Studies on Tertiary Amine Oxides. LIV. Reaction of Quinoline N-Oxides with Potassium Cyanate and Tosyl Chloride in Ethanol

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(Received March 3, 1975)

Quinoline 1-oxide (Ia) reacted with potassium cyanate and tosyl chloride in ethanol at $-10^\circ$ to give ethyl N-(2-quinolyl)carbamate (Iia) in 70% yield. The reaction under reflux caused decrease of the yield of Ia (11%) and additional formation of 2-ethoxyquinoline (IIIa) (54%) and carbostyril (IV) (29%). Unless ethanol was used, no definite product was isolated. Reactions of some derivatives of Ia as well as that of isoquinoline 2-oxide were also examined under the same conditions.

Previous papers have described the reaction of aromatic N-oxide with cyanogen bromide in alcohol producing alkoxycarbonylamino derivatives by nucleophilic attack of cyanate ion on cyanogen bromide-adduct of N-oxide and participation of alcohol. These results suggest the possibility that treatment of aromatic N-oxide with an acylating agent and cyanate ion in alcohol would afford N-heteroarylcarbamate. This paper deals with the reaction of quinoline N-oxides with tosyl chloride and potassium cyanate in ethanol.

To a solution of quinoline 1-oxide (Ia) and excess potassium cyanate (6 equiv.) in ethanol, an equivalent amount of tosyl chloride was added by portions under cooling with freezing mixture and the reactants were stirred around $-10^\circ$ for 5 hours. The basic fraction obtained from the reaction mixture was purified by column chromatography on alumina with ether to give ethyl N-(2-quinolyl)carbamate (Iia), colorless prisms, mp 99—100°, in a good yield of 70% [1] in Chart 1.

On the other hand, when the reaction was carried out under reflux for 5 hours, the yield of Iia decreased to only 11% and 2-ethoxyquinoline (IIIa) and carbostyril (IV) were additionally formed in respective yields of 54 and 29% [2] in Chart 1.

Further, the reaction in the absence of ethanol was examined by vigorously agitating a heterogeneous mixture of a solution of Ia and tosyl chloride in chloroform and the cyanate solution under cooling with freezing mixture. Although no resinous substances were formed differently from the reaction of Ia with cyanogen bromide in chloroform, the attempted purification of products by distillation under reduced pressure gave a viscous oil which readily solidified to amorphous mass, no definite product being characterized. However, treatment of the fraction containing products with ethanol at room temperature overnight instead of distillation afforded Iia though in a small yield of 17.1% [3] in Chart 1.

The results of these experiments indicate that the tosyl-adduct of Ia (A) reacts with isocyanate anion to give the 1,2-dihydro intermediate (B) which is in turn converted into 2-quinolyl isocyanate (C) by releasing p-toluenesulfonic acid. Nevertheless, the original presence of ethanol is essential for the smooth formation of the carbamate Iia, and it is not necessarily clear in which step ethanol participates in the first reaction despite of the observation obtained from the third one (see Chart 2).

2) Location: Maidashi, Higashi-ku, Fukuoka
On the other hand, cyanate anion seemingly acts as a base rather than a nucleophile at higher temperature and ethoxy group attacks at α-position of A to give IIIa via another 1,2-dihydro intermediate (D); the reason for such a marked temperature dependency is not yet elucidated (Chart 2).

The formation of carbostyril (IV) seems to result from nucleophilic attack by water present in the reaction system, but the hydrolysis of IIIa or a path involving nucleophilic attack of oxygen atom of cyanate ion may not be excluded.

Subsequently, reactions of some derivatives of Ia were similarly carried out at low temperatures (about −10°C).

Lepidine 1-oxide (Ib) and 4-chloroquinoline 1-oxide (Ic) gave the corresponding 2-quinolylcarbamate (IIb and IIc) in somewhat lower yields of 39 and 59%, respectively. From the reaction of 4-ethoxyquinoline 1-oxide (IId), 2,4-diethoxyquinoline (IIId) (19%) was produced besides the 2-quinolylcarbamate (IIId) (15%) in spite of the low reaction temperature. Reduction of IIc with hydrogen over palladium-charcoal gave IIa. The identity of IIId was confirmed by comparison with an authentic sample prepared from 2,4-dibromoquinoline and ethanolic sodium ethoxide.

The reaction of 4-quinolinol 1-oxide (Ie) resulted in the formation of a mixture of 3-, 6- and 8-tosyloxy-4-quinolinol (V) in a good yield of 86%, the formation of quinolylcarbamate being not detected. This result is apparently contrast to that of the reaction with cyanogen bromide and ethanol which gave a mixture of quinolylcarbamates in good yields. However, the formation patterns of products in both cases are essentially the same; they originated

from 1-tosyloxy- (E) or 1-cyanato-4-quinolone (F) by rearrangement of the respective 1-substituents, tosylxy or cyanato group.

4-Nitroquinoline 1-oxide was inert to the reaction under this condition and largely recovered, no definite product being isolated.

The reaction of 2-chloroquinoline 1-oxide (VI) afforded ethyl 4-(2-chloro-4-quinolyl)allophanate (VII) as a sole product in a small yield of 6.5% accompanied by 70% recovery of VI. The structure of VII was assigned from elemental analysis, infrared (IR) and unclear magnetic (NMR) spectra.

Similar reaction of quinaldine 1-oxide (VIII) gave no carbamate but 3-ethoxyquinaldine (IX) as a main product in 40.6% and 3-tosyloxy- (Xa) and 6- or 8-tosyloxyquinaldine (Xb) as by-products in respective yields of 1.9 and 2.5%. Treatment of IX with hot concentrated hydroiodic acid afforded 3-hydroxyquinaldine. The reaction can be well explained by the following courses involving an anhydro base (G) as an intermediate similarly to many β-substitution reactions of aromatic N-oxide derivatives.

\[
\text{VIII} \rightleftharpoons \text{N} \quad \text{TsO} \quad \text{N} \quad \text{OEt} \quad \text{TsO} \\
\text{Cl}^- \quad \text{CH}_2 \quad \text{Ts} \quad \text{CH}_2 \quad \text{Ts} \quad \text{Cl}^- \\
\text{G} \\
\]

In view of the easy formation of ω-chloroquinaldine from VIII and tosyl chloride, the predominant formation of 3-ethoxy derivative, IX, in this case is very significant. Apparently cyanate ion acts as a base, and this result suggests the possibility that an appropriate combination of acylating agent, base and nucleophile would open a new route to β-substituted products of quinaldine. However, attempted reaction using potassium hydroxide in place of potassium cyanate failed, and no visible sign of formation of IX or Xa was noticed.

In connection with the previous report, 8-ethoxycarbonylaminoquinoline N-oxide (XI) was similarly treated with potassium cyanate and tosyl chloride in ethanol. The reaction readily took place and 2,8-bis(ethoxycarbonyl)aminoquinoline (XII) was obtained in fairly better yield of 51% as compared with the reaction with cyanogen bromide which gave XII in only 8% yield.

Finally, the reaction of isoquinoline 2-oxide (XIII) under the same condition was found to give ethyl N-(1-isoquinoly)carbamate (XIV) in 44% yield as a sole product, no 4-substituted product being isolated in contrast to the reaction with cyanogen bromide.

These results are shown in Chart 3.

Reaction was carried out also with N-oxides of 4-chloropyridine and 2-picoline, but resulted in recovery of the starting material in each case.

9) H. Tanida, *Yakugaku Zasshi*, 78, 611 (1958); Whereas Tanida has obtained ω-chloroquinaldine by the reaction of VIII with tosyl chloride in the presence of boron trifluoride, this reaction was shown to proceed also in the absence of boron trifluoride: Motoyoshi Yamazaki, private communication.
Various preparative methods for amino derivatives of heteroaromatics have been reported which involve nucleophilic reaction of heteroaromatic N-oxides.\textsuperscript{11,12} The above-mentioned reaction is also useful for such means in benzopyridine series. Further work on extending this type of reaction to pyridine series is in progress.

**Experimental\textsuperscript{13}**

**Reaction of Quinoline 1-Oxide (Ia)—1** To a combined solution of Ia·2H\textsubscript{2}O (0.91 g) in EtOH (30 ml) and KOCN (2.43 g) in H\textsubscript{2}O (4 ml) was added TsCl (1.06 g) by small portions under cooling with freezing mixture and stirring, and the stirring was continued at the same temperature (ca. −10°) for 5 hr. The

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13) All melting and boiling points are uncorrected. NMR spectra were measured with JNM-3H-60 spectrometers at 60MC using trimethyl silane (TMS) as internal reference.
reaction mixture was concentrated under reduced pressure, mixed with H₂O and extracted with CHCl₃. The extracted fraction was chromatographed on an alumina column with ether to give 0.76 g (70%) of the 2-quinolylcarbamate IIa, 2a-g) colorless pillars, mp 90—100° (ether).

2) A mixture of Ia (1.45 g), KOCN (1.22 g) and TsCl (2.86 g) in EtOH (20 ml) was refluxed for 5 hr and worked up as above. Ether elution of alumina column afforded successively 0.53 g (54%) of 2-ethoxyquinoline IIa and 0.23 g (11%) of IIa. IIa: colorless liquid, bp 87—89° (2 mmHg). Picrate: yellow prisms, mp 139—142° (MeOH). The fraction eluted with CHCl₃—MeOH (20:1) gave 0.42 g (29%) of carboxylic acid, colorless needles, mp 195—196° (MeOH).

3) To a vigorously stirred mixture of Ia·2H₂O (1.81 g) in CHCl₃ (30 ml) and KOCN (2.43 g) in H₂O (10 ml), TsCl (2.12 g) was added under cooling with freezing mixture. After stirring was continued further 2.5 hr, the CHCl₃ layer was separated, washed with H₂O and dried over Na₂SO₄. The residue from the CHCl₃ solution was chromatographed on an alumina column with ether, and the effluent was distilled under reduced pressure to give colorless viscous oil, bp 180—182° (2 mmHg), which readily solidified to amorphous mass conceivably to be some polymer of 2-quinolyl isocyanate.

The above ether effluent from another run was kept overnight with EtOH (5 ml). The residue from EtOH solution was chromatographed on alumina with petr. ether—ether (1:1) to give 0.37 g (17.1%) of IIa.

**Reaction of Leptidin 1-Oxide (Ib)** — A solution of Ib (0.84 g), KOCN (2.43 g) and TsCl (1.06 g) in EtOH (30 ml)—H₂O (4 ml) was allowed to react and worked up in the same way as the foregoing experiment 1). Chromatography on alumina with CHCl₃ gave 0.45 g (39%) of the carbamate Ib, colorless prisms, mp 135° (acetone).

**Reaction of 4-Chloroquinoline 1-Oxide (Ic)** — 1 Reaction: The same procedure using Ic (0.90 g), KOCN (2.43 g), TsCl (1.06 g) in EtOH (30 ml)—H₂O (4 ml) gave 0.74 g (59%) of the carbamate Ic, colorless prisms, mp 104—105° (acetone). *Anal. Calcd. for C₁₅H₁₇O₂N₂Cl: C, 57.49; H, 4.39; N, 11.18. Found: C, 57.47; H, 4.16; N, 10.86.*

2) Hydrogenation of Ic: A solution of Ic (0.10 g) in MeOH (15 ml) was hydrogenated at ordinary temperature and pressure over 10% Pd·C (0.05 g) in the presence of AcONa (0.05 g). After uptake of ca. 10 ml of H₂, the filtered solution was concentrated under reduced pressure, treated with H₂O, made alkaline with K₂CO₃ and extracted with ether to give 0.08 g (93%) of Ia.

**Reaction of 4-Ethoxyquinoline 1-Oxide (Id)** — 1 Reaction: A mixture of products obtained from the reaction of Id (1.13 g) with KOCN (2.43 g) and TsCl (1.06 g) in EtOH (30 ml)—H₂O (4 ml) was chromatographed on alumina. Elution with petr. ether—ether (3:1) afforded successively 0.30 g (19%) of 2,4-diehdroxyquinoline (IIId) and 0.20 g (15%) of the carbamate (IIId). IIId: colorless needles, mp 52—54° (MeOH—H₂O). *Anal. Calcd. for C₁₅H₁₇O₃N: C, 71.85; H, 6.97; N, 6.45. Found: C, 71.43; H, 6.90; N, 6.15. Picrate: yellow needles, mp 196° (MeOH).* *Anal. Calcd. for C₁₅H₁₇O₃N·C₆H₅O₂Na₂: C, 51.12; H, 4.04; N, 12.56. Found: C, 51.35; H, 4.11; N, 12.38.* It was proved identical with an authentic sample prepared as below. IIId: colorless needles, mp 124° (ether). It was proved identical with an authentic sample.³⁰

2) Synthesis of IIId: To an ethanolic sodium ethoxide prepared from sodium (0.05 g) and EtOH (10 ml) was added 2,4-dibromoquinoline (0.29 g), and the whole was refluxed for 5 hr. Chromatography on alumina with ether gave 0.20 g (90%) of IIId, colorless prisms, mp 52—54° (MeOH—H₂O).

**Reaction of 4-Quinolinol 1-Oxide (Ie)** — A mixture of products obtained from the reaction of Ie (0.81 g) with KOCN (2.43 g) and TsCl (1.06 g) in EtOH (30 ml)—H₂O (4 ml) was recrystallized from MeOH to give 1.35 g (80%) of a crystalline mixture of 3-, 6- and 8-tosloyl-4-quinolinol (V). Its thin-layer chromatogram on silica gel showed three spots, each of which was identified by comparison with the chromatogram of the respective authentic sample. Further exploration of its composition was not carried out.

**Reaction of 2-Chloroquinoline 1-Oxide (VI)** — A mixture of products obtained from the reaction of VI (0.90 g) with KOCN (2.43 g) and TsCl (1.06 g) in EtOH (30 ml)—H₂O (4 ml) was chromatographed on alumina with ether to give successively 0.08 g (6.5%) of 2-chloro-4-quinoyl phenol (VII) and 0.70 g (78%) of unchanged VI. VII: colorless needles, mp 211—212.5° (acetone). *Anal. Calcd. for C₁₅H₁₇O₂N₂Cl: C, 53.15; H, 4.09; N, 14.31. Found: C, 53.37; H, 4.17; N, 14.34. IR vmax cm⁻¹: 3190, 3110 (NH), 1730, 1722 (C=O). NMR δ (CDCl₃): 1.48 (3H, t, J = 7.0 Hz, -CH₂CH₃), 4.64 (2H, q, J = 7.0 Hz, -CH₂CH₃), 8.1—9.7 (7H, m, 2 NH and aromatic protons).*

**Reaction of Quinalidine 1-Oxide (VIII)** — A mixture of products obtained from VIII (0.80 g) with KOCN (2.43 g) and TsCl (1.06 g) in EtOH (30 ml)—H₂O (4 ml) was concentrated under reduced pressure, treated with H₂O and extracted with ether. The ether solution was shaken with 10% HCl, and the HCl layer was made alkaline with K₂CO₃ and extracted with ether. The extract residue was chromatographed on alumina. Elution with petr. ether—ether (1:1) gave successively 0.30 g (40.6%) of 3-ethoxyquinoline (IX) and 0.06 g (1.9%) of 3-tosloylquinoline (Xa).³⁹ The third fraction eluted with ether gave 0.08 g (2.5%) of Xb. IX: colorless needles, mp 71.5° (petr. ether—ether). *Anal. Calcd. for C₁₅H₁₇O₂N: C, 76.97; H, 7.00; N, 7.48. Found: C, 77.43; H, 7.11; N, 7.19. NMR δ (CDCl₃): 8.50 (3H, t, J = 7.5 Hz, -CH₂CH₃), 7.23 (3H, s, C₆H₃), 5.75 (2H, q, J = 7.5 Hz, -CH₂CH₃), 1.70—2.80 (5H, m, aromatic protons). Picrate: yellow needles, mp 195—196° (MeOH).* *Anal. Calcd. for C₁₅H₁₇O₂N·C₆H₅O₂Na₂: C, 51.92; H, 3.87; N, 13.46. Found: C, 51.31; H, 3.71; N, 13.55. Xa: colorless pillars, mp 117—118° (ether). *Anal. Calcd.
for C_{11}H_{18}O_{2}NS: C, 65.16; H, 4.83; N, 4.47. Found: C, 65.34; H, 4.74; N, 4.40. It was proved identical with an authentic sample. Xb: colorless pillars, mp 104—105°. Anal. Calcd. for C_{12}H_{19}O_{2}NS: C, 65.16; H, 4.83; N, 4.47. Found: C, 65.25; H, 4.58; N, 4.35. Xb could be assumed to be 6- or 8-troyloxyquinaldine, but further structure elucidation was not achieved.

2) Hydrolysis of IX: A mixture of IX (1.2 g) and conc. HI (1.5 ml) was refluxed for 3.5 hr, concentrated under reduced pressure and taken up in CHCl_{3}. The CHCl_{3} solution was washed with 10% NaHSO_{3}—5% NaHCO_{3}, saturated NaCl solution and H_{2}O and dried. The residue from the CHCl_{3} solution was chromatographed on alumina with ether and MeOH. The ether eluate gave 0.72 g (60%) of IX and the MeOH eluate gave 0.06 g (6%) of 3-hydroxyquinaldine, colorless needles, mp 255° (decomp.) (MeOH) which was proved identical with an authentic sample.\(^{6,7}\)

**Reaction of 8-Ethoxycarbonylaminoquinoline 1-Oxide (XI)**—The reaction of XI (1.0 g) with KOCN (2.1 g) and TsCl (0.92 g) was carried out in EtOH (30 ml)—H_{2}O (4 ml) under the same condition. The basic fraction separated from the reaction mixture was chromatographed on alumina with ether to give 0.66 g (51%) of the dicarbamate XII,\(^{38}\) colorless needles, mp 153—153.5°. Anal. Calcd. for C_{14}H_{19}O_{2}N_{2}: C, 59.39; H, 5.65; N, 13.86. Found: C, 59.40; H, 5.49; N, 13.82.

**Reaction of Isoquinoline 2-Oxide (XIII)**—The reaction of XIII (0.91 g) with KOCN (2.43 g) and TsCl (1.06 g) was carried out in EtOH (30 ml)—H_{2}O (4 ml) under the same condition. The basic fraction was chromatographed on alumina with CHCl_{3} to give 0.48 g (44%) of 1-isoquinolylicarbamate XIV,\(^{38}\) colorless needles, mp 138—139°.