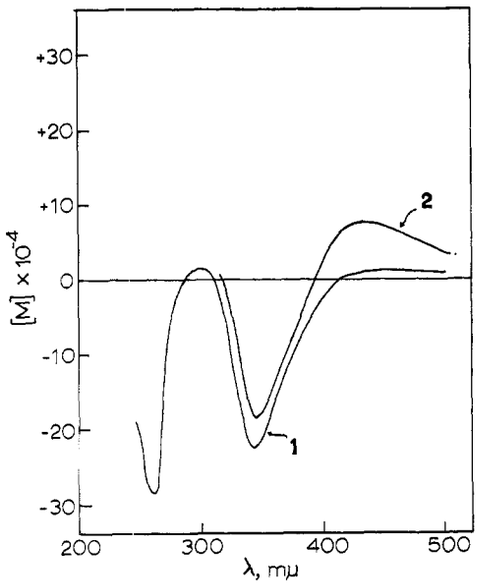


Figure 2.—The optical rotatory dispersion spectra of 1 and 2 in chloroform solution at 25°.

molecule with solvent dipoles. Elevation of the temperature would also tend to diminish the anomaly, by facilitating interconversion of rotomers. The exact nature of the proposed dipole interaction is speculative, but determination of the favored conformation of the aryl group, by X-ray crystallographic analysis, would provide useful evidence on this point.

It has already been shown[1] that the reversal of Hudson's rule for **1** and **2** in chloroform solution holds true over the wavelength range 500–700 mμ; observations at shorter wavelengths were prevented by the strong absorptions of the 2,4-dinitrophenyl chromophore. With the use of a more sensitive spectropolarimeter, measurements over the range 300–500 mμ have been made (Figure 2). It is seen that β-D anomer **2** remains more dextrorotatory than α-D anomer **1** over this whole spectral range. Both anomers show an optically active absorption, of the same sign, in the region 345–360 mμ, and in the case of **1** a second optically active absorption at 260 mμ is observed.

The feasibility of ORD measurements with 2,4-dinitrophenyl derivatives suggests that it might be possible to assign the configuration of amino groups attached to asymmetrically substituted carbon atoms, by means of ORD data on the *N*-(2,4-dinitrophenyl) derivatives.

## Experimental Section

**1,3,4,6-Tetra-*O*-acetyl-2-deoxy-2-(2,4-dinitroanilino)-α- (and β-) D-glucopyranose (1 and 2).**—The anomers were prepared by the procedure previously described,[1] and each product was recrystallized several times. The compounds were chromatographically homogeneous, anomerically pure by nmr, and had melting points and specific rotations in exact agreement with the given values.[1]

**Rotation Measurements.**—The specific rotations of **1** and **2** were measured in the solvents chloroform, benzene, pyridine, acetone, and methanol. A jacketed, center-filling, 1-dm polarimeter tube was used; the jacket was connected to water circulating from a thermostatically controlled water bath, and measurements were made at various temperatures between 20 and 60°. The polarimeter tube was closed with a plastic stopper fitted with an open capillary tube, to allow for thermal expansion while preventing evaporation, and the specific rotations at room temperature were redetermined after the measurements at higher temperatures had been made. Solute concentrations used were approximately 1%, except for the case of **1** in benzene, and **1** and **2** in methanol, where solubility limitations necessitated the use of lower concentrations. The results are given in Table I and Figure 1.

Optical rotatory dispersion measurements were made with chloroform solutions and a Bendix Model 460 C recording spectropolarimeter (Bendix Corp., Cincinnati, Ohio).

**Acknowledgment.**—The authors thank Mr. J. O. Grote of the Bendix Corp., Cincinnati, Ohio, for the spectropolarimetric measurements.

# Use of *p*-Nitrophenyl Chloroformate in Blocking Hydroxyl Groups in Nucleosides[1,2]

ROBERT L. LETSINGER AND KELVIN K. OGILVIE

*Department of Chemistry, Northwestern University Evanston, Illinois*

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*p*-Nitrophenyl chloroformate reacts with hydroxyl groups in nucleosides and nucleoside derivatives at room temperature to give two useful types of O-blocked derivatives. Compounds with "isolated" hydroxyl groups are converted into the *p*-nitrophenyl carbonate esters; those with adjacent *cis*-hydroxyl groups (ribonucleosides) are converted into cyclic carbonates. Specific examples include the formation of *p*-nitrophenyl 5′-O-trityl-thymidine 3′-carbonate from 5′-O-tritylthymidine, *p*-nitrophenyl thymidine 5′-carbonate from thymidine, and uridine 2′,3′ cyclic carbonate from uridine. The O-blocking groups are stable to conditions used for phosphorylation reactions and may be removed in weakly basic solutions (*e.g.*, imidazole in aqueous organic solvents for the nitrophenyl esters and dilute sodium hydroxide or hot aqueous pyridine for the cyclic carbonates).

For the synthesis of oligonucleotides and other complex substances from nucleosides, a variety of selective blocking agents for hydroxyl groups are desirable. Acetyl,[3,4] benzoyl,[4,5] triarylmethyl (triphenylmethyl and mono-, di-, and trimethoxytriphenylmethyl),[4-6] and alkylidene[4,7] groups have been widely used. The acyl groups are removed by alkaline hydrolysis and the triarylmethyl and alkylidene groups by acid hydrolysis. Recently, 2,4-dinitrobenzenesulfenyl chlo-

(1) Part V in the series on Nucleotide Chemistry. For part IV, see R. L. Letsinger and V. Mahadevan, *J. Am. Chem. Soc.*, **88**, 5319 (1966).

(2) This work was supported by the Division of General Medical Sciences, National Institutes of Health, Grant G10265.

(3) For representative examples, see P. T. Gilham and H. G. Khorana, *J. Am. Chem. Soc.*, **80**, 6212 (1958).

(4) P. A. Levene and R. Tipson, *J. Biol. Chem.*, **121**, 131 (1937).

(5) M. Smith, D. H. Rammler, I. H. Goldberg, and H. G. Khorana, *J. Am. Chem. Soc.*, **84**, 430 (1962).

(6) G. Weimann and H. G. Khorana, *ibid.*, **84**, 4329 (1962).

(7) P. A. Levene and R. S. Tipson, *J. Biol. Chem.*, **111**, 313 (1935); A. Hampton, *J. Am. Chem. Soc.*, **83**, 3641 (1961); S. Chladek and J. Smrt; *Collection Czech. Chem. Commun.*, **28**, 1301 (1963).

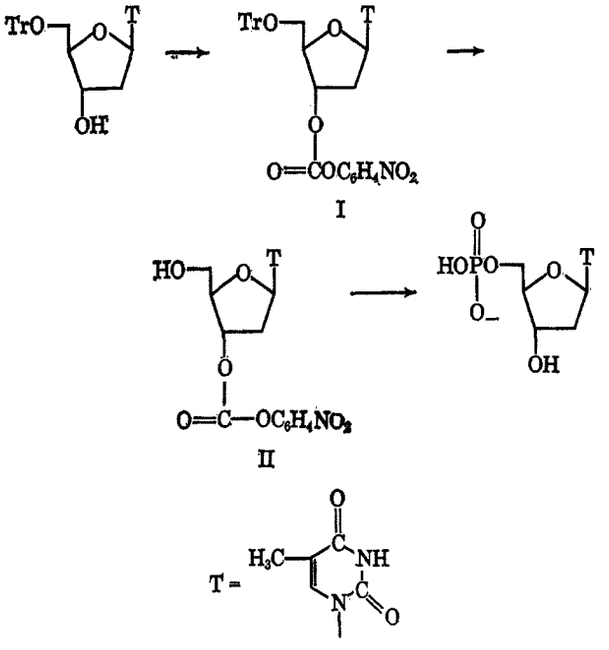
ride was suggested as a reagent for blocking hydroxyl functions.[8,9] The derivatives obtained from it are resistant to the reagents used in phosphorylation reactions, yet may be readily cleaved, unblocking the hydroxyl group, with thiophenol in pyridine[8] or by hydrogenolysis with Raney nickel[9] under conditions where acyl esters and the acid-labile blocking groups are stable.

In searching for new blocking groups which would increase the potential for work on polyhydroxy compounds we have investigated the reaction of *p*-nitrophenyl chloroformate with several nucleosides and nucleoside derivatives. This reagent was selected since *p*-nitrophenyl esters are known to be relatively stable in acidic and neutral solution and to be labile in solutions containing imidazole. We report in this paper the formation of two different types of derivatives, the nature of the product depending on whether the substrate is a ribonucleoside with adjacent *cis*-hydroxyl groups or a deoxyribonucleoside. Both types of derivatives have attractive possibilities for synthetic work in the nucleoside and nucleotide field.

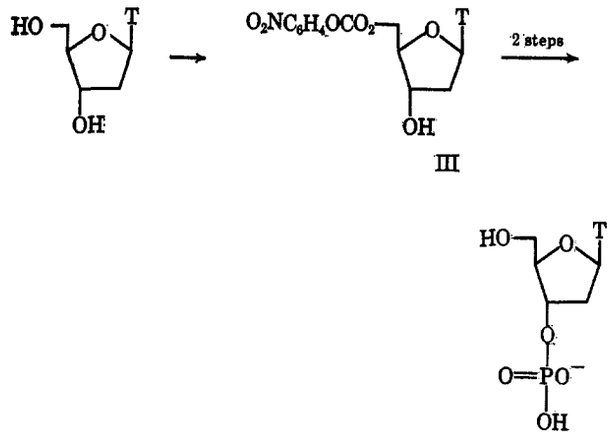
The reaction of *p*-nitrophenyl chloroformate with "isolated" hydroxyl groups in nucleosides is typified by the reaction with 5′-O-tritylthymidine and thymidine. In the former case direct esterification occurred to give *p*-nitrophenyl 5′-O-tritylthymidine 3′-carbonate (I) in 89% yield. On hydrolysis in refluxing aqueous acetic acid this compound gave (90%) the 3′-blocked nucleoside, *p*-nitrophenyl thymidine 3′-carbonate (II). As characteristic of nitrophenyl esters, I and II (Scheme I) were converted rapidly and quantitatively into 5′-O-tritylthymidine and thymidine, respectively, by imidazole in organic solvents. Acetate and benzoate derivatives of thymidine are not hydrolyzed under these conditions. That the *p*-nitrophenyloxycarbonyl group is sufficiently stable to serve as a blocking group was demonstrated by phosphorylation of *p*-nitrophenyl thymidine 3′-carbonate with β-cyanoethyl phosphate and dicyclohexylcarbodiimide in pyridine. Hydrolysis of the product afforded a good yield of thymidine 5′-phosphate. The nitrophenyl carbonate derivatives resemble the dinitrobenzenesulfenic esters in utility in synthetic work. They have the advantage that they are easily preparable in high yields.

From the reaction of *p*-nitrophenyl chloroformate with thymidine was obtained a 33% yield of *p*-nitrophenyl thymidine 5′-carbonate (III). In addition there was obtained a mixture of two substances which appeared to be carbonate esters involving two or more thymidine units per molecule. Since these materials could be hydrolyzed quantitatively to thymidine in alkaline solution, a high conversion of thymidine into III (Scheme II) could be achieved by recycling the thymidine recovered from these esters. Like the 3′ derivative, *p*-nitrophenyl thymidine 5′-carbonate could be phosphorylated at the free hydroxyl position. Phosphorylation was effected successfully with both *p*-nitrophenyl phosphorodichloridate and a mixture of β-cyanoethyl phosphate and N,N′-dicyclohexylcarbodiimide. Alkaline hydrolysis yielded in both

SCHEME I




SCHEME II







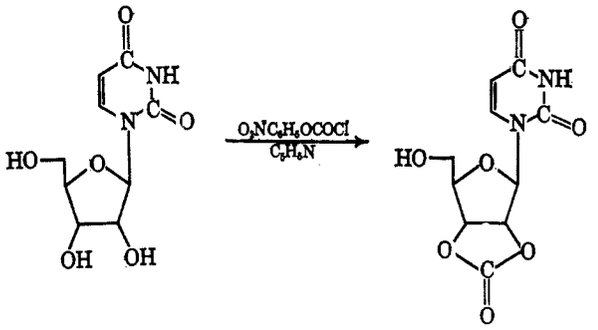
cases thymidine 3′-phosphate, characterized by paper chromatography in a system which differentiates between the 3′- and 5′-phosphate derivatives.

The reaction of *p*-nitrophenyl chloroformate with ribonucleosides took a different course. From equimolar amounts of *p*-nitrophenyl chloroformate and uridine in pyridine at room temperature was obtained *p*-nitrophenol (100%), uridine (20% recovery), and a new compound which was identified as uridine cyclic carbonate (72% yield) by elemental analysis, the infrared spectrum (a strong band at 5.57 μ, absence of bands indicative of $NO_2$), and hydrolysis to uridine. Evidence that this product (IV, Scheme III) was a 2′,3′ rather than a 3′,5′ cyclic carbonate was gained from the reaction with triphenylmethyl chloride in pyridine, which furnished in good yield a trityluridine cyclic carbonate (V) that gave 5′-O-trityluridine on alkaline hydrolysis. Benzoylation of uridine 2′,3′-carbonate produced (71%) a dibenzoyluridine cyclic carbonate (VI). When uridine was treated with a 0.5-fold excess of *p*-nitrophenyl chloroformate, the yield of IV was increased to 89%; no evidence for organic products other than nitrophenol and recovered uridine was found. This reaction probably involves

(8) R. L. Letsinger, J. Fontaine, V. Mahadevan, D. A. Schexnayder, and R. E. Leone, *J. Org. Chem.*, **29**, 2615 (1964).

(9) F. Eckstein, *Tetrahedron Letters*, No. 53, 1 (1965).

SCHEME III



formation of a nitrophenyl 2′- or a 3′-carbonate derivative which, in the presence of pyridine, interacts with the neighboring hydroxyl group to produce the cyclic ester.

N-Benzoyladenosine reacted with *p*-nitrophenyl chloroformate like uridine, yielding N-benzoyladenosine 2′,3′-carbonate. Triphenylmethyl chloride likewise reacted with this cyclic carbonate to give the 5′-ether, N-benzoyl-5′-O-trityladenosine 2′,3′-carbonate. Adenosine itself reacted readily with *p*-nitrophenyl chloroformate; however, attempts to isolate a pure, crystalline product from the reaction mixture were unsuccessful.

An interesting feature of the 2′,3′ cyclic carbonates is the facile hydrolysis by alkaline solutions. Thus, uridine 2′,3′-carbonate was completely hydrolyzed to uridine by 0.5 *M* sodium hydroxide in 50% aqueous dioxane within 5 min at room temperature and by refluxing aqueous pyridine within 15 min. Therefore, since the cyclic carbonates are easily prepared and are also readily hydrolyzed under alkaline condition, they should serve as useful derivatives for synthetic work on ribonucleosides. A disadvantage of the alkylidene groups which have been used widely for blocking 2′,3′-O positions in ribonucleosides is that hydrolysis of the glycoside function, with removal of the purine or pyrimidine moiety, may occur under the acidic conditions employed in the unblocking step. With the cyclic carbonate as a blocking group this difficulty would be avoided.

Since completion of this work Hampton and Nichol have reported the preparation of inosine 2′,3′-carbonate and adenosine 2′,3′-carbonate and have pointed out the utility of these derivatives in synthetic work.[10,11] These workers utilized the reaction of phenyl carbonate with the ribonucleoside in dimethylformamide at 130–150° (bath temperature). Sodium bicarbonate or phenol was used as a catalyst. Under these rather vigorous conditions uridine failed to give a cyclic carbonate, being converted instead to 2,2′-anhydro-1-β-D-arabinofuranosyluracil. For preparation of cyclic carbonates from substances which can form 2′-anhydro derivatives, therefore, *p*-nitrophenyl chloroformate is the reagent of choice.

(10) A. Hampton and A. W. Nichol, *Biochemistry*, **5**, 2076 (1966). An example of phosphorylation of a ribonucleoside cyclic carbonate was also provided (inosine 2,3 cyclic carbonate → inosine 5′-phosphate).

(11) Also of interest is the fact that B. R. Baker, P. M. Tanna, and G. D. F. Jackson [*J. Pharm. Sci.*, **54**, 987 (1965)] obtained from the reaction of phenyl chloroformate and thioinosine in pyridine a mixture which exhibited two carbonyl bands in the infrared (1810 and 1760 $cm^{-1}$). They attributed these bands to a substance in the mixture which contained both the carbophenoxy group (5′ position) and a cyclic carbonate ester.

## Experimental Section

*p*-Nitrophenyl chloroformate was obtained from K & K Chemicals and purified by sublimation, mp 80–81°. Nucleosides were purchased from the Nutritional Biochemicals Corp. Pyridine was purified by successive distillation from *p*-toluenesulfonyl chloride and calcium hydride and was stored over Linde Molecular Sieves.

Thin layer chromatography was carried out on Eastman chromatogram sheets, type K 301r, in ethyl acetate, unless otherwise noted. Descending paper chromatography was carried out on Whatman 3MM paper with the solvent systems: A, isopropyl alcohol–ammonium hydroxide–water (7:1:2, v/v); B, *n*-butyl alcohol–acetic acid–water (5:2:3); C, 1 *M* ammonium acetate in water–ethanol (3:7); and D, 2 *M* aqueous hydrochloric acid–*n*-propyl alcohol (1:3).

Infrared spectra were obtained with a Baird recording spectrophotometer, Model AB2-196, with the sample in potassium bromide. A Cary 14 spectrophotometer was used for the ultraviolet spectra. Elemental analyses were performed by the Micro-Tech Laboratories, Skokie, Ill.

***p*-Nitrophenyl 5′-O-Tritylthymidine 3′-Carbonate (I).**—A mixture of 0.562 g (1 mmole) of the benzene adduct of 5′-O-tritylthymidine[12] and 0.200 g (1 mmole) of *p*-nitrophenyl chloroformate in 10 ml of pyridine was stirred 27 hr at room temperature. Pyridine was then evaporated at reduced pressure, benzene was added to the residual gum, and the benzene was evaporated. Recrystallization of the residual solid from benzene afforded 0.450 g of *p*-nitrophenyl 5′-O-tritylthymidine 3′-carbonate (I), mp 116.5–117.5°. Additional material, bringing the total weight of I to 0.575 g (89%), was recovered from the mother liquors by concentration and chromatography on silica gel (25 × 2 cm) with benzene–ether mixtures as eluent. Prominent peaks in the infrared spectrum were found at 5.69, 5.94, 6.53, and 7.41 μ.

*Anal.* Calcd for $C_{36}H_{31}N_3O_9$: C, 66.55; H, 4.80; N, 6.47. Found: C, 66.45; H, 4.97; N, 6.44.

***p*-Nitrophenyl thymidine 3′-carbonate (II)** was prepared by refluxing a solution of 0.330 g (0.51 mmole) of the trityl ether (I) in 20 ml of 80% acetic acid for 0.5 hr. After the solution was poured onto ~200 g of crushed ice, triphenyl carbinol was separated by filtration and by two extractions of the filtrate with hexane. Concentration and lyophilization of the aqueous solution yielded 0.188 g (99%) of II: mp 97.5–98.5°; prominent infrared peaks at 2.85, 5.71, 5.94, 6.54, 7.36, 7.92, 8.19, 8.32, 9.04, and 11.66 μ.

*Anal.* Calcd for $C_{17}H_{17}N_3O_9$: C, 50.12; H, 4.21; N, 10.31. Found: C, 49.70; H, 4.46; N, 9.96.

**Thymidine 5′-Phosphate (Phosphorylation 1).**—Compound II (0.070 g, 0.17 mmole) and 1.0 mmole of pyridinium β-cyanoethyl phosphate[13] (1.0 ml of 1.0 *M* solution) were dried by evaporation under vacuum three times from pyridine and then stirred with 0.426 g (2.07 mmoles) of N,N′-dicyclohexylcarbodiimide in 5 ml of pyridine for 4 days at room temperature. Excess dicyclohexylcarbodiimide was converted into the urea by addition of 3 ml of water followed by 16 hr of stirring. Dicyclohexylurea was separated by filtration and the filtrate, after washing with hexane (two 25-ml portions), was warmed with 10 ml of 1 *M* sodium hydroxide under gentle reflux for 40 min to remove the cyanoethyl group from the phosphate derivative. After neutralization with Dowex 50 resin (pyridinium form) the solution was concentrated at 25° under reduced pressure. Chromatography of a sample along with samples of thymidine, thymidine 5′-phosphate, thymidine 3′-phosphate, and *p*-nitrophenol as controls revealed two organic components: thymidine 5′-phosphate and *p*-nitrophenol (see Table I, phosphorylation 1). In solvent A two additional faint spots were also found at $R_f$ 0.013 and 0.38. Chromatography of the bulk of the solution on Whatman 3MM paper (46 × 47 cm) in solvent A and elution of the band at $R_f$ 0.11 with water yielded, on lyophilization of the extract, 0.045 g (73%) of ammonium thymidine 5′-phosphate: infrared peaks at 2.94, 3.15, 6.0, 6.24, and 7.12 μ.

***p*-Nitrophenyl Thymidine 5′-Carbonate (III).**—Thymidine (0.484 g, 2 mmoles) and *p*-nitrophenyl chloroformate (0.400 g, 2 mmoles) were stirred for 3 days in 10 ml of pyridine at room temperature. Pyridine was removed at reduced pressure, leaving a gummy residue which was dissolved in a minimum volume of ethanol and acetone (3 ml) and applied to a silica gel column

(12) G. Weimann and H. G. Khorana, *J. Am. Chem. Soc.*, **84**, 419 (1962).

(13) Phosphorylation method of G. M. Tener, *ibid.*, **83**, 159 (1961).

TABLE I

$R_f$ VALUES FOR PRODUCTS OF PHOSPHORYLATION REACTIONS[a]

| Compounds | Solvent systems A | B | D |
|---|---|---|---|
| Products from phosphorylation 1 | 0.11 | 0.33 | 0.78 |
| | 0.84 | 0.92 | 0.95 |
| Products from phosphorylation 2 | 0.14 | | 0.84 |
| | 0.80 | | 0.96 |
| Products from phosphorylation 3 | 0.15 | | 0.83 |
| | 0.81 | | 0.94 |
| Thymidine 3′-phosphate | 0.13–0.16 | 0.36 | 0.83–0.86 |
| Thymidine 5′-phosphate | 0.11 | 0.33 | 0.76–0.78 |
| Thymidine | 0.67 | 0.67 | 0.74 |
| *p*-Nitrophenyl thymidine 3′-phosphate | 0.63 | | |
| *p*-Nitrophenol | 0.77–0.84 | 0.92 | 0.94–0.96 |

[a] The controls were run numerous times. Where variations were observed the range of $R_f$ values are indicated.

(25 × 2 cm). Elution with ethyl acetate yielded first nitrophenol ($R_f$ 0.80, thin layer) and then *p*-nitrophenyl thymidine 5′-carbonate, weight 0.268 g (33%), mp 95–95°, $R_f$ 0.43 (thin layer); major bands in infrared were found at 2.90, 5.69, 5.94, 6.54, 7.36, 7.81, and 8.12 μ.

*Anal.* Calcd for $C_{17}H_{17}N_3O_9$: C, 50.12; H, 4.21; N, 10.31. Found: C, 50.35; H, 4.56; N, 10.18.

When no further material was eluted with ethyl acetate, the column was washed with tetrahydrofuran. This treatment brought down 0.310 g of a white solid, which on further chromatography on a silica gel column with elution by tetrahydrofuran–acetonitrile (1:9, v/v) afforded approximately equal amounts of two substances, $R_f$ (thin layer) 0.30 and 0.10 in tetrahydrofuran–acetonitrile (1:9), and mp 130–135 and 165–166°, respectively. These substances did not contain the nitrophenyl group and they yielded thymidine on alkaline hydrolysis. They appeared to be esters of carbonic acid and thymidine but were not further characterized.

The yield of the *p*-nitrophenyl thymidine 5′-carbonate was not significantly improved when the reactions conditions were modified. Thus, with reaction times of 5 and 7 days the yields were 35 and 36%. When the thymidine to *p*-nitrophenylchloroformate ratio was 2:1 the yield of III was 17%; when the ratio was 1:1.5, the yield was 21%.

**Phosphorylation of *p*-Nitrophenyl Thymidine 5′-Carbonate. A. With β-Cyanoethyl Phosphate (Phosphorylation 2).**—*p*-Nitrophenyl thymidine 5′-carbonate (0.080 g, 0.2 mmole) and 1.5 mmole of β-cyanoethyl phosphate (pyridinium form) were rendered anhydrous by repeated evaporation from pyridine (four 5-ml portions). N,N-Dicyclohexylcarbodiimide (0.70 g, 3.4 mmole) in 2.5 ml of pyridine was added and the reaction mixture was stirred at room temperature for 76 hr. Following addition of water (3 ml) and 30 min of stirring, the mixture was filtered to separate dicyclohexylurea. The filtrate was then washed with benzene and heated at reflux for 40 min with 10 ml of 1 *M* aqueous sodium hydroxide. After neutralization by Dowex 50 (pyridinium form) the solution was analyzed by thin layer chromatography. Only two spots were obtained, corresponding to thymidine 3′-phosphate and *p*-nitrophenol (Table I, phosphorylation 2).

**B. With *p*-Nitrophenyl Phosphorodichloridate (Phosphorylation 3).**—To 0.125 g (0.5 mmole) of *p*-nitrophenyl phosphorodichloridate in 3 ml of dioxane and 0.1 ml of pyridine was added (1.5 hr) with stirring a solution of 0.10 g (0.25 mmole) of *p*-nitrophenyl thymidine 5′-carbonate in 5 ml of purified dioxane. The mixture was stirred at room temperature for an additional 3 hr; then 3 ml of water was added and the mixture was evaporated to dryness. The residue was partitioned between chloroform and water and the chloroform layer was washed with water. Paper chromatography in solvent A of a sample of the chloroform solution showed two substances, $R_f$ 0.77 (*p*-nitrophenol) and 0.63 (*p*-nitrophenyl thymidine 3′-phosphate). Controls with authentic samples of both substances were run concurrently. The remaining chloroform solution was evaporated to a gum, which was then heated for 2 hr on a steam bath with 6 ml of 1 *M* sodium hydroxide. Neutralization with Dowex 50 ($H^+$) and paper chromatography revealed two products, *p*-nitrophenol and thymidine 3′-phosphate (Table I, phosphorylation 3). It may be noted that thymidine 3′-phosphate and thymidine 5′-phosphate separate well in solvent D and that thymidine separates well from the thymidine phosphates in solvent A.

**Hydrolysis of *p*-Nitrophenyl Thymidine 5′-Carbonate.**—*p*-Nitrophenyl thymidine 5′-carbonate (20 mg) was dissolved in dioxane (1 ml). Imidazole (50 mg) and water (0.01 ml) were added and the solution was stirred at room temperature for 30 min. As the end of this time the *p*-nitrophenyl thymidine 5′-carbonate had been completely converted into *p*-nitrophenol and thymidine as determined by thin layer chromatography in three different solvent systems (ethyl acetate, tetrahydrofuran, and acetonitrile).

**Uridine 2′,3′-Carbonate (IV).**—Uridine (0.977 g, 4 mmoles) and 0.800 g (4 mmoles) of *p*-nitrophenyl chloroformate were stirred in 10 ml of pyridine for 5 days at room temperature. After removal of the pyridine at reduced pressure, the residue was taken up in the minimum amount of acetone and chromatographed on silica (25 × 2 cm) with ethyl acetate followed by tetrahydrofuran. From the ethyl acetate fractions was obtained 0.556 g (100%) of *p*-nitrophenol and 0.775 g (72%) of uridine 2′,3′-carbonate, mp 120–125° dec. The carbonate was homogeneous in thin layer chromatography on silica with ethyl acetate ($R_f$ 0.39) and on Whatman 3MM paper in solvent B ($R_f$ 0.59). Major bands in the infrared occurred at 2.90, 5.57, and 5.94 μ.

*Anal.* Calcd for $C_{10}H_{10}N_2O$ : C, 44.45; H, 3.73; N, 10.37. Found: C, 44.70; H, 3.95; N, 9.84.

From the tetrahydrofuran fractions was recovered 0.200 g of uridine, identified from the infrared spectrum, the mp 160–165°, a mixture melting point, and paper chromatography in solvents A ($R_f$ 0.54), B ($R_f$ 0.50), and C ($R_f$ 0.71).

This experiment was repeated with the exception that the ratio of *p*-nitrophenyl chloroformate to uridine was increased from 1:1 to 1.5:1. In this case the yield of uridine 2′,3′-carbonate was 89%.

**5′-O-Trityluridine 2′,3′-Carbonate (V).**—A solution of 0.234 g (0.84 mmole) of triphenylmethyl chloride and 0.135 g (0.5 mmole) of uridine 2′,3′-carbonate in 5 ml of pyridine was stirred for 2 days at room temperature, heated for 2 hr on a steam bath, and poured onto crushed ice. The solid was collected, dried under vacuum, and recrystallized from benzene to give 0.177 g (68%) of 5′-O-trityluridine 2′,3′-carbonate, mp 134.5–135.5°; strong infrared bands were at 5.57, 5.94, 9.22, and 14.15 μ.

*Anal.* Calcd for $C_{29}H_{24}N_2O_7$: C, 67.96; H, 4.72; N, 5.47. Found: C, 67.81; H, 4.97; N, 5.55.

**Dibenzoyluridine 2′,3′-Carbonate (VI).**—To 0.270 g (1 mmole) of uridine 2′,3′-carbonate in 5 ml of pyridine was added with stirring at room temperature 1 ml (9 mmoles) of benzoyl chloride. After 14 hr the solution was poured onto 100 g of ice. The gum which separated was taken up in chloroform and the resulting solution was dried over sodium sulfate, concentrated, and chromatographed on silica (20 × 2 cm column). Elution with chloroform yielded 0.340 g (71%) of the dibenzoyluridine 2′,3′-carbonate, mp 208–209°; the principle bands in the infrared were at 5.55, 5.75, 5.88, 6.0, 7.82, and 14 μ.

*Anal.* Calcd for $C_{24}H_{18}N_2O_9$: C, 60.25; H, 3.79; N, 5.86. Found: C, 59.66; H, 3.84; N, 5.65.

**Hydrolysis of Cyclic Carbonates.**—(a) 5′-O-Trityluridine 2′,3′-carbonate (0.060 g) was hydrolyzed by stirring with 5 ml of 0.5 *M* sodium hydroxide in 50% aqueous dioxane for 10 min at room temperature. Excess base was neutralized by a stream of carbon dioxide and the solution was concentrated to 0.5 ml. Extraction with ethyl acetate and chromatography on silica gel (10 × 2 cm) furnished, after recrystallization from ethyl acetate, 0.047 g (83%) of 5′-O-trityluridine. The product melted at 119–121° and did not depress the melting point of an authentic sample prepared by the procedure of Michelson and Todd.[14] When the sample was recrystallized from benzene it melted at 109°, as did the authentic sample when treated similarly. The product was further characterized by the infrared spectrum, which was identical with that of the authentic sample, and by thin layer chromatography in ethyl acetate ($R_f$ 0.59).

(b) A solution of 20 mg of uridine 2′,3′-carbonate in 2 ml of pyridine and 2 ml of water was heated under gentle reflux for 15 min. The solvent was then removed under reduced pressure and the remaining solid was dissolved in water and characterized by thin layer and paper chromatography. In each case a single fluorescent spot, corresponding to uridine, was observed (Table II).

(14) A. M. Michelson and A. R. Todd, *J. Chem. Soc.*, 3459 (1956).

TABLE II

CHROMATOGRAPHY OF PRODUCTS FROM HYDROLYSIS OF IV

| Solvent | $R_f$ values: Hydrolysis product | Uridine | IV |
|---|---|---|---|
| A[a] | 0.46 | 0.46 | |
| B[a] | 0.49 | 0.49 | |
| Ethyl acetate[b] | 0.015 | 0.015 | 0.35 |
| Dioxane[b] | 0.73 | 0.72 | 0.87 |
| Tetrahydrofuran[b] | 0.63 | 0.63 | 0.83 |

[a] Paper chromatography. [b] Thin layer chromatography on silica sheets.

**N-Benzoyladenosine 2′,3′-Carbonate.**—A solution made from 0.371 g (1 mmole) of N-benzoyladenosine[15] and 0.300 g (1.5 mmole) of *p*-nitrophenyl chloroformate and 10 ml of dry pyridine was stirred for 3 days at room temperature and then mixed with 150 ml of cold ether. The resulting precipitate was dissolved in a minimum volume of ethanol and chromatographed on silica gel by elution successively with ethyl acetate, ethyl acetate–tetrahydrofuran (9:1, v/v), and tetrahydrofuran. The ether solution was concentrated to a volume of ~2 ml and also chromatographed on silica gel with the same solvents. From the ethyl acetate fractions was obtained a total of 0.200 g (50%) of N-benzoyladenosine 2′,3′-carbonate, mp 164–165.5°; principal bands in the infrared were at 5.57, 5.92, 6.18, and 6.29 μ.

*Anal.* Calcd for $C_{18}H_{15}N_5O_6$: C, 54.42; H, 3.80; N, 17.62. Found: C, 54.35; H, 3.74; N, 17.59.

From the pure tetrahydrofuran fractions was recovered 0.160 g of N-benzoyladenosine. On the basis of the benzoyladenosine unrecovered the yield of N-benzoyladenosine 2′,3′-carbonate was 90%.

**N-Benzoyl-5′-O-trityladenosine 2′,3′-Carbonate.**—A solution of 0.30 g (1.1 mmole) of triphenylmethyl chloride and 0.300 g (0.75 mmole) of N-benzoyladenosine 2′,3′-carbonate in 10 ml of pyridine was stirred for 7 days at room temperature and then poured onto crushed ice. The gummy precipitate which formed was taken up in chloroform and the aqueous solution was extracted twice with chloroform. After drying with sodium sulfate, the chloroform solutions were combined and concentrated. Recrystallization of the resulting gum from ethyl acetate gave 0.350 g (73%) of N-benzoyl-5′-O-trityladenosine 2′,3′-carbonate, mp 134–135° with prior softening. After further purification by chromatography on silica gel with ethyl acetate, the product melted at 134–135.5° and exhibited bands in the infrared spectrum at 5.56, 5.92, 6.2, 9.2, and 14.2 μ.

*Anal.* Calcd for $C_{37}H_{29}N_5O_6$: C, 68.08; H, 4.57; N, 10.95. Found: C, 68.61; H, 4.46; N, 11.00.

$R_f$ values for chromatography of the adenosine derivatives on silica thin layer slides are presented in Table III.

TABLE III

THIN LAYER CHROMATOGRAPHIC DATA FOR ADENOSINE DERIVATIVES

| Solvent | N-Benzoyladenosine | N-Benzoyladenosine 2′,3′-carbonate | N-Benzoyl-5′-O-trityladenosine 2′,3′-carbonate |
|---|---|---|---|
| Ethyl acetate | 0.05 | 0.45 | 0.83 |
| Acetonitrile | 0.15 | 0.71 | 0.84 |
| Acetone | 0.55 | 0.83 | 0.98 |
| Ethanol | 0.64 | 0.72 | 0.75 |
| Dioxane | 0.68 | 0.80 | 0.87 |

(15) Prepared by procedure of R. H. Hall, *Biochemistry*, **3**, 769 (1964).

# Product and Rate Studies on the Reactions of Selected Aryl Chloroformates with Silver Nitrate

MATTHEW J. ZABIK[1] AND ROBERT D. SCHUETZ

*Department of Chemistry and the Institute of Biology and Medicine, Michigan State University, East Lansing, Michigan*

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The reactions of 13 aryl chloroformates prepared from phosgene and various phenols with silver nitrate in acetonitrile were examined. The reaction products, obtained in high yield from the 4-substituted phenyl chloroformates, were 4-substituted 2-nitrophenols. The 2,6-disubstituted phenyl chloroformates yielded two products; the expected 4-nitro-2,6-disubstituted phenols and biphenylquinones, while the 2,4,6-trimethylphenyl chloroformate yielded, as the major product, a substituted stilbenequinone. At equal molar concentrations the initial reaction rates of the 4-substituted phenyl chloroformates with silver nitrate at 10, 21, and 31° were second order. With a fivefold molar excess of silver nitrate, the initial rates at 21° were pseudo first order. The change in entropy, $\Delta S^*$, was negative ranging from −40.7 for the 4-nitro to −5.1 for the 4-methoxy substituent. Good Hammett correlation was obtained for $\rho$ values of 1.5017 (10°), 1.1482 (21°), and 0.9211 (31°) for the reactions at equal molar concentrations of reactants and 0.9383 (21°) for the reaction with excess silver nitrate.

Wolfrom and Chaney[2] in 1961, reported an attempt to prepare phenyl nitrate by the interaction of phenyl chloroformate with silver nitrate. They obtained *o*-nitrophenol in a 65% yield as a rearrangement product instead of the expected aryl nitrate. Since their initial report, no further studies on this aromatic chloroformate rearrangement reaction have appeared in the literature. The present investigation was undertaken to obtain information concerning the products and kinetics of the reactions of aryl chloroformates with silver salts to consider possible mechanisms for this type of rearrangement reaction.

Considerable research has been reported on the reactions of aliphatic chloroformates and some bears on on the reactions of aryl chloroformates with silver salts. Boschan,[3] in 1959, reported the preparation, in high yields, of aliphatic nitrate esters from the reaction of silver nitrate with aliphatic chloroformates. He demonstrated that 75% of the alkyl–oxygen (R–O) bond in the chloroformate remained intact by $O^{18}$-labeling experiments and that the reaction proceeded mainly with retention of configuration (70% retention, 30% inversion) in the migrating R group. Hence, it was postulated that an SN1 type of decomposition of this intermediate was operative with some action also occurring by an ionic mechanism. Mortimer[4] in a study of alkyl nitratocarbonates, found that reaction 2 paralleled roughly reaction 1 in velocity at moderate temperature (40°), but was much slower than 1 below 0°.

$$ROCCl + AgNO_3 \xrightarrow{CH_3CN} ROCONO_2 + AgCl \qquad (1)$$

(1) Abstracted in part from the Ph.D. Dissertation of M. J. Zabik, Michigan State University, 1965.

(2) A. Chaney and M. L. Wolfrom, *J. Org. Chem.*, **26**, 2998 (1961).

(3) R. Boschan, *J. Am. Chem. Soc.*, **81**, 3341 (1959).

(4) G. A. Mortimer, *J. Org. Chem.*, **27**, 1876 (1962).