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Intramolecular Cyclization of Alkylhydroxylamines in Acids

MASAMI KAWASE and YASUO KIKUGAWA*

Faculty of Pharmaceutical Sciences, Josai University, 1-1 Keyakidai, Sakado-shi, Saitama 350-02, Japan

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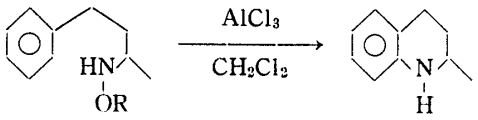
Alkylhydroxylamines having a benzene ring in the molecule were subjected to intramolecular cyclization in trifluoroacetic acid or in the presence of Lewis acids, and benzene-fused six-membered heterocycles were obtained in moderate yields from the cyclization reaction of O-acylhydroxylamines. The effect of a methoxyl group on the benzene ring was also investigated. The *m*-methoxy compound (**1j**) cyclized to give 6-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (**2e**), while the *p*-methoxy compound (**1k** or **1l**) cyclized to give the same product (**2e**). These unusual results could be explained in terms of a spiro-intermediate (**3a**).

Keywords——alkylhydroxylamines; electron-deficient nitrogen; intramolecular cyclization; synthesis of 1,2,3,4-tetrahydroquinolines; Lewis acid; trifluoroacetic acid; spiro-intermediate; methoxyl group

Although aromatic aminations and other electrophilic reactions with hydroxylamine derivatives, such as O-mesitylenesulfonylhydroxylamine, have been considerably investigated,[1] those with alkylhydroxylamines have scarcely been investigated, probably for the following reasons: 1) alkylhydroxylamines are not easily obtainable by usual procedures; 2) the aminating ability of alkylhydroxylamines is much weaker than that of hydroxylamine derivatives. Kovacic *et al.*[2] investigated the aminating ability of O,N-dimethyl-, O,N,N-trimethyl-, and N,N-dimethylhydroxylamines in the toluene–aluminium chloride system and obtained alkylaminotoluenes in yields of 24%, 0%, and 2%, respectively. It is evident that the yield of aromatic amines decrease with increasing alkyl substitution on nitrogen, and that the intermolecular alkylamination reaction is not practically useful due to the low yields.

Previously we reported a convenient synthesis of alkylhydroxylamines by the reduction of oximes,[3] and this time we have investigated the synthesis of benzene-fused heterocycles through the intramolecular cyclization of alkylhydroxylamines to a suitably situated benzene ring in the molecule.

TABLE I. Cyclization of O-Substituted Hydroxylamines[a]



1a—e **2a**

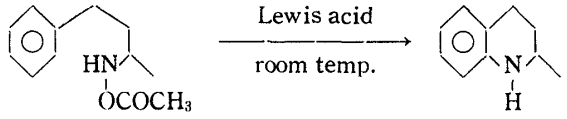
Compound	R	Yield of **2a** (%)
1a	H	0
1b	CH_3	0
1c	$COCH_3$	57
1d	$COC(CH_3)_3$	48
1e	COC_6H_5	24

a) Reaction conditions: molar ratio of $AlCl_3$ to 1=3; 6 hr at room temperature; solvent, CH_2Cl_2.

Cyclization Reaction of Alkylhydroxylamines by Lewis Acids

As intermolecular aminations with alkylhydroxylamines did not give satisfactory results for synthetic use, we investigated the intramolecular cyclization of alkylhydroxylamines by the use of Friedel–Crafts catalysts for the synthesis of benzene-fused heterocycles. N-Hydroxy-4-phenyl-2-butylamines (**1a**—**e**), synthesized in good yields by the pyridine-borane reduction[3] of the corresponding oximes, were tested for cyclization in the presence of aluminium chloride. The results are summarized in Table I. The O-acetylhydroxylamine (**1c**) cyclized to 2-methyl-1,2,3,4-tetrahydroquinoline (**2a**) in moderate yield. Theoretical consideration of the reaction mechanism is complicated by the possibility of coordination with the catalyst on nitrogen, oxygen, and/or acyl oxygen, but it is assumed that coordination on acyl oxygen is necessary to increase the cationic character of nitrogen for a concerted intramolecular displacement mechanism, because O-acylhydroxylamines (**1c**—**e**) alone can cyclize to give **2a**. A number of reaction variables were investigated—catalysts, molar ratio of catalyst to **1c**, solvents, and reaction time. As shown in Table II, the yield of **2a** was not improved.

Table II. Cyclization Reaction in the Presence of Lewis Acids



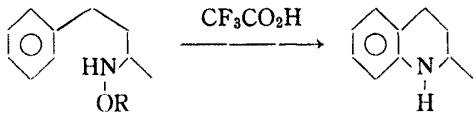
1c **2a**

Lewis acid	Molar ratio of Lewis acid/**1c**	Solvent	Reaction time (hr)	Yield of **2a** (%)
$AlCl_3$	2	CH_2Cl_2	6	41
$AlCl_3$	3	CH_2Cl_2	6	57
$AlCl_3$	5	CH_2Cl_2	24	40
$AlCl_3$	3	CH_3NO_2	6	0
$AlCl_3$	3	CS_2	6	41
$SnCl_4$	3	CH_2Cl_2	24	34
$TiCl_4$	3	CH_2Cl_2	24	0

Cyclization of Alkylhydroxylamines in Protic Acids

We have examined the intramolecular cyclization of alkylhydroxylamines (**1a**—**c**) in protic acids in a similar way to the reaction of arylhydroxylamines with a benzene ring, which was reported[4] to be catalyzed by strong protic acids such as tetrafluoroboric acid, trifluoro-

Table III. Cyclization of Hydroxylamines in Trifluoroacetic Acid



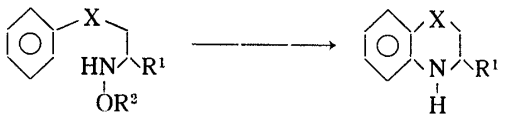
1a—**c** **2a**

Compound	Reaction conditions temp., time	Yield of **2a** (%)[a]
1a	Room temp., 24 hr	(76)
1a	Reflux, 15 hr	61
1b	Reflux, 15 hr	(87)
1c	Reflux, 15 hr	12

a) Figures in parentheses indicate recovery (%) of the starting compound.

acetic acid, or sulfuric acid. **1a** and **c** cyclized to **2a** in refluxing trifluoroacetic acid, while the O-methylhydroxylamine (**1b**) did not react, as was the case with the cyclization by Lewis acids. Table III shows the results. As **1a** should be trifluoroacetylated in refluxing trifluoroacetic acid before cyclization, the mode of cyclization in protic acid is similar to that caused by Lewis acids, and O-acylhydroxylamines alone are effective for this reaction. Of a number of catalysts (tetrafluoroboric acid, sulfuric acid, polyphosphoric acid, and trifluoromethanesulfonic acid), only trifluoroacetic acid was found to be effective. Several hydroxylamines (**1f—i**) were subjected to the cyclization reaction. Table IV shows the results.

TABLE IV. Cyclization of Various Hydroxylamines



1 **2**

Starting compound	R^1	R^2	X	Conditions: catalyst-solvent, temp., time	Product	Yield (%)
1f	H	H	CH_2	CF_3CO_2H, reflux, 15 hr	**2b**	55
1g	CH_3	H	$C(CH_3)_2$	CF_3CO_2H, reflux, 15 hr	**2c**	48
1h	CH_3	H	O	CF_3CO_2H, reflux, 15 hr	**2d**	31
1i	CH_3	$COCH_3$	O	$AlCl_3$–CH_2Cl_2, room temp., 46 hr	**2d**	31

Effect of a Methoxyl Group on the Cyclization Reaction

It is not easy to decide whether the cyclization reaction proceeds *via* a nitrenium ion intermediate[5] or by a concerted process catalyzed by a Lewis acid or a proton which coordinates on the acyl oxygen to increase the cationic character of the nitrogen, although the concerted mechanism is consistent with the experimental data. An electron-donating substituent on the benzene ring should facilitate the cyclization reaction because it is evident that an electron-deficient nitrogen must play an important role in this reaction. To investigate the substituent effect of a methoxyl group on the benzene ring, the *m*-methoxy compound (**1j**) was subjected

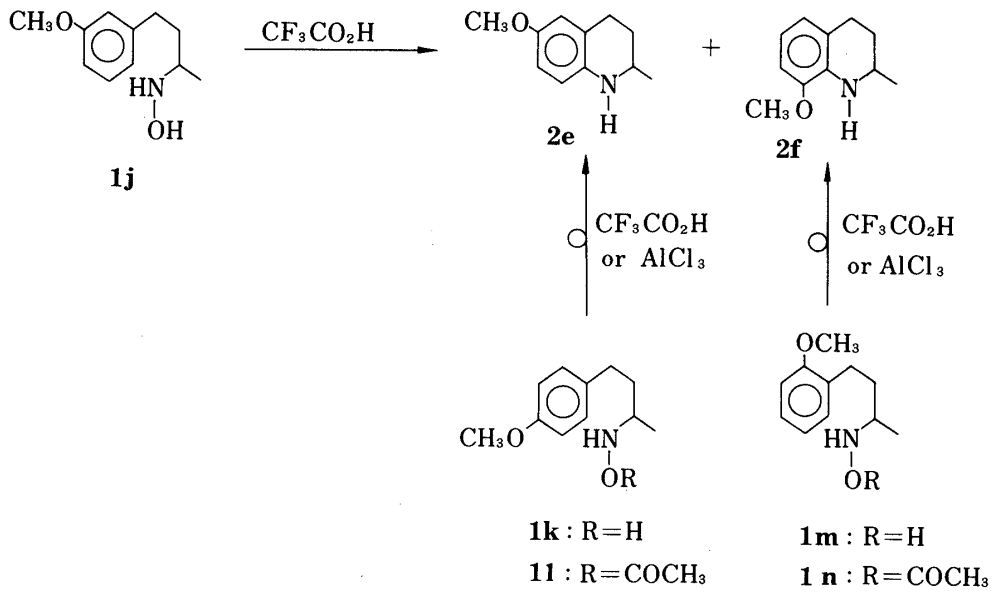
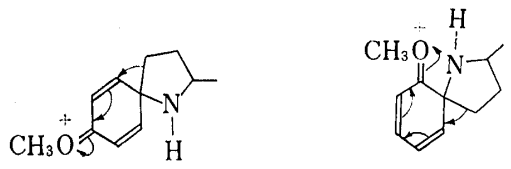


Chart 1

to the cyclization reaction in trifluoroacetic acid, to give the expected products (**2e**) (60%) and (**2f**) (10.3%). The mode of cyclization was altered dramatically when the *p*-methoxy compound (**1k**) was used as a starting material. In this case, **2e** and the 6-hydroxy compound (**2g**), the demethylated product of **2e**, were obtained from **1k** in yields of 8% and 20—35%, respectively. 7-Methoxy-2-methyl-1,2,3,4-tetrahydroquinoline, the expected product, was not detected in the reaction mixture by gas chromatographic analysis. The yield of **2e** was increased to 78% by the reaction of the O-acetylhydroxylamine (**1l**) with aluminium chloride in methylene chloride. This abnormal cyclization can be explained by assuming the presence of a spiro intermediate (**3a**) and subsequent dienone-phenol type rearrangement to give the stable six-membered ring, due to the considerable electron-donating effect of the methoxyl group, as shown in Chart 2. Formation of the spiro intermediate (**3b**) is also evident in the cyclization of the *o*-methoxy compounds (**1m** and **n**). Demethylation of **2e** can be explained by the nucleophilic attack of trifluoroacetic acid on the methyl group of the spiro intermediate (**3a**), because **2e** was not demethylated under the same reaction conditions.



3a **3b**

Chart 2

Attempted Synthesis of Indolines and Benzazepines

Attempts to synthesize indolines and benzazepines were carried out in a manner similar to that described above. Unfortunately, no desired products were obtained; instead, an unexpected product was obtained in the cyclization reaction of N-hydroxy-1-(3-methoxyphenyl)-2-propylamine (**1o**) in trifluoroacetic acid-trifluoroacetic anhydride. The new compound was elucidated as 6-methoxy-3-methyl-1-trifluoromethyl-3,4-dihydroisoquinoline 2-oxide (**2j**) by elemental analysis and chemical reactions as shown in Chart 3. The position (C-6) of the methoxyl group of **2j** was confirmed by comparison of the NMR data of **2m** with those of 1,3-dimethyl-6-methoxyisoquinoline.[6] The formation of **2j** was explained by considering the presence of N-trifluoroacetylated **1o** as an intermediate, which underwent Bischler–Napieralski type reaction to give **2j**. Smooth cyclization of **1o** under mild conditions is particularly interesting, because an acyl group having an electron-withdrawing group such as a trifluoro group[7] prevents smooth cyclization in the Bischler–Napieralski reaction.

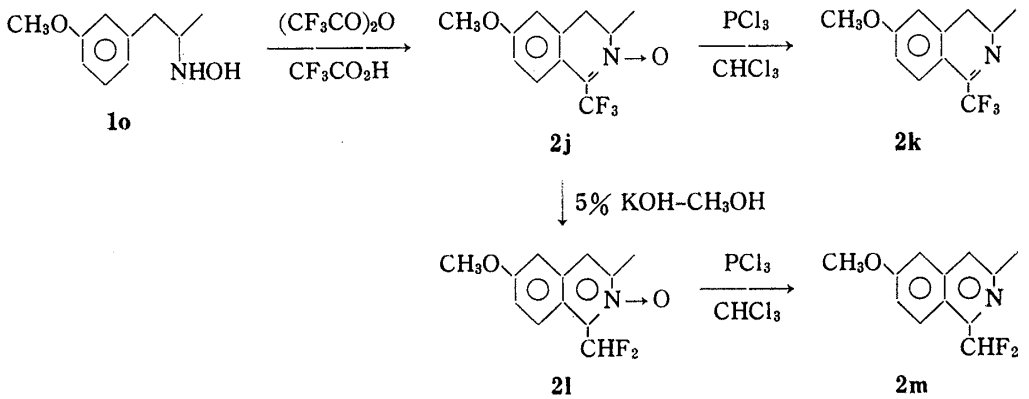


Chart 3

Experimental

All melting points are uncorrected. The following instruments were used to obtain physical data: infrared (IR) spectra, Shimadzu IR-400; nuclear magnetic resonance (NMR) spectra (tetramethylsilane as an internal standard), JNM-C-60HL; gas chromatography, Shimadzu GC-4BM; mass spectra (MS), Shimadzu LKB-9000.

Materials——(i) Aldehydes and Ketones: Benzylacetone, β-phenylpropionaldehyde, and phenoxyacetone were purchased from Tokyo Kasei Co. Ltd., Tokyo. 4-(2-Methoxyphenyl)-2-butanone, bp 106—112°/2 Torr (lit.[8] bp 125°/7 Torr), 4-(3-methoxyphenyl)-2-butanone, bp 138—142°/2 Torr (lit.[8] bp 155—156°/4 Torr), 4-(4-methoxyphenyl)-2-butanone, bp 124—127°/4 Torr (lit.[9] bp 120—122°/3 Torr), 4-methyl-4-phenyl-2-pentanone, bp 96—100°/3 Torr (lit.[10] bp 124—125°/14 Torr), and 1-(3-methoxyphenyl)-2-propanone, bp 106—112°/3 Torr (lit.[11] bp 95—102°/0.8—1 Torr) were prepared by the cited methods.

(ii) Oxime Derivatives: Benzylacetone oxime, mp 80—84° recrystallized from 50% aq. EtOH (lit.[12] mp 85°). Benzylacetone O-methyloxime, bp 96—98°/5 Torr. *Anal.* Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.56; H, 8.60; N, 7.88. Benzylacetone O-acetyloxime, bp 148—153°/5 Torr. *Anal.* Calcd for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37; N, 6.82. Found: C, 70.14; H, 7.16; N, 6.84. Benzylacetone O-pivaloyloxime, bp 142—146°/3 Torr. *Anal.* Calcd for $C_{15}H_{21}NO_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.62; H, 8.37; N, 5.68. Benzylacetone O-benzoyloxime, mp 55—56° recrystallized from ligroin. *Anal.* Calcd for $C_{15}H_{21}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.31; H, 6.34; N, 5.08. β-Phenylpropionaldehyde oxime, mp 92—96° recrystallized from hexane (lit.[13] mp 93—94.5°). 4-Methyl-4-phenyl-2-pentanone oxime, mp 61—64° recrystallized from petroleum ether (lit.[14] mp 62—63.5°). 4-(2-Methoxyphenyl)-2-butanone oxime, bp 150—160°/6 Torr. *Anal.* Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.15; H, 7.73; N, 7.15. 4-(2-Methoxyphenyl)-2-butanone O-acetyloxime, bp 146—152°/2 Torr. *Anal.* Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.40; H, 7.18; N, 5.98. 4-(3-Methoxyphenyl)-2-butanone oxime, bp 138—143°/7 Torr. *Anal.* Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.45; H, 7.71; N, 7.30. 4-(4-Methoxyphenyl)-2-butanone oxime, bp 152—156°/3 Torr (mp 76—79° recrystallized from ligroin) (lit.[15] mp 77°). 4-(4-Methoxyphenyl)-2-butanone O-acetyloxime, bp 172—176°/4 Torr. *Anal.* Calcd for $C_{13}H_{17}NO_3$: C, 66.36; H, 7.28; N, 5.95. Found: C, 66.36; H, 7.07; N, 5.95. 1-(3-

Table V. Yields and NMR Spectral Data of Alkylhydroxylamines

Compound	Yield of 1 (%)	NMR (δ) in $CDCl_3$
1a	92	1.15 (d, 3H, J=6.4 Hz), 1.35—2.17 (m, 2H), 2.71 (t, 2H, J=8.1 Hz), 2.88—3.27 (m, 1H), 5.85[a] (s, 2H), 7.36 (s, 5H)
1b	83	1.13 (d, 3H, J=6.4 Hz), 1.45—2.00 (m, 2H), 2.50—3.25 (m, 3H), 3.56 (s, 3H), 4.38—5.47[a] (br s, 1H), 7.30 (s, 5H)
1c	82	1.15 (d, 3H, J=6.4 Hz), 1.53—1.97 (m, 2H), 2.10 (s, 3H), 2.73 (t, 2H, J=8.1 Hz), 3.12 (m, 1H), 7.30 (s, 5H)
1d	94	1.07 (d, 3H, J=6.4 Hz), 1.26 (s, 9H), 1.50—2.04 (m, 2H), 2.70 (t, 2H, J=7.5 Hz), 3.08 (m, 1H), 7.21 (s, 5H), 7.50—7.68[a] (br s, 1H)
1e	52	1.20 (d, 3H, J=6.4 Hz), 1.56—2.13 (m, 2H), 2.77 (t, 2H, J=7.5 Hz), 3.09—3.50 (m, 1H), 7.55 (s, 5H), 7.37—7.67 (m, 3H), 7.97—8.25 (m, 2H)
1f	95	1.56—2.18 (m, 2H), 2.51—3.12 (m, 4H), 6.28[a] (br s, 2H), 7.25 (s, 5H)
1g	48[b]	0.86 (d, 3H, J=6.4 Hz), 1.33, 1.35 (s, 3H each), 1.49—1.96 (m, 2H), 2.67—2.95 (m, 1H), 4.71—5.97[a] (br s, 2H), 7.07—7.50 (m, 5H)
1h	96	1.21 (d, 3H, J=6.4 Hz), 3.11—3.71 (m, 1H), 3.96 (d, 2H, J=6 Hz), 6.39[a] (br s, 2H), 6.79—7.13 (m, 3H), 7.26—7.54 (m, 2H)
1i	76	1.24 (d, 3H, J=6.4 Hz), 2.06 (s, 3H), 3.25—3.80 (m, 1H), 3.95 (d, 2H, J=5.8 Hz), 6.78—7.35 (m, 5H)
1j	96	1.08 (d, 3H, J=6.4 Hz), 1.42—2.16 (m, 2H), 2.49—2.76 (t, 2H, J=8.4 Hz), 2.80—3.20 (m, 1H), 3.76 (s, 3H), 5.42—6.52[a] (br s, 2H), 6.64—6.86, 7.28—7.42 (m, 2H each)
1k	93	1.12 (d, 3H, J=6.4 Hz), 1.25—1.96 (m, 2H), 2.59 (t, 2H, J=8.1 Hz), 2.84—3.15 (m, 1H), 3.77 (m, 3H), 5.03—6.18[a] (br s, 2H), 6.73—6.89, 7.01—7.18 (m, 2H each)
1l	84	1.16 (d, 3H, J=6.4 Hz), 1.50—2.05 (m, 2H), 2.10 (s, 3H), 2.70 (t, 2H, J=8.2 Hz), 2.86—3.39 (br s, 1H), 3.78 (s, 3H), 6.90—7.26 (m, 4H)
1m	97	1.14 (d, 3H, J=6.4 Hz), 1.39—2.01 (m, 2H), 2.65 (t, 2H, J=8.1 Hz), 2.94— 3.03 (m, 1H), 3.80 (s, 3H), 5.59—6.33[a] (br s, 2H), 6.69—6.97, 6.97—7.27 (m, 2H each)
1n	89	1.16 (d, 3H, J=6.4 Hz), 1.53—1.93 (m, 2H), 2.08 (s, 3H), 2.74 (t, 2H, J=8.1 Hz), 2.93—3.24 (m, 1H), 3.81 (s, 3H), 6.85—7.09, 7.20—7.40 (m, 2H each), 7.49—7.72[a] (br s, 1H)
1o	95	1.12 (d, 3H, J=6.4 Hz), 2.68 (t, 2H, J=6.4 Hz), 2.92—3.43 (m, 1H), 3.77 (s, 3H), 5.58—6.57[a] (br s, 2H), 6.59—6.93, 7.05—7.37 (m, 2H each)

a) Exchangeable with D_2O.
b) The starting material was recovered in 45% yield.

Methoxyphenyl)-2-propanone oxime, bp 136—142°/3 Torr. *Anal.* Calcd for $C_{10}H_{13}NO_2$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.93; H, 7.29; N, 8.05. Phenoxyacetone oxime and its O-acetate were purified by silica gel column chromatography with benzene–acetone (10: 1) for elution and were used without further purification.

(iii) Others: 8-Hydroxyquinaldine was purchased from Tokyo Kasei Kogyo Co. Ltd.

General Procedure for the Reduction of Oxime Derivatives with Pyridine-Borane——A mixture of an oxime (3 mmol) and pyridine–borane (10 mmol) in EtOH (5 ml) was kept below 5°. To this solution, 10% HCl (10 ml) was added dropwise, and the mixture was stirred for 20 min at room temperature. The solution was made alkaline with 10% Na_2CO_3 with cooling and the aqueous solution was extracted with benzene. The combined benzene extracts were dried over anhyd. Na_2SO_4 and removal of benzene by evaporation gave the corresponding hydroxylamine in high yield. **1j, k, m,** and **q** were purified by washing them with hexane, **1c—e, i, l, n,** and **p** were purified by column chromatography over Florisil (Wako Pure Chemical Ind. Ltd.) using benzene–acetone (20: 1) for elution, and other hydroxylamines were used without further purification. Table V lists NMR data for the hydroxylamines.

Cyclization of O-Acetylhydroxylamines (1c and i)——$AlCl_3$ (960 mg, 7.2 mmol) was added to a solution of an O-acetylhydroxylamine (2.4 mmol) in CH_2Cl_2 (8 ml) with ice cooling. After being stirred for 6 hr at room temperature, the reaction mixture was poured into ice-water (30 ml). The aqueous solution was basified with 10% NaOH, and then extracted with CH_2Cl_2. The combined extracts were washed with sat. NaCl and dried over anhyd. Na_2SO_4. After removal of CH_2Cl_2 by evaporation, the residue was purified by column chromatography on silica gel (Merk, Art. 7734) using benzene for elution. The results are shown in Tables I and IV.

Cyclization of 1l and n——The procedure described above was used except for the replacement of 10% NaOH with 10% Na_2CO_3. The following eluents were used for silica gel column chromatography: benzene for **2f**, benzene–acetone (50: 1) for **2e**, and benzene–acetone (10: 1) for **2g**.

Cyclization of Hydroxylamines (1a, f, g, h, j, k, and m)——A solution of a hydroxylamine (2.5 mmol) in trifluoroacetic acid (6 ml) was refluxed for 15 hr, then the solvent was evaporated off under reduced pressure. The residue was basified with 10% Na_2CO_3 with cooling and the aqueous solution was extracted with benzene. Purification of the products was carried out by the procedure just described above. The results are shown in Table VI.

5-Methoxyquinaldine——5-Nitroquinaldine (mp 78—81° recrystallized from MeOH; lit.[16] mp 82°) prepared by the reported method,[16] was reduced to 5-aminoquinaldine (mp 97—103° after recrystallization from ether) with Fe-HCl. The amino compound was diazotized with nitrous acid in hydrobromic acid, and subsequent treatment with cuprous bromide gave 5-bromoquinaldine in 81% yield. After purification of the bromo compound by silica gel column chromatography using benzene–acetone (20: 1) for elution, it was subjected to methoxylation (8 hr reflux)[17] to give 5-methoxyquinaldine (bp 136—138°/13 Torr) in 94% yield; picrate, mp 202° (dec.) recrystallized from EtOH. *Anal.* Calcd for $C_{17}H_{14}N_4O_8$: C, 50.75; H, 3.51; N, 13.93. Found: C, 50.83; H, 3.53; N, 13.77.

6-Methoxyquinaldine——6-Bromoquinaldine (mp 99.5—101° recrystallized from ligroin, lit.[18] mp 96—97°), prepared by the reported method,[18] was subjected to methoxylation to give 6-methoxyquinaldine, mp 64—67° after recrystallization from hexane (lit.[19] mp 64°), in 91% yield.

7-Methoxyquinaldine——7-Bromoquinaldine (mp 75—77° after recrystallization from ligroin) prepared from *m*-bromoaniline and paraldehyde was subjected to methoxylation to give 7-methoxyquinaldine, which was distilled in a Kugelrohr apparatus (oven temp. 140°, vacuum 3 Torr) in 84% yield; oxalate, mp 215° (dec.) after recrystallization from EtOH (lit.[20] mp 217°).

8-Methoxyquinaldine——8-Hydroxyquinaldine was methylated with dimethyl sulfate to give 8-methoxyquinaldine, mp 122—124° after recrystallization from benzene (lit.[21] mp 125°).

5-Methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (2h)——The reduction of 5-methoxyquinaldine was carried out by the method reported previously.[22] A mixture of 5-methoxyquinaldine (514 mg, 2.97 mmol), pyridine-borane (1.1 ml, 12 mmol), and acetic acid (8 ml) was stirred for 18 hr at room temperature then for an additional 2 hr at 50°. After the reaction, 10% HCl (10 ml) was added to the reaction mixture with cooling and the mixture was stirred for 20 min at room temperature to decompose excess pyridine–borane. The aqueous layer was made alkaline with NaOH pellets and ice water, and it was extracted with benzene. The combined extracts were washed with sat. NaCl and dried over anhyd. Na_2SO_4. After the removal of benzene by evaporation the residue was purified by column chromatography over silica gel. First elution with benzene–hexane (1: 2) gave 1-ethyl-5-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (53.8 mg, yield 8.8%), which was identified by comparison of the spectral data with those of an authentic sample prepared by ethylation of **2h** with C_2H_5I–$NaHCO_3$–H_2O. Second elution with benzene gave 5-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (**2h**) (295 mg, yield 56%), bp 132—136°/24 Torr; picrolonate, mp 197° (dec.) after recrystallization from EtOH. *Anal.* Calcd for $C_{21}H_{23}N_5O_6$: C, 57.13; H, 5.25; N, 15.87. Found: C, 57.16; H, 5.27; N, 15.73. MS *m/e*: 177 (M^+). NMR ($CDCl_3$) δ: 1.18 (d, 3H, J=6.2 Hz), 1.40—2.25 (m, 2H), 2.48—2.85 (m, 2H), 3.05—3.53 (m, 2H, one proton was exchangeable with D_2O), 3.78 (s, 3H), 6.13, 6.21 (dd, 1H each, J=1.5, 8.0 Hz), 6.93 (t, 1H, J=8.0 Hz). IR ν_{max}^{film} cm^{-1}: 3400 (NH). Third elution with benzene–acetone (10: 1) gave the starting material (93.8 mg, yield 18%).

TABLE VI. Yields and Physical Constants of Cyclized Products

Starting compound	Reaction conditions[a]	Product	Yield (%)	mp (°C) (recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	Others
1g	A	**2c**[b]	48	219 (dec.)[c] (ethanol)	$C_{22}H_{25}N_5O_5$	60.12 (60.10	5.73 5.70	15.94 15.95)	MS *m/e*: 175 (M^+); NMR ($CDCl_3$) δ: 1.17 (d, 3H, J=6.2 Hz), 1.24, 1.32 (s, 3H each), 1.48—1.58 (m, 2H), 3.21—3.74[h] (m, 2H), 6.36—7.25 (m, 4H); IR ν_{max}^{film} cm^{-1}: 3380 (NH)
1h	A	**2d**[d]	31	195 (dec.)[c] (ethanol)	$C_{19}H_{19}N_5O_6$	55.20 (55.02	4.63 4.68	16.94 16.81)	MS *m/e*: 149 (M^+); NMR ($CDCl_3$) δ: 1.12 (d, 3H, J=6.2 Hz), 3.13—3.63[h] (m, 2H), 3.63—4.28 (m, 2H), 6.28—6.87 (m, 4H); IR ν_{max}^{film} cm^{-1}: 3380 (NH)
1i	B	**2d**	31						
1j	A	**2e**[e]	60	214 (dec.)[c] (ethanol)	$C_{21}H_{23}N_5O_6$	57.13 (57.03	5.25 5.35	15.87 15.83)	MS *m/e*: 177 (M^+); NMR ($CDCl_3$) δ: 1.18 (d, 3H, J=6.2 Hz), 1.43—2.15 (m, 2H), 2.61—3.00 (m, 2H), 3.11—3.58[h] (m, 2H), 3.71 (s, 3H), 6.28—6.76 (m, 3H); IR ν_{max}^{film} cm^{-1}: 3390 (NH)
		2f[f]	10.3	201 (dec.)[g] (methanol–ether)	$C_{11}H_{16}NOCl$	61.82 (61.58	7.55 7.25	6.55 6.57)	MS *m/e*: 177 (M^+); NMR ($CDCl_3$) δ: 1.21 (d, 3H, J=6.2 Hz), 1.40—2.10 (m, 2H), 2.65—2.98 (m, 2H), 3.08—3.55 (m, 1H), 3.65—4.23[h] (br s, 1H), 3.96 (s, 3H), 6.60 (s, 3H); IR ν_{max}^{film} cm^{-1}: 3410 (NH)
1k	A	**2e**	8						
		2g	35	103—105 (benzene–hexane)	$C_{10}H_{13}NO$	73.59 (73.58	8.03 7.97	8.58 8.51)	MS *m/e*: 163 (M^+); NMR (DMSO-d_6) δ: 1.09 (d, 3H, J=6.2 Hz), 1.33—2.05 (m, 2H), 2.45—2.83 (m, 2H), 3.00—3.50[h] (m, 2H), 6.34 (s, 3H), 8.25[h] (s, 1H); IR ν_{max}^{Nujol} cm^{-1}: 3280 (NH, OH)
1l	B	**2e**	78						
		2g	0.4						
1m	A	**2f**	6.4						
1n	B	**2f**	8						

a) A: CF_3CO_2H; B: $AlCl_3$–CH_2Cl_2.
b) bp 108—109°/14 Torr.
c) Picrolonate.
d) bp 116—120°/4 Torr [lit., bp 97—98°/2 Torr, G. Barker, G.P. Ellis, and D.A. Wilson, *J. Chem. Soc.* (*C*), **1971**, 2079].
e) Distilled in a Kugelrohr apparatus (oven temp. 170°, vacuum 9 Torr).
f) Distilled in a Kugelrohr apparatus (oven temp. 130°, vacuum 3 Torr).
g) HCl.
h) One proton was exchangeable with D_2O.

6-Methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (**2e**)——The procedure was the same as described above. First elution with benzene on silica gel column chromatography gave 6-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (**2e**) (yield 44%, physical constants, see Table VI). Second elution with benzene–acetone (50: 1) gave the starting material (yield 42%).

7-Methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (**2i**)——The procedure was the same as described above. First elution with benzene on silica gel column chromatography gave 1-ethyl-7-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (yield 32%), which was identified by comparison of the spectral data with those of an authentic sample prepared by ethylation of **2i**. Second elution with benzene–acetone (50: 1) gave 7-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (**2i**) (yield 28%), mp 66—68° after recrystallization from hexane. *Anal.* Calcd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53; N, 7.90. Found: C, 74.37; H, 8.59; N, 7.62. MS *m/e*: 177 (M^+). NMR ($CDCl_3$) δ: 1.18 (d, 3H, J=6.2 Hz), 1.38—2.12 (m, 2H), 2.58—2.91 (m, 2H), 3.05—3.63 (m, 2H, one proton was exchangeable with D_2O), 3.74 (s, 3H), 6.03 (d, 1H, J= 2.7 Hz), 6.20 (dd, 1H, J=2.7, 8.0 Hz), 6.86 (d, 1H, J= 8.0 Hz). IR ν_{max}^{Nujol} cm^{-1}: 3380 (NH). Third elution with benzene–acetone (10: 1) gave the starting material (yield 34%).

8-Methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (**2f**)——The same procedure was used except for a change of the reaction time (16 hr at room temperature). Elution with benzene on silica gel column chromatography gave 8-methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (**2f**) (yield 82%; physical constants, see Table VI). A gas chromatogram of four methoxy-2-methyl-1,2,3,4-tetrahydroquinolines is shown in Fig. 1.

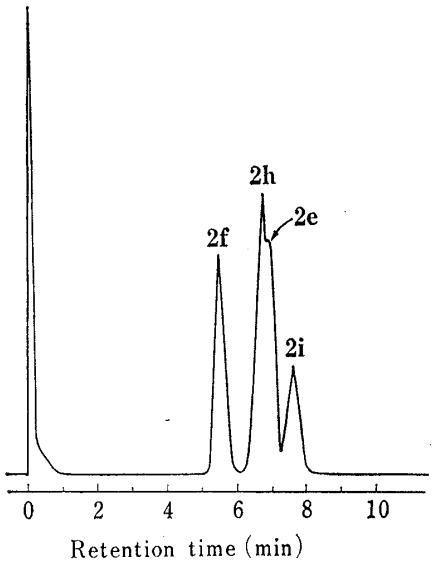


Fig. 1. Gas Chromatogram of Methoxy-2-methyl-1,2,3,4-tetrahydroquinolines

Conditions were as follows: glass column (2 m); 10% SE-30 on Chromosorb W (60—80 mesh); temperature, 160°; carrier gas, N_2 at a flow rate of 50 ml/min.

6-Hydroxy-2-methyl-1,2,3,4-tetrahydroquinoline (**2g**)——A CH_2Cl_2 solution (5 ml) of boron tribromide (500 mg, 2.08 mmol) was added carefully to a CH_2Cl_2 solution (10 ml) of **2e** (222 mg, 1.25 mmol) at −80° (dry ice-acetone) under an argon atmosphere. The reaction mixture was stirred at room temperature overnight. Water was added to the reaction mixture, and then it was basified with 10% Na_2CO_3. The aqueous solution was extracted with CH_2Cl_2. The combined extracts were washed with sat. NaCl and dried over anhyd. Na_2SO_4. After the removal of CH_2Cl_2 by evaporation, the residue was purified by silica gel column chromatography. First elution with benzene–acetone (50: 1) gave the starting material (12 mg, yield 5.4%) and second elution with benzene–acetone (10: 1) gave 6-hydroxy-2-methyl-1,2,3,4-tetrahydroquinoline (**2g**) (122 mg, yield 59%; for physical constants, see Table VI).

Cyclization of N-Hydroxy-(3-methoxyphenyl)-2-propylamine (**1o**) **in Trifluoroacetic Acid and Trifluoroacetic Anhydride**——A mixture of **1o** (459 mg, 2.5 mmol) in trifluoroacetic acid (5.8 ml) and trifluoroacetic anhydride (2.8 ml) was refluxed for 15 hr, then the reaction mixture was evaporated to dryness under reduced pressure. The residue was basified with 10% Na_2CO_3 and extracted with benzene. The combined extracts were washed with sat. NaCl and dried over anhyd. Na_2SO_4. After the removal of benzene by evaporation, the residue was purified by silica gel column chromatography using benzene–acetone (20: 1) for elution to give 6-methoxy-3-methyl-1-trifluoromethyl-3,4-dihydroisoquinoline 2-oxide (**2j**) (570 mg, yield 86%), mp 77—78.5° after recrystallization from petroleum ether. *Anal.* Calcd for $C_{12}H_{12}F_3NO_2$: C, 55.60; H, 4.67; N, 5.40. Found: C, 55.63; H, 4.44; N, 5.68. MS *m/e*: 259 (M^+). NMR ($CDCl_3$) δ: 1.36 (d, 3H, J=6.4 Hz), 2.74, 3.40 (dd, 1H each, J=5.2, 16 Hz), 3.88 (s, 3H), 4.00—4.46 (m, 1H), 6.78—7.00 (m, 2H), 7.36—7.65 (m, 1H). IR ν_{max}^{Nujol} cm^{-1}: 1610 (C=N).

1-Difluoromethyl-6-methoxy-3-methylisoquinoline 2-Oxide (**2l**)——A mixture of **2j** (434 mg, 1.7 mmol) in 5% aq. KOH (15 ml) and MeOH (5 ml) was refluxed for 1 hr then the reaction mixture was extracted with benzene. The combined extracts were washed with sat. NaCl and dried over anhyd. Na_2SO_4. After the removal of benzene by evaporation, the residue was purified by silica gel column chromatography using benzene–acetone (10: 1) for elution to give 1-difluoromethyl-6-methoxy-3-methylisoquinoline 2-oxide (**2l**) (269 mg, yield 67%), mp 151—154° after recrystallization from benzene–hexane. *Anal.* Calcd for $C_{12}H_{11}F_2NO_2$: C, 60.25; H, 4.63; N, 5.86. Found: C, 60.02; H, 4.82; N, 6.11. MS *m/e*: 239 (M^+). NMR ($CDCl_3$) δ: 2.60 (s, 3H), 3.95 (s, 3H), 6.99 (d, 1H, J=2.7 Hz), 7.25 (dd, 1H, J=9.8, 2.7 Hz), 7.60 (s, 1H), 7.99 (t, 1H, J=54 Hz), 8.23 (d, 1H, 9.8 Hz). IR ν_{max}^{Nujol} cm^{-1}: 1610 (C=N).

6-Methoxy-3-methyl-1-trifluoromethyl-3,4-dihydroisoquinoline (**2k**)——PCl_3 (0.5 ml) was added to an ice-cooled $CHCl_3$ solution (5 ml) of **2j** (420 mg, 1.62 mmol) and the mixture was heated for 1 hr at 80°. After cooling, water was added to the reaction mixture and then it was basified with NaOH pellets and extracted

with $CHCl_3$. The combined extracts were washed with sat. NaCl and dried over anhyd. Na_2SO_4. After the removal of $CHCl_3$ by evaporation, the residue was purified by silica gel column chromatography using benzene–acetone (20: 1) for elution to give 1-trifluoromethyl-6-methoxy-3-methyl-3,4-dihydroisoquinoline (**2k**) (315 mg, yield 80%), mp 47—50°; picrate, mp 127—128° after recrystallization from EtOH. *Anal.* Calcd for $C_{18}H_{15}F_3NO$: C, 45.77; H, 3.20; N, 11.86. Found: C, 46.04; H, 3.32; N, 11.73. MS *m/e*: 243 (M^+). NMR ($CDCl_3$) δ: 1.41 (d, 3H, J=6.4 Hz), 2.52—2.88 (m, 2H), 3.50—4.14 (m, 1H), 3.90 (s, 3H), 6.75—7.00 (m, 2H), 7.61 (d, 1H, J=7.5 Hz). IR ν_{max}^{Nujol} cm^{-1}: 1630 (C=N).

1-Difluoromethyl-6-methoxy-3-methylisoquinoline (**2m**)——The procedure was the same as described previously. The product was purified by silica gel column chromatography using CH_2Cl_2 for elution to give 1-difluoromethyl-6-methoxy-3-methylisoquinoline (**2m**) (yield 65%), mp 113—115° after recrystallization from hexane. *Anal.* Calcd for $C_{12}H_{11}F_2NO$: C, 64.57; H, 4.97; N, 6.27. Found: C, 64.63; H, 4.76; N, 6.41. MS *m/e*: 223 (M^+). NMR ($CDCl_3$) δ: 2.69 (s, 3H), 3.93 (s, 3H), 7.00 (t, 1H, J=54 Hz), 7.03 (d, 1H, J=2.3 Hz), 7.24 (dd, 1H, J=9.0, 2.3 Hz), 7.51 (s, 1H), 8.38 (d, 1H, J=9.0 Hz). IR ν_{max}^{Nujol} cm^{-1}: 1630 (C=N).

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