AMINO-GROUP EXCHANGE AND RING-CLEAVAGE REACTIONS IN FUSED 1,2,6-THIADIAZINE DIOXIDE DERIVATIVES

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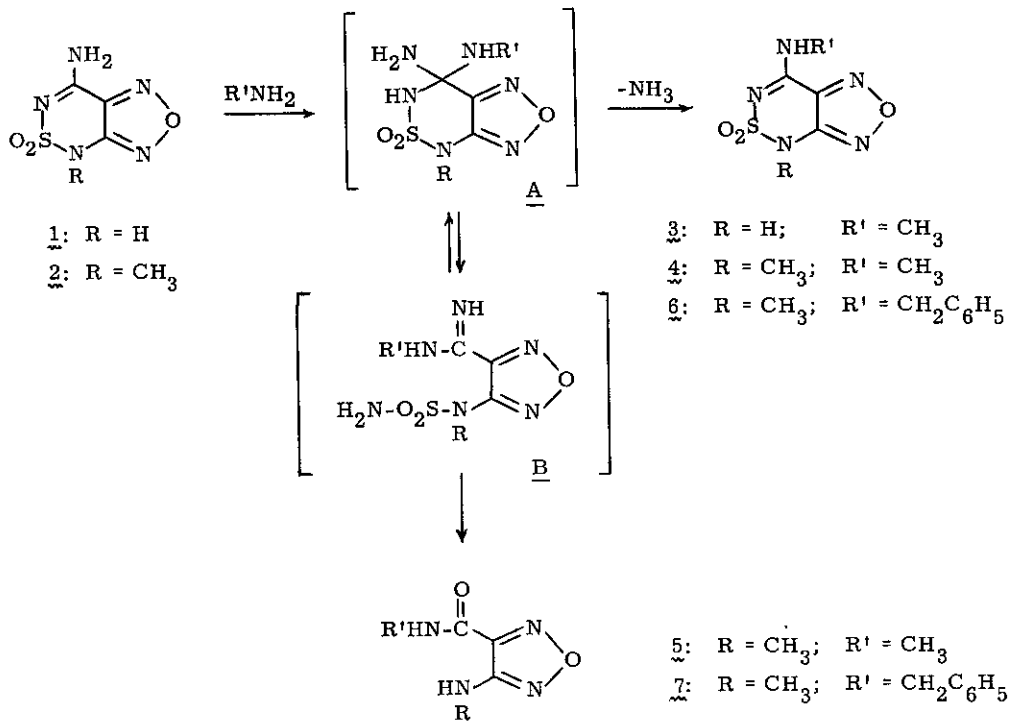
Abstract – Reactions of 7-amino-4H-furazano [3,4-c][1,2,6] thiadiazine 5,5-dioxide (1) and its 4-methyl derivative (2) with nucleophilic agents under different conditions, are described. Besides the products resulting from the displacement of the 7-amino group, those produced by cleavage of the thiadiazine ring have also been obtained.

Continuing with our work on the preparation of 1,2,6-thiadiazine derivatives and related products[1], we now wish to report our results on amino-group exchange and ring cleavage reactions in fused furazano-thiadiazine derivatives.

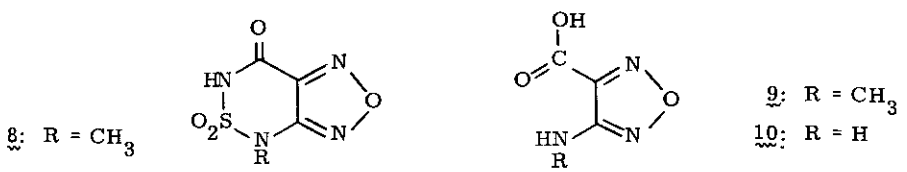
Facile nucleophile displacement of the amino group in position 7 of several fused heterocyclic systems like [1,2,5] thiadiazolo [3,4-d] pyrimidines[2] and furazano [3,4-d] pyrimidines[3] has been described. During the preparation of 2S dioxo isosteres of purines we had previously observed that, in a similar manner, the amino group of 7-amino-4H-furazano [3,4-c][1,2,6] thiadiazine 5,5-dioxide (1)[4] and its 4-methyl derivative (2)[5] smoothly (room temperature) underwent nucleophilic displacement with aqueous methylamine to give the corresponding 7-methylamino derivatives (3) and (4)[5]. When this same reaction was performed with 2 under more vigorous conditions (sealed tube, 100°C), besides nucleophilic displacement of the amino group, cleavage of the thiadiazine ring took place and 3-methylamino-4-(N-methylcarboxamido) furazan (5) was obtained.

As an extension of this reaction other nucleophilic agents were used. Benzylamine gave similar results as methylamine and thus 7-benzylamino-4-methylfurazano [3,4-c][1,2,6] thiadiazine 5,5-dioxide (6) and 3-methylamino-4-(N-benzylcarboxamido) furazan (7) were obtained. Mechanisms involving ring opening and subsequent reclosure have been proposed for amino group displacement (exchange amination) in pyrimidines and fused pyrimidines[6]. For a similar amino group exchange in the 7-aminofurazano [3,4-c] pyrimidine series, Taylor[3] has proposed an sp^3 intermediate, which in the case of the furazanothiadiazine would be A (see Scheme I). Loss of ammonia from A would give rise to the substitution products (amino-exchange) 3, 4 or 6. On the other hand, A could be in equilibrium with the ring-opened form B. This N-disubstituted sulfamide, under the more vigorous reaction conditions could suffer an amine-induced and/or hydrolytic cleavage[7] and thus give 5 or 7.



Scheme I

When sodium hydroxide was used as a nucleophilic agent, compound 2 gave at room temperature, both the substitution product 4-methylfurazano [3,4-c] [1,2,6] thiadiazin-7 (6H)-one 5,5-dioxide 8 (which was isolated as the sodium salt) and 3-methylaminofurazan-4-carboxylic acid 9, which resulted from the thiadiazine cleavage, whilst the same reaction under reflux afforded only 9. (It is worth mentioning that up to now, it had not been possible to obtain 8 following the procedure used for the 7-aminofurazano-thiadiazines [4,5]). On the other hand, compound 1 reacted with sodium hydroxide only under reflux, and, in these conditions, the ring-opened derivative 3-aminofurazan-4-carboxylic acid 10 [8] was isolated.



The structures of all these compounds were established according to their analytical and spectroscopic data. In the ^{1}H nmr spectra of the substitution products, the signals belonging to the methyl groups appear at a lower field than the corresponding ones in the ring-opened derivatives. (See Table I).

Compound	Yield %	Mp (°C)	Cryst. solvent	λ_{max}^{nm} (ε)		δ^1H nmr (DMSO-d_6) NR	NHR'
3	74	237 (dec.)	water	(water)	210 (10,600) 240(sh) (5,450) 260(sh) (4,600) 272(sh) (3,800) 334 (2,500)	--	3.00
4	56	215	water	(water)	209 (9,750) 273 (4,900) 300(sh) (3,600)	3.40	3.00
5	60	186	water			2.87	2.55
6	81	190-191	ethanol	(ethanol-water)	217 (8,450) 280 (4,650)	3.45	4.75($C\underline{H}_2$-$C_6\underline{H}_5$) 7.50($C\underline{H}_2$-$C_6\underline{H}_5$)
7	35	125	ethanol-water	(ethanol)	232 (8,050) 250 (3,200)	2.90	4.55($C\underline{H}_2$-$C_6\underline{H}_5$) 7.45 ($C\underline{H}_2$-$C_6\underline{H}_5$)
8	18 (sodium salt)	250 (dec.)	ethanol	(methanol)	210 (2,800) 262 (2,650)	3.35	
9	79 (sodium salt)	170	water	(methanol)	214 (2,600) 303 (1,500)	2.80	
10	52	200	water	(methanol)	209 (2,600) 287 (2,150)	--	

The results here described open a new route for the synthesis of furazan carboxamide derivatives. The extension of these reactions to other fused thiadiazine systems and related glycosides is under study.

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