REACTIONS OF AROMATIC HETEROCYCLES INVOLVING THE CATALYTIC ACTION OF THE CYANIDE ION

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The condensation of two benzaldehyde or substituted benzaldehyde molecules, the so-called benzoin condensation, has long been known to be specifically catalyzed by the cyanide ion and many reports on the benzoin condensation have been published. However, reports regarding the catalytic action of the cyanide ion in reactions other than the benzoin condensation have rarely been published. In the past several years the present authors have gained knowledge of many catalytic reactions of aromatic heterocycles with the cyanide ion and this article summarizes them.

CONTENTS

1. The Condensation between Aromatic Heterocycles and Aromatic Aldehydes in the Presence of the Cyanide Ion (the Extension of the Benzoin Condensation)

The mechanism of the benzoin condensation is believed to be as shown in Chart 1.[1] The cyanide ion has strong nucleophilicity and attacks the carbonyl carbon of the aromatic aldehyde (11) to form the intermediate (a). The intermediate (d) containing the cyano group loses cyanide ion to give the benzoin (10). The catalytic action of the cyanide ion might be due to its abilities to easily bind to

and leave an active site. The condensation between two different aromatic aldehydes was also found in the literature and is called the cross benzoin condensation.

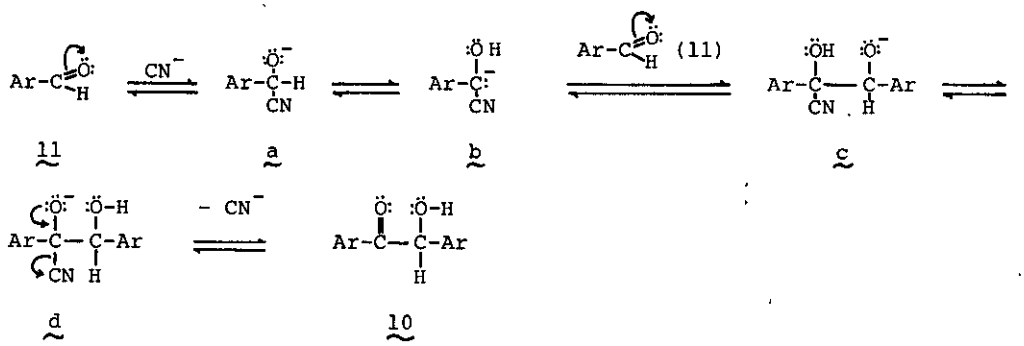
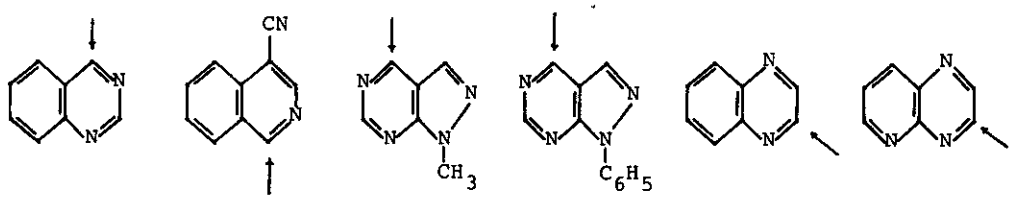
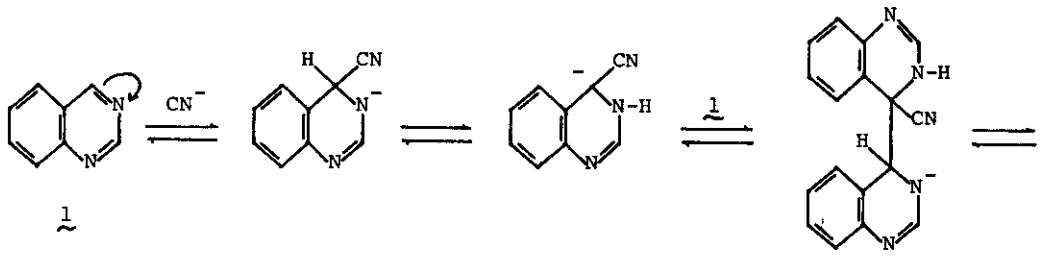


Chart 1

It has been reported by Armarego and Willette that quinazoline (1) dimerized in aqueous sodium cyanide to give 4,4'-biquinazoline (2).[2] We also found that 4-isoquinolinecarbonitrile (3)[3], 1-methyl-1H-pyrazolo[3,4-d]pyrimidine (4)[4], 1-phenyl-1H-pyrazolo[3,4-d]pyrimidine (5)[4], quinoxaline (6)[4], and pyrido[2,3-b]pyrazine (7)[4] dimerized by the action of potassium cyanide in dimethyl sulfoxide (DMSO). Armarego et al. did not explain the mechanism of dimerization in detail. From the fact that dimerization proceeded in the presence of the cyanide ion, its mechanism may well be of the benzoin condensation type followed by oxidation to the fully aromatic system. For example, the dimerization mechanism of 1 may be written as Chart 2.



(The symbol of the arrow shows that the dimerization takes place at this position)



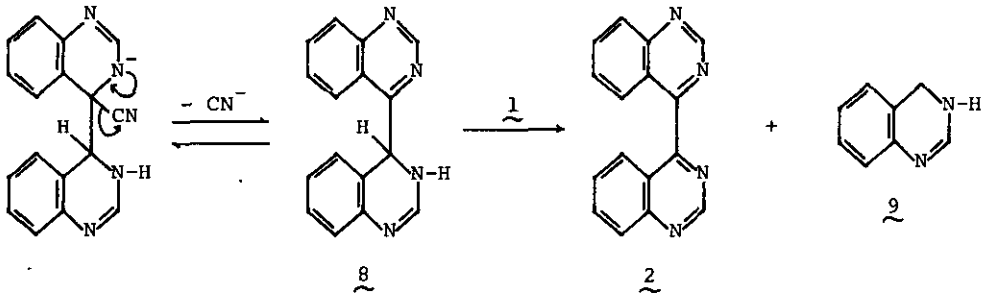
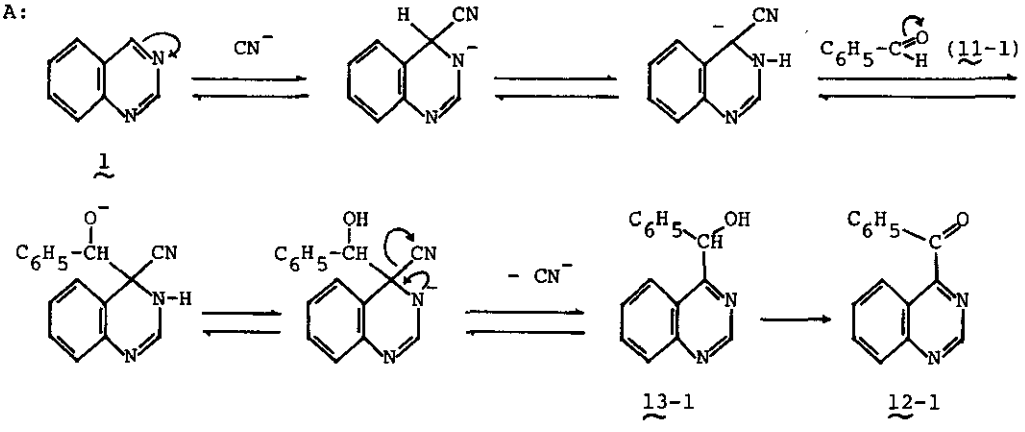


Chart 2

In Chart 2, the intermediate 8, corresponding to the benzoin (10), undergoes oxidation to give the dimerized 2. In this oxidation, 1 probably acts as hydride ion acceptor and is reduced to 3,4-dihydroquinazoline (9).

If the dimerization mechanism is similar to that of the benzoin condensation, it is expected that the presence of aromatic aldehydes (11) in the reaction system would make it undergo the cross benzoin condensation-like reaction between aromatic heterocycles and 11. In fact we found that this expected cross benzoin condensation-like reaction occurred. For example, when a solution of 1, benzaldehyde (11-1) and potassium cyanide in methanol was allowed to stand overnight in a refrigerator, the formation of phenyl 4-quinazolinyl ketone (12-1) was recognized.[5] It is considered that there are two reaction processes, paths A and B, for the formation of 12-1. Both paths A and B, as shown in Chart 3, are similar to that of the cross benzoin condensation. In path A the cyanide ion first attacks 1, whereas in path B the cyanide ion attacks 11-1. Our conclusion, based on several experimental data, is that path A is more likely than path B. In path A alcohol (13-1), corresponding to benzoin (10-1), is formed as an intermediate which is oxidized to 12-1.

Path A:



Path B:

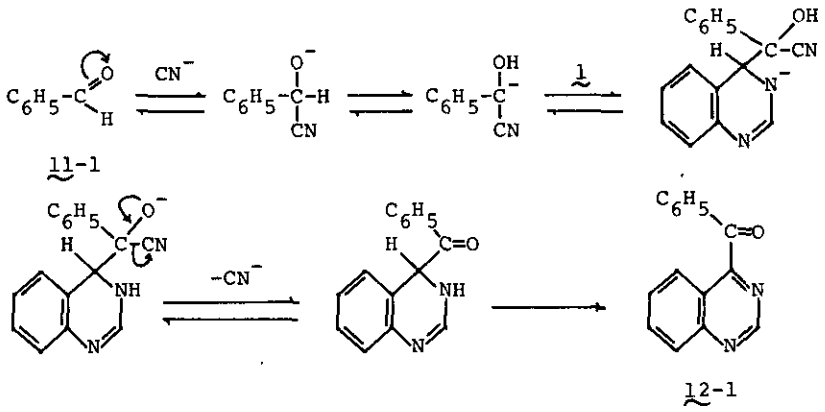


Chart 3

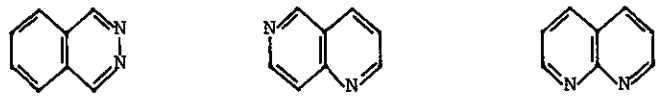
Similarly, the reaction of 1 with substituted benzaldehydes (11) such as o- (11-2), m- (11-3), p-methoxybenzaldehyde (11-4), o- (11-5), m- (11-6), p-chlorobenzaldehyde (11-7), o- (11-8), m- (11-9), p-tolualdehyde (11-10), and p-acetamidobenzaldehyde (11-11) gave ketones (12) corresponding to 12-1 together with 2. In the case of 11-2 and 11-7 the corresponding alcohol (13-2, 13-7) was formed together with ketone (12-2, 12-7) and 2. Similar reaction was also found to occur between 1 and heteroaromatic aldehydes such as furfural (11-12) and isonicotinoaldehyde (11-13). When the electron-attracting nitro and cyano groups, or electron-donating N,N-dimethylamino and hydroxyl groups, were substituted para, ortho and meta to the aldehyde group in 11-1, the reaction failed. In other words, aromatic aldehydes (11) which undergo the benzoin condensation react with 1 to give the products such as the alcohol (13) or the ketone (12).

When DMSO rather than methanol was used as solvent, the formation of the alcohol (13) markedly predominated over the ketone (12).[6] This is one of the facts that make path A preferable.

Aromatic heterocycles 3 - 7, which were dimerized by the catalytic action of the cyanide ion as mentioned above, reacted with aromatic aldehydes (11) to give the corresponding alcohols and ketones, in varying yields.[4] The aromatic heterocycle which is dimerized undergoes the cross-benzoin condensation-like reaction, but this is not the case with the non-dimerized one. In fact, phthalazine (14), 1,6-naphthyridine (15), and 1,8-naphthyridine (16) gave neither the corresponding dimer nor the corresponding alcohol or ketone.

The reaction products could be obtained in considerable yield from the combination of aromatic heterocycles and aromatic aldehydes (11). This reaction is

thus considered to be a very effective method for preparing aromatic heterocyclic alcohols or ketones.



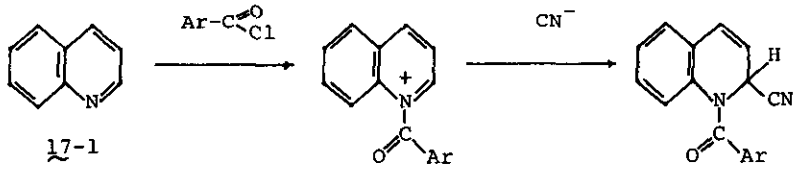
14 15 16

Chart 4

2. The Reaction of Aromatic Heterocyclic N-Oxides with Carboxylic Acid Chlorides in the Presence of Potassium Cyanide (the Extension of the Reissert-Henze Reaction)

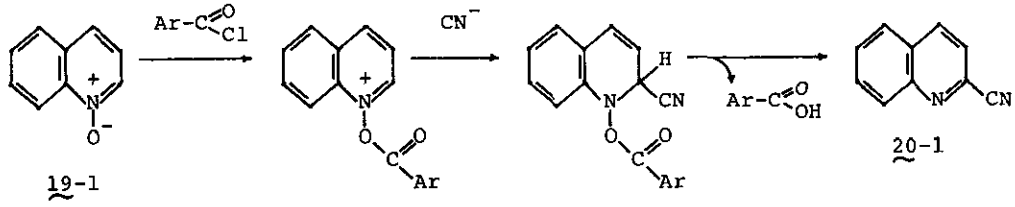
The reaction of quinoline (17-1) with aroyl chlorides in the presence of potassium cyanide forms the 1,2-dihydroquinoline derivative, the so-called Reissert compound (18), and this reaction is called the Reissert reaction.[7] Application of the Reissert reaction to quinoline 1-oxide (19-1) resulted in concurrent deoxygenation of the N-oxide group to form 2-quinolinecarbonitrile (20-1). This reaction, which is called the Reissert-Henze reaction[8], can be used to synthesize the substituted 2-quinolinecarbonitriles (20) from the substituted quinoline 1-oxides (19), and is very useful for the introduction of the cyano group into the α-position of the ring nitrogen of aromatic heterocycles.

The Reissert reaction:



17-1 18

The Reissert-Henze reaction:

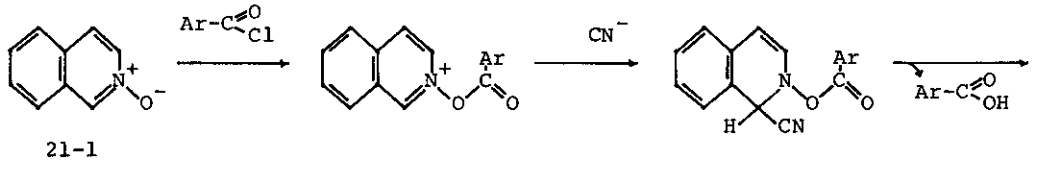


19-1 20-1

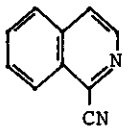
Chart 5

Application of the Reissert-Henze reaction to isoquinoline 2-oxide (21-1) was also carried out and resulted in the formation of 1-isoquinolinecarbonitrile

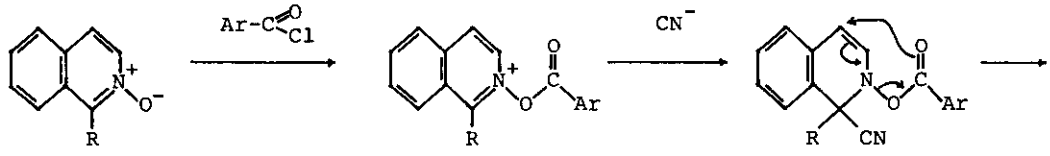
(22-1), but no report on 1-substituted isoquinoline 2-oxides (21-2), which is not expected to form the product corresponding to 22-1, has been published. What results can be obtained from the Reissert-Henze reaction of 21-2? This question motivated us to do "the Extension of the Reissert-Henze Reaction" described in the title of this section. Thus, several 1-substituted isoquinoline 2-oxides (21-2) reacted with benzoyl chloride in the presence of potassium cyanide to result in the concurrent deoxygenation of the N-oxide group and in the formation of 1-substituted 4-benzoyloxyisoquinolines (23-1)[9]. From this fact it becomes clear that even when the Reissert-Henze reaction is not expected to occur, another reaction can take place. Although 23-1, formed here, does not have a cyano group, if there is no potassium cyanide present in the reaction medium, the reaction does not occur. For example, the reaction with potassium carbonate instead of potassium cyanide did not result in the formation of any product. In the case of p-methoxy- or p-nitrobenzoyl chlorides used as the acid chloride, the result of the reaction was similar to that with benzoyl chloride. Benzyl and butyl groups substituted at the 1-position of 21-2 gave 1,4-dihydroisoquinoline derivatives (23'), where the cyano group was introduced into the 1-position and the aroyloxy group was located at the 4-position, with or without formation of 23. As it seems that 23' is a precursor of 23, a possible reaction process is presented as shown in Chart 6.



21-1



22-1



21-2

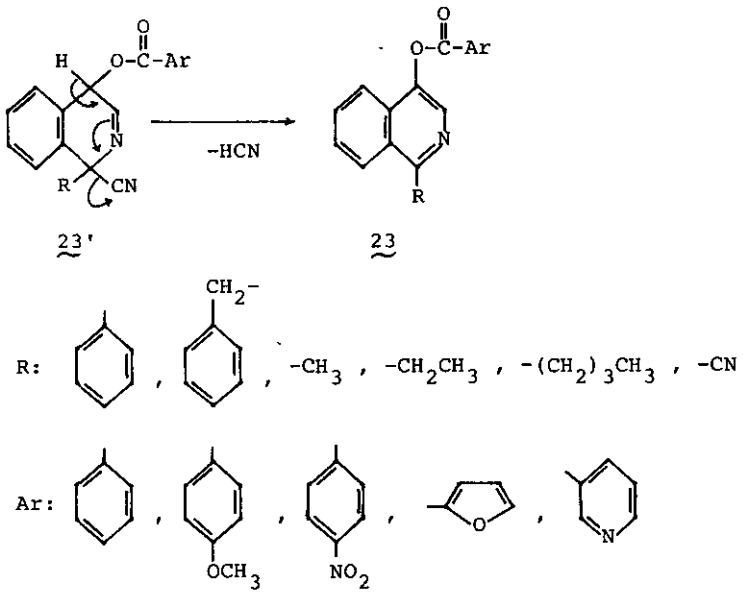


Chart 6

The reaction of 1,4-disubstituted isoquinoline 2-oxides (21-3)[9] gave 1,4-dihydroisoquinoline derivatives (24) (Chart 7) corresponding to 23' from 21-2.

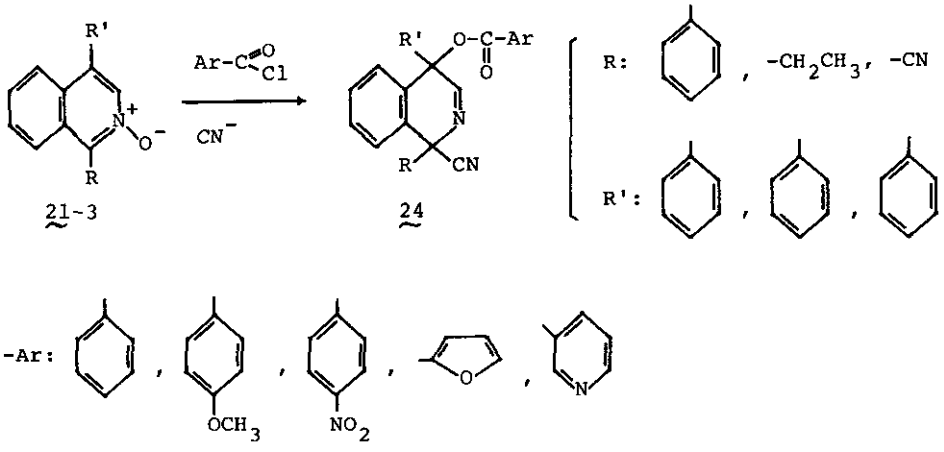


Chart 7

Application of the Reissert-Henze reaction to 2-substituted or 2,3-disubstituted quinoline 1-oxides (19-2)[10] resulted in the concurrent deoxygenation of the N-oxide group to form 1,2,3,4-tetrahydroquinoline derivatives (25) where the hydroxyl, aroyloxyl, and cyano groups were introduced into the 2-, 3-, and 4-positions respectively. When the substituent at the 2-position of 19-2 was phenyl group, the reaction resulted in the concurrent deoxygenation of the N-oxide group to give 6- or 8-aroyloxyquinolines (26), together with formation of 25 (Chart 8).

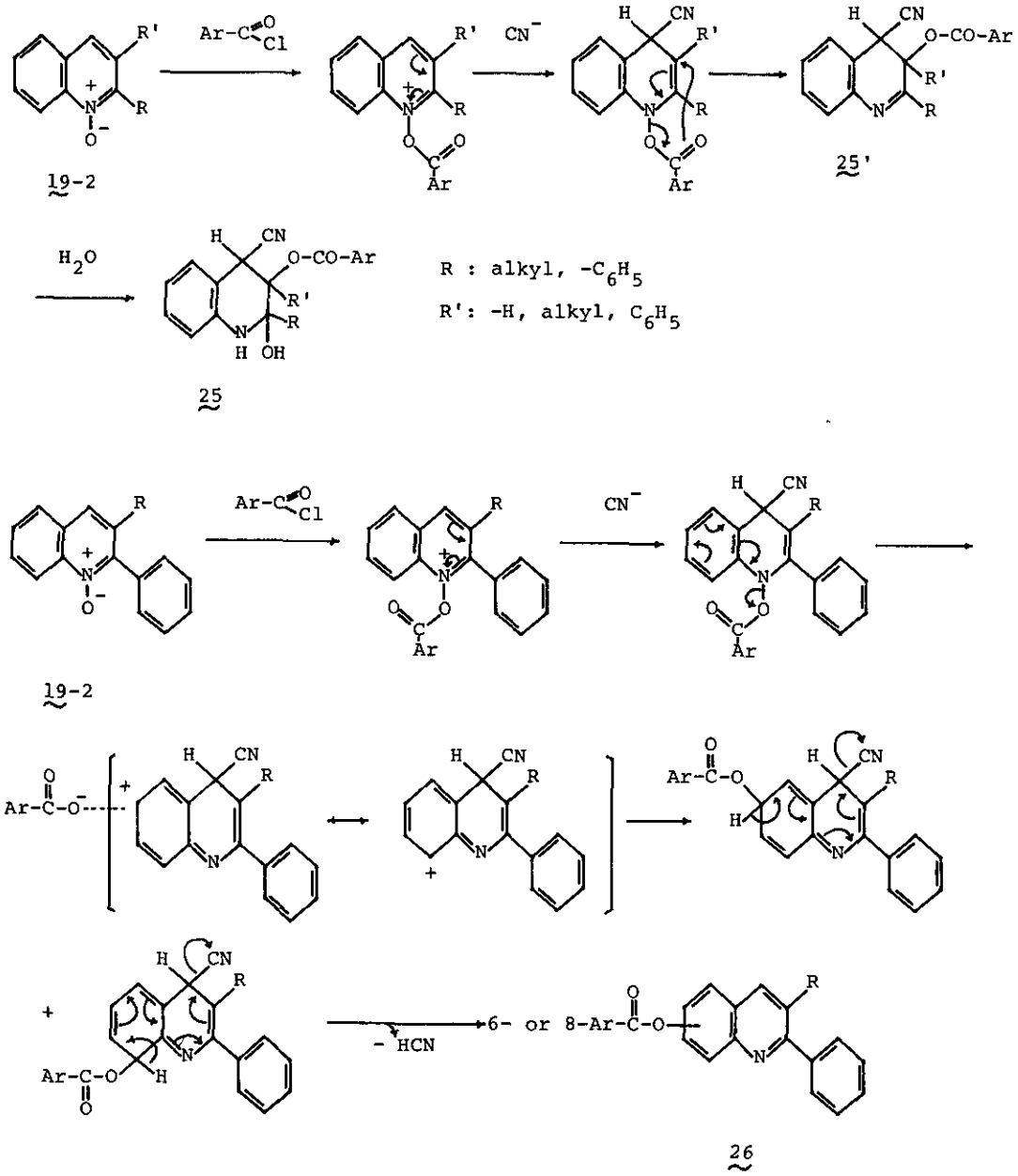


Chart 8

The compound 25', which seems to be an intermediate of the product 25, corresponds to 24 from 1,4-disubstituted isoquinoline 2-oxides (21-3), but it could still not be isolated. And the formation of 26 is the same result as obtained with 2,4-diphenylquinoline 1-oxide[11], already reported by Hamana et al. As already mentioned in this section, the extension of the Reissert-Henze reaction

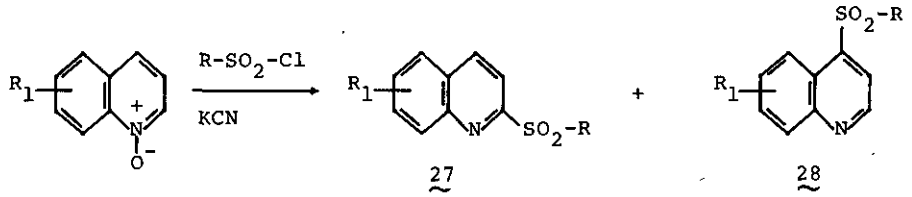
proceeds in the following two ways; one is the introduction of the cyano group into the heteroaromatic ring, and the other does not involve its introduction . In the latter case the cyanide ion attacks a nucleophilically active site to form an intermediate. Then this precursor loses the cyanide ion to form the final product. From this it can be said that the cyanide ion, similar to that in the benzoin condensation, acts as a catalyst.

3. The Reaction of Aromatic Heterocyclic N-Oxides with Sulfonic Acid Chlorides in the Presence of Potassium Cyanide

All acid chlorides in the Reissert-Henze reaction and its extension, described in section 2, were carboxylic acid chlorides. However the reaction of aromatic heterocyclic N-oxides with sulfonic acid chlorides, in the presence of the cyanide ion, took place in a different way from those of the Reissert-Henze reaction or its extension. When sulfonyl chloride was added to an aqueous acetone solution of quinoline 1-oxide (19-1), or its variously substituted derivatives, and potassium cyanide, and the mixture was stirred at room temperature, the following results were obtained. (i) In the case of quinoline 1-oxides (19-3) unsubstituted at the 2-position[12] the reaction resulted in the concurrent deoxygenation of the N-oxide group, and the sulfonyl group was introduced into the 2-position to form 2-sulfonylquinolines (27). In a few cases the 4-sulfonylquinoline (28) was formed as a minor product together with 27 (major product). (ii) In the case of quinoline 1-oxides (19-4) having substituents at the 2-position but not at the 4-position[12] the reaction proceeded in the deoxygenation of the N-oxide group and resulted in the introduction of the sulfonyl group into the 4-position to form 28 as major product, together with the 3-sulfonylquinoline (29) as a minor product. (iii) In the case of quinoline 1-oxides (19-5) substituted at both the 2- and 4-positions [13] the formation of 29, which was derived by introduction of the sulfonyl group into the 3-position, was recognized through the concurrent deoxygenation of the N-oxide group.

Although the reaction products obtained here do not contain the cyano group, the absence of the cyanide ion in the reaction does not allow formation of the products. For example, the reaction of 19-1 with sulfonyl chlorides in the presence of potassium carbonate, instead of potassium cyanide, resulted in the formation of carbostyril only in good yield, and 27 was not formed. We then examined the action of the cyanide ion in various ways and reached the following conclu-

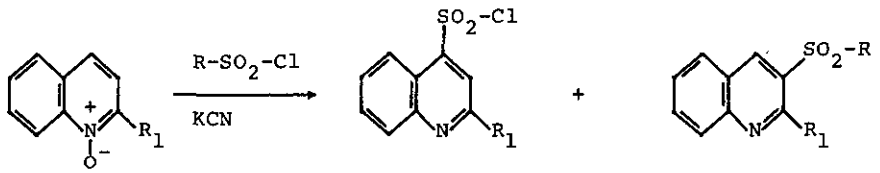
(i)



19-3 27 28

R_1: H-, 3-Br-, 3-CN-, 4-CH_3O-, 4-CH_3, 4-Cl-, 4-CN-, 6-CH_3O-, 6-Cl, 6-Br-, 6-CN-, 6-NO_2-, 7-Cl

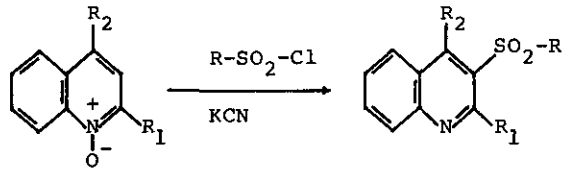
(ii)



19-4 28 29

R_1: CH_3-, C_6H_5-

(iii)



19-5 29

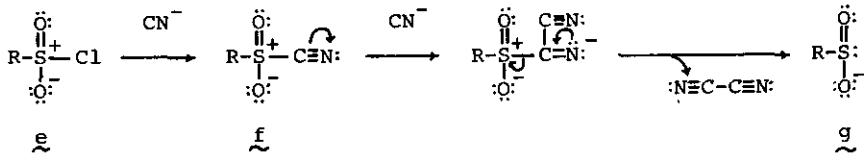
R_1: CH_3-, CH_3-, CH_3CH_2-, C_6H_5-

R_2: C_6H_5-, CH_3-, CH_3- , CH_3-

R : CH_3-, CH_3CH_2-, C_6H_5-, p-CH_3-C_6H_4-

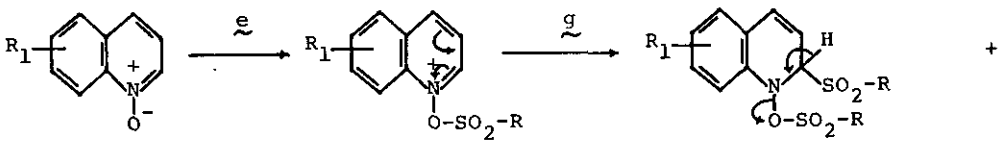
Chart 9

sions. The cyanide ion reacts with sulfonyl chloride (e) to form the sulfonyl cyanide (f) which leads to cyanogen and sulfinate ion (g) by cleavage of the S-C bond by attaching the cyanide ion to the carbon of the cyano group of f. The sulfinate ion (g) as a nucleophile is concerned with the following processes to 27, 28, and 29, as shown in Chart 10, and the reactions are classified as type A for the formation of 27 and 28, and type B for that of 29, according to the structure of the product.

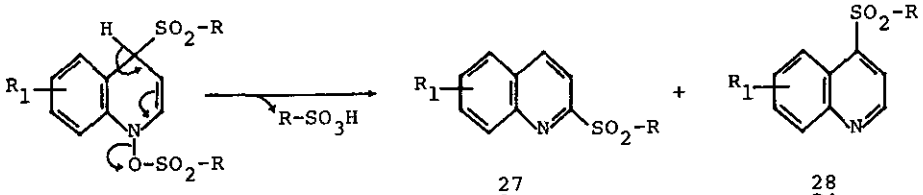


e f g

A type of the reaction:

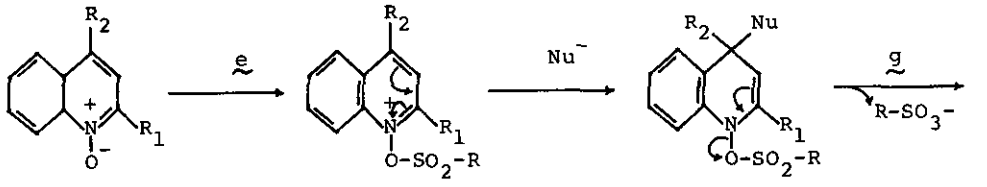


19-3, 19-4

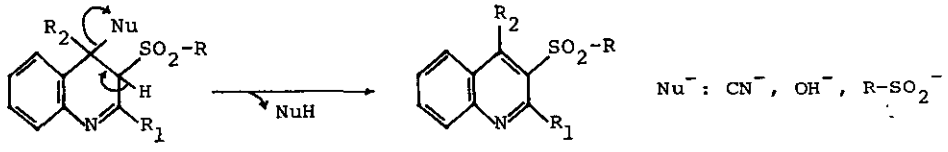


27 28

B type of the reaction:



19-5



29

Chart 10

In the mechanism of the A type the sulfinate ion (g) seems to correspond to the cyanide ion in the Reissert-Henze reaction. In fact, 19-1 reacted with acid chlorides such as benzoyl chloride, methanesulfonyl chloride, or p-toluenesulfonyl chloride in the presence of sodium p-toluenesulfinate to give 2-(p-tolylsulfonyl)quinoline (27-1). Stable sulfinates such as higher alkane- and arenesulfinates can be used as reagent instead of the cyanide ion, but the unstable ones such as lower alkanesulfinates can not. From this it can be said that the reaction with sulfonyl chloride in the presence of the cyanide ion is very useful for the synthesis of lower alkylated sulfonylheterocycles.

The title "Reactions of Aromatic Heterocycles Involving the Catalytic Action of the Cyanide Ion" does not express properly the changing of the cyanide ion into cyanogen. But we are very interested in the unique reactions which do not involve the introduction of the cyano group but still depend on the presence of cyanide ion.

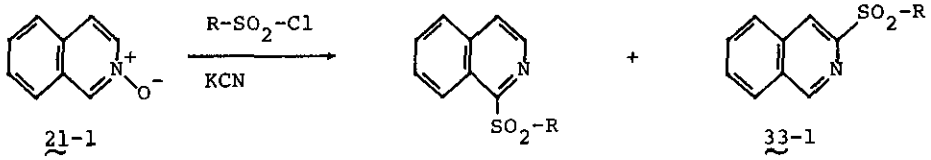
The reaction of 19-5, which both R_1 and R_2 are alkyl group, resulted in the rearrangement of R_1 into the 3-position and 3,4-dialkylcarbostyril (30) was formed as a by-product. This rearrangement is not known in the chemistry of aromatic heterocyclic N-oxides. We do not however explain it in detail as the cyanide ion is not directly concerned in this rearrangement.

19-5 30

R_1: $-CH_3$, $-CH_2CH_3$
R_2: $-CH_3$, $-CH_3$

Chart 11

Application of this reaction to isoquinoline 2-oxide (21-1)[14] and phenanthridine 5-oxide (31)[15] resulted in the concurrent deoxygenation of the N-oxide group, and 1- (32-1) or 3-(alkylsulfonyl)isoquinoline (33-1) and 6-(alkylsulfonyl)phenanthridine (34) were obtained by the A type mechanism. It is known that there are very few reports of successful introduction of substituents into the 3-position from the reaction of 21-1 with acid chlorides. Pyridine 1-oxide (35)[16] also gave the products by both A and B type reactions, even though the yields were poor. In the former the sulfonyl group was introduced into the 2- or 4-positions, and in the latter it was introduced into the 3-position. It is also known that the Reissert-Henze reaction is unsuccessful in the case of the pyridine 1-oxide series, other than for the 4-chloro derivative.



21-1 32-1 33-1

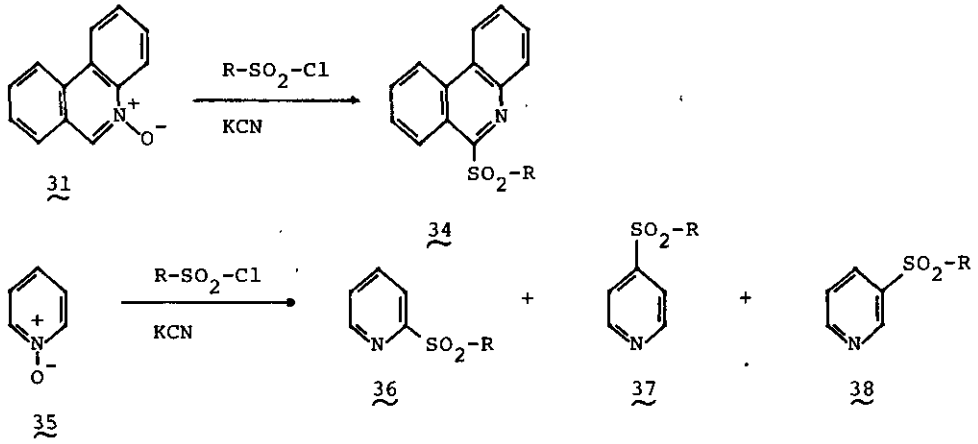


Chart 12

In the case of quinoxaline 1-oxide or 2-substituted quinoxaline 4-oxides (39), 1-substituted phthalazine 3-oxides (40), and 4-substituted quinazoline 1-oxides (41), the formation of the corresponding sulfones (42, 43, 44) was recognized.[17]

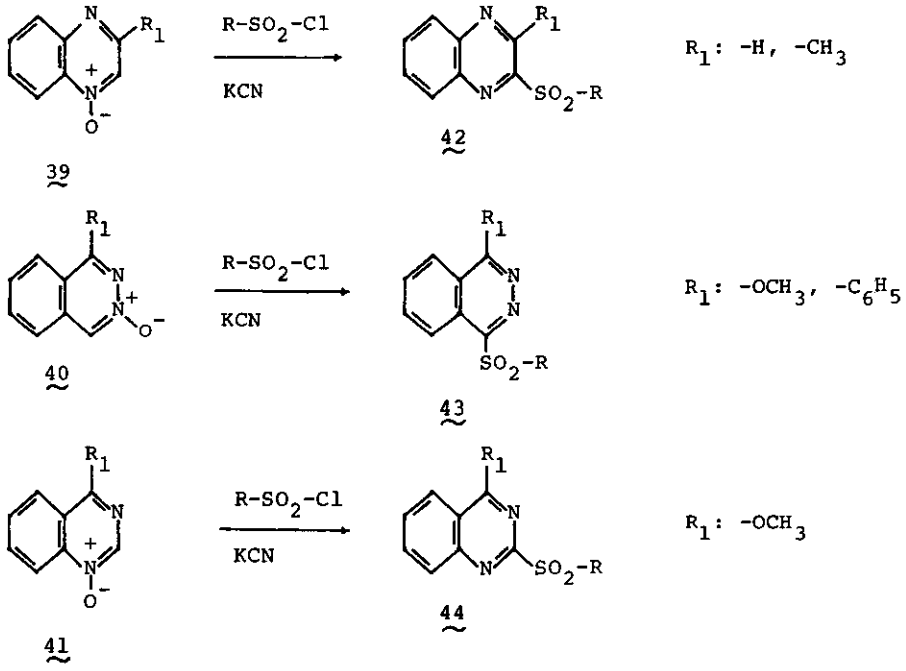


Chart 13

In sulfone formation mentioned in this section, the introduction of the hydroxyl group with the concurrent deoxygenation of the N-oxide group occurred and the carbostyril type of the compound was always formed together with the sulfone. And in some cases the cyano compound, corresponding to the product of the Reissert-

Henze reaction, was also obtained.

When the reaction of 1-phenyl-1H-pyrazolo[3,4-d]pyrimidine 5-oxide (45)[18] with methanesulfonyl chloride in the presence of potassium cyanide was carried out in aqueous acetone, introduction of the acetonyl group, originating from acetone, into the 4-position occurred with the concurrent deoxygenation of the N-oxide group to give 46 in good yield, and did not result in the formation of any of the expected sulfone. Moreover, the reaction in aqueous dioxane gave the nitrile (47), while the Reissert-Henze reaction of 45 gave the ring opening product (48) and did not give 47.[19] It seems outwardly that cyanide ion acts as a base catalyst for the formation of 46. Similar reaction was also found for 4-isoquinolinecarbonitrile 2-oxide (21-4) giving sulfone (32-2) and isocarbostyril derivative (49) together with 50 as the major product.[14]

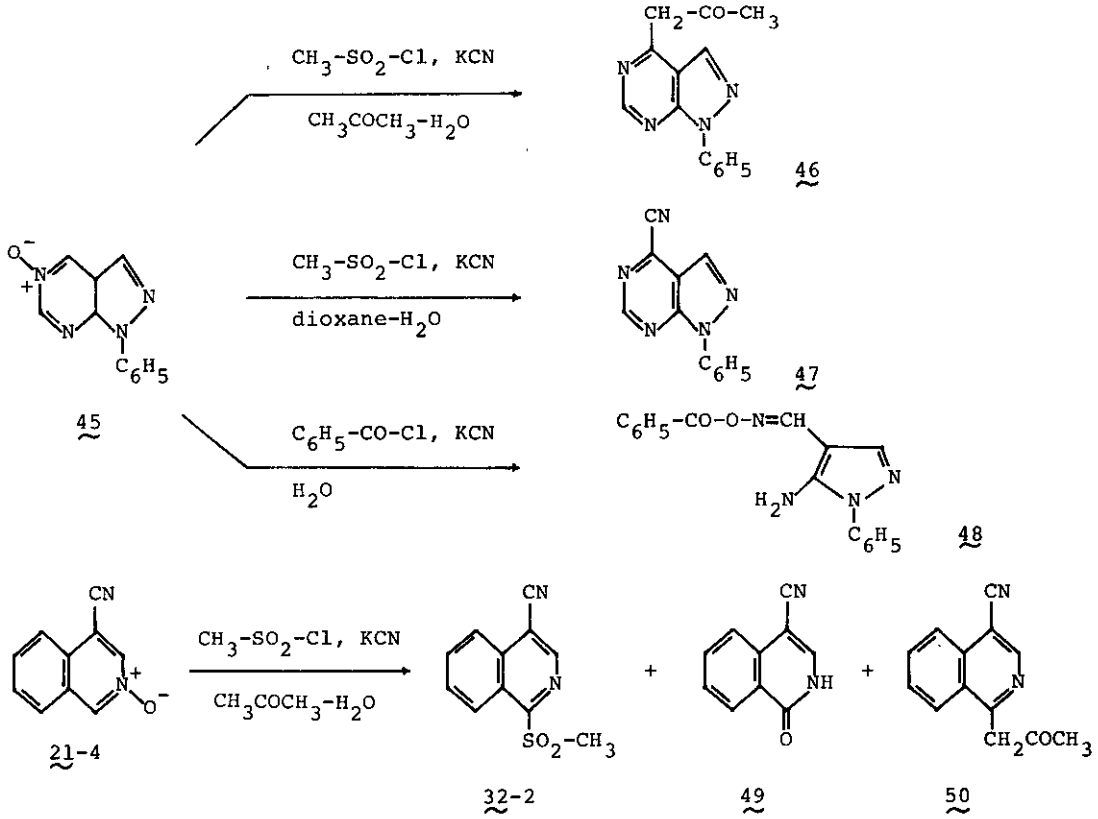


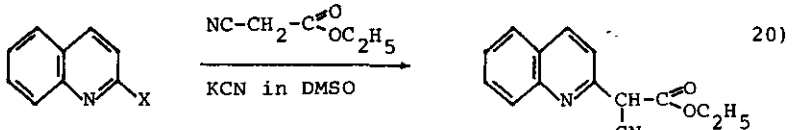
Chart 14

4. Reactions Involving Base Catalytic Action of the Cyanide Ion

It is well known that the leaving atom or group, bonded to a π-deficient position of the aromatic heterocyclic ring system, is easily displaced by several

nucleophiles. Nucleophilic substitution on halo aromatic heterocycles, especially chloro derivatives in which the chloro group is the leaving one, has long been examined in several ways and has been used for many chemical syntheses. The sulfonyl, nitro, and cyano groups often act as leaving group, and substitution proceeds smoothly. Even in the case of hydrogen as leaving group, that is, in the absence of any substituent at the π-deficient position, nucleophilic substitution often proceeds if a suitable hydride ion acceptor is present in the reaction system. Substitution by carbanion provides us with a facile method for the introduction of a carbon chain into the aromatic heterocyclic ring system. In general the substitution by carbanion is carried out in a mixture of active methylene compound or ketone, and base such as sodium amide, potassium hydroxide or sodium hydride. It was also found that substitution was successful in many aromatic heterocycles using potassium cyanide and several active methylene compounds in DMSO. Based on the structure of the substrate and that of the product, it seems that the cyanide ion behaves in the reaction somewhat like a base catalyst. In many of the cases in which the ordinary method, using sodium amide as base, failed to give substitution, the use of potassium cyanide often gave successful results. However, the yield of product is so variable that improvement of the reaction conditions is neccessary before using this method for chemical synthesis.

(1) Quinolines:

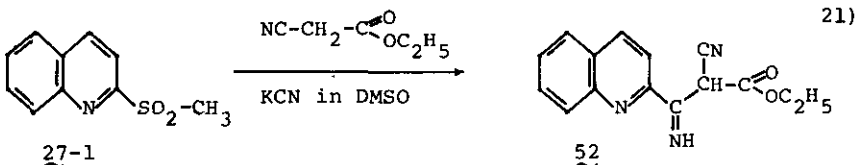


20)

X: $-NO_2$, 17-2

$-I$, 17-3

51

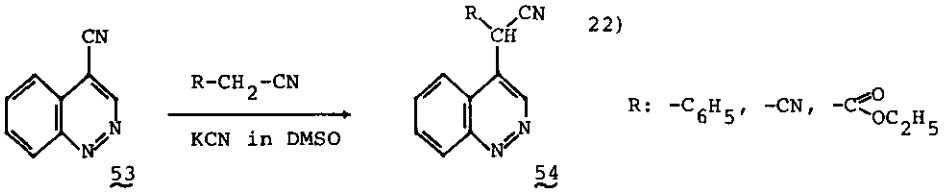


21)

27-1

52

(2) Cinnolines:

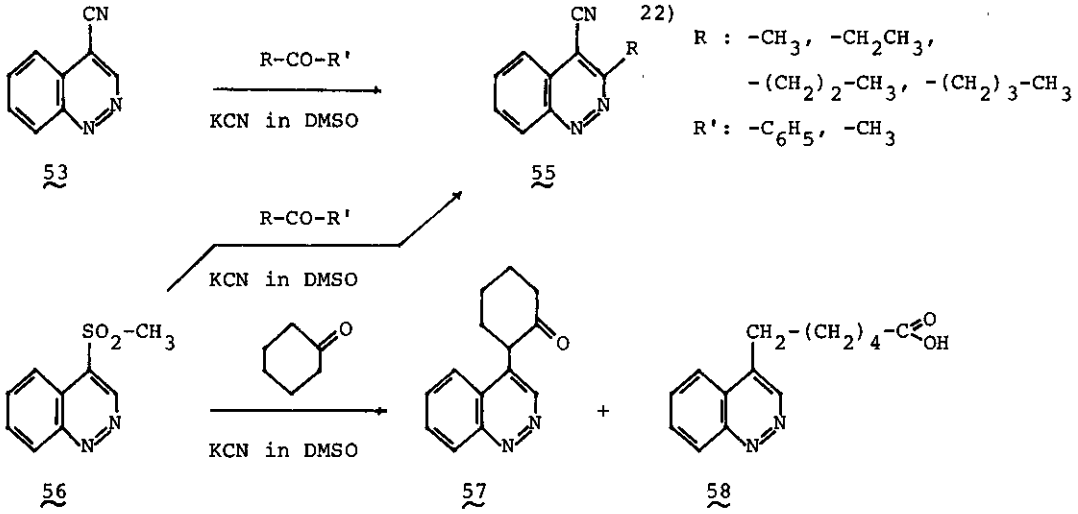


22)

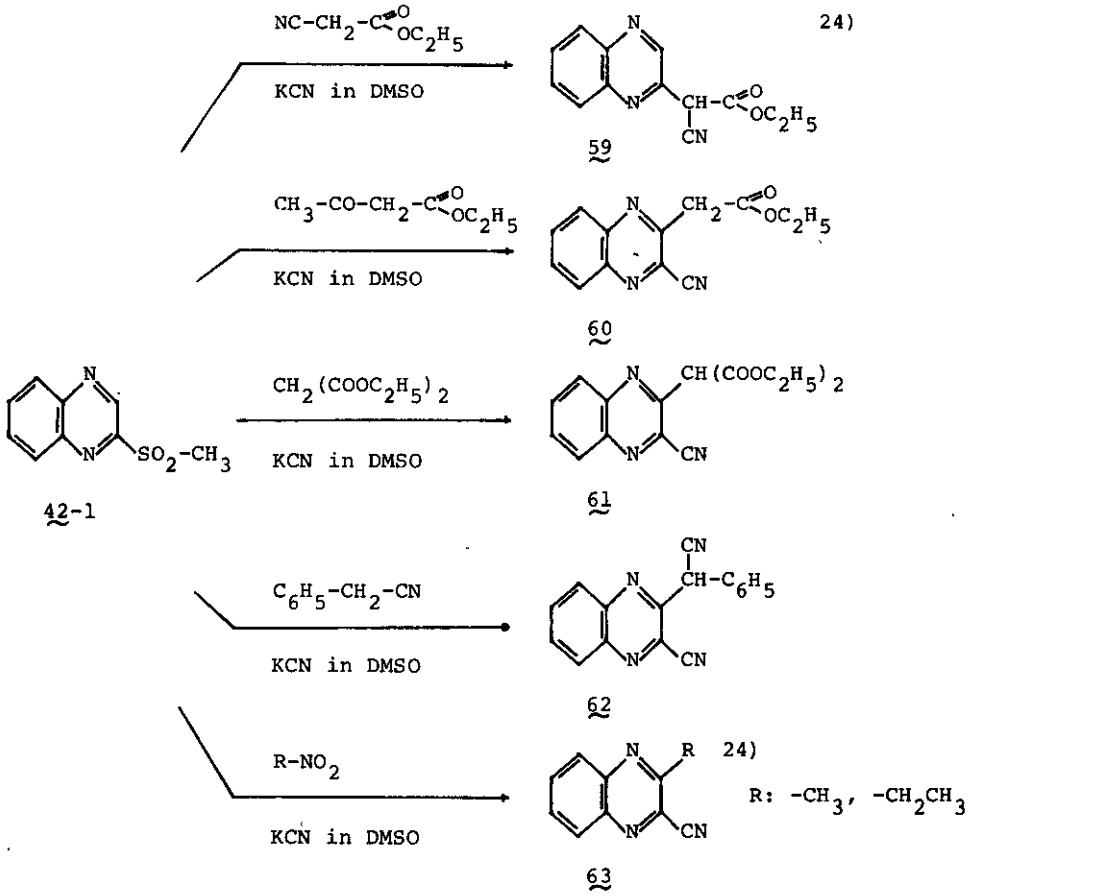
R: $-C_6H_5$, $-CN$, $-C(=O)OC_2H_5$

53

54



(3) Quinoxalines:



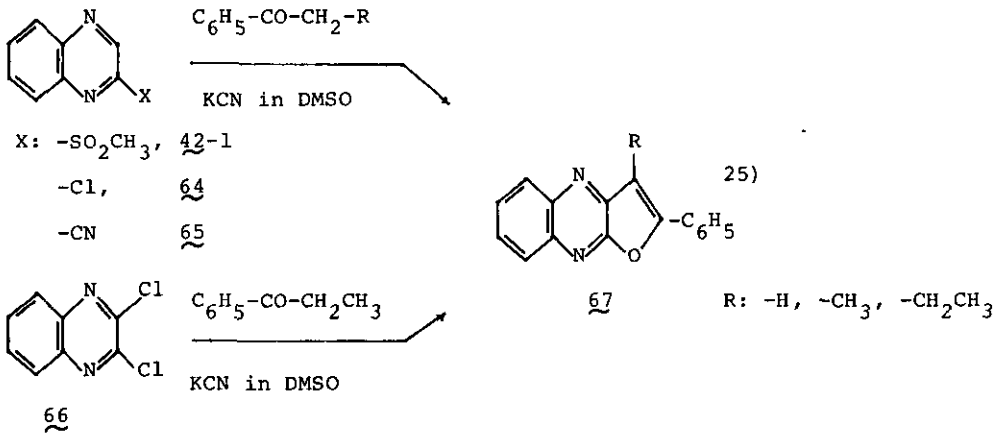


Chart 15

(1) The nitro and iodo groups in 2-nitroquinoline (17-2) or 2-iodoquinoline (17-3) were displaced by carbanion, but the methylsulfonyl group in 2-(methylsulfonyl)quinoline (27-1) was first displaced by cyanide ion followed by addition of the active methylene compound to the resulting cyano group to give the adduct (52). This fact shows that the direction of substitution depends on the nature of the leaving group.

(2) When 4-cinnolinecarbonitrile (53) reacted with active methylene compound in the presence of the cyanide ion in DMSO, the cyano group was displaced by carbanion, while the reaction with ketone resulted in the introduction of an alkyl group, which originated from ketone, into the carbon atom next to the carbon bonding the cyano group, that is, the 3-position of the cinnoline ring. This fact shows that the direction of substitution depends on the nature of the carbanion. Cyclohexanone used as ketone did not react with 53. But its reaction with 4-(methylsulfonyl)cinnoline (56) gave the product of substitution of methylsulfonyl group by cyclohexanone, and its hydrolyzed product, 4-cinnolinehexanoic acid (58). In the case of the reaction of 56 with methyl ketone or phenyl ketone, the methylsulfonyl group was first displaced by the cyanide ion and the following reaction which took place was the same as that for 53. It is to be noted that the introduced alkyl groups originating from ketone, are not methyl or phenyl groups, but are the *other alkyl groups*.

(3) There are two directions for nucleophilic substitution in the case of reaction of 2-(methylsulfonyl)quinoxaline (42-1) with carbanion: One is the displacement of the methylsulfonyl group by carbanion, and the other is the intro-

duction of carbanion at the carbon next to the one first substituted by the cyanide ion. Phenyl ketone reacted with 42-1, 2-chloroquinoxaline (64), or 2-quinoxalinecarbonitrile (65) to give furo[2,3-b]quinoxaline derivatives (67), although the yield was very poor. Application of this reaction to 2,3-dichloroquinoxaline (66) also gave the furo[2,3-b]quinoxaline derivative (67) in moderate yield.

REFERENCES

1) (a) Ide, W. S., Buck, J. S.: "Organic Reactions" Vol. IV, John Wiley & Sons, Inc., New York (1948), p. 269.; (b) Gould, E. S.: "Mechanism and Structure in Organic Chemistry", Henry Holt and Company, Inc., New York (1959), p. 394.
2) Armarego, W. L. F., Willette, R. E.: J. Chem. Soc., 1965, 1258.
3) Hayashi, E., Makino, H., Higashino, T.: Yakugaku Zasshi, 94, 1041 (1974).
4) Higashino, T., Goi, M., Hayashi, E.: Chem. Pharm. Bull. (Tokyo), 24, 238 (1976).
5) Higashino, T., Goi, M., Hayashi, E.: Chem. Pharm. Bull. (Tokyo), 22, 2493 (1974).
6) Higashino, T., Goi, M., Hayashi, E.: Yakugaku Zasshi, 96, 397 (1976).
7) (a) McEwen, W. E., Cobb, R. L.: Chem. Rev., 55, 511 (1955); (b) Popp, F. D.: "Advances in Heterocyclic Chemistry", Vol. 9, Academic Press, London (1965), p.1.
8) (a) Ochiani, E.: "Aromatic Amine Oxides", Elsevier Publishing Company, Amsterdam (1976), p. 269 ; (b) Katritzky, A. R., Lagowski, J. M.: "Chemistry of the Heterocyclic N-Oxides", Academic Press, London (1971), p. 300.
9) Hayashi, E., Miyashita, A.: Yakugaku Zasshi, 97, 1334 (1977).
10) Hayashi, E., Miyashita, A.: Yakugaku Zasshi, 96, 968 (1976).
11) Hamana, M., Shimizu, K.: Yakugaku Zasshi, 86, 59 (1966).
12) Hayashi, E., Shimada, N.: Yakugaku Zasshi, 97, 627 (1977).
13) Hayashi, E., Shimada, N.: Yakugaku Zasshi, 97, 641 (1977).
14) Hayashi, E., Shimada, N.: Yakugaku Zasshi, 97, 1345 (1977).
15) Hayashi, E., Shimada, N.: Yakugaku Zasshi, 98, 136 (1978).
16) Hayashi, E., Shimada, N.: Yakugaku Zasshi, 98, 95 (1978).
17) Sano, K.: "Thesis for the Master of Science in Shizuoka College of Pharmacy" (1976).

18) Hayashi, E., Higashino, T., Shimada, N.: Yakugaku Zasshi, 98, 234 (1978).

19) Higashino, T., Iwai, Y., Hayashi, E.: Chem. Pharm. Bull. (Tokyo), 24, 3120 (1976).

20) Hayashi, E., Saito, T.: Yakugaku Zasshi, 89, 108 (1969).

21) Hayashi, E., Saito, T.: Yakugaku Zasshi, 89, 74 (1969).

22) Hayashi, E., Utsunomiya, I.: Yakugaku Zasshi, 94 1159 (1974).

23) Hayashi, E., Watanabe, T.: Yakugaku Zasshi, 89, 1092 (1969).

24) Hayashi, E., Miyagishima, T: Yakugaku Zasshi, 87, 1103 (1967).

25) Hayashi, E., Utsunomiya, A.: Yakugaku Zasshi, 95, 774 (1975).

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