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Characterization of a Perhydro-5,6-di(methylene)-2,4-dioxopyrimidine Intermediate and Its Cycloaddition Reactions Leading to Quinazoline Derivatives[1)]

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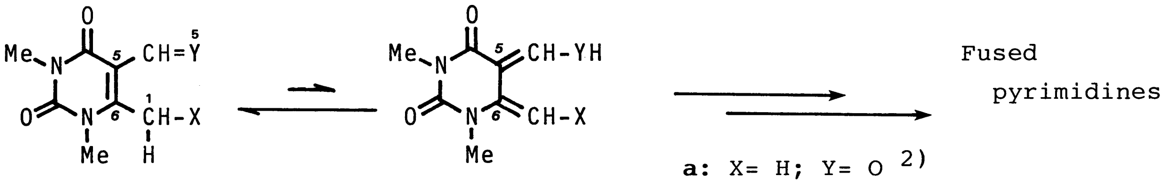
Perhydro-5,6-di(methylene)-2,4-dioxopyrimidine derivative, a useful intermediate for the synthesis of some fused pyrimidines, was characterized as the [4+2] cycloadduct to N-methylmaleimide.

Recently, we have proposed the perhydro-5,6-di(methylene)-2,4-dioxopyrimidine derivatives **2** as key intermediates for the synthesis of fused pyrimidines such as pyrido[3,4-d]pyrimidine[2)] and pyrrolo[3,4-d]pyrimidine.[1b)] These intermediates **2** would be generated via thermal [1,5] hydrogen shift of the corresponding precursors **1**. However, any evidence to elucidate the existence of such intermediates has not been obtained.



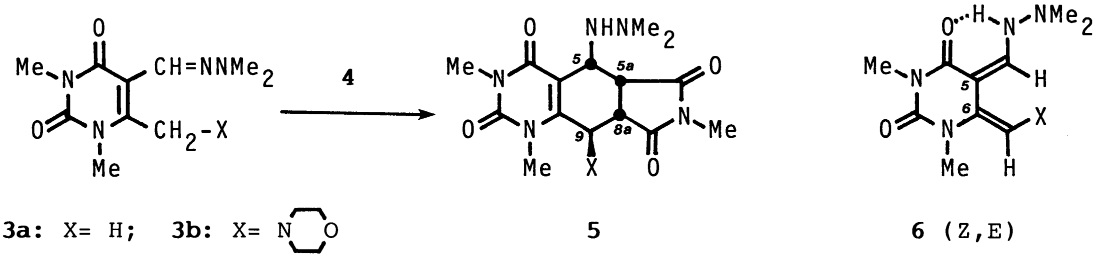
1 **2**

a: X= H; Y= O [2)]
b: X= NR^1R^2; Y= NR^3 [1b)]

In this communication, we wish to describe the characterization of a similar type of intermediate and the synthetic utility of its cycloaddition reactions leading to quinazoline derivatives.

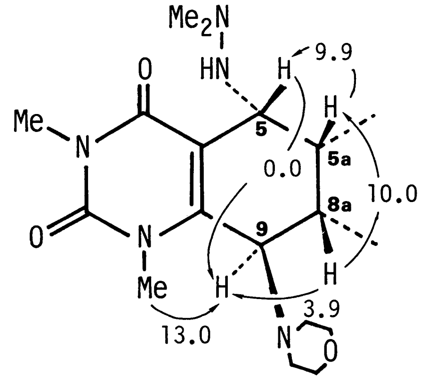
The reaction of 1,2,3,4-tetrahydro-1,3,6-trimethyl- (**3a**) and 1,2,3,4-tetrahydro-1,3-dimethyl-6-morpholinomethyl-2,4-dioxopyrimidine-5-carbaldehyde N,N-dimethylhydrazone (**3b**) with N-methylmaleimide (**4**)(1.1 equiv.) under reflux in toluene for 2 d gave 1:1 adducts **5a** and **5b** in 95 and 76% yields, respectively. The 2,4,6,8-tetraoxo-1,2,3,4,5a,6,7,8,8a,9-decahydro-5H-pyrrolo[3,4-g]quinazoline structure for **5** was confirmed on the basis of analytical and spectral data.[3)]

The stereochemistries of cycloadducts **5a** and **5b** were also accomplished by


3a: X= H; **3b:** X= N O

5

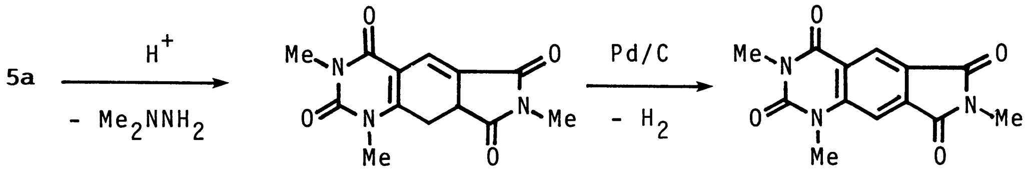
6 (Z,E)



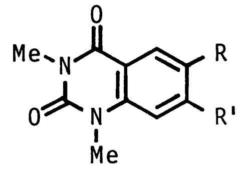
Results of NOE measurements
(%: enhancement of signal area)

comparing the coupling constants with those of the related systems:$^{4)}$ 5,5a-cis configuration for **5a** ($J_{5,5a}$= 3.7 Hz) and 5,5a-cis-8a,9-trans one for **5b** ($J_{5,5a}$= 4.4 and $J_{8a,9}$= 1.0 Hz). These assignments were supported by the NOE measurements of **5b** and the inspection using molecular models. This means that the diene moiety of intermediate **6** has Z,E-configuration. The pathway to **6** would be explainable as below: the [1,5] hydrogen shift of **3b** yields another intermediate diene with E,E- or E,Z-configuration, which is converted to the more stable isomer, **6**.$^{5)}$

The treatment of **5a** with hydrochloric acid in ethanol gave a deaminated product **7** in 92% yield, which was dehydrogenated with Pd/C in refluxing dioxane to afford 2,4,6,8-tetraoxo-1,2,3,4,7,8-hexahydro-6H-pyrrolo[3,4-g]quinazoline **8** in 85% yield. One-pot method (68% yield from **3a**) as well as the reaction at higher temperature (e.g., in refluxing diglyme **8a** was obtained in 78% yield from **3a**) was effective for the direct preparation of **8**. Some examples of cycloaddition reactions of **6a** with olefinic dienophiles in refluxing diglyme are summarized below.



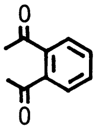
7 **8**



9: R= R'= CO$_2$Me (Y. 42%)

10: R= R'= COPh (Y. 35%)

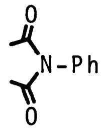
11: R= R'=



(Y. 76%)

12: R= CN; R'= H (Y. 38%)
(from fumaronitrile)

13: R= R'=



(Y. 84%)

References

1) a) Studies on Fused Pyrimidine Derivatives. Part VI; b) Part V of this series: M. Noguchi, Y. Kiriki, and S. Kajigaeshi, Bull. Chem. Soc. Jpn., 62, 3043 (1989).
2) M. Noguchi, K. Sakamoto, S. Nagata, and S. Kajigaeshi, J. Heterocycl. Chem., 25, 205 (1988).
3) All new compounds in this paper gave satisfactory analytical and spectral data. **5b**: mp 251-254 °C(dec); IR(KBr): 3510(NH); ^{1}H NMR(CDCl$_3$): 2.20(s, 6H, -CH$_3$), 3.05, 3.37, 3.61(3s, 3H each, -CH$_3$), 2.3-2.6(m, 4H, -CH$_2$-), 2.7(dd, 1H, 5a-H, J= 8.0, 4.4 Hz) 3.1(dd, 1H, 8a-H, J= 8.0, 1.0 Hz), 3.6-3.8(m, 4H, -CH$_2$-), 4.35(br d, 1H, 9-H, J= 1.0 Hz), 4.78(br d, 1H, 5-H, J= 4.4 Hz); ^{13}C NMR(CDCl$_3$): 25.1, 28.4(5a-, 8a-C), 35.5, 38.1, 42.8, 47.0(-CH$_3$), 47.6(9-C), 48.2(5-C), 54.8, 66.7(-CH$_2$-), 110.2(4a-C), 149.9(9a-C), 152.4(2-C), 161.1(4-C), 176.4, 177.9(6-, 8-C); MS(m/z): 420(M$^+$).
4) S. Senda, T. Asao, I. Sugiyama, and K. Hirota, Tetrahedron Lett., 21, 531 (1980).
5) The hydrogen bond of **6** would play an important role for the stabilization of the system; P. G. Sammes, Tetrahedron, 32, 405 (1976).

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