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Studies on Reaction of Alkali-fusion of Haloquinolones *via* Aryne Intermediates[1]

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In the course of preparing 4-hydroxycarbostyril by potassium hydroxide–fusion of 4-chlorocarbostyril, a novel reaction was found. This reaction was explained by the formation of aryne intermediate. This prediction was confirmed by investigating reactions of other haloquinolones with molten potassium hydroxide.

Aryl halides having no activating group such as NO_2 or CN may be converted into arylamines accompanied by rearrangement when treated with metallic amides. It is now clear that the mechanism by which these conversions generally occur is very different from the normal substitution reaction. Indeed, these reactions are not simple substitutions at all, but are a combination of elimination and addition. The intermediates in these reactions are designated as aryne. It became evident that this kind of reaction takes place not only in benzene or the related aromatic compounds, but also in heteroaromatic compounds and the chemistry concerning aryne-like mechanism in pyridine or quinoline has been developing.[3] For example, treatment of 3- chloroquinoline with lithium piperidine in ether yields a mixture of 3- and 4-piperidinoquinolines.[4] Similarly, upon reaction with potassium amide 3-bromo-4-ethoxypyridine affords 2-amino-4-ethoxypyridine.[5] Those products are considered to arise from the elimination–addition reactions. The competitive direct substitution is unlikely to take place in these starting materials because the transition state for it cannot be stabilized by conjugation.[6] The above examples are to be compared with the reaction of 4-chloropyridine with lithium piperidine, which proceeds entirely in a direct substitution (*i.e.* addition–elimination) manner.[6] Not only the metallic amides, but also strong alkali causes the similar rearrangement reactions. An example is that *o*-chlorotoluene gives a mixture of *o*-cresol (48%) and *m*-cresol (52%) when heated with molten sodium hydroxide.[7] This is also considered to be an elimination–addition reaction.

In the course of our work designed to prepare 4-hydroxycarbostyril according to the method of Friedländer,[8] we have found an evidence which led us to believe that the aryne-like reactions also occur in the carbostyril derivatives. While we were preparing this manuscript, similar observations were made in the same system: A reaction of 3-halocarbostyrils with piperidine at 180° gave rise to 3- and 4-piperidino products while 4-bromocarbostyril yielded

1) A portion of this work was presented at 82nd Annual Meeting of the Pharmaceutical Society of Japan, Nov. 1962.
2) Location: *Hongo, Bunkyo-ku, Tokyo.*
3) For general review, H.H. Zeiss (ed.), "Organometallic Chemistry," Reinhold Publishing Corp., 1960; R.W. Hoffmann, "Dehydrobenzene and cycloalkyne," Academic Press, New York, 1967.
4) T. Kauffmann and F.P. Boettcher, *Angew. Chem.*, **73**, 341 (1961).
5) R.J. Martens and H.J. Hertog, *Tetrahedron Letters*, **15**, 643 (1962).
6) T. Kauffmann and F.P. Boettcher, *Chem. Ber.* **95**, 1528 (1962).
7) A.T. Bottini and J.D. Roberts, *J. Am. Chem. Soc.*, **79**, 1458 (1957).
8) P. Friedländer and A.W. Weinberg, *Ber.*, **15**, 2679 (1882).
9) T. Kauffmann, A. Risberg, J. Schultz and R. Weber, *Tetrahedron Letters*, 3563, (1964).
10) T. Kauffmann and J. Schultz, *Chem. Ber.*, **98**, 1837 (1966).

only 4-piperidino compound.[9,10] The latter reaction was explained as resulting from the direct substitution. Herein, we wish to report our results which suggests that the elimination–addition pathway can occur in some nucleophilic reactions of 4-chlorocarbostyril.

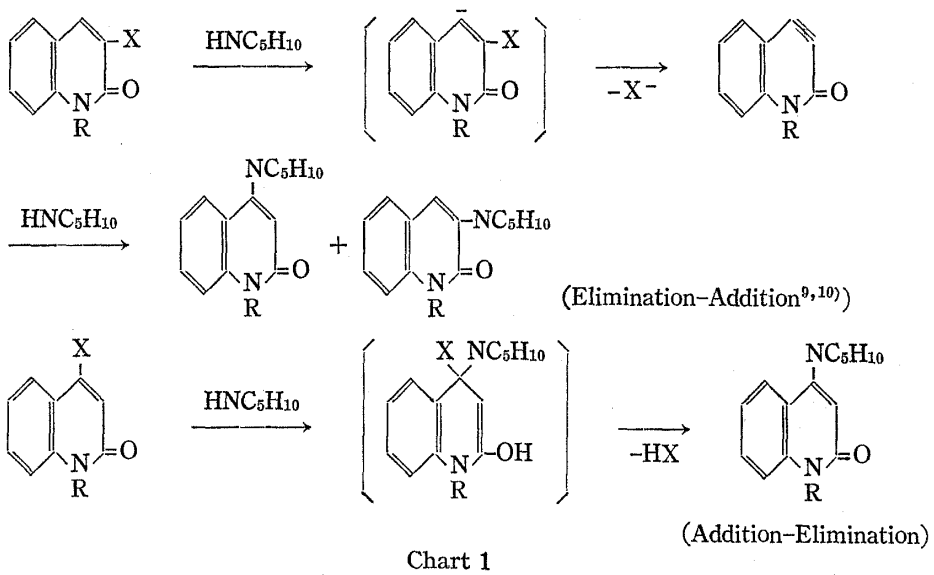


Chart 1

When 4-chlorocarbostyril (I) was heated with molten KOH at 200°,[8] two different hydroxycarbostyrils, mp 256° (II) and mp 320° (III), were isolated in 57% and 25% yield, respectively. These two isomers were separated by fractional recrystallization from methanol, (III) precipitated first, followed by (II). The compound (III) gave a monoacetate (IIIa), mp 210° with Ac_2O–pyridine and a monomethyl ether (IIIb), mp 253.5° with diazomethane. Similarly, (II) gave a monoacetate (IIa), mp 214° and a monomethyl ether (IIb), mp 190°. The less soluble carbostyril (III) and its derivatives were identical to the authentic 4-hydroxycarbostyril and its derivatives, respectively, by admixture test and comparison of their infrared spectra. The more soluble carbostyril (II) was proved to be 3-hydroxycarbostyril. The monomethyl ether (IIb) was identical to 3-methoxycarbostyril synthesized in a following independent route.

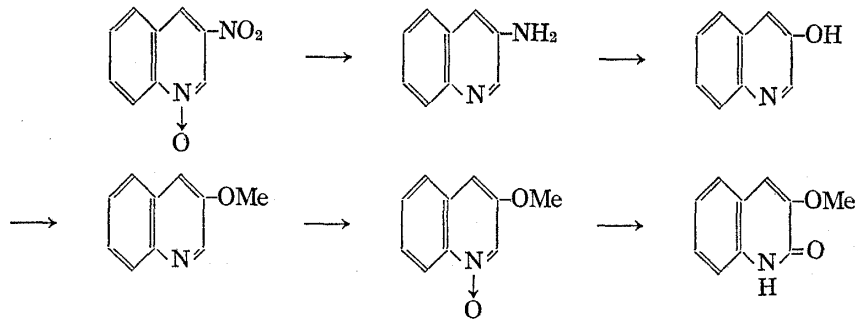


Chart 2

It was found that both 3- and 4-hydroxycarbostyrils are stable under the reaction conditions. Thus, only the elimination–addition mechanism will account for the formation of a mixture of (II) and (III) from 4-chlorocarbostyril. It is interesting to compare our results with Kauffmann's report that 4-halocarbostyril reacted with piperidine at 100° within 4 hr, giving exclusively the direct substitution product.[10] Potassium hydroxide in our experiments hardly attacked 4-chlorocarbostyril below 150°. Apparently, the basicity of KOH is such that the carbostyril exists as an anion (IV), which lessens the inductive effect at 4-position by the nitrogen and makes the direct attack by OH^- quite unfeasible. The only

other reaction mode is the attack of OH^- at C_3-hydrogen to yield (V), yielding eventually 3,4-dehydrocarbostyril. The final products are thus 3- and 4-hydroxycarbostyrils. On the other hand piperidine is not basic enough to give rise to an anion (IV) and hence the inductive effect by the nitrogen at C_4 of the carbostyril will remain effective. The result is direct attack of piperidine at C_4.

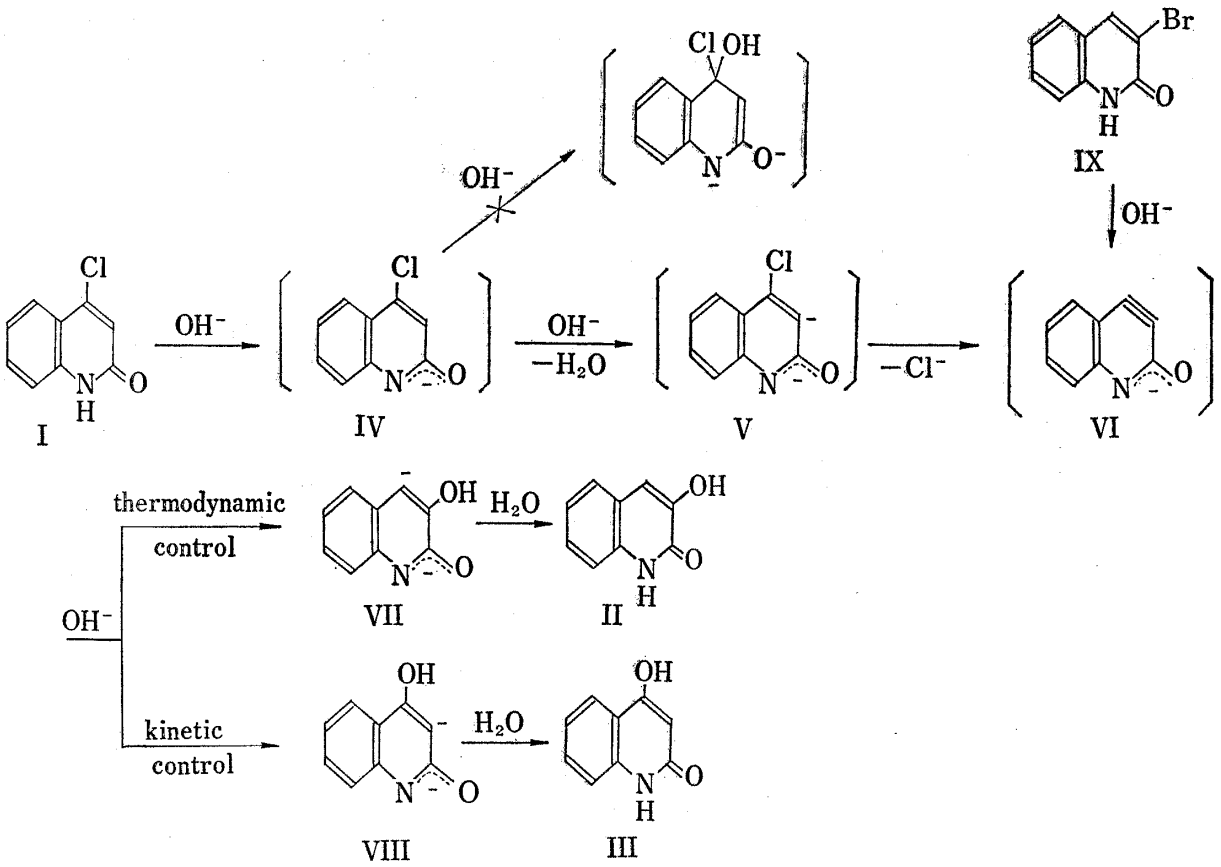


Chart 3

In order to see wether the direct nucleophilic attack is still partially responsible for the formation of 4-hydroxycarbostyril (III), 3-bromocarbostyril (IX) was subjected to the same reaction. If a considerable increase of the product ratio (II/III) is observed, then one might suspect some role of the direct attack. The experimental results, however, did not give any definite conclusion due to a lack of accurate reproducibility.

At the stage of OH^- addition to the aryne (VI), two possible ways are envisaged. When the stability of the resulting adduct is the decisive factor (thermodynamic control), (VII)

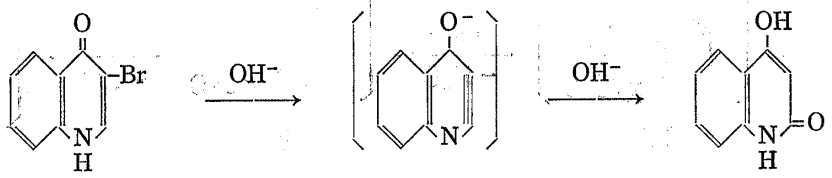
Table I. Reaction of Halocarbostyril with Molten Potassium Hydroxide

Reaction conditions Temp (°C)	Time (min)	Yield (%)	Product ratio (II)/(III)
4-Chlorocarbostyril (I)			
165	45	0	
180	90	12	1/1
200	40	82	2.3/1
230	35	61	2.5/1
3-Bromocarbostyril (IX)			
205	60	64	1.3/1
222	35	94	3.5/1

should be formed in preference to (VIII) since the negative charge is further away from the center of the carbostyril anion. When the electron density at the two ends of the dehydro bond determines the addition ratio (kinetic control), the OH^- would attack at the 4-position. Our observations, though qualitatively, seem to suggest the former factor favorable. The similar trend was found in the reaction of bromophenol with potassium amide, where *o*-aminophenol is formed predominantly over the *m*-isomer.[11]

The results of those KOH-fusion reactions were summarized on the following Table.

It was anticipated that a similar elimination-addition mechanism might prevail in other quinolones. In fact, when 3-bromo-4-quinolone(X) was subjected to the same reaction, 4-hydroxycarbostyril (III) was obtained in 58% yield as a sole product. Other expected product, 3,4-dihydroxyquinoline, if any formed, might be decomposed under the reaction condition as it is quite unstable in alkali. The rearranged product (III) will be obtained through 2,3-dehydroquinolone.



X III

Chart 4

Experimental

Reaction of 4-Chlorocarbostyril (I) with Molten KOH——To molten KOH prepared from KOH (9 g) and H_2O (0.5 ml), 1.25 g of I was added in small portions. The mixture was heated with stirring for 30 min at 200°. The reaction mixture was poured into ice–water and neutralized with *conc.* HCl. The resulting precipitate was collected by filtration and washed with water. Fractional crystallization from MeOH gave, first 0.28 g (yield, 25%) of white powder, mp 316° (decomp.), and then 0.64 g (yield, 57%) of yellowish crystals, mp 253—256° (decomp.). Each was further recrystallized to afford III, mp 320° (decomp.), and II, mp 256° (decomp.), which were acetylated with Ac_2O and pyridine to give the corresponding monoacetates, IIIa, mp 210°, and IIa, mp 214°. III and II were treated with CH_2N_2 in ether to afford monomethyl ethers, IIIb, mp 253.5°, and IIb, mp 190°, respectively. *Anal.* Calcd. for $C_{10}H_9O_2N$ (IIIb): C, 68.56; H, 5.18; N, 8.00. Found: C, 68.52; H, 5.38; N, 8.11. UV $\lambda_{max}^{95\%\ EtOH}$ mμ (ε): 264 (7600), 274 (7400), 313 (6500).

III, IIIa, and IIIb showed no depression on admixture with the authentic 4-hydroxycarbostyril and its derivatives. *Anal.* Calcd. for $C_{10}H_9O_2N$ (IIb): C, 68.56; H, 5.18; N, 8.00. Found: C, 68.67; H, 5.25; N, 7.95 UV $\lambda_{max}^{95\%\ EtOH}$ mμ (ε): 273 (6900), 316 (11500), 329 (8800).

Upon admixture with 3-methoxycarbostyril synthesized by the route as described below, (IIb) showed no depression.

4-Chlorocarbostyril (I)——Acidic hydrolysis of 2,4-dichloroquinoline[12] (mp 66—67°) gave I, mp 247.5—248°.

Preparation of Authentic 4-Hydroxycarbostyril (III)——Its preparation followed that of Ziegler.[13] The crude, without recrystallization, was acetylated with Ac_2O and pyridine. Recrystallization of the product from EtOH gave a monoacetate (IIIa), mp 211—212° (reported mp 214—215°). This acetate was hydrolyzed with 10% KOH soln. to afford 4-hydroxycarbostyril (III), mp 317—320° (decomp.) (reported mp 352—354°). 4-Methoxycarbostyril (IIIb), mp 255° was obtained from III and CH_2N_2. *Anal.* Calcd for $C_{10}H_9O_2N$: C, 68.56; H, 5.18. Found: C, 68.30; H, 5.20.

Independent Synthesis of 3-Methoxycarbostyril (IIb)——1) 3-Nitroquinoline 1-Oxide: Prepared by the method of Ochiai,[14] mp 186—192°.

2) 3-Aminoquinoline: Raney–Nickel catalyst, prepared from 1 g of Ni–Al alloy, was added to a solution of 0.995 g of 3-nitroquinoline 1-oxide dissolved in 30 ml of MeOH and 0.6 ml of AcOH, and the mixture was reduced at ordinary temperature and hydrogen pressure. The catalyst was filtered off. After passed

11) G.B.R. deGraaff, H.J. der Hertog and W.C. Melger, *Tetrahedron Letter*, **1965**, 963.
12) E. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **7**, 146 (1959).
13) Ziegler, *Monatsh*, **1959**, 822.
14) E. Ochiai, A. Ota, *Chem. Pharm. Bull.* (Tokyo), **10**, 349 (1962).

through Amberlite IRA-410, the filtrate was evaporated *in vacuo* to dryness. The residue was chromatographed over alumina using $CHCl_3$ as a solvent. From the eluate subsequent to syrupy residue, 0.363 g (yield, 48%) of 3-aminoquinoline mp 81—83°, was obtained.

3) 3-Hydroxyquinoline: Starting from 1.183 g of 3-aminoquinoline, 0.761 g (yield, 64%) of 3-hydroxyquinoline, mp 197—198.5°, was obtained by the method of Mills, *et al.*[15]

4) 3-Methoxyquinoline: Prepared from 3-hydroxyquinoline and CH_2N_2. Picrate, mp 219°.

5) 3-Methoxyquinoline 1-Oxide: One gram of 3-methoxyquinoline was treated with perphthalic acid in ether and allowed to stand overnight in a refrigerator. The ether solution was washed with 10% Na_2CO_3 soln. and dried over Na_2SO_4. The solvent was evaporated and the residue was passed through alumina column, using benzene and $CHCl_3$ in 1:1 ratio as an eluent to give white crystals of mp 93° (228 mg). The same compound of mp 90—93° (187 mg) was obtained from 10% Na_2CO_3 soln. layer. These were recrystallized from benzene–ether to afford colorless prisms of mp 94—96°. *Anal.* Calcd. for $C_{10}H_9O_2N \cdot H_2O$: C, 62.16; H, 5.74; N, 7.25. Found: C, 62.60; H, 5.90; N, 7.48. UV $\lambda_{max}^{95\%\ EtOH}$ mμ (ε): 297 (4700), 309 (5400), 345 (5700), 359 (6300).

6) **3-**Methoxycarbostyril (IIb): To a solution of 3-methoxyquinoline (60 mg) in 15 ml of $CHCl_3$ containing a few drops of water, TsCl (86 mg) was added in small portions. The reaction mixture was refluxed for 25 min. After cooling, 10 ml of 10% Na_2CO_3 was added and warmed. The $CHCl_3$ layer was taken up, dried, and evaporated. The crude product (85 mg) was separated by alumina chromatography. From less adsorbing fractions, 69 mg of some unknown substance was obtained. Next came 3 mg of the starting material. Then, 13 mg of light yellow crystals were eluted, which were recrystallized from ether to prisms, mp 191—192.5°. This sample showed no depression on admixture with IIb derived from the reaction of 4-chlorocarbostyril. The infrared spectrum of this sample was also superimposable with that of IIb. *Anal.* Calcd. for $C_{10}H_9O_2N$: C, 68.56; H, 5.18. Found: C, 68.75; H, 5.10.

Reaction of 3-Bromocarbostyril (IX) with Molten KOH——The reaction was carried out similarly to the procedure described for the reaction of 4-chlorocarbostyril (I).

3-Bromocarbostyril (IX)——The preparation followed that of Ochiai[16] mp 258° (reported mp 255°).

Reaction of 3-Bromo-4-quinolone (X) with Molten KOH——The method used here was virtually identical with that described for the reaction of I. From 500 mg of the starting material (X), 275 mg of a crude substance was obtained, which was recrystallized from MeOH, giving 160 mg (yield, 58%) of 4-hydroxycarbostyril (mp 324°) as yellowish plates. From the mother liquid, the starting material (X) (115 mg) was recovered. Thus obtained 4-hydroxycarbostyril was acetylated to a monoacetate, mp 210.5—212°, which was identified with the authentic (IIIa) using infrared spectrum and admixture test.

3-Bromo-4-quinolone (X)——The preparation followed that of Riegel,[9] in which the starting material, 4-hydroxyquinoline was prepared according to the procedure of Hayashi.[12] mp 278—279° (reported 288—289°).

15) W.H. Mills and W.H. Watson, *J. Chem. Soc.*, **97**, 753 (1910).
16) E. Ochiai and T. Okamoto, *Yakugaku Zasshi*, **68**, 88 (1948).