[Chem. Pharm. Bull. 18(1) 26—31 (1970)]

UDC 547.831.1.07.04

Studies on Tertiary Amine Oxides. XXXVII.[1] Reactions of Aromatic N-Oxides with Enol Ethers in the Presence of Benzoyl Chloride

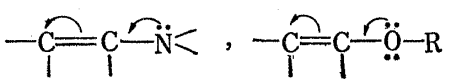
Masatomo Hamana and Hiroshi Noda

Faculty of Pharmaceutical Sciences, Kyushu University[2]

(Received May 16, 1969)

Reaction of aromatic N-oxide with enol ether in the presence of benzoyl chloride was examined. 2-Ethoxycyclohexene (II) reacted readily with quinoline 1-oxides (I, IV) and isoquinoline 2-oxide (VI), producing α-2-cyclohexanonyl derivatives (III, V, VII) in fairly good yields. Similarly, the reaction of I with 2-ethoxypropene (IX), methyl vinyl ether (XI) and dihydropyrane (XIV) gave 2-acetonyl- (X), 2-(2-methoxyvinyl)- (XII) and 2-(5-dihydropyranyl)-quinolines (XV), respectively. Nucleophilic reactivity of enol ether in this reaction was considerably lower compared with that of enamine; no satisfactory result was obtained with II and pyridine 1-oxide and also with I and furan, thiophene and anisole under similar conditions.

Previous papers from our laboratory have shown that the acyl-adducts of N-oxides of pyridine series readily undergo nucleophilic attack not only by enamines of cyclohexanone[3] or isobutyraldehyde,[1] but also by indoles[4] and antipyrine[5] which can be regarded as aromatic analogs of enamine.[6] From these results it may be well presumed that the enol ether system, having polarization similar to that of enamine, would enter into reaction with an acyl adduct of aromatic N-oxide. The subject of this report deals with reactions of some enol ethers and aromatic N-oxides in the presence of benzoyl chloride.



When benzoyl chloride (1.2 eq) was added dropwise to an ice-cooled solution of quinoline 1-oxide (I) and 1-ethoxycyclohexene (II) (2 eq) in chloroform, the solution turned gradually to reddish black. The reaction mixture was allowed to stand overnight at room temperature, followed by treatment with 20% hydrochloric acid to give expected 2-(2-quinolyl)cyclohexanone (III)[3a] in about 58% yield. An alternative procedure involving the reverse addition of II to the benzoyl chloride-adduct of I (VIII) gave essentially the same result. In the same way 2-(4-chloro-2-quinolyl)cyclohexanone (V)[3c] was obtained in good yield (73%) from 4-chloroquinoline 1-oxide (IV), and isoquinoline 2-oxide (VI) also smoothly afforded 2-(1-isoquinolyl)cyclohexanone (VII)[3a] in 40% yield.

On the other hand, no reaction was observed with pyridine 1-oxide and II even when tosyl chloride was used as an acylating agent.

Similar application of 2-ethoxypropene (IX) to benzoyl chloride-adduct of quinoline 1-oxide (VIII) in chloroform followed by treatment of the reaction mixture with hydrochloric acid gave 2-acetonylquinoline (X)[7] in 44% yield (Chart 1).

Subsequently, the reaction of methyl vinyl ether (XI) with I was examined. A large excess of XI was added at −13° to a solution of VIII in chloroform, and then the temperature

1) Part XXXVI: M. Hamana and H. Noda, *Yakugaku Zasshi*, **89**, 641 (1969).
2) Location: *Katakasu, Fukuoka.*
3) *a*) M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), **13**, 912 (1965); *b*) *Idem, ibid.*, **14**, 762 (1966); *c*) *Idem, ibid.*, **15**, 474 (1967).
4) M. Hamana and I. Kumadaki, *Chem. Pharm. Bull.* (Tokyo), **15**, 363 (1967).
5) M. Hamana and H. Noda, *Chem. Pharm. Bull.* (Tokyo), **15**, 1380 (1967).
6) J. Szmuskovicz, "Advances in Organic Chemistry: Methods and Results," Vol. 4, ed. by R.A. Raphael, E.C. Taylor, and H. Wynberg, Interscience Publishers, Inc., New York, N.Y., 1963.
7) T. Okamoto and H. Takayama, *Chem. Pharm. Bull.* (Tokyo), **11**, 514 (1965).

NII-Electronic Library Service

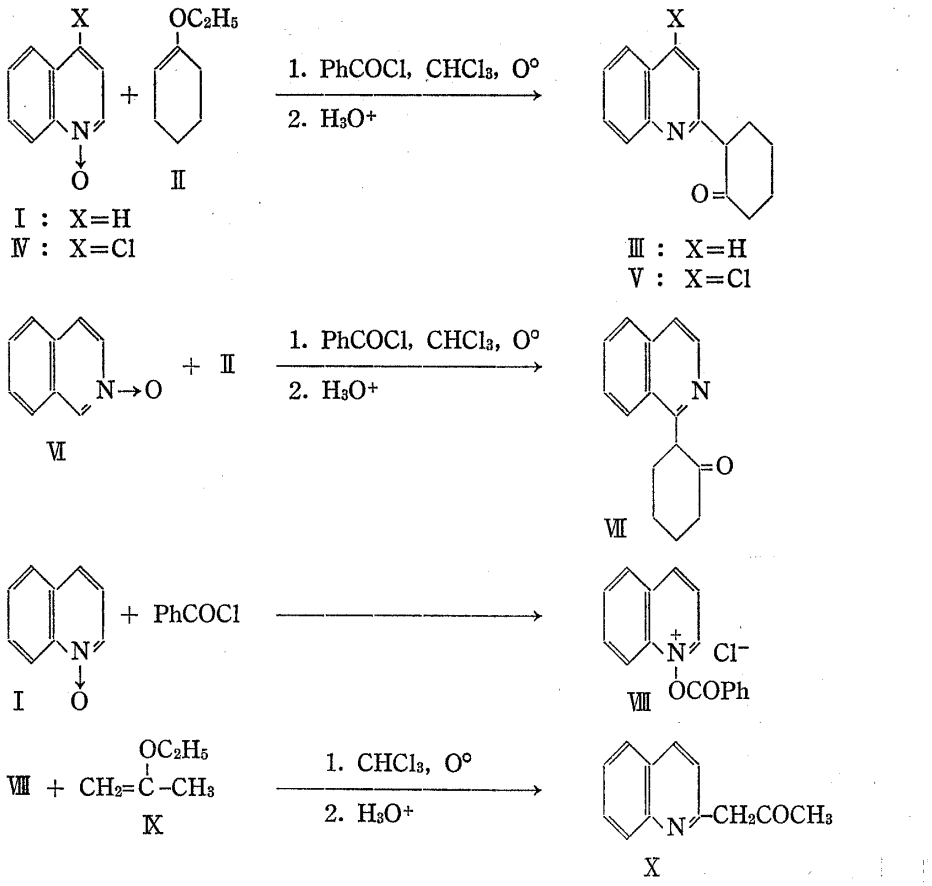


Chart 1

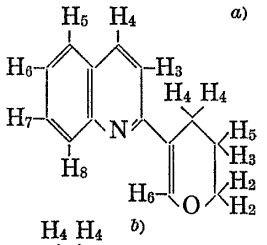
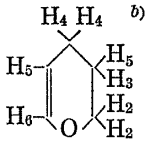
of the mixture was gradually raised to 0° for two hours. The rapid raising of the temperature was unfavorable because of forming large amounts of resinous substances. After standing overnight in a refrigerator, methanol and a catalytic amount of *p*-toluenesulfonic acid were added to the reaction mixture, which was kept at room temperature for further two days. The solution was basified with triethylamine and the volatile substances were removed under reduced pressure at a low temperature. The residue was completely basified with saturated sodium bicarbonate solution and extracted with ether. Vacuum distillation of the extracted substances afforded methyl benzoate (51%) and 2-(2-methoxyvinyl)quinoline (XII) (50%, bp 140—145° (4 mmHg)) as a greenish yellow, viscous oil. Since XII was so unstable as to polymerize to black resines on standing at ordinary temperature, proof of the proposed structure was provided by elemental analysis of its picrate (mp 165—168°, $C_{12}H_{11}ON \cdot C_6H_3O_7N_3$) and also by transformation to quinaldic acid 1-oxide[3a] with peracetic acid. Although in a small yield, XII was also obtained together with benzoic acid on vacuum distillation of the basic fraction obtained by shaking the reaction mixture with 5% hydrochloric acid for a short time, followed by making alkaline with sodium bicarbonate and extracting with chloroform. These observations may be accounted for by the reaction sequences shown in Chart 2. The ether, XI, attacks on the 2-position of quinoline ring of VIII in the usual way followed by elimination of benzoic acid to give the compound XIII as the preliminary product. The compound XIII is not appreciably hydrolyzed by dil. hydrochloric acid under the condition employed here, but decomposes thermally through distillation to XII and benzoic acid. On the other hand, when XIII is treated with methanol, it is converted to methyl benzoate and dimethylacetal of 2-quinolylacetaldehyde from which methanol is eliminated through vacuum distillation to give XII.

2,3-Dihydro-4*H*-pyrane (XIV) was shown to react with benzoyl chloride-adduct of I (VIII) in the same manner as methyl vinyl ether (XI). The chloroform solution of VIII and

NII-Electronic Library Service

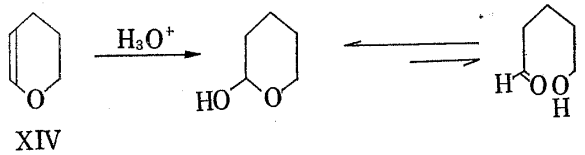
XIV was kept standing at room temperature for three days. The reaction mixture was treated with anhydrous methanol, made alkaline with 10% sodium hydroxide solution, extracted with chloroform and the crude products obtained from the extract were subjected to vacuum distillation to give methyl benzoate and 5-(2-quinolyl)-2,3-dihydro-4*H*-pyrane (XV) as a yellow oil of bp 145—155° (0.45 mmHg). Further purification of XV was effected by chromatography over alumina in ether. Its picrate, mp 200—202°, gave analytical values in agreement with the empirical formula $C_{14}H_{13}ON \cdot C_6H_3O_7N_3$. While peracetic acid oxidation of XV gave no satisfactory result, XV was oxidized with concentrated nitric acid (D 1.4) to quinaldic acid in a good yield.

Table I. NMR Spectra of 3-(2-Quinolyl)-2,3-dihydro-4*H*-pyrane and of 2,3-Dihydro-4*H*-pyrane

Compound	Quinoline nucleus		Dihydropyrane nucleus				
	C_2–H	C_{3-8}–H	C_6–H	C_5–H	C_4–H	C_3–H	C_2–H
 *a)*	—	1.97—2.74 (7H: m)		—	7.29 (2H: t) (J=5.25)	7.98 (2H: q) (J=5.25)	5.92 (2H: t) (J=5.25)
 *b)*	—	—	3.63	5.35	7.8—8.5		6.03

a) Spectrum was determined on $CDCl_3$ solution, using TMS as internal reference by JMN-3H-60 spectrometer operated at 60 Mc.
chemical shifts in τ, and J value in cps
t: triplet, q: quintet, m: multiplet
b) ref. 8

The structure of XV was confirmed by the nuclear magnetic resonance (NMR) spectrum in deuteriochloroform (Table I). The spectrum lacks signals attributable to the proton of the 5-position as well as that of the 6-position in dihydropyrane moiety; in the spectrum of the dihydropyane itself, those signals appear at 5.35 and 3.63 τ, respectively.[8] In the aromatic region, there were observed complex peaks due to seven protons, but the signal of the proton of the 2-position of quinoline ring was not noticed. These facts may indicate that the proton of the 6-position of dihydropyrane ring is deshielded by the quinoline ring attached to the adjacent carbon atom, its signal being shifted to the aromatic region. Whereas dihydropyrane itself shows the complex signals attributable to the protons of the 4-, 3- and 2-positions, the dihydropyrane ring of XV gives the typical first order pattern system; namely, the replacement of the proton of the 5-position with 2-quinolyl group causes the chemical shift of the proton of the 4-position to separate from that of the proton of the 3-position and, in addition, the coupling constants, $J_{4,3}$ and $J_{3,2}$, become practically the same (5.25 cps) to make the peaks triplet, quintet and triplet, respectively.



XIV

It is generally noticed that cyclic unsaturated ether such as dihydropyrane (XIV) is easily hydrated by the catalytic action of acid to form the hemiacetal

8) Varian High Resolution NMR Spectra Catalog, Vol. 1, 1962, Spectrum No. 111.

NII-Electronic Library Service

which comes rapidly to equilibrium with its open-chain aldehyde-alcohol form[9] as shown above.

In an attempt to transfer XV into the hemiacetal (XVI) a solution of XV in 10% hydrochloric acid was refluxed for 2 hours, followed by neutralization with sodium hydroxide, but the starting material, XV, was quantitatively recovered upon purification of the product by chromatography over alumina. This result apparently shows that the hemiacetal (XVI), even if be formed, is difficult to be isolated because XVI contains a labile hydroxyl group at β-position of the side chain attached to the 2-position of the quinoline ring to eliminate a component of water so readily during the processing.

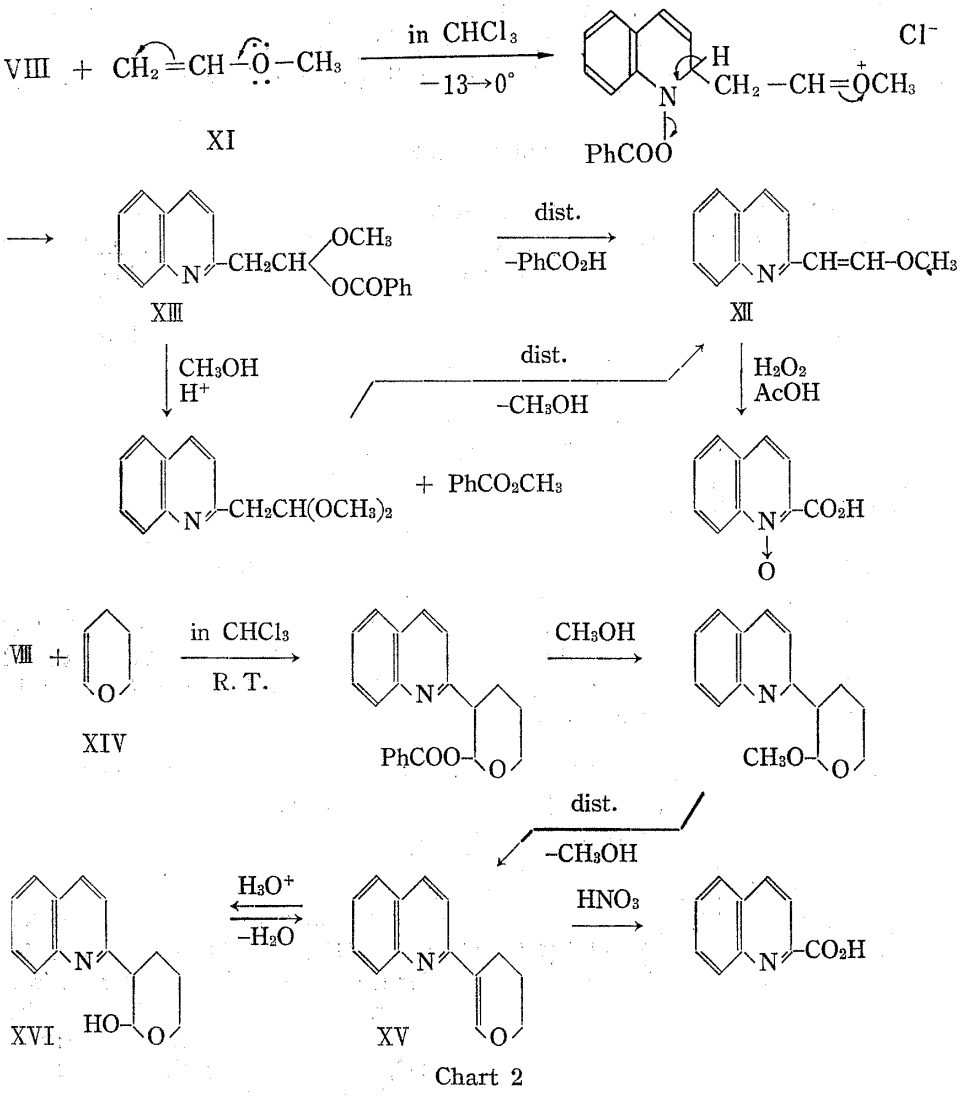


Chart 2

Finally, reactions of furan, thiophen and anisole with VIII were carried out in order to explore the reactivities of aromatic analogs of enol ether. Reaction of furan with VIII in chloroform under refluxing for 5 hours resulted in formation of carbostyril (12.4%), 1-benzoyloxy-2-hydroxy-1,2-dihydroquinoline[10] (11%) and quinoline (10%) along with recovery of I (25%), no expected product being detected. On the other hand, a prolonged reaction of 4 days at a low temperature afforded carbostyril in high yield of 94% as the sole product.

9) L.E. Schniepp and H.H. Geller, *J. Am. Chem. Soc.*, **68**, 1646 (1946); C.D. Hurd and W.H. Sanders, *ibid.*, **74**, 5324 (1952); B. Helferich and M. Gehrke, *Ber.*, **54**, 2640 (1921).
10) M. Hamana and K. Funakoshi, *Yakugaku Zasshi*, **80**, 1031 (1960).

NII-Electronic Library Service

No expected product could be obtained from similar treatment of thiophen and anisole, too; a small amount of carbostyril was produced in some cases. Attempted reaction of anisole using *p*-nitrobenzoyl chloride as an acylating agent was also unsuccessful.

From the results mentioned above it may be concluded that nucleophilic reactivity of aliphatic enol ether such as II, IX, XI or XIV is large enough to react with the benzoyl chloride-adduct of quinoline 1-oxide of naphthoid character, but considerably lower compared with that of enamine as shown by the failure to react with pyridine 1-oxide of benzenoid character. This aspect is in accordance with the fact that aromatic analogs of enol ether, furan, thiophen and anisole, could not enter into the reaction with quinoline 1-oxide in contrast to successful reactions of the comparable nitrogen compounds, indole, antipyrine and also dimethylaniline[11] with quinoline 1-oxide. However, enamines of acetaldehyde or acetone are so unstable that it is unfavorable for synthetic application. From this point of view, the corresponding enol ethers seem to be more usefull for synthesis of quinoline derivatives in some cases.

Experimental[12]

Reaction of Quinoline 1-Oxide (I) with 1-Ethoxycyclohexene (II)——1) To an ice-cooled solution of I (1.45 g, 0.01 mole) and II (2.53 g, 0.02 mole) in $CHCl_3$ (10 ml), PhCOCl (1.69 g, 0.012 mole) was added dropwise with stirring. After standing overnight at room temperature, the reaction mixture was mixed with 20% HCl (10 ml) and concentrated on a water-bath under reduced pressure. The residue was again dissolved in 20% HCl, washed with benzene–ether, made alkaline with K_2CO_3 and extracted with $CHCl_3$. Removal of $CHCl_3$ left a solid which was recrystallized from methanol to yield 0.59 g of 2-(2-quinolyl)cyclohexanone (III).[3a] The methanolic mother liquor was evaporated and the residue was dissolved in benzene and passed through an alumina column to give an additional 0.71 g of III. The total yield of III was 1.3 g.

2) To a solution of I (1.45 g) in $CHCl_3$ (20 ml), PhCOCl (1.69 g) was added under ice-cooling and the whole was kept standing at room temperature for 15 min. To this solution of VIII was added II (2.53 g), and the mixture was kept standing overnight and processed as above to yield 1.31 g of III.

Reaction of 4-Chloroquinoline 1-Oxide (IV) with II——To an ice-cooled solution of IV (1.8 g, 0.01 mole) and II (2.53 g) in $CHCl_3$ (10 ml), PhCOCl (1.69 g, 0.012 mole) was added dropwise with stirring. After ice-cooling for 3 hr, the reaction mixture was kept standing for 2 days at room temperature, and then shaken with 20% HCl (10 ml) for 1 hr, concentrated *in vacuo* below 40° of bath-temperature, washed with benzene–ether, basified with solid K_2CO_3 and extracted with $CHCl_3$. Evaporation of $CHCl_3$ left a solid, which was recrystallized from MeOH to give 1.37 g of 2-(4-chloro-2-quinolyl)cyclohexanone (V)[3c], red needles, mp 97—98°. From the methanolic mother liquor an additional 0.53 g of V was obtained by chromatography on alumina with benzene.

Reaction of Isoquinoline 2-Oxide (VI) with II——To an ice-cooled solution of VI (1.45 g, 0.01 mole) and II (2.53 g, 0.02 mole) in $CHCl_3$ (20 ml), PhCOCl (1.69 g, 0.012 mole) was added, and the reaction mixture was kept standing overnight at room temperature, and treated in the same manner as above. Recrystallization of the crude product from EtOH afforded 0.43 g of 2-(1-isoquinolyl)cyclohexanone (VII),[3a] mp 141.5—143.5°. From the mother liquor an additional 0.47 g of VII was obtained.

Reaction of Quinoline 1-Oxide (I) with 2-Ethoxypropene (IX)——To a solution of PhCOCl-adduct of I (VIII) prepared from PhCOCl (1.69 g) and I (1.45 g) in $CHCl_3$ (10 ml), IX (1.7 g, 0.022 mole) was added, and the deeply red-colored reaction mixture was kept under ice-cooling for 5 hr and then in a refrigerator overnight. The reaction mixture was treated in usual manner, and an oil obtained as a basic product was distilled under reduced pressure to collect a fraction of bp 120—135° (6 mmHg). Picrate: mp 183—184.5° (decomp.) (EtOH). *Anal.* Calcd. for $C_{12}H_{11}ON \cdot C_6H_3O_7N_3$: C, 52.18; H, 3.41; N, 13.52. Found: C, 52.34; H, 3.61; N, 13.68. No depression of the mp was noted upon admixture with an authentic sample.[7]

Reaction of Quinoline 1-Oxide (I) with Methyl Vinyl Ether (XI)——To a solution of VIII (3.38 g of PhCOCl and 2.9 g of I) in $CHCl_3$ (10 ml), XI (10 ml) was added at −13° and the reaction temperature was gradually raised to 0° for 2 hr. After standing overnight in a refrigerator, the reaction mixture was concentrated under reduced pressure, and the residue was mixed with $TsOH \cdot H_2O$ (0.19 g) and MeOH (10 ml), followed by keeping at room temperature for 2 days. Et_3N (8.3 g) was added, and the mixture was evaporated *in vacuo* below 40°, basified with saturated $NaHCO_3$ solution, and extracted with ether. Distillation of the extracted oil under reduced pressure gave 1.38 g of methyl benzoate, bp∼52° (5 mmHg) and 1.85 g of 2-(2-methoxyvinyl)-quinoline (XII) as a greenish yellow, viscous oil, bp 140—145° (4 mmHg). Picrate: mp 165—168° (MeOH). *Anal.* Calcd. for $C_{12}H_{11}ON \cdot C_6H_3O_7N_3$: C, 52.14; H, 3.41; N, 13.52. Found: C, 52.39; H, 3.80; N, 13.16.

11) M. Hamana and O. Hoshino, *Yakugaku Zasshi*, **84**, 35 (1964).

12) All melting and boiling points are uncorrected.

NII-Electronic Library Service

Peracetic Acid Oxidation of XII——A mixture of XII (0.5 g), 30% H_2O_2 (5 ml), and glacial AcOH (20 ml) was heated at 70—80° on a water-bath. After 3 hr, further 3 ml of H_2O_2 was added and the whole was kept at the same temperature for 7 hr. The reaction mixture was evaporated under reduced pressure and treated with water to give a white precipitate which was collected, washed with water and recrystallized from EtOH to afford 0.21 g of quinaldic acid 1-oxide of mp 168—169°.

Reaction of Quinoline 1-Oxide (I) with 2,3-Dihydro-4*H*-pyrane (XIV)——A mixture of I (2.9 g, 0.02 mole), PhCOCl (3.4 g, 0.024 mole) and XIV (6.8 g, 0.081 mole) in $CHCl_3$ (20 ml) was stirred at room temperature for 1.5 hr. After standing for 3 days, 10 ml of anhyd. MeOH was added under ice-cooling to the reaction mixture, which was stirred for 40 min and then kept standing at room temperature for 5 days. The mixture was shaken with 24 ml of 10% NaOH under ice-cooling and $CHCl_3$ layer was separated from aqueous layer which was further extracted with $CHCl_3$. The combined $CHCl_3$ extract was evaporated, and the residue was distilled at reduced pressure to give methyl benzoate (2.5 g, bp~75° (0.45 mmHg)) and a yellow oil of bp 145—155° (0.45 mmHg). The latter was purified by chromatography on alumina in ether to afford 2.16 g of 5-(2-quinolyl)-2,3-dihydro-4*H*-pyrane (XV) as a light yellow liquid. Picrate: yellow prisms, mp 200—202° (acetone). *Anal.* Calcd. for $C_{14}H_{13}ON \cdot C_6H_3O_7N_3$: C, 54.55; H, 3.66; N, 12.72. Found: C, 54.59; H, 3.64; N, 12.72.

Oxidation of XV with Nitric Acid——To 20 ml of concentrated HNO_3 (D 1.4), 1.43 g of XV was added under ice-cooling, and the resultant solution was heated on a water-bath to ensue a vigorous reaction. After it ceased, heating was continued further 10 hr, and the reaction mixture was concentrated under reduced pressure, treated with water and deposited black resines were filtered off. The filtrate was made alkaline with solid K_2CO_3, filtered, and the filtrate was made weakly acidic with AcOH. To this was added hot saturated solution of $Pb(OAc)_2$, and resulting white precipitates were collected, washed with water and suspended in water, through which was passed H_2S to deposite PbS. The filtrate and washings from PbS was evaporated under reduced pressure and the residue was recrystallized from benzene to afford 0.73 g of quinaldic acid as pale brown needles of mp 157—159°, undepressed on admixture with an authentic sample. *Anal.* Calcd. for $C_{10}H_7O_2N$: N, 8.10. Found: N, 8.06.

Hydrolysis of XV with Hydrochloric Acid——A solution of XV (0.53 g) in 10% HCl (10 ml) was refluxed for 2 hr, concentrated under reduced pressure and neutralized with solid K_2CO_3, and a resulting oil was extracted with $CHCl_3$. The extract was purified by chromatography on alumina, and proved completely identical with XV by IR spectral examination.

Reaction of Quinoline 1-Oxide with Furan——1) A solution of I (1.45 g), furan (4 ml) and PhCOCl (1.69 g) in $CHCl_3$ (30 ml) was kept standing in a refrigerator for 4 days. Usual processing gave 1.36 g of carbostyril.

2) A solution of I (2.9 g), furan (8 ml) and PhCOCl (3.38 g) in $CHCl_3$ (30 ml) was refluxed for 15 hr, and then the reaction mixture was concentrated *in vacuo*, treated with 20% K_2CO_3 and extracted with $CHCl_3$. Vacuum distillation of the extracted substances afforded two fractions of bp 125—133° (0.15 mmHg) and bp 140—165° (0.2 mmHg), respectively. The first was chromatographed over alumina using $CHCl_3$, AcOEt and EtOH–AcOEt (1:5) successively to give benzioc acid (1.74 g), quinoline (0.26 g) and I (0.72 g), respectively. The second fraction was treated with ether and undissolved substance was recrystallized from EtOH to give 0.36 g of carbostyril. The ether solution was evaporated and the residue was recrystallized from water to afford 0.6 g of *N*-benzoyloxy-2-hydroxy-1,2-dihydroquinoline[10] as colorless needles of mp 121—123°, which was proved identical with an authentic sample by admixture and by comparison of their IR spectra.

Acknowledgement A part of expenses for this work was defrayed by the Grant-in-Aid for Scientific Research from the Ministry of Education, which is gratefully acknowledged. Thanks are also due to Messrs. M. Shido, K. Ishimura, Y. Inoue, Miss Y. Takahashi and Miss T. Tahara for elemental analysis, to Mr. H. Matsui and Miss K. Soeda for the measurement of IR and UV absorption spectra, and to S. Takeo for the measurement of NMR spectra.

NII-Electronic Library Service