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# REACTION OF 2,3-BUTANEDIONE WITH PROPYLENEDIAMINE OBSERVED BY $^1$H-NMR SPECTROSCOPY

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**Abstract** - 2,3-Butanedione reacted with propylenediamine to form an initial intermediate : acetylated methyl-*N*-(3-aminopropyl) imine, which was a geometrical mixture of *syn* - and *anti*- isomers. The intermediate isomerized to *anti*- or *syn*-form *via* pyrimidine ring flip on heating. A steric factor of the isomers affected the formation of the final products. The mechanism based on NMR spectroscopy and molecular orbital calculation is proposed.

Some dihydropyrazines (DHPs) have revealed DNA strand-breakage activity.[1] In the course of our attempt to synthesize new DHPs having this activity, a few interesting facts also have become apparent.[2,3] The new reaction products and the pathway of 2,3-butanedione (BD) with ethylenediamine (ED) were already described in our previous paper.[4] All products showed DNA strand-breakage activity[1,4] by generating hydroxyl and carbon-centered radicals.[5] Therefore, we attempted to obtain certain products expected to be DNA strand-breakable compounds from a reaction of BD with propylenediamine (PD) instead of ED. Although the reaction of diketones with diamines is well known[6] and a number of products is obtained,[7] there has been no discussion about an imine derivative in *anti/syn*-form as an intermediate as will be reported herein. In this communication, we would like to show several products from a reaction of BD with PD and the reaction pathways based on NMR spectroscopy and molecular orbital calculation.

It was interesting that 2-acetyl-2-methylhexahydropyrimidine (**1**) was one of the products from the reaction of BD with PD,[4] because 2-acetyl-2-methylimidazolidine, similar to **1**, could not be isolated in a reaction with ED, indicating the high reactivity. The other products except for **1** were investigated in the present study. The successive procedures of the reaction are, first, a mixing of the starting substances in a solvent under cooling, followed by stirring at room temperature, refluxing and then post-treatment. Under the several reaction conditions (reaction temperature, reaction time, solvent, post-treatment, etc.), the main product changed into an alternate compound. The high reactivity of the products should be predictable similarly to the case with ED.

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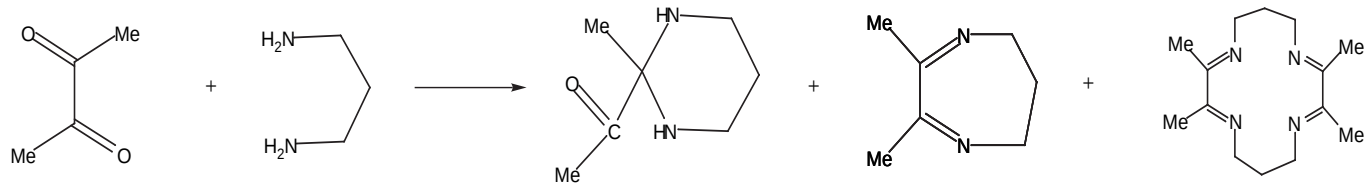
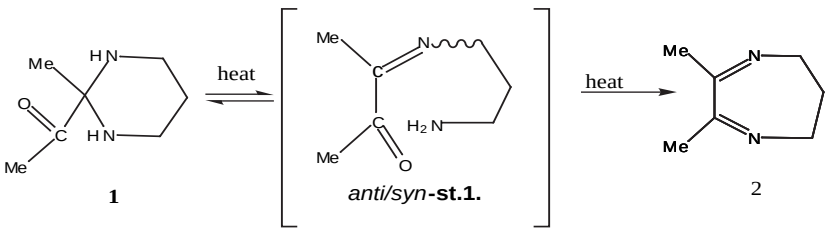
Consequently, isolation of each product from the reaction mixture was expected to be very difficult, and accordingly, NMR spectral analyses were attempted. Each product shown in Scheme 1 was independently obtained from a separate reaction. The isolated yields of the products (**1**), 6,7-dihydro-2,3-dimethyl-5*H*-1,4-diazepine[8] (**2**) and 2,3,9,10-tetramethyl-1,4,8,11-tetraazacyclotetradeca-1,3,8,10-tetraene[9] (**3**) were 89, 20, and 6%, respectively. It is easily predicted that **2** is formed as the main product. However, the reaction mixture in ether used as a solvent at the first trial gave **1** in high yield as the sole product. Since the preparation of **2** has not previously been described in the literature, it was particularly interesting to learn why **2** was not obtained in this case. When the reaction mixture was refluxed in $CHCl_3$ for prolonged time, the appearance of **2** increased sluggishly. Although the existence of **2** in more than 95% yield was detected in an NMR spectrum of the reaction mixture which was refluxed for 7 days in $CHCl_3$, the isolated yield (20%) was very low . One reason is that significant amounts of the product were lost during distillation under high reduced pressure (1 mmHg) in the post-treatment.




Scheme 1

In the NMR spectra of the reaction mixture after addition of **BD** into a chloroform-$d_3$ solution of **PD** under cooling by ice bath, the mixture showed the signals due to the starting substances : **BD** and **PD** only, and then began to represent signals of a product : acetyl, methyl, *N*-(3-aminopropyl)imine (**st.1**) as the sole product under stirring for 10 min after removing the ice bath. The mixture at room temperature proceeded to give a product (**1**), and the production of **1** further progressed under heating at 60 °C. Thus, the heating of the reaction mixture for a short time affected the yield of **1**. However, prolonged heating of the mixture showed furthermore a conversion in NMR signals and, an additional product (**2**) appeared as shown in Scheme 5 below.

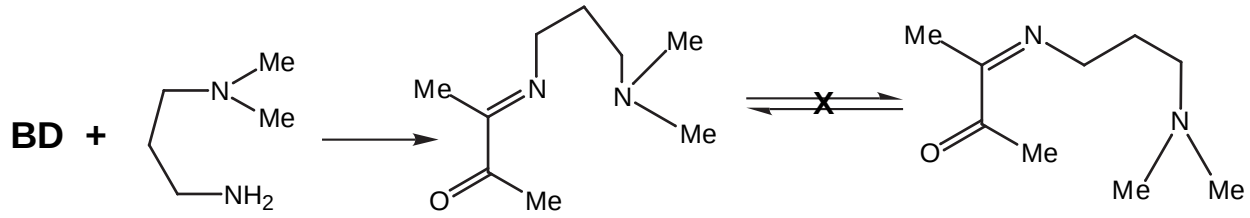
Thus, the remarkable fact became clear that **1** changed into **2** when isolated **1** was refluxed for a few hours in $CHCl_3$ ; in other words, a ring-expansion reaction proceeded on heating (Scheme 2).




Scheme 2

A detailed study of the ring-expansion reaction showed that the initial transformation was ring-opening of **1** to **st.1** before the formation of **2**, that is, **st.1** was first produced. This indicated a route whereby **2** was reconstructed *via* **st.1** from **1** as shown in Scheme 2. It is very attractive that the proportion of *anti*- and *syn*-forms[10] in the reproduced **st.1** was 1 : 1. On the other hand, **st.1** resulting in the first stage (step 1) of the reaction was shown in a proportion of *anti*- : *syn*-forms = 10 : 1 at 10 min when stirring of the reaction mixture

was started at room temperature after mixing of the starting substances under ice cooling. In another case which was stirred for a few hours under continuous ice cooling, the *syn*-form was not detected. The proportion underwent various changes in the progress of the reaction, while it is assumed that the steric factor of the *anti*- and *syn*-forms affected the formation of alternate products. **St.1** at *syn*-form can produce **1** and **2** without steric hindrance. Contrary to the *syn*-form, although the *anti*-form of **st.1** is advantageous for producing **1** to the *syn*-form of **st.1** on inspection of the PM3 heats of formation (ΔHf) by energy difference (49.2 - 48.0 = 1.2 kcal/mol) as mentioned below, **st.1** at *anti*-form can not yield **2** since the N-atom of the amino group can not achieve the distance to enable binding with the C-atom of the carbonyl group. Therefore, it is inferred that the transformation of **1** to **2** under the heating condition requires a conversion of the *anti*-form to *syn*-form of **st.1**. As an analogous case to **st.1**, acetyl, methyl, *N*-(3-dimethylaminopropyl)imine (**st.1'**), which can not cyclize into a ring-closing compound such as **1** and **2**, was examined to see if a mutual conversion of *anti*- and *syn*-forms occurred by heating without conversion *via* a pyrimidine ring such as **1**. It was confirmed by NMR analysis that the *anti*-form of the imine (**st.1'**) resulting from a reaction of **BD** with *N*,*N*-dimethyl-propylenediamine could not convert to *syn*-form by heating as shown in Scheme 3. This result indicated that the conversion of the *anti*-form to *syn*-form in **st.1** was impossible.

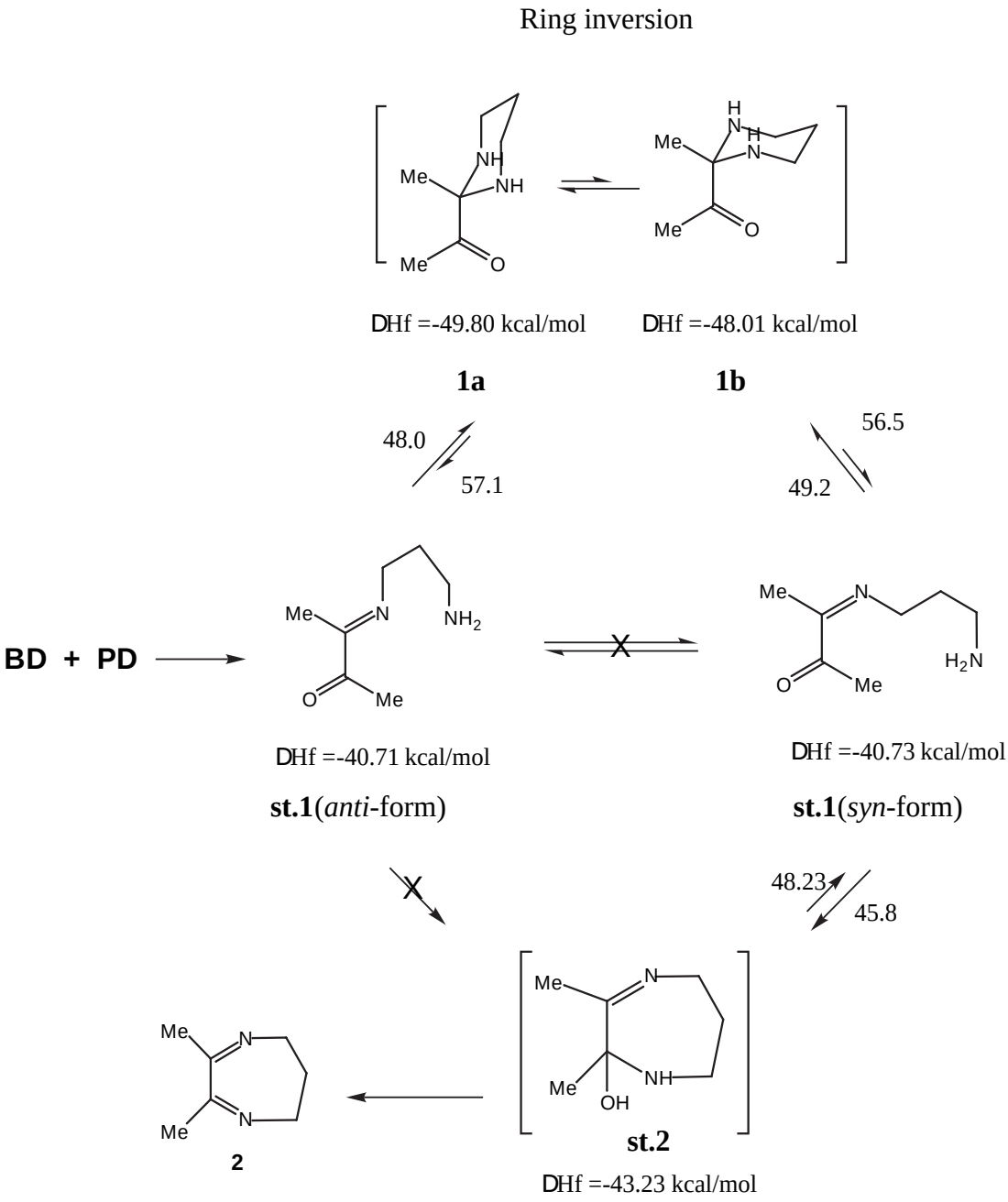



**st.1'** (*anti*-form) **st.1'** (*syn*-form)

Scheme 3

The slow-paced appearance of the *syn*-form of **st.1** in the reaction mixture was recognized by detection of the NMR signals and the process was postulated by PM3 calculation as mentioned below. The heating reaction of **1** in $CHCl_3$ for prolonged time gave the ring-opened **st.1**, which contained nearly the same proportion of *anti*- and s*yn*-forms. This fact explained that the ring flip (**1a** <--> **1b**) of the pyrimidine ring in **1** achieved the conversion of the *anti*-form to *syn*-form, which could be convertible to **2**. The reaction system such as { **st.1** (*anti*-form) <--->[ **1a** <---> **1b** ] <---> **st.1** (*syn*-form) <---> **st.2**} approached the reaction end to yield **2** by the existence of an unreversible stage ( **st. 2** ---> **2** ) as shown in Scheme 4. The PM3-calculated heats of reaction (ΔE) and heats of formation (ΔHf) support the preceding assumption. The ΔE of the formation of each step is depicted in Scheme 4. It is estimated that the insignificant difference (0.6 kcal/mol) between 56.5 kcal/mol for the formation **st.1** (*syn*-form) from **1b** and 57.1 kcal/mol for **st.1** (*anti*-form) from **1a**, required a suitably prolonged heating. Also, the PM3 calculation indicated that the formation of **3** (ΔHf = 28.129 kcal/mol) from the *syn*-form of **st.1** was more stable than that (ΔHf = 32.52 kcal/mol) from the *anti*-form of **st.1**.

The total reaction pathway is expressed as shown in Scheme 5 involving the compound (**2'**), which was identified by NMR spectra. The reaction proceeded at cool or room temperature, and on further refluxing for a



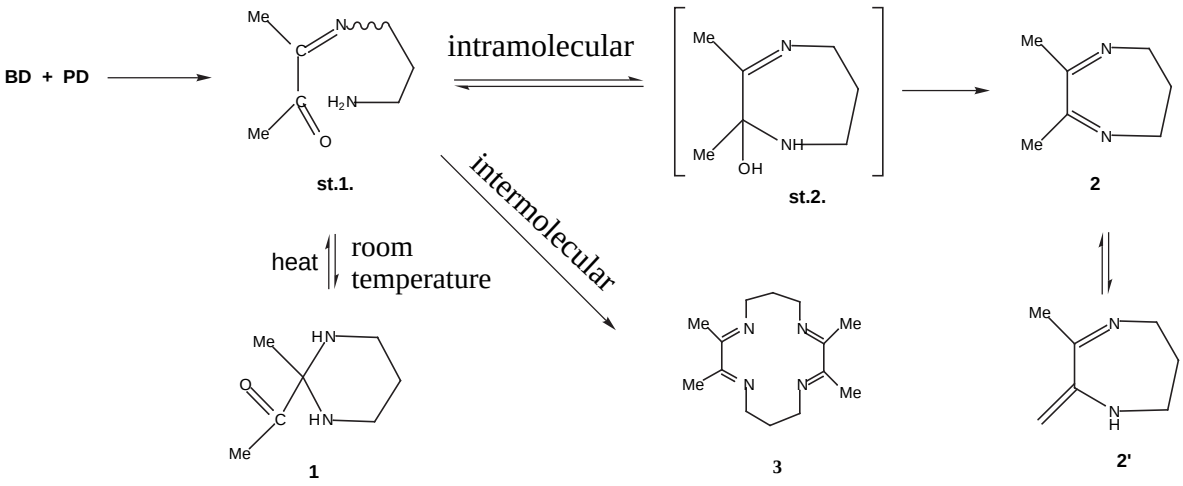

Scheme 4

short time gave the sole product (**1**), and the reaction under refluxing for a prolonged time gave the plural products, mainly **2** and small amounts of **2'** and **3**. Using a solvent with higher boiling point increased the formation of **3** and **2'**.

Successive research for the synthesis of a new DNA strand-breakable compound is in progress. Compound (**2**) was already recognized to be a DNA strand-breakage agent. The reactions of various diketones with **PD** have been already performed and a number of novel products were obtained. The detailed data and biological activity of the products will be described in a following paper.

**ACKNOWLEDGMENT**

This work was supported in part by a Grant-in-Aid for Scientific Research (B) from Japan Society for the Promotion of Science (JSPS).




Compounds (**1**, **2**, and **3**) were isolated. **St.1** and **2'** were identified by NMR spectra

Scheme 5

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8. bp 60-65°C (1 mmHg) by Kugel Role distillation Instrument equipped with a vacuum gauge : DVR2 (Vaccbrand).

   Colorless odor oil. FAB-MS : m/z 249 ($2M+H^+$, 24%), 125 ($M+H^+$, 19%), 99 (100%). $^1H$ (500 MHz) / $^{13}C$ (125 MHz)-NMR (δ, $CDCl_3$) : $CH_3$- ; 2.08 / 22.90, -C-$\underline{CH_2}$-C- ; 2.18 / 32.14, =N-$CH_2$- ; 3.21 / 47.91, >C=N- ; - / 168.60 ppm.
9. mp 66-67°C (ether). FAB-MS : m/z 249 ($M+H^+$, 32%), 99 (100%). $^1H$ (500 MHz) / $^{13}C$ (125 MHz)-NMR (δ, $CDCl_3$) : $CH_3$- ; 2.06 / 12.64, -C-$\underline{CH_2}$-C- ; 2.02-2.09 / 31.86, =N-$CH_2$- ; 3.54 / 50.27, >C=N; - / 168.15 ppm. The metal complex of **3** has been reported,[11] however **3** as a metal-free compound was not found in the literature.
10. $^1H$-NMR (δ, 500 MHz, $CDCl_3$) : *anti*-form [ 1.95 (d, J = 1.2 Hz, $CH_3$-C=N-), 2.35 (s, $CH_3$-CO-), 3.54

(dt, J =1.2, 6.7 Hz, >C=N-$CH_2$-)] : *syn*-form [ 1.96 (d, J = 1.2 Hz, $CH_3$-C=N-), 2.38 (s, $CH_3$-CO-), 3.59 (dt, J = 1.2, 6.7 Hz, >C=N-$CH_2$-)]. The NOE was observed between the methyl ($CH_3$-C=N-) and the methylene (>C=N-$CH_2$-) signals of **st.1** indicating an *anti*-form.

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