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A Novel Beckmann Fission Reaction of 2-Aminocyclohexanone Oxime

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Synopsis. 2-(4-Cyanobutyl)-4,5,6,7-tetrahydrobenzimidazole was obtained by treating 2-aminocyclohexanone oxime with ethyl acetimidate hydrochloride in acetic acid at below 50 °C, though only 2-methyl-4,5,6,7-tetrahydrobenzimidazole was produced by the reaction of 2-aminocyclohexanone oxime and free ethyl acetimidate in neutral solvents. A novel Beckmann fission reaction of dimeric 2-aminocyclohexanone oxime is presumed to participate in the formation of 2-(4-cyanobutyl)-4,5,6,7-tetrahydrobenzimidazole.

2-Aminocyclohexanone oxime (**1**) reveals an electrophilic property at the nitrogen atom of its amino group and a nucleophilic one at the carbon atom bearing hydroxyimino group and thus reacts readily with reagents having reactive functional groups to give various kinds of heterocyclic compounds, such as 2-mercaptoimidazoles,[1] phenazines,[2] and 2-amino-ε-caprolactam.[3] In this study we describe the reactions of **1** with ethyl acetimidate and its hydrochloride, and we continue the structure elucidation.

Results and Discussion

We have obtained **2** as a sole product in 89.2% yield by heating a mixture of **1** and ethyl acetimidate in methanol and/or chloroform under reflux. When we used ethyl acetimidate hydrochloride in chloroform, methanol or a mixture of chloroform and pyridine, only a small amount of 1,2,3,4,6,7,8,9-octahydro phenazine (**4**) was obtained with virtual recovery of the starting materials. When ethyl acetimidate hydrochloride was used in acetic acid at above 80 °C, **4** was obtained as a major product.[2] However, **3** was mainly obtained at below 50 °C.[4] The structure of this new compound **3** has been studied by various means. This material has a molecular formula $C_{12}H_{17}N_3$ and must be formed by the condensation of two molecules of **1** with the elimination of 1 mol of ammonia and 2 mol of water. In the ^{1}H-NMR spectrum, two kinds of 8H multiplets were observed at δ 1.6—2.1 and δ 2.2—2.9, and a 1H doublet, which was replaced by deuterium. oxide, was observed at δ 7.3—8.1. The 1H doublet at low field was assumed to be an imino proton adjacent to olefin or electron-withdrawing groups. The UV spectrum showed an absorption maximum at 226 nm. The MS spectrum showed the parent peak at m/z 203 and fragment peaks at 175, 163, 150, 137, 108, 95, and 77, but these peaks are not highly informative. Since constructive structural data were not obtained merely from these data, an X-ray

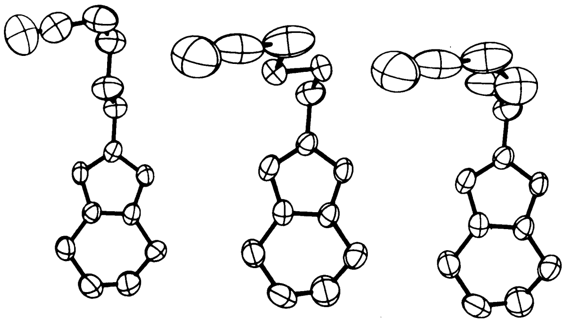
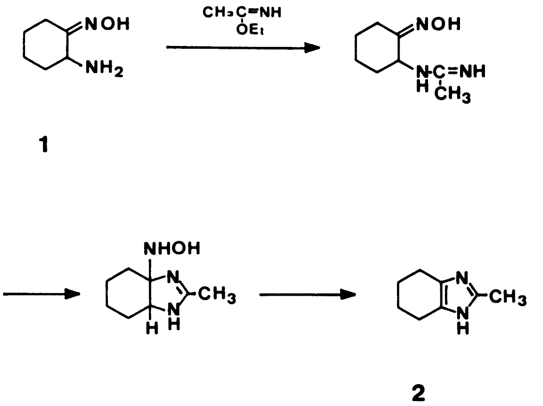
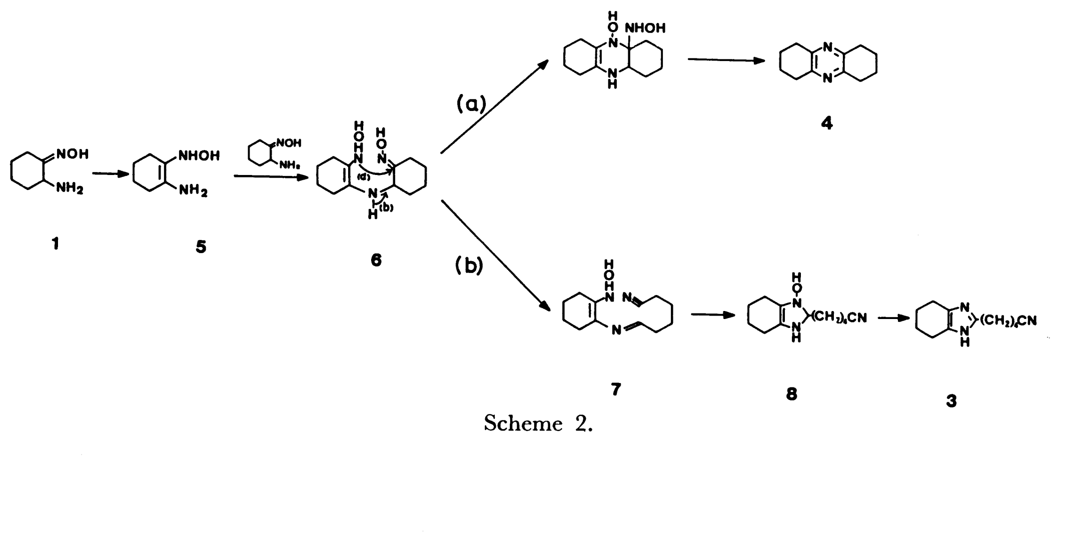


Fig. 1. ORTEP drawings of the molecule **3** determined by X-ray structure analysis.[5] Three conformers of the side chain exist in a monoclinic crystal. The ellipsoids are drawn to enclose 50% probability.



Scheme 1.



Scheme 2.

crystal structure analysis was then carried out with a single crystal grown from a ethyl acetate solution and the structure was established as **3** (Fig. 1).

The formation of 2-(4-cyanobutyl)-4,5,6,7-tetrahydro benzimidazole from 2 mol of 2-aminocyclohexanone oxime is quite unexpected and unusual. A plausible mechanism to account for its formation is depicted in Schemes 1 an 2.

By treating **1** with ethyl acetimidate in usual solvents such as chloroform and/or methanol, **2** was obtained as the expected product. When ethyl acetimidate hydrochloride was used in acetic acid, the reaction rate became slower and **1** was isomerized to 1-amino-2-(hydroxyamino)cyclohexene (**5**), and **5** reacted with another **1** to give 1-[2-(hydroxyimino)cyclohexylamino]-2-(hydroxyamino)cyclohexene (**6**). At above 80 °C, the carbon atom bearing hydroxyimino group was attacked by the nitrogen of hydroxyamino group to give **4** (path *a* in Scheme 2). When the reaction conditions were milder (at below 50 °C), on the contrary, a Beckmann fission reaction of **6** proceeded to give 1-(6-nitrilohexylideneamino)-2-(hydroxyamino)cyclohexene (**7**), which was converted to **8** by ring closure and finaly to **3** by dehydration (path *b* in Scheme 2).

Although the details of the role of ehtyl acetimidate hydrochloride in this reaction remain to be clarified, no such Beckmann fission reaction has ever been reported to the best of our knowledge.

Experimental

Measurements. The IR, UV, and mass spectra were recorded on Shimadzu IR-40, Shimadzu UV-220, and Hitachi RMU-7M spectrometers respectively. The ^{1}H-NMR spectra were recorded on Hitachi R-24B (60 MHz) spectrometer, using TMS as the internal standard. The X-ray diffraction data were obtained on a Rigaku automated four-circle diffractometer. The details of the crystal structure was reported by a separate cover.[5]

Preparations. 2-Aminocyclohexanone oxime (**1**) was prepared by the method described in the patent.[6]

2-Methyl-4,5,6,7-tetrahydrobenzimidazole (**2**): To a solution of 2-aminocyclohexanone oxime 64 g (0.5 mol) in methanol (500 ml) was added dropwise an ethyl acetimidate 43.5 g (0.5 mol) in the solution of methanol (50 ml) under reflux during 1 h, and the reaction mixture was heated under reflux for additional 6 h. After the reaction, the solvent was evaporated out, and the crude product was purified by recrystallization from ethyl acetate to give 60.7 g (89.2%) of **2** as a white solid; mp 225—226 °C. ^{1}H-NMR (CDCl$_3$), δ=1.6—2.1 (m, 4H), 2.33 (s, 3H), 2.1—2.8 (m, 4H), 8.7—9.3 (m, 1H); IR (KBr) 3190, 3100, 3000, 2940, 2850, 2760, 1630, 1540, 1460, 1440, 1420, 1240, 1040, 940 cm^{-1}. Found: C, 70.63; H, 8.79; N, 20.50%. Calcd for $C_8H_{12}N_2$: C, 70.55; H, 8.88; N, 20.57%.

2-(4-Cyanobutyl)-4,5,6,7-tetrahydrobenzimidazole (3): A mixture of 2-aminocyclohexanone oxime 12.8 g (0.1 mol), ethyl acetimidate hydrochloride 12.4 g (0.1 mol) and acetic acid 100 ml was heated at 40 °C. After 3 h, acetic acid was removed under reduced pressure, water (30 ml) was added to the residue, and the solution was extracted with benzene (50 ml). The water layer was adjusted to pH 10 with 2 M (1 M=1 mol dm^{-3}) sodium hydroxide solution and the solution was extracted with three 100 ml portions of benzene and then dried over anhydrous magnesium sulfate. After removal of the benzene, the residue was purified by recrystallization from ethyl acetate to give 8.6 g (84.6%) of **3** as a white solid; mp 177—178 °C. ^{1}H-NMR (CDCl$_3$) δ=1.5—2.1 (m, 8H), 2.2—2.8 (m, 8H), 7.3—8.2 (m, 1H); IR (KBr) 3180, 3100, 3020, 2950, 2860, 2770, 2260, 1630, 1440, 1240, 1040 cm^{-1}. Found: C, 70.88; H, 8.49; N, 20.63% . Calcd for $C_{12}H_{17}N_3$; C, 70.90; H, 8.43; N, 20.67%.

References

1) Toray Industries, Inc., Japan Patent Kokai 79-103870 (1979).

2) Toray Industries, Inc., Japan Patent Kokai 83-23679 (1983).

3) Toray Industries, Inc., Japan Patent 66-18087 (1966).

4) In the absence of ethyl acetimidate hydrochloride, **3** was not obtained in acetic acid at 50 °C.

5) Y. Kitano, H. Sato, S. Imamura and T. Ashida, *Acta Crystallogr., Sect. C.* **39**, in press (1983).

6) Toray Industries, Inc., U. S. Patent 3839448 (1974).