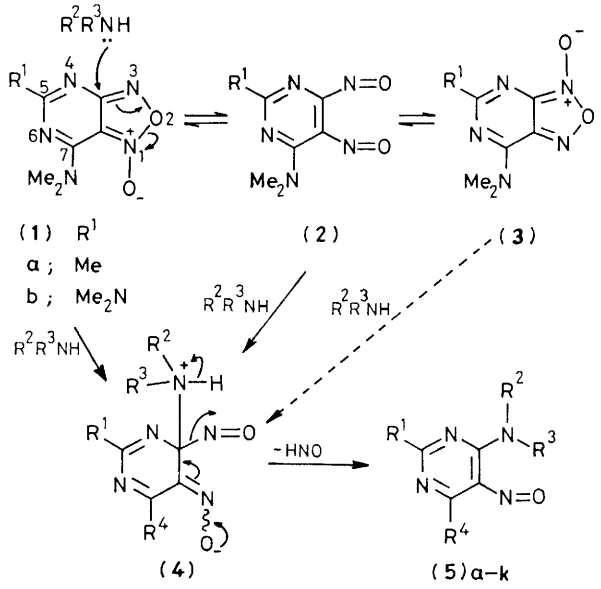
Unprecedented Aminative Ring-opening Reactions of [1,2,5]Oxadiazolo[3,4-*d*]pyrimidine 1-Oxides (Pyrimidofuroxans)

George Tennant* and Graeme M. Wallace

Department of Chemistry, University of Edinburgh, West Mains Road, Edinburgh EH9 3JJ, U.K.

Reaction of 5-substituted 7-dimethylamino-[1,2,5]oxadiazolo[3,4-*d*]pyrimidine 1-oxides with ammonia and amines results in unprecedented aminative furoxan ring-opening to the corresponding 4-amino-5-nitrosopyrimidines, whereas [1,2,5]oxadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one 1-oxide reacts with amines to afford 4-alkylaminomethylideneaminofuroxan-5-carboxamide derivatives.

Nitroso-derivatives formed by initial nucleophilic opening of the furoxan ring are plausible intermediates[1,2] in transformations of benzofuroxans which lead to a variety of heterocyclic ring systems.[1,3] However, though amines effect the simple ring-opening of benzofuroxans to 2-nitrophenylhydrazine derivatives,[4,5] the nucleophilic opening of annelated furoxans to nitroso-products has not been reported hitherto.† It is now shown that the reaction of 5-substituted 7-dimethylamino-[1,2,5]oxadiazolo[3,4-*d*]pyrimidine 1-oxides with ammonia and amines under mild conditions results in unprecedented furoxan ring-opening to the corresponding 4-amino-5-nitrosopyrimidine derivatives. In contrast, amines react with [1,2,5]oxadiazolo[3,4-*d*]pyrimidin-7(6*H*)-one 1-oxide by aminolytic opening of the pyrimidine ring giving 4-alkylaminomethylideneaminofuroxan-5-carboxamide derivatives.‡



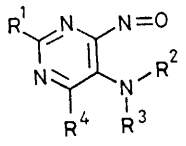
Scheme 1

(5)	R^1	R^2	R^3	R^4	M.p. /°C	Yield /%
a;	Me	H	H	Me_2N	187	44
b;	Me	H	Et	Me_2N	68	45
c;	Me	H	Ph	Me_2N	148	80
d;	Me	H	PhCHMe	Me_2N	93	84
e;	Me	Me	Me	Me_2N	125	90
f;	Me	H	Me	MeNH	204	73
g;	Me	H	$PhCH_2$	$PhCH_2NH$	123	42
h;	Me	$-[CH_2]_4-$		$CH_2[CH_2]_3N-$	143	85
i;	Me	$-[CH_2]_5-$		Me_2N	100	62
j;	Me	$-[CH_2]_2O[CH_2]_2-$		Me_2N	gum	95
k;	Me_2N	$-[CH_2]_4-$		Me_2N	118	41

The pyrimidofuroxans [Scheme 1; (**1a**)], m.p. 129 °C, and (**1b**), m.p. 169 °C, studied were readily synthesised in high yield (94—99%) by the orthodox thermal decomposition of the requisite azido-nitropyrimidine or nitrotetrazolo[1,5-*c*]-pyrimidine, respectively. The assignment of 1-oxide (as opposed to tautomeric 3-oxide) structures (**1a**) and (**1b**) to these products is based on the temperature invariance of their ^1H n.m.r. spectrum, which in both cases shows the presence of only a single species, and the greater stability of the 4-aza- (as opposed to 7-aza-) tautomeric structure anticipated on electronic grounds.[6] Both compounds (**1a**) and (**1b**) reacted smoothly at room temperature with ethanolic solutions of ammonia and a variety of primary and secondary amines giving moderate to excellent yields (Scheme 1) of blue or blue-green products whose properties are consistent with the 4-amino-5-nitrosopyrimidine structures (**5**). In the reactions of the pyrimidofuroxan (**1a**) with methylamine, benzylamine, and pyrrolidine, furoxan ring-opening was accompanied by aminative replacement of the 7-dimethylamino-substituent giving the nitrosopyrimidine products (**5f—h**). Alternative 5-amino-4-nitrosopyrimidine structures (**6**) for the products of the reactions of the pyrimidofuroxans (**1a**) and (**1b**) with ammonia and amines are specifically excluded by the symmetrical nature of the compounds (**5e—h**) as revealed by their ^1H n.m.r. absorption.

Formation of the nitrosopyrimidine products (**5**) from the pyrimidofuroxans (**1**) requires the unprecedented excision of an N–O unit from a furoxan ring. A possible course (Scheme 1) for these transformations involves initial aminative ring-opening of the pyrimidofuroxan reacting in its most stable tautomeric form (**1**)[6] to give a nitroso-intermediate (**4**) convertible by loss of the elements of monomeric hyponitrous acid into the observed products [(**4**) → (**5**)]. Analogous pathways originating in the alternative tautomeric forms (**2**) and (**3**) of the pyrimidofuroxan would also account for the observed nitrosopyrimidine products (**5**) but the involvement of the less stable tautomer (**3**) in particular is unlikely in view of the significant hindrance to nucleophilic attack imposed by the proximity of the 1-oxide oxygen atom.

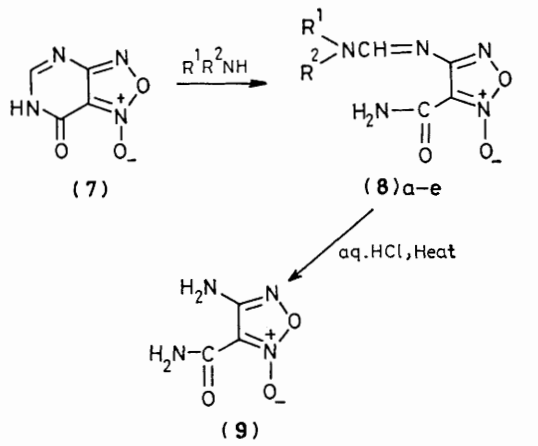
The known[7] oxadiazolopyrimidinone [Scheme 2; (**7**)] also reacted readily with amines. However, in marked contrast with the pyrimidofuroxans (**1a**) and (**1b**), the products, formed in moderate to excellent yield (Scheme 2), were the corresponding 4-alkylaminomethylideneaminofuroxan-5-carboxamides (**8**)



(**6**)

† The conversion of benzofuroxan into 2-nitrosoaniline described in ref. 5 appears to involve preliminary reductive and not direct nucleophilic opening of the furoxan ring.

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



(7) (8)a–e (9)

Scheme 2

(8)	R^1	R^2	M.p/°C	Yield/%
a;	H	Et	152	58
b;	Et	Et	137	41
c;	$-[CH_2]_4-$		187	84
d;	$-[CH_2]_5-$		193	85
e;	$-[CH_2]_2O[CH_2]_2-$		147	81

derived by aminolytic opening of the pyrimidine ring. In accord with their assigned structure, the compounds (**8c**) and (**8d**) underwent acidic hydrolysis to afford 4-aminofuroxan-5-carboxamide (**9**) (69%), colourless plates, m.p. 205 °C, thus providing a viable route to this hitherto unknown but potentially useful synthetic intermediate.

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