STUDY OF THE REACTIVITY OF 3-OXO-1,2,6-THIADIAZINE 1,1-DIOXIDES

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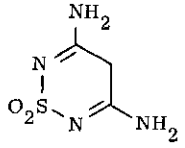
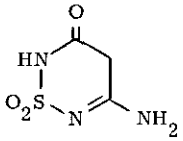
Abstract - Alkylation and glycosidation reactions of 5-amino-3-oxo-2H, 4H-1,2,6-thiadiazine 1,1-dioxide[1] and 3,5-dioxo-2H, 4H, 6H-1,2,6-thiadiazine 1,1-dioxide[1], which is only isolable as salt form[2] are reported. The structures of the newly synthesized compounds are discussed on the basis of their spectroscopic data.

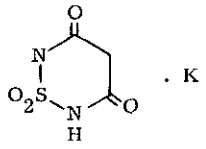
In connection with our previous reports on the preparation of 2-S-dioxo isosters of purine and pyrimidine derivatives[3] we now wish to report our results on thiadiazine derivatives II and III. These type of compounds are of interest since they and their nucleosides may be regarded as potential transition state analogs in the biosynthesis of purine and pyrimidine nucleosides[4].



I



II



III

Methylation of II with dimethyl sulfate in $NaHCO_3$ at room temperature afforded the monomethyl derivative (IIa : 28%) together with traces of IIb. The ^1H nmr spectrum (DMSO-d_6) showed two singlets: one at δ 3.15 was attributed to a methyl group attached to the N-2 position, since another at δ 3.8 corresponding to the methylenic protons remains unchanged in comparison with the starting material.

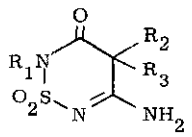
When the reaction was performed in 1N NaOH only the dimethyl derivative (IIb : 35%) was obtained. The ^1H nmr spectrum (DMSO-d_6) showed two distinct signals for the methyl groups: a singlet at δ 3.15 assigned to the N-2 position and a doublet at δ 1.55 indicating a C-CH_3 group coupled with the H-4. This doublet collapsed to a singlet after addition of D_2O. The spectrum showed also a multiplet at δ 3.65, with the same coupling constant as that of the C-CH_3, that disappeared on addition of D_2O and which was attributed to the H-4. Attempts to prepare a trimethyl derivative starting from IIb were unsuccessful.

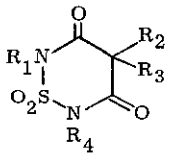
Methylation of III both in 1N NaOH and in $NaHCO_3$ afforded only the dimethyl derivative (IIIa : 58%) ^1H nmr (DMSO-d_6) δ : 3.3 (6H, s, CH_3), 4.15 (2H, s, CH_2).

It should be pointed out that the behaviour of II and III towards dimethyl sulfate is quite different to that reported for I [5], where methylation always started at C-4 position to continue at N-2.

Reaction of II with benzyl chloride did not take place in $NaHCO_3$ but when it was performed in 1N NaOH the dibenzyl derivative (IIc : 20%) was isolated, even when working with equimolar amounts of the reagents. ^1H nmr (DMSO-d_6) δ : 7.37 (10H, s, C_6H_5), 3.45 (4H, s, C-$C\underline{H}_2$-C_6H_5).

In a similar reaction, when III was the starting material a C-monobenzyl derivative (IIIb : 18%) together with a C-dibenzyl derivative (IIIc : 26%) could be isolated. IIIb ^1H nmr (DMSO-d_6) δ : 7.38 (5H, s, C_6H_5), 3.75 (1H, m, CH), 3.1 (2H, d, C-$C\underline{H}_2$-C_6H_5); IIIc ^1H nmr (DMSO-d_6) : 7.31 (10H, s, C_6H_5), 3.40 (4H, s, C-$C\underline{H}_2$-C_6H_5).





IIa : $R_1 = CH_3$, $R_2 = R_3 = H$

IIb : $R_1 = R_2 = CH_3$, $R_3 = H$

IIc : $R_1 = H$; $R_2 = R_3 = C_6H_5$-CH_2

IId : R_1 = 2,3,4,6-tetra-O-acetyl-β-D-glucopyranosyl;
$R_2 = R_3 = H$

IIIa : $R_1 = R_4 = CH_3$, $R_2 = R_3 = H$

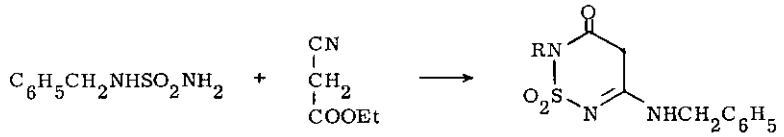
IIIb : $R_2 = C_6H_5CH_2$, $R_1 = R_3 = R_4 = H$

IIIc . $R_1 = R_4 = H$; $R_2 = R_3 = C_6H_5$-CH_2

Products *	mp °C	λ_{max} nm (ε) in H_2O
IIa	195-196	223 (6,600) , 280 (4,200)
IIb	211-213	227 (5,900)
IIc	260-261	211 (18,300)
IId	165-166	220 - ; 270 -
IIIa	92-93	205 (8,700) ; 273 (3,200)
IIIb	159-160	206 (14,200)
IIIc	189-190	205 (22,500)
IVa	239-240	- - - -
IVb	193-194	217 - - -

* Satisfactory data of elemental analysis were obtained for all new products.

In an attempt to obtain an N-6 alkyl derivative, N-benzyl sulfamide was made to react with ethyl cyanacetate in a similar manner as that described for the preparation of II[1]. Thus, only a benzylamino derivative could be isolated from the reaction mixture as its monopotassium salt (IVa · 46%) which on acidification yielded the free compound (IVb : 39%).



R = K IVa
R = H IVb

The fact that the benzyl rest had migrated to the exocyclic amino group was evident from the ^{1}H nmr spectrum (DMSO-d_6). IVb δ : 4.25 (2H, d, NH-C<u>H</u>$_2$-C_6H_5), 8.6 (1H, m, N<u>H</u>-CH_2-C_6H_5).

In order to consider this behaviour as a Dimroth rearrangement, other alkyl sulfamides were made to react with ethyl cyanacetate, resulting in the formation of complex reaction mixtures.

Using the different alkylated derivatives as model substances, nucleoside preparation was attempted. Thus, II was first silylated with HMDS and then made to react with 1,2,3,4,6-penta-O-acetyl-β-D-glucopyranose, at room temperature, in the presence of $SnCl_4$ according to the procedure described by Vorbrüggen et al[6]. From the reaction mixture the N-2-glucosyl derivative (IId : 25%) could be isolated. The uv spectrum of IId was similar to that of the N-2 methyl derivative IIa, indicating that glycosidation had taken place at that position. The β configuration was assigned on the basis of mechanistic considerations[7] as well as on the basis of the coupling constant $J_{1'-2'}$ = 9 Hz, indicating a <u>trans</u> diaxial arrangement for H-1' and H-2'. IId ^{1}H nmr δ: 5.75 (1H, d, H-1'), 5.5 (2H, m, H-2', H-3'), 4.9 (1H, t, H-4'), 4.15 (3H, m, H-5', H-6'), 3.8 (2H, s, CH_2), 2.00 (12H, m, $COCH_3$).

Due to its insolubility and taking advantage of its acidic character compound III had to be silylated in pyridine. However glycosidation was unsuccessful.

The difference in behaviour of II and III towards alkylating agents reflects the softness of the alkylating agent[8]. Surprisingly no O-alkylation could be detected although other 3-oxo-thiadiazine derivatives showed competitive O- <u>vs</u> N- and C-alkylation[5,9].

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