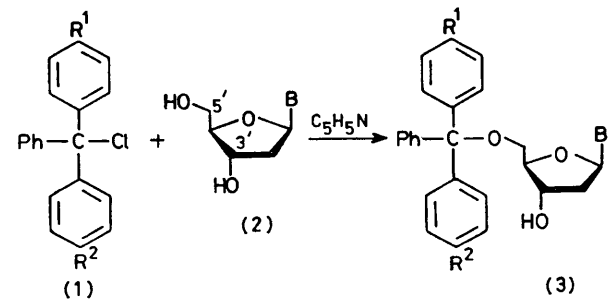
The 9-Phenylxanthen-9-yl Protecting Group

By JYOTI B. CHATTOPADHYAYA and COLIN B. REESE*
(*Department of Chemistry, King's College, Strand, London* WC2R 2LS)

Summary 9-Chloro-9-phenylxanthene (**4b**) reacts with the 5′-hydroxy groups of 2′-deoxyribonucleosides (**2**) (and their *N*-acyl derivatives) to give crystalline 9-phenylxanthen-9-yl (pixyl) derivatives (**5**) in satisfactory to good yields; the pixyl group may be removed by acidic hydrolysis under very mild conditions.

THE triphenylmethyl (trityl) group has been used very widely[1] to protect primary hydroxy functions in sugar, nucleoside, and steroid chemistry; it may be introduced by treating the substrate alcohol (*e.g.* **2**, Scheme) with chlorotriphenylmethane (**1a**) in pyridine solution. The mono- and di-methoxytrityl protecting groups (as in **3b** and **3c**, respectively), which are removable under milder conditions of acidic hydrolysis, may similarly be introduced[2] by treating the substrate alcohol with (*p*-methoxyphenyl)chlorodiphenylmethane (**1b**) and chlorodi(*p*-methoxyphenyl)-phenylmethane (**1c**), respectively. Chlorotriphenylmethane (**1a**) and the latter reagents (**1b** and **1c**) display a high selectivity towards the primary hydroxy groups of polyols.

In recent years, both the mono- and di-methoxytrityl protecting groups have found much use in oligodeoxyribonucleotide synthesis.[3]



a; $R^1 = R^2 = H$
b; $R^1 = H$; $R^2 = OMe$
c; $R^1 = R^2 = OMe$

SCHEME

Although the reactions between (**1c**) and 2′-deoxyribonucleosides (**2**) appear to occur with a relatively high degree of regioselectivity, 5′-*O*-dimethoxytrityl-2′-deoxyribonucleosides (**3c**) do not appear to crystallize readily.[2] The latter derivatives are usually isolated[2] as precipitated solids and it is therefore uncertain whether or not they are contaminated with small quantities of the isomeric 3′-*O*-dimethoxytrityl derivatives.† It occurred to us that the use of the more compact and presumably more polar 9-phenylxanthen-9-yl (pixyl)‡ protecting group (as in **5**) might lead to derivatives with better crystallization properties than the corresponding dimethoxytrityl ethers (*e.g.*, **3c**). We now report that this indeed appears to be the case and that the acid lability of the pixyl group is closely similar to that of the dimethoxytrityl protecting group.

TABLE. 5′-*O*-Pixyl derivatives of 2′-deoxyribonucleosides

Derivative[a] (5)	Yield[b] (%)	M.p. (°C)	Crystallization solvent[c]
a	68(56)[d]	194—195	A
b	87	224—225	B
c	74(65)[d]	159	C
d	83	149	D

[a] These crystalline compounds are characterized as 5′-*O*-pixyl derivatives (**5**) on the basis of satisfactory microanalytical and ^{1}H n.m.r. spectroscopic [in $(CD_3)_2SO$] data. Signals in the region of δ 4·25—4·55 (1H, m) and 3·2 (2H, m) may be assigned to the resonances of H-3′ and H-5′, respectively. [b] Isolated crystalline material, based on 2′-deoxyribonucleoside or *N*-acyl derivative. [c] A, methanol–methylated spirit; B, methanol; C, ethanol; D, benzene. [d] Yields in parentheses are based on 3′,5′-di-*O*-acetyl-2′-deoxy-adenosine or -guanosine.

Treatment of a 2′-deoxyribonucleoside or its *N*-acyl derivative with an excess of 9-chloro-9-phenylxanthene[4] (**4b**) in pyridine solution gives the corresponding 5′-*O*-pixyl derivative (**5**). Satisfactory to good yields (Table) of (**5a—d**), the 5′-*O*-pixyl derivatives of 6-*N*-*p*-t-butylbenzoyl-2′-deoxyadenosine, 4-*N*-benzoyl-2′-deoxycytidine, 2-*N*-*p*-t-butylphenylacetyl-2′-deoxyguanosine, and thymidine, respectively, have been obtained in this way.§ Each of the latter derivatives has been isolated as an analytically pure crystalline solid but yields have not yet been optimized.

In 80% acetic acid at 20 °C, removal of the pixyl groups from (**5a—d**) is complete within *ca.* 15, 12, 8, and 12 min, respectively. Under the same conditions, removal of the dimethoxytrityl group from (**3c**; B = **9**) is complete within 16 min. Compounds (**5a—d**) were designed as building blocks for the synthesis of oligodeoxyribonucleotides by the phosphotriester approach and are currently being used successfully for this purpose.[5] As fully-protected phosphotriester intermediates tend to become less soluble in organic solvents with increasing molecular weight,[6] two of the building blocks (**5a,c**) have been provided with lipophilic acyl protecting groups. The *p*-t-butylphenylacetyl group, used to protect guanine residues (as in **8**), is both lipophilic and removable under conveniently mild conditions (*ca.* 5 M-NH_3–MeOH, 20 °C, 5 h).

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† Compound (**1c**) has been shown (ref. 2) also to react with the 3′-hydroxy groups of 2′-deoxyribonucleoside derivatives.

‡ We suggest that 9-phenylxanthen-9-yl should be abbreviated to 'pixyl' and that the symbol Px (corresponding to Tr for trityl) should be used to represent the pixyl group in chemical formulae.

§ The following procedure which was used for the preparation of (**5d**) is typical. Thymidine (20·6 mmol), (**4b**) 31 mmol [prepared by the action of acetyl chloride on 9-phenylxanthen-9-ol (**4a**) (M. Gomberg and L. H. Cone, *Annalen*, 1909, **370**, 142) in benzene solution], and anhydrous pyridine (35 ml) were stirred together at room temperature. After 80 min, when t.l.c. (silica gel) indicated that no thymidine remained, methanol (15 ml) was added and the products were partitioned between choroform (100 ml) and saturated aqueous sodium hydrogen carbonate (150 ml). Evaporation of the dried organic layer and crystallization of the residue from benzene gave (**5d**), 8·53 g (see Table). If the reaction time is prolonged or a larger excess of (**4b**) is used, some 3′,5′-di-*O*-pixyl derivative is likely to be formed.

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[6] R. Arentzen and C. B. Reese, *J.C.S. Perkin I*, 1977, 445.