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The Reaction of Nucleophilic Reagents at the β-Position of 3-Bromo-4-nitropyridine *N*-Oxide

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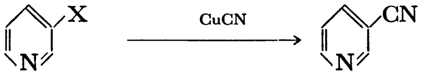
Some nucleophilic substitutions on the β-position of the pyridine nucleus were carried out. The reactions of 3-bromo-4-nitropyridine *N*-oxide(**1**) with diethyl sodiomalonate, ethyl sodiocyanoacetate, and ethyl sodioacetoacetate in diethyl carbonate or pyridine afforded 3-bis-(ethoxycarbonyl)methyl-4-nitropyridine *N*-oxide (**2**), 3-cyano(ethoxycarbonyl)methyl-4-nitropyridine *N*-oxide (**3**), and 3-acetyl(ethoxycarbonyl)methyl-4-nitropyridine *N*-oxide (**4**) respectively, and ethyl sodioacetoacetate, when treated at a higher temperature, gave 3-ethoxycarbonyl-2-methyl-furo(3,2-*c*)pyridine *N*-oxide (**5**). A probable mechanism of the reaction was presented.

The nucleophilic substitution reaction of pyridine homologues and their *N*-oxides have been widely investigated for a long time, and there are several reviews on the subject.[1–3] Most of such substitutions of the pyridine ring take place at the α or γ-position, especially with the carbanions. In this connection, several carbanion sources, such as active methylenes, enamines, Grignard reagents, alkyl metals, and metal cyanides, have been developed,[4] but only a few examples of the introduction of carbanions to the β-position of the pyridine ring have been reported, among which are the followings.[5,6]



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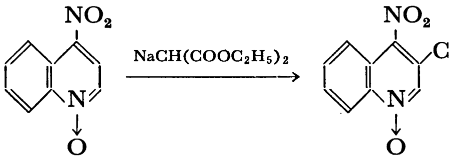

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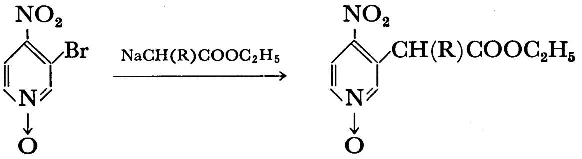
In the present investigation, since the authors' interests focussed on the carbanion introduction to the β-position of the pyridine ring, the reactions of 3-bromo-4-nitropyridine *N*-oxide with several active methylene compounds were worked out. The choice of the substrate was based on the following considerations; in the case of a nucleophilic attack, a bromide anion is a better leaving group than a hydride anion, and the β-carbon occupied by the bromine is activated by the inductive and tautomeric effects of the neighbouring nitro group.[7]

Results and Discussion

Diethyl malonate, ethyl cyanoacetate, and ethyl acetoacetate were employed as nucleophilic reagents.

The Reaction of 3-Bromo-4-nitropyridine N-*Oxide (1) with Diethyl Sodiomalonate.* On the treatment of **1** with diethyl sodiomalonate in diethyl carbonate at 50 °C, pale yellow needles (**2**) were obtained in a satisfactory yield after purification through a silica gel column. The NMR spectrum of Compound **2** showed four different kinds of hydrogens; a triplet at δ 1.28 and a quartet at 4.27 (CH_3CH_2OCO), a singlet at 5.31($CHPy(COOEt)_2$), and several peaks between 7.93—8.25 (aromatic hydrogens) in an area ratio of 6 : 4 : 1 : 3. The infrared spectrum of **2** indicated the presence of ester carbonyl, nitro, and *N*-oxide groups. The treatment of **2** with 20% sulfuric acid at 130 °C for 3 hours gave 3-(1-oxido-4-nitro)pyridylacetic acid. On the basis of these data, **2** was proved to be 3-bis(ethoxycarbonyl)methyl-4-nitropyridine *N*-oxide (**2**), showing that the malonate anion was introduced into the β-position of the pyridine nucleus.



(**1**)

(**2**, **3**, and **4**)
2: R=$COOC_2H_5$
3: R=CN
4: R=$COCH_3$

*The Reaction of **1** with Ethyl Sodiocyanoacetate.* When **1** was treated with ethyl sodiocyanoacetate, the reaction proceeded similarly, and 3-cyano(ethoxycarbonyl)methyl-4-nitropyridine *N*-oxide (**3**) was obtained. The NMR spectrum of **3** was analogous to that of **2** with the exception of the fact that the methine proton at δ 5.58 was exchangeable with deuterium. The acidity of **3** was also shown by the capacity to form a deeply-coloured quaternary ammonium salt, even with aqueous ammonia.

*The Reaction of **1** with Ethyl Sodioacetoacetate.* The treatment of **1** with ethyl sodioacetoacetate had results different from those of the two preceding reactions.

At a lower temperature (30—35 °C), the reaction proceeded much as in the above two reactions to give 3-acetyl(ethoxycarbonyl)methyl-4-nitropyridine *N*-oxide

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[1] H. S. Mosher, "Heterocyclic Compounds," Vol. 1, Chap. 8, ed. by R. C. Elderfield, John Wiley & Sons, New York, 1950.

[2] E. Ochiai, "Aromatic Amine Oxides," Elsevier Publishing Co., Amsterdam (1967).

[3] A. R. Katritzky and J. M. Lagowski, "Chemistry of the Heterocyclic N-oxides," Academic Press, London (1970).

[4] For example, M. Hamana, "The Chemistry of the Heterocycles," Vol. 3, ed. by Y. Kitahara, T. Kametani, and T. Kato, Nankodo & Co., Tokyo (1971).

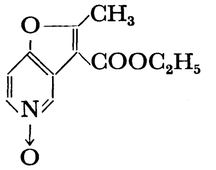
[5] S. M. McElvain and M. A. Goese, *J. Amer. Chem. Soc.*, **63**, 2283 (1941); W. T. Caldwell, F. T. Tyson, and L. Lauer, *ibid.*, **66**, 1479 (1944).

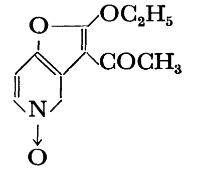
[6] H. J. Richter and N. E. Rustad, *J. Org. Chem.*, **29**, 3381 (1964).

[7] *Cf.* Th. J. de Boer and I. P. Dirdx, "The Chemistry of the Nitro and Nitroso Groups," Chap. 8, ed by H. Feuer, Interscience Publishers, New York (1969).

(**4**). However, the NMR spectrum of **4** showed a different aspect from the two preceding products (**2** and **3**). The singlet due to the methine proton was weakened to a negligible intensity, and a new D_2O-exchageable singlet corresponding to one proton appeared at δ 13.07, indicating that **4** exists as an enol, but the O–H absorption band was not observed in the IR spectrum. The fact that the methylene signal, which should originally be a quartet, splits into twelve peaks suggests that **4** exists in more than two enol forms. It seems also that the reactivity of the methine proton might act as a driving force to further the reaction.

When the reaction was followed by further treatment at a higher temperature (80—90 °C), colourless crystals (**5**) were obtained which had the empirical formulas of $C_{11}H_{12}NO_{4.5}$ and $C_{11}H_{11}NO_4$ after drying over phosphorus pentoxide. The IR spectrum of **5** indicated the subsistence of the carbonyl group and the *N*-oxide group and the lack of a nitro group. The NMR spectrum of **5** showed 6 different kinds of hydrogens. From the above data, **5** was assumed to be either **5a**, or **5b**.

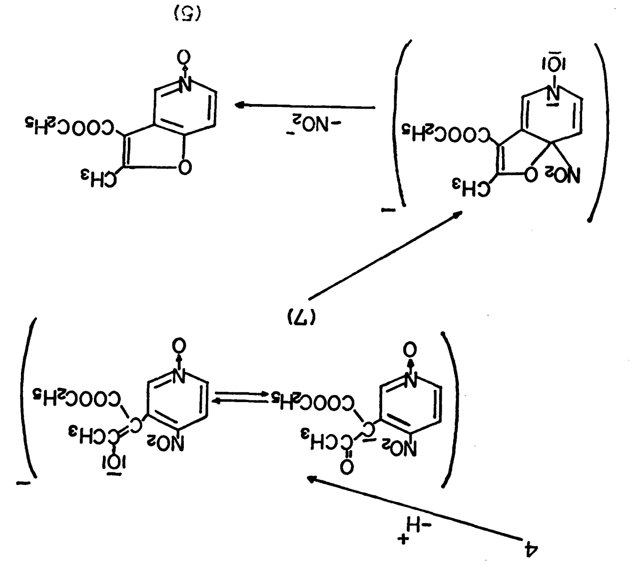

(**5a**)


(**5b**)

The reaction of **1** with diethyl sodiomalonate and ethyl sodiocyanoacetate did not produce a compound corresponding to **5**, even at a higher temperature. This fact suggests that the acetyl carbonyl group rather than the ester carbonyl group takes part in the reaction and that **5** might be **5a** rather than **5b**. This inference was supported by the fact that the treatment of **5** with 10% hydrochloric acid gave a colourless carboxylic acid (**6**), $C_9H_7NO_4$. Thus, **5** was proved to be **5a**, 3-ethoxycarbonyl-2-methylfuro(3,2-*c*)pyridine *N*-oxide, and **6** was proved to be 2-methyl-5-oxidofuro-(3,2-*c*)pyridine-3-carboxylic acid.

The above results prove that ethyl sodioacetoacetate behaved, at a higher temperature, differently from the other reagents and gave a fused heterocyclic compound; this was because of the outstanding activity of the methine proton and the acetyl carbonyl group of **4** as has been mentioned above. The judgment that **5** was formed *via* **4** was supported by the facts that **4** was obtained at a lower temperature, that **5** was a preferential product at a higher temperature, and the fact that a deep red-purple in colour of the reaction mixture as was common to all the reactions yielding **2**, **3**, and **4**, faded in the case of **5** with a rise in the temperature. A probable course of the formation of **5** was proporsed as in the following scheme.

A methine proton of the preliminary product, **4**, is extracted by the excess base to give an anion, **7**, which is shown as a resonance of two canonical formula. The *O*-anion internally attacks the 4–*C*, which is activated by the nitro and *N*-oxide group; this is followed by the departure of the nitrate anion to give **5**.



Scheme

Consequently, the introduction of carbanion to the β-position of the pyridine ring was successfully achieved by the displacement of the bromide anion activated by the *ortho*-nitro group. The results were of great value not only in the point of the accomplishment of the introduction of the *C*-anion into the β-position of the pyridine nucleus with ease, but also in the point of the use of the product (**2**, **3**, and **4**) as synthetic intermediates, because the 4-nitro group of the products was still active in response to the nucleophilic attack. Further work is in progress on this point.

Experimental

All the melting points are uncorrected. The IR spectra were obtained on a Hitachi Infrared Spectrophotometer, EPI–S2, as Nujol mulls. The NMR spectra were recorded on a Hitachi High Resolution NMR Spectrometer, 20B, with TMS as the internal standard.

3-Bromo-4-nitropyridine N-*oxide (**1**).* 3-bromopyridine[8] was treated with 5 equivalent amounts of 30% hydrogen peroxide and 100 equivalent amounts of glacial acetic acid at 70—80 °C for 20 hr to give 3-bromopyridine *N*-oxide in a 92.3% yield as hydrochloride. 3-Bromo-4-nitropyridine *N*-oxide (**1**) (mp 152—152.5 °C) was obtained in a 57.5% yield from 3-bromopyridine *N*-oxide by the method of Jujo.[9]

*The Reaction of **1**. (a) With Diethyl Sodiomalonate*: Into a solution of 1.0 g of 3-bromo-4-nitropyridine *N*-oxide (**1**) in 50 ml of diethyl carbonate, a solution of diethyl sodiomalonate, which had been formed from 0.3 g of sodium and 2.2 g of diethyl malonate in 50 ml of diethyl carbonate, was stirred from a dropping funnel at 15—20 °C over a period of an hour; then the mixture was heated at 50—60 °C for 5 hr. The resulting mixture was neutralized with dil hydrochloric acid to pH 3. The organic layer was separated, and the water layer was extracted with chloroform. After drying over anhydrous sodium sulfate, the combined organic layers were evaporated; the residue was dissolved in 10 ml of chloroform and refined through a silica gel (Wakogel C–300) column. After the elution of diethyl malonate with chloro-

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[8] S. M. McElvain and M. A. Goese, *J. Amer. Chem. Soc.*, **65**, 2227 (1943).

[9] R. Jujo, *Yakugaku Zasshi*, **66**(**B**), 49(1946).

form, the evaporation of the ethereal elute gave 1.25 g (91.9%) of 3-bis(ethoxycarbonyl)methyl-4-nitropyridine *N*-oxide (**2**) as pale yellow needles; mp 97—98 °C (recrystallized from acetone–isopropyl ether). Found: C, 48.08; H, 4.51; N, 9.19%; Calcd for $C_{12}H_{14}N_2O_7$: C, 48.33; H, 4.73; N, 9.39%. IR: 1750 cm^{-1} (C=O), 1520 and 1350 (NO_2), and 1245 (N→O). NMR($CDCl_3$): δ 1.28 (6H, t), 4.27 (4H, q), 5.31 (1H, s), and 7.93—8.25 (3H, m).

(b) With Ethyl Sodiocyanoacetate: A similar treatment of **1** with ethyl sodiocyanoacetate formed from 0.3 g of sodium and 2.0 g of ethyl cyanoacetate in pyridine at 0 °C, but with the solvent being evaporated before the neutralization, gave 0.92 g (80.3%) of 3-cyano(ethoxycarbonyl)-methyl-4-nitropyridine *N*-oxide (**3**) as pale yellow needles; mp 147 °C (recrystallized from methyl alcohol). Found: C, 47.75; H, 3.65; N, 16.57%; Calcd for $C_{10}H_9N_3O_5$: C, 47.81; H, 3.59; N, 16.73%. IR: 2225 cm^{-1} (CN), 1745 (C=O), 1520 and 1340 (NO_2), and 1240 (N→O). NMR($CDCl_3$): δ 1.34 (3H, t), 4.34 (2H, q), 5.58 (1H, s), and 8.06—8.45 (3H, m).

(c) With Ethyl Sodioacetoacetate at a Lower Temperature: A solution of 1.0 g of **1** and ethyl sodioacetoacetate from 0.3 g of sodium and 2.1 g of ethyl acetoacetate in 100 ml of diethyl carbonate was kept at 30—35 °C for 12 hr; then the reaction mixture was treated as above to give 0.8 g (65.4%) of 3-acetyl(ethoxycarbonyl)methyl-4-nitropyridine *N*-oxide (**4**) as yellow leaflets; mp 95—96 °C (recrystallized from ethyl ether). Found: C, 49.46; H, 4.48; N, 10.26%; Calcd for $C_{11}H_{12}N_2O_6$: C, 49.25; H, 4.48; N, 10.26%. IR: 1645 cm^{-1} (C=O), 1620 (C=C), 1510 and 1350 (NO_2), and 1260 (N→O). NMR($CDCl_3$): δ 1.13 (3H, t), 1.96 (3H, s), 4.24 (2H, m), 7.90—8.27 (3H, m), and 13.07 (1H, s).

(d) With Ethyl Sodioacetoacetate at a Higher Temperature: The reaction mixture of the above reaction was further heated at 80—90 °C for an additional 5 hr. The resulting mixture was treated by the same procedure, and from the alcoholic elute, 0.82 g (78.2%) of 3-ethoxycarbonyl-2-methylfuro(3,2-*c*)pyridine *N*-oxide (**5**) semihydrate was obtained as colourless prisms; mp 150 °C (recrystallized from acetone). Found: C, 57.31; H, 5.23; N, 5.92%; Calcd for $C_{11}H_{11}NO_4\cdot 1/2\,H_2O$: C, 57.39; H, 5.22; N, 6.09%, after drying over phosphorus pentoxide, Found: C, 59.64; H, 4.88; N, 6.08%; Calcd for $C_{11}H_{11}NO_4$: C, 59.28; H, 4.96; N, 6.33%. IR: 1695 cm^{-1}(C=O) and 1245 (N→O). NMR($CDCl_3$): δ 1.42 (3H, t), 2.78 (3H, s), 4.40 (2H, q), 7.31 (1H, d), 8.10 (1H, dd), and 8.82 (1H, d).

*Hydrolysis of **5***. A mixture of **5** and 10 ml of 10% hydrochloric acid was refluxed for 5 hr, and then cooled. The crystalline precipitates were collected and recrystallized from 0.1% hydrochloric acid to give 0.15 g (89.4%) of 2-methyl-5-oxidofuro(3,2-*c*)pyridine-3-carboxylic acid (**6**) as colourless needles; mp 254 °C (decomp.). Found: C, 55.69; H, 3.46; N, 7.06%; Calcd for $C_9H_9NO_4$: C, 55.96; H, 3.65; N, 7.25%. IR: 1690 cm^{-1}(broad)(COOH), 1245 (N→O). NMR(CD_3COOD): δ 2.83(3H, s), 7.71 (1H, d), 8.55 (1H, dd), and 9.10 (1H, d).

*Hydrolysis of **2***. A mixture of 1.0 g of **2** and 10 g of 30% sulfuric acid was heated at 130 °C for 3 hr; the reaction mixture was then neutralized with sodium carbonate to pH 2. The precipitates were collected by filtration and recrystallized from methyl alcohol to give 0.5 g (81.0%) of 3-(1-oxide-4-nitro)pyridylacetic acid as colourless needles; mp 161—162 °C. Found: C, 42.65; H, 2.56; N, 14.21%; Calcd for $C_7H_4N_2O_5$: C, 42.68; H, 2.58; N, 14.08%. IR: 1530 and 1350 cm^{-1}(NO_2), 1710 (C=O), and 1260 (N→O).

*Ammonium Salt of **3***. A tenth gram of **3** was dissolved in 10 ml of concd. ammonium hydroxide; then the mixture was evapolated to dryness, and recrystallized from acetone-isopropyl ether to give 0.09 g of ammonium salt of **3** as dark violet needles; mp 160—161 °C. Found: C, 44.75; H, 4.42; N, 20.57%. Calcd for $C_{10}H_{12}N_4O_5$: C, 44.77; H, 4.48; N, 20.89%.