Ring Transformation of 1,3-Dinitroquinolizin-4-one with Enolate Anions[1)]

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Synopsis. The ring transformation of 1,3-dinitroquinolizin-4-one, which is one of the condensed ring compounds of 1-substituted 3,5-dinitro-2-pyridone series, with enolate anions, $R^1CH_2COCHCOR^2$, gave the corresponding 2-COR^2-6-R^1-4-nitrobenzene-1,3-diols. The results show that carbonyl carbon of the quinolizinone behaves as reaction site in the ring transformation.

In a previous paper,[2)] we reported the substituent effects of 4- and 6-methyl or 4-methoxyl groups on the regio-orientation of the nucleophilic ring transformation of 1-substituted 3,5-dinitro-2-pyridones with enolate anions.

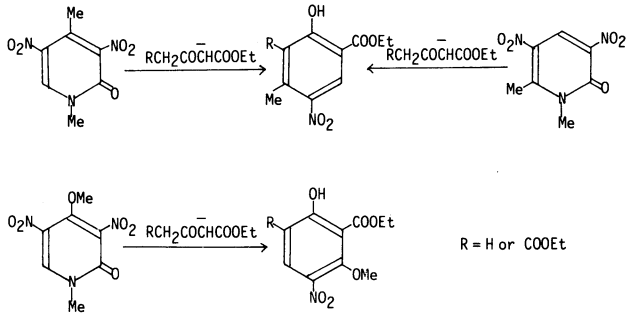

Fig. 1.

We wish to extend examinations to quinolizinone ring in order to investigate the scope and limitation of the reaction. 1,3-Dinitroquinolizin-4-one (**1**) is a 1,6-disubstituted 2-pyridone, of which 1- and 6-positions are linked with conjugated 1,3-butadiene unit, and the conjugation bonds in pyridone ring extend to pyridine unit. These structural features may cause a new type of reaction of electron-deficient 2-pyridone derivatives.

Results and Discussion

1,3-Dinitroquinolizin-4-one (**1**) was obtained by the known procedure.[3)] Treatment of **1** with 3 times equimolar ethyl sodio-3-oxobutanoate in DMF at −15—−10 °C gave colorless needles (**2a**) of mp 112.0—113.0 °C. The ^{1}H NMR spectra of **2a** indicated the presence of two aromatic *ortho*-protons and two hydroxyl protons in addition to methylene and methyl protons of ethoxycarbonyl group. From this result and IR spectra, **2a** was assigned to ethyl 2,6-dihydroxy-3-nitrobenzoate, and identified as that by comparison of spectral data with those of the sample prepared from 2,6-dihydroxy-3-nitrobenzoic acid.[4)]

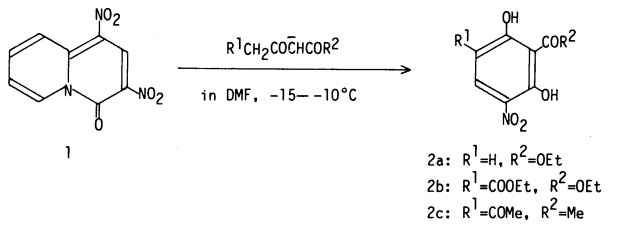

Fig. 2.

Similar reaction of **1** with 1.5 times equimolar diethyl sodio-3-oxopentanedioate gave diethyl 2,4-dihydroxy-5-nitro-1,3-benzenedicarboxylate (**2b**) in a good yield (76%).

Sodium salt of 2,4,6-heptanetrione also reacted in the similar conditions to give 3-acetyl-2,4-dihydroxy-5-nitroacetophenone (**2c**) in a moderate yield (57%).

The reaction of **1** with ethyl sodio-3-oxobutanoate was attempted to reveal appropriate reaction conditions, but no improvement of the yield of **2a** was achieved (Table 1). Diethyl 3-oxopentanedioate and 2,4,6-heptanetrione were sufficiently active to give reasonable yield of the products by using 1.5 mol of each reagent. However, the reaction of 3 molar amounts of ethyl 3-oxobutanoate did not show a good yield probably because the nucleophilic center of the reagent is methyl group which is less reactive than methylene group between two carbonyl groups.

The reaction of sodio-2,4-pentanedione in the conditions similar to those of the reaction of ethyl sodio-3-oxobutanoate gave only an unidentified resinous material.

Our previous results of the ring transformation of 3,5-dinitro-2-pyridones showed that the reaction centers were 4- and 6-positions (vinyl positions of carbonyl carbon) and not 2-position (carbonyl carbon) of 2-pyridone. In the present reaction, however, it is obvious that the product **2** consists of the reagent and C_2–C_3–C_4 part of quinolizinone ring and that carbonyl carbon (C_4 of the substrate **1**, corresponding to the 2-position of 2-pyridone) behaves as reaction site in the ring transformation. The fact is the first example

Table 1. Ring Transformation of 1,3-Dinitroquinolizin-4-one

Reagent[a)]	Reaction conditions		Products (Yields/%)	
	mol. ratio	temp/°C		
a	3.0	−15—−10	**2a** (25.6)	
b	1.5	−15—−10	**2b** (76.2)	
c	1.5	−15—−10	**2c** (56.8)	
a	3.0	25	**2a** (trace)	
a	1.5	−15—−10	**2a** (trace)	**1** (42.5)

a) **a**: ethyl sodio-3-oxobutanoate, **b**: diethyl sodio-3-oxopentanedioate, **c**: sodio-2,4,6-heptanetrione.

in 2-pyridone series.

Another product, 2-(nitromethyl)pyridine, which is supposedly derived from the rest of **1** in the ring transformation was not isolated. With reference to the report that 2-(nitromethyl)pyridine is an acidic and unstable compound,[5] it will give only a resinous material under the conditions of the present work.

From these results, a plausible course of the reaction is suggested as path(b) in the following scheme. The initial attack of enolate anion of β-dicarbonyl compound at the 2-position of substrate **1** (corresponding to the 4-position of 2-pyridone) was followed by the intramolecular nucleophilic attack of another nucleophilic center of introduced reagent at the 4-position of parent quinolizinone unit (carbonyl carbon) to give an intermediate **4**, of which reconstruction leads to the product **2**.

An alternative path(a) may be suggested, where the enolate anion attacks at the electrophilic centers of the quinolizinone in reverse sequence to path(b) to form the same intermediate **4** as is formed in path(b). It is well known that the nucleophilic attack generally occurs at a conjugated position and not at the carbonyl carbon in a conjugated carbonyl system, as the case of path(b). So, we prefer the path(b) as probable reaction course.

In the case of the reaction of ethyl sodio-3-oxobutanoate, a σ-complex, **3d**, may be initially formed, but direct conversion of **3d** to **4d** is unlikely, since it requires abstraction of a proton from less acidic center. Then **3d** is likely to transform to **3a** through equilibrium with **1** in view of easy cyclization to tricyclic intermediate by deprotonation from the most acidic methylene carbon in **3a**, and finally **4a** is given predominantly.[2,6,7]

The results mentioned above suggest that carbony carbon acts as electrophilic center in the intramolecular nucleophilic cyclization step of the ring transformation of 1,3-dinitroquinolizin-4-one. The fact is different from the case of 3,5-dinitro-2-pyridone, and may be explained as follows. If the reaction proceeds in the same way as 3,5-dinitro-2-pyridone,[2,8] an unfavorable crowded tricyclic intermediate, **5**, will be formed through path(c) or (d). Althogh the intermediate **5** appears to be not so unstable to be formed, its reconstruction to stable aromatic product such as **2** in path(b) is impossible. These factors will result in forming the intermediate **4** through path(b).

Experimental

All the melting points were uncorrected. ^{1}H NMR spectra were recorded by a Hitachi R-20B Spectrometer with TMS as the internal standard. IR spectra were obtained by a Hitachi 260-10 Spectrometer.

Reaction of 1 with Ethyl Sodio-3-oxobutanoate. To a solution of 500 mg (2.1 mmol) of **1** in 100 cm^3 of DMF was added dropwise ethyl sodio-3-oxobutanoate sulution, prepared from 150 mg (6.5 mmol) of sodium and 950 mg (7.3 mmol) of ethyl 3-oxobutanoate in 30 cm^3 DMF for 5 h at −15—−10 °C with stirring, and the mixture was allowed to stand at the same temperature overnight. After being quenched by addition of 3.5 cm^3 of 1 mol dm^{-3} HCl, the solvent was evaporated in vacuo, the residual oil was dissolved in 20 cm^3 water, and extracted with chloroform at pH 3.0. After the extract was dried over anhydrous magnesium sulfate chloroform was distilled off, and the residual syrup was column-chromatographed on silica gel (Wakogel C-200). From benzene elute, was obtained 126 mg

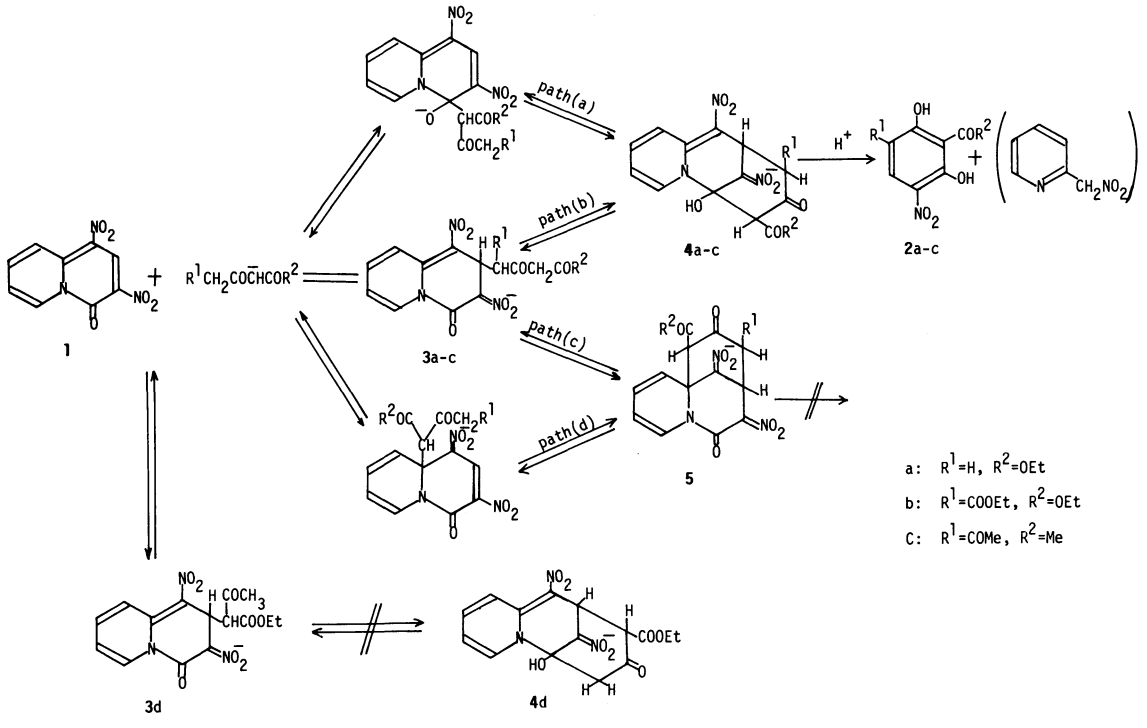

Fig. 3.

(27.7%) of ethyl 2,6-dihydroxy-3-nitrobenzoate (**2a**), which was recrystallized from petroleum benzine of bp 65—75 °C. IR(nujol) ν 3100 (OH), 1750, (C=O), 1540, 1350 (NO_2). ^1H NMR ($CDCl_3$) δ=1.44 (t, J=7.0 Hz, 3H), 4.48 (q, J=7.0 Hz, 2H), 6.52 (d, J=9.0 Hz, 1H), 8.15 (d, J=9.0 Hz, 1H), 12.43 (s, 1H), 12.61 (s, 1H). Found: C, 47.51; H, 3.81; N, 6.08%. Calcd for $C_9H_9NO_6$: C, 47.58; H, 3.99; N, 6.17%.

Reaction of 1 with Diethyl Sodio-3-oxopentanedioate. Treatment of 500 mg (2.1 mmol) of **1** with diethyl sodio-3-oxopentanedioate, prepared from 73 mg (3.2 mmol) of sodium and 720 mg (3.6 mmol) of diethyl 3-oxopentanedioate in the similar procedure as described above, gave 485 mg (76.2%) of diethyl 2,4-dihydroxy-5-nitro-1,3-benzenedicarboxylate (**2b**); colorless plates (petroleum benzine), mp 85.0—86.0 °C. IR(nujol) ν 3200 (OH), 1750 (C=O), 1540, 1350 (NO_2). ^1H NMR ($CDCl_3$) δ=1.40 (t, J=7.0 Hz, 3H), 1.43 (t, J=7.0 Hz, 3H), 4.43 (q, J=7.0 Hz, 2H), 4.44 (q, J=7.0 Hz, 2H), 8.71 (s, 1H), 11.94 (s, 1H), 12.26 (s, 1H). Found: C, 48.31; H, 4.44; N, 4.61%. Calcd for $C_{12}H_{13}NO_8$: C, 48.17; H, 4.38; N, 4.70%.

Reaction of 1 with Sodio-2,4,6-heptanetrione. According to the preliminary expriments, 500 mg (2.1 mmol) of **1** was made to react with sodio-2,4,6-heptanetrione prepared from 73 mg (3.1 mmol) sodium and 500 mg (3.6 mmol) of 2,4,6-heptanetrione to give 290 mg (56.8%) of 3-acetyl-2,4-dihydroxy-5-nitroacetophenone (**2c**); colorless columns (ethanol), mp 142.0—143.0 C. IR(nujol): ν 3100 (OH), 1620 (C=O), 1580 (C=O), 1550, 1345 (NO_2). ^1H NMR ($CDCl_3$) δ=2.69 (s, 3H), 2.82 (s, 3H), 8.73 (s, 1H), 14.94 (s, 2H). Found: C, 50.31; H, 3.89; N, 5.76%. Calcd for $C_{10}H_9NO_6$: C, 50.21; H, 3.79; N, 5.86%.

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