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Studies on Tertiary Amine Oxides. XLV.[1] Reaction of Quinoline N-Oxide with Cyanogen Bromide

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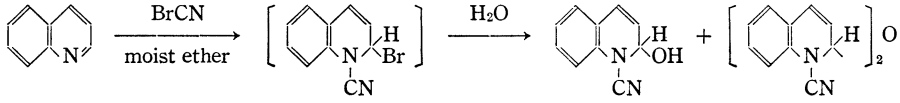
Quinoline N-oxide (I) reacted with cyanogen bromide in ethanol solution to give ethyl N-(8-quinolyl)carbamate (IIa), ethyl N-(2-quinolyl)carbamate (III), N-(α-quinolyl)carbostyril (IV), carbostyril (V) and quinoline (VI). Similar results were obtained from reactions in methanol and *n*-propanol (Table II). The presence of alcohols is essential for the smooth proceeding of the reaction, no definite product being isolated unless alcohols are present. The effect of the reaction temperatures (Table I) and that of other additives (Table III) were examined, and the reaction mechanism was discussed.

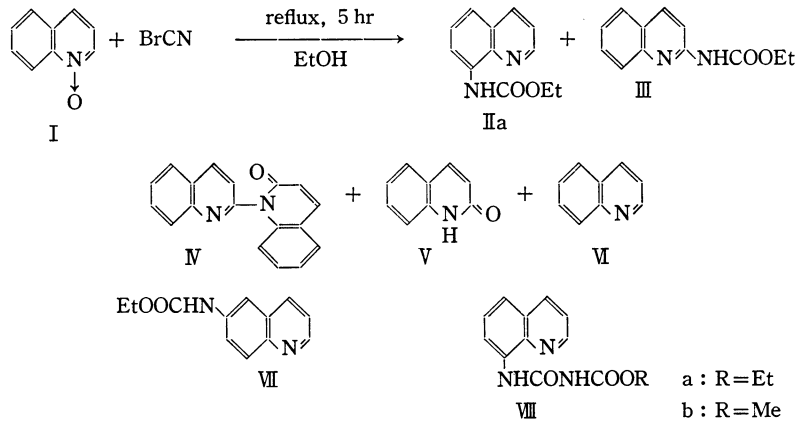
One of the authors (M. H.) and his co-workers have extensively studied the nucleophilic reaction of acyl-adducts of pyridine and benzopyridine N-oxides under various conditions and succeeded in developing many interesting and novel reactions.[3] As an extension of this work, we examined the reaction of quinoline N-oxide with cyanogen bromide which is well expected to act as an electrophile similar to acylating agents and form an adduct with the N-oxide function.

While Mumm and Ludwig[4] have described that cyanogen bromide adds to the C=N bond of pyridine and quinoline nuclei to afford the products derived from the 1-cyano-2-bromo-1,2-dihydro intermediate as exemplified below, there is no report on the reaction of cyanogen bromide with aromatic N-oxides.



In the beginning, cyanogen bromide was applied to quinoline N-oxide (I) in various solvents such as chloroform, dioxane, dimethylformamide, acetonitrile and water, at room temperatures or under heating. Although some reaction apparently occurred, only dark-brownish resinous substances were formed in each case and no definite product could be isolated. After many attempts, however, it was found that a reaction took place smoothly when ethanol was employed as the solvent. A solution of the N-oxide (I) and 1.5 equivalent of cyanogen bromide in ethanol was refluxed for 5 hours on a water-bath, and the products were carefully separated by chromatography on alumina to give ethyl N-(8-quinolyl)carbamate (IIa),[5] ethyl N-(2-quinolyl)carbamate (III),[6] N-(α-quinolyl)carbostyril (IV),[7] carbostyril (V) and quinoline (VI) in yields of 25, 2, 25, 16 and 7%, respectively (Chart 1). The structures of these products were confirmed by direct comparison with the respective authetic samples.

1) Part XLIV: M. Yamazaki, K. Noda, and M. Hamana, *Chem. Pharm. Bull.* (Tokyo), **21**, 712 (1973).
2) Location: *Katakasu, Higashi-ku, Fukuoka.*
3) Ref. 1) and earlier papers of this series.
4) *a*) O. Mumm and H. Ludwig, *Ann.*, **514**, 34 (1934); *b*) H.A. Hageman, "Organic Reactions" Vol. 7, ed. by R. Adams, John Wiley and Sons Inc., New York, 1953, p. 218.
5) R.E. Damschroeder and R.L. Shriner, *J. Am. Chem. Soc.*, **58**, 1610 (1936).
6) A.R. Katritzky, *J. Chem. Soc.*, **1957**, 4365.
7) *a*) K. Takeda and K. Hamamoto, *Yakugaku Zasshi*, **73**, 1158 (1953); *b*) T. Kajiwara, *Nippon Kagaku Zasshi*, **86**, 1060 (1965).



I IIa III IV V VI VII VIII

Chart 1

The formation of quinolylcarbamates, IIa and III, is very noteworthy in view of the evident participation of ethanol in the reaction, although their yields are rather unsatisfactory. In order to explore the essential features of the reaction, the reaction was investigated in some detail.

The effect of reaction temperature was first examined by carrying out the reaction separately at 0—5°, at room temperature and under reflux, and the results shown in Table I were obtained. Apparently, the higher temperature, the better total yield was obtained; while the reaction proceeded even at low temperatures, considerable amount of I was recovered.

Table I. Effects of Reaction Temperature[a)]

Reaction condition		Products (%)					
Temp.	Time	IIa	III	IV	V	VI	I
0—5°	3 days	15.3	3.7	1.32	—	—	49.5
room temperature	3 days	13.9	3.7	29.4	9.6	—	33.0
reflux	5 hr	25.0	1.9	25.0	16.4	7.0	—

a) All reactions are carried out in ethanol.

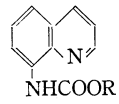
Subsequently, the reaction was carried out by using methanol and *n*-propanol in place of ethanol as the solvent. As Table II shows, the nature of alcohol does not affect so much the proportion of products, so far as lower alcohols are used. 8-Quinolyl-carbamates (IIb[5)] and IIc[5)]) were produced in 28 and 30% yields, respectively. The amounts of IV, V and VI were also essentially the same with those obtained from the reaction in ethanol, but any 2-quinolylcarbamates corresponding to III were not detected in these cases. It was further found that the reaction in boiling chloroform gave no resinous substance when 3 equivalent of ethanol was added, and yielded not only IIa and III but also ethyl N-(6-quinolyl)carbamate (VII)[8)] as a minor product, IV and V being formed only in very small amounts.

Since the formation of IV may be explained by the interaction between the unchanged I and 2-bromoquinoline initially formed during the reaction,[7)] it may be reasonably presumed that the formation of IV would be hindered by adding some reagents capable of trapping bromide anion and the yield of II or III would accordingly increase. In order to examine this possibility the reaction was carried out in the presence of sodium acetate and sodium

8) C.G. Raison, *J. Chem. Soc.*, **1949**, 2070.

Table II. Effects of the Nature of Alcohol

Solvent	Products (%)					
	II	III	VII	IV	V	VI
MeOH	IIb : 27.7	—	—	14.7	16.4	6.2
EtOH	IIa : 25.0	1.9	—	25.0	16.4	7.0
$CHCl_3$–EtOH (3 eq)	IIa : 27.3	2.8	2.3	small	amsll	—
n-PrOH	IIc : 29.6	—	—	22.1	11.0	12.4

II  a: R=Et, b: R=Me, c: R=*n*-Pr

benzoate. As Table III shows, the formation of IV was expectedly suppressed, but carbostyril was produced conversely in more than twice the amount, and the yield of II did not change so much; furthermore a small amount of alkyl 4-(8-quinolyl)allophanate (VIII) was also isolated. Differently from the fact that the reactions listed in Table II gave approximately the same amounts of 8-quinolylcarbamates (II) independent of the nature of alcohol, their yields were appreciably affected by the nature of alcohol in these cases and the amount of II decreased in the following order: IIc>IIa>IIb. Although the effect of potassium carbonate seems similar to that of the acetate or benzoate, the considerable increase of the yield of 2-quinolylcarbamate III was observed (Table III).

Table III. Effects of Additive

Reaction condition			Products (%)				
Solvent	Additive	Temp.	II	III	VIII	V	I
MeOH	AcONa	reflux	IIb : 13.9	—	—	41.4	3.4
EtOH	AcONa	reflux	IIa : 27.3	1.9	VIIIa : 1.9	44.8	9.0
n-PrOH	AcONa	reflux	IIc : 36.5	—	—	9.0	10.3
MeOH	C_6H_5COONa	reflux	IIb : 15.3	—	VIIIb[a]: 4.9	40.0	—
EtOH	C_6H_5COONa	reflux	IIa : 23.1	—	VIIIa : 4.6	38.6	—
EtOH	K_2CO_3	reflux	IIa : 21.3	11.1	VIIIa : 8.5	19.2	—
EtOH[b]	KCN	50—60°	—	—	—	—	72.0
EtOH[b]	KCN	reflux	—	—	—	—	96.0
EtOH[b]	KOCN	−10°	IIa : 1.4	12.5	VIIIa : 3.1	—	43.7
EtOH[b]	KOCN	reflux	IIa : 0.5	15.8	VIIIa : 2.3	—	28.7
EtOH	NH_2CO_2Et	reflux	IIa : 20.8	6.5	—	—	—

a) mp 182—186°, *Anal.* Calcd. for $C_{12}H_{11}O_3N_3$: C, 58.79; H, 4.52; N, 17.14. Found: C, 59.40; H 4.53; N, 17.23. IR cm^{-1}: ν_{N-H} 3330, 3190, $\nu_{C=O}$ 1748, 1710, ν_{C-O} 1220 (Nujol)
b) Containing a small amount of water.

Finally in order to gain some insight into the reaction mechanism, the reaction was examined in the presence of potassium cyanide, potassium cyanate and urethane in ethanol.

An ethanol solution of cyanogen bromide was added to a mixture prepared from a saturated aqueous solution of potassium cyanide and ethanol solution of I, and the resultant mixture was warmed at 50—60° or refluxed for 5 hours. The formation of 2-cyano-quinoline was expected, but no reaction was observed and only the unchanged I was recovered in 72 and 90% yields, respectively.

Then the reaction in the presence of potassium cyanate was carried out in a similar way at −10° or under reflux. Although the total yield of products was not so good, it is noticeable that the main product was 2-quinolylcarbamate III, and 8-quinolyl-allophanate VIIIa and

8-quinolylcarbamate IIa were formed as minor products in very small amounts, the latter being the least one.

A similar reaction in the presence of urethane resulted in a very slight increase of the formation of III and the corresponding decrease of that of IIa (Table III).

From the above-mentioned results it was revealed that the reaction of quinoline N-oxide with cyanogen bromide in alcohols led to formation of quinolylcarbamates accompanied by deoxygenation of the N-oxide function. The characteristic points of the reaction may be enumurated as follows.

(1) Alcohols are essential for the smooth proceeding of reaction in participating in the reaction to produce the stable products; unless alcohols are present, resinification is remarkable and no definite product is obtainable.

(2) Among quinolylcarbamates (II, III and VII), the 8-quinolyl derivative (II) is always the predominant product and the 2- and 6-quinolyl derivatives (III and VII) are isolated as minor products in some cases. So far as lower alcohols are employed, the nature of alcohol does not essentially affect the reaction course or the yields of the products.

(3) N-(α-Quinolyl)carbostyril (IV) and carbostyril (V) are formed as the fairly common by-products.

(4) Formation of IV is suppressed and conversely the amount of V is increased with the reaction in the presence of sodium acetate or sodium benzoate. At the same time the yield of 8-quinolylcarbamate is slightly increased with the number of carbon atoms of the alcohol in these cases; *i. e.* IIb<IIa<IIc.

All these observations apparently indicate that the first step of the reaction is the electrophilic attack by cyanogen bromide at the N-oxide oxygen atom to give 1-cyanatoquinolinium bromide (IX), an adduct similar to an acyl-adduct of quinoline N-oxide, as shown in Chart 2. The formation of resinous substances in the absence of alcohol must be due to the inherent instability of this IX, however in the presence of alcohol, IX successively undergo appreciablly smooth transformations producing a variety of products.

The formation of 2-quinolylcarbamate III may be initiated by nucleophilic attack with isocyanate anion or some equivalent nucleophilic species at the electron-deficient 2-position of IX to give an 1,2-dihydroquinoline intermediate such as XI. The next step is the elimination of a component of cyanic acid from XI; the isocyanate anion acting as a nucleophile at the first step may originate from this elimination step. Isocyanate, XII, thus formed might easily react with ethanol giving the carbamate III, although it is not clear yet in which step ethanol participates in the reaction. The fact that the formation of III is superior to that of 8-quinolyl derivatives, IIa and VIIIa, in the presence of potassium cyanate contrary to the reactions without potassium cyanate apparently supports this pathway; the lower total yield in these cases may be partly due to some interaction of cyanogen bromide with potassium cyanate besides the main path. The role of urethane as a nucleophile attacking at IX seems to be very small from the result of the reaction in the presence of urethane. An alternative course proceeding through a cyclic transition state (XIII) seems improbable from the above-mentioned observations.

It is evident from the positions undergone substitution that the formation of 8- and 6-substituted products (II, VIII and VII) follows a different path from that of III. The crucial step is the extrusion of a cyanate ion from a 1,2-dihydroquinoline intermediate such as X initially formed from IX. Subsequently the cyanate anion attacks at the electron-deficient 8- or 6-position of quinoline ring, probably through ion pairs (XIV), followed by elimination of hydrogen bromide and by attack of alcohols to afford II or VII. As for the mechanism of II formation, a concerted path such as XV may be also conceivable from the fact that II is always the predominant product among quinolylcarbamates except for the reaction in the presence of potassium cyanate. However, the detailed mechanism involving this point and the step of participation of alcohols remains to be explored.

It is evident that N-(α-quinolyl)carbostyril (IV) is produced by the reaction of 2-bromoquinoline formed from the 1,2-dihydro intermediate X with the unchanged I as the results given in Table III show. As for the mechanism of the formation of carbostyril (V), we tentatively postulate a course involving nucleophilic attack of the oxygen atom of cyanate anion at the electron-deficient 2-position of IX.

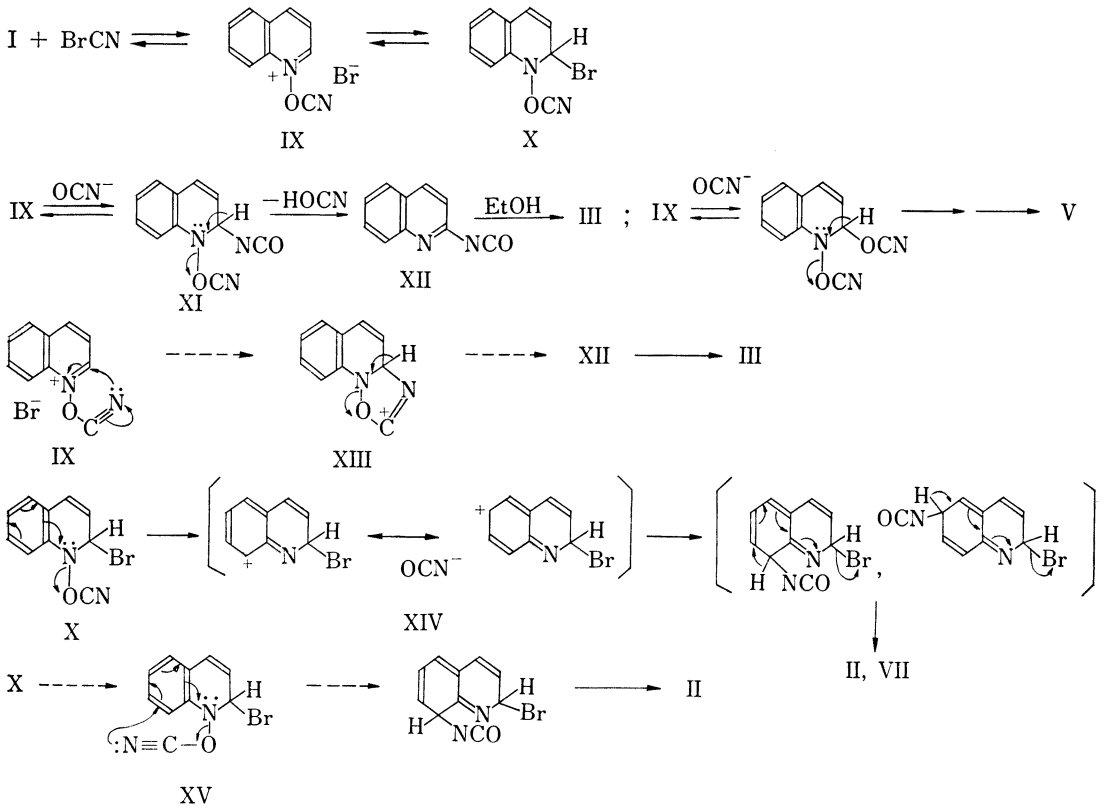


Chart 2

It has been shown previously shown that ethanol can be used as the solvent without any difficulties in the reaction of quinoline N-oxides with potassium cyanide in the presence of tosyl chloride to give 2-cyanoquinolines, because the formation of acyl-adducts of aromatic N-oxide is a highly reactive reaction.[9] Further, it is now disclosed that the participation of alcohols is essential for the smooth proceeding of the reaction in the above cases. There is no precedent for such an observation in the reaction of aromatic N-oxides with acylating agents or reagents of similar character.

Experimental[10]

Reaction of Quinoline N-Oxide (I) with Cyanogen Bromide——1) To a solution of I (0.75 g) in EtOH (10 ml) was added BrCN (0.80 g), and the mixture was refluxed for 5 hr. After EtOH was removed under reduced pressure, the residue was treated with H_2O, made alkaline with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ extract was dried over Na_2SO_4 and evaporated to give a syrupy residue, which was chromatographed on alumina column using petr. ether–ether (3: 1), ether ,$CHCl_3$ and MeOH as eluents. From the

9) M. Hamana and T. Matsumoto, *Yakugaku Zasshi*, **91**, 269 (1971).
10) All melting and boiling points are uncorrected.

petr. ether–ether eluate, ethyl N-(8-quinolyl)carbamate (IIa), quinoline (VI) and ethyl N-(2-quinolyl)carbamate (III) were successively obtained. IIa: colorless prisms, mp 67—69° (petr. ether), 0.27 g (25%). *Anal.* Calcd. for $C_{12}H_{12}O_2N_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 67.11; H, 5.39; N, 12.87. VI: bp 160—165° (20 mmHg) (bath temp.), 0.045 g (7%). Picrate: yellow needles, mp 201—202° (MeOH). III: colorless pillars, mp 97° (ether), 0.02 g (2%). The ether eluate gave 0.10 g of urethane, mp 51—52°, bp 84° (18 mmHg). From the $CHCl_3$ eluate, 0.17 g (25%) of N-(α-quinolyl)carbostyril (IV) was obtained. Colorless pillars (acetone). IR cm^{-1}: $\nu_{C=O}$ 1665 (Nujol). *Anal.* Calcd. for $C_8H_{12}ON_2$: C, 79.39; H, 4.44; N, 10.29. Found: C, 78.89; H, 4.46; N, 10.33. The MeOH eluate gave 0.12 g (16%) of carbostyril (V), colorless needles, mp 195—196° (MeOH). IIa, III, IV, and V were proved to be identical with the respective authentic samples by admixture and IR spectral examination. Hydrolysis of IIa with hot conc. HCl afforded quantitatively 8-aminoquinoline.

2) To a solution of I (0.73 g) in EtOH (10 ml) was added BrCN (0.8 g), and the mixture was allowed to stand for 3 days at room temperature. In another run the same mixture was kept for 3 days in a refrigerator. Each of the reaction mixtures was treated as in 1) and the results shown in Table I were obtained.

The Reaction in Methanol——A mixture of I (0.73 g) and BrCN (0.80 g) in MeOH (10 ml) was refluxed for 5 hr. The reaction mixture was concentrated under reduced pressure, treated with H_2O, made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The extracted substances were chromatographed on an alumina column using ether, $CHCl_3$ and MeOH as eluents. The fraction eluted with ether was distilled under reduced pressure to give 0.04 g (6%) of quinoline, bp 160—165° (2 mmHg) (bath temp.) and an oil of bp 165—175° (2 mmHg) bath (temp.), which soon crystallized. Recrystallization of the latter compound from MeOH–H_2O gave 0.28 g (28%) of methyl N-(8-quinolyl)carbamate (IIb), colorless scales, mp 52—53°. *Anal.* Calcd. for $C_{11}H_{10}O_2N_2$: C, 65.35; H, 4.98; N, 13.86. Found: C, 65.54; H, 5.14; N, 13.54. Hydrolysis of IIb with hot conc. HCl afforded 8-aminoquinoline in 84% yield. From the $CHCl_3$ and MeOH eluates, 0.10 g (14%) of IV and 0.12 g (16%) of V were obtained, respectively.

The Reaction in *n*-Propanol——A mixture of I (0.73 g) and BrCN (0.80 g) in *n*-PrOH (10 ml) was refluxed for 5 hr. The reaction mixture was concentrated under reduced pressure, treated with H_2O, made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The extracted substances were chromatographed on an alumina column using ether, $CHCl_3$ and MeOH as eluents. The fraction eluted with ether was distilled under reduced pressure to give 0.08 g (12%) of quinoline, bp 160—165° (20 mmHg) (bath temp.) and a colorless oil of bp 165—170° (0.2 mmHg) (bath temp.), which soon solidified. Recrystallization from petr. ether gave 0.34 g (30%) of *n*-propyl N-(8-quinolyl)carbamate (IIc), colorless needles, mp 59—60°. *Anal.* Calcd for $C_{13}H_{14}O_2N_2$: C, 67.81; H, 6.31; N, 12.17. Found: C, 67.72; H, 6.32; N, 12.16. Heating of IIc with conc. HCl afforded 8-aminoquinoline in 96% yield. From the $CHCl_3$ and MeOH eluates, 0.15 g (22%) of IV and 0.08 g (11%) of V were obtained, respectively.

The Reaction in the Presence of Ethanol in Chloroform——A mixture of I (1.45 g), BrCN (1.5 g) and EtOH (1.38 g) in $CHCl_3$ (20 ml) was refluxed for 5 hr. The reaction mixture was processed in the same manner to give the result shown in Table II.

The Reaction in the Presence of Sodium Acetate, Sodium Benzoate or Potassium Carbonate——1) A mixture of I (1.45 g), BrCN (1.59 g) and AcONa (1.23 g) in EtOH (20 ml) was refluxed for 5 hr. The reaction mixture was evaporated under reduced pressure, treated with H_2O, made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The extract was concentrated and chromatographed on an alumina column using petr. ether–ether (1: 1), ether ,$CHCl_3$ and MeOH as eluents. The fraction eluted with petr. ether–ether (1: 1) afforded 0.59 g (27%) of IIa. From the ether eluate 0.04 g (2%) of III and 0.05 g (2%) of ethyl 4-(8-quinolyl)allophanate (VIIIa) were obtained successively. VIIIa: colorless needles, mp 162° (acetone). IR cm^{-1}: ν_{N-H} 3200, 3100; ν_{C-O} 1722, 1685—1670; ν_{C-O} 1245 (Nujol). *Anal.* Calcd. for $C_{13}H_{13}O_3N_3$: C, 60.22; H, 5.05; N, 16.21. Found: C, 60.21; H, 5.04; N, 16.24. Hydrolysis of VIIIa with hot conc. HCl afforded 8-aminoquinoline in 68% yield. The $CHCl_3$ eluate gave 0.05 g of urethane and 0.14 g (9.0%) of unchanged I. From the MeOH eluate 0.65 g (44.8%) of V was obtained.

2) Similar reactions in MeOH and *n*-PrOH and those in the presence of C_6H_5COONa or K_2CO_3 were carried out and the results shown in Table III were obtained.

The Reaction in the Presence of Potassium Cyanide——1) To a mixture of I·$2H_2O$ (1.81 g)–EtOH (10 ml) and KCN (1.95 g)–H_2O (5 ml) was added BrCN (1.59 g)–EtOH (10 ml). The whole was stirred at room temperature for 1 hr and then at 50—60° for 5 hr. The reaction mixture was concentrated under reduced pressure, treated with H_2O and extracted with $CHCl_3$. The extract was concentrated to a small volume and passed through an alumina column. The first eluate afforded 0.50 g of oil, bp 125° (18 mmHg); its structure was not elucidated. The second fraction gave 1.30 g (72%) of recovered I.

2) A similar reaction under reflux for 5 hr resulted in recovery of I in 96% yield.

The Reaction in the Presence of Potassium Cyanate——1) A mixture of I·$2H_2O$ (1.81 g)–EtOH (20 ml), KOCN (2.43 g)–H_2O (5 ml) and BrCN (1.59 g)–EtOH (10 ml) was refluxed for 5 hr. The reaction mixture was concentrated, treated with H_2O and extracted with $CHCl_3$. The extracted substances were chromatographed on an alumina column using petr. ether, ether, $CHCl_3$ and MeOH as eluents. At first, 0.01 g (0.5%) of IIa was obtained from the petr. ether–ether (3: 1) eluate. The next fraction eluted with petr. ether–

ether (1 : 1) afforded successively 0.34 g (16%) of IV and 0.06 g (2%) of VIIIa. The $CHCl_3$ eluate gave 0.52 g (29%) of unchanged I, and the $CHCl_3$–MeOH (3 : 1) eluate yielded 0.30 g of crystals, its structure being not elucidated.

2) The same mixture was stirred for 5 hr under cooling with ice and salt and treated in the similar manner to give the result shown in Table III.

The Reaction in the Presence of Urethane——A mixture of $I \cdot 2H_2O$ (1.81 g), BrCN (1.59 g) and urethane (1.07 g) in EtOH (30 ml) was refluxed for 5 hr. The reaction mixture was treated in the similar manner, and 0.45 g (21%) of IIa and 0.14 g of III were isolated.

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