PREPARATION OF 2S-DIOXO ISOSTERS OF N-METHYLATED ISOGUANINES

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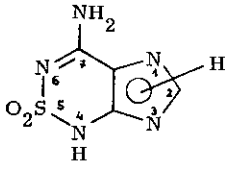
Abstract. Preparation of 7-amino-3,6- dimethylimidazo [2,3-c] -1,2,6-thiadiazine 5,5-dioxide which involves formylation of the corresponding furazano [3,4-c] thiadiazine derivative, reductive cleavage of the furazan moiety and subsequent cyclization to the imidazole ring is described. For the synthesis of 1-methyl- and 3-methyl-7-amino-4H-imidazo [2,3-c]-1,2,6-thiadiazine 5,5-dioxide, the corresponding 4-benzyl-imidazo [2,3-c] thiadiazine was prepared and methylated to give a mixture of the 4-benzyl-1-methyl and 4-benzyl-3-methyl isomers which were finally debenzylated by catalytic hydrogenation. The structures of the newly synthesized compounds are discussed on the basis of their spectroscopic data.

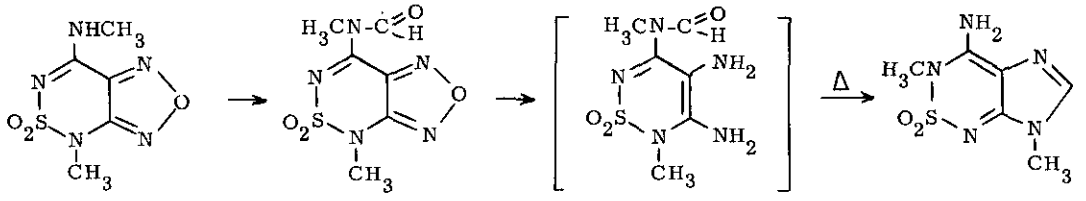
Continuing with our studies on the 2S-dioxo isosters of purines [1,2] and pyrimidines [3] we have previously reported some N-methyl derivatives [4] of 7-amino-1H, 4H-imidazo [2,3-c] -1,2,6-thiadiazine 5,5-dioxide (1) [1], an isoster of isoguanine. These derivatives, incorporated with a tetrahedral sulfur, may be regarded as transition-state analogs of tetrahedral intermediates formed in the course of enzymatic reactions in the biosynthesis of nucleic acids, and can therefore be potential inhibitors of those enzymes [5].



1

In the present paper, we wish to extend our results on this series including the preparation of some of its mono- and di-methyl derivatives which could not be obtained by direct methylation of 1.

In order to obtain the corresponding 3,6-dimethyl derivative, we made use of the elegant procedure described by Taylor for the preparation of 9-substituted adenines [6]. This procedure has the advantage that all reactions proceed under mild conditions and that substituents are introduced unambiguously.



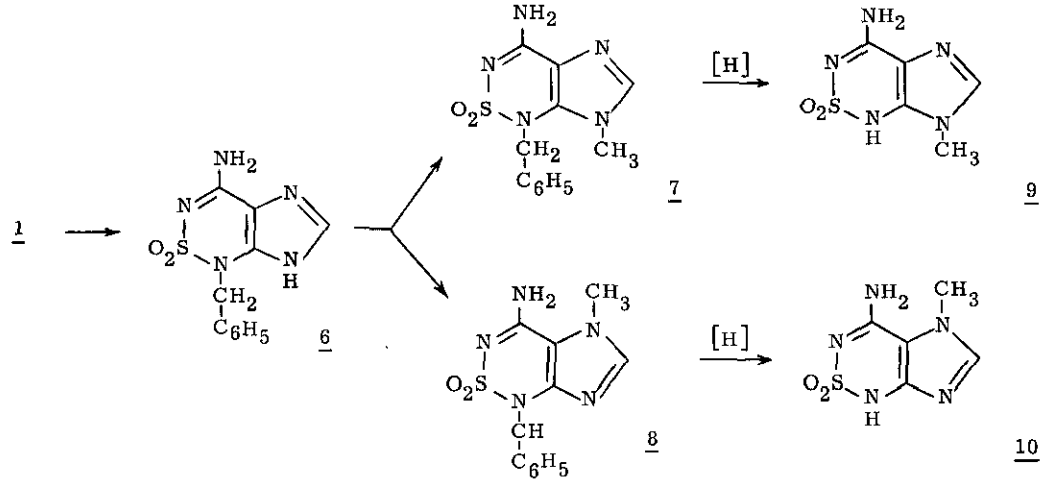
2 3 4 5

Scheme I

The requisite methylamino derivative 2 is readily available from the corresponding furazano [3,4-c] thiadiazine derivative[4]. Formylation of 2 with formic acid/acetic anhydride afforded 3 which was reduced with zinc dust in acetic acid and heated to give the desired 7-amino-3,6-dimethyl imidazo [2,3-c]-1,2,6-thiadiazine 5,5-dioxide (5) (mp 263-264°C). Compound 3 was isolated from the reaction mixture and immediately used in the next step due to the lability of the formylamino rest. The conversion of 2 into 5 involves the reductive cleavage of the furazan ring to give the intermediate 3-formylamino-thiadiazine 4 which then cyclizes to the imidazothiadiazine. *The structure of* 5 *was established according* to its analytical and spectroscopic data, in comparison with those of the corresponding 1,4 and 3,4-dimethyl derivatives[4]. The ^{1}H nmr spectrum showed two very close signals for the methyl groups and another singlet at δ 7.6 corresponding to the imidazole proton which confirmed the fact that conversion of the furazan into the imidazole ring had taken place. The uv spectrum of 5 was, as expected, very different to those of the 1,4- and 3,4-dimethyl derivatives (see Table I).

Application of this procedure to selectively prepare the 6-methyl-imidazothiadiazine failed because the key intermediate 7-amino-4-*methyl furazano* [3,4-*c*]-1,2,6-*thiadiazine* 5,5-dioxide[4] could not be formylated. In this case, the behaviour of the furazanothiadiazine is in contrast to that of the 5-substituted 7-amino-furazanopyrimidines which are readily formylated[6].

For the preparation of the 1-methylimidazothiadiazine 10 the following synthetic approach was used.



Scheme II

Reaction of 1 with benzyl chloride, in alkaline medium, selectively yielded 7-amino-4-benzyl-3H-imidazo [2,3-c] -1,2,6-thiadiazine 5,5-dioxide (6) [mp 242-244°C (dec)]. This is a rather unusual behaviour of the thiadiazine ring in which N- and O-benzylation are not favoured[7,8]. The structure of the 4-benzyl derivative 6 was established according to its analytical and spectroscopic data (uv and ^{1}H nmr) in comparison with those of the 4-methyl derivative[4]. Thus, the signal corresponding to the imidazole proton in the ^{1}H nmr of 6 had the same chemical shift as that of the 4-methyl derivative (see Table I).

Table I. Spectroscopic data of the 7-aminoimidazo [2,3-c] -1,2,6-thiadiazine 5,5-dioxides

Products [a]	λ_{max}^{nm} (ε)	δ ^{1}H nmr (DMSO-d_6) >CH	-N-CH_3
1,4-dimethyl-	214 (4,500); 230 sh (4,000); 243 (3,800); 297 (3,700) [b]	7.90	3.15 (N^4); 3.90 (N^1)
3,4-dimethyl-	218 (13,000); 235 sh (5,800); 287 (5,900) [b]	7.70	3.20 (N^4); 3.75 (N^3)
3,6-dimethyl- (5)	222 (12,300); 305 (10,300) [b]	7.60	3.30; 3.40
1-methyl- (10)	225 (8,400); 305 (5,900) [c]	7.90	3.95 (N^1)
3-methyl- (9)	209 (14,700); 302 (8,500) [b]	7.70	3.55 (N^3)
4-methyl-	230 (8,100); 239 sh (7,500); 297 (7,600) [b]	7.95	3.30 (N^4)
4-benzyl- (6)	222 sh (7,600); 232 (8,200), 298 (7,100) [c]	7.95	--
4-benzyl-3-methyl- (7)	220 sh (10,900); 230 (11,900); 283 (7,100) [d]	7.75	3.65 (N^3)
4-benzyl-1-methyl- (8)	218 (4,800); 235 sh (4,600); 248 sh (4,000); 297 (4,500) [d]	7.95	3.95 (N^1)

[a] Satisfactory data of elemental analyses were obtained for all new products. Yields 50-70 %.
[b] in H_2O; c) in H_2O/EtOH; d) in EtOH.

Compound 6 was then treated with dimethyl sulfate to give a mixture, from which 7-amino-4-benzyl-3-methylimidazo [2,3-c]-1,2,6-thiadiazine 5,5-dioxide (7) [mp 248-250°C (dec)] was obtained by recrystallization from EtOH. 7-Amino-4-benzyl-1-methylimidazo [2,3-c] -1,2,6-

thiadiazine 5,5-dioxide (8) [mp 150-152°C (dec)] had to be separated from the reaction mixture by tlc (7:1 $CHCl_3$: EtOH). The structures of 7 and 8 were established on the basis of their spectroscopic data in comparison with those of the 1,4- and 3,4-dimethyl derivatives (see Table I) and of subsequent chemical conversions.

Catalytic hydrogenation of 8 afforded the desired 7-amino-1-methyl-4H-imidazo [2,3-c]-1,2,6-thiadiazine 5,5-dioxide (10) [mp 262-263°C (dec)], while that of 7 afforded the 3-methyl imidazothiadiazine 9 which had previously been obtained following the procedure described for 5[4].

Finally, attempts were done to hydrolyze the 7-amino group of these derivatives in order to obtain the corresponding structural analogs of N-methylated xanthines, since it is well known that isoguanine derivatives can be converted to the xanthine analogs by mineral acid hydrolyses[9,10]. When the 4-benzyl monomethyl derivatives 7 and 8 were boiled with 2N HCl, only benzylamine hydrochloride could be isolated, as result of the cleavage of the thiadiazine ring.

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