthalene by $AsCl_3$ and paraformaldehyde. Thus it is proposed that arsenic trihalides react with DMF in a manner similar to $SOCl_2$.

On the basis of this information we have synthesized both **2a** and **2b** by the method of Bosshard, *et al.*,[10] and used them for the halogenation of **1** and **6**. In all cases paper chromatography and thin layer chromatography indicated a quantitative conversion into the corresponding 5′-deoxy-5′-halogeno nucleoside. Isolation and purification gave yields in the range of 80–90%. (See Table I.)

In the reactions of **2a** and **2b** with uridine, fast moving (R_f 0.80–0.85, paper chromatography) uv absorbing substances were found when the reaction mixture was not refluxed with NH_4OH. These rather unstable compounds gave a negative *cis*-glycol test,[12]

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(3) Recipient of Career Award RC 31-63 from the National Cancer Institute, National Institutes of Health.

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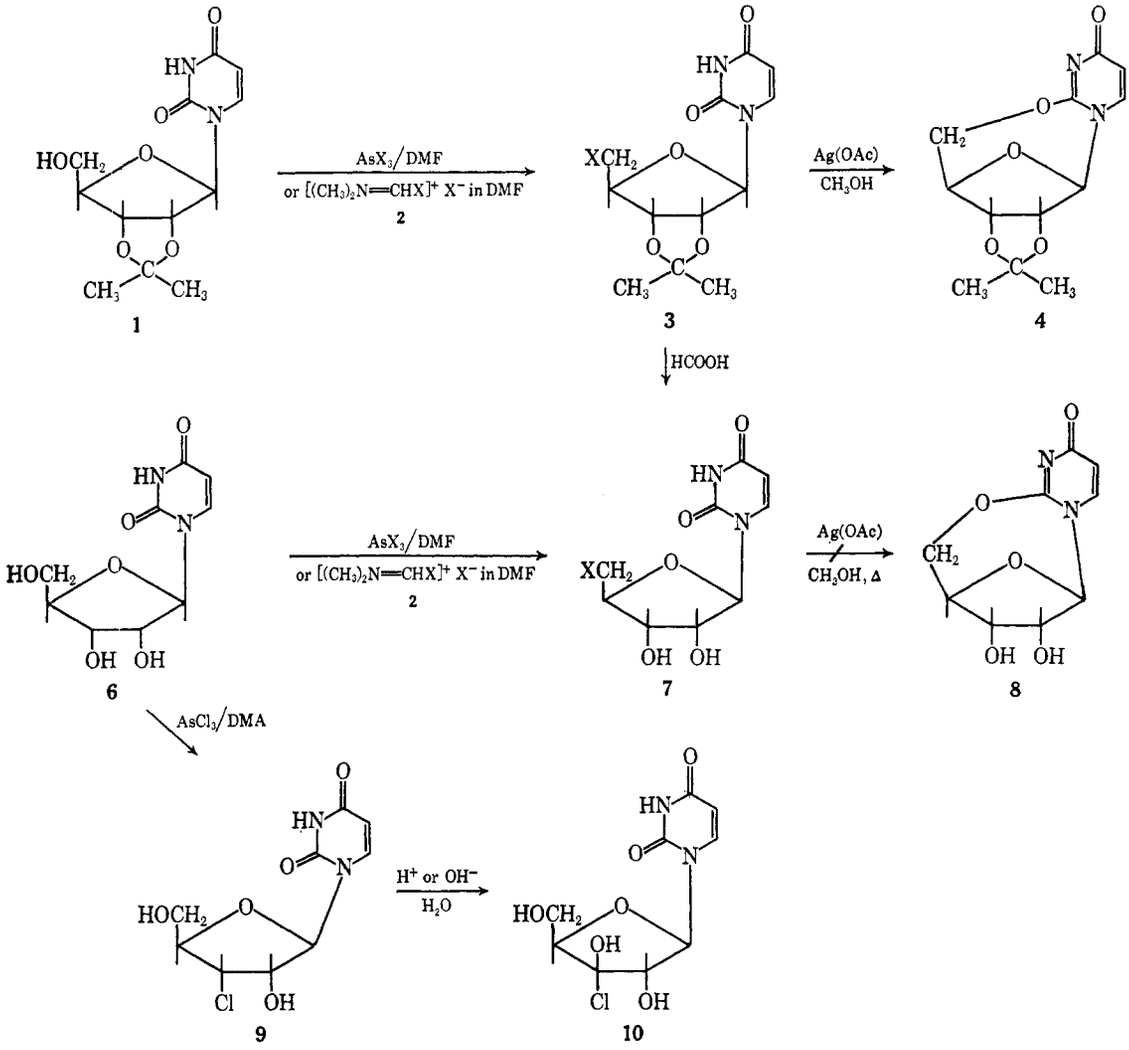
SCHEME I



a, X = chloro
b, X = bromo
c, X = iodo

and a positive ferric hydroxamate test[13] and were rapidly converted on treatment with base into the desired halogenouridine compound. We believe these substances to be the 2′,3′-O-diformate esters of **7a** and **7b.** Compound **2a** has been reported[14] to react with both primary and secondary alcohols to give formates.

It was also interesting to study the ease with which the 5′-deoxy-5′-halogenated derivatives synthesized in this study could be cyclized to the 5′-O^2-cyclo nucleosides. The results of this experiment appear in Table II. Only the bromo and iodo derivatives reacted under the conditions used. It was interesting to note that the product of the cyclization reaction of **7b** was O^2-methyluridine. Nevertheless the formation of O^2-methyluridine must have proceeded *via* a 5′-O^2-cyclo intermediate. This suggests that the difference between **7b** and its 2′,3′-acetonide **3b** in cyclo nucleoside formation lies in the stability of the corresponding cyclo nucleoside. 5′-O^2-cyclouridine is less stable and therefore more reactive with the solvent, methanol, than 2′,3′-O-isopropylidene-5′-O^2-cyclouridine.

Codington, *et al.*,[15] reported 2.5-mμ hypsochromic shifts relative to uridine for their 2′-deoxy-2′-halogenouridine compounds. The shifts were the same regardless of which halogen was present. In the present study 1.0-mμ hypsochromic shifts were found in the 5′-deoxy-5′-halogenouridine series. However the 5′-deoxy-5′-halogeno-2′,3′-O-isopropylideneuridine compunds showed hypsochromic shifts whose magnitude depended on the nature of the halogen present.

Recently reports have appreared which indicate the possible formation of nucleoside arsenates in certain biological systems.[16,17] As indicated earlier the original aim of this study was the chemical synthesis of arsenonucleosides. In the previously described arsenic trihalide reactions in DMF and DMA there were no indications that such a derivative had formed. Reactions of arsenic trihalides with **1** and **6** in solvents other than DMF anf DMA did not produce the desired arseno nucleosides. Since cyclo nucleosides have been

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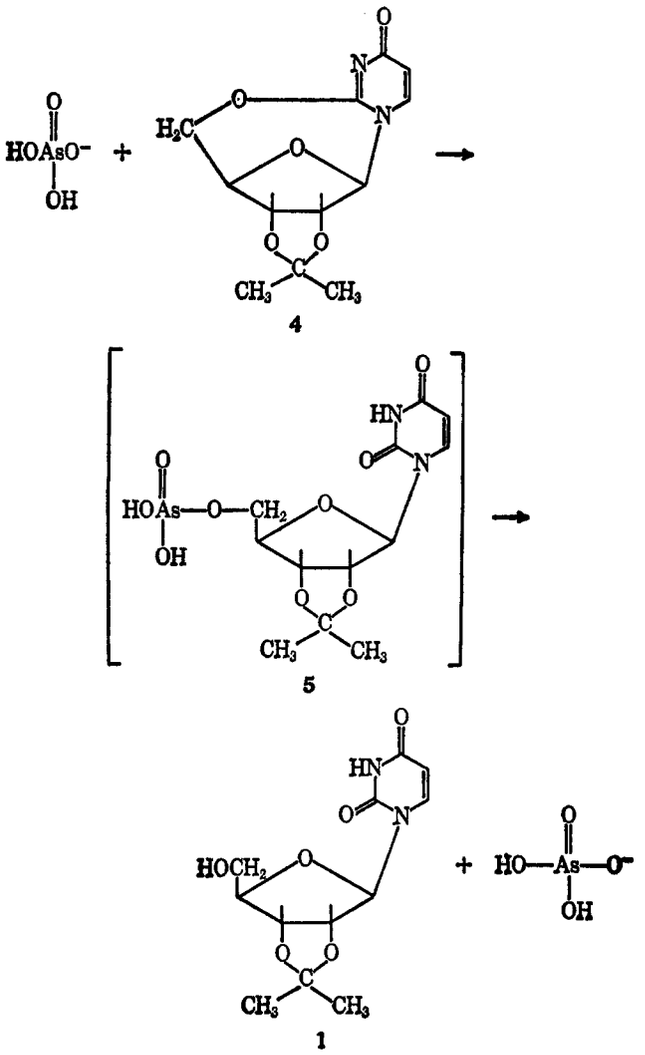
TABLE I

REACTIONS OF ARSENIC TRIHALIDES AND HALOMETHYLENEDIMETHYLAMMONIUM HALIDES WITH NUCLEOSIDES

Nucleoside, g (mmol)	Halogenating agent, g (mmol)	Solvent DMF, ml	Temp, °C	Time, hr	Product	R_f (paper)	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % X	Calcd, % N	Found, % C	Found, % H	Found, % X	Found, % N
1, 0.500 (1.76)	$AsCl_3$, 0.360 (2.00)	15	160	0.5	**3a**	0.80	52	174–178	$C_{12}H_{15}ClN_2O_5$	47.60	5.03	11.71	9.58	47.55	4.92	11.71	9.04
1, 0.500 (1.76)	$AsBr_3$, 0.630 (2.00)	15	90	48	**3b**	0.84	62	179–181	$C_{12}H_{15}BrN_2O_5$	41.50	4.32	23.20	8.07	41.62	4.46	23.28	8.07
6, 2.00 (8.20)	$AsCl_3$, 1.73 (9.61)	25	160	4	**7a**	0.42	51	170–172	$C_9H_{11}ClN_2O_5$	41.15	4.22	13.50	10.67	40.96	4.29	13.50	10.75
6, 2.00 (8.20)	$AsBr_3$, 3.01 (9.56)	25	160	2	**7b**	0.47	40	172–175	$C_9H_{11}BrN_2O_5$	35.20	3.64	26.03	9.13	35.25	3.60	26.15	9.13
1, 0.500 (1.75)	**2a**, 0.230 (1.81)	10	90	1.5	**3a**	0.80	90	175–177									
1, 0.50 (1.75)	**2b**, 0.391 (1.80)	10	90	1.5	**3b**	0.84	85	179–181									
6, 2.00 (8.20)	**2a**, 1.04 (8.19)	20	120	8	**7a**	0.42	81	170–172									
6, 2.00 (8.20)	**2b**, 1.78 (8.20)	20	120	8	**7b**	0.47	78	173–175									

SCHEME II



reported[18] to show a high degree of reactivity toward certain nucleophiles including phosphates, an attempt was made at the synthesis of 2′,3′-O-isopropylideneuridine 5′-arsenate (**5**) by reaction of arsenate with cyclo nucleoside **4** (Scheme II). Arseno nucleoside **5** was rapidly hydrolyzed by traces of water during attempts at isolation. The inability to synthesize an arseno nucleoside is consistent with reports of the instability of sugar arsenates.[19]

Experimental Section[20]

Synthesis of 2a and 2b.[10]—Equimolar proportions of dry DMF and $SOCl_2$ or $SOBr_2$ were allowed to react together at room tem-

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TABLE II

EASE OF CYCLIZATION AND ULTRAVIOLET SPECTRA OF 5′-DEOXY-5′-HALOGENO NUCLEOSIDES

Compound	Cyclization[a]	Ultraviolet spectra: pH 1–7 Max	ϵ_{max}[b]	Min	ϵ_{min}[b]	pH 12 Max	Min
Uridine series							
5′-Deoxy-5′-fluoro-[c]		261		230		262	242
7a	Unchanged	207 261	9.99 10.3	230	2.46	262	242
7b	Forms of O^2-methyluridine	207 261	10.0 10.7	230	2.68	262	242
5′-Deoxy-5′-iodo-[d]	*e*	261		230			
2′-3′-O-Isopropylideneuridine series							
3a	Unchanged	260.5	11.5	230	2.73	260	240
3b	100% conversion into **4** in 40 min	258	11.8	230	6.45	259	240
3c[f]	100% conversion into **4** in 10 min	258		229		258	240

[a] Cyclization of the halo nucleosides to **4** or **8** was carried out by the reaction of 13 μmol of halogeno nucleoside with 56 μmol of silver acetate in 1.20 ml of dry methanol at 67°. The reactions were followed by tlc using butanol saturated with water as solvent and HF_{254} silica gel as the stationary phase. [b] ϵ_{max} and ϵ_{min} (10^{-3}) were determined in water (pH 5). [c] H. M. Kissman, and M. J. Weiss, *J. Amer. Chem. Soc.*, **80**, 5559 (1958). [d] D. M. Brown, A. R. Todd, and S. Varadarajan, *J. Chem. Soc.*, **868** (1967). [e] Forms a compound "too insoluble to permit complete purification." [f] Sample kindly supplied by Dr. B. Otter.

perature for 30 min. The reaction mixture was evaporated to dryness (40°). The residue was washed thoroughly with dry ether and again dried *in vacuo*.

Isolation and Purification of 3a and 3b.—The solution was cooled and then made basic with 1 *N* NH_4OH. The reaction mixture was refluxed 0.5 hr and then evaporated to dryness *in vacuo*. Water (15 ml) was added to the residue and the water suspension was extracted with $CHCl_3$. The $CHCl_3$ extracts were combined, extracted with water, and then dried with Na_2SO_4. After filtration from the drying agent the solution was evaporated to 5 ml. The addition of hexane to a point of slight turbidity resulted in the crystallization of **3a** or **3b**. The solid was recrystallized twice from $CHCl_3$–hexane.

Isolation and Purification of 7a and 7b.—The reaction flask was cooled and its contents were evaporated to a brown oil *in vacuo*. Water (20 ml) was added to the oil and the resulting mixture was made basic with 1 *N* NH_4OH. The solution was refluxed 0.5 hr and then evaporated *in vacuo* to yield a solid which was then dissolved in 100 ml of methanol. Norit A (neutral), 2 g, was added and the mixture stirred at 27° for 3 hr before filtration. The filtrate was evaporated *in vacuo* to 10 ml. The solid deposited at this time was filtered from the solution and did not contain any nucleoside. The liquid was thick layer chromatographed using four plates. Compound **7a** appeared at R_f 0.65 and **7b** at 0.70. The 0.65 band (or 0.70 band) was removed from the plates and the silica gel was then extracted with boiling methanol. The suspension was filtered and the filtrate was then evaporated to 10 ml. The solution was allowed to stand for 3 days at 10° whereupon a white precipitate of product was deposited. The supernatant was evaporated to 5 ml and allowed to stand for 1 day at 10°. An additional yield of product precipitated. The solid was recrystallized twice from acetone.

Synthesis of 3′-Deoxy-3′-chlorouridine (9).—The procedure employed was the same as that used in the reaction of **6** and $AsCl_3$ except that 25 ml of dry DMA was used and the reaction was carried out at 127° for 12 hr. Thick layer chromatography gave four uv absorbing bands at R_f 0.20, 0.43, 0.54 and 0.80. Paper chromatography of the same methanol solution gave the following uv absorbing bands: 0.26 (10%), 0.36–0.42 (60%), 0.52 (5%), and 0.76 (25%). Each tlc band was removed and compared by paper chromatography and uv absorption spectrum to a pure sample of possible reaction components. As anticipated the tlc band at 0.20 was found to be **6**. The band at 0.43 resolved, upon paper chromatography, into two uv absorbing spots, 0.36 and 0.42, uracil and **7a**, respectively. The band at 0.52 was probably 1-β-D-xylofuranosyluracil (**10**) as indicated by its uv spectrum, a negative *cis*-glycol test and its electrophoretic mobility.[21] The band at 0.80 was removed and extracted with 100 ml of boiling methanol. The mixture was filtered and the filtrate was evaporated to dryness. An analytical sample of this rather unstable product was obtained by recrystallization from methanol. A yield of 430 mg (20%) was obtained, mp 177–179°, R_f (paper) 0.78. Compound **9** gave a negative *cis*-glycol test and could be converted into 10 by 6 *N* HCl or 6 *N* NaOH on standing at 25° for 24 hr: uv spectrum, $\lambda_{max}^{CH_3OH}$ 258 (ε 7400), $\lambda_{min}^{CH_3OH}$ 229.

Anal. Calcd for $C_9H_{11}ClN_2O_5$: C, 41.15; H, 4.22; Cl, 13.50; N, 10.67. Found: C, 41.25; H, 4.30; Cl, 13.70; N, 9.70.

Attempts at the Synthesis of Arseno Nucleosides. A. The Reaction of Monopyridinium Arsenate with 5′-O^2-Cyclo-2′,3′-O-isopropylideneuridine (4).—Arsenic acid (1.10 ml of a 4.16 mg/ml aqueous solution) was evaporated to dryness *in vacuo* and then further dried by evaporation thrice with 2 ml of dry pyridine. Dry DMA (2 ml) was added and the mixture evaporated to 0.2 ml. In a second test tube, 4 mg (0.0150 mmol) of **4** was dried by evaporation with dry pyridine thrice. Under a stream of N_2 0.20 ml of dry DMA was added to the nucleoside. The flask was then evacuated, filled with N_2 and immediately sealed. The solution was maintained at 25° for 3 hr. A sample removed for paper chromatography showed that **4** was completely converted into **1**. In a control experiment the above steps were followed exactly as described except that water (1 ml) was used instead of arsenic acid. Paper chromatography showed that there had been no conversion of **4** into **1**.

B. The Reaction of Morpholine-N,N′-dicyclohexylcarboxamidinium Arsenate with 4.—Equimolar quantities (0.0134 mmol) of morpholine-N,N′-dicyclohexylcarboxamidinium arsenate and **4** were allowed to react in 0.20 ml of dry DMA at 25° for 3 hr. A control solution containing morpholine-N,N′-dicyclohexylcarboxamidine,[22] **4**, and DMA but no arsenate was also allowed to stand at 25° for 3 hr. Paper chromatography of the two reaction solutions showed conversion of **4** into **1** only in the reaction containing arsenate.

Registry No.—**3a**, 19556-51-5; **3b**, 19556-52-6; **3c**, 14671-65-9; **7a**, 19556-54-8; **7b**, 19556-55-9; **9**, 18810-36-1.

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