NEW SYNTHESES OF 1-AMINO- AND 1-(2-AMINOETHYL)-2,6-DICYANOPIPERIDINES AND DIAZABICYCLO COMPOUNDS BY A STRECKER REACTION USING GLUTARALDEHYDE AND DIAMINES, AND THEIR STEREOCHEMISTRY

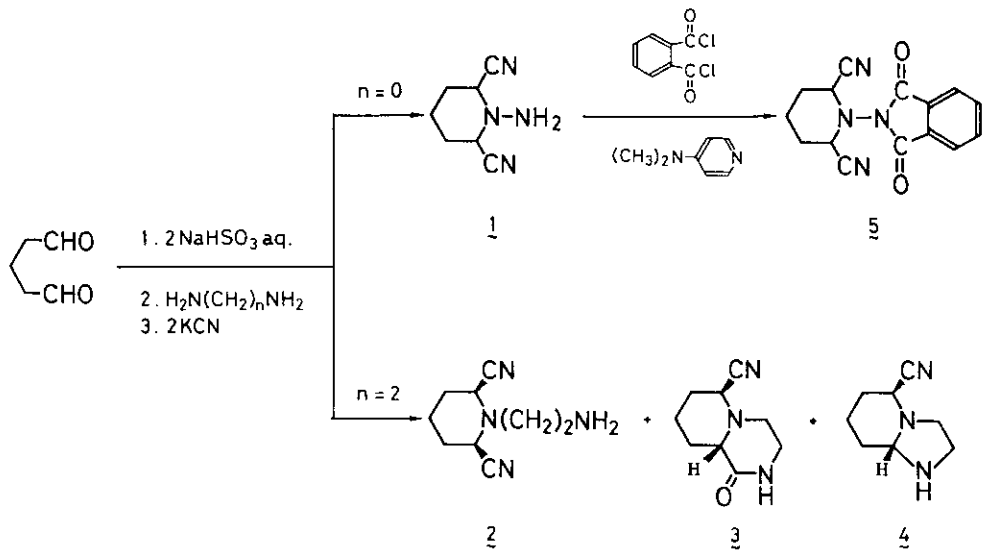
Kazumasa Takahashi,* Akira Tachiki, Katsuyuki Ogura, and Hirotada Iida
Department of Synthetic Chemistry, Faculty of Engineering, Chiba University, Yayoi-cho, Chiba 260, Japan

Abstract ——— An efficient sequence proposed here involves a simple Strecker reaction of glutaraldehyde with hydrazine or 1,2-diaminoethane, which gives 1-amino- or 1-(2-aminoethyl)-2,6-dicyanopiperidines, 2-cyano-1,7-diazabicyclo[4.3.0]nonane, and 10-cyano-1,4-diazabicyclo[4.4.0]decan-5-one. Their stereochemistry is also elucidated. Moreover, treatment of 1-amino-2,6-dicyanopiperidine and phthaloyl dichloride in the presence of 4-(N,N-dimethylamino)pyridine quantitatively gives 1-phthalimido-2,6-dicyanopiperidine.

The only study related to our present work has been reported for the synthesis of 1-amino-2,6-dicyanopiperidine (1)[1]. However, the stereochemistry of 1 has not been explicitly elucidated, and there is no information about the Strecker reaction of glutaraldehyde with 1,2-diaminoethane either. We report here that the Strecker reaction of glutaraldehyde with hydrazine or 1,2-diaminoethane gives 1-amino- or 1-(2-aminoethyl)-2,6-dicyanopiperidines (i.e., 1 or 2), 10-cyano-1,4-diazabicyclo[4.4.0]decan-5-one (3), and 2-cyano-1,7-diazabicyclo[4.3.0]nonane (4), and the treatment of 1 with phthaloyl dichloride quantitatively gives 1-phthalimido-2,6-dicyanopiperidine (5). Moreover, their stereochemistry is also elucidated.

The Strecker reaction of glutaraldehyde with hydrazine using sodium hydrogen sulfite and potassium cyanide gave, under optimum conditions, two stereoisomers of 1-amino-2,6-dicyanopiperidine (1) in 34% yield. On the other hand, the Strecker reaction using 1,2-diaminoethane gave three products, 1-(2-aminoethyl)-2,6-

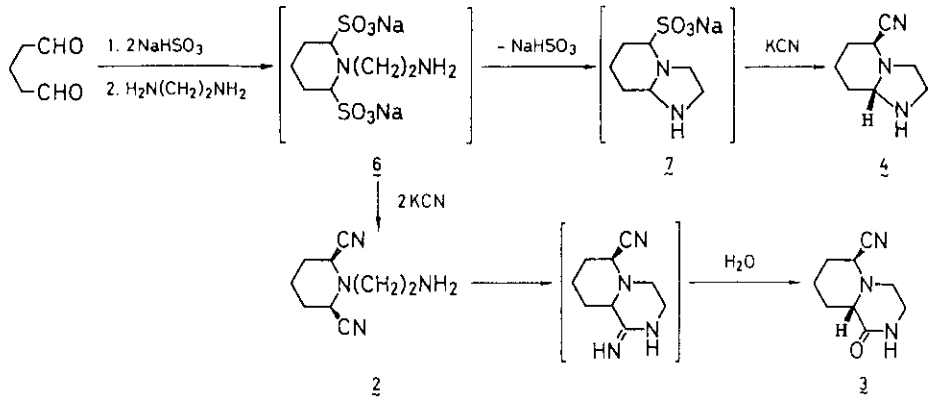
Scheme 1. Preparation of piperidine derivatives (1, 2, 3, 4, and 5)



dicyanopiperidine (2), 10-cyano-1,4-diazabicyclo[4.4.0]decan-5-one (3), and 2-cyano-1,7-diazabicyclo[4.3.0]nonane (4). The yields of 2, 3 and 4 depended on the concentration of glutaraldehyde and the time allowed for cyclization after the addition of 1,2-diaminoethane: When the concentration and the time were 0.05 M and 48 h, the yields of 2, 3 and 4 were 10%, 11% and 28%, respectively. Likewise, under conditions of 0.05 M and 72 h, their yields were ca. 2%, 11% and 48%, respectively. Thus, the formation of 4 increased with longer time for cyclization. The formation of polymers increased with higher glutaraldehyde concentrations. These results suggest that the formation mechanism for 2, 3 and 4 is as depicted in Scheme 2: The longer time for cyclization incresaes conversion from the intermediate 6 to 7. On the other hand, the formation of 3 is conducted from 2 after the addition of potassium cyanide.

In the case of 1, two kinds of stereoisomers were isolated in a molar ratio of 3:2. The configuration of the two cyano groups of each stereoisomer was examined by ^{1}H-NMR (270 MHz, see Table 2). The difference of the chemical shift between the axial and equatorial methine protons, α to the CN group, of the two isomers and the spin-spin coupling constant between the methine and the vicinal methylene protons provide definitive evidence for the CN configuration, which are similar to that of 1-benzyl-2,6-dicyanopiperidine reported in our previous paper[2]: The methine proton of 1a afford two overlapping doublets (J < 4Hz), and that of 1b,

Scheme 2. Formation-mechanism for piperidine derivatives (2, 3 and 4)

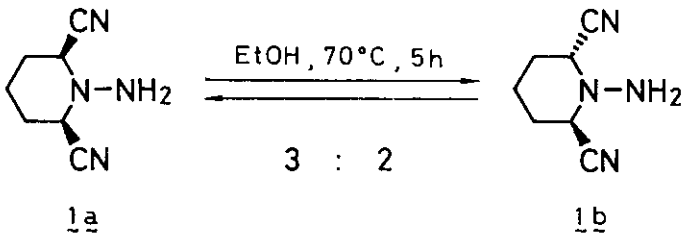


on the other hand, gives rise to two distinguishable doublets with coupling constants of 6.9 and 3.9 Hz at δ 3.82. The configuration of the two CN groups of 1a is assigned to axial-axial orientation, since the coupling constant is the same as the reported that in 1-benzyl-2,6-dicyanopiperidine[2], and the diaxial conformation is preffered as in this conformation of stabilizing anomeric effects between the peri-antiplanar nitrile groups and the nitrogen lone pair of electrons[3]. On the other hand, the configuration of 1b may be contrued as being cis-form, if that would be assigned by only data of the coupling constant and the chemical shift. However, that is confirmed to be trans-form on the basis of the following data[4]: (1) A careful observation for IR spectrum of 1b shows the existence of two different CN groups (2240 and 2250 cm^{-1}). (2) The chemical shift (δ 3.82) and the coupling constant (6.9 and 3.9 Hz) measured at 27 °C are obviously observed as "the average value" between axial and equatorial methine protons owing to conformational interconversion of the piperidine ring: When 1b was examined at -60 °C by ^{1}H-NMR (270 MHz, $CDCl_3$/TMS), two different methine protons resonated at δ 3.53 and δ 4.26, respectively, and are clearly distinguished. The chemical shift (δ 3.82) at 27 °C is just an average position between each one of axial (δ 3.53) and equatorial (δ 4.26) methine protons fixed at -60 °C. In the case of 2, 3 and 4, on the other hand, a single stereoisomer was obtained, and its axial configuration was determined likewise.

When 1a in ethanol was heated at 70±5 °C for 5 h, partial conversion of 1a into 1b (40%) was confirmed by means of thin layer chromatography (TLC) and ^{1}H-NMR spectroscopy. Under similar conditions, 1b was also converted into 1a (60%). The molar ratio of 1a vs. 1b obtained after the equilibration experiment was 3 : 2.

On the other hand, the conversion of 3 and 4 under similar conditions was not observed.

The reaction of 1a or 1b with phthaloyl dichloride in the presence of triethylamine and 4-(N,N-dimethylamino)pyridine in dichloromethane smoothly took place to give each stereoisomer of 1-phthalimido-2,6-dicyanopiperidine (5a or 5b) in 91%-95% yield. The yield in the absence of 4-(N,N-dimethylamino)pyridine was 43%-63%, but above 90% in the presence of more than 1% on the molar quantity of 1a or 1b (see Table 1). The configuration of the two cyano groups of each stereoisomer (5a or 5b) was examined by means of ^{1}H-NMR and IR as in the case of 1a or 1b (see Table 2).



1a 1b

Table 1. Preparation of 1-phthalimido-2,6-dicyanopiperidine (5)

DMAP[a]	Yield of 5a	Yield of 5b
none	63%	43%
1% mole	91%	83%
10% mole	82%	95%

a) DMAP is an abbreviation of 4-(N,N-dimethylamino)pyridine, and the amount used is shown as a molar ratio (%) to 1a or 1b.

EXPERIMENTAL

(I) Preparartion of 1-amino-2,6-dicyanopiperidine (1): To a solution of sodium hydrogen sulfite (12.5 g, 0.12 mol) in 200 ml of water was added a 50% aqueous solution of glutaraldehyde (10 g, 0.05 mol). The mixture was stirred for 1 h at room temperature and then diluted to 900 ml with water. An aqueous solution (100 ml) of 90% hydrazine hydrate (2.79 g, 0.05 mol) was added dropwise to the solution. After the solution was stirred for 16 h at room temperature, solid potassium cyanide (6.51 g, 0.10 mol) was added to the solution. After being stirred for 4 h, the solution was extracted with dichloromethane (4 x 250 ml). The combined organic layers were washed with brine and dried over anhydrous sodium sul-

fate. After removal of the sodium sulfate and the solvent, the residue was purified by column chromatography (silica gel/a mixture of benzene and ethyl acetate) to give 1a and 1b in 21% (1.563 g) and 13% (0.977 g) yields, respectively. Their physical properties are listed in Table 2. Since the melting point reported for 1 in the literature[1] is 101-103 °C, the compound reported is assumed to be a mixture of 1a and 1b (see Table 2).

(II) Preparation of 1-(2-aminoethyl)-2,6-dicyanopiperidine (2), 10-cyano-1,4-diazabicyclo[4.4.0]decan-5-one (3), and 2-cyano-1,7-diazabicyclo[4.3.0]nonane (4) by Strecker reaction using 1,2-diaminoethane: By the same procedure, the reaction among sodium hydrogen sulfite (12.4 g, 0.12 mol), a 50% aqueous solution of

Table 2. Physical properties of new products (1, 2, 3, 4, and 5)

Compd.	Configuration[a]	Yield (%)	IR(KBr), cm^{-1} ν_{CN}	IR(KBr), cm^{-1} ν_{NH}	M.p. (°C)	^{1}H-NMR($CDCl_3$/Me_4Si): δ units CH (α position to CN)	NH
1a	ax-ax	21	2240	3360	101-101.5	eq-CH: 3.94(2H, t-like, J= 3.9 Hz)	3.75 (s, 2H)
1b	ax-eq	13	2250 2240	3370	105.5-106.5	CH[b]: 3.82(2H, d-d, J=6.9 and 3.9 Hz)	3.69 (s, 2H)
2a	ax-ax	2-10	2240	3550 3370	180.0-180.5[c]	eq-CH: 4.37(2H, t-like, J= 3.6 Hz)	7.95 (br, 2H)
3a	ax	11	2250	3250	117.0-118.0	eq-CH[d]:3.45(1H, t-like, J= 3.6 Hz)	1.66[e] (s, 1H)
4a	ax	28-48	2230 (neat)	3400 (neat)	oil	eq-CH[f]:3.94(1H, t-like, J= 3.6 Hz)	6.24 (s, 1H)
5a	ax-ax	91	2260	-	242-243	eq-CH: 4.68(2H, d-d, J=11.2 and 3.6 Hz)	-
5b	ax-eq	95	2250 2240	-	229-230	CH[g]: 4.80(2H, d-d, J= 7.1 and 3.9 Hz)	-

a) The configuration is for CN. These compounds gave satisfactory microanalyses. b) These data were measured at 27 °C. At -60 °C, ax-CH and eq-CH resonated at δ 3.53 and δ 4.26, respectively. c) The colorless crystal changed in color to brown at about 160 °C. d) Another methine proton resonates at δ 2.37(1H, d-d, J=13.5 and 2 Hz), and the configuration for the proton is assumed to be axial. Moreover, ^{13}C-NMR spectra of 3a are assigned as follows: δ 169.971(s, C=O), 115.665(s, CN), 60.064(d, CH), 54.478(d, CH), 49.151(t, CH_2), 28.304(t, CH_2), 26.864(t, CH_2). e) The signal disappeared by addition of D_2O. f) Another methine proton resonates at δ 2.10(1H, d-d, J=12.0 and 2.3 Hz), and the configuration for the proton is assumed to be axial. g) Data of 5b are similar to those of 1b.

glutaraldehyde (10 g, 0.05 mol), 1,2-diaminoethane (3.76 g, 0.06 mol), and potassium cyanide (6.52 g, 0.10 mol) was carried out to give products 2, 3 and 4 in 10% (0.896 g), 11% (0.986 g) and 28% (2.12 g) yields, respectively. The yields of 2, 3 and 4 depended on the concentration of glutaraldehyde and the time allowed for cyclization after the addition of 1,2-diaminoethane (see Text). Their physical properties are listed in Table 2.

(III) Preparation of 1-phthalimido-2,6-dicyanopiperidine (5): Under a nitrogen atmosphere, to a mixture of 1a (0.751 g, 5 mmol), triethylamine (2.52 g, 25 mmol), 4-(N,N-dimethylamino)pyridine (0.5 mmol, 10% equimolar to 1a), and dichloromethane (20 ml) cooled in an ice bath was added dropwise phthaloyl dichloride (1.043 g, 5.1 mmol). After the addition, the ice bath was removed, and then the mixture was stirred for 16 h at room temperature. The mixture was poured into water (50 ml), and then extracted with dichloromethane (2 x 100 ml). The combined organic layers were washed with water, and dried over anhydrous sodium sulfate. After removal of the solvent, the residue was purified by means of column chromatography (silica gel/ a mixture of benzene and ethyl acetate) to give 5a, whose configuration for two CN groups is assigned to axial-axial orientation, is obtained in 91% yield (1.276 g).

Likewise, the reaction using 1b gave 5b in 95% yield (1.338 g), whose two CN groups are in axial-equatorial orientation. Their physical properties are summarized in Table 2.

REFERENCES

1. H. E. Johnson and D. G. Crosby, J. Org. Chem., 1962, 27, 1298.
2. K. Takahashi, T. Mikajiri, H. Kurita, K. Ogura, and H. Iida, J. Org. Chem., 1985, 50, 4372.
3. P. Deslongchamps,"Stereoelectronic Effects in Organic Chemistry" PERGAMON PRESS (1983).
4. The data given in the present work are promoting us to reinvestigate the configurational determination for products having equatorial-equatorial orientations which were prepared as minor products within 1-substituted-2,6-dicyanopiperidines described in ref. 2.

Received, 9th June, 1986