# PRODUCTS FROM A NOVEL REACTION OF DIHYDROPYRAZINES WITH VICHINALDIAMINES

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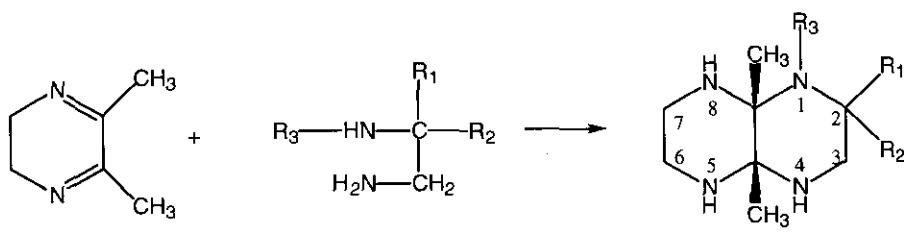
**Abstract** - Dihydropyrazines such as 2,3-dihydro-5,6-dimethylpyrazine reacted with 1,2-diamines like ethylenediamine to form *cis*-tetraazadecalins (TADs) as crystalline products. The NMR spectra of the products in $CDCl_3$ or $CD_3CN$ at -20 ~ -60°C exhibited the signals due to TAD. However, the NMR spectra at room temperature showed that the TAD had dissociated into its parent materials. Seven TADs were obtained by only a mixing operation at a low temperature.

We recently found that dihydropyrazines have DNA strand-breaking activity[1] and reported a new phenomenon that dihydropyrazines transformed into dimeric compounds[2,3] and generated certain carbon-centered radicals[4,5] in their water solution. Further, we unexpectedly found a new reaction whereby

Scheme 1




1

**2a** : $R_1$=$R_2$=$R_3$=H
**2b** : $R_1$=$CH_3$, $R_2$=$R_3$=H
**2c** : $R_1$=$R_2$=$CH_3$, $R_3$=H
**2d** : $R_1$=$R_2$=H, $R_3$=$CH_3$

**3a** : $R_1$=$R_2$=$R_3$=H (77.6%)
**3b** : $R_1$=$CH_3$, $R_2$=$R_3$=H (41.3%)
**3c** : $R_1$=$R_2$=$CH_3$, $R_3$=H (35.3%)
**3d** : $R_1$=$R_2$=H, $R_3$=$CH_3$ (52.7%)

dihydropyrazines react with vicinal diamines to give tetraazadecalins (TADs) which also revealed DNA

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strand-breaking activity the same as dihydropyrazines. To our knowledge, there has been only one report[6] regarding angularly substituted TADs, the steric information and reaction mechanism of which, however, were not described. Preparation methods of various angularly nonsubstituted TADs have been reported,[7] in which the *trans*-fused TADs were isolated as stable crystals in the reaction of glyoxal with diamines. The angularly substituted TADs shown in this communication apparently differ from the previously reported TADs in terms of physical properties and chemical stability.

Mixing 2,3-dihydro-5,6-dimethylpyrazine (**1**) with ethylenediamine (**2a**) at room temperature gave a very unstable crystalline compound (**3a**) which could be recrystallized from benzene or acetonitrile at a lower temperature. The $^1$H-NMR spectrum of **3a** in $CD_3CN$ at room temperature showed only the sum of signals due to its components, i.e., a mixture of **1** and **2a**. However, the NMR spectra of **3a** in $CD_3CN$ in -40°C or in $CDCl_3$ at -60°C showed the signals due to a TAD ; a higher field signal (δ: 1.95 ppm) due to angularly methyls of TAD appeared with disappearance of both methyl signals (δ: 2.13 ppm, $CH_3$-C=N- ) of **1** and the methylene signal (δ: 2.73 ppm) of **2a**. The $^{13}$C-NMR spectrum of **3a** exhibits four signals at 23.45 (methyl carbon), 40.40 and 44.06 (methylene carbon) and 67.95 ppm (quarternary carbon). Analyses of two-dimensional H-C coherence (HMQC and HMBC) at the lower temperatures depicted the structure of **3a** as TAD. The methylene carbons of C2 (C6) and C3 (C7) resonate at different positions,[8] suggesting that the A and B rings of the TAD skeleton are *cis*-fused in conjunction with each other. In addition, **3d** gave us a clue about the structural determination. The $^1$H-NMR spectrum of **3d** showed three methyl signals at δ: 1.07 and 1.38 (angularly substituted methyl), and δ: 2.18 (*N*-methyl). Owing to the presence of *N*-Me, angularly substituted methyl groups resonate at unequivalent positions[9] and the NOE was observed between the methyl signals of C8a and C4a, indicating that **3d** has a *cis*-fused skeleton. Single-crystal X-Ray analysis[10] of **6a** mentioned later supported these structural assignments (see Figure 1.).

Thus, **3a** was characterized to be *cis*-4a,8a-dimethyl-1,4,5,8-tetraazadecalin and the TAD analogs in a series of the present reaction were also characterized to have the *cis*-fused skeleton. Other types (**3b**,**3c** and **3d**) of TAD derivatives were prepared by the reaction of **1** with the ethylenediamine derivatives (**2b**, **2c** and **2d**) (Scheme 1).

Similarly, *trans*-2,3-dimethyl-5,6,7,8,9,10-hexahydroquinoxaline(**4**)[1] reacted with *trans*-

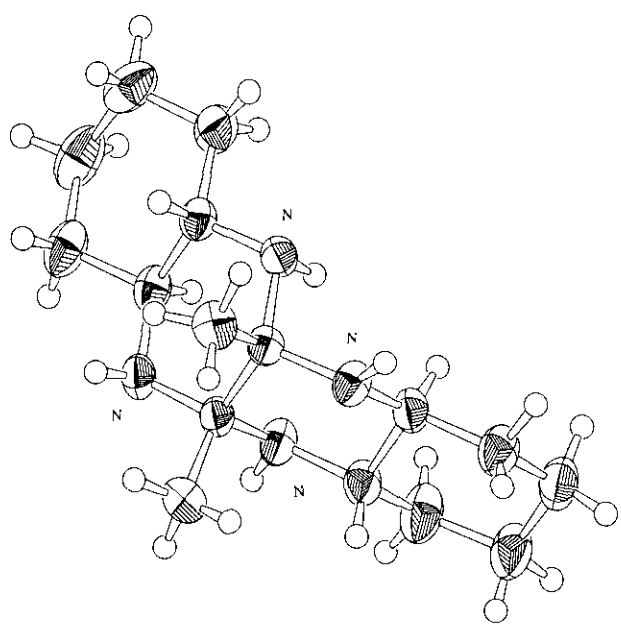
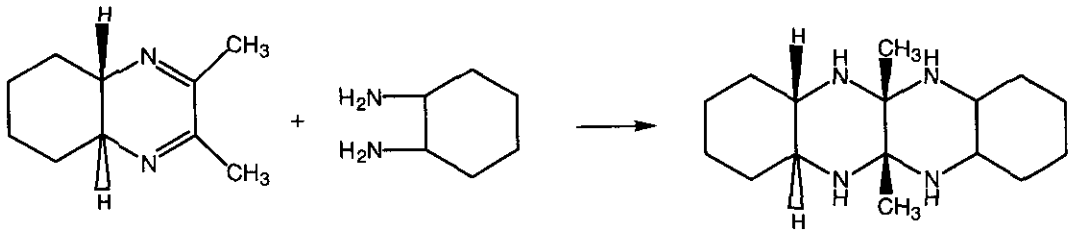



Figure 1. ORTEP Drawing of **6a**.

1,2-diaminocyclohexane (**5a**) and *cis*-isomer (**5b**) in $CH_3CN$ under a low temperature condition to give *trans*-2,3-*trans*-6,7-bis (tetramethylene)-*cis*-4a,8a-dimethyl-1,4,5,8-tetraazadecalin (**6a**) and *cis*-2,3-*trans*-6,7-bis (tetramethylene)-*cis*-4a,8a-dimethyl-1,4,5,8-tetraazadecalin (**6b**), respectively, which could be isolated as stable crystals even at room temperature (Scheme 2).

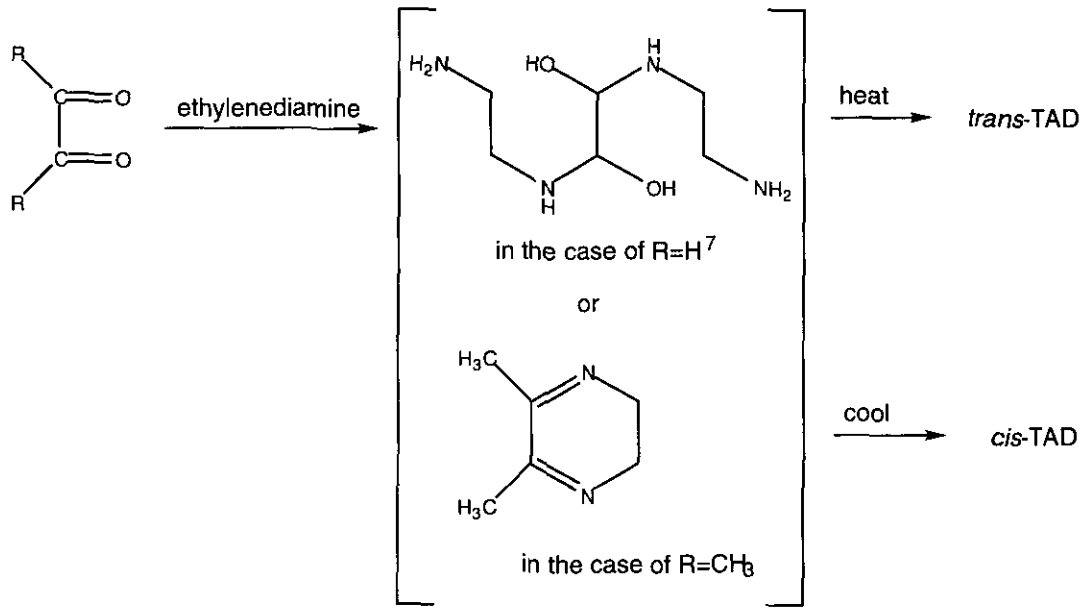
Scheme 2



**4** **5a**: *trans*-isomer **6a**: *trans-cis-trans* (60.6%)
**5b**: *cis*-isomer **6b**: *trans-cis-cis* (61.7%)

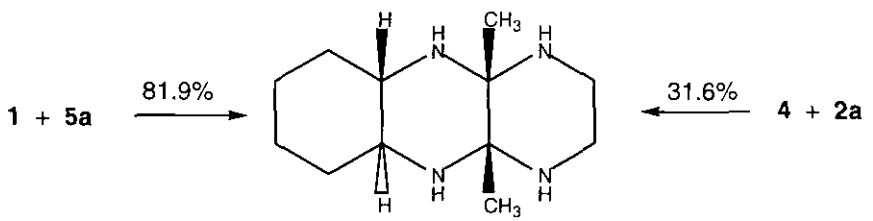
Angularly nonsubstituted *trans*-TADs and the *N*-substituted *trans*-TADs were reported[7] as very stable compounds prepared by refluxing ethanol solutions of glyoxal and diamines. Even in a variety of conditions starting with ethylenediamine and α-diketone, angularly substituted TADs were not obtained by the reported synthetic method. In our reactions, angularly substituted TADs were obtained by only mixing dihydropyrazines with diamines at a low temperature (4°C ~-30°C), and then they were easily dissociated into their starting materials in $CHCl_3$ or $CH_3CN$ solution at room temperature. Consequently, 2,3-butanedione reacted with ethylenediamine in refluxing $CH_3CN$ to give intermediary dihydropyrazine. When this reaction mixture was allowed to stand at -30°C, the dihydropyrazine reacted again with excess ethylenediamine to give *cis*-TAD (>24.8% yield) and other products.[3]

Scheme 3



The reaction mechanism for 2,3-butanedione is considered to differ from that[7] for glyoxal because the intermediary dihydropyrazine could not be detected by NMR spectrometry during the course of the reaction, although *trans*-TAD was obtained in 65.4% yield on the reaction of glyoxal with **2a** according to the reported methods[7] (Scheme 3).

Scheme 4

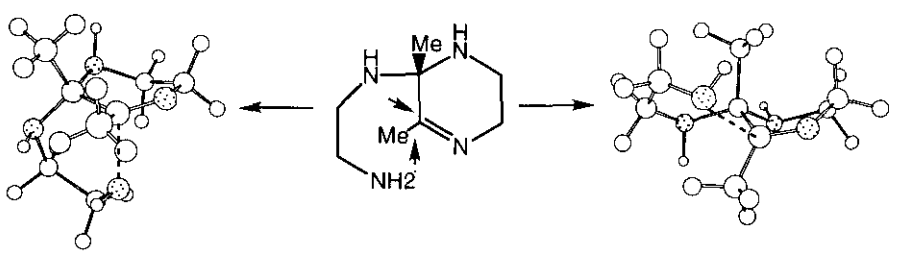



**7**

In alternative reactions of **1** with **5a** and **4** with **2a**, *trans*-2,3-tetramethylene-*cis*-4a,8a-dimethyl-1,4,5,8-tetraazadecalin (**7**) was also obtained together with other products.[11]

At the present stage, it is not clear whether the cyclization reaction is simultaneous or stepwise. In a simultaneous reaction process, formation of the *cis*-isomer is considered to progress one-sidedly. Even in a stepwise addition reaction with more steric flexibility than the simultaneous reaction, predominant formation of the *cis*-isomer is also predictable. The transion state (TS) geometries leading to the *cis*-fused and *trans*-fused TADs were located by AM1 semiempirical MO method[12] using TS option. The heats of formation of the *cis*-fusion TS and *trans*-fusion TS are 61.075 and 75.173 kcal/mol , respectively. The heat of formation of *cis*-fusion TS[13] is about 14 kcal/mol smaller than that of *trans*-fusion TS as shown in Figure 2. Further work on the novel formation reaction of dihydropyrazines is in progress.

Figure 2. Possible Reaction Mechanism and AM1-Calculated Transition States for the Addition Reaction




*cis*-fusion TS Intermediate (A) *trans*-fusion TS

## ACKNOWLEDGMENT

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8.Four methylene carbons of angularly nonsubstituted *trans*-TAD were equivalent and detected as a sole signal at δ: 46.53 ppm.

9.The high-field shift of the C8a-Me may be ascribed to steric reasons involving the effect of the lone-pair electrons of the nitrogen atom, in which facile conformation distortion can not occur by introduction of the *N*-methyl group.

10.Crystal data for **6a**. *M* 278.4, monoclinic, space group *C2/c*, $a$ = 38.6295(9)Å, $b$ = 8.9386(2)Å, $c$ =18.4721(4) Å, $\beta$ =98.3375(4)°, $V$=6310.9(2) Å$^3$, $Z$=16, $D$c=1.172 g cm$^{-3}$, $D$m=1.268 g cm$^{-3}$. The reflection data were measured on a Rigaku RAXIS-RAPID Imaging Plate diffractometer with graphite monochromated Mo-$K\alpha$ radiation ($\lambda$=0.7107 Å). The structures were solved by direct method. The hydrogens atoms were placed in calculated positions. The non-hydrogen atoms were refined anisotropically and the hydrogen atoms were not refined. The final cycle of full-matrix least-square refinement was based on 7216 observed reflections ($I$>-10.00σ$I$) and 361 variable parameters and converged with unweighted ($R$) and weighted agreement factors ($R$w) of 0.095 and 0.118, respectively [$R$1=0.049 for 3148 reflections with $I$>2.0σ ($I$)]. All calculations were performed using the teXsan crystallographic software Package of Molecular Structure Corporation (1985 & 1999).

11. The by-products contained **2a**, **6a** and other products; detailed data will be described in a succeeding paper.

12. M. J. S. Dewar, E. G. Zoebisch, E. F. Healy, and J. J. P. Stewart, *J. Am. Chem. Soc.*, 1985, **107**, 3902: AM1 calculations are performed using MOPAC (version 6.0), J. J. P. Stewart, *QCPE program* No. 455. The calculations were performed in the gas phase.

13. The *cis*-adduct is predicted to be 5.50 kcal/mol more stable than the *trans*-adduct by *ab initio* calculation ( HF/6-31G*//HF/6-31G*).

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