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Chemistry of Diborane and Sodium Borohydride. VIII.[1] Imidate Formation from Nitriles with Sodium Borohydride

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The reaction of heteroaromatic nitriles with trace of sodium borohydride in alcohol was examined. Cyano group substituted at α-position of heteroatoms was easily converted to the corresponding imidate. It was also possible to convert selectively one cyano group to the ester group without any change of the other cyano groups.

The cyano group is generally not reduceable with sodium borohydride under the usual reduction conditions, but some nitriles (2- or 4-pyridinecarbonitrile, *etc.*) are found to be reduced to amines with sodium borohydride in ethanol.[3]

During the investigation of the reduction mechanisms, ethyl imidates were obtained in some cases when the reaction was quenched by the addition of water at the early stage of the reaction. Not only large amounts of sodium borohydride but also catalytic amounts were effective in the imidate formation. Various kinds of heteroaromatic nitriles were submitted to the same reaction conditions to find the specific role of sodium borohydride in this reaction, and it was found that the cyano group substituted at the α-position to a heteroatom is easily converted to an imidate.

The Formation of Ethyl Imidates from Nitriles

From Table I it is recognized that a cyano group substituted at the α-position to the ring-nitrogen or-oxygen atom is converted to the corresponding imidate except for the cyano group of 1-isoquinolinecarbonitrile.

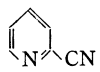
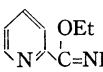
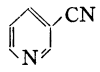
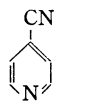
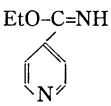
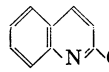
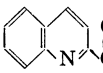
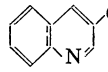
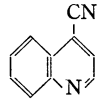
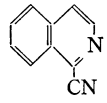
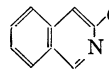
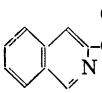
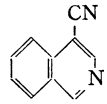
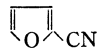
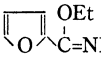
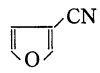
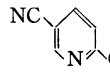
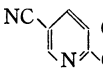
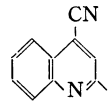
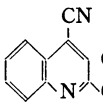
The usual method of forming imidates from nitriles is to introduce dry hydrogen chloride gas into the alcohol-nitrile mixture.[4] On the other hand it is not so common to synthesize imidates in alkaline medium, Nef[5] having reported the formation of an imidate with potassium cyanide and Schaefer, *et al.*[6] reporting on the equilibriums between nitriles and their

1) Part VII: I. Saito, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.* (Tokyo), **18**, 1731 (1970).
2) Location: *Hongo, Bunkyo-ku, Tokyo*; *a*) To whom inquiries should be addressed.
3) A part of this work was presented at the Meeting (Chemistry of Heterocyclic Compounds) of the Society of Synthetic Organic Chemistry, Japan, Tokyo, November 27, 1967. S. Yamada and Y. Kikugawa, *Chem. Ind.* (London), **1967**, 1325.
4) A. Pinner, Die Imidoäther und iher Derivate, Robert Oppenheim (Gustav Schmidt), Berlin, Germany, 1892.
5) J.U. Nef, *Ann.*, **287**, 265 (1895).
6) F.C. Schaefer and G.A. Peters, *J. Org. Chem.*, **26**, 412 (1961).

corresponding imidates in the presence of sodium alcoholate. In the latter case electrostatically activated nitriles were converted to the corresponding imidates with little positional selectivity as compared to the reaction under our conditions. For example, according to them[6] both 2- and 3-pyridinecarbonitriles were converted to the imidates in good yields, but under our conditions only 2-pyridinecarbonitrile (I) was converted to the imidate (II)

Table I. The Formation of Ethyl Imidates from Nitriles with $NaBH_4$

$$ArCN \xrightarrow[\text{the starting material in EtOH(10ml)}]{NaBH_4\ 1/16\ \text{molar equivalent to}} Ar\overset{\displaystyle OEt}{\underset{\displaystyle |}{C}}{=}NH$$

Number[a]	Starting compounds		m mole	Reflux time (hr)	Products (yield %)	
1		I	4.8	2		II (49), I (10)
2		III	4.8	6	III (74)	
3		IV	4.8	6		V (12), IV (67)
4		VI	3.2	2		VII (64)
5		VIII	3.2	2	VIII (70)	
6		IX	3.2	2	IX (90)	
7		X	3.2	6	X (91)	
8		XI	3.2	6		XII (62), XI (21)
9		XIII	3.2	6	XIII (92)	
10		XIV	5.4	6		XV (62), XIV (36)
11		XVI	5.4	6	XVI (95)	
12		XVII	3.8	2		XVIII (70)
13		XIX	2.8	2		XX (84)

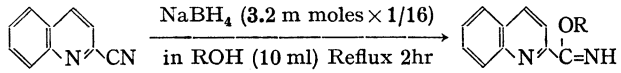
a) The numbers correspond to the experimental numbers described in Experimental.

while 3-pyridinecarbonitrile (III) was inert. It is clear that sodium borohydride plays a special role in the formation of imidates, however the mechanism is obscure at present.

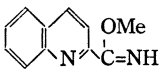
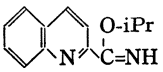
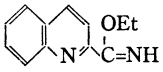
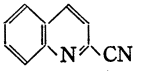
The Formation of Several Kinds of Imidates from 2-Quinolinecarbonitrile

Table II shows the results when the solvent was changed. The imidate formation occurred in methanol, ethanol and isopropyl alcohol but in *tert*-butyl alcohol the starting material was recovered quantitatively. This might show that the oxygen atom of *tert*-butyl alcohol could not attack the carbon of the nitrile because of steric hindrance by the *tert*-butyl group. When solvent was changed to tetrahydrofuran or pyridine each containing 4 molar equivalents of ethanol to the starting material, the nitrile was recovered quantitatively. Hence it is concluded that this reaction needs a large excess of alcohol.

TABLE II. The Formation of Several Kinds of Imidates in Alcohols



3.2 m moles

Number[a]	Solvent	Product (yield %)	Number[a]	Solvent	Product (yield %)
14	MeOH	 XXI (65)	15	iso-PrOH	 XXII (62)
4	EtOH	 VII (64)	16	*tert*-BuOH	 VI (92)

a) The numbers correspond to the experimental numbers described in Experimental.

The Equilibrium Reaction

The imidate formation from 2-furocarbonitrile (XIV) was followed by the gas chromatographic method to confirm whether this reaction involves an equilibrium or not. As Fig. 1 (A)

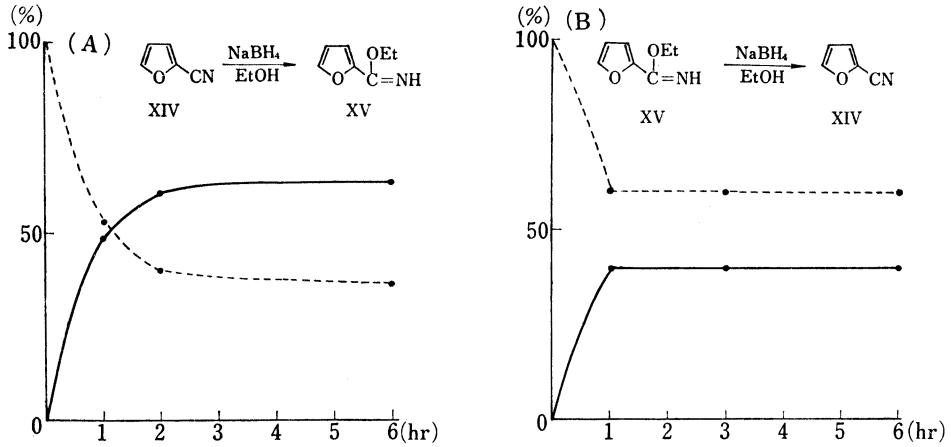


Fig. 1. (A) Plot of the Decrease of the Nitrile (---) and the Increase of the Imidate (—)
(B) Plot of the Decrease of the Imidate (---) and the Increase of the Nitrile (—)

shows, the conversion of nitrile (XIV) to imidate (XV) did not complete even after 6 hours, an equilibrium mixture composed of 36% of (XIV) and 62% of XV being apparently formed.

The same procedure was applied to ethyl 2-furoimidate (XV) prepared by another method.[4] As shown in Fig. 1 (B) 40% of the starting imidate was converted to its corresponding nitrile while 60% remained unreacted. These results prove that an equilibrium is involved in the reaction.

On the other hand some nitriles were not converted to imidates at all under the same reaction conditions. For example, 3-pyridinecarbonitrile (III) was not converted to its corresponding imidate. However, when ethyl 3-pyridineimidate prepared by the usual method[4] was submitted to the same procedure, the starting imidate was consumed completely after 1 hour and 3-pyridinecarbonitrile (III) was obtained in 91% yield. In this case it might be assumed that the equilibrium was one-sided to the nitrile.

Selective Conversion of Nitriles to Esters *via* Imidates

As an application of the above reaction, it may be well expected that only one cyano group in a compound having two or more cyano groups might be selectively converted to an another functional group through the imidate without affecting the other cyano groups. This was realized as shown in Chart 1. When 2,5-pyridinedicarbonitrile (XVII) was submitted to this reaction ethyl 2-(5-cyanopyridine) imidate (XVIII) was obtained in 70% yield. This imidate was hydrolysized to the ester (XXIII) in 86% yield. For the identification of the ester, the ester was hydrolized with dilute sodium hydroxide solution to the carboxylic acid, which was then decarboxylated in refluxing acetic acid to 3-pyridinecarbonitrile, which in turn was identfied by comparison with an authentic sample.

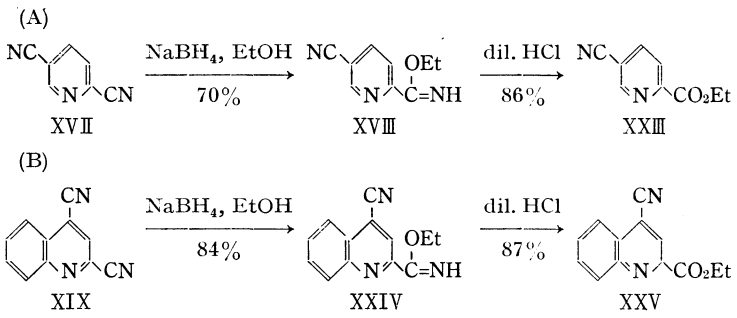


Chart 1. Selective Conversion of One of the Two Cyano Groups to Ester Group

2,4-Quinolinedicarbonitrile (XIX) was also submitted to this reaction and the corresponding monoimidate (XXIV) and its corresponding ester (XXV) were obtained as shown in Chart 1 (B). This ester was converted to 4-quinolinecarbonitrile in the same way as described above and the product was identified by comparison with an authentic sample.

Experimental[7]

Materials——Sodium borohydride was purchased from Kawaken Fine Chemicals Co., Ltd. and dried completely before use. 3-Pyridinecarbonitrile was obtained from Aldrich Chemical Co., Ltd. and purified by the recrystallization from ether–pet. ether. Other nitriles were prepared by the similar methods describ-

7) 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 measurements of gas chromatography were performed with Yanagimoto Gas Chromatograph Model GCG-3D.

ed in the literature,[8-19] except 3-furonitrile (XVI), 2,5-pyridinedicarbonitrile (XVII) and 2,4-quinolinedicarbonitrile (XIX), each of which was prepared by the procedure mentioned below. The authentic imidates were prepared by the Pinner method.[4,8,9] The physical constants of these compounds are listed in Table III, V, and VI.

TABLE III. Physical Constants of the Starting Compounds

Numbers of the compds	bp(°C/mmHg) or mp(°C)	lit[a]	Numbers of the Lit.[b]
I	26.5— 27.0	(26)[11]	10)
III	47.0— 48.0	(48—49)[21]	—
IV	78.5— 80.0	(79)[11]	11)
VI	93.0— 94.0	(94)[12]	12)
VIII	107.0—107.5	(106)[13]	13)
IX	101.0—102.0	(102)[14]	14)
X	87.0— 88.5	(87—88)[15]	15)
XI	122.0—123.0	(124—125)[16]	16)
XIII	101.5—103.0	(104)[17]	17)
XIV	143.0—144.5/760	(145—146/760)[18]	18)
XVI	143.0—148.0/760	(81—82/72)[23]	19,20)
XVII	107.5—109.0	—	—
XIX	164.0—165.0	—	21)

a) Physical constants listed in the literatures.
b) These literatures were consulted in the preparation of the starting materials.

3-Furonitrile (XVI)——An anhydrous benzene solution (20 ml) of phosgen (3.9 g, 0.397 moles) and pyridine (6 ml, 0.058 moles) were added dropwise at the same time to an anhydrous benzene suspension (20 ml) of 3-furancarboxamide (2.88 g, 0.0264 moles) under ice cooling. The reaction mixture was left at the room temperature for 3 hr with stirring. The precipitated pyridine–HCl salt was filtered by suction and washed with anhydrous benzene. The combined benzene solutions were washed with cold 10% Na_2CO_3 and satd. NaCl and dried over anhyd. Na_2SO_4. After careful evaporation of the solvent, the residual oil was distilled under 760 mmHg to give 3-furonitrile as a colorless oil (720 mg, Yield 30%). The physical constants are listed on Table III.

2,5-Pyridinedicarbonitrile (XVII)——This was prepared by the same method as the preparation of 3-furonitrile and recrystallized from ethanol to give colorless plates (Yield 43%). *Anal.* Calcd. for $C_7H_3N_3$: C, 65.11; H, 2.34; N, 32.55. Found: C, 64.93; H, 2.44; N, 32.8.

2,4-Quinolinedicarbonitrile (XIX)——Pure $POCl_3$ (18.4 ml, 0.12 moles) was added to a pyridine solution (12.8 ml, 0.08 moles) of 2,4-quinolinedicarboxamide (2.15 g, 0.01 mole) and it was refluxed for 30 min. After the reaction, $POCl_3$ and pyridine were removed under reduced pressure, and to the residue were added H_2O and 10% Na_2CO_3 to make the solution alkaline. This was extracted with ether which was washed with satd. NaCl and dried over anhydrous Na_2CO_4. The solvent was removed and the residue was recrystallized from ethanol to give pale yellow needles of 2,4-quinolinedicarbonitrile. (650 mg, Yield 36%), *Anal.* Calcd. for $C_{11}H_5N_3$: C, 73.73; H. 2,81; N, 23.45. Found: C, 73.73; H, 2.78; N, 23.35.

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9) J. Bertrand, C. Dobritz, and H. Beerens, *Bull. Soc. Pharm. Lille.*, **1956**, 39; *Chem. Abstr.*, **51**, 1168 (1957).
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14) A. Kaufmann, *Chem. Ber.*, **51**, 119, 121 (1918).
15) J.M. Wefer, A. Catalla, and F.D. Popp, *Chem. & Ind.*, 140 (1965).
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18) O. Wallach, *Chem. Ber.*, **14**, 751 (1881).
19) H.A. Smith and J.B. Conley, *J. Am. Chem. Soc.*, **73**, 4633 (1951).
20) H. Gilman and R.R. Burtner, *J. Am. Chem. Soc.*, **55**, 2906 (1933).
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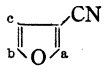
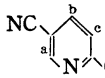
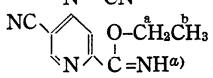
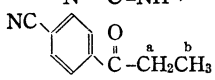
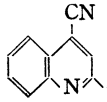
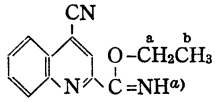
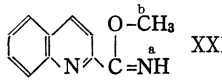
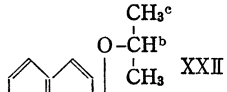
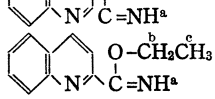
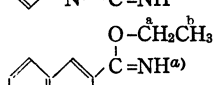
22) O. Fischer, *Chem. Ber.*, **15**, 63 (1882).
23) S. Gronowitz and G. Sorlin, *Arkiv. Kemi.*, **19**, 515 (1962).

Table IV. Conditions of Gas Chromatography

Number[a]	Column	Temp. °C	Carrier gas He: Pressure kg/cm²	Carrier gas He: Rate of flow ml/min	Retention time (min): Product	Retention time (min): Diphenyl ether
1	15% SE 30, 3m on Diasolid L	160	1.0	40	(I) 1.7, (II) 4.4	7.4
2	15% SE 30, 3m on Diasolid L	160	1.0	40	(III) 1.8	7.4
3	15% SE 30, 3m on Diasolid L	160	1.0	40	(IV) 1.8, (V) 4.5	7.4
5	15% Carbowax 20M 3m on Diasolid L	200	1.0	80	(VIII) 6.5	3.8
6	15% Carbowax 20M 3m on Diasolid L	200	1.0	80	(IX) 11.7	3.8
7	15% SE 30, 3m on Diasolid L	200	1.0	25	(X) 2.4	4.4
9	15% SE 30, 3m on Diasolid L	200	1.0	25	(XIII) 2.5	4.4
10	15% Carbowax 20M 3m on Diasolid L	160	1.0	40	(XIV) 1.6, (XV) 2.5	12.5
11	15% Carbowax 20M 3m on Diasolid L	160	1.0	40	(XVI) 1.6	12.5

a) These numbers correspond to the experimental numbers described in Experimental.

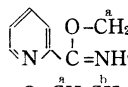
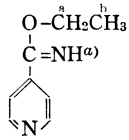
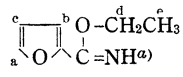
Table V. Physical Constants of Starting Materials and Products

Compounds	bp(°C/mmHg) or mp (°C)	IR cm⁻¹	NMR τ value
 XVI	143.0—148.0/760	2270 (C≡N)	a: 1.96(s), b: 2.40(d) c: 3.27(d) J_{bc}=2cps
 XVII	107.5—109.0	2260 (C≡N) 1595 (arom)	a: 1.15(d), b: 1.85(q) c: 2.15((d) J_{ab}=2cps
 XVIII		2260 (C≡N) 1645 (C=N)	a: 5.55(q) b: 8.56(t) J_{ab}=7 cps
 XXIII	73.0— 74.0	2260 (C≡N) 1735 (C=O)	a: 5.55(q) b: 8.50(t) J_{ab}=7 cps
 XIX	164.0—165.0	2260 (C≡N)	1.60—2.20(m)
 XXV	136.0—137.0	2260 (C≡N) 1730 (C=O)	a: 5.46(q) b: 8.46(t) J_{ab}=7 cps
 XXI	142.0—145.0/6.0	3320 (NH) 1655 (C=N)	a: 0.65(s) b: 5.95(s)
 XXII	141.0—147.0/6.0	3350 (NH) 1650 (C=N)	a: 0.56(s) b: 4.60(m) c: 8.58(d) J_{bc}=6 cps
 VII	134.0—140.0/5.0	3320 (NH) 1660 (C=N)	a: 0.35(s) b: 5.50(q) c: 8.53(t) J_{bc}=6 cps
		3340 (NH) 1640 (C=N)	a: 5.55(q) b: 8.58(t) J_{ab}=7 cps

a) These protons were not detected by NMR (τ: −4—10).

General Procedure for the Formation of Imidates——(A) The experiments (1) (2) (3) (4) (5) (6) (7) (9) (10) and (11) were performed in this procedure A: The nitrile (3.2—4.8 mmoles, See Table I), diphenyl ether (500 mg the internal standard)and $NaBH_4$ (3.2—4.8 mmoles × 1/16) were dissolved in anhydrous ethanol (10 ml) and it was refluxed for 2—6 hr. A small portion of the solution was taken for the gas chromatographic measurements to find the ratios of the nitrile, the imidate and diphenyl ether. The detailed conditions of the gas chromatographic method were listed on Table IV.

Table VI. Physical Constants of Authentic Imidates

Compounds	bp (°C/mmHg)	IR cm^{-1}	NMR τ value
	107.0—109.0/24.0	3320 (NH) 1660 (C=N)	a: 5.55(q) b: 8.55(t) J_{ab}=7 cps
	130.0—133.0/25.0	3250 (NH) 1645 (C=N)	a: 5.60(q) b: 8.55(t) J_{ab}=7 cps
	174.0—177.0/760	3350 (NH) 1655 (C=N)	a: 2.56(d) b: 3.27(d) c: 3.66(d) d: 5.68(q) e: 8.62(t) J_{ac}=2 cps J_{bc}=4 cps J_{de}=7 cps

a) These protons were not detected by NMR (τ: −4—10).

(B) The experiments (4) (8) (12) '13) (14) (15) and (16) were performed in this procedure B: The nitrile (2.8—4.8 mmoles, See Table I and II) diphenyl ether (500 mg) and $NaBH_4$ (2.8—4.8 mmoles × 1/16) were dissolved in alcohol (10 ml See Table II) and it was refluxed for 2—6 hr. After the reaction, the solvent was removed under reduced pressure and water was added to the residue. The water solution was extracted with ether which was washed with satd. NaCl and dried over anhydrous Na_2SO_4. The ether was removed and the yield of the imidate was calculated by the comparison of the ether protons of the imidate and the methyl protons of acetophenone which was mixed for the internal standard before the measurement of NMR.

Ethyl 5-Cyanopicolinate (XXII)——2,5-Pyridinedicarbonitrile (500 mg, 3.8 mmoles) and $NaBH_4$ (9 mg, 3.8 mmoles × 1/16) were dissolved in ethanol (10 ml) and it was refluxed for 2 hr. After cooling, this solution was added dropwise to 1% HCl and it was stirred for 2 hr at room temperature. 10% Na_2CO_3 was added to the solution under cooling to make it alkaline and it was extracted with ether which was washed with satd. NaCl and dried over anhyd. Na_2SO_4. After the evaporation of ether, the residue was purified by column chromatography (SiO_2, $CHCl_3$) and ethyl 5-cyanopicolinate was obtained as colorless needles. (410 mg, Yield 60% based on XVII). *Anal.* Calcd. for $C_9H_8O_2N_2$: C, 61.36; H, 4.58; N, 15.90. Found: C, 61.11; H, 4.60; N, 16.04.

If necessary, it is also possible to isolate the imidate which was hydrolyzed without isolation in this procedure. Chart 1 shows the isolation per cent of the imidate.

The Identification of Ethyl 5-Cyanopicolinate——(1) Ethyl 5-cyanopicolinate (260 mg, 1.48 mmoles) obtained from the above reaction was suspended in 1% NaOH (6 ml) and it was stirred for 8 hr. After the reaction it was extracted with ether, and from the ether layer the starting material was recovered (110 mg, Yield 42%). The water layer was acidified to pH 4 by 10% HCl to give white precipitates which were filtered by suction and dried in vacuum. 5-Cyanopicolinic acid was obtained (110 mg, Yield 51% mp 195—225°, IR ν_{max}^{KBr} cm^{-1}: 2260 (C≡N), 1710 (C=O)).

(2) 5-Cyanopicolinic acid obtained from (1) was dissolved in acetic acid (20 ml) and it was refluxed for 3 hr. After the evaporation of the solvent, 5% NaOH was added under cooling to the residue and it was extracted with ether which was washed with satd. NaCl and dried over anhyd. Na_2SO_4. The solvent was removed to give 3-pyridinecarbonitrile (60 mg, Yield 34%, mp 47.0—48.0° (ether–pet. ether)). It was identified as 3-pyridinecarbonitrile by the mixed melting points measurement with an authentic sample.

Ethyl 4-Cyanoquinaldinate (XXV)——2,4-Quinolinedicarbonitrile (500 mg, 2.8 mmoles) and $NaBH_4$ (7 mg, 2.8 mmoles × 1/16) were dissolved in ethanol (10 ml) and it was refluxed for 2 hr. After the reaction, it was added dropwise to 1% HCl solution under cooling and stirred for 2 hr at a room temperature. 10% Na_2CO_3 was added to the solution under cooling to make it alkaline and it was extracted with ether 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 (SiO_2, ether: *n*-hexane=1: 1). Ethyl 4-cyanoquinaldinate thus obtained was recrystallized from ethanol. (460 mg, mp 136—137°, Yield 74% based on XIX).

The Identification of Ethyl 4-Cyanoquinaldinate——(1) Ethyl 4-cyanoquinaldinate obtained from the above reaction (450 mg, 2.0 mmoles) and KOH (110 mg, 2.0 mmoles) were dissolved in ethanol (20 ml) and it was refluxed for 5 hr. The precipitated potassium salt was filtered by suction and it was dissolved in H_2O. This water solution was acidified to pH 4 by 10% HCl to give the white precipitate which was filtered and dried in vacuum. 4-Cyanoquinaldinic acid (250 mg, Yield 63%, mp 220—235°, IR ν_{max}^{KBr} cm^{-1}: 2260 (C≡N), 1700 (C=O)).

(2) 4-Cyanoquinaldinic acid obtained from (1) (240 mg, 1.2 mmoles) was dissolved in acetic acid (20 ml) and it was refluxed for 5 hr. After the evaporation of the solvent, water was added to the residue and 10% Na_2CO_3 was added to the solution to make it alkaline. It was extracted with ether which was washed with satd. NaCl and dried over anhyd. Na_2SO_4.

Ether was removed to give 4-cyanoquinoline which was recrystallized from ether–ligroin (70 mg, Yield 29%, mp 101.0—102.0°). It was identified as 4-cyanoquinoline by the mixed melting points measurement with an authentic sample.