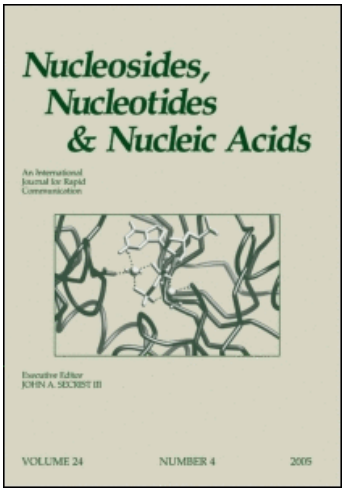

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Synthesis of Novel Polycyclic Nucleoside Analogs

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Synthesis of Novel Polycyclic Nucleoside Analogs

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We have synthesized polycyclic nucleoside derivatives by a novel, one pot procedure by reacting 4-*O*-TPS-pyrimidine nucleosides with aromatic diamines. The reaction is limited in scope but provides easy access to certain previously unknown heterocyclic ring systems.[2] 4-*O*-Triisopropylphenylsulfonyl-pyrimidine nucleosides were reacted with aromatic diamines leading to fused, polycyclic ring systems: *o*-phenylenediamine yielded the pyrimido[1,6-a]benzimidazole, 2,3-diaminonaphthalene gave the naphth[2',3':4,5]imidazo [1,2-f]pyrimidine and 1,8-diaminonaphthalene led to the pyrimido[1,6-a]perimidine ring system. The reaction is unique because two connected nucleophilic centers react with the pyrimidine nucleoside to form an extended ring system. However, reactions of pyrimidine nucleosides with electrophiles are well known. E.g., reaction of cytidine and adenosine with bromoacetaldehyde yields ethenocytidine and ethenoadenosine[3] and on reaction of cytidine with 1'-methylthiaminium salts dipyrimido[1,6-a:4',5'-d]pyrimidine derivatives are obtained.[4] Other polycyclic bases have been made from cytidine and adenosine by photochemical reactions.[5]

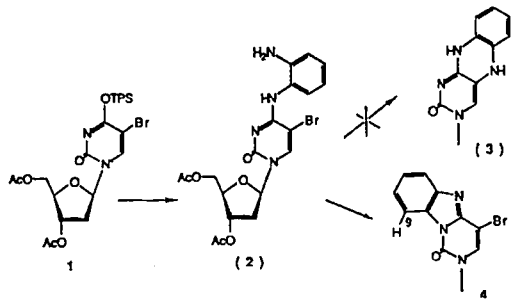


Figure 1

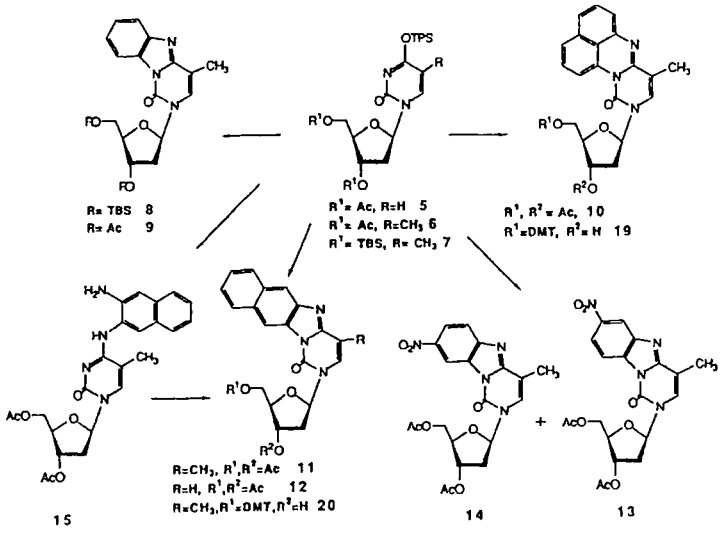
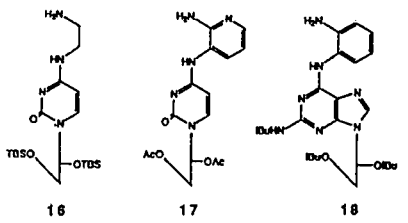


Figure 2

In an attempt to synthesize the tricyclic nucleoside derivative **3**, the 4-*O*-TPS pyrimidine derivative **1**[6] was treated with *o*-phenylenediamine in refluxing THF and a slower moving spot was observed on TLC, corresponding presumably to the adduct **2** (see Fig. 1). The reaction did not stop at that stage, however, and a new fluorescent product of higher R_f formed and was isolated in 49% yield. Quite unexpectedly this product still contained Br but had lost NH_3 according to MS and elemental analyses. The λ_{max} in the UV spectrum was shifted to longer wavelengths relative to the starting *o*-phenylenediamine (λ_{max} = 294 nm) and exhibited a well resolved vibrational structure. On the basis of these data, the product was subsequently assigned structure **4**. This assignment was also confirmed by the ^{1}H NMR spectrum in which the signal of the H-C9 is shifted to high-field due to the anisotropy of the neighboring carbonyl group.[7]

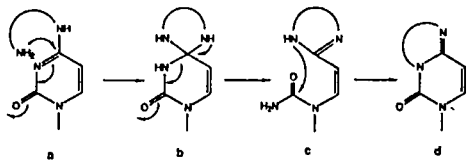
In order to examine the generality of the rather unusual reaction the 4-*O*-TPS-thymidine and -deoxyuridine derivatives **5**, **6**, and **7** were reacted with various aromatic diamines and the cyclized products **8** (from *o*-phenylenediamine), **10** (from 1,8-diaminonaphthalene), **11** and **12** (from 2,3-diaminonaphthalene) and the isomeric compounds **13** and **14** (from 4-nitro-*o*-phenylenediamine) were isolated in modest to good yields (see Fig. 2).

When the reaction was carried out in the presence ot base none of the cyclized compounds were obtained but the reaction stopped at the intermediate stage, *e.g.*, treatment of **6** with 2,3-diaminonaphthalene in the presence of 1 equivalent of ethyldiisopropylamine yielded **15** in 60% yield. **15** was slowly converted to **11** in refluxing THF, more rapidly in the presence of acetic acid demonstrating that this second cyclization step is acid catalyzed.



16 17 18

Figure 3



a b c d

Figure 4

Alternatively, the reaction was carried out in two steps by first treating the 4-*O*-TPS derivative with the diamine in the presence of base and then affecting the cyclization with acid. By treating *o*-phenylenediamine and **7** with potassium hexamethyldisilazane in THF at -78°C, work up and subsequent reflux of the crude product in THF in the presence of 0.8 equivalents of acetic acid the cyclized product **9** was obtained in 60% overall yield.

On the other hand, reaction of **7** with ethylene diamine and of **6** with 2,3-diaminopyridine led only to the adducts **16** and **17**, respectively (see Fig. 3) which could not be cyclized under a variety of reaction conditions. Also attempts to extend this reaction to purine nucleosides failed. The reaction of *o*-phenylenediamine with N^2, 3',5'-triisobutyryl-6-O-TPS-dG resulted only in the formation of **18** which did not undergo any cyclization.

A possible mechanism of this novel cyclization is shown in Fig. 4. It might involve initial Michael addition of the primary amine in **a** to form **b**, followed by ring opening (**b**→**c**) and cyclization with loss of NH_3 to give the cyclized product (**c**→**d**). These extended heterocycles are stable to the conditions of deoxyoligonucleotide synthesis. Of interest is the incorporation of such analogs into oligomers and the investigation of the hybridization properties with complemenary sequences.

References and Notes

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