Nucleophilic Addition Reactions of [1,2,5]Oxadiazolo[3,4-*d*]pyrimidine 1-Oxides (Pyrimidofuroxans)

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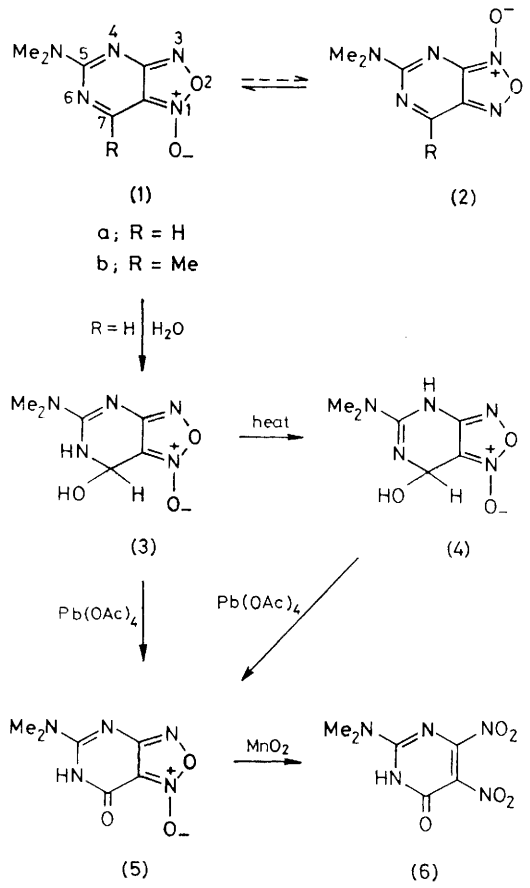
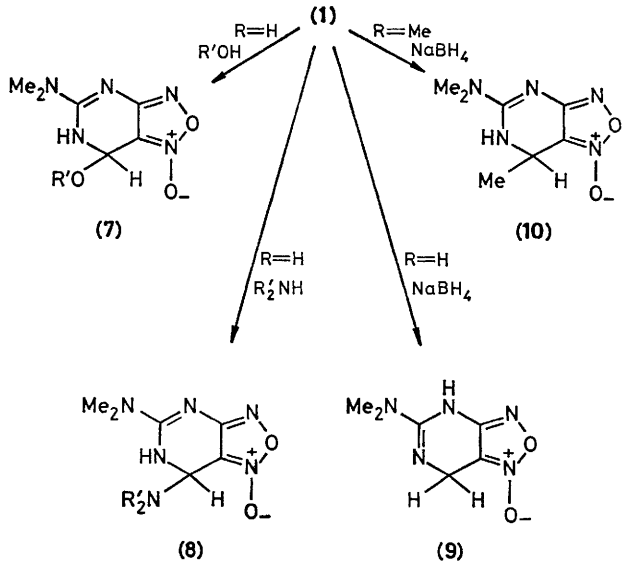
5-Dimethylamino-[1,2,5]oxadiazolo[3,4-*d*]pyrimidine 1-oxide reacts preferentially at the C-7 position of the pyrimidine ring with nucleophilic reagents (water, alcohols, amines, and the hydride ion) giving readily isolable covalent adducts in which the furoxan ring remains intact, but in the case of the water adduct this ring can be opened oxidatively under mild conditions to afford the corresponding 5,6-dinitropyrimidin-4(3*H*)-one derivative.

Nucleophilic opening of the furoxan ring in benzofuroxans provides the basis for the exceptional utility of these molecules in heterocyclic synthesis.[1] Competing nucleophilic attack at the benzene nucleus in simple benzofuroxans is rarely observed,[2] though not unexpectedly this mode tends to predominate in the case of benzofuroxans activated by electron-withdrawing substituents.[3] Derivatives of the [1,2,5]-oxadiazolo[3,4-*d*]pyrimidine 1-oxide (pyrimidofuroxan) ring



Scheme 1



Compound	R′	M.p./°C	Yield/%
(7a)	Me	125	91
(7b)	Et	118	93
(8a)	Me	77	78
(8b)	Et	56	78
(9)	—	196	81
(10)	—	187	33

Scheme 2

system,[4] whose susceptibility to nucleophilic attack has not previously been reported, are now shown to react preferentially at the C-7 position of the pyrimidine ring with a variety of nucleophiles giving covalent adducts in which the furoxan ring remains intact.†

The pyrimidofuroxans (Scheme 1) (**1a**), m.p. 136 °C, and (**1b**), m.p. 140 °C, chosen for study were readily formed in high yield (70—90%) as orange crystalline solids, by the orthodox cyclisative decomposition of the corresponding 4-azido-5-nitropyrimidine derivatives. The formulation of the pyrimidofuroxans as 1-*N*-oxides (**1**) rather than 3-*N*-oxides (**2**) is based firstly on their ^{1}H n.m.r. spectrum which in each case shows a single species and lacks temperature dependence, and secondly on the greater stability of the 4-aza tautomer (**1**) anticipated on electronic grounds.[5] Despite the presence of the electron-donating and hence deactivating dimethylamino substituent, merely stirring the pyrimidofuroxan (**1a**) in aqueous dioxan at room temperature resulted in the formation of a readily separated mixture of the colourless covalent hydrates (**3**) (92%), m.p. 135 °C,‡ and (**4**) (8%), m.p. 135 °C.‡ The adduct (**3**) was unstable to crystallisation being readily converted quantitatively into the isomer (**4**). The structures assigned to the covalent adducts (**3**) and (**4**) are based on their i.r. and ^{1}H n.m.r. spectra and on their oxidation by lead tetra-acetate to give the yellow crystalline oxadiazolopyrimidinone (**5**) (46—56%), m.p. 207 °C. Further oxidation of the latter compound or of the adduct (**3**) or (**4**) occurred on treatment with manganese dioxide in dimethylformamide giving a yellow crystalline product (54—91%), m.p. 190 °C (violent decomp.) whose properties are consistent with its formulation as the hitherto unknown dinitropyrimidinone (**6**). The mildness of the oxidative furoxan ring-opening [(**5**) → (**6**)] is particularly noteworthy in view of the relatively harsh conditions required to effect analogous ring-opening in nitrobenzofuroxans,[6] and indicates that manganese dioxide is a potentially useful reagent for the oxidative conversion of furoxan rings into otherwise inaccessible 1,2-dinitro-products. This aspect is being further investigated.

Formation of the adducts (**3**) and (**4**) from the pyrimidofuroxan (**1a**) is akin to the well documented[7] covalent hydration of the structurally related quinazolines. The pyrimidofuroxan (**1a**) was also converted in cold methanol and ethanol in high yield (Scheme 2) into the relatively stable covalent adducts (**7a** and **b**). On the other hand reaction of (**1a**) with dimethylamine in ethanol or with neat diethylamine afforded good yields (Scheme 2) of colourless products which decomposed back to the pyrimidofuroxan (**1a**) on dissolution in organic solvents but whose covalent adduct structures (**8a** and **b**) may be tentatively inferred from their i.r. absorption.

The propensity of the pyrimidofuroxan (**1a**) to undergo nucleophilic attack at the C-7 position of the pyrimidine nucleus is further emphasised by its reaction with the hydride ion, sodium borohydride in diglyme converting it into a dihydro-product whose ^{1}H n.m.r. spectrum allows its unequivocal formulation as the 4,7-dihydro derivative (**9**). The reduction of the pyrimidine ring in preference to the furoxan ring observed in this transformation contrasts with the well known[8] susceptibility of the furoxan ring in benzofuroxans to sodium borohydride reduction, but parallels the behaviour reported[9] for pyrimidofurazans.

The methylpyrimidofuroxan (**1b**) was recovered unchanged from aqueous and alcoholic media thus demonstrating the inhibiting effect on nucleophilic addition of a C-7 substituent. However, the presence of the C-7 methyl group in the pyrimidofuroxan (**1b**) did not prevent the addition of hydride ions,

† Satisfactory analyses and spectral data were obtained for all new compounds.

‡ Corresponds to thermal reversion to the pyrimidofuroxan (**1a**).

reduction with sodium borohydride in diglyme giving the 6,7-dihydro-derivative (**10**), albeit in low yield.

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