76–78° (8 mm) and its nmr spectrum included signals at −0.25 (cyclopropane CH_2, 2 H) and at −0.45 ppm (bridgehead H, 2 H).

Anal.[17] Calcd for $C_{11}H_{20}$: C, 86.8; H, 13.2. Found: C, 86.4; H, 13.1.

Registry No.—*trans*-Bicyclo[8.1.0]undecane, 15840-80-9.

(17) By R. Seab in these laboratories.

N^6,3′-O-Disubstituted Deoxyadenosine[1]

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Deoxyadenosine derivatives possessing alkali or hydrazine labile protecting groups at the N^6 and 3′-O positions are attractive intermediates for use in synthesizing oligonucleotides by the phosphotriester method.[1,2] A route to such compounds is to block the reactive 5′ oxygen of N^6-acyl- or benzoyldeoxyadenosine, introduce the desired substituent on the 3′ oxygen, and then remove selectively the protecting group on the 5′ oxygen. Since N^6-benzoyldeoxyadenosine derivatives readily undergo depurination in acidic media,[3,4] the protecting group on the 5′-oxygen atom should be one that can be removed without resort to acidic conditions. At the same time, strong alkaline conditions for removal of this group are precluded if an acyl group is to be retained on the 3′ oxygen.

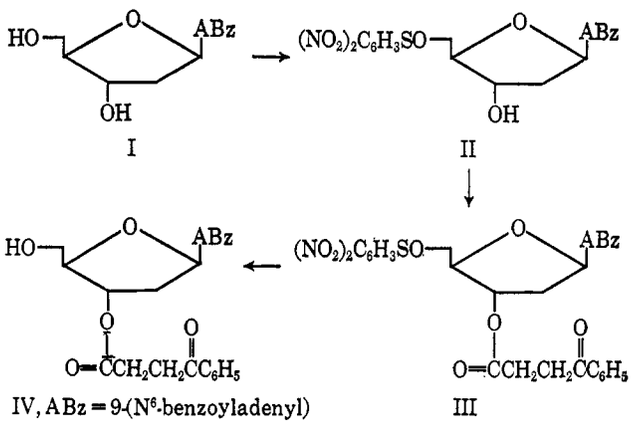
The 2,4-dinitrobenzenesulfenyl group, which protects oxygen of hydroxyl groups during acylation reactions and can be removed readily by the action of thiophenol in pyridine,[5] appeared to have the requisite properties for protecting the 5′-oxygen of deoxyadenosine derivatives. As a test of this approach we explored the synthesis of 3′-O-(β-benzoylpropionyl)-N^6-benzoyldeoxyadenosine *via* 5′-O-(2,4-dinitrobenzenesulfenyl)-N^6-benzoyldeoxyadenosine.

Preliminary experiments were conducted with thymidine to see if the 5′ oxygen of a nucleoside with free 3′- and 5′-hydroxyl groups could be preferentially sulfenylated. At room temperature the degree of selectivity was low. However, when the reaction was carried out with slightly less than 1 equiv of 2,4-dinitrobenzenesulfenyl chloride at 0°, a 37% yield of 5′-O-(2,4-dinitrobenzenesulfenyl)thymidine was obtained along with small amounts of the 3′-O-dinitrobenzenesulfenyl isomer (10%) and a higher sulfenylated product (~8%). The 3′ isomer has been prepared previously from 5′-O-tritylthymidine.[5]

N^6-Benzoyldeoxyadenosine underwent reaction with 2,4-dinitrobenzenesulfenyl chloride considerably more slowly than did thymidine. A suitable method for formation of the 5′-oxygen derivative was found to be treatment of N^6-benzoyldeoxyadenosine with 1.5 equiv of 2,4-dinitrobenzenesulfenyl chloride in pyridine at 20° for 1.5 hr. Under these conditions a 45% yield of 5′-O-(2,4-dinitrobenzenesulfenyl)-N^6-benzoyldeoxyadenosine, a 12% yield of the corresponding 3′-O isomer, and a 13% yield of a disulfenylated derivative were obtained.

A flowsheet depicting the formation of 5′-O-(2,4-dinitrobenzenesulfenyl)-N^6-benzoyldeoxyadenosine (II), introduction of a β-benzoylpropionyl group at the 3′ oxygen to give III, and cleavage of the dinitrobenzenesulfenyl group to yield 3′-O-(β-benzoylpropionyl)-N^6-benzoyldeoxyadenosine (IV) is shown in Chart I.

CHART I



Compound III was obtained in 54% yield by reaction of II with excess β-benzoylpropionic acid and dicyclohexylcarbodiimide. The dinitrobenzenesulfenyl group could be cleaved from the 5′ oxygen cleanly with thiophenol in pyridine, as in the case of the thymidine derivatives.[5] We used hydrogen sulfide in pyridine in the preparative experiment for this purpose, however, since it was found that hydrogen sulfide effects the cleavage and the reaction mixture can be worked up more conveniently than one containing excess thiophenol.

In the case of the mono(dinitrobenzenesulfenyl) derivatives of thymidine the assignment of structure is clear as the higher melting isomer is known from independent synthesis[5] to be the 3′-oxygen derivative. Two lines of evidence point to the fact that the lower melting isomer of mono(dinitrobenzenesulfenyl)-N^6-deoxyadenosine is the 5′-oxygen derivative: (1) The lower melting isomer was obtained in preponderate amount, in accord with the observation that the 5′-oxygen of nucleoside derivatives is in general attacked more readily than the 3′-oxygen. (2) The R_f value of the lower melting isomer (in ethyl acetate on silica slides) is less than that for the higher melting isomer, in agreement with the observation that the R_f values for 5′-oxygen derivatives of nucleosides are less than the R_f values of the corresponding 3′-oxygen derivatives (*e.g.*, for the 2,4-dinitrobenzenesulfenyl, the *p*-monomethoxytrityl, and the isobutyloxycarbonyl derivatives[6] of thymidine). Proof that the β-benzoylpropionyl group in IV is joined at the 3′-oxygen, and therefore that the 2,4-dinitroben-

(1) Part XI in series on Nucleotide Chemistry. Part X: R. L. Letsinger, M. H. Caruthers, P. S. Miller, and K. K. Ogilvie, *J. Amer. Chem. Soc.*, **89**, 7146 (1967). This research was supported by the Division of General Medical Sciences, National Institutes of Health (GM-10265).

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zenesulfenyl group in II is joined at the 5′-oxygen, is provided by the synthesis of thymidylyl-(3′–5′)-deoxyadenosine from compound IV and 5′-O-monomethoxytritylthymidine.[7] This compound was completely hydrolyzed by snake venom phosphodiesterase, an enzyme specific for oligonucleotides possessing a terminal 3′-hydroxyl group and 3′–5′ phospho diester links.

Experimental Section

Infrared spectra were determined in potassium bromide with a Baird recording spectrophotometer. Thin layer chromatography was performed on Eastman Chromagram sheets, 6060 silica gel, with ethyl acetate; R_f values are indicated in text. Elemental analyses were made by the Micro-Tech Laboratories, Skokie, Ill.

5′-O-(2,4-Dinitrobenzenesulfenyl)thymidine.—Thymidine (2.00 g, 8.28 mmol) was dissolved in 150 ml of anhydrous pyridine and cooled to 0°. 2,4-Dinitrobenzenesulfenyl chloride (1.94 g, 7.62 mmol) in 50 ml of anhydrous pyridine was added dropwise over a period of 1 hr with stirring; then, after the mixture had stood for 4 hr at 0°, it was allowed to warm to room temperature. The mixture was diluted with 1 l. of ice–water and extracted three times with $CHCl_3$. The organic layer was washed twice with water, dried with Na_2SO_4, and concentrated. The residue was taken up in warm methanol and the solution was filtered while hot. Methanol was then distilled off and the residue was dissolved in ethyl acetate and chromatographed on silica gel (12 × 50 cm) using ethyl acetate as an eluent. The first fraction yielded 0.19 g of a yellow solid, mp 122–128°, R_f 0.85, which is probably 3′,5′-bis-O-(2,4-dinitrobenzenesulfenyl)thymidine. The second fraction contained 0.35 g (10%) of 3′-O-(2,4-dinitrobenzenesulfenyl)thymidine,[5] mp 182–184° dec, R_f 0.62. Finally, elution with 50% ethyl acetate–acetone yielded 5′-O-(2,4-dinitrobenzenesulfenyl)thymidine, isolated by stripping off the solvent, dissolving the residue in ethyl acetate, and precipitation by addition of hexane: weight 1.25 g (37%); mp 102–110°; R_f 0.43; prominent infrared bands at 2.90, 5.95, 6.28, 6.60, 7.47, and 12.08 μ. The spectrum was very close to that of the 3′-O isomer, differing primarily by absence of a shoulder at 9.0 μ.

Anal. Calcd for $C_{16}H_{16}N_4O_9S$: C, 43.64; H, 3.66; N, 12.72; S, 7.28. Found: C, 43.65; H, 3.93; N, 11.78; S, 7.06.

5′-O-(2,4-Dinitrobenzenesulfenyl)-3′-O-(β-benzyoylpropionyl)-N⁶-benzoyldeoxyadenosine (III).—To 0.366 g (1.03 mmol) of dry N⁶-benzoyldeoxyadenosine in 10 ml of pyridine at 20° was added 0.350 g (1.49 mmol) of 2,4-dinitrobenzenesulfenyl chloride in 5 ml of pyridine. After 1.5 hr the mixture was poured over 300 g of ice and allowed to stand 1 hr. The insoluble material was extracted into chloroform which, after drying over Na_2SO_4, was stripped *in vacuo*. Ethanol was added and stripped to remove traces of pyridine, and the gummy residue was dissolved in hot $CHCl_3$. Column chromatography on silica gel with ethyl acetate yielded on concentration and precipitation with hexane 0.097 g of a yellow solid, mp 115–125°, R_f 0.85, which is probably the bis-2,4-dinitrobenzenesulfenyl derivative. From the second chromatographic fraction was obtained 0.066 g (12%) of 3′-O-(2,4-dinitrobenzenesulfenyl)-N⁶-benzoyldeoxyadenosine: mp 151–153°; R_f 0.66; prominent infrared bands at 2.93, 5.82, 6.24, 6.55, 7.44, and 11.96 μ.

Anal. Calcd for $C_{23}H_{19}N_7O_8S$: C, 49.90; H, 3.46; N, 17.72; S, 5.79. Found: C, 49.64; H, 3.80; N, 17.58; S, 5.61.

Continued elution of the column yielded 0.253 g (45%) of II: mp 115–125°; R_f 0.32; prominent infrared bands at 2.95, 5.84, 6.24, 6.55, 7.44, and 11.97 μ. A mixture of 0.244 g (0.44 mmol) of compound II, 0.451 g (2.53 mmol) of β-benzoylpropionic acid, and 0.6 g (3 mmol) of dicyclohexylcarbodiimide in 2 ml of pyridine was stirred for 2 hr at room temperature, diluted with 1 ml of water, and stirred an additional hour. The insoluble dicyclohexylurea was filtered off and washed with $CHCl_3$ (50 ml) and the combined filtrate and $CHCl_3$ washings were washed with saturated $NaHCO_3$. After drying over Na_2SO_4 the solution was stripped in a rotatory evaporator, diluted with ethanol, and stripped again to a gummy residue. This material was dissolved in hot ethyl acetate and, after standing overnight, was filtered to remove the crystalline acylurea. On chromatography on a silica gel column with ethyl acetate the filtrate yielded compound III: mp 94–96°; weight 0.170 g (54% from II); R_f 0.67; prominent infrared bands at 2.98, 3.48, 5.78 (s), 5.93, 6.27, 6.60, 7.48, and 12.00 μ (w).

Anal. Calcd for $C_{33}H_{27}N_7O_{10}S$: C, 55.53; H, 3.81; N, 13.74; S, 4.49. Found: C, 55.59; H, 4.12; N, 13.63; S, 4.41.

3′-O-(β-Benzoylpropionyl)-N⁶-benzoyldeoxyadenosine (IV).—The preparation of compound III was repeated on a fourfold scale to the point where the products were dissolved in ethyl acetate and separated by chromatography. In this case, in place of the chromatographic separation, the gummy products were dissolved in pyridine and H_2S was slowly bubbled through the solution for 16 hr. Following the usual work-up procedure (stripping of the solvent, addition of ethanol, stripping of the ethanol, etc.) the solid products were chromatographed on silica gel with ethyl acetate–methanol (90/10). Compound IV was recovered by concentrating the appropriate fraction and was recrystallized from ethyl acetate: mp 111–112.5°; weight 0.532 g (57%); R_f 0.57; prominent infrared bands at 2.96, 5.76, 5.93, 6.24, 6.87, and 8.63 μ. That the 2,4-dinitrobenzenesulfenyl group was absent was shown by absence of bands at ~6.6 and 7.4 (nitro groups) and 12.0 μ (characteristic for 2,4-dinitrobenzenesulfenyl derivatives).

Anal. Calcd for $C_{27}H_{25}N_5O_6$: C, 62.90; H, 4.89; N, 13.59. Found: C, 62.96; H, 4.99; N, 13.52.

Registry No.—5′-O-(2,4-Dinitrobenzenesulfenyl)thymidine, 16243-75-7; 3′-O-(2,4-dinitrobenzenesulfenyl)-N⁶-benzoyldeoxyadenosine, 16243-76-8; III, 16281-89-3; IV, 16243-74-6.

(7) Experiments of K. K. Ogilvie, Northwestern University, Evanston, Ill.

Reactions of Phosphorus Compounds. XVI. The Reaction of Several Hydroxyphosphonium Ylides

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The preparation of 2,3-dihydro-1-benzoxepin may be readily accomplished by treating 3(O-formylphenoxy)-propyltriphenylphosphonium bromide (I) in a nonprotonic solvent under basic conditions.[1] As an extension to this work, and due to the recent interest in the oxepin ring system,[2-7] we have first examined the feasibility of preparing 1-phenoxy-4-phenylbutadiene (VI) from 2-hydroxy-3-phenoxypropyltriphenylphosphonium bromide (III) and benzaldehyde. Finding this first reaction successful, we turned to the corresponding reaction of 2-hydroxy-3(2-formylphenoxy)propyltriphenylphosphonium bromide (XII) which we hoped would give 1-benzoxepin (XVII).

The salt III was allowed to react with base to form the ylide IV, and addition of benzaldehyde followed (Scheme I). The expected products of this reaction

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