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STUDIES ON TERTIARY AMINE OXIDES—LII[1]

REACTION OF 4-NITROQUINOLINE 1-OXIDE WITH ENAMINES OF ISOBUTYRALDEHYDE. A NOVEL CYCLIZATION REACTION INVOLVING PARTICIPATION OF THE NITRO GROUP

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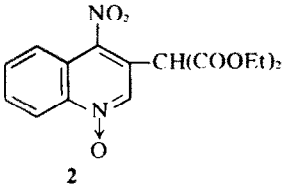
Abstract—When a chloroform solution of 4-nitroquinoline 1-oxide (**1**) and 2 equivalents of an enamine of isobutyraldehyde (**4**) is kept at room temp for a prolonged time, a novel cyclization reaction occurs to produce 1-hydroxy-2-oxo-3,3-dimethylpyrrolido[4,5-c]quinoline 5-oxide (**5**) or/and the corresponding 1-deoxy compound (**6**). Their structures were established by spectral and chemical examinations. The reaction mechanisms are also discussed.

It is well documented that the nitro group of 4-nitroquinoline 1-oxide (**1**) is readily replaced with various nucleophilic reagents to afford a large number of 4-substituted quinoline 1-oxides.[2,3] On the other hand, some nucleophiles are found to attack at the *ortho*-position to the 4-nitro group either with retention or with simultaneous displacement of the nitro group to produce 3,4-disubstituted quinoline derivatives; the first example is the base-catalyzed reaction of **1** with diethyl malonate which gives diethyl (4 - nitro - 3 - quinolyl)malonate 1-oxide (**2**)[4] and the second one is represented by the formation of ethyl α - (3 - cyano - 4 - quinolyl) - cyanoacetate (**3**) from the reaction of **1** with ethyl cyanoacetate and potassium cyanide.[5] In the course of studies on reaction of aromatic N-oxides with enamines,[6] we happened to come across a novel reaction of **1** with enamines of isobutyraldehyde which involved nucleophilic attack by enamines at the 3-position of **1** and consecutive cyclization between the N atom of the 4-nitro group and the enamine moiety thus introduced.



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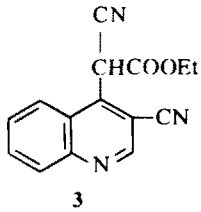

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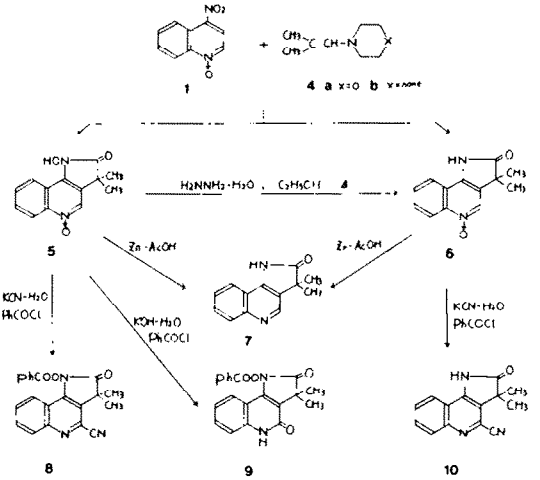
When a chloroform solution of **1** and two equivalents of 1 - morpholinoisobutene (**4a**) was kept at room temp, the mixture became light yellow and began to deposit yellow feathers of 1 - hydroxy - 2 - oxo - 3,3 - dimethylpyrrolido[4,5 - c]quinoline 5-oxide (**5**), m.p. 250° (dec), after few days. On further standing, orange crystals of the corresponding 1-deoxy compound, 2 - oxo - 3,3 - dimethylpyrrolido[4,5 - c]quinoline 5-oxide (**6**), m.p. 300° (dec), appeared accompanied by decrease of **5**. From reactions under reflux in dichloromethane and those at room temperatures in dimethylformamide or tetrahydrofuran, only **6** was obtained, no **5** being detected. The use of 1-pyrrolidinoisobutene (**4b**) in place of **4a** in dichloromethane similarly afforded **6** as a sole product. Table 1 lists these results.

Further, the application of the components of **4a**, i.e. isobutyraldehyde and morpholine, instead of **4a** itself, was found to give **6** although in a small yield of 8·3%; nevertheless, a similar reaction in the presence of molecular sieve 4A resulted in the formation of **5** in a moderate yield of 31%. The use of diethylamine as an amine proceeded similarly to give **5** in respective yields of 4·9 and 31 per cent depending upon the absence or the presence of the molecular sieve. Apparently, the corresponding enamines were initially formed and then the reaction with **1** occurred in these cases (Table 2).



Scheme 1.

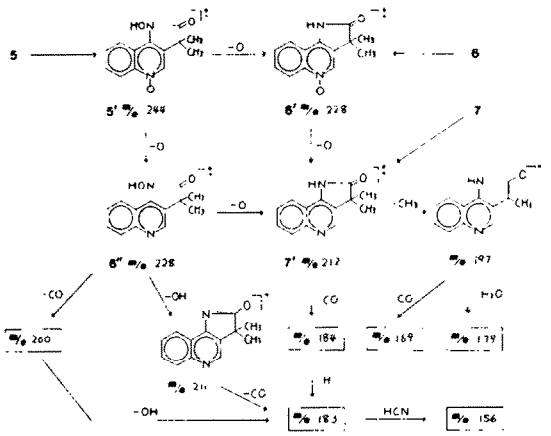
Compounds **5** and **6** gave analytical values in agreement with empirical formulae $C_{13}H_{12}O_3N_2$ and $C_{13}H_{12}O_2N_2$, and their mass spectra exhibited molecular ions at *m/e* 244 (**5'**) and 228 (**6'**), respectively. The first fragment peak produced by elimination of one O atom from **5'** seemed to consist of two ions, **6'** and **6''**, and the fragment patterns of **5'**, **6'** and **6''** could be reasonably explained as shown in Scheme 2.

Table 1. Reactions of 4-nitroquinoline 1-oxide with enamines of isobutyraldehyde

Exp. No.	Base of Enamine	Solvent	Reaction Temp. (°C)	Reaction Time (day)	Product (%) 5	Product (%) 6
1	morpholine	$CHCl_3$	room temp.	4	49	
2	morpholine	$CHCl_3$	room temp.	10	29.5	2.6
3	morpholine	$CHCl_3$	room temp.	20	16.4	13.2
4	morpholine	CH_2Cl_2	40	2		17.6
5	morpholine	CH_2Cl_2	40	4		8.8
6	morpholine	DMF	room temp.	10		14
7	morpholine	THF	room temp.	10		22
8	pyrrolidine	CH_2Cl_2	room temp.	10		17.5
9	pyrrolidine	CH_2Cl_2	0	10		9.6

Table 2. Reactions of 4-nitroquinoline 1-oxide with secondary amines and isobutyraldehyde

Exp. No.	Secondary Amine	Dehydrating Agent	Solvent	Reaction Temp. (°C)	Reaction Time (day)	Product (%) 5	Product (%) 6
10	morpholine	-	$CHCl_3$	room temp.	10		8.3
11	morpholine	molecular sieve 4A	$CHCl_3$	room temp.	10	31	
12	diethylamine	-	$CHCl_3$	room temp.	10	4.9	
13	diethylamine	molecular sieve 4A	$CHCl_3$	room temp.	10	31	

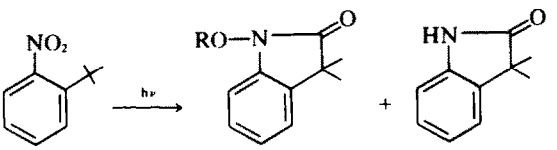


Scheme 2.

Their IR and NMR spectra were also consistent with the assigned structures. The IR spectrum of **5** displayed bands attributable to OH group (3640–2200 cm^{-1}) and a CO band (1740 cm^{-1}) but no absorption due to NO_2 group. The NMR spectrum of **5** showed C_3–H of quinoline ring as a singlet at 9·0 ppm and four protons at its C_5–C_8 as a complex multiplet at 7·5–8·5 ppm, but any signals due to C_3–H of quinoline ring and an aldehyde proton were not noticed. Compound **6** exhibited bands in the IR spectrum attributable to NH (3700–2100 cm^{-1}) and a CO band (1730 cm^{-1}), and its NMR spectrum closely resembled that of **5**.

Conversion of **5** to **6** was effected easily by heating with hydrazine hydrate in ethanol. On treatment with zinc powder and acetic acid, **5** as well as **6** afforded the same compound, 2 - oxo - 3,3 - dimethylpyrrolido[4,5 - c]-quinoline (**7**). When **5** was treated with potassium cyanide or potassium hydroxide in the presence of benzoyl chloride, a cyano or hydroxyl group was introduced into the 2-position of quinoline ring accompanied by deoxygenation of the N-oxide function as well as benzoylation of the 1-OH group to give 1 - benzoyloxy - 2 - oxo - 3,3 - dimethyl - 4 - cyanopyrrolido[4,5 - c]quinoline (**8**) or the corresponding 4-hydroxy compound (**9**). A similar reaction of **6** with potassium cyanide also smoothly produced 4-cyano-derivative (**10**), but no benzoylation of the lactam NH group was noticed in this case; compound **7** was recovered unchanged under similar conditions as expected (Scheme 1).

Döpp has obtained 1 - hydroxy - 3,3 - dimethyl - 3H - indolone (**11a**) and its deoxygenated product (**12**) from the photoreaction of *o* - nitro - t-butylbenzene in an alkaline solution and examined the IR and mass spectra of **11a**, **12** and the acetate of **11a** (**11b**).[7] The spectral properties of all products described in this paper are consistent with those reported by Döpp.



11a: R = H
b: R = Ac

12

Although the details of the reaction mechanism have not been established, the first step of the reaction must be nucleophilic attack by enamines at the electron-deficient 3-position of the quinoline ring to form a 3,4-dihydroquinoline intermediate (**13**).

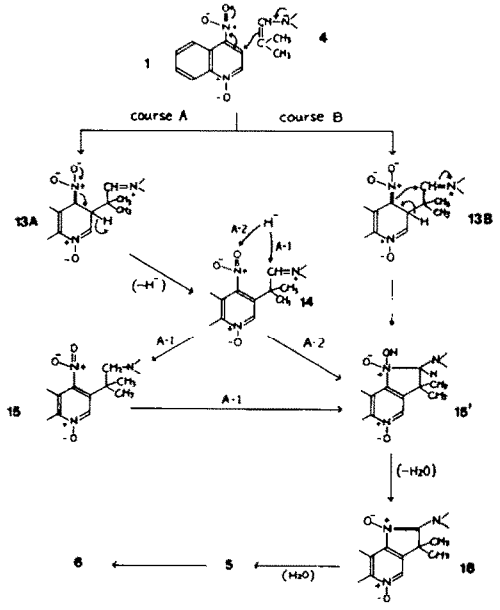
If a hydride ion is eliminated from **13** in the usual way observed in many nucleophilic substitution reactions on aromatic nuclei[8] such as the reaction of **1** with diethyl malonate, the formation of **5** might be explained either by course A–1 or by course A–2. The eliminated hydride ion attacks the immonium moiety of **14** formed at the same time, producing **15** followed by condensation between the nitro group and the methylene group via **15'** to give **16** in course A–1. Course A–2 involves the attack by the hydride ion at the oxygen atom of nitro group and concerted N–C bond formation to give **15'** which is dehydrated to **16**. Hydrolysis of **16** affords product **5**. With respect to the mode of attack of the hydride ion, the capture by the nitro group (course A–2) seems less likely than the reduction of the immonium group (course A–1). However, in spite of the well-known fact that aromatic nitro groups undergo condensation with carbanions to give nitrones or N-oxides,[9] the formation of **16** from **15** via this type of condensation seems highly improbable in this case because of the absence of strong base and the weakly acidic character of the methylene group.

On the contrary, if the elimination of a proton could occur from the first intermediate **13**, the formation of **5** may be explicable by course B which involves a concerted N–C bond formation between the nitrogen atom of the nitro group and the immonium carbon to give **15'** (Scheme 3).

Whereas there has been no precedent for such a proton shift in nucleophilic reactions of aromatic nitro compounds,[8] an attack by a N atom of nitro group on an electron-deficient carbon has been advanced in formation of benzimidazole N-oxides from N,N-disubstituted o-nitroanilines via an *aci*-nitro intermediate,[9] the fact of which seems to support the plausibility of course B in our reactions.

From the results of reactions of **1** with **4a** in chloroform (Table 1) and also the report by Danishefsky[10] on the reduction of aromatic nitro compounds with enamines, it seemed likely that the 1-deoxy compound **6** was produced from **5** by the reduction with excess enamines. However, separately attempted reduction of **5** with **4a** under practically the same conditions was unsuccessful. Of course, there is another possibility that some reduction might occur during the reaction course; for example, the reduction of the nitro group by a hydride ion may not be excluded. Information on this aspect is also lacking at present.

The elucidation of the problems unclarified here and the extension of the reaction are now under way in our laboratory.



Scheme 3.

EXPERIMENTAL

M.ps and b.ps are uncorrected. NMR spectra were run on a JNM-3H-60 spectrometer, using trifluoroacetic acid, deuteriodimethylsulfoxide or $CDCl_3$ as solvent, and TMS as internal standard. Mass spectra were recorded at 75 eV on a JMS-01SG spectrometer.

Quinoline 1-oxide.[11] A mixture of quinoline (129 g, 1 mole), $Na_2WO_4 \cdot 2H_2O$ (5 g), EDTA (5 g) and 30% H_2O_2 (100 ml) was carefully warmed at 70° with stirring. As an exothermic reaction ensued, the reaction vessel was externally cooled with water at need. After 2 hr, another 100 ml of 30% H_2O_2 was added, and warming at the same temp. was continued further 2 hr. The resulted clear soln was treated with powdered MnO_2 to decompose excess peroxide, concentrated *in vacuo* and extracted with CH_2Cl_2. The extract was dried over anhyd K_2CO_3, and the extract residue was purified by distillation under reduced pressure to give 140 g (96·5%) of quinoline 1-oxide, b.p. 166–170° (3 mm Hg).

Reactions of 4-nitroquinoline 1-oxide (**1**) *with enamines of isobutyraldehyde*

(1) (*Exp. No.* 1). A soln of **1** (0·95 g, 5 mmole) and **4a** (1·54 g, 11 mmole) in $CHCl_3$ (15 ml) was kept at room temp. After 4 days the resultant ppt was filtered, washed with $CHCl_3$ and dissolved in 10% KOH. This alkaline soln was filtered and then neutralized with 10% HCl to give yellow feathers of **5**, which was collected, washed with water and dried *in vacuo*, 0·6 g, m.p. 247–250° (dec). (Found: C, 63·52; H, 4·85; N, 11·04. Calc. for $C_{13}H_{12}O_3N_2$: C, 63·92; H, 4·95; N, 11·47%); IR(KBr) cm^{-1}: 3640–2200(b), 1740; NMR(CF_3COOH) ppm: 1·75 (6H, s, C_3–$(CH_3)_2$), 7·5–8·7 (4H, m, C_{6-9}–Hs), 9·0 (1H, s, C_4–H).

(2) (*Exp. No.* 3). A same $CHCl_3$ soln of **1** and **4a** as described above was kept at room temp. for 20 days to afford the mixture containing yellow feathers (**5**) and orange crystals. Further 10 ml of $CHCl_3$ was added, and the $CHCl_3$ soln was decanted with gentle shaking to separate $CHCl_3$ soln containing suspension of **5** from orange crystals. The isolation and purification of **5** was carried out as described in (1); yield, 0·22 g. Remained orange crystals were dissolved in 10% KOH, filtered to remove insoluble dust, and the filtrate was neutralized with 10% HCl. Precipitated powder was washed with water and recrystallized from EtOH to give 0·15 g of **6**, m.p. 297–300° (dec). (Found: C, 68·68; H, 5·40; N, 12·17. Calc. for $C_{13}H_{12}O_2N_2$: C, 68·41; H, 5·30; N, 12·27%); IR (KBr) cm^{-1}: 3700–2100 (b), 1730; NMR (CF_3COOH) ppm: 1·78 (6H, s, C_3–$(CH_3)_2$), 8·0–8·75 (4H, m, C_{6-9}–Hs), 9·2 (1H, s, C_4–H).

(3) (*Exp. No.* 4). A soln of **1** (0·95 g) and **4a** (1·54 g) in CH_2Cl_2 (30 ml) was refluxed for 2 days. The mixture was treated as above to give 0·2 g of **6**.

(4) (*Exp. No.* 8). A soln of **1** (0·95 g) and **4b** (1·8 g, 5 mmole) in CH_2Cl_2 (15 ml) was kept at room temp for 10 days to give 0·2 g of **6**.

Reaction of **1** *with isobutyraldehyde and diethylamine in the presence of molecular sieve* 4A (*Exp. No.* 13)

A mixture of **1** (0·95 g, 5 mmole), isobutyraldehyde (1 g, 14 mmole), diethylamine (2 g, 27 mmole) and molecular sieve 4A (1 g) in $CHCl_3$ (15 ml) was kept at room temp. for 10 days, and treated as in the above cases to give 0·30 g of **5**.

Another runs listed in Table 2 were carried out in practically the same way.

Reactions of 1 - *hydroxy* - 2 - *oxo* - 3,3 - *dimethylpyrrolido*[4,5 - c]*quinoline 5-oxide* (**5**)

(1) *Reaction with hydrazine.* A mixture of **5** (0·244 g), $NH_2NH_2 \cdot H_2O$ in EtOH (20 ml) was refluxed for 5 hr, and concentrated under reduced pressure. The residue was dissolved in a small amount of water, treated with 10% HCl, and the resulted yellow crystals were collected and recrystallized from EtOH to give 0·1 g (44%) of **6**, yellow needles, m.p. 297–300° (dec).

(2) *Reaction with zinc and acetic acid.* To a stirred soln of **5** (0·488 g) in AcOH (25 ml) was gradually added Zn powder (1 g). After 1 hr another 1 g of Zn powder was added and the mixture was stirred for 2 hr. Zn powder was removed by suction and the filtrate was concentrated under reduced pressure. The residue was purified by dry column chromatography on silica gel with AcOEt followed by recrystallization from AcOEt to give 0·345 g (81·2%) of **7**, colorless needles, m.p. 219–220°. (Found: C, 73·33; H, 5·68; N, 13·06. Calc. for $C_{13}H_{12}ON_2$: C, 73·56; H, 5·70; N, 13·20%); IR (KBr) cm^{-1}: 3600–2300, 1730; NMR (DMSO–d_6) ppm: 1·43 (6H, s, C_3–$(CH_3)_2$), 7·5–8·25 (4H, m, C_{6-9}–Hs), 8·77 (1H, s, C_4–H), 11·4 (1H, bs, N_1–H).

(3) *Reaction with potassium cyanide and benzoyl chloride.* A mixture of **5** (0·488 g), KCN (1·63 g), H_2O (20 ml), CH_2Cl_2 (20 ml) and PhCOCl (0·71 g) was stirred for 12 hr. The CH_2Cl_2 layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined CH_2Cl_2 layer was dried over anhyd Na_2SO_4 followed by evaporation to give a residue which was chromatographed on silica gel with benzene, and recrystallized from isopropyl ether to give 0·57 g (80%) of **8**, colorless needles, m.p. 170–171°. (Found: C, 70·63; H, 4·25; N, 11·99. Calc. for $C_{21}H_{15}O_3N_3$: C, 70·58; H, 4·23; N, 11·76%); IR (Nujol) cm^{-1}: 2225, 1781, 1763; NMR ($CDCl_3$) ppm: 1·78 (6H, s, C_3–$(CH_3)_2$), 7·34–8·30 (9H, m, C_{6-9}– and phenyl–Hs); MS: *m/e* 357 (M^+).

(4) *Reaction with potassium hydroxide and benzoyl chloride.* A mixture of **5** (0·488 g), 10% KOH (13 ml), CH_2Cl_2 (20 ml) and PhCOCl (0·71 g) was stirred for 12 hr. The mixture was treated as in the foregoing experiment and the crude product was chromatographed on silica gel with AcOEt and EtOH. The fraction eluted with EtOH was recrystallized from EtOH to give 0·1 g (14%) of **9**, colorless granular crystals, m.p. 239–240°. (Found: C, 68·58, H, 4·67; N, 8·02. Calc. for $C_{20}H_{16}O_4N_2$: C, 68·96; H, 4·63; N, 8·04%); IR (KBr) cm^{-1}: 3200–2400 (b), 1785, 1753, 1655; NMR (DMSO–d_6) ppm: 1·55 (6H, s, C_3–$(CH_3)_2$), 6·95–8·0 (8H, m, C_{7-9}– and phenyl–Hs), 8·1–8·4 (1H, m, C_6–H), 8·1 (1H, bs, N_5–H); MS: *m/e* 348 (M^+).

Reaction of 2 - *oxo* - 3,3 - *dimethylpyrrolido*[4,5 - c]*quinoline 5-oxide*

(1) *Reaction with zinc and acetic acid.* As described for the reaction of **5**, **6** (0·456 g) was treated with Zn powder and AcOH to give 0·191 g (45%) of **7**.

(2) *Reaction with potassium cyanide and benzoyl chloride.* A mixture of **6** (0·228 g), KCN (1·5 g), H_2O (10 ml), $CHCl_3$ (10 ml) and PhCOCl (1 g) was stirred for 12 hr. The $CHCl_3$ layer was separated, dried over anhyd Na_2SO_4 and passed through a silica gel column to give 0·110 g (46·3%) of **10**, colorless granular crystals, m.p. 232–233° (CH_2Cl_2–isopropyl ether). (Found: C, 70·63; H, 4·75; N, 17·53. Calc. for $C_{14}H_{11}ON_3$: C, 70·87; H, 4·67; N, 17·71%); IR (KBr) cm^{-1}: 3600–2600 (b), 2245, 1725; NMR ($CDCl_3$) ppm: 1·79 (6H, s, C_3–$(CH_3)_2$), 7·7–7·93 (2H, m, $C_{7,8}$–Hs), 8·0–8·2 (2H, m, $C_{6,9}$–Hs), 11·42 (1H, bs, N_1–H); MS: *m/e* 237 (M^+).

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