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Some Aspects of the Reaction of Arenesulfenyl chlorides with Hydroxyl Functions of Ribonucleosides

HERVÉ BAZIN, JARMO HEIKKILÄ and JYOTI CHATTOPADHYAYA *

Bioorganic Chemistry Laboratory, Department of Microbiology, Box 581, Biomedical Center, University, S-751 23 Uppsala, Sweden

Reaction of benzene, 4-toluene, 2-pyridine, 4-nitrobenzene, 4-chlorobenzene, and 2-toluenesulfenyl chloride with 6-*N*-phthaloyl-2′,3′-isopropylideneadenosine (*1*) in dry pyridine solution, at 0 to −10 °C, gave a diastereomeric mixture of arenesulfinates, *2*–*7*, along with 6-N-phthaloyl-5′-chloro-5′-deoxy-2′,3′-isopropylideneadenosine (*8*); while the reaction of 2-nitrobenzene, 2,4-dinitrobenzene, 2-nitro-4-toluene and triphenylmethylsulfenyl chloride with (*1*), under an identical set of condition, gave pure arenesulfenate esters *9*–*12* without any trace of 5′-chloro derivative (*8*). A suitable mechanism has been proposed to account for above chemoselective reactions. Finally, 2-nitrobenzenesulfenyl- group has been employed for selective protection of either 2′- or 3′-hydroxyl functions of a ribonucleoside derivative.

Letsinger *et. al.*[1] first demonstrated that the reaction of an excess of 2,4-dinitrobenzenesulfenyl (Dnbs) chloride with thymidine in pyridine furnished a tris-2,4-Dnbs derivative; the Dnbs groups could be removed by nucleophilic agents like sodium cyanide, sodium thiosulfate, sodium sulfide or thiophenol. We have been interested in protecting the primary and secondary hydroxyl functions of ribonucleosides by the formation of sulfenate esters and to use these selectively protected ribonucleoside blocks for the synthesis of oligoribonucleotides. This communication reports our preliminary studies on the reaction of a variety of arenesulfenyl chlorides with a substrate containing hydroxyl groups. Such a study is deemed important to elucidate the applicabilities of these arenesulfenyl chlorides as prospective hydroxyl protective groups.

Reaction of an excess of benzene, 4-toluene, 2-pyridine, 4-nitrobenzene, 4-chlorobenzene or 2-toluenesulfenyl chloride with 6-*N*-phthaloyl-2′,3′-isopropylideneadenosine (*1*) in *dry* pyridine solution, under an atmosphere of argon at 0 to −20 °C, gave a diastereoisomeric mixture (1:1 ratio) of the corresponding 5′-arenesulfinates, (*2*) to (*7*), in 37, 31, 44, 20, 28 and 58 % yield, respectively. It should be added that 6-*N*-phthaloyl-5′-deoxy-5′-chloro-2′,3′-isopropylideneadenosine (*8*) was also obtained in 39, 13, 28, 3, 31 and 36 % yields from the above reaction mixtures. No attempts were made to separate the diastereoisomeric mixture of arenesulfinates (*2*) to (*7*). However, a complete ^{1}H–NMR assignment has been made for each isomer of 6-*N*-phthaloyl-5′-(4-toluenesulfinyl)-2′,3′-isopropylideneadenosine by the help of a two dimensional chemical shift correlated spectroscopic (COSY) experiment at 400 MHz, as shown in Fig. 1. This confirmed the

* To whom correspondence should be addressed.

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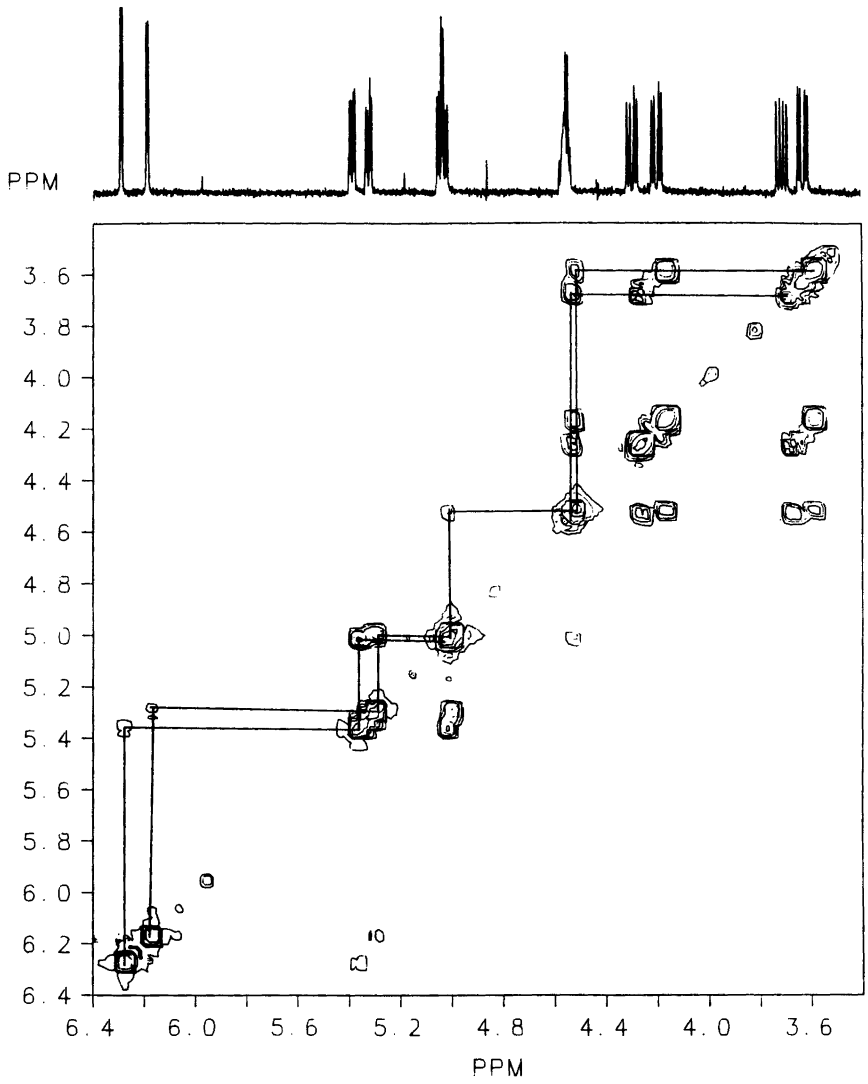
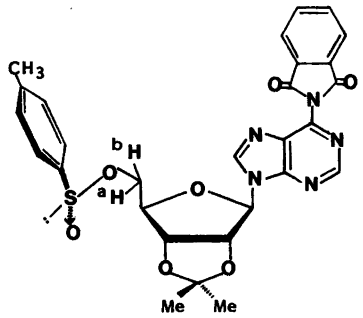
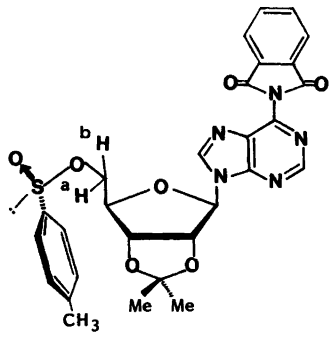


Fig. 1. Two dimensional shift correlated ^{1}H NMR spectrum at 400 MHz in $CDCl_3$.

stereochemistry of each isomer to be (*3a*) and (*3b*). Such stereochemical assignments have been arrived at by comparing the chemical shifts of of 5′-^{a}H and 5′-^{b}H protons, in (*3a*) and (*3b*), with respect to the orientation of the benzene ring attached to the sulfur atom. The steric proximity of 5′-^{b}H along the perpendicular axis to the plane of the benzene ring, as shown in (*3a*), may be attributed to its shielding to the extent of 0.50 ppm, as is evident from a comparison with (*3b*). A similar argument would explain that the 5′-^{a}H in (*3a*) is deshielded by 0.67 ppm with respect to the 5′-^{a}H in (*3b*) because it is close to the plane of the benzene ring. Such stereochemical assignments of resonance absorptions to each isomer from a diastereoisomeric mixture is only possible when the chemical shifts from each component can be correlated as in case of a COSY experiment shown in Fig. 1.



(3a)

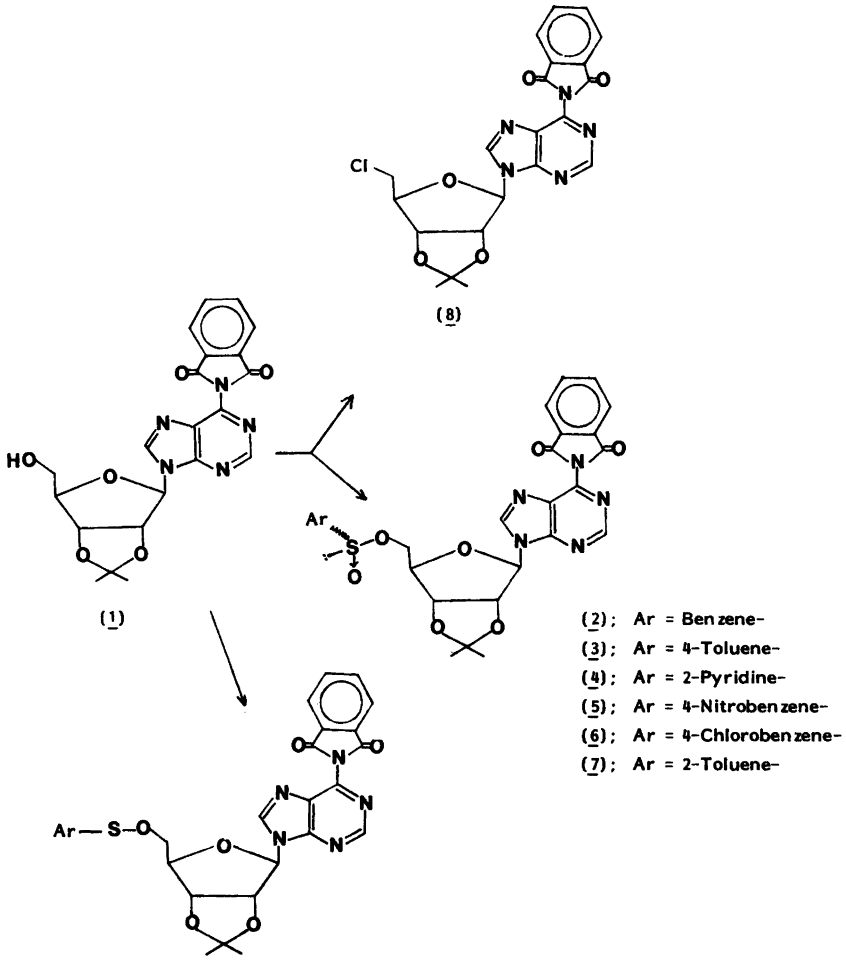


(3b)

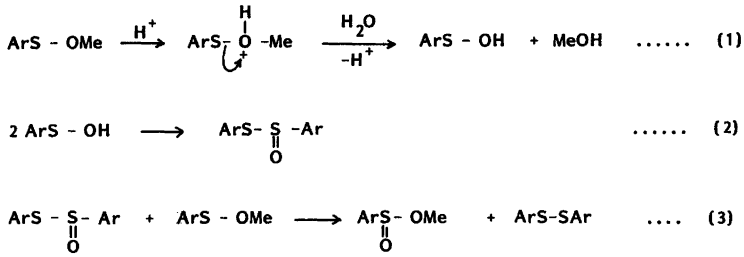
It is interesting to note that, while the above reaction gave exclusively arenesulfinate esters, the reaction of (*1*) with 2-nitrobenzene (Nbs), 2,4-dinitrobenzene (Dnbs), 2-nitro-4-toluene (Nts) and triphenylmethyl-(trityl) sulfenyl chlorides (*ca.* 2 equiv.), under condition identical to those of the first set of reactions, gave the corresponding arenesulfenates, *9–12*, in 63, 66, 56 and 44 % yields, respectively. No trace of the corresponding arenesulfinates or the 5′-chloro-5′-deoxy derivative (*8*) was detected in the latter reaction mixtures. We have subsequently attempted to understand such remarkably chemoselective formation of sulfinates, *2–7*, on one hand, and the sulfenates, *9–12*, on the other, in view of the literature reports.[7]

A comparison of the first and the second set of reactions seems to suggest that the presence of an *ortho* nitro group as a substituent, as in Nbs-, Dnbs- and Nts-chlorides, or a bulky group, as in triphenylmethanesulfenyl chloride, are some of the essential structural requirements for the formation of the sulfenate ester *9–12*.

A perusal of the literature[7] shows that 4-toluenemethylsulfenate has been actually isolated as a pure compound and was found to decompose almost instanteneously in the presence of traces of moisture to give methanol and 4-tolunemethylsulfinate at room temperature. The authors provided experimental evidence in support of a mechanism (Scheme 1) which involves the formation of thiolsulfinate, as a transient intermediate from sulfenic acid in the acid hydrolysis of 4-toluenemethylsulfenate [eqns. (1) and (2)], followed by its reaction with the unchanged sulfenate giving the sulfinate ester [eqn. (3)]. However, such a reaction mechanism does not completely explain our observation that the formation



of the sulfinates, *2*–*7*, invariably accompanies the formation of the 5′-chloro-5′-deoxy derivative (*8*) with benzene, 4-toluene, 2-pyridine, 4-nitrobenzene, 4-chlorobenzene or 2-toluene sulfenyl chloride; while *stable* sulfenate esters can be easily isolated, with no traces of (*8*), with 2-nitro-substituted arenesulfenyl chlorides. The following reaction mechanism (Scheme 2) is thus proposed which explains the formation of all isolated compounds. In such a reaction pathway, it is conceived that the transient sulfenate ester (*a*), upon protonation on the sulfenate-oxygen, undergoes a nucleophilic attack by the chloride ion (*b*) to give alkyl chloride (*d*) and arenesulfenic acid (*c*) which gives thiolsulfinate as an intermediate. This thiolsulfinate subsequently reacts with unchanged sulfenate, in a usual way as shown in eqns. (2) and (3) of Scheme 1, to give the sulfinate ester.

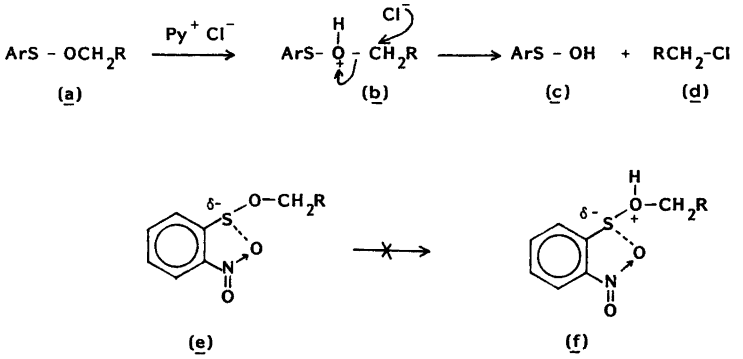


Scheme 1.

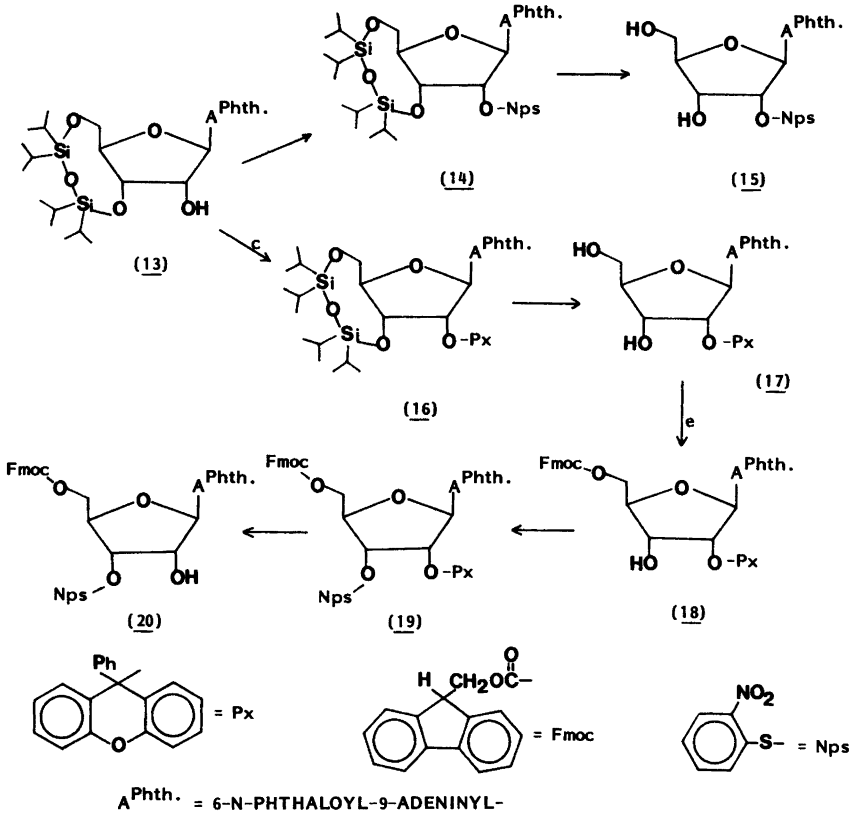
It has not been clearly elucidated[7] whether in the first step of the acid hydrolysis of the arenesulfenate ester the sulfur–oxygen or the carbon–oxygen bond cleavage takes place upon protonation and an attack by a molecule of water. It is, however, very likely[7,9] that it is the sulfur-oxygen bond that cleaves in such an acid hydrolysis in view of the known electrophilic character of the bivalent sulfur in the sulfenate ester. The basic mechanistic difference between the literature report of the sulfenate ester hydrolysis[7] and our reaction under a *dry* condition [compare eqn. (1) in Scheme 1 with *b* in Scheme 2] is that, in the latter, a carbon-oxygen bond cleavage takes place, upon a protonation step and a subsequent nucleophilic attack on the alkyl-carbon as opposed to the literature example where, most probably, a sulfur-oxygen bond cleavage takes place upon protonation and an attack by a molecule of water on the electrophilic sulfur. It thus emerges that the oxygen in our sulfinate ester seems to be originating from alcohol, whereas the source of oxygen is water in the hydrolysis of arenesulfenate.

The proposed mechanistic route (Scheme 2) has been proved experimentally by an independent NMR experiment, at an ambient temperature, using freshly distilled (under argon) 4-tolueneethylsulfenate[7] in *dry* deuterochloroform and an excess of *dry* pyridinium hydrobromide (*ca.* 10 fold). In such an experiment, under a complete dry condition, the formations of 4-tolueneethylsulfinate (*ca.* 70 %) and ethylbromide (*ca.* 30 %) were complete within 10 min. The products were also independently analyzed by GLC (GP 10 % SP-2100 on 100/200 Suppelcoport).

It may be recalled that an *ortho*-nitro arenesulfenate ester (*9*) is exclusively formed with 2-nitrobenzenesulfenyl chloride and (*1*) in dry pyridine solution at 20 °C while with



Scheme 2.



Scheme 3.

4-nitrobenzenesulfenyl chloride, under identical conditions, a diastereomeric mixture of sulfinates (*5*) are formed, along with (*8*). It is interesting to note in this context that the 2-toluenesulfenyl chloride behaved in a very similar way as 4-toluenesulfenyl chloride and gave the 5′-chloro derivative (*8*) and the corresponding diastereomeric mixture of sulfinate esters (*7*).

Therefore, it seems to be clear that the *ortho*-nitro group in the benzene ring indeed plays an important role in the stability of the sulfenate esters *9*–*11*. It is conceivable that an *ortho*- nitro substituent, enhances the nucleophilic character of sulfur (as shown in an intermediate like (*e*) in Scheme 2 by a week charge transfer mechanism. A nucleophilic sulfur, as in (*e*), with its expanded d orbitals, would be able to accomodate one of the oxygen lone pairs and thus a protonation step of the sulfenate-oxygen, to give (*f*), would not be expected to be favoured; which, in turn, would stabilize the sulfenate esters, (*9*) to (*11*). The requirement of coplanarity for such a charge transfer process to take place is expected to be less severe if *d* orbitals of sulfur atom are involved.[8]

As a further proof of the identity of the arenesulfinate ester (*2*), we have carried out an unambiguous chemical synthesis of diastereoisomeric mixture of 6-*N*-phthaloyl-5′-benzenesulfinyl-isopropylideneadenosine (*2*) in 95 % yield using benzenesulfinyl chloride[2] and 6-*N*-phthaloyl-2′,3′-isopropylidene adenosine (*1*) in dry pyridine solution.

Having established these chemoselective reactions with various arenesulfenyl chlorides, we have subsequently employed the 2-nitrobenzenesulfenyl (Nbs) group for the selective protection of either 2'- or 3'-hydroxyl functions of the sugar moiety of a ribonucleoside to give partially protected building blocks like(*15*) and (*20*) which are useful for the oligoribonucleotide synthesis. The synthesis of such building blocks are outlined in Scheme 3 starting from 3',5'-*O*-1,1,3,3-tetraisopropyldisilyloxy-6-*N*-phthaloyladenosine (*13*) (Experimental). The Nbs group has been found to be stable under the conditions of normal manipulations and yet it could be quantitatively removed with the desired selectivity from either (*15*) or (*20*) by a brief treatment of triethylammonium thiocresolate (2 equiv. in dry acetonitrile (5 ml/mM) at 20 °C for 15 min. Further work is in progress.

EXPERIMENTAL

^{1}H NMR spectra were measured at 60 MHz with a Perkin-Elmer R600 spectrometer and at 90 MHz with a Jeol FX 90Q spectrometer; tetramethylsilane was used as an internal standard. UV absorption spectra were measured either with Waters DMS 100 or with a Cary 2200 double beam scanning spectrometer. Merck silica gel 60 F_{254} pre-coated plates were used for monitoring TLC in the following solvent systems: (A) chloroform–methanol (95:5; v/v) and (B) chloroform–methanol (9:1; v/v). Merck Kieselgel G was used for short column chromatography.

Dioxan, pyridine and acetonitrile were dried by heating under reflux with Calcium hydride for *ca.* 3 h; these solvents were then distilled at atmospheric pressure and stored over molecular sieves (4Å) in dark bottles.

Arenesulfenyl chlorides have been freshly prepared using literature procedures.[6]

5'-O-Benzenesulfinyl-2'-3'-O-isopropylidene-6-N-phthaloyladenosine (2): a general procedure. To a dry pyridine solution (10 ml) of 6-*N*-phthaloyl-2',3'-*O*-isopropylideneadenosine (*1*) (437 mg, 1 mmol) at *ca.* −15 °C, benzenesulfenyl chloride (217 mg, 1.5 mmol) was added under stirring in an atmosphere of argon. After 3 h, the mixture was poured to a separating funnel containing cold saturated sodium bicarbonate solution (25 ml). The mixture was extracted with chloroform (3×40 ml). Organic layers were pooled and evaporated to obtain a glass which was co-evaporated with toluene. The residue was then purified over a short column of silica gel using first methylene chloride and then 2 % ethanol – chloroform mixture to afford (*2*) as diastereomeric mixture (1:1) (269 mg, 47 %) and *8* (213 mg, 47 %). Compounds *3*, *4*, *5*, *6*, *7*, *9*, *10*, *11* and *12* were similarly obtained. During the preparations of compounds *2*–*7*, the 5'-chloro derivative *8* was invariably formed. These compounds were characterized by ^{1}H NMR, UV and mass spectroscopy as described below:

Compound (1). ^{1}H NMR ($CDCl_3$): δ 9.06 (*s*,1 H) H-8; 8.33 (*s*, 1 H) H-2; 7.94 (*m*, 4 H) phthaloyl; 6.05 (*d*, 3.6, 1 H) H-1'; 5.23 (*dd*, 5.8, 1 H) H-2'; 4.94 (*dd*, 1.6, 1 H) H-3'; 4.85 (br*s*, 1 H) OH; 4.54 (*m*, 1 H) H-4'; 3.85 (*m*, 2 H) H-5'5''; 1.65 (*s*, 3 H), 1.39(*s*, 3 H) isopropylidene.

Compound (2). R_f=0.29 (system A). U.V. (95 % EtOH): λ_{max} (pH 3) 271(ε=11, 800) 246 (ε=11, 800); λ_{max} (pH 12) 303 (ε=11, 800). Mass spectrum (chemical ionization, NH_3) at $MH^{\cdot+}$ at *m/z* 562 (1 %) ^{1}H NMR ($CDCl_3$): δ 9.01 (*s*, 1 H), 8.88 (*s*, 1 H) H-8; 8.41 (*s*, 1 H), 8.22 (*s*, 1 H) H-2; 7.95 (*m*, 8 H) phthaloyl; 7.28 (*m*, 1 OH) aryl; 6.29 (*d*, 2.4, 1 H), 6.19 (*d*, 2.4, 1 H) H-1'; 5.35 (*m*, 6.0, 2 H) H-2'; 5.04 (*dd*, 3.0, 2 H), H-3'; 4.50 (*m*, 2 H) H-4'; 4.25 (*m*, 2 H), 3.72 (*m*, 2 H) H-5'5''; 1.40 (*s*, 6H), 1.36(*s*,6H) isopropylidene.

Compound (3). R_f=0.33 (system A). UV (95 % EtOH): λ_{max} (pH3) 269 (ε=12,000), 248 (ε=13,700); λ_{max} (pH 12) 304 (ε=11,800).

Mass spectrum (chemical ionization, NH_3): $MH_2^{\cdot+}$ at *m/z* 577 (2 %) ^{1}H NMR ($CDCl_3$): δ 9.02 (*s*, 1 H), 8.94 (*s*, 1 H) H-8; 8.41 (*s*, 1 H), 8.24 (*s*, 1 H) H-2; 7.90 (*m*, 8 H) phthaloyl; 7.45 (*m*, 8 H) aryl; 6.28 (*d*, 1 H), 6.18 (*d*, 1 H) H-1'; 5.35 (*m*, 2 H) H-2'; 5.04 (*m*, 2 H) H-3'; 4.53 (*m*, 2 H) H-4'; 4.24 (*m*, 2 H), 3.65 (*m*, 2 H) H-5'5''; 2.42 (*s*, 3 H), 2.38 (*s*, 3 H) tolyl-CH_3; 1.63 (*s*, 6 H), 1.40 (*s*, 6 H) isopropylidene.

However, it has been possible, by a 400 MHz ^{1}H NMR experiment (COSY) (Fig. 1) to

assign sugar resonance absorptions of each of the component of the diastereoisomeric mixture.

Diastereoisomer. (3a). δ 6.31 (*d*, 1 H, J=2.7 Hz), H-1′; 5.41 (*dd*, 1 H, J=2.7 & 6.4 Hz) H-2′; 5.07 (*dd*, 1 H, J=2.7 & 6.4 Hz), H-3′; 4.59 (*m*, 1 H), H-4′; 4.32 (*dd*, 1 H, J_{gem}=11 and J_{vic}=4.6 Hz), 5′-^{a}H; 3.73 (*dd*,1H, J_{gem}=11 & J_{vic}=5.5 Hz), 5′-^{b}H.

Diastereoisomer. (3b). δ 6.21 (*d* ,1 H, J=2.4 Hz), H-1′; 5.35 (*dd*, 1 H, J=2.4 & 6.1 Hz), H-2′; 5.05 (dd, 1 H, J=2.7 & 6.4 Hz), H-3′; 4.57 (*m*, 1 H), H-4′; 4.23 (*dd*, 1 H, J_{gem}=11.3 and J_{vic}=4 Hz), 5′-^{b}H; 3.65 (*dd*, 1 H, J_{gem}=11.3 and J_{vic}=3.4 Hz), 5′-^{a}H.

Compound (4). R_f=0.36 (system A). UV (95 % EtOH): λ_{max} (pH3); 270 (ε=14,400); λ_{max}(pH 12) 303 (ε=15,400); ^{1}H NMR ($CDCl_3$): δ 8.95(*s*, 1 H), 8.82 (*s*, 1 H) H-8; 8.57 (*m*, 2 H), pyridyl; 7.98 (*m*, 8 H) phthaloyl; 7.82 (*m*, 4 H), 7.37 (*m*, 2 H) pyridyl; 6.22 (*d*, 2.6, 1 H), 6.18 (*d*, 2.6, 1 H) H-1′; 5.57 (*m*, 2 H) H-2′; 5.07 (*m*, 2 H), H-3′; 4.55 (*m*, 2 H) H-4′; 4.36 (*m*, 2 H), 3.83 (*m*, 2 H) H-5′5″; 1.63 (*s*, 6 H), 1.42 (*s*, 3 H), 1.38 (*s*, 3 H) isopropylidene.

Compound (5). UV (95 %) EtOH): λ_{max} (pH3) 252 (ε=18,700), 269 (ε=18,400); λ_{max} (pH 12) 299 (ε=18,700). ^{1}H NMR ($CDCl_3$): δ 9.04 (*s*, 1 H), 8.94 (*s*, 1 H) H-8; 8.33 (*s*, 1 H), 8.20 (*s*, 1 H) H-2; 7.92 (*m*, 8 H) phthaloyl; 7.79 (*m*, 8 H) aryl; 6.26 (*d*, 2.4, 1 H), 6.18 (*d*, 2.4, 1 H) H-1′; 5.46 (*dd*, 6.5, 2 H) H-2′; 5.08 (*dd*, 3.0, 2 H) H-3′; 4.50 (*m*, 2 H) H-4′; 4.23 (*m*, 2 H), 3.84 (*m*, 2 H) H-5′5″; 1.60 (*s*, 6 H), 1.39 (*s*, 6 H) isopropylidene.

Compound (6). R_f=0.42 (system A). UV (95 % EtOH): λ_{max} (pH 3) 250 (ε=16 500), 270 (15 800); λ_{max} (pH 12) 303 (ε=16 800). ^{1}H NMR ($CDCl_3$): δ 9.04 (*s*, 1 H), 8.98 (*s*, 1H) H-8; 8.37 (*s*, 1 H), 8.22 (*s*, 1 H) H-2; 7.92 (*m*, 8 H) phthaloyl; 8.25–7.79 (*m*, 8 H) aryl; 6.26 (*d*, 2.4, 1 H), 6.18 (*d*, 2.4, 1 H) H-1′; 5.45 (*dd*, 5.9, 1 H), 5.36 (*dd*, 5.9, 1 H) H-2′; 5.04 (*dd*, 3.5, 2 H) H-3′; 4.51 (*m*, 2 H) H-4′; 4.25 (*m*, 2 H), 3.70 (*m*, 2 H) H-5′5″; 1.60 (*s*, 6 H), 1.39 (*s*, 6 H) isopropylidene.

Compound (7). R_f=0.4 (system A). UV (95 % EtOH): λ_{max} (pH 3) 271 (ε=25,000), 249 (ε=23,400) λ_{max} (pH 12) 303 (ε=26,500). ^{1}H NMR ($CDCl_3$): δ 9.0 (*s*, 1 H), 8.86 (*s*, 1 H), H-8; 8.41 (*s*, 1 H), 8.18 (*s*, 1 H), H-2; 7.96 (*m*, 10 H), phthaloyl and arene; 7.38 (*m*, 6 H), arene; 6.28 (*d, 2.7, 1 H), 6.15 (d*, 2.0, 1 H), H-1′; 5.40 (*dd*, 6.6, 1 H), 5.33 (*dd*, 5.1, 1 H), H-2′; 5.04 (*dd*, 2.9, 2 H), H-3′; 4.53 (*m*, 2 H), H-4′; 4.23 (*m*, 2 H), 3.63 (*m*, 2 H), H-5′,5″; 2.39 (*s*, 3 H), 2.26 (*s*, 3 H), tolyl-CH_3; 1.63 (*s*, 6 H) & 1.39 (*s*, 6 H), isopropylidene.

Compound (8). R_f=0.45 (system A). UV (95 % EtOH): λ_{max} (pH 3) 271 (ε=14,600), λ_{max} (pH 12) 303 (ε=14,600). Mass spectrum (chemical ionization, NH_3): MH^{+} at *m/z* 456 (9 %) ^{1}H NMR ($CDCl_3$): δ 9.08 (*s*, 1 H), H-8; 8.93 (*s*, 1 H), H-2; 7.95 (*m*, 4 H), phthaloyl; 6.28 (*d*, 2.4, 1 H) H-1′; 5.48 (*dd*, 6.5, 1 H) H-2′; 5.17 (*dd*, 3.0, 1 H), H-3′; 4.57 (*m*, 6.0, 1 H) H-4′; 4.57 (*m*, 2 H) H-5′5″; 1.64 (*s*, 3 H), 1.4 (*s*, 3 H), isopropylidene.

Compound (9). R_f=0.65 (system A). UV (95 % EtOH): λ_{max} (pH 3) 271 (ε=17,200), 395 (ε=3 360); λ_{max} (pH 12) 300 (ε=15 398), 398 (ε=2 500).

Mass spectrum (chemical ionization, NH_3): MH^{+} at *m/z* 591 (19.3 %) (^{1}H NMR ($CDCl_3$) δ 9.02 (*s*, 1 H) H-8; 8.39 (*s*, 1 H) H-2; 7.94 (*m*, 4 H) phthaloyl; 8.2–7.28 (*m*, 4 H) aryl; 6.36 (*d*, 2.4, 1 H) H-1′; 5.51 (*dd*, 5.4, 1 H); 5.20 (*dd*, 3.0, 1 H) H-3′; 4.65 (*dt*, 3.6, 1 H) H-4′; 4.19 (*d*, 2 H) H-5′5″; 1.68 (*s*, 3 H), 1.43 (*s*, 3 H) isopropylidene.

Compound (10). R_f=0.49 (system A). UV (95 % EtOH): λ_{max} (pH 3) 270 (ε=22 700), 327 (ε=9 740); Mass spectrum (chemical ionization, NH_3): MH^{+} at *m/z* 636 (19.5 %) ^{1}H NMR ($CDCl_3$): δ 9.07 (*d*, 1 H) aryl; 9.02 (*s*, 1 H) H-8; 8.35 (*s*, 1 H) H-2; 8.16 (*dd*, 1 H) aryl; 7.95 (*m*, 4 H) phthaloyl; 7.59 (*d*, 1 H) aryl; 6.37 (*d*, 2.4, 1 H) H-1′; 5.65 (*dd*, 6.0, 1 H) H-2′; 5.25 (*dd*, 3.9, 1 H) H-3′; 4.65 (*m*, 1 H) H-4′; 4.20 (*m*, 2 H) H-5′5″; 1.68 (*s*, 3 H), 1.45 (*s*, 3 H) isopropylidene.

Compound (11). R_f=0.55 (system A). UV (95 % EtOH): λ_{max}(pH 3) 269 (ε=17,300) 406 (ε=3,370); λ_{max}(pH 12) 300 (ε=16,600), 406 (ε=3,020). Mass spectrum (chemical ionization, NH_3): MH^{+} at *m/z* 605 (11.9 %) ^{1}H NMR ($CDCl_3$): δ 9.02 (*s*, 1 H) H-8; 8.37 (*s*, 1 H) H-2; 8.03 (*m*, 2 H) aryl; 7.92 (*m*, 4 H) phthaloyl; 7.28 (*m*, 1 H) aryl; 6.34 (*d*, 2.4, 1 H), H-1′; 5.42 (*dd*, 6.6, 1 H) H-2′; 5.16 (*dd*, 3.6, 1 H) H-3′; 4.61 (*dt*, 4.6, 1 H) H-4′; 4.13 (*d*, 2 H) H-5′5″; 2.36 (*s*, 3 H) CH_3; 1.66 (*s*, 3 H), 1.43 (*s*, 3 H) isopropylidene.

Compound (12). R_f=0.58 (system B). UV (95 % EtOH): λ_{max} (pH 3) 270 (ε=14 700), λ_{max} (pH13) 302 (ε=15 300). ^{1}H NMR ($CDCl_3$): δ 8.86 (*s*, 1 H) H-8; 8.26 (*s*, 1 H) H-2; 7.92 (*m*, 4 H) phthaloyl; 7.30 (*m*, 15 H) trityl; 6.20 (*d*, 2.40, 1 H) H-1′; 5.44 (*dd*, 6.2, 1 H) H-2′; 4.98 (*dd*, 3.1, 1 H) H-3′; 4.56 (*m*, 6.6, 1 H) H-4′; 3.35 (*d*, 2 H) H-5′5″; 1.62 (*s*, 3 H), 1.39 (*s*, 3 H) isopropylidene.

6-N-*Phthaloyl-3',5'-O*-1,1,3,3-tetraisopropyl-1,3-disiloxyladenosine (*13*). To a dry pyridine solution (100 ml) of 6-*N*-phthaloyladenosine (4.37 g, 10 mmol) 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane[5] (3.47 g, 11 mmol) was added under stirring at room temperature. After 45 min the mixture was poured into aqueous saturated sodium bicarbonate solution (200 ml). The mixture was extracted with chloroform (3×100 ml). The organic layers were collected, evaporated and co-evaporated with toluene. The residue was purified over a short column of silica gel using first chloroform and gradually changing to 4 % ethanol-chloroform mixture. The desired compound (*13*) was isolated in 69.5 % yield (4.53 g). UV(EtOH) λ_{max}274 nm.

^{1}H NMR ($CDCl_3$): δ 9.0 (*s*, 1 H) H-8; 8.37 (*s*, 1 H), H-2; 7.94 (*m*, 4 H) Phthaloyl; 6.10 (*d*,1.0, 1 H), H-1'; 4.61 (*dd*, 5.4, 1 H) H-2'; 5.04 (*dd*, 4.0, 1 H) H-3'; 4.19 (*m*, 1 H) H-4'; 4.12 (brs, 2 H) H-5'5"; 1.08 (*m*, 28 H) isopropyl.

6-N-*Phthaloyl-3',5'-O*-1,1,3,3-tetraisopropyl-1,3-disiloxyl-2'-O-*(2-nitrobenzenesulfenyl)-adenosine* (*14*). To a dry pyridine solution (50 ml) of (*13*) (3.26 g, 5 mmol) 2-nitrobenzenesulfenyl chloride (1.04 g, 5.5 mmol) was added under stirring. After 30 min the mixture was poured to a separating funnel containing saturated sodium bicarbonate aqueous solution (100 ml). The mixture was extracted with chloroform (3×60 ml). The organic layers were collected and the volatile matters were evaporated and the residue co-evaporated with toluene and was purified over a short column of silica gel using 2 % ethanol–chloroform mixture as an eluent giving (*14*) as a glass (3.54 g, 88 %). UV (EtOH) λ_{max} 270 nm.

^{1}H NMR ($CDCl_3$): δ 8.98 (*s*, 1 H) H-8; 8.45 (*s*, 1 H) H-2; 8.25–7.4 (*m*, 4 H) Nbs group; 7.91 (*m*, 4 H) phthaloyl; 6.07 (*s*, 1 H) H-1'; 4.93 (*dd*, 4.0, 1 H) H-3'; 4.50 (*d*, 6.0, 1 H) H-2'; 4.34 (*m*, 1 H) H-4'; 4.21 (brs, 2 H) H-5'5"; 1.0 (*m*, 28 H) isopropyl.

6-N-*Phthaloyl-2'*-O-*(2-nitrobenzenesulfenyl)adenosine* (*15*). To compound *14* (1.61 g, 2 mml) in tetrahydrofuran (36 ml) was added 1 M tetrabutylammonium fluoride (4 ml in dry tetrahydrofuran, 4 mmol) at room temperature. After 15 min the volatile matters were evaporated and the residue was co-evaporated with toluene. The residue was purified over a short column of silica gel using a gradient of 4 to 6 % ethanol–chloroform mixture as an eluent. Yield: (991 mg, 91 %). UV (EtOH) λ_{max} 270 nm.

^{1}H NMR (DMSO-d_6) δ 9.10 (*s*, 1 H) H-8; 8.98 (*s*, 1 H) H-2; 8.25–7.4 (*m*, 4 H) Nbs group; 8.08 (*m*, 4 H) phthaloyl; 6.62 (*d*, 4.7, 1 H) H-1'; 4.86 (*dd*, 8.0, 1 H) H-2'; 4.68 (*dd*, 6.0, 1 H) H-3'; 4.15 (*m*, 1 H) H-4'; 3.74 (brs, 2 H) H-5'5".

6-N-*Phthaloyl-2'*-O-*(9-phenylxanthen-9-yl)adenosine* (*17*). To a dry pyridine solution (25 ml) of 6-*N*-phthaloyladenosine (1 g, 2.5 mmol) was added 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane (0.87 g, 2.7 mmol), and the mixture was stirred for 60 min at room temperature. Then 9-chloro-9-phenylxanthene[3] (1.1 g, 3.75 mmol) was added and the reaction mixture was stirred for 2 h and poured into a cold saturated sodium bicarbonate solution (100 ml). The mixture was extracted with chloroform (2×50 ml) and evaporated to dryness. After co-evaporation with toluene (4×25 ml), the residue was dissolved in dry tetrahydrofuran (50 ml) and 1 M solution of tetrabutylammonium fluoride (5 ml) in dry tetrahydrofuran was added. After 15 min all volatile matters were removed *in vacuo*; the residue was co-evaporated with toluene and purified on a short column of silica gel using 1 % triethylamine in dichloromethane as an eluent. The fractions were concentrated and the residue was redissolved in a small amount of dichloromethane and precipitated from cyclohexane giving (*17*). Yield (965 mg, 59 %). R_f: 0.61 (System B). UV (EtOH) λ_{max} (pH 3) 273 nm (ε=12 500); λ_{max} (pH 12) 307 nm (ε=12.600) and 283 nm (ε=13 500).

^{1}H NMR ($CDCl_3$): δ 8.78 (*s*, 1 H) H-8; 8.07 (*s*, 1 H) H-2; 7.95 (*m*, 4 H) phthaloyl; 7.35 (*m*, 9 H), 6.84 (*m*, 2 H), 6.30 (*m*, 2 H) Pixyl; 5.90 (*d*, 7.8, 1 H) H-1'; 4.7 (*d*, 4.6, 1 H) H-2'; 3.1 (*d*, 1 H) H-3'; 4.16 (brs, 1 H) H-4'; 3.67 (*m*, 2 H) H-5'5".

6-N-*Phthaloyl-2'*-O-*(9-phenylxanthen-9-yl)-5'*-O-*(fluoren-9-yl-methoxycarbonyl)adenosine* (*18*). To a dry pyridine solution (10 ml) of (*17*) (635 mg, 1 mmol) was added dropwise a dry acetonitrile solution (5 ml) of 9-fluorenylmethylchloroformate[4] (Fmoc-Cl 336 mg, 1.3 mmol). The reaction mixture was stirred for 4.5 h at room temperature and then the reaction mixture was poured into a cold saturated sodium bicarbonate solution (100 ml) and the mixture was extracted with chloroform (2×50 ml). The organic layers were concentrated *in vacuo* and the residue after co-evaporation with toluene (4×25 ml) was dissolved in dichloromethane; precipitation from cyclohexane gave (*18*). Yield (717 mg, 82 %). R_f=0.77

(system B).

^{1}H NMR ($CDCl_3$) δ 9.02 (*s*, 1 H) H-8; 8.82 (*s*, 1 H) H-2; 7.91 (*m*, 4 H) phthaloyl; 7.30 (*m*, 17 H) Pixyl and Fmoc; 6.84 (*m*, 2 H), 6.30 (*m*, 2 H) Pixyl; 6.06 (*d*, 7.2, 1 H) H-1′; 4.77 (*dd*, 4.7, 1 H) H-2′; 4.40 (*m*, 1 H) H-4′; 4.30 (*m*, 5 H) H-5′5″, Fmoc-CH_2 & CH; 3.26 (*d*, 1 H) H-3′.

6-N-Phthaloyl-2′-O-(9-phenylxanthen-9-yl)-3′-O-(2-nitrobenzene sulfenyl)-5′-O-(fluoren-9-methoxycarbonyl)adenosine (*19*). To a dry pyridine solution (2 ml) of (*18*) (175 mg 0.2 mmol) was added 2-nitrobenzenesulfenyl chloride (42 mg, 0.22 mmol) and the mixture was stirred 2 h at room temperature. The reaction mixture was then poured into a saturated sodium bicarbonate solution (25 ml) and extracted with chloroform (3×15 ml). The organic layers were evaporated *in vacuo* and chromatographed over a short column of silica gel using 2 % ethanol-chloroform mixture as an eluent. Evaporations of the desired fractions gave a yellow foam. yield (118 mg, 57 %); R_f 0.77 (system B).

^{1}H NMR ($CDCl_3$): δ 8.86 (*s*, 2 H) H-8 and H-2; 8.28–7.4 (*m*, 20 H) Nbs and Fmoc; 7.91 (*m*, 4 H) phthaloyl; 6.2 (*d*, 7.2, 1 H) H-1′; 5.24 (*dd*, 4.2, 1 H) H-2′; 4.45 (*m*, 1 H) H-4′; 4.30 (*m*, 5 H) H-5′5″ and Fmoc-CH_2 & CH; 3.5 (*d*, 1 H) H-3′.

6-N-Phthaloyl-3′-O-(2-nitrobenzenesulfenyl)-5′-O-(fluoren-9-yl-methoxycarbonyl) adenosine (*20*). To a dichloromethane solution (5 ml) of (*19*) (188 mg, 0.115 mmol) was added 2 % solution of toluenesulfonic acid monohydrate in dichloromethane–methanol 7:3 (v/v) (3.5 ml). After 15 min at room temperature, the reaction mixture was diluted with chloroform (25 ml) and washed with saturated aqueous sodium bicarbonate solution (100 ml). The organic layer was concentrated and the residue dissolved in dichloromethane; precipitation from cyclohexane gave (*20*) as a bright yellow powder (75 mg, 86 %). R_f=0.57 (system B).

^{1}H NMR ($CDCl_3$: δ 8.98 (*s*, 1 H) H-8; 8.38 (*s*, 1 H) H-2; 8.28–7.4 (*m*, 12 H) Nbs and Fmoc; 7.90 (*m*, 4 H) phthaloyl; 6.24 (*d*, 6.3, 1 H) H-1′; 5.13 (*d*, 5.4, 1 H) H-2′; 4.77 (*m*, 1 H) H-4′; 4.38 (*m*, 5 H) H-5′5″, Fmoc-CH_2 & CH; 4.20 (*dd*, 4.0) H-3′.

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REFERENCES

1. Letsinger, R.L., Fontaine, J., Mahadevan, V., Schexnayder, D.A. and Leone, R.E. *J. Am. Chem. Soc. 86* (1964) 2615.
2. Douglas, I.B. and Poole, D.R. *J. Am. Chem. Soc. 22* (1957) 536.
3. Chattopadhyaya, J. and Reese, C.B. *J. Chem. Soc. Chem. Commun.* (1978) 639.
4. Gioeli, C. and Chattopadhyaya, J. *J. Chem. Soc. Chem. Commun.* (1982) 672.
5. Markiewicz, W.T. *J. Chem. Res. 24 (S)* (1979).
6. Kühle, E. *Synthesis* (1970) 561; (1971) 617 and references therein.
7. Ciuffarin, E., Gambarotta, S. and Isolo, M. *J. Chem. Soc. Perkin Trans. 2* (1978) 554.
8. Oae, S. and Zalnut, C. *J. Am. Chem. Soc. 82* (1960) 5359 and references therein.
9. Douglas, I.B. and Kopp, D.A. *J. Org. Chem. 27* (1962) 1398.

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