FORMATION OF TRICYCLIC HETEROCYCLES FROM THE CONDENSATION REACTION OF 1,2-DIAMINES WITH 1,2-DIKETONES

Tadatoshi YAMAGUCHI,*[,a] Masashi ETO,[c] Kenji WATANABE,[b] Nobuhiro KASHIGE,[b] and Kazunobu HARANO*[,c]

Department of Hygiene, Miyazaki Medical College,[a] Kiyotake-cho, Miyazaki-gun, Miyazaki 889-16, Japan, Faculty of Pharmaceutical Science, Fukuoka University,[b] Nanakuma, Jounan-ku, Fukuoka 814-80, Japan, and Faculty of Pharmaceutical Sciences, Kumamoto University,[c] 5-1 Oe-hon-machi, Kumamoto 862, Japan. (E-mail: harano@gpo.kumamoto-u.ac.jp)[c]

Condensation of 1,2-diamines with 1,2-diketones yielded unexpected tricyclic heterocycles. The structures were determined by single-crystal X-ray analysis.

KEY WORDS dihydropyrazine; X-ray analysis; DNA strand breakable compound; tricyclic compound

In the course of study of the activity of new types of DNA strand breakable compounds,[1] we tried to synthesize substituted dihydropyrazine derivatives by condensation of 1,2-diamines with 1,2-diketones.[2] However, we obtained unexpected tricyclic compounds as the main products.

This paper describes the single-crystal X-ray analyses of the tricyclic compounds (**4**) and their formation mechanisms.

An equimolar mixture of ethylenediamine (**1a**) and diacetyl (**2**) was treated with KOH in ether to obtain 2,3-dimethyldihydropyrazine (**3a**)[1] (5%) and a crystalline product (**4a**) (71%). The ratio of these two products varied according to the reaction conditions. The ^{1}H- and ^{13}C-NMR spectra of **4a** in $CDCl_3$ showed complex spectral patterns, suggesting that decompositions took place in solutions.

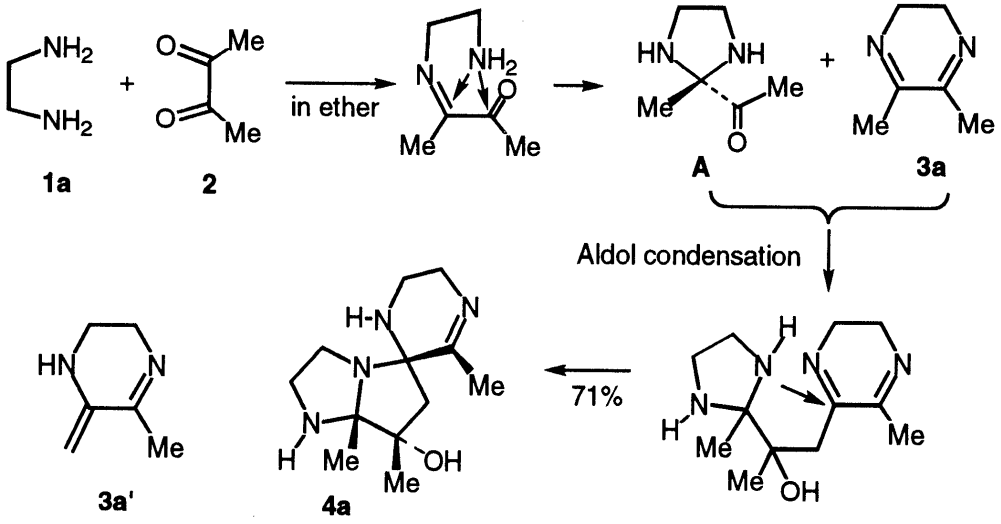

Chart 1

The structure of **4a** was clarified by single-crystal X-ray analysis and solved by the direct method. Full-matrix least-squares refinement gave a final R of 0.057.[3a] The ORTEP[3b] drawing and numbering system of **4a** used in this paper are shown in Fig. 1.

* To whom correspondence should be addressed.

As shown in Fig. 1, the molecule consists of a tetrahydropyrazine ring and a tetrahydropyrrole ring condensed with an imidazolidine ring, which are joined through a spiro-carbon atom. Intramolecular short contacts are observed in O15•••N1 (2.700Å) and O15•••N9 (2.880 Å), which form hydrogen bonds.

Table 1. Heats of Formation of the Reaction Products

Compound	ΔHf (kcal/mol)
A	-48.3
3a	16.2
3a + H_2O	-37.3
Exocyclic isomer of **3a** (**3a'**)	24.4

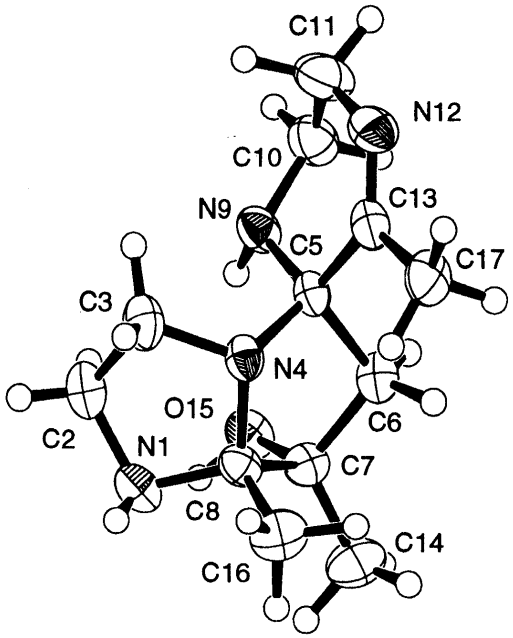

Fig. 1. ORTEP Drawing of **4a**

The spiro compound is assumed to be formed from the ring closure of the condensation product of **3a** and the imidazolidine derivative (**A**).The intermediate **A** could not be isolated from the reaction mixture. However, we can safely say that the formation of **A** is plausible because the reaction of glyoxal with diamines gave both the five- and six-membered derivatives.[4] To determine the possibility of the formation of **A**, PM3 calculations[5] on the related compounds were carried out. Inspection of the heats of formation (ΔHf) indicates that **A** is more stable than **3a**+H_2O, predominant in an equilibrium mixture of the initial condensation reaction. The imidazolidine **A** may react with **3a** to give **4a**. The PM3 calculatation indicates that the formation of **3a'** is energetically unfavorable. However, the 1,3-shift is considered to be promoted in a basic condition, indicating that the formation mechanism of **4a** *via* an enamine **3a'** cannot be ruled out.

Condensation of 2,3-diaminobutane (**1b**) with **2** gave **3b** (85%) which dimerized in a refrigerator to give **4b** whose structure was verified by X-ray analysis (R=0.041). As shown in Fig. 2, the molecular structure has a center of symmetry. Careful inspection of the ^{1}H-NMR spectrum of the crude product indicates the absence of stereoisomers of **4b**, suggesting that the dimerization proceeds stereoselectively. To obtain information about the mechanism, the transition structure (TS) calculation was performed. The TS1 for the intermolecular ene reaction of **3b'**+ **3b'** was successfully located using the TS option implemented in MOPAC. The interacting interatomic distances for H-N and C-C bonds were calculated to be 1.740 and 1.881 Å, respectively. The successive ring closure probably proceeds through a similar mechanism. From these observations, **4b** is considered to be formed *via* thermally-allowed reactions [2π (C=C)+2π(C=N) +2σ(N-H)] involving inter- and intramolecular processes (Chart 2).

A similar reaction behavior was observed in the reaction of 1,2-diaminopropane (**1c**) and **2** (see Chart 3).

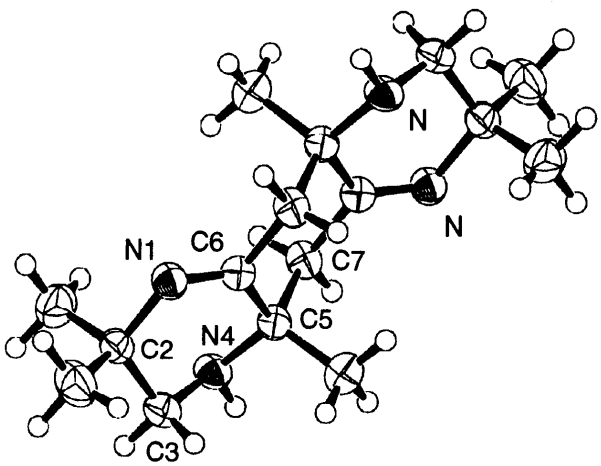

Fig. 2. ORTEP Drawing of **4b**

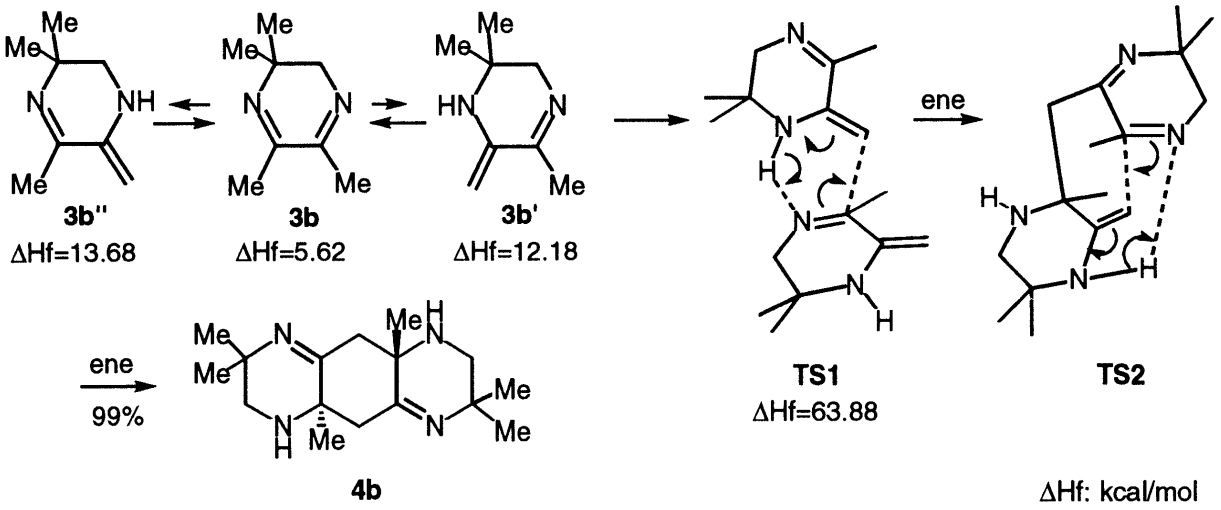

Chart 2

Recently, Sustmann and coworkers obtained a similar product from treatment of 2,2-diethyl-4,5-dimethyl-2*H*-imidazole with trifluoroacetic acid in dichloromethane at 60°C.[6] The formation mechanism has not yet been clarified.

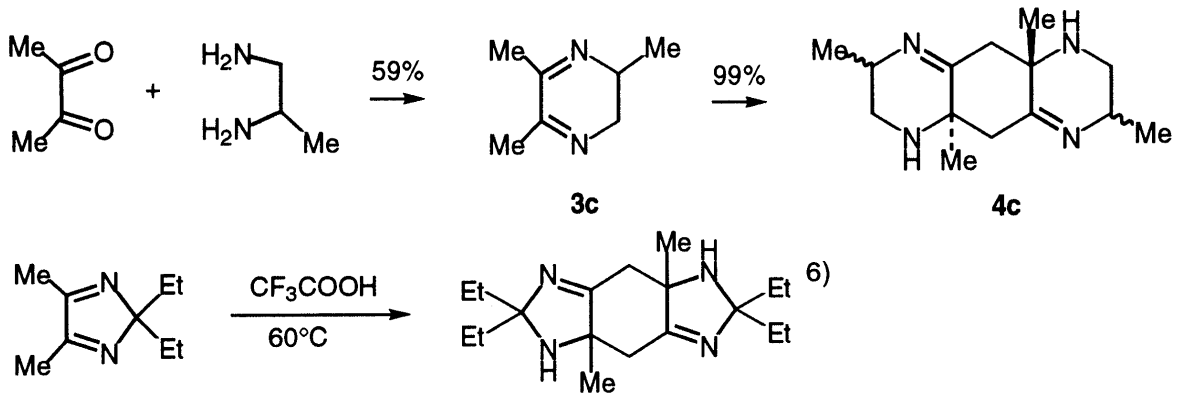

Chart 3

Studies on the formation mechanism and biological activity of the dimeric compounds are in progress.

REFERENCES AND NOTES

1) Yamaguchi T., Kashige N., Mishiro N., Miake F., Watanabe K., *Biol. Pharm. Bull.* (in press, No. 1693).
2) a) Ishiguro T., Matsuura M., *Yakugaku Zasshi*, **78**, 229-231 (1958).
b) Arnold D. R., Abraitys V.Y., McLeod J. Jr., *Can. J. Chem.*, **49**, 923-935 (1970): Kliegmen J. M., Barnes R. K., *Tetrahedron Lett.*, **24**, 1953-1956 (1969).
3) a) Johnson C. K., ORTEP, Report ORNL-3794, Oak Ridge National Laboratory, Oak Ridge, TN, 1965. b) teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 and 1992). Crystal Data; **4a**: monoclinic, Space group $P2_1/c$, a=7.156 (2), b=15.314 (2), c=11.689 (2)Å, ß=94.70 (2)°, V=1276.5 (2)Å^3, Dc=1.240 gcm^{-3}, Z=4, Mo Kα radiation (50 kV-150 mA), λ=0.7107 Å, Num of RD=3045, Num of F_{obs}=2000, R_f=0.058; **4b**: tetragonal, Space group $I4_1/a$ a=12.078 (4), c=21.995 (7)Å, V=3208(1)Å^3, Dc=1.144 gcm^{-3}, Z=16, Mo Kα radiation (50 kV-150 mA), λ=0.7107 Å, Num of RD=1906, Num of F_{obs}=1076, R_f=0.041.
4) Willer R. L., Moore D. W., *J. Org. Chem.*, **50**, 2365 and 2368 (1985) and cited therein.
5) Stewart J. J. P., *QCPE Bull.*, **9**, 10 (1989): *idem, J. Comp. Chem.*, **10**, 209, 221 (1989).
6) Felderhoff M., Sustmann R., Steller I., Boese R., *Libigs Ann.*, 1697-1698 (1995).

(Received July 15, 1996; accepted September 3, 1996)