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NITROGEN-OXYGEN AND OXYGEN-OXYGEN ALKYL GROUP MIGRATIONS. SYNTHESIS OF 1,2,4-TRIAZINE HYDROXAMIC ACID ESTERS

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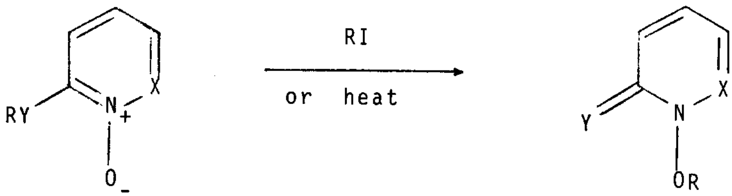
Abstract: Novel 1,2,4-triazine hydroxamic acid esters and alkylated 2,3-dihydro-1,2,4-triazine N-oxides were prepared by rearrangement and selective alkylations of 3-alkoxy and 3-alkylamino-1,2,4-triazine N-oxides.

In light of the current interests and the extensive research on pyrimidine bases, we want to report a facile alkylation of 6-azapyrimidine N-oxides (1,2,4-triazines). It is well known that amino and alkoxypyridine, 1, and pyridazine N-oxides, 2, undergo rearrangements upon treatment with alkyl halides, with bases, or when heated.[1] However, there are few, if any, such reports on these rearrangements with heterocyclic rings containing the 1,3-diazine moiety (pyrimidines, 1,3,5- and 1,2,4-triazines). This is primarily due to the high reactivity of these systems which are prone to ring opening, ring contraction, and decomposition reactions under very mild conditions.



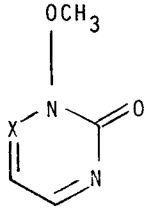
1 X = CH; Y = NH,O

2 X = N; Y = NH,O

3 X = CH; Y = NH,O

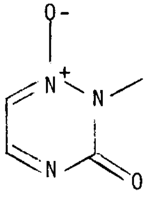
4 X = N; Y = NH,O

Recently, we reported the isolation of 1-methoxy-1,2-dihydropyrimidine-2-one, 5, during the N-oxidation of 2-methoxypyrimidine, 6.[2] This prompted an examination of their 6-aza analogs to determine whether similar cyclic hydroxamic acid derivatives (such as 5, X=N) could be prepared.

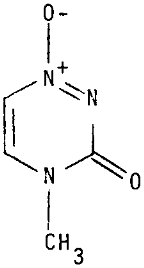


5 X = CH

Treatment of 3-methoxy-1,2,4-triazine 1-oxide, 7, with methyliodide in methanol at room temperature for 10 days produced compound 8, whose ^{1}H nmr spectrum consisted of two doublets in the aromatic region (δ8.14 and δ8.80) and a three-proton singlet at δ3.81. The molecular weight (127 amu) and elemental analysis ($C_4H_5H_3O_2$) confirmed that compound 8 was isomeric with the starting material. The infrared carbonyl absorption at 1685 cm^{-1} coupled with the above information made it clear that this product was either 8a or 8b. In view of the fact that the N_2-CH groups of various 2,3-dihydro-N_2-methyl-1,2,4-triazine-3-ones are much more deshielded[3-5] (δ3.70-3.83) than the N_4-CH_3 group of 3,4-dihydro-N_4-methyl-1,2,4-triazine-3-ones[3-5] (δ3.41-3.50), we have assigned structure 8a to the above product. In addition, the NOE experiments support these assignments. When compound 8 was dissolved in d_6-benzene and the N-CH_3 signal irradiated at its frequency, no increase in intensity of either of the two doublets was observed. If the methyl group was at N_4 rather than N_2, a significant augmentation in intensity of H_5 doublet would occur.

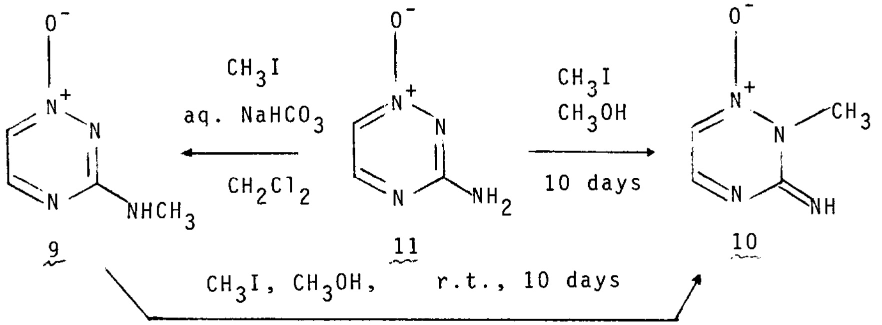


8a

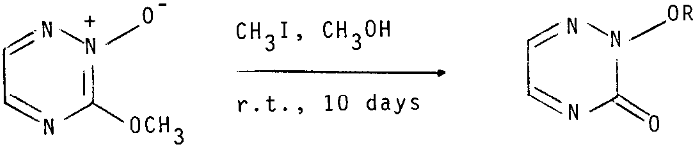


8b

Similarly, 3-monomethylamino-1,2,4-triazine 1-oxide, 9, rearranged to 2,3-dihydro-N_2-methyl-3-imino-1,2,4-triazine 1-oxide, 10. The 3-amino-1,2,4-triazine 1-oxide, 11, yielded the kinetic product 9 when rapidly stirred into the non-polar solvent (CH_2Cl_2/hexane) containing methyliodide in an immiscible aqueous bicarbonate solution, but gave the alkylated imide 10 in the polar solvent (CH_3OH). The 3-dimethylamino derivative did not rearrange since it cannot tautomerize to the imino compound.



The 3-amino-1,2,4-triazine 2-oxide, 12, did not react under similar conditions and 3-methoxy-1,2,4-triazine 2-oxide, 13, yielded the desired cyclic hydroxamic acid, 14. The O-methyl ester 14a was isolated in the presence of a base (Na_2CO_3) and the parent 2-hydroxy-2,3-dihydro-1,2,4-triazine-3-one, 14b, without neutralization. Therefore, it seems that 14b arose via the hydrolysis of 14a.

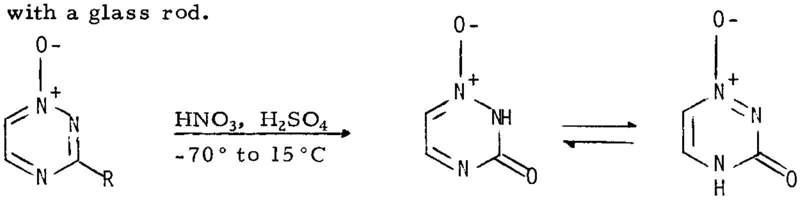


13

14a R = CH_3

14b R = H

Alternatively, parent hydroxamic acids 15 and 14b were prepared by hydrolysis of the corresponding 3-methoxy and/or 3-amino derivatives in strong mineral acids. When 3-methoxy-, 7, or 3-amino-1,2,4-triazine 1-oxide, 11, were treated with the mixture of concentrated nitric and sulfuric acids under carefully monitored conditions, they were converted to 2,3-dihydro-1,2,4-triazine-3-one 1-oxide, 15, in good yields (ca. 50-60%). Under the same reaction conditions, 3-amino-1,2,4-triazine 2-oxide, 12, yielded 14b. The initial reaction is exothermic and, if carried out at room temperature, starting materials decompose rapidly with the evolution of nitrogen oxides. The desired compounds 14b and 15, otherwise not easily accessible, are obtained if the reaction mixture is frozen to -70 °C and the triazine is added slowly to this slurry (temperature never to exceed 15 °C). The stirring was accomplished with a glass rod.

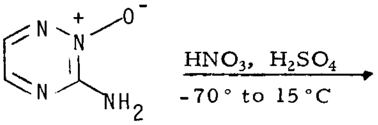


7 R = OCH_3

11 R = NH_2

15a

15b



14b R = H

12

The structural assignment for compound **15** designated as the 2,3-dihydro- isomer **15a** rather than the 3,4-dihydro- isomer **15b** was based on the comparison of its ^1H nmr spectrum with that of the alkylated derivative, **8a**. However, it should be kept in mind that this is only a tentative assignment and further studies are needed to establish whether the two isomers exist in equilibrium in solution and in the solid state.

Experimental: Starting materials were prepared according to the literature methods described in ref. 1 and references (**7**[6], **11**[7], **12**[8], **13**[8]) therein. Physical and analytical data: **8**, nmr (d_6-DMSO), 8.80 (d), 8.14 (d), 3.81 (s 3H); mp 160-161 °C. Anal. Calcd. for $C_4H_5N_3O_2$: C, 37.79; H, 3.97; N, 33.06. Found: C, 37.70; H, 3.91; N, 32.88. **9**, $C_4H_6N_4O$, mp 163-165 °C (lit.[1] 164-165 °C). **10**, nmr (d_6-DMSO), 8.78(d), 8.12(d), 3.69)s3H) mp 87 °C (dec.). Anal. Calcd. for $C_4H_6N_4O$: C, 38.08; H, 4.80; N, 44.27. Found: C, 38.17; H, 4.81; N, 44.20. **14a**, nmr ($CDCl_3$, d_6-acetone), 8.47(d), 8.38(d), 4.67(s 3H); mp 169-171 °C. Anal. Calcd. for $C_4H_5N_3O_2$: C, 37.79; H, 3.97; N, 33.06. Found: C, 37.69; H, 3.76; N, 32.79. **14b**, nmr (d_6-DMSO), 8.30(d), 8.20(d); mp 222-225 °C. Anal. Calcd. for $C_3H_3N_3O_2$: C, 31.86; H, 2.60; N, 37.16. Found: C, 31.73; H, 2.31; N, 37.17. **15**, nmr (d_6-DMSO), 8.70(d), 8.05(d); mp 201-203.5 °C. Anal. Calcd. for $C_3H_3N_3O_2$: C, 31.86; H, 2.68; N, 37.17. Found: C, 31.71; H, 2.88; N, 36.86. The ^1H coupling constant for **7** ($J_{5,6}$=4.0 Hz) as compared to **15** ($J_{5,6}$= 6.2 Hz) also offers continuing evidence that compound **15** exists as a 3-one rather than the 3-hydroxy tautomer.

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