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

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The reaction of 2- or 4-substituted pyridines and quinolines and 1- or 3-substituted isoquinolines with sodium borohydride was examined. The substituent groups which are usually resistant to reduction with sodium borohydride were reducible through the electronic influence of the heteroaromatic ring. The solvent effects on the reduction with sodium borohydride were also examined.

In the previous report,[1] the reaction of pyridine, quinoline and isoquinoline derivatives with sodium borohydride was examined and the reduction of the pyridine nucleus, which has a strong electron withdrawing group on the *meta* position to the ring nitrogen, was observed.

This article reports the reaction of *ortho* or *para* substituted derivatives to the ring nitrogen of pyridine, quinoline and isoquinoline with sodium borohydride.

Table I tabulates the results of the reduction of pyridine derivatives with sodium borohydride in ethanol. Substituent groups, which cannot be reduced with sodium borohydride under the usual reduction,[5] were selected for the investigation. The cyano group cannot be reduced with sodium borohydride except in very special cases;[6] the nitro group can be reduced with sodium borohydride only when the nitrobenzenes have a $\delta+$ substituent on the *para* position of nitro group in the benzene ring.[7] It was reported recently that nitrobenzenes are reducible with sodium borohydride with the use of pyridine as solvent.[8] The ester group is also resistant to reduction but can be reduced in the presence of a large quantity of sodium borohydride.[9]

According to Table I, the cyano and nitro groups (III), (IV), (VII), and (VIII), were reduced with sodium borohydride in ethanol. On the other hand benzonitrile and nitrobenzene examined under the same reduction conditions were recovered unchanged. So it is apparent that the pyridine ring has a strong effect on the reduction of these substituent groups. Because of the electronic effect of the ring nitrogen the carbon atoms at the 2- and 4- positions of the pyridine ring are more electron deficient than the correponding carbon atoms in the benzene ring; consequently an enhancement of the electrophilicity of the substituent group on the

1) Part IX: Y. Kikugawa, M. Kuramoto, I. Saito, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 1914. (1973).
2) A part of this work was published before as a Communication to the Editor. S. Yamada and Y. Kikugawa, *Chem. Ind.* (London), **1967**, 1325; S. Yamada, M. Kuramoto, and Y. Kikugawa, *Tetrahedron Letters*, **1969**, 3101.
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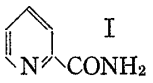
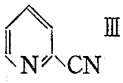
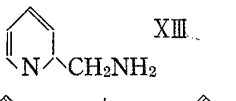
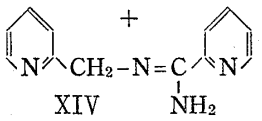
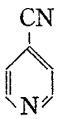
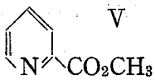
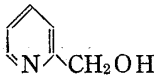
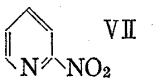
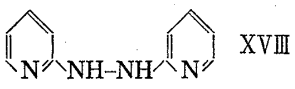
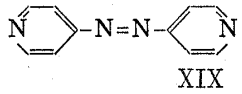
5) E. Schenker, *Angew. Chem.*, **73**, 81 (1961).
6) *a*) J.A. Meschino and C.H. Bond, *J. Org. Chem.*, **28**, 3129 (1963); *b*) S.E. Ellzey, Jr., J.S. Wittman III and W.J. Connick, Jr., *J. Org. Chem.*, **30**, 3946 (1965).
7) H.J. Shine and H.E. Mallory, *J. Org. Chem.*, **27**, 2390 (1962).
8) G. Otani, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 1840 (1968).
9) M.S. Brown and H. Rapoport, *J. Org. Chem.*, **28**, 2361 (1963).

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	5	5	recovery of starting material	85
 II	5	5	recovery of starting material	76
 III	5	4	 XIII	43
			 XIV	40[b]
 IV	5	5	 XV	53
 V	3	4	 XVI	70
 VI	3	4	 XVII	69
 VII	3	1	 XVIII	69
 VIII	3	1	 XIX	54

a) S.M.: starting material
b) The yield was obtained under the condition (molar ratio $NaBH_4$/starting material=5, reflux time 1 hr)

pyridine ring results. The ester group, (V) and (VI), was easily reduced and the amide group, (I) and (II) was not reduced, and the starting materials were recovered.

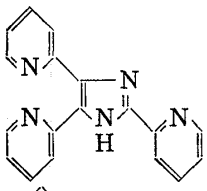
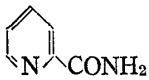
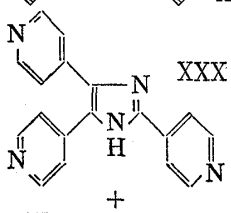
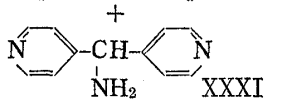
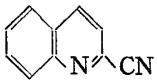
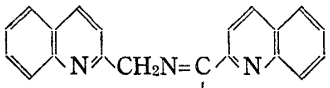
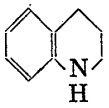
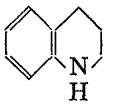
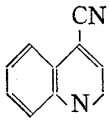
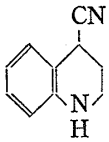
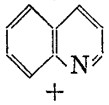
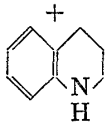
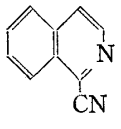
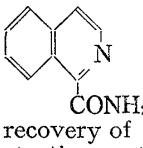
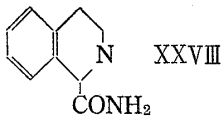
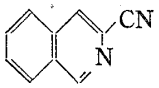
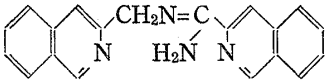
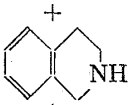
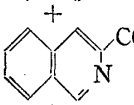
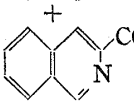
According to our previous investigations of the reducibility with sodium borohydride, the results depend considerably upon the solvent used. Cyano heterocyclic compounds were chosen for this investigation of the solvent effects upon the reduction reaction. Table II shows the results.

The Use of Ethanol as Solvent

It has been reported[10] that catalytic amounts of sodium borohydride can convert the cyano group to the corresponding ethyl imidate in ethanol. For the reduction conditions of the present investigation, excess sodium borohydride (5 molar equivalents) has been employed, thus it was expected that different results from the former[10] might be observed. In the case of III, small amounts of the reaction mixture were taken during the reaction and submitted to gas chromatographic measurements.[11] The small peaks of the starting compound and its corresponding amine were detectable, but the peak of the corresponding imidate

10) H. Watanabe, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **21**, 465 (1973).
11) SE-30 (Diasolid 10%), 3 m, Carrier Gas He, 0.95 kg/cm², 160°.

TABLE II. The Reduction of Cyanoheterocycles with $NaBH_4$ in Various Solvents

Starting materials	In EtOH Molar ratio: $NaBH_4$/S.M.[a] = 5 Reflux time: 5 hr		In pyridine or diglyme Molar ratio: $NaBH_4$/S.M.[a] = 3			In pyridine or diglyme + EtOH[b] or H_2O[b] Molar ratio: $NaBH_4$/S.M. = 3 Reaction temperature: 90—100°		
	Products	Yield (%) (isolated)	Products	Reflux time (hr)	Yield (%) (isolated)	Products	Reaction time (hr)	Yield (%) (isolated)
 III	see Table I		 XXIX	8	20	 I	5	39
 IV	see Table I		 XXX +  XXXI	8	2.1 1.5	 II	5	46
 IX	 XX +  XXI	61 small	 XXI + tar	8	2	XXI	10	39
 X	 XXII	48	XXII +  XXVII +  XXI	10	15 25 6	XXII + XXVII + XXI	5	52 2 4.5
 XI	 XXIII recovery of starting material XI	6 49	 XXVIII + XXIII	5	24 12	XXVIII + XXIII	10	34 16
 XII	 XXIV +  XXV +  XXVI +  XXXII	17 22 18 10	XXVI	5	24	XXV	10	34

a) S.M.: starting material
b) 3—4 molar equivalents of EtOH or H_2O toward starting material were added.

could not be observed. On the other hand the same sample was mixed with water and it was extracted with ether. The ether layer was submitted to gas chromatographic measurements under the same conditions and at this time the peak of the corresponding imidate was outstanding. So it can be assumed that the intermediate, before water treatment, might be the unvolatile borane adduct which is shown in Fig. 1, and the reaction of this intermediate with the reduced amine might form amidine. Reduction of III with sodium borohydride in ethanol gave XIII (43% yield) and XIV (40% yield).

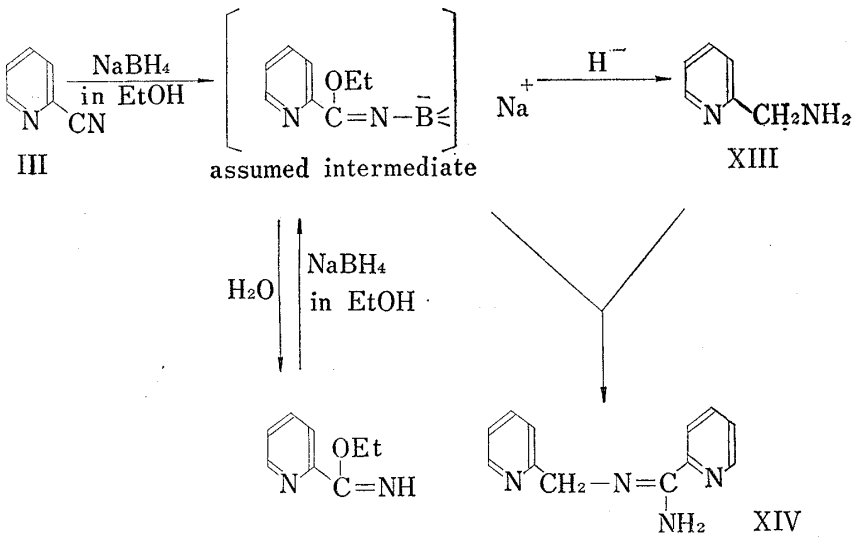


Fig. 1. Assumed Mechanism

When the ethyl imidate which was prepared by another route was reduced with sodium borohydride under the same reaction conditions as for the nitrile (III), same products (the amine (XIII) 31% and the amidine (XIV) 20%) were obtained, so the reaction pathway which is described in Fig. 1 can be assumed. When the solvent was changed from ethanol to pyridine or to pyridine containing a small amount of ethanol (4 molar equivalents to the starting material), the corresponding imidate was not observed[12] and the products were also different from those observed when ethanol was used as solvent. The results will be described in the following part.

The reduction of IV with sodium borohydride in ethanol only gave the reduced amine (XV) and amidine type compound was not detected. However, 2-quinolinecarbonitrile (IX), under the similar conditions, gave mainly the amidine type compound (XX).

According to our findings,[10] 4-quinolinecarbonitrile (X) and 1-isoquinolinecarbonitrile (XI) could not be converted to the corresponding imidate with sodium borohydride in ethanol, so in these cases the corresponding amines and amidines were not obtained. Table II shows that 4-quinolinecarbonitrile (X) was reduced to the tetrahydro compound (XXII) without the reduction of the cyano group. Since the cyano group cannot be converted to the imidate, it remained and the quinoline ring was attacked by a hydride ion to form the tetrahydro compound (XXII). For the determination of the reduction mechanism, EtOD was used to check the position in which deuterium was incorporated during the reaction.

According to the nuclear magnetic resonance (NMR) of the product, deuterium was incorporated in the 4-position and no other. So it was concluded that a hydride ion attacked

12) The imidate could not be detected at all by NMR and gas chromatography (SE-30, 15% Diasolid L, 3 m, He gas 1.0 kg/cm^2, 160°, the retention time of the authetic imidate (III) is 4.4 min).

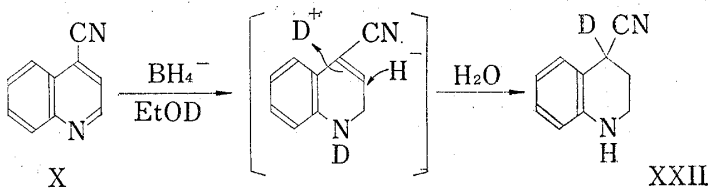


Fig. 2. Reduction Mechanism

the 2-position of the quinoline ring first and the 3-position next[13] under the influence of the cyano group.

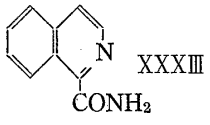
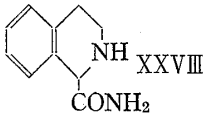
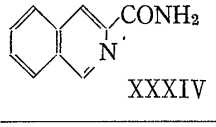
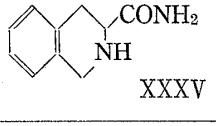
In the case of isoquinolinecarbonitriles, (XI) and (XII), the former resulted in the recovery of starting material and the latter gave various kinds of products under low yields. However, it is worth noting that the decyanised product (XXV) was obtained among the products.

In the case of the isoquinolinecarboxamides (XXXIII) and (XXXIV) (Table III), the starting materials were recovered unchanged under the same reduction conditions but the corresponding esters (XXXII) and (XXXVI) were reduced to the isoquinolinemethanols (XXXVII) and (XXXIX) and the 1,2,3,4-tetrahydroisoquinolinemethanols (XXXVIII) and (XL) (Table IV). 1-Isoquinolinemethanol (XXXVII) was resistant to the further reduction of the nucleus with sodium borohydride, accordingly in the formation of the tetrahydro compounds (XXXVIII) and (XL), the isoquinoline ring was reduced first through the influence of the electron withdrawing ester group forming the α-amino ester which was reduced to the alcohol with ease as anticipated from the literature.[14] On attempt to carry out the nuclear reduction of 1-methyl- or 1-benzyl-isoquinoline under the same reaction conditions was unsuccessful. This results supports the above explanation.

The Use of Pyridine or Diglyme as Solvent

The reaction in these solvents was not as simple as in ethanol. Usually several products, which were very difficult to purify, were formed. 2-Pyridinecarbonitrile (III) was not reduced to the corresponding amine instead surprisingly 2,4,5-tris(2-pyridyl)imidazole (XXIX) which may have been formed by the reductive condensation of 3 moles of the starting compounds,

Table III. The Reduction of Isoquinolinecarboxamides with $NaBH_4$

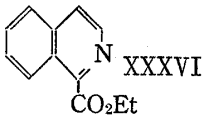
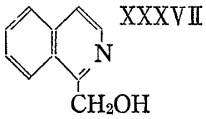
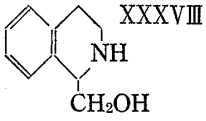
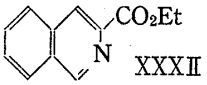
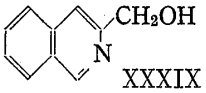
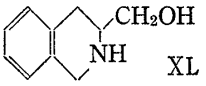
Starting materials	In EtOH Molar ratio: $NaBH_4$/S.M.[a] = 5 Reflux time: 5 hr		In pyridine Molar ratio: $NaBH_4$/S.M. = 3 Reflux time: 5 hr	
	Product	Yield % (isolated)	Products	Yield % (isolated)
 XXXIII	recovery of starting material	93	 XXVIII	33
 XXXIV	recovery of starting material	92	 XXXV	9

a) S.M.: starting material

13) In the case of quinoline itself, 1,2-dihydroquinoline, which was formed by the first attack of a hydride ion, is converted to 1,4-dihydroquinoline by the migration of the double bond, and then is reduced to the tetrahydro compound. See the previous report.[1]

14) H. Seki, K. Koga, H. Matsuo, S. Ohki, I. Matsuo, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **13**, 995 (1965).

Table IV. The Reduction of Ethyl Isoquinolinecarboxylate with $NaBH_4$ in EtOH

Starting materials	Molar ratio $NaBH_4$/S.M.[a]	Reflux time	Products	Yield (isolated)
 XXXVI	3	5	 XXXVII +  XXXVIII	50 + 47
 XXXII	3	5	 XXXIX +  XL	49 + 16

a) S.M.: starting material

was obtained in 20 per cent yield.[2] It was impossible to elucidate the structures of other viscous products because of the difficulty of their purification. The structure of the imidazole (XXIX) was supported by infrared (IR), ultraviolet (UV), mass spectra and elemental analysis. The imidazole (XXIX) was chemically oxidized by cromic acid[15] to form α-picolinamide in low yield.

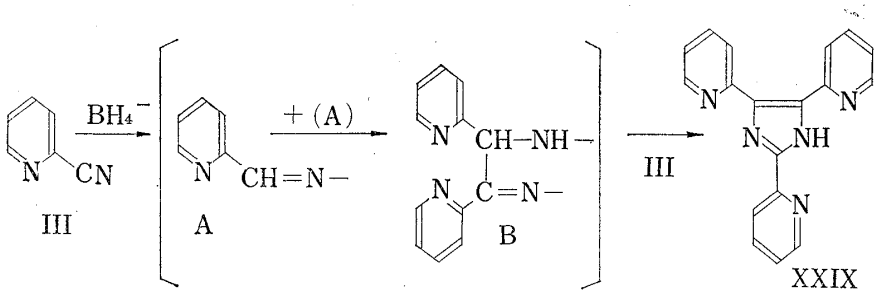


Fig. 3. Assumed Mechanism

The assumed mechanism for the formation of the imidazole derivative is described in Fig. 3. The aldimine (A), which was formed from the nitrile by the attack of a hydride ion, was condensed to compound (B) similarly as for a benzoin condensation and the imidazole may have been formed from (B) and the starting compound (III).

In the case of 4-pyridinecarbonitrile (IV) the corresponding amine was not obtained but the imidazole derivative (XXX) was isolated in 2.1 per sent yield and 1,1-bis(4-pyridyl)methylamine (XXXI) in 1.5 per cent yield from the tarry mixture. The formation mechanism of XXXI is not clear at present. In the cases of 2- or 4-quinolinecarbonitrile (IX or X) and of 1- or 3-isoquinolinecarbonitrile (XI or XII), the formation of imidazole derivatives was expected but in most of these cases a hydride ion attacked the ring in stead of the cyano group to give the tetrahydro compounds in low yield.

15) F.R. Japp, *Ber.*, **15**, 2410 (1882).

4-Quinolinecarbonitrile (X) was reduced to 1,2,3,4-tetrahydroquinoline-4-carbonitrile (XXII), quinoline (XXVII) and 1,2,3,4-tetrahydroquinoline (XXI) which were identified by gas chromatography. The reduction mechanism is obscure at present.

1-Isoquinolinecarbonitrile (XI) was reduced to 1,2,3,4-tetrahydroquinoline-1-carboxamide (XXVIII) without the recovery of any starting nitrile. In this instance the nitrile might have been converted during the reaction to an active group (ex. ketenimine) labile to hydrolysis since generally nitriles cannot be hydrolysed by water after the sodium borohydride reaction.

The Use of Pyridine or Diglyme Plus Small Amounts[16] of Ethanol or Water as Solvent

In aprotic solvents like pyridine or diglyme the reduction was not as smooth as in ethanol, therefore small amounts of protic solvents (ethanol or water) were added to the solvent as proton donnors to improve the yield[17] of the reaction products.

2- or 4-Pyridinecarbonitrile (III) or (IV) was not reduced to the amine but the corresponding amide was isolated probably because of activation of nitrile for hydrolysis.

In the cases of 2- or 4-quinolinecarbonitrile (IX or X) and 1- or 3-isoquinolinecarbonitrile (XI or XII), the yields of the products were improved by the presence of water or alcohol (See Table II). 2-Quinolinecarbonitrile (IX) and 3-isoquinolinecarbonitrile (XII) were reduced to the tetrahydro compounds and decyanated at the same time. The cyano group was not converted to the imidate because only small amounts of ethanol were employed under these reaction conditions, thus a hydride ion attacked the ring forming the tetrahydro compounds (α-amino nitriles).

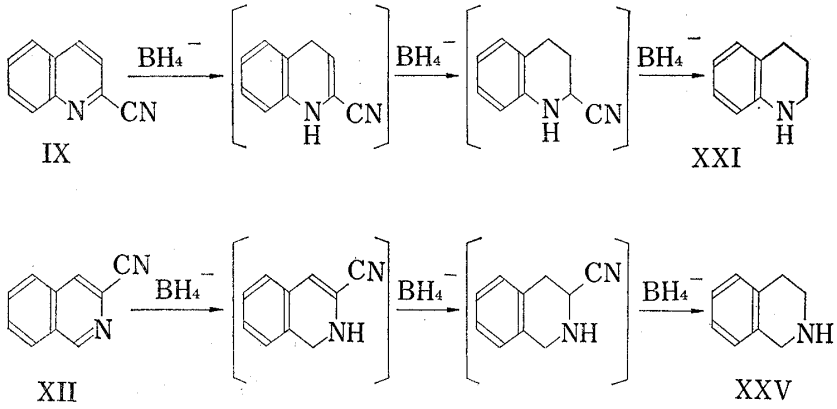


Fig. 4. Assumed Reduction Mechanism

Recently it has been reported[18] that α-amino nitriles are decyanated with sodium borohydride in good yield, consequently the final products in the examples above were tetrahydroquinoline (XXI) and -isoquinoline (XXV) as listed in Table II. The reaction mechanism is postulated in Fig. 4.

Experimental[19]

Materials——$NaBH_4$ was purchased from Kawaken Fine Chemicals Co., Ltd. and used without further purification. Methyl Isonicotinate (VI) was obtained commercially and purified as usual. Other starting

16) 3—4 molar equivalents of ethanol or water based on the starting material were added to the solvent.
17) Y. Kikugawa, S. Ikegami, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **17**, 98 (1969).
18) S. Yamada and H. Akimoto, *Tetrahedron Letters*, **1969**, 3105.
19) All melting points and boiling points were uncorrected. NMR Spectra were taken on Model J.N.M. 3H 60 spectrometer with Me_4Si as the internal standard. IR spectra measurements were performed with a Spectrometer, Model DS-402, Japan Spectroscopic Co., Ltd. The measurement of UV spectra was carried out with a Cary Model 11 recording spectrophotometer.

materials were prepared by the method described in literatures listed in Table V. Commercially available ethanol and diglyme were dehydrated with sodium metal and distilled. Pyridine was purified as described in the literature.[17]

General Procedure——The mixture of starting material and $NaBH_4$ in the solvent was treated under the conditions listed in Table I—IV. After the reaction, the solvents were removed *in vacuo* under the

Table V. Physical Constants of the Starting Compounds

Starting compounds	bp °C/mmHg or mp °C	Literature bp°C/mmHg or mp °C	Starting compounds	bp °C/mmHg or mp °C	Literature bp °C/mmHg or mp °C
I	105.5—106.5	107[a]	XII	123.5—124.5	124—125[j]
II	117 —120	117—120[b]	XXXII	45 — 45.5	40— 46[k]
III	26.5— 28	29[c]	XXXIII	166 —168	168—170[l]
IV	77 — 78.5	79[d]	XXIV	204.5—205.5	206[m]
V	95 — 96/5	232/760[a]	XXXVI	148 —150/2.5	197—199/20[n]
VII	67 — 68	70[e]	XLI	146/22	picrate[o]
VIII	47.5	50[f]		picrate mp 238	mp 225—226
IX	94 — 95	94[g]		sulfate	sulfate[p]
X	99 —101	95[h]		mp 248—250	mp 248—250
XI	87 — 88.5	87— 88[i]	XLII	170/2	164—166/0.1[q]

a) O. Engler, *Chem. Ber.*, **27**, 1785 (1890)
b) R. Camps *Arch. Pharm.*, **240**, 361 (1902)
c) R. Camps, *Arch. Pharm.*, **240**, 367 (1902)
d) R. Camps, *Arch. Pharm.*, **240**, 368 (1902)
e) A. Kirpal and W. Böhm, *Chem. Ber.*, **64**, 767 (1931)
f) E. Ochiai, *J. Org. Chem.*, **18**, 534 (1952)
g) M. Henze, *Chem. Ber.*, **69**, 1566 (1936)
h) A. Kaufman and R. Widmer, *Chem. Ber.*, **44**, 2058 (1911)
i) J.M. Wefer, A. Catala, and E.D. Popp, *Chem. Ind.*, **1965**, 140
j) G.A. Swan, *J. Chem. Soc.*, **1958**, 2038
k) G.A. Swan, *J. Chem. Soc.*, **1950**, 1536
l) J.M. Wefer, A. Catala, and F.D. Popp, *J. Org. Chem.*, **30**, 3075 (1965)
m) F.H. Case, *J. Org. Chem.*, **12**, 471 (1952)
n) J.J. Padbury and H.G. Lindwall, *J. Am. Chem. Soc.*, **67**, 1268 (1945)
o) E. Späth, F. Berger, and W. Kuntara, *Chem. Ber.*, **63**, 134 (1930)
p) A. Galat, *J. Am. Chem. Soc.*, **75**, 1738 (1953)
q) S. Sugasawa and R. Tachikawa, *Tetrahedron*, **4**, 205 (1958)

Table VI

The Use of Ethanol as Solvent

The method of the purification of the product		The starting compound
Recrystallization from a proper solvent listed in Table VI		I, II, VII, VIII, IX, XXXIII and XXXIV
Column Chromatography	SiO_2, $CHCl_3$	XXXII, XXXVI, XLI and XLII
	Al_2O_3, $CHCl_3$	XI and XII
Distillation		III, IV, V, VI and X

The Use of Pyridine or Diglyme as Solvent

The method of the purification of the product		The starting compound
Column Chromatography	SiO_2, $CHCl_3$	III, IV, IX, X, XXXIII and XXXIV
	Al_2O_3, $CHCl_3$	XI and XII

The Use of Pyridine or Diglyme Plus Small Amounts of Ethanol or Water

The method of the purification of the product		The starting compound
Column Chromatography	SiO_2, $CHCl_3$	III, IV and XI
	Al_2O_3, $CHCl_3$	IX and XII[a]

a) In these cases it is necessary to break B-N bonding by the addition of dil. HCl and next to make the solution alkaline with 10% NaOH. The aqueous layer was extracted with $CHCl_3$ which was washed with H_2O and dried over anhyd. Na_2SO_4. After the evaporation of $CHCl_3$, the residue was purified by the column chromatography.

nitrogen atmosphere. After cooling, water was added to the residue. The aqueous layer was extracted with a proper solvent (chloroform, benzene, ether or ethyl acetate), which was washed with H_2O and dried over anhyd. Na_2SO_4. The solvent was removed and the residue was purified as follows.

The physical constants of the products were listed in Table VI.

The Formation of Ethyl 2-Pyridylimidate——2-Pyridinecarbonitrile (III) (6 g, 0.058 moles) and $NaBH_4$ (2.9 g, 0.076 moles) were dissolved in ethanol (50 ml) and it was refluxed for 30 min. After the reaction completed, ethanol was removed under the N_2 atmosphere and water was added to the residue. The aqueous layer was extracted with ether which was washed with satd. NaCl and dried over anhyd. Na_2SO_4. After the evaporation of ether, the residual oil was distilled to give ethyl 2-pyridylimidate. 3.4 g, yield 40%, bp_{16} 98—100°, IR γ_{max}^{cap} cm^{-1} 3320 (NH), 1660 (C=N), NMR ($CDCl_3$) τ: 5.55 (2H, quartet), 8.55 (3H, triplet). The spectra of this compound was superimposable with the authentic imidate (bp_{17} 105—107°) which was prepared from HCl–EtOH method.

The Reduction of Ethyl 2-Pyridylimidate with $NaBH_4$——Ethyl 2-pyridylimidate (1.5 g, 0.01 mole) and $NaBH_4$ (1.9 g, 0.05 moles) were dissolved in ethanol (30 ml) and it was refluxed for 4 hours. After the reaction completed, ethanol was removed under the N_2 atmosphere and to the residue water was added to give 2 layers (the lower was the decomposition product of $NaBH_4$). The upper layer was extracted with ether which was washed with satd. NaCl and dried over anhyd. Na_2SO_4. After the evaporation of the solvent the crystalline was out. It was filtered and washed with cold benzene to give the amidine (XIV). 230 mg yield 20%, 126—127° (benzene–hexane). The residual oil was distilled under the N_2 atmosphere to give 2-aminomethylpyridine (XIII). 330 mg yield 31%, bp_{17} 85°. The spectral data of these compounds were the same to those of the authentic compounds (XIII) and (XIV) listed in Table I.

The Oxidation of 2,4,5-Tris(2-pyridyl)imidazole (XXIX) by Chromic Acid——CrO_3 (2 g, 2×10^{-2}moles) dissolved in CH_3COOH (2 ml) was added dropwise to the CH_3COOH (10 ml) containing the imidazole (XXIX) (1 g, 3.4×10^{-3}moles) under ice cooling for 10 min. The mixture was kept at 60—70° for 24 hours and water (30 ml) was added to the reaction mixture. The solution was made alkaline by conc. Na_2CO_3 and it was extracted with ethyl acetate which was washed with satd. NaCl and dried over Na_2SO_4. After the evaporation of the solvent the residue was purified by the column chromatography (SiO_2) to give α-picolinamide 35 mg, yield 8.4%, mp 104—106°. The starting material was recovered in 17% (170 mg) yield.

The Reduction of 1-Isoquinolinemethanol (XXXVII) with $NaBH_4$——The compound (XXXVII) (479 mg, 0.003 moles) and $NaBH_4$ (342 mg, 0.009 moles) was dissolved in ethanol (15 ml) and it was refulxed for 6 hours. From the thin layer chromatography of the reaction mixture, it was realized that the starting material remained. So $NaBH_4$ (228 mg) was added to the reaction mixture and it was refluxed for 4 hours. After the reaction completed, water 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 the solvent the residual oil was purified by the column chromatography to yield 1,2,3,4-tetrahydro-1-isoquinolinemethanol (XXXVIII) 271 mg, yield 55%, and the starting material 144 mg. Yield 30%. These compounds were identified by the comparison of the IR of the authentic compounds.

Table VI. Physical Constants of the Products

Product numbers	bp °C/mmHg or mp °C (literature) [recrystallization solvent]	Derivatives mp °C (literature) [recrystallization solvent]	Formula	Analysis (%) Calcd. (Found) C	H	N	Spectral data
XIII	84—85/15 (78—80/12)[a]	2HCl[b] 216—220 [MeOH] (209—212)[a]	$C_6H_{10}N_2Cl_2$	39.80 (40.07)	5.57 (5.68)	15.47 (15.23)	IR $\nu_{max}^{cap.}$ cm^{-1}: 3400—3300 (NH_2), 1600 (aromatic); NMR τ(CCl_4): 7.91 (s, NH_2), 6.21 (s, $-CH_2-$)
XIV	127—127.5 [benzene–hexane]		$C_{12}H_{12}N_4$	67.90 (67.79)	5.70 (5.64)	26.40 (26.32)	IR ν_{max}^{KBr} cm^{-1}: 3480 (NH_2), 1670 (C=N); NMR τ (CCl_4): 5.33 (s, CH_2), 3.62 (s, NH_2); Mass. Calcd. M.W. 212, Found M.W. 216 (bromocamphor)
XV	87—90/6 (120—125/12)[c]	pic.[d] 179—180 [EtOH–acetone] (179—180)[c]	$C_{12}H_{11}O_7N_5$	42.73 (42.87)	3.29 (3.37)	20.77 (20.58)	
XVI	113/20 (135—140/30)[c]	pic.[d] 158—158.5 [EtOH] (157—158)[c]	$C_{12}H_{10}O_8N_4$	42.61 (42.48)	2.98 (3.13)	16.57 (16.59)	

Product numbers	bp C°/mmHg or mp °C (literature) [recrystallization solvent]	Derivatives mp °C (literature) [recrystallization solvent]	Formula	Analysis (%) Calcd. (Found) C	H	N	Spectral data
XVII	150/16 (152—154/16)[e]	pic.[d] 159—160 [EtOH] (162)[e]	$C_{12}H_{10}O_8N_4$	42.61 (42.44)	2.98 (3.10)	16.57 (16.84)	
XVIII	167—168 (dec.)[f] [EtOH–H_2O] (168)[g]		$C_{10}H_{10}N_4$	64.50 (64.67)	5.41 (5.36)	30.09 (29.90)	IR ν_{max}^{KBr} cm^{-1}: 3250 (NH)
XIX	106—107.5 [EtOH–H_2O] (107.5—108)[h]		$C_{10}H_8N_4$	65.20 (65.00)	4.38 (4.32)	30.42 (30.12)	
XX	146—148 (dec.) [benzene–hexane]		$C_{20}H_{16}N_4$	76.90 (76.96)	5.16 (5.42)	17.94 (17.66)	IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 1655 (C=N)
		pic.[d] 201—202 (dec.)[f] [EtOH–acetone]	$C_{26}H_{19}O_7N_7$	57.67 (57.67)	3.52 (3.46)	18.11 (18.28)	
	N-(2-quinolylmethyl)-2-quinolinecarboxamide 106—106.5 [iso-PrOH]		$C_{20}H_{15}ON_3$	76.60 (76.38)	4.83 (4.95)	13.41 (13.97)	IR ν_{max}^{KBr} cm^{-1}: 3370 (NH), 1660 (C=O) Mass Calcd. M.W. 313 Found M.W. 320 (bromocamphor)
XXI[i,j]	HCl[k] 179.5—180.5[l] [EtOH–ether] (181—180)[f]						
XXII	155/6						IR $\nu_{max}^{cap.}$ cm^{-1}: 3400 (NH), 2225 (C≡N) NMR τ (CCl_4): 2.88—3.80 (m, 4H, aromatic)
		benzoate 117.5—118 [iso Pro ether–AcOEt]	$C_{17}H_{14}ON_2$	77.84 (77.83)	5.38 (5.33)	10.68 (10.95)	6.06 (s, 1H, NH) 6.25 (t, 0.3H, γ-position) 6.83 (m, 2H, α-position) 8.01 (m, 2H, β-position) UV λ_{max}^{EtOH} mμ: 242, 254, 307
XXIII	164—165.5[l] [benzene] (168—170)[m]						
XXIV		pic.[d] 204 (dec.)[f]	$C_{26}H_{19}O_7N_7$	57.67 (57.96)	3.52 (3.65)	18.11 (17.24)	IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (NH) 1600 (C=N)
XXV[i]	pic.[d] 208—210[l] [EtOH] (208)[n]						
XXVI[i]	204.5—205.5 [EtOH] (206)[o]						
XXVII[p]							
XXVIII	178—180 [AcOEt]		$C_{10}H_{12}ON_2$	68.15 (67.80)	6.80 (6.90)	15.90 (16.00)	IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3520, 3380 (NH), 1685 (C=O) NMR τ ($CDCl_3$): 5.40 (s, 1H one position)
XXIX	113—114 [benzene–petr. ether]		$C_{18}H_{13}N_5$	72.22 (72.01)	4.38 (4.67)	23.40 (23.23)	IR ν_{max}^{KBr} cm^{-1}: 3430 (NH), 1587 (aromatic) UV λ_{max}^{EtOH} mμ(ε): 320 (51800) Mass. Calcd. M.W. 299 Found *m/e* 299 (M$^+$)
XXX	>300 [dioxane–MeOH]		$C_{18}H_{13}N_5$	72.22 (72.09)	4.38 (4.60)	23.40 (23.46)	IR ν_{max}^{KBr} cm^{-1}: 3440 (NH), 1605 (aromatic) UV λ_{max}^{EtOH} mμ(ε): 315 (51800) Mass. Calcd. M.W. 299 Found *m/e* 299 (M$^+$)

Product numbers	bp °C/mmHg or mp °C (literature) [recrystallization solvent]	Derivatives mp °C (literature) [recrystallization solvent]	Formula	Analysis (%) Calcd. (Found) C	H	N	Spectral data
XXXI	92— 93 [benzene–peter. ether]		$C_{11}H_{11}N_3$	71.33 (71.72)	5.99 (6.13)	22.67 (22.99)	IR ν_{max}^{EtOH} cm^{-1}: 3380 (NH_2), 1595 (aromatic) UV λ_{max}^{EtOH} $m\mu(\varepsilon)$: 265(2900), 278(2240) Mass. Calcd. M.W. 185 Found: *m/e* 185 (M^+) NMR τ ($CDCl_3$) 1.41 (q, 4H, α-position) 2.65 (q, 4H, β-position) 4.80 (s, 1H, –CH–) 7.97 (s, 2H, NH_2)
XXXII	43— 44[b] [EtOH] (45—45.5)[q]						
XXXVII	71— 72 [benzene–hexane] (65)[r]	phenylurethane 153—155 [MeOH–ether-hexane]	$C_{17}H_{14}O_2N_2$	73.36 (73.39)	5.07 (5.19)	10.07 (10.25)	
XXXVIII		HCl[k] 198—200 [EtOH]	$C_{10}H_{14}ONCl$	60.15 (59.57)	7.07 (7.02)	7.02 (7.15)	
XXXIX	75 [benzene–peter ether] (81)[s]						
XL		HCl[k] 186—188 [EtOH–ether] (185—186)[t]					

a) R. Graf, *J. Prakt. Chem.*, **140**, 39 (1934)
b) 2HCl=dihydrochloride
c) B. Prijs, A.H. Lutz, and H. Erlenmeyer, *Helv. Chim. Acta*, **31**, 571 (1948)
d) pic.=picrate
e) M. Protiva, *Chem. Listy.*, **45**, 20 (1951)
f) dec.=decomposition
g) H. Beyer, H.J. Hasse, and W. Widgrude, *Chem. Ber.*, **91**, 256 (1956)
h) H.J. den Hertog and W.P. Combe, *Rec. Trav. Chim.*, **70**, 581 (1951)
i) identified by the comparison of the spectral data of the authentic sample
j) E.A. Braude, J. Hannah, and R.P. Linstead, *J. Chem. Soc.*, **1960**, 3249
k) HCl=hydrochloride
l) identified by the comparison of the mixed melting point test with the authentic sample
m) J.M. Wefer, A. Catala, and F.D. Popp, *J. Org. Chem.*, **30**, 3075 (1965)
n) O. Hibino, K. Kinoshita, S. Hashimoto, and K. Okada, *Kogyokagaku Zasshi*, **68**, 1703 (1965)
o) F.H. Case, *J. Org. Chem.*, **17**, 471 (1952)
p) identified by the comparison of the gas chromatograms with the authentic sample
q) G.A. Swan, *J. Chem. Soc.*, **1950**, 1536
r) B.R. Brown, D.L. Hammick, and B.H. Thewlis, *J. Chem. Soc.*, **1951**, 1145
s) H. Erlenmeyer, H. Baumann, and E. Sorkin, *Helv. Chim. Acta*, **31**, 1978 (1948)
t) R.T. Papala, E.R. Lavagnino, E.R. Shepard, and E. Frarkas, *J. Am. Chem. Soc.*, **79**, 3770 (1957)