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Chemistry of Diborane and Sodium Borohydride. IX.[1] The Reduction of 3-Substituted Pyridines and Quinolines, and 4-Substituted Isoquinolines with Sodium Borohydride[2]

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Reductions of 3-substituted pyridines, quinolines and 4-substituted isoquinolines with sodium borohydride were examined. The reduction of the nucleus occurred and the reduction mechanisms were investigated.

Pyridine, quinoline and isoquinoline derivatives have greater affinity toward nucleophilic reagents than the corresponding carbocyclic aromatics because of electronic effects of the nitrogen atom in the ring.[4] But these effects are not sufficient enough to enhance the reactivity of these compounds to mild nucleophilic reagents such as sodium borohydride. The most common method for the enhancement of their reactivity involves their conversion to quarternary salts by alkyl halides and there are many examples in the literatures concerning the reduction of quaternary salts of heteroaromatic compounds by sodium borohydride.[5] On the other hand there are few reports referring to the reduction of tertiary bases of pyridine, quinoline and isoquinoline derivatives with sodium borohydride[6] because of the reason mentioned above. It might be expected that these heteroaromatic tertiary bases could have high reactivity toward sodium borohydride, if electron-withdrawing groups are properly substituted (except on a nitrogen atom) so as to cooperate electronically with the ring nitrogen for the reduction. Therefore, it might be also expected that it becomes easy to obtain various hydroheteroaromatic compounds which are hardly obtainable from other routes.

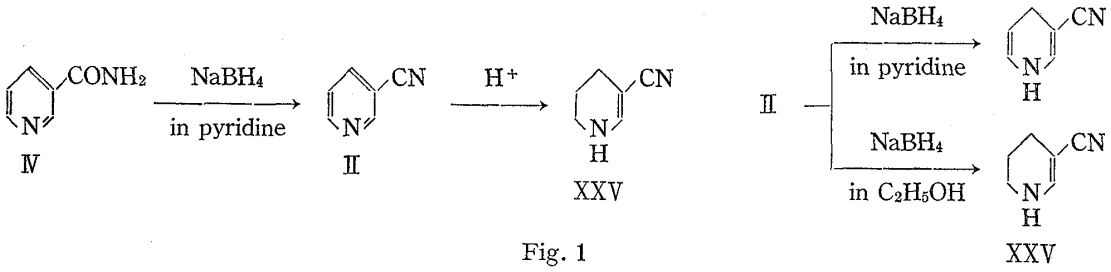


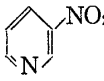
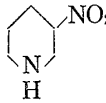
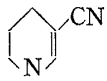
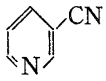
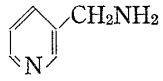
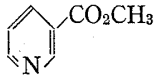
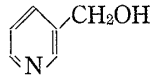
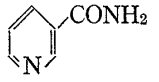
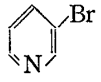
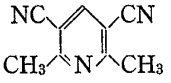
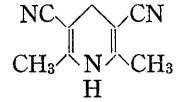
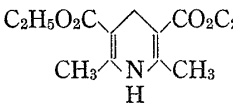
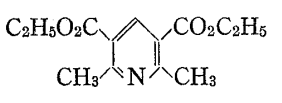
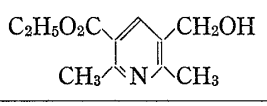
Fig. 1

1) Part VIII: H. Watanabe, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 465 (1973).
2) A part of this work was published before as a Communication to Editor: S. Yamada and Y. Kikugawa, *Chem. Ind.* (London), **1966**, 2169.
3) Location: *Hongo, Bunkyo-ku, Tokyo.*
4) E. Klingsberg, "Pyridine and Its Derivatives," Part I, Interscience Publishers, Inc, New York, 1960, p. 12.
5) *a*) K. Schenker and J. Druey, *Helv. Chim. Acta*, **42**, 1960 (1959); *b*) N. Kinoshita, M. Hamana, and T. Kawasaki, *Chem. Pharm. Bull.* (Tokyo), **10**, 753 (1962); *c*) N. Kinoshita and T. Kawasaki, *Yakugaku Zasshi*, **83**, 123 (1963); *d*) A.R. Katritzky and A.J. Boulton, "Advances in Heterocyclic Chemistry," Vol. 6, Academic Press, 1966, p. 45.
6) *a*) G.N. Walker and B.N. Weaver, *J. Org. Chem.*, **26**, 4441 (1961); *b*) J. Kuthan and E. Janeckova, *Collect. Czech. Chem. Comm.*, **29**, 1654 (1964); *c*) Y. Kawazoe and M. Tachibana, *Chem. Pharm. Bull.* (Tokyo), **13**, 1103 (1965).

In the course of investigating new reactions with readily available sodium borohydride, this article reports an attempt to reduce pyridine, quinoline and isoquinoline derivatives with sodium borohydride. A previous paper[7] described that nicotinamide (IV) was reduced to 1,4,5,6-tetrahydronicotinonitrile (XXV) with sodium borohydride in pyridine solution. Considering the mechanism of this reaction it is probable that the amide group was first dehydrated to the nitrile group followed by the reduction of pyridine nucleus to give XXV (Fig. 1). So we examined the reduction of nicotinonitrile (II) with sodium borohydride and, as expected, could get 1,4-dihydronicotinonitrile in anhydrous pyridine[8] and further reduced 1,4,5,6-tetrahydronicotinonitrile (XXV) in ethanol.[2] Reduction of various kinds of 3-substituted pyridine derivatives was carried out as shown in Table I. Since the quinoline and isoquinoline rings are much reactive as compared with the pyridine rine, their derivatives were expected to react more easily with sodium borohydride. The reduction of these compounds was examined and the results were summarized in Table II and III a, b.

These results demonstrate that the reduction of heterocyclic ring occurred when a substituent could cooperate electronically with the ring nitrogen atom, that is, an electron-withdrawing substituent was attached on the carbon atom *meta* to the ring nitrogen. It is in-

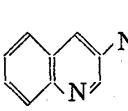
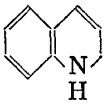
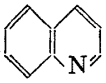
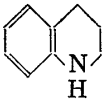
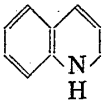
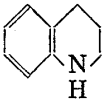
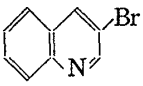
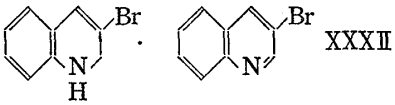
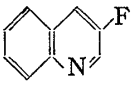
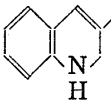
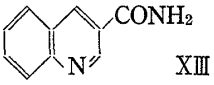
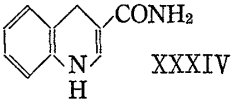
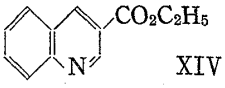
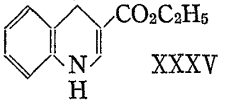
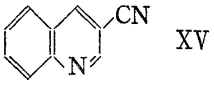
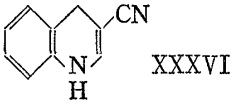
Table I. The Reduction of Pyridine Derivatives with $NaBH_4$ in EtOH

Starting materials	Molar ratio $NaBH_4$/S.M.[a]	Reflux time (hr)	Products	Yield % (isolated)
 I	3	0.5	 XXIV	42
			 XXV	60
 II	3	4	+  XXVI	15
 III	3	4	 XXVII	43
 IV	3	5	recovery of starting material	66
 V	3	7	recovery of starting material	26
 VI[b]	3	7	 XXVIII	60
			 XXIX	12
 VII	3	1	+  XXX	37

a) S.M.: starting material
b) The reduction of 3,5-dicyanopyridine derivatives was reported in the literature.[6b]

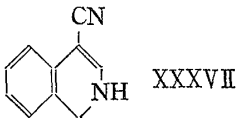
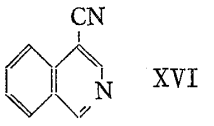
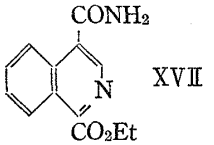
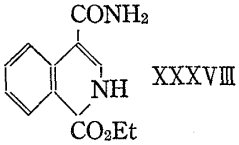
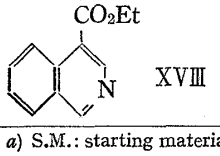
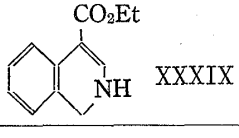
7) Y. Kikugawa, S. Ikegami, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **17**, 98 (1969).
8) S. Yamada, M. Kuramoto, and Y. Kikugawa, *Tetrahedron Letters*, **1969**, 3101.

Table II. The Reduction of Quinoline Derivatives with $NaBH_4$ in EtOH

Starting materials	Molar ratio $NaBH_4$/S.M.[a]	Reflux time (hr)	Products	Yield % (isolated)
 VIII	10	5	recovery of starting material	86
			 X	35[b]
 IX	10	5	+	
			 XXXI	20[b]
 X	10	5	 XXXI	34[b]
 XI	10	5	 XXXII	40
 XII	10	5	 XXXIII	30[b]
 XIII	1	1	 XXXIV	86
 XIV	1	0.5	 XXXV	86
 XV	0.5	1	 XXXVI	95

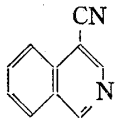
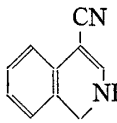
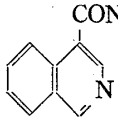
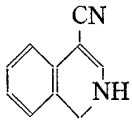
a) S.M.: starting material
b) These values were determined by NMR spectroscopy.

Table IIIa. The Reduction of Isoquinoline Derivatives with $NaBH_4$ in EtOH

Starting materials	Molar ratio $NaBH_4$/S.M.[a]	Reflux time (hr)	Products	Yield % (isolated)
			 XXXVII	39
 XVI	5	5	+	
			recovery of starting material	37
 XVII	5	5	 XXXVIII	39
 XVIII	5	5	 XXXIX	64

a) S.M.: starting material

Table IIIb. The Reduction of Isoquinoline Derivatives with $NaBH_4$ in Pyridine

Starting materials	Molar ratio $NaBH_4$/S.M.[a]	Reflux time (hr)	Products	Yield % (isolated)
 XVI	3	5	 XXXVII	86
 XVII	3	5	 XXXVII	41

a) S.M.: starting material

teresting to confirm what kinds of substituents are the most effective for the reduction of the ring and where is the first position to be attacked by a hydride ion on the reduction of the ring.

Pyridine itself was not reduced with sodium borohydride in ethanol. However, as shown in Table I, 3-nitro-(I) and 3-cyano-(II) pyridines were reduced to the corresponding piperidine (XXIV) and tetrahydropyridine (XXV) derivatives in ethanol. In the latter case, the product in which only nitrile group was reduced, was abnormally obtained as a by-product. In the case of methyl nicotinate (III), only the ester group was reduced leaving the pyridine nucleus intact, while neither pyridine nucleus nor substituent was reduced in the case of nicotinamide (IV) and 3-bromopyridine (V) in ethanol solution, and starting materials were recovered. Two products were obtained from VII, that is, one was 1,4-dihydropyridine derivative (XXIX) and the other was XXX in which one of ester groups was reduced leaving the pyridine nucleus intact. The comparison of the reduction of III with that of VII shows that the participation of ester group for the nucleus reduction is weaker than nitro and cyano groups.

Of the quinoline derivatives (Table II), 3-dimethylaminoquinoline (VIII), which has an electron-releasing group at the 3 position, was not reduced with sodium borohydride in alcohol, and the starting material was recovered, but quinoline (IX) itself was reduced to give two products, 1,2-dihydroquinoline (X) and 1,2,3,4-tetrahydroquinoline (XXXI). The former (X) was again reduced to (XXXI) under the similar reduction condition. The detailed reduction mechanism will be discussed in the following section. Quinoline derivatives, which have an electron-withdrawing group such as amide (XIII), ester (XIV) and nitril (XV) groups at the position 3, were all reduced to the corresponding 1,4-dihydroquinoline derivatives (XXXIV, XXXV and XXXVI) in good yields without reduction of the substituents, It is realized from these results that the position 4 of quinoline nucleus is the most reactive toward a hydride ion in these reductions.

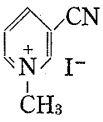
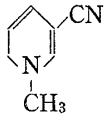
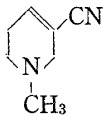
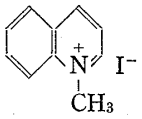
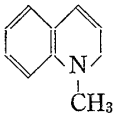
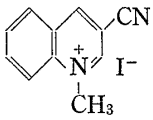
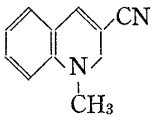
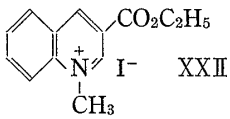
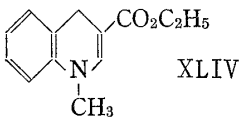
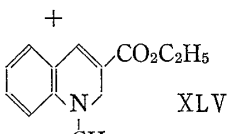
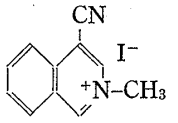
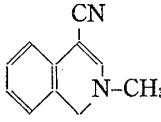
On the other hand, when 3-bromo-(XI) and 3-fluoro-(XII) quinolines were reduced under the same reduction conditions, the corresponding 1,2-dihydroquinoline derivatives (XXXII and XXXIII), were obtained and formation of 1,4-dihydro- of 1,2,3,4-tetrahydroquinoline derivative was not detected even though the crude product was checked by nuclear magnetic resonance (NMR) spectra. These results show that the 2 position of 3-haloquinoline derivatives is more reactive toward a hydride ion than the 4 position of quinoline nucleus.

The reduction product of 3-bromoquinoline (XI) was recognized as a molecular complex (XXXII) of the starting compound and 1,2-dihydro-3-bromoquinoline judging from the data described below. The NMR spectrum shows 2 protons (τ: 5.67 aliphatic protons of the *ortho* position of a 1,2-dihydroquinoline) and 1 proton (τ: 1.82 aromatic proton of the *ortho* position of 3-bromoquinoline). The infrared spectrum shows a N-H bond at 3340 cm^{-1} and the ultraviolet (UV) absorption shows an absorption maximum at 352 mμ which is typical for 1,2-dihydroquinolines. The analytical data and the result of gas chromatography listed in Table VII also support this structure.

Reduction of isoquinoline derivatives, which have an electron-withdrawing group such as cyano (XVI), carbamoyl (XVII) and ethoxycarbonyl (XVIII) at the 4 position, with sodium borohydride in a protic solvent, ethanol, and an aprotic solvent, pyridine is shown in Table III a, b. Isoquinoline having no substituent is generally inert to the reduction with sodium borohydride in ethanol and pyridine. However, as shown in Table III a, b, isoquinoline derivatives (XVI, XVII, and XVIII) having as electron-withdrawing group at the 4 position, always gave 1,2-dihydroisoquinoline derivatives (XXXVII, XXXVIII, and XXXIX) in both solvents. Reduction of XVII in pyridine gave 1,2-dihydro-4-isoquinolinecarbonitrile (XXXVII) which was a dehydrated and reduced product of XVII. This is similar to the formation of 1,4,5,6-tetrahydronicotinonitrile (XXV) from nicotinamide (IV) under the same reaction condition.[7]

It has been reported[5] that the reduction of quaternary salts of pyridine, quinoline, isoquinoline derivatives with sodium borohydride always give the corresponding 1,2-dihydro compounds by the attack of a hydride ion at the 2 position of pyridine and quinoline neclei and at the 1 position of isoquinoline derivative. We repeated the reduction of these quaternary salts with sodium borohydride in ethanol (Table IV) for the comparison with our reduction

Table IV. The Reduction of Quarternary Salts of Heterocycles with $NaBH_4$ in EtOH

Starting materials	Molar ratio $NaBH_4$/S.M.[a]	Reaction time (min) at 0°	Products	Yield % (isolated)
 XIX[b]	1.2	60	 XL	35
			 XLI	38
 XX	1	10	 XLII	87
 XXI	1	10	 XLIII	87
 XXII	1	10[d]	 XLIV +  XLV	23[c] 72[c]
 XXIII	1	10	 XLVI	86

a) S.M.: starting material
b) The reaction was carried out according to the method described in the literature.[5a]
c) These value were determined by NMR spectroroscopy.
d) at −7°

of heterocyclic tertiary base having an electron-withdrawing substituent. Most of quaternary salts tested gave the corresponding 1,2-dihydro compounds since the electron-attracting effect of the quaternary nitrogen atom becomes so strong that a borohydride ion can attack only at the *ortho* position of quaternary nitrogen atom. However the compound (XXII) gave two reduced products, 1,2-dihydro compound (XLV) and 1,4-dihydro compound (XLIV). This shows that the effect of a substituent still operates in the reduction of quaternary salt.

From Table I—III, the electrophilic position of heteroaromatic compounds is dependent on the nature of the substituent, and the real reaction mechanism seems to be very complicated. But judging from the products in the Tables, it can be speculated that when a strong electron-attracting substituent is located at the 3 position of pyridine and quinoline nuclei, the 4 position of these nuclei becomes more electrophilic than the 2 position as shown in Fig. 2. On the other hand, 3-halogeno-quinolines and quinoline itself do not have such a substituent effect which orients strongly reduction position, and the carbon of the 2 position in quinoline nucleus is the most electrophilic toward a hydride ion because of electronic effect of the nitrogen atom in the nucleus.

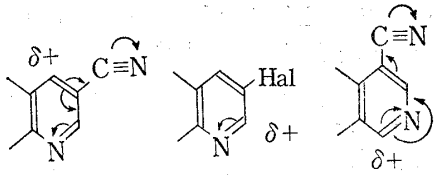


Fig. 2

In the case of isoquinoline derivatives which have an electron-withdrawing group at the 4 position, the 1 position of isoquinoline nucleus becomes reactive toward a hydride ion as shown in Fig. 2. Since the *para* position to a nitrogen atom of isoquinoline is fused to a benzene ring, a hydride ion can attack only at the 1 position of isoquinoline nucleus.

Reduction Mechanism of Nicotinonitrile (II) to 1,4,5,6-Tetrahydronicotinonitrile (XXV)

For the exploration of the reduction mechanism it is important to determine which position is most reactive toward a borohydride ion when the product is a tetrahydro compound. In the case of 3-nitropyridine (I), the reaction is very vigorous and only the hexahydro compound was obtained, and it is impossible to postulate the position first attacked. However, in the case of nicotinonitrile (II), it can be assumed that first a hydride ion attacks the 4 position to form the 1,4-dihydro derivative which is further reduced to the tetrahydro compound (XXV) by the attack of a hydride ion at the 6 position as shown in Fig. 3.

There is, however, another possibilities that 1,2- or 1,6-dihydro compound first formed by an attack of hydride ion at the 2 or 6 position is converted to the tetrahydro compound

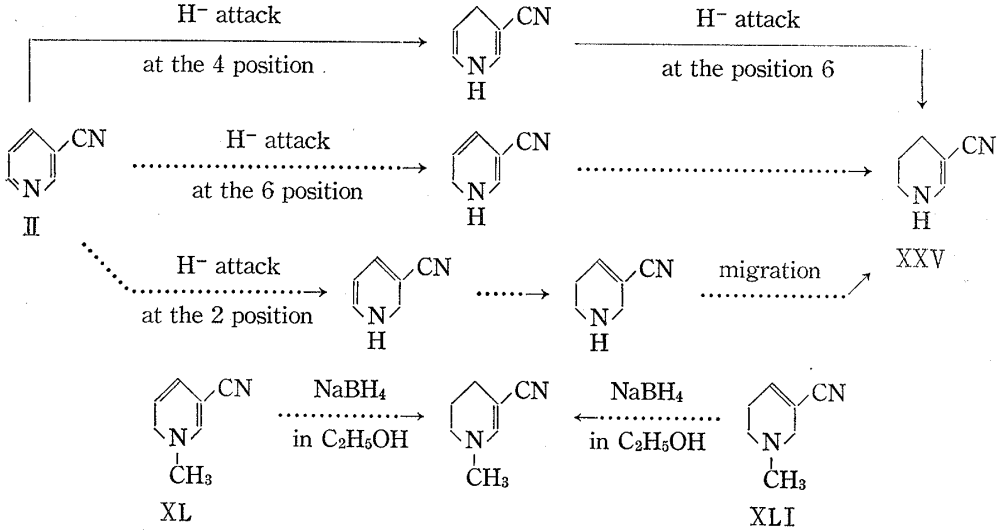


Fig. 3. Reduction Mechanism of Nicotinonitrile (II) to 1,4,5,6-Tetrahydronicotinonitrile (XXV)

(XXV) by further reduction and migration of double bond or *vice versa*. To deny these possibilities 1-methyl-1,6-dihydronicotinonitrile (XL), and 1-methyl-1,2,5,6-tetrahydronicotinonitrile (XLI) were synthesized,[9,10] and both of them were submitted to the same reduction as the case of II. The starting material was recovered in 95% yield in the former case. In the latter case, the migration of the double bond was not observed by checking the UV absorption spectrum of the reaction products,[11] although the hexahydro compound was obtained in low yield with the recovery of the starting material. As the double bond of XXV was not reduced at all in this reduction, it can be supported by the above mentioned experiments that the first attack of a hydride ion at the 2 or 6 position of II is precluded. The mechanism shown in Fig. 3 is also supported by the formation of 1,4-dihydronicotinonitrile from the reduction of nicotinonitrile with sodium borohydride in pyridine.[8]

Reduction Mechanism of Quinoline (IX) to 1,2,3,4-Tetrahydroquinoline (XXXI) with Sodium Borohydride in Alcohol

When quinoline (IX) was reduced with sodium borohydride in ethanol, two products, 1,2-dihydroquinoline (X) and 1,2,3,4-tetrahydroquinoline (XXXI) were obtained (Fig. 4), X being further reduced to XXXI in 34% yield under the same reduction conditions as shown in Table II. Accordingly, the reduction of IX to XXXI seems to proceed by way of X, and the first attack of a hydride ion to IX occurs at the 2 position to give X. On the other hand, lithium aluminum hydride, the most strongly reducing hydride reagent, reduces IX to X in quantitative yield,[12] and no further reduction occurs. This is quite different characteristics of these two hydride reagents.

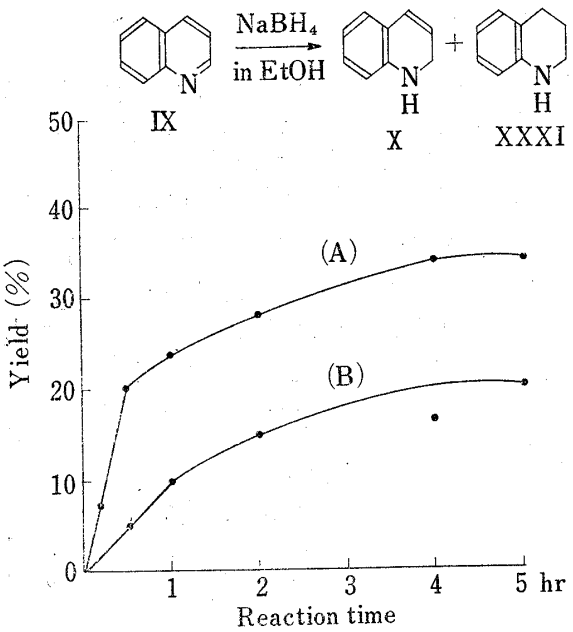


Fig. 4. (A): Yield of 1,2-Dihydroquinoline (X), (B): Yield of 1,2,3,4-tetrahydroquinoline (XXXI)

Yields were determined by NMR spectroscopy using anisol as an internal standard.

Then, we investigated the reduction mechanism from X to XXXI with sodium borohydride in ethanol in details. Sodium borodeuteride was employed as the reducing agent in a mixture of diglyme and ethanol, and it was found that deuterium was incorporated into the 2 position of XXXI. This result can be explained by the interesting migration of the double bond from the 3,4-positions to the 2,3-positions as shown in Fig. 5. To confirm this conclusion, X was reduced with sodium borohydride in diglyme containing deuterated ethanol and 3-deuterio-1,2,3,4-tetrahydroquinoline was obtained which could indicate the presence of enamine-imine tautomerism in the reduction course as shown in Fig. 5.

Reduction Mechanism of Isoquinoline (LI) with Sodium Borohydride in Aqueous Solution

The reduction of isoquinoline (LI) with sodium borohydride did not proceed in ethanol, pyridine or diglyme, but surprisingly LI was reduced to 1,2,3,4-tetrahydroisoquinoline

9) It is very difficult to obtain 1,6-dihydro- and 1,2,5,6-tetrahydro-nicotinonitriles, and the corresponding N-methyl derivatives were synthesized and examined.
10) They were synthesized by the procedures reported in Ref. 5*a*).
11) According to 5*a*), 1-methyl-1,4,5,6-tetrahydronicotinonitrile has an absorption maximum at 278 mμ (*ε*: 18300).
12) E.A. Braude, J. Hannah, and R. Linstead, *J. Chem. Soc.*, **1960**, 3249.

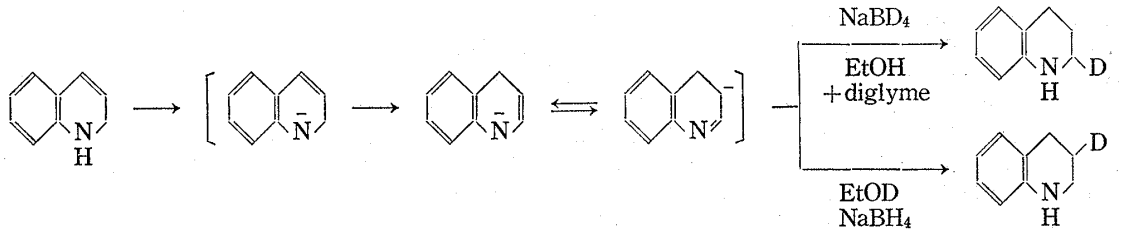


Fig. 5. Reduction Mechanism of 1,2-Dihydroquinoline (X) to 1,2,3,4-Tetrahydroquinoline (XXXI)

(XLVII) in water or diglyme-water as shown in Table V. To investigate the reduction mechanisms, deuterium oxide was used as the solvent and 1,2,3,4-tetrahydroisoquinoline containing 1.5 deuteriums in the 4 position, was obtained, which fact indicates the presence of 1,4-dihydroisoquinoline as an intermediate. So a borohydride ion must attack the 1 position of isoquinoline first, and the 4 position was attacked next as show in Fig. 6.

Table V. Reduction of Isoquinoline (LI) with Sodium Borohydride in Various Solvents

LI XLVII

Solvents	Product, XLVII yields %	Recovery of starting material (LI) %
EtOH	8	70
Pyridine	15	60
Diglyme	—	72
Diglyme+H_2O	70	—
H_2O	71	—

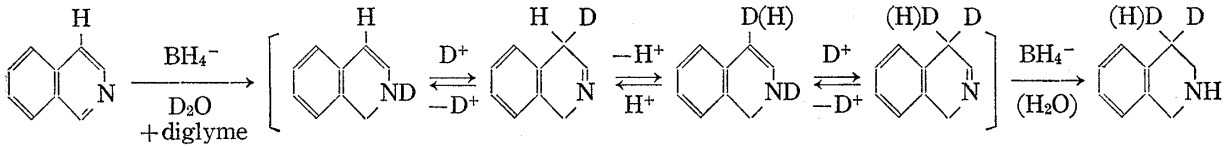


Fig. 6. Reduction Mechanism of Isoquinoline (LI) with Sodium Borohydride in D_2O

It was realized that a pyridine nucleus was easily reduced with sodium borohydride when a proper group was substituted on the pyridine ring. An attempt was made to reduce benzene ring of quinoline of isoquinoline with sodium borohydride, and 5-nitro-, 6-nitro-, 8-nitro- and 6,8-dinitro-quinolines were prepared, and submitted to the reduction with sodium borohydride in ethanol. The reaction was very vigorous even under cooling and the starting material was consumed completely after 10 minutes, but only tarrs were formed.

In the case of 6-quinolinecarbonitrile (XLVIII) and 8-quinolinecarbonitrile (XLIX), only the pyridine ring was reduced with sodium borohydride and corresponding 1,2,3,4-tetrahydro compounds were obtained.

Experimental[13]

Materials——$NaBH_4$ was purchased from Kawaken Fine Chemicals Co., Ltd., and used without further purification. Compounds II, IV, IX, and LI were obtained commercially and purified as usual. Other starting materials were prepared by the methods described in the literatures listed in Table VI and VII. Commercially available ethanol and diglyme were dehydrated with sodium metal and distilled. Pyridine was purified as described in the previous literature.[7]

13) All melting points and boiling points were uncorrected. NMR spectra were taken on Model J.N.M. 3H 60 spectrometer with Me_4Si as an internal standard. IR spectra measurements were performed with a Spectrometer, Model DS-402, Japan Spectroscopic Co., Ltd. The measurements of UV spectra were carried out with a Cary Model II recording spectrophotometer.

General Procedure[14]——A mixture of a starting material (0.01 mole) and $NaBH_4$ in solvents (20—30 ml) was treated under the condition described in Table I—IV. After the reaction completed, solvents were removed *in vacuo* under nitrogen atomosphere. After cooling H_2O was added to the residue, the aqueous layer was extracted with the proper solvents (ether, benzene, $CHCl_3$, or ethyl acetate) which were washed with satd. NaCl and dried over anhyd. Na_2SO_4. The solvent was removed and the residue was purified by column chromatography (SiO_2, $CHCl_3$, for the products (X, XXXI, XXXIX, and XLIX): Al_2O_3, $CHCl_3$, for the compounds (XXXVII, XXXVIII, and XLVII)) or distillation (compounds (XXIV, XXV, XXVI, and XXVII)) or recrystallization (compounds (XXVIII, XXXIV, XXXV, XXXVI, XXXIX, and L)).

Table VI. Physical Constants of the Starting Compounds

Numbers[a]	bp °C/mmHg or mp °C	Literature bp °C/mmHg or mp °C	Numbers[a]	bp °C/mmHg or mp °C	Literature bp °C/mmHg or mp °C
I	40	41[b]	XIV	66—68	65[c]
III	38	38[d]	XV	105—106	107[e]
V	55—60/13	61—63/15[f]	XVI	101.5—103.5	104[g]
VI	107—108	112[h]	XVII	165—169	168—172[i]
VII	67—68	72—73[j]	XVIII	48—49	47—49[k]
X	63—67	62—65[l]	XIX	194 (dec.)[m]	198 (dec.[n])[m]
XI	147/13	158—162/24[o]	XXX	133	133[p]
XII	80/7	102/15[q]	XLVIII	133—134	135[r]
XIII	198	198—199[s]	XLIX	83—84	84[t]

a) The number is corresponding to the number of the compound in this report.
b) O. Schickh, A. Binzund, and A. Schulz, *Chem. Ber.*, **69**, 2605 (1939)
c) K.W. Rosenmund, *Chem. Ber.*, **87**, 1229 (1954)
d) C. Engler, *Chem. Ber.*, **27**, 1787 (1894)
e) H. Gilman and S.M. Spatz, *J. Am. Chem. Soc.*, **63**, 1556 (1941)
f) S.M. McElvain and M.A. Goese, *J. Am. Chem. Soc.*, **65**, 2227 (1943)
g) F.T. Tyson, *J. Am. Chem. Soc.*, **61**, 183 (1939)
h) V. Meyer, *J. Prakt. Chem.*, **78**, 509 (1908)
i) G. Thuillier, B. Marcot, A. Vilar, and P. Rumpf, *Bull. Soc. Chim. France*, **1966**, 1763
j) Nippon Kagakukai, "Zikken Kagaku Koza," Vol. 21 (III), ed. by E. Ochiai, S. Fujise, Maruzen, Tokyo, 1966, p. 280
k) J.J. Padbury and H.G. Lindwall, *J. Am. Chem. Soc.*, **67**, 1268 (1945)
l) R.F. Collins, *J. Chem. Soc.*, **1954**, 3642
m) dec.=decomposition
n) K. Schenker and J. Druey, *Helv. Chim. Acta*, **42**, 1960 (1959)
o) R.R. Renskaw and H.L. Friedman, *J. Am. Chem. Soc.*, **61**, 3321 (1939)
p) A. Kaufmann and A. Albertini, *Chem. Ber.*, **42**, 3776 (1909)
q) A. Roe and G.F. Hawkins, *J. Am. Chem. Soc.*, **71**, 1785 (1945)
r) J. Biedermann, *Chem. Ber.*, **22**, 2762 (1889)
s) W.H. Mills and W.H. Watson, *J. Chem. Soc.*, **97**, 745 (1910)
t) L.F. Fieser and E.B. Hershberg, *J. Am. Chem. Soc.*, **62**, 1640 (1940)

Table VII. Physical Constants of the Starting Compounds

Numbers[a]	bp °C/mmHg or mp °C (literature)	Derivative mp °C	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
VIII	145—146/3.5 (126—128/0.1)[c]	pic.[b] 224—225 [EtOH][d]	$C_{17}H_{15}O_7N_5$	50.87	3.77	17.15	50.98	3.91	17.31
XXI	207 (dec.)[e]		$C_{11}H_9N_2I$	44.61	3.06	9.49	44.83	3.33	9.60
XXII	203—204		$C_{13}H_{14}O_2NI$	45.50	4.11	4.08	45.52	4.23	4.14
XXIII	290 (dec.)[e]		$C_{11}H_9N_2I$	44.61	3.06	9.49	44.90	3.36	9.34

a) The number is corresponding to the number of the compound in this report.
b) pic.=picrate
c) S. Okuda, *Chem. Pharm. Bull.* (Tokyo), **4**, 261 (1956)
d) recrystallization solvent
e) dec.=decomposition

14) Yields and other reaction conditions are listed in Table I—IV. The physical constants and spectral data are listed in Table VIII and IX.

Modified Procedures——a) The Reduction of VII : After the reaction completed, the solvent was removed and the residue was recrystallized from ethanol to give XXIX. The filtrate was removed and the residue was recrystallized from benzene–hexane to give XXX.

b) The Reduction of XI : After the reaction completed, the solvent was removed and H_2O was added to the residue. The insoluble material was gathered by suction and washed with 50% methanol–H_2O. This was recrystallized from hexane to give XXXII.

c) The Reduction of XVI : For XVI it is necessary to break B–N bonding by adding dil. HCl and to make the solution alkaline with 10% NaOH for extraction.

d) The Reduction of Quaternery Salts : After the reaction completed, H_2O was added and it was extracted with $CHCl_4$ which was washed with satd. NaCl and dried over anhyd. Na_2SO_4. After the evaporation of $CHCl_3$ the residue was purified by distillation (compounds (XL and XLI)) or column chromatography (Al_2O_3, $CHCl_3$, for the compounds (XLII, XLIII, and XLVI)). In the case of XXII, the residue was submitted to the NMR measurement to confirm the structures of the compounds (XLIV and XLV).

e) The Reduction of 6-Quinolinecarbonitrile (XLVII) : 6-Quinolinecarbonitrile (XLVII) (770 mg, 0.005 moles) and $NaBH_4$ (570 mg, 0.015 moles) were mixed in ethanol (690 mg, 0.015 moles) and diglyme (20 ml) and it was heated at 100° for 10 hr. After the reaction completed, H_2O (30 ml) was added and it was acidfied with 6NHCl to pH 5 at 0°. H_2O was removed *in vacuo* and the residue was made alkaline (pH 10) by aq. conc. K_2CO_3. It was extracted with $CHCl_3$ which was washed with satd. NaCl and dried over anhyd. Na_2SO_4. After the evaporation of the solvent under N_2 atmosphere, the residue was subjected to column chromatography (SiO_2, $CHCl_3$) to separate an oily product and the starting material (XLVII). The oily product was distilled to give pure 1,2,3,4-tetrahydroquinoline-6-carbonitrile (XLIX) (310 mg, yield 39.2%) bp 105—108° (4 mmHg). UV λ_{max}^{EtOH} mμ: 263, 301. IR ν_{max}^{Cap} cm^{-1} 3410 (NH), 2210 (C≡N), 1608 (benzene ring). NMR (CCl_4) τ: 8.16 (2H, quartet, 3-position), 7.38 (2H, triplet, 4-position), 6.83 (2H, triplet, 2-position), 6.11 (1H, singlet, N–H), 3.03—3.93 (3H, multiplet, benzene ring).

f) The Reduction of 8-Quinolinecarbonitrile (XLVIII) : Under the same procedure described in e), 8-quinolinecarbonitrile (XLVIII) was reduced to 1,2,3,4-tetrahydroquinoline-8-carbonitrile (L) which was recrystallized from benzene–pet. ether to give a pure compound (L) (240 mg, yield. 30.4%) mp 74—75°. UV λ_{max}^{EtOH} mμ (ε): 261 (6400), 348 (4900). IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 2202 (C≡N), 1601 (benzene ring). NMR (CCl_4) τ: 8.11 (2H, quartet, 3-position), 7.28 (2H, triplet, 4-position), 6.60 (2H, triplet, 2-position), 5.02 (1H, singlet, N–H), 2.79—3.78 (3H, multiplet, benzene ring). *Anal.* Calcd. for $C_{10}H_{10}N_2$: C, 75.92; H, 6.37; N, 17.71. Found: C, 75.91; H, 6.26; N, 17.66.

g) The Reduction of 1,2-Dihydroquinoline (X)[15] with $NaBD_4$: 1,2-Dihydroquinoline (X) (655 mg, 0.005 moles), $NaBD_4$ (630 mg, 0.015 moles) and ethanol (920 mg, 0.02 moles) were added to diglyme solution (35 ml) and it was heated at 100—105° for 10 hr. After the reaction completed, H_2O (150 ml) was added to the reaction mixture and it was extracted with $CHCl_3$ which was washed with satd. NaCl and dried over anhyd. Na_2SO_4. After the evaporation of $CHCl_3$ the residue contained the starting material (70%)[16] and 1,2,3,4-tetrahydroquinoline (XXXI) (160 mg, 24%) which was separated by column choromatography (SiO_2, $CHCl_3$). NMR ($CDCl_3$) τ: 8.20 (2H, triplet, 3-position), 7.85 (2H, triplet, 4-position), 6.90 (1H, triplet, 2-position), 6.25 (1H, singlet, N–H), 3.45 (4H, multiplet, benzene ring).

h) The Reduction of 1,2-Dihydroquinoline (X) with $NaBH_4$ in Diglyme-EtOD : The same procedure was taken as described above and 1,2,3,4-tetrahydroquinoline was obtained (24%). NMR ($CDCl_3$) τ: 8.20 (1.2H, multiplet, 3-position), 7.85 (2H, doublet, 4-position), 6.85 (2H, doublet, 2-position), 6.30 (1H, singlet, N–H), 3.45 (4H, multiplet, benzene ring).

The Reduction of Nicotinonitrile (II) with $NaBH_4$ in Pyridine——The mixture of nicotinonitrile (II) (5.2 g, 0.05 moles) and $NaBH_4$ (5.7 g, 0.15 moles) in pyridine (150 ml) was refluxed for 8 hr. The solvent was removed *in vacuo* under N_2 atmosphere. H_2O was added to the residue and it was extracted with $CHCl_3$ which was washed with satd. NaCl and dried over anhyd. Na_2SO_4. The solvent was evaporated under N_2 atmosphere to give the product which was purified by column chromatography (SiO_2, AcOEt) to give 1,4-dihydronicotinonitrile mp 74—75°. yield 52% λ_{max}^{EtOH} mμ (ε) 330 (5600); ν_{max}^{KBr} cm^{-1}: 3380 (NH), 2220 (C≡N), 1690, 1630 (>N–CH=Ċ–CN); NMR ($CDCl_3$): 3.41 (1H, 2-pisition), 4.20 (2H, 6-position and N–H, 2H, was decreased to 1H when N–H was deuterated,)5.40 (1H, 5-position) and 6.90 (2H, 4-position).

The Reduction of Isoquinoline (LI) with $NaBH_4$ in Various Solvents[17]——(i) In Ethanol: Isoquinoline (LI) (1.29 g, 0.01 mole) and $NaBH_4$ (3.8 g, 0.1 mole) were dissolved in ethanol (50 ml) and it was refluxed for 5 hr. After the reaction completed, ethanol was removed and H_2O (10 ml) was added to the residue and it was extracted with $CHCl_3$ which was washed with satd. NaCl and dried over anhyd. Na_2SO_4. After the evaporation of the solvent, the residue was purified by column chromatography (Al_2O_3, $CHCl_3$) to give 1,2,3,4-

15) The starting 1,2-dihydroquinoline was synthesized by the literature procedure (Ref. 12).
16) The yield was determined by gas chromatography (30% SE-30, on Diasolid L, 2.25 m, 1 kg/cm^2, 200°). 1,2-Dihydroquinoline which was identified by NMR was converted to quinoline in a column at high temperature.
17) Yields are listed in Table V.

tetrahydroisoquinoline (XLVII).

(ii) In Pyridine: Isoquinoline (LI) (1.29 g, 0.01 mole) and $NaBH_4$ (1.14 g, 0.03 moles) were dissolved in pyridine (50 ml) and it was refluxed for 5 hr. After the reaction the same procedure was taken as described in (i).

(iii) In Diglyme–H_2O: Isoquinoline (LI) (1.29 g, 0.01 mole) and $NaBH_4$ (3.8 g, 0.1 mole) were dissolved in diglyme (25 ml) and H_2O (1 ml) and it was heated at 90° for 5 hr. After the reaction completed, the same procedure was taken as described in (i) and the product was purified by column chromatography (Al_2O_3, $CHCl_3$) to give 1,2,3,4-tetrahydroquinoline (XLVII) (429 mg, yield 32.3%) and its borane adduct (502 mg, yield 38.5%) which was easily hydrolysed to 1,2,3,4-tetrahydroisoquinoline with hot 10% HCl and ethanol in quantitative yield. Physical constants of the borane adduct, mp 135—137° (EtOH). IR ν_{max}^{KBr} cm^{-1}: 3180 (NH), 2400—2500 (BH). UV λ_{max}^{EtOH} mμ: 262, 272. *Anal.* Calcd. for $C_{19}H_{14}NB$: C, 73.53; H, 9.59; N, 9.53. Found: C, 73.24; H, 9.49; N, 9.69.

(iv) In Diglyme: Isoquinoline (LI) (1.29 g, 0.01 mole) and $NaBH_4$ (3.8 g, 0.1 mole) were dissolved in diglyme (25 ml) and it was heated at 90° for 5 hr. After the reaction the same procedure was taken as described in (i).

(v) In H_2O: Isoquinoline (LI) (1.29 g, 0.01 mole) and $NaBH_4$ (3.8 g, 0.1 mole) were dissolved in H_2O (25 ml) and dioxane (5 ml) and it was heated at 90° for 5 hr. After the reaction it was extracted with $CHCl_3$ which was washed with satd. NaCl and dried over anhyd. Na_2SO_4. After the evaporation of $CHCl_3$, CCl_4 was added to the residual oil to give a crystalline which was identified as 1,2,3,4-tetrahydroisoquinoline borane (yield 71.5%) by the comparison of IR and mp of the authentic sample.[18]

(vi) In Diglyme: The same procedure was taken as described in (iii) of this section and deuterium was incorporated in the 4-position. NMR ($CDCl_3$) τ: 7.22 (0.5 H, singlet, 4-position), 6.93 (2H, singlet, 3-position), 6.06 (2H, singlet, 1-position), 4.75 (1H, singlet, NH), 3.05 (4H, singlet, benzene part).

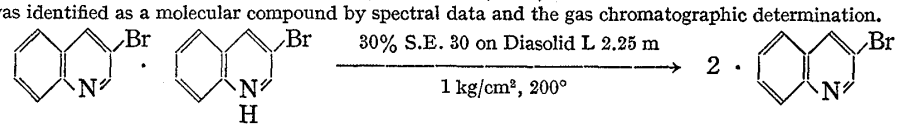
Table VIII. Physical Constants of the Products

Number	bp °C/mmHg or mp °C (literature) [recrystallization solvent]	Derivatives mp °C (literature) [recrystallization solvent]	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
X	63—67[a] (62—65)[b]								
XXIV	95—98/14	pic.[c] 146.5—147.5 [H_2O]	$C_{11}H_{13}O_9N_5$	36.77	3.65	19.49	37.04	3.89	19.60
XXV	145/3, 40—41 [ether–pet. ether]	benzoate 103—104 [EtOH]	$C_6H_8N_2$ $C_{13}H_{12}ON_2$	66.64 73.56	7.46 5.71	25.91 13.20	66.24 73.82	7.45 5.59	25.83 13.43
XXVI	82—83/13	HCl[d] 221—223 [EtOH] (HCl[d] 223)[e]	$C_6H_9N_2Cl$	39.80	5.57	15.47	40.01	5.71	15.67
XXVII	112—114/3 (154—156/20)[f]	pic.[c] 157.5—158 [EtOH]	$C_{12}H_{10}O_8N_4$	42.61	2.98	16.57	42.77	3.25	16.52
XXVIII	215—220 [EtOH] (222)[g]		$C_9H_9N_3$	67.90	5.70	26.40	67.68	5.77	26.44
XXIX	175—178 [EtOH] (185—187)[h]								
XXX	104—105 [benzene–hexane]		$C_{11}H_{15}O_3N$	63.14	7.23	6.69	62.85	7.25	6.92
XXXI		HCl[d] 179.5—180.5[i] [EtOH–ether] (HCl[d] 181—182)[j]							
XXXII	81—82 [hexane]		$C_{18}H_{14}N_2Br_2$[k]	51.70	3.38	6.70	51.23	3.40	6.78
XXXIII[a]									
XXXIV	224 [EtOH]		$C_{10}H_{10}ON_2$	68.95	5.79	16.08	69.10	5.96	15.85
XXXV	142—143 [benzene]		$C_{12}H_{13}O_2N$	70.90	6.45	6.89	70.70	6.35	7.12
XXXVI	130—131.5 [benzene–hexane]	acetate 101—102 [isopro. ether]	$C_{10}H_8N_2$ $C_{12}H_{10}ON_2$	76.90 72.71	5.16 5.09	17.94 14.13	76.97 72.89	5.28 5.10	17.74 14.34
XXXVII	101.5—103.5 [ether–pet. ether]	pic.[c] 166—168 (dec).[l] [EtOH]	$C_{16}H_{11}O_7N_5$	49.87	2.88	18.18	49.70	2.63	18.41
XXXVIII	196—197 [EtOH]		$C_{10}H_{10}ON_2$	68.95	5.79	16.08	68.90	5.70	15.89
XXXIX	80—82 [ether]	pic.[c] 140 [EtOH]	$C_{18}H_{16}O_9N_4$	50.00	3.73	12.96	50.07	3.47	13.15
XL	92—93/12[a] (92—93/11)[m]								

18) This sample was obtained from the experiment (iii).

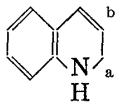
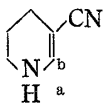
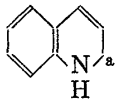
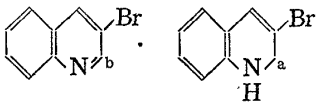
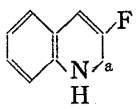
Number	bp °C/mmHg or mp °C (Literature) [recrystallization solvent]	Derivatives mp °C (literature) [recrystallization solvent)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XLI	115/2[a] (90—92/0.08)[m]								
XLII[a]	(52—53/0.08)[j]	pic.[c] 165—165.5 [acetone–EtOH]	$C_{16}H_{14}O_7N_4$	51.34	3.77	14.97	51.30	3.40	14.95
XLIII[a]		1-methyl-3-cyano-carbostyril >230 [EtOH]	$C_{11}H_8ON_2$	71.92	4.38	15.21	72.06	4.55	15.31
XLIV } XLV }[n]		pic.[c] 167—168.5[o] [EtOH]	$C_{19}H_{18}O_9N_4$	51.12	4.06	12.55	51.22	3.80	12.70
XLVI		pic.[c] 203—205 (dec.)[l] [MeOH] 2-methyl-4-cyano-isoscarbstyril 200—201 [EtOH]	$C_{17}H_{13}O_7N_5$	51.13 71.72	3.28 4.38	17.54 15.21	51.43 71.66	3.04 4.47	17.72 15.05
XLVII		pic.[c] 208—210 [EtOH] (pic.[c] 208)[p]							
L	74—75		$C_{10}H_{10}N_2$	75.92	6.37	17.71	75.91	6.26	17.66

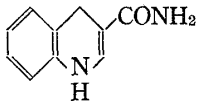
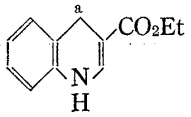
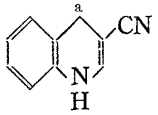
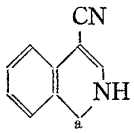
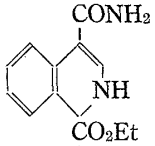
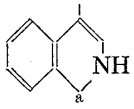
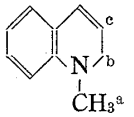
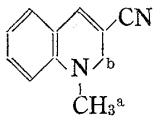
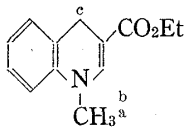
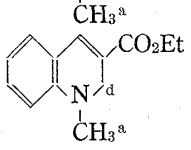
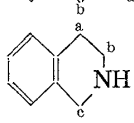
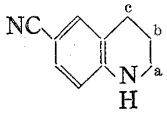
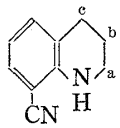
a) identified by the comparison of the spectral data of the authentic sample
b) R.F. Collins, *J. Chem. Soc.*, **1954**, 3642
c) pic.: picrate
d) HCl: HCl salt
e) K. Fromherz and H. Spiegelberg *Helv. Physiol et Pharm. Acta*, **6**, 42 (1948)
f) H.J. den Hertog and W.P. Combe, *Rect. Trav. Chim.*, **70**, 581 (1951)
g) V. Meyer, *J. Prakt. Chem.*, **78**, 509 (1908)
h) "Nippon Kagakukai, Zikken Kagaku Koza," Vol. 21 (III), ed. by E. Ochiai, S Fujise, Maruzen, Tokyo, 1960, p. 280
i) identified by the comparison of the mixed melting point test with the authentic sample
j) F.A. Braude, J. Hannah, and R.P. Linstead, *J. Chem. Soc.*, **1960**, 3249
k) It was identified as a molecular compound by spectral data and the gas chromatographic determination.



1,2-Dihydroquinoline derivatives are easily aromatized by heat when they are submitted to gas chromatography.
l) dec.: decomposition
m) K. Schenker and J. Druey, *Helv. Chim. Acta*, **42**, 1960 (1959)
n) identified by the spectral data (see Table IX)
o) It is impossible to distinguish the picrate of 1,2-dihydro or 1,4-dihydro compound by the spectral data.
p) O. Hibino, K. Kinoshita, S. Hashimoto, and K. Okada, *Kogyo Kagaku Zasshi*, **68**, 1703 (1965)

TABLE IX. Spectral Data of the Products

Number[a]	Compounds	IR ν cm^{-1}	UV λ_{max}^{EtOH} mμ (ε)	NMR τ value
X		KBr: 3375 (NH), 1640 (C=C)	340	CCl_4: a: 5.90(q) b: 4.52(six)
XXV		$CHCl_3$: 3475 (NH), 2180 (C≡N) 1630 (C=C)	265 (14600)	CCl_4: a: 4.23(s) b: 2.96(d)
XXXI		Cap.: 3375 (NH)	299	CCl_4: a: 6.81(t)
XXXII		KBr: 3340 (NH), 1640 (C=C) 1600 (aromatic)	352	CCl_4: a: 5.67(d) b: 1.82(d)
XXXIII			340—350	$CDCl_3$+3-fluoro-quinoline[b] a: 6.00(s)

Number[a)]	Compounds	IR ν cm^{-1}	UV λ_{max}^{EtOH} mμ (ε)	NMR τ value
XXXIV		KBr: 3480 (NH), 1675 (C=O) 1630 (C=C)	337	
XXXV		KBr: 1680—1650 (N–C=C–CO_2Et)	338(13500)	$CDCl_3$: a: 6.25(s)
XXXVI		KBr: 3275 (NH), 2080 (C≡N) 1640 (C=C)	325(11500)	$CDCl_3$: a: 6.28(s)
XXXVII		KBr: 3320 (NH), 2180 (C≡N) 1610 (C=C)	330(5900)	$CDCl_3$: a: 5.40(d)
XXXVIII		KBr: 3370 (NH) 1620—1612 (C=C–$CONH_2$)	272, 329	
XXXIX		KBr: 3280 (NH) 1655 (C=C–CO_2Et)	326	$CDCl_3$: a: 5.60(d)
XLII		Cap.: 1644 (C=C)	345	CCl_4: a: 7.43(s) b: 6.12(q) c: 4.51(six)
XLIII		Cap.: 2180 (C≡N), 1655 (C=C)	295, 410	$CDCl_3$: a: 7.32(s) b: 6.10(d)
XLIV		Cap.: 1720—1690 (C=O) 1640—1645 (C=C)	305, 348	$CDCl_3$: a: 7.23(s) b: 6.84(s) c: 6.26(s)
XLV			422	d: 5.83(s)
XLVI		KBr: 2220 (C≡N), 1630 (C=C)	236, 241, 335	$CDCl_3$: a: 7.10(s) b: 5.55(s)
XLVII		Cap.: 3260 (NH)	265, 272	CCl_4: a: 7.18(t) b: 6.93(m) c: 5.91(s)
XLIX		KBr: 3410 (NH), 2210 (C≡N) 1608 (C=C)	263, 301	CCl_4: a: 6.83(t) b: 8.16(m) c: 7.38(t)
L		KBr: 3400 (NH), 2202 (C≡N) 1601 (C=C)	261(6400) 348(4900)	CCl_4: a: 6.60(t) b: 8.11(m) c: 7.28(t)

a) The number is corresponding to the number of the compound in this report.
b) It was impossible to isolate pure 3-fluoroquinoline and the reaction mixture was submitted to the NMR measurement.