Nucleoside Studies. IV.[1] The Synthesis of 2',5'-Dideoxycytidines and Other Derivatives of 2'-Deoxycytidine

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N-Benzoyl-2'-deoxycytidine 3'-acetate 5'-*p*-toluenesulfonate (**15**) and the corresponding 3'-benzoate **13** undergo nucleophilic displacement of tosylate to yield, from **13**, *N*-benzoyl-2'-deoxy-5'-iodocytidine 3'-benzoate (**14**) and, from **15**, the following derivatives of *N*-benzoyl-2'-deoxycytidine 3'-acetate: 5'-iodo (**16**), 5'-thio 5' acetate (**23**), 5'-phthalimido (**18**), and 5'-aizdo (**19**). Iodo derivative **14** results alternately by interaction of methyltriphenoxyphosphonium iodide and *N*-benzoyl-2'-deoxycytidine 3'-benzoate (**11**). Hydrolysis of **14** and **16** gives 2',5'-dideoxy-5'-iodocytidine (**17**) which, on catalytic hydrogenation, gives 2',5'-dideoxycytidine (**20**). Hydrolysis of **19** gives 5'-azido-2',5'-dideoxycytidine (**22**). *N*-Benzoyl-2'-deoxycytidine 5'-benzoate 3'-methanesulfonate (**2**) suffers glycosyl cleavage when subjected to conditions of nucleophilic displacement of methanesulfonate.

The usefulness of certain synthetic 2'-deoxynucleosides as chemotherapeutic agents is now well established. 5-Iodo-2'-deoxyuridine has marked antiviral activity[2-6]; 5-fluoro-2'-deoxyuridine and 5-fluoro-2'-deoxycytidine are potentially useful antitumor agents.[7,8] These discoveries have led to the preparation of many analogs of the naturally occurring compounds by total and partial synthesis.[9]

Total synthesis of pyrimidine deoxyribosides is feasible by the direct coupling of a deoxyribosyl halide with the mercury salt of the appropriate pyrimidine,[10] but this method has limitations[11] since the mercury salts are often insoluble or unreactive. Partial synthesis[9] has been used to modify the carbohydrate moiety of thymidine,[12] and some derivatives of 2'-deoxyuridine have recently been described.[13] We have now carried out a series of transformations of 2'-deoxycytidine (**7**) which has received little attention so far (see Scheme I).

Some derivatives of 2'-deoxycytidine were prepared by the Cambridge group[14,15] to demonstrate the β-glycosylic linkage of the natural nucleoside. More recently some protected derivatives have been prepared as part of a program of deoxypolynucleotide synthesis.[16] Our first objective was to prepare analogs in which the 5'-hydroxyl group is replaced by halogen, hydrogen, nitrogen, and sulfur. The methods employed were analogous to the methods used for the preparation of the corresponding thymidine[12] and 2'-deoxyuridine compounds.[13]

Michelson and Todd[14] had converted 5'-trityl ether **8** to *N*-acetyl-2'-deoxy-5'-*O*-tritylcytidine 3'-acetate but found that brief acid treatment to cleave the trityl ether caused some glycosyl cleavage with concurrent hydrolysis of the labile *N*-acetyl group. In the hope that it would be more resistant to such side reactions the *N*,3'-dibenzoate **9**, obtained by benzoylation of **8**, was treated with hot 80% acetic acid[14] which effectively cleaved the trityl ether without amide hydrolysis to give the 5' alcohol **11** in 60% yield. However, repetition of this hydrolysis on a large scale led to glycosyl cleavage, giving *N*-benzoylcytosine (**6**) in high yield. With hydrogen chloride in ether,[17] trityl ether **9** was efficiently cleaved to give the crystalline hydrochloride of **11**, which was easily converted to the free base by treatment with water. Tosylation of the latter in pyridine gave 49% of dibenzoyl tosylate **13**.

N-Benzoyl-2'-deoxycytidine (**10**) was the major product isolated when 2'-deoxycytidine (**7**) was allowed to react with 1 equiv. of benzoic anhydride in pyridine. In addition, a dibenzoyl derivative **4** was isolated in low yield and its physical properties differed from the well-characterized *N*,3'-dibenzoate **11**. The ultraviolet absorption spectrum of **4** showed a maximum at 305 mμ, indicative of *N*-acylation,[18] and this served to eliminate the alternative 3',5'-dibenzoate structure. *N*-Benzoyl-2'-deoxycytidine had been previously prepared[16] by a two-step sequence involving tribenzoylation of 2'-deoxycytidine and then hydrolysis under controlled alkaline conditions.

Treatment of *N*-benzoyl derivative **10** with 1 equiv. of *p*-toluenesulfonyl chloride in pyridine gave 45% of the 5'-tosylate **12** whose structure was confirmed by its benzoylation to dibenzoyl tosylate **13**.

When *N*-benzoyl 5'-tosylate **12** was subjected to a displacement reaction with sodium iodide in refluxing 2-butanone, glycosyl cleavage and liberation of free iodine occurred. The fully protected 5'-tosylate **13**, however, when allowed to react with sodium iodide in refluxing 2-butanone, gave 53% of 5' iodo derivative

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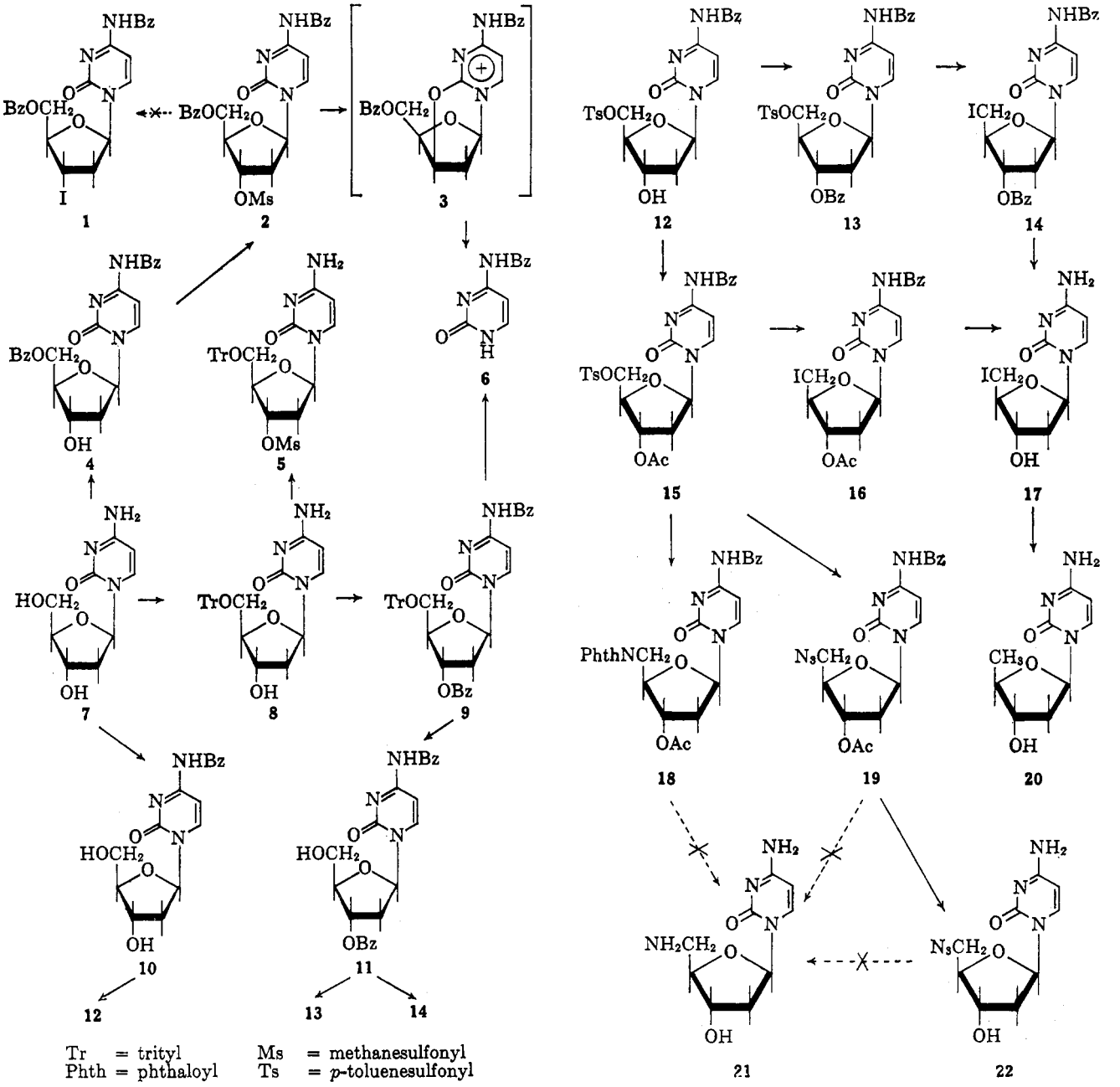
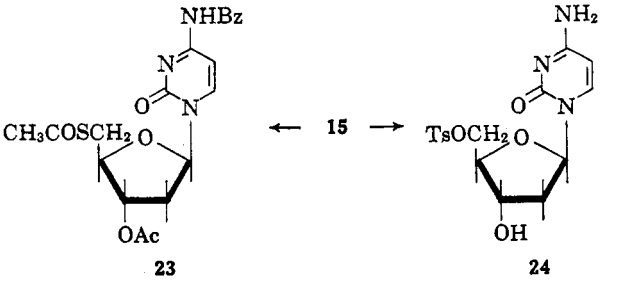
SCHEME I



14. This compound, which was difficult to purify, was obtained in 41% yield by reaction of 5′-alcohol **11** directly with methyltriphenoxyphosphonium iodide[19] in *N*,*N*-dimethylformamide.[20]

Acetylation of *N*-benzoyl 5′-tosylate **12** gave the *N*-benzoyl 3′-acetate **15**, the structure of which was confirmed by conversion to the known 2′-deoxycytidine 5′-tosylate[14] (**24**) with methanolic ammonia. The tosylate group of **15** was readily displaced with iodide to give the 5′-iodo derivative **16** in 90% yield. Removal of the protecting groups of 5′-iodo derivatives **14** and **16** with cold methanolic ammonia gave 2′,5′-dideoxy-5′-iodocytidine (**17**) in 90 and 95% yields. Hydrogenation of **17** in the presence of 5% palladium on barium sulfate at pH 10[12a] gave the desired 2′,5′-dideoxycytidine (**20**) as the hydriodide salt, which was converted to the free base by treatment with 1 equiv. of triethylamine.

Displacement of tosylate from **15** with potassium thiolacetate in acetone at room temperature gave 40% of the 5′-thio derivative **23**; the 5′-phthalimido derivative **18** was obtained by a displacement reaction on **15** with potassium phthalimide in *N*,*N*-dimethylformamide at 110°.[21] Treatment of **18** with butylamine



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in methanol at reflux[1] gave a gum from which no 5′-amine **21** could be isolated. Another widely applied route for the synthesis of amino sugars employs an intermediate azide.[22] Displacement of tosylate from **15** with sodium azide in *N*,*N*-dimethylformamide at 110°[22] gave 70% of the desired 5′-azide **19**. Reduction of **19** with hydrogen and a variety of catalysts or with sodium borohydride in isopropyl alcohol failed to give protected derivatives of the 5′-amine **21**. Catalytic reduction of the deacylated azide **22** also failed to give **21**.

A desirable derivative of 2′-deoxycytidine of potential biological significance is 2′,3′-dideoxycytidine. We expected to be able to prepare this compound by catalytic hydrogenation of the 3′-iodo compound, a method analogous to our synthesis of the 2′,5′-dideoxy derivative **20**. Treatment of 2′-deoxy-5′-*O*-tritylcytidine (**8**) with 1 equiv. of methanesulfonyl chloride gave, in fair yield, a product which is assigned the 3′-mesylate structure **5**. The mesylate function of **5** was displaced with sodium iodide in refluxing 2-butanone with formation of sodium methanesulfonate, thus eliminating the alternate *N*-mesylate structure. Further work-up of the reaction was unpromising. We therefore decided to work with a fully protected compound. *N*,5′-Dibenzoate **4** was allowed to react with excess methanesulfonyl chloride in pyridine to give 3′-mesylate **2** in 35% yield. Interaction of this secondary sulfonate with sodium iodide in 2,4-pentanedione at 100° failed to give the desired iodo derivative **1** but yielded, instead, 70% of *N*-benzoylcytosine (**6**). The mesylate group was displaced, but the presumed intermediate cyclonucleoside **3** was so unstable under these conditions that elimination of the sugar residue occurred.[23]

Experimental

Melting points were determined on a Fisher-Johns melting point apparatus and are uncorrected. Ultraviolet spectra were determined with a Cary recording spectrophotometer.

2′-Deoxy-5′-*O*-tritylcytidine (8) was prepared in 62% yield by the method of Michelson and Todd[14] and had m.p. 230–232° (lit.[14] m.p. 239°), $[\alpha]^{25}D$ +56° (*c* 1.04, EtOH), λ_{max}^{EtOH} 272 mμ (ε 8450), $\lambda_{max}^{0.1\,N\,NaOH}$ 270 mμ (ε 8450), $\lambda_{max}^{0.1\,N\,HCl}$ 280 mμ (ε 12,200). An attempt to prepare this compound by heating the reaction mixture at 100° for 0.5 hr.[12c] resulted in glycosyl cleavage.

N-Benzoyl-2′-deoxy-5′-*O*-tritylcytidine 3′-Benzoate (9).—To a solution of 1.00 g. (0.00213 mole) of **8** in 50 ml. of pyridine was added 2.32 ml. (2.80 g., 0.020 mole) of benzoyl chloride and the solution was stirred at room temperature for 6 hr. With vigorous stirring the reaction mixture was poured into 1 l. of ice–water; the insoluble solid was collected by filtration and washed with water. After air drying, 1.02 g. (71%) of product was obtained as a yellow solid, m.p. 100–105°. The product was dissolved in ethanol and refrigerated. Compound **9** was obtained by filtration as a colorless amorphous solid: m.p. 113–115°; $[\alpha]^{25}D$ +29° (*c* 0.72, EtOH); λ_{max}^{EtOH} 226, 256, and 306 mμ (ε 35,800, 29,000, and 9500).

Anal. Calcd. for $C_{42}H_{38}N_3O_6$: C, 74.4; H, 5.21; N, 6.20. Found: C, 74.8; H, 5.17; N, 5.59.

***N*-Benzoyl-2′-deoxycytidine 3′-Benzoate (11). A. Use of 80% Acetic Acid.**—A suspension of 1.02 g. (0.00147 mole) of **9** in 20 ml. of 80% acetic acid was placed in an oil bath preheated to 100°. The mixture was heated with occasional swirling for 5 min. by which time a clear colorless solution was obtained. The solvent was removed *in vacuo* to yield a semisolid residue. After trituration with ether and filtration, 0.51 g. of crude product was obtained as a tan solid, m.p. 190–210° dec. Two recrystallizations from absolute ethanol gave 0.271 g. (42%) of **11** as colorless plates: m.p. 222–224° dec.; $[\alpha]^{25}D$ +1° (*c* 0.96, DMF); λ_{max}^{EtOH} 232, 260, and 305 mμ (ε 21,400, 24,800, and 10,000).

Anal. Calcd. for $C_{23}H_{21}N_3O_6$: C, 63.4; H, 4.86; N, 9.65. Found: C, 63.9; H, 5.10; N, 9.59.

B. Use of Hydrogen Chloride.—Crude **9** (7.2 g., 0.0106 mole) was dissolved in 30 ml. of anhydrous ether and was cooled to 0°. Hydrogen chloride was bubbled through the cold solution for 10 min. The mixture was then diluted with ether and filtered to remove 3.22 g. (64%) of a colorless solid, m.p. >250°. The solid was stirred vigorously with 75 ml. of water for 2 hr. and the insoluble material was then filtered off. Recrystallization from absolute ethanol gave 2.02 g. (44%) of **11** as colorless plates, m.p. 213–216° dec.

Anal. Found: C, 63.0; H, 5.17; N, 9.96.

N-Benzoyl-2′-deoxycytidine (10) and N-Benzoyl-2′-deoxycytidine 5′-Benzoate (4).—To a suspension of 13.0 g. (0.0616 mole) of 2′-deoxycytidine (**7**) in 250 ml. of pyridine was added 14.02 g. (0.062 mole) of benzoic anhydride, and the mixture was stirred at room temperature for 4 hr. The pyridine was removed *in vacuo* to leave a semisolid residue which was poured with vigorous stirring into 1 l. of ice–water. The solution was extracted once with ether and the aqueous fraction was evaporated to dryness *in vacuo* to yield 14.93 g. of crude product. After recrystallization from absolute ethanol, 11.7 g. (57%) of **10** was obtained as colorless crystals, m.p. 205–207° (lit.[16] m.p. 194°), $[\alpha]^{25}D$ +82° (*c* 0.61, EtOH), $\lambda_{max}^{H_2O}$ 258 and 301 mμ (ε 20,500 and 10,900).

Anal. Calcd. for $C_{16}H_{17}N_3O_5$: C, 58.0; H, 5.17; N, 12.7. Found: C, 57.7; H, 5.48; N, 12.3.

The ether extract was held at room temperature, and the resulting colorless crystalline solid was collected and recrystallized from absolute ethanol to give 0.468 g. (2%) of **4** as colorless crystals: m.p. 145.5–147.5°; $[\alpha]^{25}D$ +70° (*c* 1.03, DMF); $\lambda_{max}^{H_2O}$ 230, 260, and 305 mμ (ε 18,700, 20,400, and 8700).

Anal. Calcd. for $C_{23}H_{21}N_3O_6 \cdot 0.5H_2O$: C, 62.2; H, 4.99; N, 9.46. Found: C, 62.2; H, 4.77; N, 9.97.

***N*-Benzoyl-2′-deoxycytidine 5′-*p*-Toluenesulfonate (12).**—A suspension of 9.00 g. (0.0272 mole) of **10** in 100 ml. of pyridine was cooled to 0°, 5.18 g. (0.0272 mole) of *p*-toluenesulfonyl chloride was added, and the mixture was stirred at 3° for 18 hr. About two-thirds of the pyridine was removed *in vacuo* and the resulting sirup was treated with 500 ml. of ice–water and then extracted with ethyl acetate. After drying over magnesium sulfate, the solvent was removed *in vacuo* to give 10.8 g. of a colorless solid, m.p. 143–150° dec. One recrystallization from 250 ml. of absolute ethanol yielded 5.87 g. (46%) of colorless needles, m.p. 146–149° dec. Further recrystallization from absolute ethanol gave **12** as colorless needles: m.p. 149.5–151° dec.; $[\alpha]^{25}D$ +105° (*c* 0.55, EtOH); λ_{max}^{EtOH} 223, 260, and 305 mμ (ε 21,800, 22,300, and 9700).

Anal. Calcd. for $C_{23}H_{23}N_3O_7S$: C, 56.8; H, 4.97; N, 8.64; S, 6.59. Found: C, 56.8; H, 4.73; N, 8.16; S, 6.58.

***N*-Benzoyl-2′-deoxycytidine 3′-Benzoate 5′-*p*-Toluenesulfonate (13). A. From N-Benzoyl-2′-deoxycytidine 5′-*p*-Toluenesulfonate (12).**—To a solution of 1.00 g. (0.00205 mole) of **12** in 20 ml. of pyridine was added 0.40 ml. (0.485 g., 0.0034 mole) of benzoyl chloride. The solution was stirred at room temperature for 6 hr. and then poured with vigorous stirring into 500 ml. of ice–water, whereupon a gum separated. The gum was extracted into chloroform and dried over magnesium sulfate. Removal of the solvent *in vacuo* gave a yellow liquid which solidified on trituration with ether. The colorless solid was removed by filtration and air dried to yield 0.453 g. of **13** as colorless plates, m.p. 149–151° dec. One recrystallization from absolute ethanol gave 0.316 g. (26%) of **13**: m.p. 155–159° dec.; λ_{max}^{MeOH} 227, 260, and 302 mμ (ε 35,000, 27,100, and 11,200).

Anal. Calcd. for $C_{30}H_{27}N_3O_8S$: C, 61.1; H, 4.61; N, 7.13; S, 5.44. Found: C, 61.4; H, 4.79; N, 7.21; S, 5.34.

B. From N-Benzoyl-2′-deoxycytidine 3′-Benzoate (11).—A solution of 1.00 g. (0.0023 mole) of **11** in 25 ml. of pyridine was cooled to 0° and 0.534 g. (0.0028 mole) of *p*-toluenesulfonyl chloride was added. The solution was slowly brought to room temperature, maintained there for 18 hr., and then poured with

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(23) To our knowledge the only cyclocytidine salt reported in the literature is 2′,3′-*O*-isopropylidene-O^2,5′-cyclocytidine: V. M. Clark, A. R. Todd, and J. Zussman, *J. Chem. Soc.*, 2952 (1951). No 2′-deoxycyclocytidines have been described. Andersen, *et al.*,[15] tried to prepare a cyclonucleoside from 2′-deoxycytidine by heating its 5′-tosylate in acetone, but were unable to isolate it. However, the fact that *p*-toluenesulfonate anion was produced led them to conclude that an unstable cyclonucleoside was formed and that this decomposed to cytosine and the sugar moiety.

vigorous stirring into 3 l. of ice–water. The resulting colorless solid was removed by filtration to yield 1.044 g. of crude product, m.p. <100° dec. One recrystallization from ethanol gave 0.662 g. (49%) of **13** as colorless plates, m.p. 156–159° dec.

N-**Benzoyl-2′,5′-dideoxy-5′-iodocytidine 3′-Benzoate (14). A. From 5′-Tosylate 13.**—A stirred solution of 0.500 g. (0.00085 mole) of **13** and 0.160 g. (0.0011 mole) of sodium iodide in 15 ml. of 2-butanone was refluxed for 2 hr. under nitrogen. The mixture was filtered to remove 0.067 g. (34%) of sodium *p*-toluenesulfonate, and the filtrate was evaporated *in vacuo* to leave a yellow glass. The glass was triturated with absolute ethanol and the crude colorless solid (0.349 g., m.p. 170°) was collected by filtration. Recrystallization from ethanol gave 0.246 g. (53%) of **14** as a colorless solid, m.p. 162–168° dec. This was dissolved in a small volume of chloroform and was chromatographed on 5 g. of neutral alumina (Woelm, grade I). The first three fractions (total 25 ml.) were evaporated separately to give colorless solids which were combined. The resulting 0.107 g. of product was triturated with 50 ml. of ethanol to give 0.029 g. of **14** as colorless needles, m.p. 171–175° dec. Recrystallization from ethanol gave colorless needles, m.p. 174–176° dec.

Anal. Calcd. for $C_{23}H_{20}IN_3O_5 \cdot 0.25C_2H_5OH$: C, 50.7; H, 3.88; I, 22.8; N, 7.55. Found: C, 51.4; H, 3.91; I, 22.7; N, 7.45.

B. From *N*-Benzoyl-2′-deoxycytidine 5′-Benzoate (11).—A solution containing 0.500 g. (0.00155 mole) of **11** and 0.794 g. (0.0024 mole) of methyltriphenoxyphosphonium iodide[17] in 10 ml. of *N*,*N*-dimethylformamide was stirred at room temperature for 18 hr. The solvent was removed *in vacuo* to leave a dark red gum which was dissolved in chloroform, washed with 5% sodium thiosulfate and water, then dried over magnesium sulfate. Removal of the solvent *in vacuo* gave a yellow oil which solidified on trituration with ether to yield 0.343 g. (41%) of crude **14**, m.p. 164–171° dec. After recrystallization from absolute ethanol, 0.225 g. (27%) of **14** was obtained as colorless crystals: m.p. 171–174° dec.; $[\alpha]^{25}D$ +6° (*c* 1.00, DMF); λ_{max}^{MeOH} 230, 260, and 302 mμ (ε 24,500, 26,400, and 11,170).

Anal. Found: C, 51.9; H, 3.68; I, 21.0; N, 7.89.

N-**Benzoyl-2′-deoxycytidine 3′-Acetate 5′-*p*-Toluenesulfonate (15).**—A solution containing 1.00 g. (0.00206 mole) of **12**, 1.0 ml. (1.08 g., 0.01 mole) of acetic anhydride, and 10 ml. of pyridine was stirred at room temperature for 18 hr. Methanol (5 ml.) was added and after 0.5 hr. the solvent was removed *in vacuo* to leave a gel which solidified on trituration with water. The solid was removed by filtration and recrystallized from absolute ethanol to yield 0.772 g. (71%) of **15** as colorless plates: m.p. 160–163° dec.; $[\alpha]^{25}D$ +48° (*c* 1.0, DMF); λ_{max}^{MeOH} 224, 260, and 302 mμ (ε 24,200, 24,700, and 10,500).

Anal. Calcd. for $C_{25}H_{25}N_3O_8S$: C, 56.9; H, 4.78; N, 7.97; S, 6.08. Found: C, 56.9; H, 4.88; N, 8.12; S, 6.14.

2′-Deoxycytidine 5′-*p*-Toluenesulfonate (24).—A suspension of 0.500 g. (0.00095 mole) of **15** in 25 ml. of half-saturated methanolic ammonia was stirred at 3° for 18 hr. Evaporation of the clear solution *in vacuo* left a colorless gum which solidified on trituration with ether. Filtration and air drying gave 0.319 g. (88%) of **24** as a colorless amorphous solid, m.p. 120–123° (lit.[14] m.p. 120°), $[\alpha]^{25}D$ +70° (*c* 1.04, EtOH), λ_{max}^{MeOH} 270 mμ (ε 8010).

N-**Benzoyl-2′,5′-dideoxy-5′-iodocytidine 3′-Acetate (16).**—A suspension of 4.00 g. (0.0076 mole) of **15** and 2.28 g. (0.0152 mole) of sodium iodide in 200 ml. of 2-butanone was refluxed under nitrogen for 2 hr. The solution was cooled to room temperature and was filtered to remove 1.5 g. (100%) of sodium *p*-toluenesulfonate. The filtrate was evaporated to dryness *in vacuo* to yield an orange gum which solidified on trituration with ethanol. The solid was crystallized from ethanol to give 3.10 g. (90%) of **16**, m.p. 177–180° dec. A sample was recrystallized from ethanol to yield colorless needles, m.p. 179–181° dec., $[\alpha]^{25}D$ +42° (*c* 1.04, DMF), λ_{max}^{MeOH} 260 and 303 mμ (ε 23,000 and 10,400).

Anal. Calcd. for $C_{18}H_{18}IN_3O_5$: C, 44.7; H, 3.76; I, 26.3; N, 8.70. Found: C, 44.7; H, 3.85; I, 26.1; N, 8.83.

2′,5′-Dideoxy-5′-iodocytidine (17). A. From N,3′-Dibenzoate 14.—Compound **14** (0.175 g., 0.00032 mole) was suspended in 10 ml. of half-saturated methanolic ammonia and the solution was stirred for 18 hr. at 3°. The solvent was removed *in vacuo* to leave a semisolid residue. Trituration with ether and filtration gave 0.097 g. (90%) of **17**, m.p. 108–115° dec. The product was recrystallized from ethanol–ether and then from ethanol to give 0.015 g. of **17** as colorless needles, m.p. 172–175° dec.

Anal. Calcd. for $C_9H_{12}IN_3O_3 \cdot 0.25C_2H_5OH$: C, 32.7; H, 3.90; I, 36.4; N, 12.1. Found: C, 33.0; H, 4.03; I, 36.8; N, 12.5.

B. From N-Benzoyl 3′-acetate 16.—A suspension of 3.10 g. (0.00642 mole) of **16** in 300 ml. of half-saturated methanolic ammonia was allowed to react as in part A, yielding 1.99 g. (95%) of **17** as colorless needles, m.p. 179–183° dec. Recrystallization from ethanol gave colorless needles, m.p. 178–180° dec., $[\alpha]^{25}D$ +41° (*c* 1.02, DMF), λ_{max}^{MeOH} 235 and 270 mμ (ε 8350 and 9260).

Anal. Found: C, 32.8; H, 4.04; I, 36.4; N, 12.4.

2′,5′-Dideoxycytidine (20).—A solution of 0.391 g. (0.00116 mole) of **17** in 20 ml. of water and 40 ml. of ethanol was adjusted to pH 10 with ammonia. The solution was then hydrogenated at room temperature and atmospheric pressure in the presence of 1.60 g. of 5% palladium on barium sulfate. After 3.75 hr., the hydrogen uptake had ceased. The catalyst was removed by filtration through diatomaceous earth and the filtrate was evaporated *in vacuo* to yield a yellow oil which was dissolved in water. The aqueous solution was extracted once with ether and was then evaporated *in vacuo* to give 0.157 g. (40%) of **20** hydriodide, m.p. 162.5–163°. A suspension of the salt in 10 ml. of chloroform and 0.06 ml. (0.047 g., 0.00046 mole) of triethylamine was stirred at room temperature for 1 hr. The insoluble solid was collected by filtration and washed with chloroform to yield 0.110 g. (45%) of colorless needles, m.p. 187.5–193°. Two recrystallizations from ethanol–ether gave 0.079 g. of **20**, m.p. 189–191°, $[\alpha]^{25}D$ +105° (*c* 1.01, EtOH), λ_{max}^{MeOH} 230 and 272 mμ (ε 7380 and 8220).

Anal. Calcd. for $C_9H_{13}N_3O_3$: C, 51.2; H, 6.20; N, 19.9. Found: C, 51.0; H, 6.41; N, 20.2.

N-**Benzoyl-2′,5′-dideoxy-5′-thiocytidine 3′,5′-Diacetate (23).**—A stirred suspension of 0.50 g. (0.00095 mole) of **15** in 10 ml. of acetone was treated with 0.424 g. (0.0038 mole) of potassium thiolacetate. After stirring at room temperature for 5 hr., the mixture was filtered to remove inorganic salts, and the acetone was removed *in vacuo* to leave a colorless oil which solidified on trituration with ether. The crude product (0.299 g.), m.p. 110–120°, was recrystallized from isopropyl alcohol–cyclohexane to give 0.165 g. (40%) of **23** as a tan solid, m.p. 131–133°, $[\alpha]^{25}D$ +62.5° (*c* 1.00, DMF), λ_{max}^{MeOH} 260 and 303 mμ (ε 22,900 and 10,100).

Anal. Calcd. for $C_{20}H_{21}N_3O_6S \cdot 0.5H_2O$: C, 54.5; H, 5.05; N, 9.55; S, 7.27. Found: C, 54.8; H, 5.31; N, 9.28; S, 7.22.

N-**Benzoyl-2′,5′-dideoxy-5′-phthalimidocytidine 3′-Acetate (18).**—A solution of 2.40 g. (0.0045 mole) of **15** and 0.852 g. (0.0046 mole) of potassium phthalimide in 60 ml. of *N*,*N*-dimethylformamide was stirred under nitrogen, then slowly heated to 110° and held there for 2 hr. The deep brown solution was cooled to room temperature and evaporated *in vacuo* to a deep brown oily residue. Trituration with acetone and filtration gave 0.816 g. (97%) of potassium *p*-toluenesulfonate. The filtrate was evaporated *in vacuo* and the residue solidified on trituration with ether to give 2.85 g. of crude product. Recrystallization of the solid from ethanol gave 0.210 g. (9%) of **18** as colorless crystals, m.p. 260–262° dec., $[\alpha]^{25}D$ +99° (*c* 1.05, DMF), λ_{max}^{MeOH} 258 and 300 mμ (ε 29,500 and 14,600).

Anal. Calcd. for $C_{26}H_{22}N_4O_7 \cdot 0.75H_2O$: C, 60.5; H, 4.59; N, 10.9. Found: C, 60.5; H, 4.52; N, 11.3.

5′-Azido-*N*-benzoyl-2′,5′-dideoxycytidine 3′-Acetate (19).—A suspension of 2.00 g. (0.00379 mole) of **15** and 0.967 g. (0.0114 mole) of sodium azide in 50 ml. of dry *N*,*N*-dimethylformamide was heated at 110–115° for 2.5 hr. under nitrogen. After cooling to room temperature, the mixture was filtered and the filtrate was evaporated *in vacuo* to leave a brown semisolid residue. After trituration with acetone, the inorganic salts were removed by filtration and the filtrate was evaporated to leave an orange oil which, on trituration with ether and water, gave 1.16 g. (70%) of **19**, m.p. 161–165.5°. Recrystallization from absolute ethanol gave **19** as colorless needles, m.p. 164–168°, $[\alpha]^{25}D$ +51° (*c* 0.51, EtOH), λ_{max}^{MeOH} 260 and 302 mμ (ε 19,900 and 9560).

Anal. Calcd. for $C_{18}H_{18}N_6O_5$: C, 54.3; H, 4.55; N, 21.1. Found: C, 54.3; H, 4.80; N, 20.9.

5′-Azido-2′,5′-dideoxycytidine (22).—A suspension of 0.200 g. (0.0005 mole) of **19** in 10 ml. of half-saturated methanolic ammonia was stirred at 3° for 20 hr. and then evaporated to dryness *in vacuo* to yield a colorless gum which solidified on trituration with ether. The crude solid, 0.107 g. (85%), m.p. 178–181°, was recrystallized from ethanol–ether to give **22** as color-

less needles, m.p. 181–184°, $[\alpha]^{25}D$ +115° (*c* 1.02, DMF), λ_{max}^{MeOH} 235 and 270 mμ (ε 7820 and 8510).

Anal. Calcd. for $C_9H_{12}N_6O_3$: C, 42.8; H, 4.80; N, 33.3. Found: C, 43.4; H, 4.98; N, 33.0.

2′-Deoxy-5′-*O*-tritylcytidine 3′-Methanesulfonate (5).—A solution of 0.100 g. (0.000213 mole) of **8** in 5 ml. of pyridine was cooled to 0° and 0.02 ml. (0.024 g., 0.000213 mole) of methanesulfonyl chloride was added; the mixture was stirred at 3° for 2 days. The solution was poured with vigorous stirring into 300 ml. of ice–water. The resulting solid was removed by filtration and air dried to give 0.086 g. of crude product, m.p. 137–154°. One recrystallization from ethyl acetate–petroleum ether (b.p. 30–60°) yielded 0.061 g. (54%) of **5** as colorless needles, m.p. 142.5–146°, $[\alpha]^{25}D$ +40.5° (*c* 0.37, EtOH), λ_{max}^{EtOH} 265 mμ (ε 7550), $\lambda_{max}^{0.1\ N\ NaOH}$ 270 mμ (ε 8650), $\lambda_{max}^{0.1\ N\ HCl}$ 270 mμ (ε 10,800).

Anal. Calcd. for $C_{29}H_{29}N_3O_6S\cdot 0.5H_2O$: C, 62.6; H, 5.42; N, 7.56; S, 5.58. Found: C, 62.5; H, 5.47; N, 7.61; S, 5.11.

***N*-Benzoyl-2′-deoxycytidine 5′-Benzoate 3′-Methanesulfonate (2).**—A solution containing 1.00 g. (0.00302 mole) of **4** and 0.688 g. (0.47 ml., 0.006 mole) of methanesulfonyl chloride in 25 ml. of pyridine was stirred for 18 hr. at 3° and then 2.5 hr. at room temperature. The solution was cooled to 0°, about 1 ml. of water was added, and the solution was stirred an additional 0.5 hr. The mixture was then poured with vigorous stirring into 200 ml. of ice–water, and the precipitated solid was removed by filtration to yield 0.94 g. of crude product, m.p. 89–95°. One recrystallization from absolute ethanol gave 0.543 g. (35%) of **2** as colorless needles: m.p. 144–149° dec.; $[\alpha]^{25}D$ +30° (*c* 1.28, DMF); λ_{max}^{MeOH} 228, 259, and 302 mμ (ε 28,000, 25,100, and 10,300).

Anal. Calcd. for $C_{24}H_{23}N_3O_8S$: C, 56.1; H, 4.51; N, 8.18; S, 6.24. Found: C, 56.5; H, 4.69; N, 8.07; S, 6.05.

Attempted Preparation of *N*-Benzoyl-2′,5′-dideoxy-3′-iodocytidine 5′-Benzoate (1).—A mixture of 0.250 g. (0.00063 mole) of **2** and 0.0189 g. (0.00126 mole) of sodium iodide in 30 ml. of 2,4-pentanedione was heated under nitrogen at 100° for 2 hr. After cooling to room temperature the mixture of sodium *p*-toluenesulfonate and *N*-benzoylcytosine (**6**) was filtered off. The latter (0.088 g., 70%) was isolated by its water insolubility. The filtrate was evaporated *in vacuo* at 80° to yield a dark red oil whose thin layer chromatogram [using silica gel G impregnated with phosphor; solvent system butanol–water (86:14)] revealed three components, R_f 0.61, 0.68, and 0.77. This material was not examined further.

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Lead Tetraacetate Oxidation of Some Thiocarbonyl Sugar Derivatives[1a]

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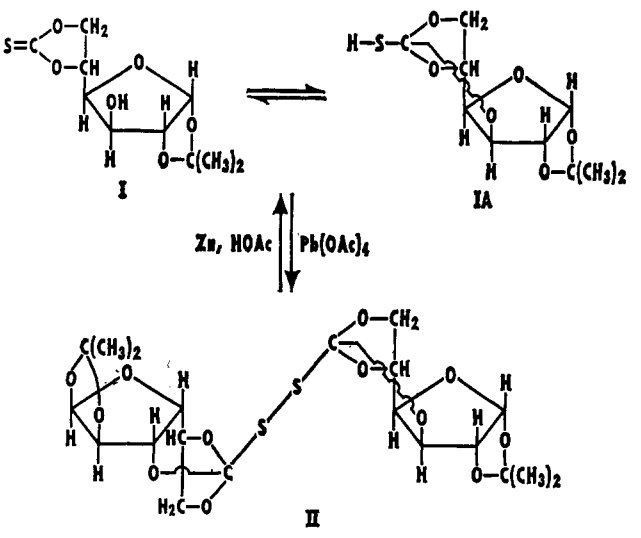
Consumption of lead tetraacetate by the sulfur atom in various sugar thiocarbonyl derivatives was traced, and the resulting oxidized products were isolated and identified. The nature of the oxidation varied with the structure of the sugar derivative used. A rapid consumption of 0.5 mole of lead tetraacetate per mole of 1,2-*O*-isopropylidene-α-D-glucofuranose 5,6-thionocarbonate (I) gave crystalline bis(1,2-*O*-isopropylidene-α-D-glucofuranose 3,5,6-orthocarbonyl) disulfide (II). The 3-*O*-acetyl (III) and 3-*O*-*p*-tolylsulfonyl (V) derivatives of I consumed one molar equivalent of the oxidant and formed elemental sulfur and the corresponding 5,6-carbonate derivatives IV and VI. Bis(1,2:5,6-di-*O*-isopropylidene-3-*O*-thiocarbonyl-α-D-glucofuranose) disulfide and bis-(1,2:3,4-di-*O*-isopropylidene-6-*O*-thiocarbonyl-α-D-galactopyranose) disulfide were virtually unaffected by the oxidant. One molecular equivalent of lead tetraacetate was consumed by 1,2-*O*-isopropylidene-5,6-dithio-β-L-idofuranose 5,6-trithiocarbonate (IX) and its 3-*O*-acetyl (XI) and 3-*O*-*p*-tolylsulfonyl (XIII) derivatives resulting in the formation of the corresponding oxythiocarbonyl compounds X, XII, and XIV.

The sulfur atom of various thio sugars is readily oxidized by periodate[2] and lead tetraacetate.[3–5] Among effects observed are the formation of sulfoxides and sulfones by periodate[2] and the cleavage of dibenzyl mercaptal groups by lead tetraacetate. In the present work the action of lead tetraacetate on sugar derivatives containing a thiocarbonyl group is investigated. The rates of consumption of the oxidant by different thiocarbonyl sugar derivatives in glacial acetic acid at 25° are shown in Figure 1.

In previous work[6] it was proposed that I is in equilibrium with an ortho ester type structure (IA, Scheme I) containing a sulfhydryl group. This proposal was based on the formation of ortho ester type structures on methylation and benzylation of I and on the detection of a sulfhydryl group with 2,2-diphenyl-1-picrylhydrazyl. The presence of such an equilibrium is now confirmed by the isolation and identification of a crystalline dimer product containing a disulfide grouping on oxidation of I with lead tetraacetate. As expected

SCHEME I



(1) (a) Presented before Division of Carbohydrate Chemistry, 149th National Meeting of the American Chemical Society, Detroit, Mich., April 1965. (b) This is a laboratory of the Northern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture. Article is not copyrighted.

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