The Use of β,β,β-Tribromoethyl Chloroformate for the Protection of Nucleoside Hydroxyl Groups

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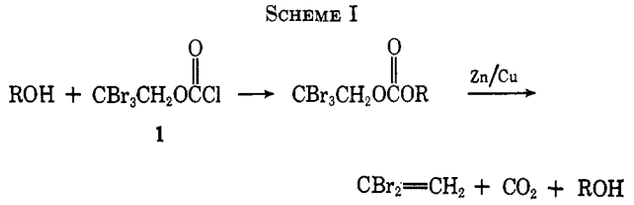
β,β,β-Tribromoethyl chloroformate (1) has been used to protect the primary or secondary hydroxyl groups of nucleosides and nucleoside derivatives. The β,β,β-tribromoethoxycarbonyl compounds were produced rapidly and generally in good yields. Both the 3′- and 5′-mono-β,β,β-tribromoethoxycarbonyl derivatives of thymidine and N-benzoyldeoxycytidine have been prepared. The β,β,β-tribromoethoxycarbonyl group was stable under acidic conditions but could be rapidly removed using a zinc–copper couple in a suitable solvent. Two types of derivative were obtained from the reaction of 1 with 5′-O-trityluridine: a 2′,3′-di-O-β,β,β-tribromoethoxycarbonyl compound and a 2′,3′-cyclic carbonate. Attempts to obtain a 2′- or 3′-mono-β,β,β-tribromoethoxycarbonyl derivative led to the production of uridine 2′,3′-cyclic carbonate. The reaction of 2′,3′-O-isopropylideneadenosine with 1 gave products corresponding to both N and O substitution.

The sensitivity of many compounds in the nucleoside and nucleotide field makes it desirable to use protecting groups which can be removed under relatively mild conditions. Primary hydroxyl groups have been protected as their *p*-methoxy-substituted trityl esters,[1] and 2′,3′-*cis*-diols have been protected by acetal,[1-3] cyclic carbonate,[4,5] or ortho ester formation.[6,7] Hydroxyl groups have also been protected by acylation,[8] by acetal formation,[9,10] and by alkoxy- or aryloxycarbonylation.[5,11] All these protecting groups could be removed with either acidic or basic treatment. More specific conditions have been employed for the removal of some hydroxyl protecting groups: 2,4-dinitrobenzenesulfenyl substituents have been removed with thiophenol,[12] dihydrothiophene adducts with silver ion,[13] and β-benzoylpropionyl groups with buffered hydrazine.[14]

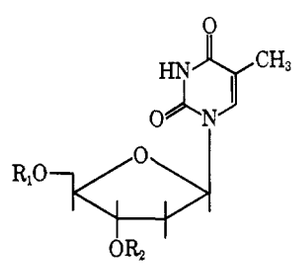
This paper describes the use of the generally applicable β,β,β-tribromoethoxycarbonyl group, a protecting group which is susceptible to nonhydrolytic removal. β,β,β-Tribromoethyl chloroformate (**1**)[15] reacted smoothly with primary and secondary hydroxyl groups of nucleosides and nucleoside derivatives, generally within 1 hr at 0° in anhydrous pyridine. The products were isolated either by crystallization or by silica column chromatography. The β,β,β-tribromoethoxycarbonyl group could be removed by a β-elimination process using a zinc–copper couple (Scheme I).

Amino compounds have been successfully protected using the 2-iodoethoxycarbonyl group, the removal of which could be accomplished by treatment with zinc dust in methanol by a similar β-elimination process.[16] Carboxylic and phosphoric acids have also been regenerated from their β,β,β-trichloroethyl esters by treatment with zinc dust or a zinc–copper couple.[17,18] A preliminary account of the use of the closely similar β,β,β-trichloroethoxycarbonyl group has also been reported.[19]

Scheme I



Treatment of thymidine with 1 equiv of **1** yielded the 5′-β,β,β-tribromoethoxycarbonyl compound **2** which was isolated by crystallization in 42% yield. The disubstituted compound **3** was also produced when thymidine was treated with 2 equiv of **1**, but, under these conditions, no trace of the mono-3′-β,β,β-tribromoethoxycarbonyl derivative could be found. The



2, R_1 = CBr_3CH_2OCO; R_2 = H
3, R_1 = CBr_3CH_2OCO; R_2 = CBr_3CH_2OCO
4, R_1 = CBr_3CH_2OCO; R_2 = CH_3CO
5, R_1 = H; R_2 = CH_3CO
6, R_1 = $(C_6H_5)_3C$; R_2 = H
7, R_1 = $(C_6H_5)_3C$; R_2 = CBr_3CH_2OCO
8, R_1 = H; R_2 = CBr_3CH_2OCO
9, R_1 = CH_3CO; R_2 = CBr_3CH_2OCO
10, R_1 = CH_3CO; R_2 = H
11, R_1 = $(C_6H_5)_2C$; R_2 = $(C_2H_5)_2NCO$
12, R_1 = CCl_3CH_2OCO; R_2 = CH_3CO

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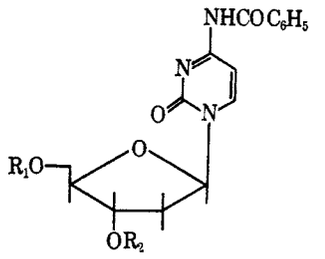
presence of the β,β,β-tribromoethoxy group in all of the β,β,β-tribromoethoxycarbonyl compounds was readily detected by nmr spectroscopy, since the methylene hydrogens of each group gave rise to a sharp singlet in the region δ 4.8–5.1. Compound **2** was converted into its 3′-acetate **4**, which was treated with a zinc–copper couple in acetic acid, and 3′-O-acetylthymidine (**5**) was isolated in 75% yield. Ethanol and N,N-dimethylformamide (DMF) were also suitable as solvents for the removal of the β,β,β-tribromoethoxycarbonyl group, although in these solvents the elimination was appreciably slower. The acetate **5** was also converted into **4** in good yield by treatment with **1**. These interconversions demonstrate that the β,β,β-tribromoethoxycarbonyl group in compound **2** is located on the 5′-carbon atom.

5′-O-Tritylthymidine (**6**) reacted with **1** very readily to give the 3′-β,β,β-tribromoethoxycarbonyl derivative **7**. Detritylation of **7** was carried out with 80% aqueous acetic acid for 35 min at 100°, and the products were isolated by silica column chromatography. The main product, 3′-O-β,β,β-tribromoethoxycarbonylthymidine (**8**) was obtained in 80% yield, and a minor product, which was isolated in 4% yield, was identified as its 5′-acetate **9**. Treatment of thymidine under the same conditions produced only traces of acetylated species after 35 min. The yield of the acetate **9** from **7** was increased to 20% by the use of a longer reaction time. Treatment of **8** with acetic anhydride in pyridine also yielded **9**, which was converted into 5′-O-acetylthymidine (**10**) using a zinc–copper couple. The reactivity of alkoxycarbonyl groups toward basic reagents was illustrated by the reaction of **7** with diethylamine. At room temperature the diethyl carbamate **11** was obtained in 57% yield, and was readily identified by the presence of signals due to two ethyl groups in its nmr spectrum. In order to compare the ease of removal of the β,β,β-tribromoethoxycarbonyl group with the published β,β,β-trichloroethoxycarbonyl group,[19] 3′-O-acetyl-5′-O-β,β,β-trichloroethoxycarbonylthymidine (**12**) was prepared from the reaction of **5** with β,β,β-trichloroethyl chloroformate.[20] Compounds **4** and **12** were treated with a zinc–copper couple in aqueous acetic acid and aliquots were removed at intervals and examined by thin layer chromatography. The removal of the β,β,β-tribromoethoxycarbonyl group was complete in 20 min, as contrasted with the β,β,β-trichloroethoxycarbonyl group which required 3.5 hr for its complete removal under the same conditions. The difference in reactivity can be attributed to the relatively greater polarizability of the bromine atom.

The reaction of deoxycytidine with **1** produced a mixture of at least five components, the separation of which was not attempted. N-Benzoyldeoxycytidine, however, reacted smoothly with **1** to give the 5′-β,β,β-tribromoethoxycarbonyl compound **13** and the 3′,5′-di-O-β,β,β-tribromoethoxycarbonyl derivative **14**.

Compound **13** was converted into its 3′-acetate **15** by treatment with acetic anhydride in pyridine. The synthesis of **15** was also accomplished by another route. 3′-O-Acetyl-N-benzoyldeoxycytidine (**16**) was prepared from N-benzoyldeoxycytidine by sequential

(20) Thanks are extended to Mr. O. Keller of these laboratories for the preparation of β,β,β-trichloroethyl chloroformate and compound **12**.

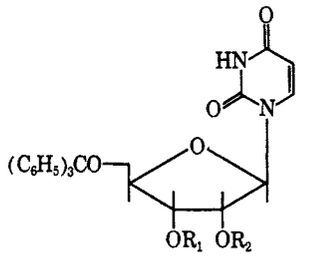


13, R_1 = CBr_3CH_2OCO; R_2 = H
14, R_1 = CBr_3CH_2OCO; R_2 = CBr_3CH_2OCO
15, R_1 = CBr_3CH_2OCO; R_2 = CH_3CO
16, R_1 = H; R_2 = CH_3CO
17, R_1 = H; R_2 = CBr_3CH_2OCO
18, R_1 = $CH_3OC_6H_4(C_6H_5)_2C$; R_2 = H

mono-*p*-methoxytritylation, acetylation, and removal of the mono-*p*-methoxytrityl group. The 3′-acetate **16** was then treated with **1** and the 5′-O-β,β,β-tribromoethoxycarbonyl compound **15** was formed in good yield. N-Benzoyl-3′-O-β,β,β-tribromoethoxycarbonyldeoxycytidine (**17**) was prepared by treatment of N-benzoyl-5′-O-mono-*p*-methoxytrityldeoxycytidine (**18**) with **1**, followed by removal of the trityl group using aqueous acetic acid. No acetylation was detected under these conditons, in contrast to the corresponding reaction of **7**. The removal of the β,β,β-tribromoethoxycarbonyl group was less satisfactory in the N-benzoyldeoxycytidine series. The reaction of **17** with a zinc–copper couple gave N-benzoyldeoxycytidine in only 30% yield, and a study on the reaction of **13** showed that a substantial loss of ultraviolet-absorbing material occurred within 15 min in 90% acetic acid. This material could not be recovered by thorough extraction of the zinc–copper couple. Treatment of N-benzoyldeoxycytidine under the same conditions resulted in a similar loss of ultraviolet-absorbing material. This reaction is being studied further, and the results will be reported at a later date.

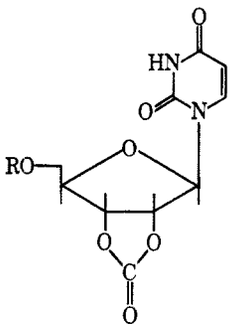
To circumvent this difficulty, an attempt was made to use iodide ion for the removal of a β,β,β-tribromoethoxycarbonyl substituent. Compound **2** was treated with sodium iodide in DMF at 100°, and aliquots were removed at intervals and examined by paper and thin layer chromatography. Although the starting material had disappeared after 3.5 hr, the major product was different from thymidine.

In the ribose series, 5′-O-trityluridine (**19**) was treated with 1.5 equiv of **1**, and two products were



19, R_1 = H; R_2 = H
21, R_1 = CBr_3CH_2OCO; R_2 = CBr_3CH_2OCO
22, R_1 = H; R_2 = $(C_6H_5)_3C$
23, R_1 = CBr_3CH_2OCO; R_2 = $(C_6H_5)_3C$

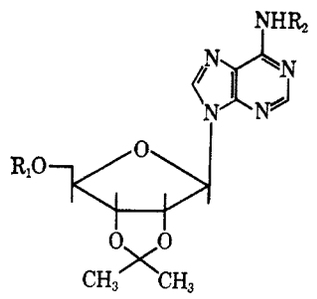
isolated. These were 5′-O-trityluridine 2′,3′-cyclic carbonate (**20**) and 2′,3′-di-O-β,β,β-tribromoethoxycarbonyl-5′-O-trityluridine (**21**).



20, R = $(C_6H_5)_3C$
24, R = H

Compound **20** was presumably formed by cyclization of a mono-β,β,β-tribromoethoxycarbonyl derivative, although no compound of this type could be detected, even when the experiment was repeated using a smaller proportion of **1**. In an attempt to isolate a mono-β,β,β-tribromoethoxycarbonyl derivative, 2′,5′-di-O-trityluridine (**22**)[21] was treated with **1**, and the 3′-β,β,β-tribromoethoxycarbonyl compound **23** was obtained. This product was easily reconverted into **22** using a zinc–copper couple in 90% aqueous acetic acid at room temperature, no detritylation being detected under these conditions. Treatment of **23**, however, with 80% aqueous acetic acid at 100° removed both trityl groups with concomitant cyclization of the β,β,β-tribromoethoxycarbonyl substituent, and uridine 2′,3′-cyclic carbonate (**24**) was obtained in good yield. The cyclic carbonates **20** and **24** were identical with samples prepared by the method of Letsinger and Ogilvie.[5]

2′,3′-O-Isopropylideneadenosine (**25**) was treated with **1** and two mono-β,β,β-tribromoethoxycarbonyl derivatives were isolated. The major product was identified as the urethan **26**, and the minor component was found to be the 5′-β,β,β-tribromoethoxycarbonyl derivative **27**. In addition, two di-β,β,β-tribromoethoxycarbonyl compounds were isolated, but the locations of the β,β,β-tribromoethoxycarbonyl substituents in these derivatives were not identified.



25, R_1 = H; R_2 = H
26, R_1 = H; R_2 = CBr_3CH_2OCO
27, R_1 = CBr_3CH_2OCO; R_2 = H

The β,β,β-tribromoethoxycarbonyl derivatives were prepared by dissolution of **1** in DMF at 0° and immediate addition of this solution to the nucleoside in pyridine. Direct addition of **1** to the nucleoside solution produced a gum, presumably a complex of **1** with pyridine, which dissolved very slowly, and longer times were necessary for complete reaction. Although **1** reacted vigorously and exothermically with DMF at room temperature, with the production of carbon dioxide and dimethylamine hydrochloride, at 0° this reaction was appreciably slower. DMF could therefore be satisfactorily used in the preparation of β,β,β-tribromoethoxycarbonyl derivatives, providing that the solution of **1** was immediately added to the nucleoside in pyridine. The use of chromatographic methods has shown that, in some cases, complete reaction occurred when only 1 equiv of **1** was used. Thus, under these conditions, the decomposition of **1** in DMF has been reduced to negligible proportions.

(21) N. C. Yung and J. J. Fox, *J. Amer. Chem. Soc.*, **83**, 3060 (1961).

Experimental Section[22]

β,β,β-Tribromoethyl Chloroformate (**1**).—This compound was prepared from the reaction of β,β,β-tribromoethanol with phosgene in benzene, using pyridine as the catalyst, bp 47–50° (0.05 mm) [lit.[15] bp 103° (10 mm)]. β,β,β-Trichloroethyl chloroformate was prepared in the same way, bp 48–50° (6 mm) [lit.[19] bp 75–76° (60 mm)].

5′-O-β,β,β-Tribromoethoxycarbonylthymidine (**2**).—A freshly prepared 0° solution of **1** (0.73 ml) in DMF (5 ml) was added to a 0° solution of thymidine (1.2 g) in pyridine (20 ml) and the mixture was stirred at 0° for 80 min. Water (0.5 ml) was added, and the solution was evaporated to dryness and dissolved in chloroform. The chloroform solution was washed three times with water, dried (Na_2SO_4), and evaporated. Crystallization from ethyl acetate–hexane gave 1.15 g (42%) of **2**: mp 96–99°; uv max (CH_3OH), 265 mμ (ε 9220); ir ($CHCl_3$), 1760 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{15}Br_3N_2O_7$: C, 28.33; H, 2.72; Br, 43.53; N, 5.09. Found: C, 28.60; H, 2.73; Br, 43.45; N, 4.88.

3′,5′-Di-O-β,β,β-tribromoethoxycarbonylthymidine (**3**).—The conditions employed were those for the preparation of **2**, except for the use of 1.5 ml of **1**. After 2 hr at 0°, water (2 ml) was added. The solution was evaporated, dissolved in chloroform, and washed and dried as before; the product (4.3 g) was applied to a silica column (230 g) and eluted with chloroform–ethyl acetate (2:1). In addition to **2**, 1.25 g (45%), compound **3**, 1.64 g (38%), was obtained as a foam: uv max (CH_3OH), 261 mμ (ε 9600); ir (KBr), 1750 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{16}Br_6N_2O_9$: C, 22.34; H, 1.86; Br, 55.78; N, 3.26. Found: C, 22.43; H, 2.06; Br, 55.73; N, 3.17.

3′-O-Acetyl-5′-O-β,β,β-tribromoethoxycarbonylthymidine (**4**).

A. From 3′-O-Acetylthymidine (**5**).—A solution of **5** (1.14 g) in pyridine (10 ml) was treated with a freshly prepared solution of **1** (1.6 ml) in DMF (10 ml) for 30 min at 0°. Water (2 ml) was added, and the product was evaporated to a syrup (4.5 g) which was applied to a silica column (250 g). Elution with chloroform–ethyl acetate (2:1) gave 1.43 g (60%) of **4**: mp 153–154°; uv max (CH_3OH), 265 mμ (ε 9560); ir ($CHCl_3$), 1730, 1760 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{17}Br_3N_2O_8$: C, 30.38; H, 2.87; Br, 40.45; N, 4.73. Found: C, 30.11; H, 3.03; Br, 40.36; N, 4.59.

B. From 2.—A solution of **2** (97 mg) in pyridine (2 ml) was treated with acetic anhydride (1 ml) for 17 hr at 0° and the solution was poured into ice–water (1 l.). The solid was collected by centrifugation, washed with cold water, dried, and recrystallized from ethyl acetate–hexane to give 72 mg (69%) of **4**, mp 153–154° alone and on admixture with the sample prepared from **5**.

Removal of the β,β,β-Tribromoethoxycarbonyl Group from 4.—A solution of **4** (400 mg) in acetic acid (7 ml) was stirred with a zinc–copper couple[23] (400 mg) for 2 hr. The couple was removed by filtration and washed with hot methanol, and the fil-

(22) Pyridine and DMF were dried by storage over Linde Molecular Sieve Type 4A. Silica column chromatography was carried out using Merck silica gel 0.05–0.2 mm. Nuclear magnetic resonance spectra were obtained using a Varian A-60 or HA-100 spectrometer, ultraviolet spectra were obtained with a Carey Model 14 instrument, and infrared spectra were determined with a Beckman IR-5 or IR-9. Melting points were determined with a Thomas–Hoover apparatus.

(23) Obtained from Alfa Inorganics Inc. The couple was activated by brief treatment with boiling acetic acid, washed with acetic acid and then ether, dried, and stored under nitrogen.

trate and washings were evaporated to dryness. The residue was extracted with hot methylene chloride and the extracts were evaporated and crystallized from chloroform–hexane to give 3′-O-acetylthymidine (**5**), 164 mg (75%), mp 176–177° alone and on admixture with authentic material (lit.[24] mp 176°).

3′-O-β,β,β-Tribromoethoxycarbonyl-5′-O-tritylthymidine (7).—A 0° solution of **1** (2.85 ml) in DMF (20 ml) was added to 5′-O-tritylthymidine (2.9 g, benzene adduct) in cold pyridine (20 ml). The mixture was stirred at 0° for 2 hr, and, after the usual extraction procedure, the product was applied to a silica column (400 g). Elution with chloroform–ethyl acetate (12:1) and recrystallization of the product from ethyl acetate–hexane gave 3.17 g (77%) of **7**: mp 171–171.5°; uv max (CH_3OH), 264 mμ (ε 9500); ir ($CHCl_3$), 1750 cm^{-1} (C=O).

Anal. Calcd for $C_{32}H_{29}Br_3N_2O_7 \cdot {}^1/_2CH_3COOC_2H_5$: C, 48.77; H, 3.94; Br, 28.64; N, 3.35. Found: C, 48.78; H, 4.16; Br, 28.58; N, 3.35.

3′-O-β,β,β-Tribromoethoxycarbonylthymidine (8).—A solution of **7** (1.0 g) in 80% acetic acid (20 ml) was heated at 100° for 35 min. The product was evaporated to dryness, applied to a silica column (200 g), and eluted with chloroform–ethyl acetate (2:1). The appropriate fractions were evaporated to give 559 mg (80%) of **8** as a foam: uv max (CH_3OH), 263 mμ (ε 9070); ir ($CHCl_3$), 1775 cm^{-1} (C=O).

Anal. Calcd for $C_{13}H_{15}Br_3N_2O_7$: C, 28.33; H, 2.72; N, 5.09. Found: C, 29.19; H, 3.08; N, 5.40.

Compound **9**, 31 mg (4%), was also obtained from the column.

5′-O-Acetyl-3′-O-tribromoethoxycarbonylthymidine (9).—A solution of **8** (100 mg) in pyridine (2 ml) and acetic anhydride (1 ml) was stored for 16 hr at 0°. Water (0.5 ml) was added, and the solution was evaporated to dryness and dissolved in chloroform. The chloroform solution was washed with water, dried (Na_2SO_4), and evaporated to give **9**, 100 mg (93%), as a foam: uv max (CH_3OH), 263 mμ (ε 9710); ir ($CHCl_3$), 1755 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{17}Br_3N_2O_8$: C, 30.38; H, 2.87; N, 4.73. Found: C, 30.38; H, 2.88; N, 4.43.

Removal of the β,β,β-Tribromoethoxycarbonyl Group from 9.—A solution of **9** (283 mg) in acetic acid (5 ml) was stirred with a zinc–copper couple (380 mg) for 7 hr. The couple was filtered off and washed with hot methanol. The filtrate and washings were evaporated to dryness, applied to a silica column (50 g) and eluted with chloroform–ethyl acetate (1:5). Crystallization of the appropriate fractions from chloroform–hexane yielded 81 mg (60%) of 5′-O-acetylthymidine, mp 146° (lit.[25] mp 146°).

3′-O-Diethylcarbamoyl-5′-O-tritylthymidine (11).—A solution of **7** in diethylamine (5 ml) was allowed to stand at room temperature for 7 hr and evaporated to dryness, and the residue was crystallized from chloroform–hexane. Recrystallization from isopropyl alcohol gave 120 mg (57%) of pure **11**: mp 203–205°; uv max (CH_3OH), 265 mμ (ε 9660); ir ($CHCl_3$), 1690 cm^{-1} (C=O); nmr ($CDCl_3$), δ 1.10 (t, 6, CH_3CH_2), 3.23 (quartet, 4, CH_3CH_2).

Anal. Calcd for $C_{34}H_{37}N_3O_6$: C, 69.98; H, 6.35; N, 7.20. Found: C, 70.10; H, 6.77; N, 6.85.

3′-O-Acetyl-5′-O-β,β,β-trichloroethoxycarbonylthymidine (12).—This material was prepared by the method employed for the preparation of **4**, except that **1** was replaced by β,β,β-trichloroethyl chloroformate:[19] mp 137–139°; uv max (CH_3OH), 264 mμ (ε 9380); ir ($CHCl_3$), 1730, 1760 cm^{-1} (C=O).

Anal. Calcd for $C_{15}H_{17}Cl_3N_2O_8$: C, 39.19; H, 3.73; N, 6.10. Found: C, 39.03; H, 3.89; N, 6.09.

Action of a Zinc–Copper Couple on 4 and 12.—Solutions of **4** (25 mg) and **12** (25 mg) in 90% acetic acid (1 ml), were each stirred with a zinc–copper couple (20 mg). Aliquots (0.03 ml) were taken at intervals, evaporated to dryness, dissolved in methanol, and examined by thin layer chromatography, using ethyl acetate as the developing solvent. The disappearance of **4** was complete in 20 min, whereas **12** required 3.5 hr for its complete reaction. In both cases thymidine was the only product detected.

Reaction of 1 with N-Benzoyldeoxycytidine.—A freshly prepared 0° solution of **1** (0.58 ml) in DMF (4 ml) was added to N-benzoyldeoxycytidine (660 mg) in pyridine (15 ml). The mixture was stirred at 0° for 1 hr, and then treated in the usual way. The product was applied to a silica column (200 g) and eluted with chloroform–ethyl acetate (2:1, 2 l.), with ethyl acetate (2 l.), and finally with ethyl acetate–methanol (20:1, 2 l.), and 25-ml fractions were collected. Fractions 60–100 were combined, evaporated, and recrystallized from ethyl acetate–hexane to give 560 mg (30%) of **14**: mp 162.5–164.5°; uv max (CH_3OH), 258 mμ (ε 25,800), 303 (10,700); ir (KBr), 1760 cm^{-1} (C=O).

Anal. Calcd for $C_{22}H_{19}Br_6N_3O_9$: C, 27.84; H, 2.00; Br, 50.55; N, 4.43. Found: C, 27.96; H, 1.98; Br, 50.47; N, 4.34.

Fractions 325–400 were pooled, evaporated, and recrystallized from methanol–water to give 530 mg (41%) of **13**: mp 198° dec; uv max (CH_3OH), 260 mμ (ε 23,700), 304 (10,600); ir (KBr), 1740 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{18}Br_3N_3O_7$: C, 35.64; H, 2.81; Br, 37.47; N, 6.56. Found: C, 35.78; H, 2.88; Br, 37.43; N, 6.56.

3′-O-Acetyl-N-benzoyldeoxycytidine (16).—A solution of N-benzoyl-5′-O-mono-*p*-methoxytrityldeoxycytidine[26] (697 mg) in pyridine (10 ml) was treated with acetic anhydride (3.5 ml) at 0° for 24 hr and then poured into ice–water (500 ml). The solid was collected, washed with water, dried, and treated with 80% acetic acid (10 ml) for 6 hr. The solution was evaporated to dryness, and the residue was extracted with ether and recrystallized from chloroform–hexane giving 308 mg (72%) of **16**: mp 202–203°; uv max (CH_3OH), 259 mμ (ε 24,000), 304 (10,800); ir (KBr), 1725 cm^{-1} (C=O).

Anal. Calcd for $C_{18}H_{19}N_3O_6$: C, 57.91; H, 5.10; N, 11.26. Found: C, 57.42; H, 5.27; N, 11.04.

3′-O-Acetyl-N-benzoyl-5′-O-β,β,β-tribromoethoxycarbonyldeoxycytidine (15). A. From N-Benzoyl-3′-O-acetyldeoxycytidine (16).—A freshly prepared 0° solution of **1** (0.1 ml) in DMF (0.5 ml) was added to a 0° solution of **16** (168 mg) in pyridine (2 ml) and the mixture was stirred at 0° for 100 min. The usual extraction procedure was followed and the product was crystallized from chloroform–hexane to give 296 mg (96%) of **15**: mp 197–199° dec; uv max (CH_3OH), 259 mμ (ε 24,100), 303.5 (10,410); ir (KBr), 1750 cm^{-1} (C=O).

Anal. Calcd for $C_{21}H_{20}Br_3N_3O_8$: C, 36.97; H, 2.93; Br, 35.17; N, 6.16. Found: C, 37.14; H, 2.80; Br, 35.10; N, 5.92.

B. By Acetylation of 13.—A solution of **13** (160 mg) in pyridine (5 ml) and acetic anhydride (2.5 ml) was stored at 0° overnight. The product was isolated in the usual way, and recrystallization from chloroform–hexane gave **15**, 150 mg (88%).

N-Benzoyl-3′-O-β,β,β-tribromoethoxycarbonyldeoxycytidine. (17).—A solution of **1** (0.73 ml) in DMF (5 ml) was added to a 0° solution of **18** (1.21 g) in pyridine (20 ml) and the mixture was stirred at 0° for 4 hr. The usual isolation procedure was followed; the product was applied to a silica column (250 g) and eluted with chloroform–ethyl acetate (8:1). The desired fractions were pooled, and evaporated to a foam (1.32 g). A 1-g sample of this material was treated with 80% acetic acid (20 ml) for 6 hr, evaporated to dryness, and extracted with ether. The residue was recrystallized from acetonitrile to give 614 mg (88%) of **17**: mp 202° dec; uv max (dioxane), 259 mμ (ε 22,450), 312 (9280); ir (KBr), 1740 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{18}Br_3N_3O_7$: C, 35.64; H, 2.81; Br, 37.47; N, 6.56. Found: C, 35.64; H, 2.75; Br, 37.23; N, 6.29.

Treatment of 17 with a Zinc–Copper Couple.—A solution of **17** (320 mg) in 95% acetic acid (10 ml) was stirred with a zinc–copper couple (200 mg) for 45 min. The couple was removed by filtration and washed with acetic acid, and the filtrate and washings were evaporated and purified by passage through a silica column (50 g) using ethyl acetate–methanol (10:1) as the solvent. Recrystallization from water gave 49 mg (30%) of N-benzoyldeoxycytidine, mp 197° (lit.[26] mp 194°).

Treatment of 5′-O-Trityluridine (19) with 1.—A 0° solution of **1** (0.44 ml) in DMF (2.5 ml) was added to a cold solution of **19** (972 mg) in pyridine (10 ml). The mixture was stirred for 30 min at 0° and the usual isolation procedure was then followed. The product was purified by silica column chromatography using chloroform–ethyl acetate [12:1 (2 l.), 1:1 (2 l.)]. Compound **21** was obtained, 783 mg (77%), as a foam: uv max (CH_3OH), 257 mμ (ε 10,490); ir ($CHCl_3$), 1760 cm^{-1} (C=O).

Anal. Calcd for $C_{34}H_{28}Br_6N_2O_{10}$: C, 37.00; H, 2.54; N, 2.54. Found: C, 36.50; H, 2.53; N, 2.35.

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Later fractions yielded 459 mg (21%) of the cyclic carbonate **20**: uv max (CH_3OH), 256 mμ (ε 8750); the ir spectrum ($CHCl_3$) was identical with that of an authentic sample.[5]

Reaction of 2′,5′-Di-O-trityluridine with 1.—A freshly prepared solution of **1** (0.88 ml) in DMF (5 ml) was added to a 0° solution of 2′,5′-di-O-trityluridine[21] (1.37 g) in pyridine (20 ml), and the mixture was stirred at 0° overnight. The usual isolation procedure was applied, and the product was purified by passage through a silica column (250 g), using chloroform–ethyl acetate (50:1). Recrystallization from ethyl acetate–hexane gave 1.15 g (60%) of **23**: mp 148–153°; uv max (dioxane), 256 mμ (ε 10,650); ir (KBr), 1750 cm^{-1} (C=O).

Anal. Calcd. for $C_{50}H_{41}Br_3N_2O_8$: C, 57.88; H, 3.96; N, 2.70. Found: C, 57.93; H, 3.98; N, 2.57.

Regeneration of 2′,5′-Di-O-trityluridine from 23.—A solution of **23** (250 mg) in 90% acetic acid (5 ml) was stirred with a zinc–copper couple (100 mg) for 35 min. The couple was removed by filtration, and washed with chloroform. The filtrate and washings were evaporated to dryness and extracted with dry benzene. The extracts were evaporated and crystallized from benzene–ether to give 156 mg (88%) of 2′,5′-di-O-trityluridine.

Treatment of 23 with 80% Acetic Acid.—A solution of **23** (518 mg) in 80% acetic acid (30 ml) was heated at 100° for 40 min, and evaporated to dryness. The residue was extracted with ether and dried *in vacuo* to give 120 mg (89%) of uridine 2′,3′-cyclic carbonate (**24**): uv max (CH_3OH), 255 mμ (ε 9780); the ir spectrum (KBr) was identical with that of an authentic sample.[5]

Reaction of 2′,3′-O-Isopropylideneadenosine with 1.—A freshly prepared solution of **1** in DMF (10 ml) was added to a 0° solution of **25** (1.2 g) in pyridine and the mixture was stirred at 0° for 1 hr. The usual isolation procedure was followed and the product was applied to a silica column (300 g) and eluted with chloroform–ethyl acetate (4:1, 2 l.) followed by ethyl acetate (2 l.).

The first compound to be eluted from the column was recrystallized from chloroform–hexane: 457 mg; mp 150°; uv max (CH_3OH), 287 mμ; ir (KBr), 1720, 1770 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{18}Br_6N_6O_8$: C, 24.66; H, 2.06; Br, 51.86. Found: C, 24.36; H, 1.95; Br, 51.93.

The second product from the column was isolated as a foam (440 mg): uv max (CH_3OH), 267 mμ; ir ($CHCl_3$), 1760 cm^{-1} (C=O).

Anal. Calcd for $C_{19}H_{19}Br_6N_6O_8$: C, 24.66; H, 2.06; Br, 51.86. Found: C, 24.94; H, 2.25; Br, 50.70.

The carbamate **26** was obtained, 736 mg (30%), and recrystallized from chloroform–hexane: mp 210–211°; uv max (CH_3OH), 279 mμ (ε 10,800); ir (KBr), 1730 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{18}Br_3N_5O_6$: C, 31.18; H, 2.92; N, 11.36. Found: C, 30.88; H, 2.87; N, 11.19.

Compound **27**, 220 mg (9%), was isolated as a foam: uv max (CH_3OH), 258 mμ (ε 14,900); ir ($CHCl_3$), 1760 cm^{-1} (C=O).

Anal. Calcd for $C_{16}H_{18}Br_3N_5O_6$: C, 31.18; H, 2.92; Br, 38.93; N, 11.36. Found: C, 31.38; H, 3.16; Br, 38.90; N, 11.26.

Registry No.—**1**, 17182-43-3; **2**, 17182-30-8; **3**, 17182-31-9; **4**, 17182-32-0; **7**, 17182-33-1; **8**, 17188-71-5; **9**, 17182-34-2; **11**, 17182-35-3; **12**, 17182-36-4; **13**, 17188-72-6; **14**, 17182-37-5; **15**, 17182-38-6; **16**, 17182-39-7; **17**, 17182-40-0; **21**, 17222-08-1; **23**, 17182-41-1; **26**, 17188-73-7; **27**, 17182-42-2.

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Nucleosides. LII. Transformations of Pyrimidine Nucleosides in Alkaline Media. I. The Conversion of 5-Halogenoarabinosyluracils into Imidazoline Nucleosides[1]

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The reactions of 1-β-D-arabinofuranosyl-5-halogenouracils in alkali have been investigated under various conditions. The 5-fluorouracil nucleoside (**1**) is stable in hot sodium methoxide solution whereas the 5-bromo analog (**4**) is converted in high yield into 2′,6-anhydro-1-(β-D-arabinofuranosyl)-6-hydroxyuridine (**5**). Compound **5** is also formed in low yield when **4** is treated with warm aqueous sodium hydroxide. The major product of this aqueous reaction was shown to be 1-β-D-arabinofuranosyl-2-oxo-4-imidazoline-4-carboxylic acid (**3**). Nucleoside **3** was also prepared under similar conditions by ring closure of the 2′,6-anhydro acyclic ureide **2**. The structure of **3** was elucidated from chemical and nmr evidence and by comparison of the ultraviolet spectral and pK_a data of **3** and its derivatives with those of model N-alkylated imidazolinecarboxylic acids. Mechanisms involving attack of the 2′-hydroxyl group on C-6 of the pyrimidine ring are suggested for these novel transformations. 1-Methyl-5-bromouracil (**29**) does not undergo rearrangement to an imidazolinecarboxylic acid when treated with aqueous alkali but is converted into 1-methylbarbituric acid. Imidazoline nucleosides have also been prepared by total synthesis. Condensation of tetraacetyl-α-D-glucopyranosyl bromide (**19**) with 2-oxo-4-imidazoline-4-carboxylic acid methyl ester (**14**) affords a mixture of N-1 and N-3 glucosylated imidazoline derivatives. As with pyrimidine nucleosides, uv spectral shifts in the high alkaline region were observed with the 3-methyl derivative of the imidazoline nucleoside (**3**). These shifts are attributed to the effects of ionization of the sugar moiety on the aglycon.

Pyrimidine nucleosides containing the 1-β-D-arabinofuranosyl moiety have been studied extensively as antiviral and antitumor[2] agents. Recent investigations[3] into the synthesis of arabinosyl nucleosides for evaluation as chemotherapeutic agents have revealed some interesting chemical properties which result from the configuration of the sugar at C-2′. This structural feature allows a facile interaction between the 2′-hydroxy group and the aglycon which can result in the formation of a 2′,6-ether linkage.[3] For example, 1-β-D-arabinofuranosyl-5-fluorouracil (**1**) and its 5-fluorocytosine analog are rapidly transformed[3a] in warm,

(1) (a) This investigation was supported in part by funds from the National Cancer Institute, National Institutes of Health, U. S. Public Health Service (Grant No. CA 08748). (b) A preliminary account of part of this work has been published: B. A. Otter and J. J. Fox, *J. Amer. Chem. Soc.*, **89**, 3663 (1967).

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