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Studies of the Reissert-Kaufmann-type Reaction of 4-Nitropyridine *N*-Oxide and Its Homologues

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The Reissert-Kaufmann-type reaction of substituted *N*-methoxy-4-nitropyridinium methylsulfates gave the corresponding 2-cyano-4-nitropyridines in satisfactory yields. When 3-methyl-4-nitropyridine *N*-oxide was used as the starting material, a cyano group was introduced not into the 6-position, but into the 2-position. This preference may be explained by proposing a hyperconjugation effect of the 3-methyl group. The resulting nitriles were quantitatively hydrolyzed to the corresponding 4-nitropicolinic acids. These reactions provided a new route for the preparation of nitropyridinecarboxylic acids from pyridine homologues. Further, some nucleophilic substitution reactions of the products were carried out.

It has recently been established that the nitration of pyridine *N*-oxides with fuming nitric acid alone provides a convenient method for the preparation of 4-nitropyridine *N*-oxides.[1]

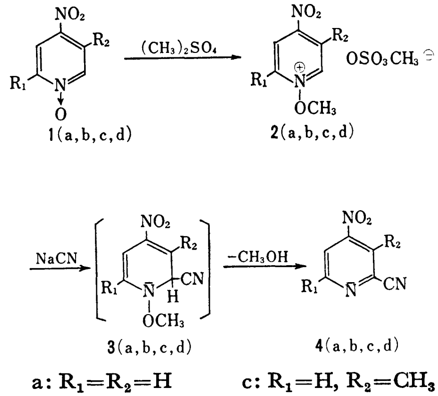
As is commonly known, the Reissert-Kaufmann reaction has offered a general synthetic method for heterocyclic nitriles in condensed heteroaromatic compounds such as quinoline and isoquinoline since it was reported by Reissert[2] and by Kaufmann *et al.*[3-6] Ochiai and Nakayama reported an example of the formation of a cyanopyridine by the nucleophilic attack of a cyanide ion on a pyridinium salt.[7] Thus, 4-chloro-2-cyanopyridine was obtained from 4-chloropyridine *N*-oxide. Further, Feely and Beavers[8] and Okamoto and Tani[9,10] independently extended the reaction to include various derivatives of pyridine *N*-oxides.

Tani also reported the reaction of 4-nitropyridine *N*-oxide,[11] but the reported neither a detailed investigation of the product nor the reaction of other homologues of 4-nitropyridine *N*-oxide.

In the present study, the Reissert-Kaufmann-type reaction of 4-nitropyridine *N*-oxide and its homologues was performed in order to prepare 2-cyano-4-nitropyridines and in order to clarify the electronic effects of the 4-nitro group in the reaction. The hydrolysis of 2-cyano-4-nitropyridines led to the corresponding acids, and the nucleophilic reactivity of the 4-nitro group of the nitriles and the carboxylic acids, were also examined.

Results and Discussion

The *N*-oxides used as starting materials were 4-nitropyridine *N*-oxide (**1a**), 2-methyl-4-nitropyridine *N*-oxide (**Ib**), 3-methyl-4-nitropyridine *N*-oxide (**Ic**), and 5-ethyl-2-methyl-4-nitropyridine *N*-oxide (**1d**). The *N*-oxides were treated at 65—70°C with 1—1.2 equivalents of dimethyl sulfate to form *N*-methoxypyridinium salts (**2**). But above this temperature the salts were liable to decompose, with the evolution of nitrogen dioxide. The resulting salts were hygroscopic crystals; they were used for subsequent reactions without purification. The



a: $R_1=R_2=H$ c: $R_1=H, R_2=CH_3$
b: $R_1=CH_3, R_2=H$ d: $R_1=CH_3, R_2=C_2H_5$

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[1] E. Matsumura, unpublished results.

[2] A. Reissert, *Ber.*, **38**, 1603, 3415 (1905).

[3] A. Kaufmann and A. Albertini, *ibid.*, **42**, 3776 (1909).

[4] A. Kaufmann and R. Widmer, *ibid.*, **44**, 2058 (1911).

[5] A. Kaufmann and H. Peyer, *ibid.*, **45**, 1805 (1912).

[6] A. Kaufmann, *ibid.*, **51**, 116 (1918).

[7] E. Ochiai and I. Nakayama, *Yakugaku Zasshi*, **65**(**ko**), 7 (1945).

[8] W. E. Feely and E. M. Beavers, *J. Amer. Chem. Soc.*, **81**, 4004 (1959).

[9] T. Okamoto and H. Tani, *Chem. Pharm. Bull.* (Tokyo), **7**, 130, 925 (1959).

[10] H. Tani, *ibid.*, **7**, 930 (1959).

[11] H. Tani, *Yakugaku Zasshi*, **80**, 1418 (1960).

aqueous solution of the salts was treated with an aqueous solution of sodium cyanide under a nitrogen atmosphere in an ice-salt mixture in order to avoid any violent reaction and excessive tar formation. From the reaction mixture, the nitriles (**4**) were obtained, in the cases of (**a**), (**b**), and (**c**), as crystals (which were subsequently purified by recrystallization), and, in the case of (**d**), as an oil (which was subsequently purified by vacuum distillation).

The infrared spectra of all of the products indicated the presence of a nitro group (1350—1360, 1530 cm^{-1}), a nitrile group (2200 cm^{-1}), and no *N*-oxide group. The results of the micro analyses of the products were in good agreement the findings on the mono cyano derivatives of 4-nitropyridine and its homologues. In order to ascertain the position of the introduced cyano group, each of the products was converted to the corresponding pyridinecarboxylic acid; **4a** was converted to picolinic acid; **4b**, to 6-methyl-4-nitropicolinic acid; **4c**, to quinolinic acid, and **4d**, to 6-methylquinolinic acid. The acids were identified by a mixed-melting-point determination and by a comparison of the infrared spectra with those of authentic samples. From the above facts, the products are identified as 2-cyano-4-nitropyridine (**4a**), 2-cyano-6-methyl-4-nitropyridine (**4b**), 2-cyano-3-methyl-4-nitropyridine (**4c**), and 2-cyano-3-ethyl-6-methyl-4-nitropyridine (**4d**) respectively. The elementary analyses and some properties of the products are summarized in Table 1.

The fact that the nucleophilic attack of the cyanide ion on the methylsulfates occurred at the 2-position to form 1,2-dihydro intermediates (**3**), which then led to the corresponding nitriles with the elimination of a molecule of methanol, can be explained by presuming that the inductive and electromeric effects of quaternary nuclear nitrogen on the methylsulfates (**2**) are greater than those of the 4-nitro group.

With the reaction of 3-methyl-4-nitropyridine *N*-oxide (**1c**), a cyano group was introduced into the 2-position, this was contrary to the expectation that the inductive and steric effects of the 3-methyl group would tend to direct the entering cyano group to the 6-position of the pyridine nucleus. Analogous results have been reported with 3-methylpyridine *N*-oxide.[8,9] The result may rationally be explained as follows. Considering the hyperconjugation of the 3-methyl group in the dihydro-type structure (**3**), which is assumed to be an intermediate, the electron density is more extensively delocalized when a cyano group is introduced into the 2-position (**A**) than when it is introduced into the 6-position (**B**), as is shown in Fig. 1. Therefore, the **A** intermediate is preferentially formed to give the 2-cyano derivative.

The hydrolysis to 4-nitropicolinic acids (**5**) was successfully carried out, and the 4-nitro group was held, by heating with 90% sulfuric acid followed by treatment with sodium nitrite. The results

TABLE 1. SUBSTITUTED 2-CYANO-4-NITROPYRIDINES

Product	Mp (bp) °C	Yield %	ν_{NO_2} cm^{-1}	ν_{CN} cm^{-1}	Formula	C%		H%		N%	
						Found	Calcd	Found	Calcd	Found	Calcd
4a	73—74*	56.9	1360 1530	2200	$C_6H_3N_3O_2$	48.57	48.33	1.78	2.03	28.02	28.18
4b	76.5—77.5	67.1	1360 1530	2200	$C_7H_5N_3O_2$	51.45	51.53	2.91	3.09	25.90	25.76
4c	64—65	85.7	1350 1530	2200	$C_7H_5N_3O_2$	51.89	51.53	3.01	3.09	25.76	25.76
4d	(94/0.05 mmHg)	82.4	1350 1530	2200	$C_9H_9N_3O_2$	56.42	56.56	4.63	4.72	21.68	21.98

* Lit, (Ref. 11) mp 72—74°C.

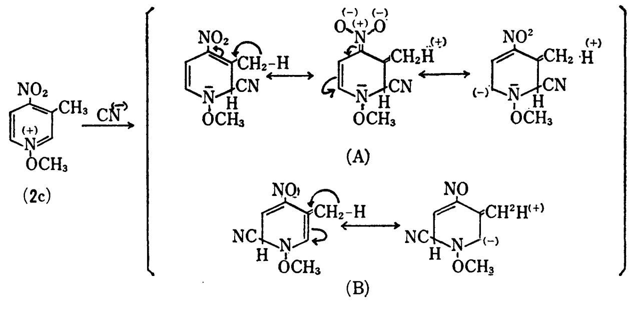
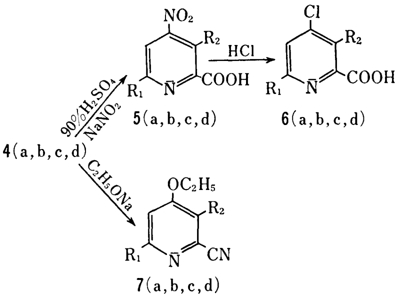


Fig. 1

and analytical data are summarized in Table 2. The sequence of the reactions starting with pyridine homologues, *N*-oxidation, nitration with fuming nitric acid alone, cyanation, and hydrolysis, provides a new rout for the preparation of 4-nitropyridine-2-carboxylic acids, which attract our attention by their antibacterial and antifungal activities[12] and which have been scarcely obtained by other methods.

These cyanonitropyridines and their carboxylic derivatives were anticipated to undergo a nucleophilic substitution at the 4-position because of the strong electron-withdrawing property of the 2-cyano or the 2-carboxyl group. A concurrent substitution of the nitro group by the chloride ion has been observed on the hydrolysis of 2-cyano-4-nitropyridine with hydrochloric acid in a sealed tube.[11]

We obtained 4-chloropicolinic acids from 4-nitropicolinic acids in good yields under milder conditions by heating them with hydrochloric acid. The results and the analytical data are summarized in Table 3. It also became clear that the substitution of 2-cyano-4-nitropyridines by sodium ethoxide at the 4-position occurred more easily than that of 4-nitropyridine which was observed on heating.[13] Thus, 2-cyano-4-ethoxypyridines (**7**) were yielded from 2-cyano-4-nitropyridines (**4**) when they were treated with ethanolic sodium ethoxide in an ice-salt mixture. The results and analytical data are



a: $R_1=R_2=H$ b: $R_1=CH_3$, $R_2=H$
c: $R_1=H$, $R_2=CH_3$ d: $R_1=CH_3$, $R_2=C_2H_5$

TABLE 2. SUBSTITUTED 4-NITROPICOLINIC ACIDS

Product	Mp °C	Yield %	ν NO2 cm^{-1}	ν COOH cm^{-1}	Formula	C% Found	C% Calcd	H% Found	H% Calcd	N% Found	N% Calcd
5a	154—155*	97.6	1360 1530	1700	$C_6H_4N_2O_4$	42.88	42.87	2.16	2.40	16.70	16.67
5b	129—130	98.5	1360 1530	1710	$C_7H_6N_2O_4 \cdot H_2O$	41.94	42.00	4.00	4.03	13.85	14.00
5c	148	97.6	1360 1530	1710	$C_7H_6N_2O_4$	46.28	46.16	3.22	3.32	15.30	15.38
5d	76—77	98.1	1350 1530	1710	$C_9H_{10}N_2O_4$	51.60	51.42	4.84	4.80	13.24	13.30

* Lit, (Ref. 12) mp 152°C (decomp.).

TABLE 3. SUBSTITUTED 4-CHLOROPICOLINIC ACIDS

Product	Mp °C	Yield%	ν COOH cm^{-1}	Formula	C% Found	C% Calcd	H% Found	H% Calcd	N% Found	N% Calcd
6a	186—187*	85.3	1700	$C_6H_4NO_2Cl$	45.85	45.71	2.48	2.52	8.78	8.89
6b	123—124	90.5	1710	$C_7H_6NO_2Cl$	48.81	49.00	3.62	3.52	7.98	8.16
6c	163—164	98.0	1710	$C_7H_6NO_2Cl$	48.75	49.00	3.26	3.52	7.97	8.16
6d	43—44	95.0	1710	$C_9H_{10}NO_2Cl \cdot 1/2H_2O$	52.08	51.80	5.20	5.33	6.95	6.71

* Lit, mp 183—183.5 °C; T. Kato, *Yakugaku Zasshi*, **83**, 352 (1963).

TABLE 4. SUBSTITUTED 2-CYANO-4-ETHOXYPYRIDINES

Product	Mp °C	Yield %	ν CN cm^{-1}	Formula	C% Found	C% Calcd	H% Found	H% Calcd	N% Found	N% Calcd
7a	66—67*	91	2200	$C_8H_8N_2O$	64.75	64.85	5.36	5.44	18.66	18.91
7b	87—88	95	2200	$C_9H_{10}N_2O$	66.36	66.65	6.22	6.22	17.14	17.27
7c	128—129	90	2200	$C_9H_{10}N_2O$	66.65	66.65	6.32	6.22	17.46	17.27
7d	89—90	92	2200	$C_{11}H_{14}N_2O$	69.37	69.44	7.52	7.42	14.49	14.73

* Lit, mp 70—72°C; Y. Nishijima, *Yakugaku Zasshi*, **82**, 1267 (1962).

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12) E. V. Brown, U. S. 2766251 (1956).

13) M. Katada, *Yakugaku Zasshi*, **67**, 20 (1947).

summarized in Table 4. The fact that nucleophilic substitution at the 4-position proceeds with such ease shows that the activity of the 4-nitro group as a leaving group toward the nucleophilic substitution and the reactivity are favoured by the inductive effects of the 2-substituents.

Experimental

All the melting points and boiling points are uncorrected. The infrared spectra were recorded on a Hitachi infrared spectrophotometer, Model EPI-S 2, as Nujol mulls.

2-Cyano-4-nitropyridine (4a). A mixture of 20.0 g of 4-nitropyridine *N*-oxide (**1a**) and 18.0 g of dimethyl sulfate was placed in a three-necked flask, equipped with a sealed stirrer, a thermometer, and a silica-gel tube. The mixture was heated at 65—70°C for 2 hr. Upon cooling, the salt crystallized out; it was then collected and dissolved in 50 m*l* of water, and the silica-gel tube was replaced by a dropping funnel. A solution of 14.6 g of sodium cyanide in 100 m*l* of water was added from the dropping funnel at −7——8°C with vigorous stirring in a slow stream of nitrogen over a period of 7 hr. After standing overnight, the crystalline precipitates were collected and recrystallized from isopropyl ether to give 12.1 g (56.9%) of 2-cyano-4-nitropyridine (**4a**).

2-Cyano-6-methyl-4-nitropyridine (4b). Twenty grams of 2-methyl-4-nitropyridine *N*-oxide (**1b**) were worked up as in the foregoing experiment with 19.7 g of dimethyl sulfate and 14.0 g of sodium cyanide to give 14.2 g (67.1%) of 2-cyano-6-methyl-4-nitropyridine (**4b**).

2-Cyano-3-methyl-4-nitropyridine (4c). The treatment of 20.0 g of 3-methyl-4-nitropyridine *N*-oxide (**1c**) with 16.4 g of dimethyl sulfate and 12.7 g of sodium cyanide in the manner as described above gave 18.1 g (85.7%) of 2-cyano-3-methyl-4-nitropyridine (**4c**).

2-Cyano-3-ethyl-6-methyl-4-nitropyridine (4d). Twenty grams of 5-ethyl-2-methyl-4-nitropyridine *N*-oxide (**1d**) were treated with 15.6 g of dimethyl sulfate and 11.9 g of sodium cyanide according to the above procedure, and the resulting mixture was extracted with chloroform. The extract was worked up in the usual manner, and the residual oil was distilled *in vacuo* to give 17.3 g (82.4%) of 2-cyano-3-ethyl-6-methyl-4-nitropyridine (**4d**).

4-Nitropicolinic Acid (5a). A solution of 5 g of 2-cyano-4-nitropyridine (**4a**) in 50 g of 90% sulfuric acid was heated at 120°C for 2 hr. Into the reaction mixture, 5.6 g of sodium nitrite in 10 m*l* of water were added dropwise with stirring at 20—25°C over a period of 30 min. The mixture was kept at 20—25°C for an hour and then heated at 80°C for an additional hour. The resulting solution was poured onto 100 g of cracked ice and neutralized to pH 1.6 with sodium carbonate. The crystalline precipitates were then separated and recrystallized from acetone to give 5.4 g (97.6%) of 4-nitropicolinic acid (**5a**).

Other 4-Nitropicolinic Acids. 6-Methyl- (**5b**) (monohydrate), 3-methyl- (**5c**), and 3-ethyl-6-methyl-4-nitropicolinic acid (**5d**) were obtained by procedure described above.

4-Chloropicolinic Acid (6a). A solution of 5.0 g of 4-nitropicolinic acid (**5a**) in 50 m*l* of concentrated hydrochloric acid was heated at 100°C for 2 hr. The reaction mixture was then evaporated to dryness under reduced pressure and neutralized to pH 2.0 with sodium carbonate. The crystalline precipitates were collected and recrystallized from methanol - water to give 4.1 g (95.3%) of 4-chloropicolinic acid (**6a**).

Other 4-Chloropicolinic Acids. 4-Chloro-6-methyl- (**6b**) and 4-chloro-3-methylpicolinic acid (**6c**) were obtained by the above method, and both of them were recrystallized from benzene. 4-Chloro-3-ethyl-6-methylpicolinic acid (**6d**) was obtained as follows. 3-Ethyl-6-methyl-4-nitropicolinic acid (**5d**) was treated with concentrated hydrochloric acid, and the reaction mixture was neutralized as above. Evaporation to dryness, the extraction of the residue with benzene, and the removal of the solvent gave 4-chloro-3-ethyl-6-methylpicolinic acid (**6d**).

2-Cyano-4-ethoxypyridine (7a). A solution of 1 g of 2-cyano-4-nitropyridine (**4a**) in 30 m*l* of absolute ethanol was placed in a three-necked flask, equipped with a sealed stirrer, a dropping funnel, a thermometer, and a silica-gel tube. A solution of sodium ethoxide prepared from 0.18 g of sodium and 20 m*l* of absolute ethanol was added dropwise with stirring at −5—0°C over a period of an hour. After having been stirred for an additional hour, the reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was extracted with benzene, and from the extract 0.9 g (91%) of 2-cyano-4-ethoxypyridine (**7a**) was obtained. This was then recrystallized from petroleum benzine.

Other 2-Cyano-4-ethoxypyridines. 2-Cyano-4-ethoxy-6-methyl- (**7b**), 2-cyano-4-ethoxy-3-methyl- (**7c**), and 2-cyano-4-ethoxy-3-ethyl-6-methylpyridine (**7d**) were obtained by the same procedure.

Picolinic Acid. The catalytic reduction of 4-chloropicolinic acid (**6a**) with 5% Pd–C in methanol at room temperature gave picolinic acid in a 90.6% yield; mp 136°C; IR 1700 cm^{-1} (COOH); (Found: C, 58.38; H, 3.92; N, 11.35%). It was identified by a mixed-melting-point determination and by a comparison of the infrared spectra with those of an authentic sample.

6-Methyl-4-nitropicolinic Acid (Monohydrate). By applying the method for the preparation of 5-ethyl-4-nitropicolinic acid,[14] authentic 6-methyl-4-nitropicolinic acid melting at 129—130°C was prepared from 6-methyl-4-nitropicolinaldehyde, which had itself been obtained according to the directions of Furukawa.[15]

Quinolinic Acid. 3-Methylpicolinic acid melting at 114—115°C was obtained from 4-chloro-3-methylpicolinic acid (**6c**) by the same method as was used for picolinic acid in a 95.8% yield. 3-Methylpicolinic acid was oxidized with aqueous potassium permanganate at 90°C to give quinolinic acid in a 74.1% yield; decomp. 187; 229—230°C; IR 1700 cm^{-1} (COOH); (Found: C, 50.50; H, 2.84; N, 8.21%). It was identified by a mixed-melting-point determination and by a comparison of the infrared spectra with those of an authentic sample prepared by the oxidation of quinoline with

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[14] M. Endo and T. Nakajima, *Yakugaku Zasshi*, **80**, 875 (1960).

[15] S. Furukawa, *ibid.*, **77**, 11 (1957).

aqueous potassium permanganate.

6-Methylquinolinic Acid. 3-Ethyl-6-methylpicolinic acid boiling at 83—84°C (0.05 mmHg) was obtained from 4-chloro-3-ethyl-6-methylpicolinic acid (**6d**) in a 97.7% yield by the procedure described above. It was oxidized with aqueous potassium permanganate at 20°C to give 6-methylquinolinic acid in an 81.2% yield; mp 166—167°C; IR 1720 cm^{-1} (COOH); (Found: C, 53.04; H, 3.90; N, 7.77%). It was identified by means of a mixed-melting-point determination and by a comparison of the infrared spectra with the authentic sample prepared from 8-hydroxyquinaldine.[16]

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[16] Anchor Chemical Co., Ltd., and H. N. Rydon, Brit. 838015 (1960).