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167. **Takeo Higashino**: On the Reaction of 4-Quinazolinecarbonitrile with Nucleophilic Reagents. II. Reaction of 4-Quinazolinecarbonitrile with Grignard Reagents.

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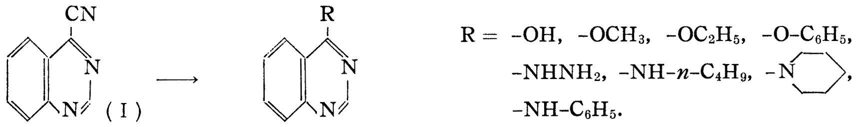
In Part I[1] of this series, it was reported that reaction of 4-quinazolinecarbonitrile (I) with 10% potassium hydroxide at room temperature afforded 4(3*H*)-quinazolinone, with sodium alkoxide, 4-alkoxyquinazolines, with sodium phenoxide, 4-phenoxyquinazoline, with hydrazine, 4-hydrazinoquinazoline, and with butylamine as an aliphatic primary amine, piperidine as an aliphatic secondary amine, or aniline as an aromatic primary amine gave 4-butylaminoquinazoline, 4-piperidinoquinazoline, or 4-anilinoquinazoline.

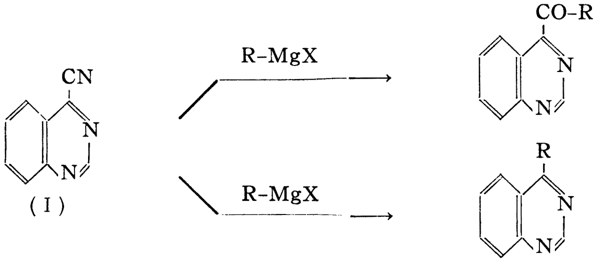
The foregoing results showed that the 4-position in (I) was very reactive to anionoid reagents.



R = -OH, -OCH$_3$, -OC$_2$H$_5$, -O-C$_6$H$_5$,
-NHNH$_2$, -NH-n-C$_4$H$_9$, -N,
-NH-C$_6$H$_5$.

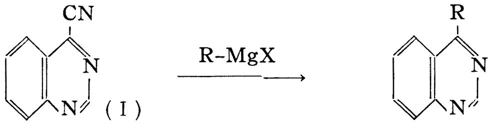
In the present series of work, reactions of (I) with Grignard reagents were studied in order to elucidate the chemical properties of the cyano group at the 4-position of (I).

Considering the fact that the 4-position of (I) is very reactive to anionoid reagents, two reaction products may be expected from the reaction of (I) with Grignard reagents. One is 4-acylquinazoline which is generally derivable by the reaction of the cyano group with Grignard reagents, and the other is 4-alkylquinazoline which is formed when Grignard reagents directly attack the 4-position of (I).



The present experiments showed that this reaction proceeded in such a manner as to produce 4-alkylquinazoline and not 4-acylquinazoline.

In an anhydrous ether, reaction of (I) with methylmagnesium iodide, ethylmagnesium bromide, isopropylmagnesium bromide, phenylmagnesium bromide, and benzylmagnesium chloride by the usual method afforded 4-methylquinazoline (II), 4-ethylquinazoline (III), 4-isopropylquinazoline (IV), 4-phenylquinazoline (V), and 4-benzylquinazoline (VI), respectively.



R = -CH$_3$ (II), -C$_2$H$_5$ (III),
-iso-C$_3$H$_7$ (IV),
-C$_6$H$_5$ (V), -CH$_2$-C$_6$H$_5$ (VI).

[*1] Oshika, Shizuoka (東野武郎).

1) T. Higasino: Yakugaku Zasshi, **80**, 1404 (1960).

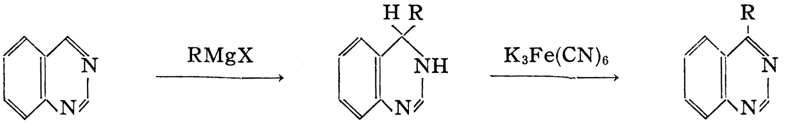
2) *Idem*: *Ibid.*, **80**, 245 (1960).

TABLE I.

Picrates	M.p. (°C)
4-Methylquinazoline picrate (IIa)	183
4-Ethylquinazoline picrate (IIIa)	170~171
4-Isopropylquinazoline picrate (IVa)	161~162
4-Benzylquinazoline picrate (VIa)	154

(II), (III), (IV), and (VI), so obtained, were converted into their picrates, (IIa), (IIIa), (IVa), and (VIa), the melting points of these picrates were listed in Table I.

These picrates were identified by admixture with those of the authentic samples[2] obtained by oxidation of the corresponding 4-alkyl-3,4-dihydroquinazolines with potassium ferricyanide, which were prepared by reaction of quinazoline with Grignard reagents,[2] as shown in Chart 1.



R = $-CH_3$ (II), $-C_2H_5$ (III), -iso-C_3H_7 (IV), $-C_6H_5$ (V), $-CH_2-C_6H_5$ (VI).

Chart 1.

Also (V) was identified on admixture with an authentic specimen prepared by oxidation of 3,4-dihydro-4-phenylquinazoline[3] with potassium ferricyanide.

The formation of 4-alkylquinazoline is considered to involve a route shown in Chart 2.

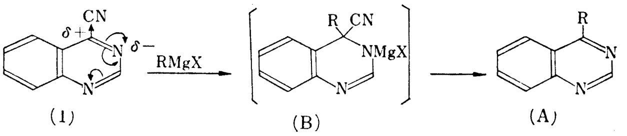
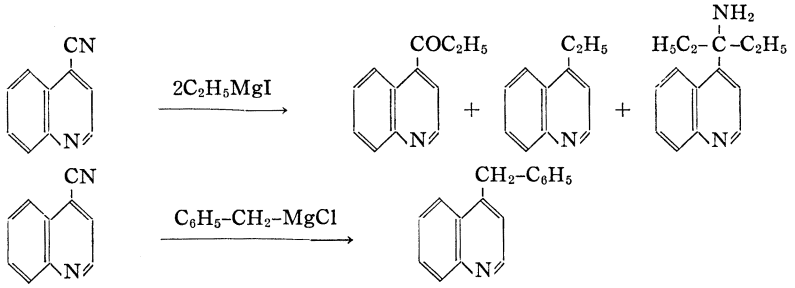


Chart 2.

Electron density of the ring-carbon atom of the 4-position of (I) due to the overlapping of the -M and -E effects of the nitrogen atoms of the rings, the -E effect of the fused benzene-ring, and the -I effect of the cyano group of the 4-position of (I), may be smaller than that of the carbon atom of the cyano group due to the -M effect of the nitrogen atom in the cyano group.

Since the 4-position of (I) is liable to an anionoid attack, the substituted compound (A) might be formed via the intermediate complex of (B) type.

Since the example of the cyano group with such a tendency among other aromatic heterocyclic compounds was only reported in the case of 4-quinolinecarbonitrile,[4] similar



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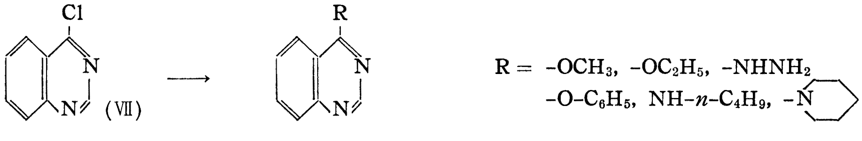
[3] K. Schofield : J. Chem. Soc., **1952**, 1927.

[4] P. Rabe, R. Pasternack : Ber., **46**, 1030 (1913).

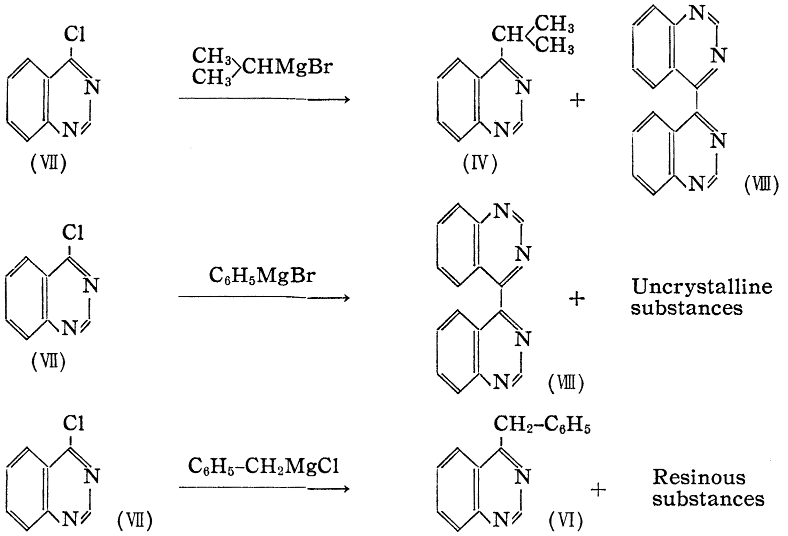
reactions were carried out on quinazoline derivatives possessing the cyano group at the 4-position of the molecule.

In Part I of this series, it was shown that the chemical behaviors of (I) toward anionoid reagents were in parallel with those of 4-chloroquinazoline (VII).[1]

Now, reactions of (VII) with Grignard reagents were carried out in order to compare them with those of (I) with the same reagents.



In an anhydrous ether, (VII), with isopropylmagnesium bromide, gave (IV) and a small amount of 4,4′-biquinazoline (VIII) as a by-product, with phenylmagnesium bromide, a small amount of (VIII) and some uncrystalline substances, and with benzylmagnesium chloride, (VI) and some resinous substances.



The results of these reactions showed that some differences in chemical properties existed between (VII) and (I).

The structure of (VIII) was deduced from the fact that its analytical values corresponded to $C_{16}H_{10}N_4$ and the same product was obtained from the reactions of (VII) with isopropylmagnesium bromide or phenylmagnesium bromide.

Experimental

Reaction of 4-Quinazolinecarbonitrile (I) with Grignard Reagents

1) **4-Methylquinazoline (II)**——The Grignard reagent was prepared by the usual method from 0.15 g. of Mg and 0.5 g. of MeI dissolved in 10 cc. of anhydrous Et_2O. This solution was added in small portions with shaking to a solution of 0.5 g. of (I) in 12 cc. of anhydrous Et_2O. After the reaction mixture was refluxed for 2 hr., 15 cc. of 2*N* H_2SO_4 was added and the solution was neutralized with K_2CO_3, and extracted with benzene. The benzene solution was dried over anhyd. K_2CO_3 and passed through a column of alumina (200 mesh, 30 cc.) to remove impurities. Evaporation of the solvent gave 0.4 g. (87%) of (II). Its picrate (IIa) crystallized as yellow needles, m.p. 183° from MeOH.

(IIa) was identified on admixture with 4-methylquinazoline picrate, m.p. 183°, prepared by another route.[2]

2) **4-Ethylquinazoline (III)**——Reaction of 0.5 g. of (I) with ethylmagnesium bromide (0.6 g. of EtBr, 0.2 g. of Mg, in 10 cc. of anhydrous Et_2O) in anhydrous Et_2O by the above described procedure afforded 0.4 g. (80%) of (III). The picrate (IIIa), formed yellow needles, m.p. 170~171°, from MeOH. *Anal.* Calcd. for $C_{16}H_{13}O_7N_5$ (4-ethylquinazoline picrate) : C, 49.62; H, 3.38; N, 18.08. Found : C, 49.72; H, 3.35; N, 17.72.

(IIIa) was identified on admixture with 4-ethylquinazoline picrate, m.p. 170~171°, described below.

3) **4-Isopropylquinazoline (IV)**——Reaction of 0.5 g. of (I) with isopropylmagnesium bromide (0.15 g. of Mg, and 0.5 g. of isopropylbromide) in anhydrous Et_2O by the same method as described above afforded 0.41 g. (74%) of (IV). The picrate (IVa), formed yellow needles, m.p. 161~162°, from MeOH. *Anal.* Calcd. for $C_{17}H_{15}O_7N_5$ (4-isopropylquinazoline picrate) : C, 50.87; H, 3.77; N, 17.45. Found: C, 50.94; H, 3.91; N, 17.38.

(IVa) was identified on admixture with 4-isopropylquinazoline picrate, m.p. 161~162°, described later.

4) **4-Phenylquinazoline (V)**——Reaction of 0.5 g. of (I) with phenylmagnesium bromide (0.6 g. of bromobenzene and 0.1 g. of Mg in 10 cc. of anhydrous Et_2O) in anhydrous Et_2O by the same method as described above afforded 0.3 g. (45%) of (V), white leaflets, m.p. 97°, from petroleum (b.p. 60~80°).

(V) was identified on admixture with 4-phenylquinazoline prepared by K. Schofield.[3)]

5) **4-Benzylquinazoline (VI)**——Reaction of 0.5 g. of (I) with benzylmagnesium chloride (0.5 g. of benzyl chloride and 0.14 g. of Mg in 10 cc. of anhydrous Et_2O) in anhydrous Et_2O by the same treatment as described above afforded 0.3 g. (42%) of (IV). The picrate (VIa), formed orange prisms, m.p. 154°, from MeOH. *Anal.* Calcd. for $C_{21}H_{15}O_7N_5 \cdot \frac{1}{2}H_2O$ (4-benzylquinazoline picrate) : C, 55.02; H, 3.51; N, 15.18. Found : C, 54.88; H, 3.58; N, 15.40.

(VIa) was identified on admixture with 4-benzylquinazoline picrate prepared below.

Preparation of 4-Alkylquinazolines

General Method——The Grignard reagent was prepared from 0.014 mole of Mg, and 0.012 mole of alkyl halide in 10 cc. of anhydrous Et_2O.

This solution was added in small portions with shaking to a solution of 0.01 mole (1.3 g.) of quinazoline in 10 cc. of anhydrous Et_2O. The reaction mixture was refluxed for 1 hr. and 15 cc. of 10% H_2SO_4 was added to the reaction mixture. The H_2SO_4 layer was neutralized with K_2CO_3, and extracted with benzene.

A solution of 7.8 g. (0.022 mole) of $K_3Fe(CN)_6$ and 20 cc. of H_2O was added in small portions with shaking at room temperature to a mixture of a KOH solution (5 g. of KOH in 10 cc. of H_2O) and the above benzene solution. After continuous shaking for 3 hr., the benzene layer was dried over anhyd. Na_2SO_4, and the benzene solution was passed through a column of alumina (200 mesh, 20 cc.) to remove impurities.

Alkylquinazolines, thus obtained, were driverted to their picrates. The results are shown in Table II. and Table III.

TABLE II.

Alkylquinazolines	Yield (g.), (%)
4-Ethylquinazoline (III)	1.2, 72
4-Isopropylquinazoline (IV)	1.1, 70
4-Benzylquinazoline (VI)	1.4, 66

TABLE III.

Picrate	Formula	Analysis (%)						
		Calcd.			Found			
		C	H	N	C	H	N	
(IIIa)	$C_{16}H_{13}O_7N_5$	49.62	3.38	18.08	49.43	3.21	17.77	yellow needles
(IVa)	$C_{17}H_{15}O_7N_5$	50.87	3.77	17.45	50.62	3.76	17.48	〃
(VIa)	$C_{21}H_{15}O_7N_5 \cdot \frac{1}{2}H_2O$	55.02	3.51	15.18	54.88	3.69	15.39	orange prisms

Reaction of 4-Chloroquinazoline (VII) with Isopropylmagnesium Bromide——The Grignard reagent was prepared from 0.65 g. of isopropyl bromide and 0.15 g. of Mg in 10 cc. of anhydrous Et_2O.

This solution was added in small portions with shaking to a solution of 0.5 g. of (VII) and 10 cc. of anhydrous Et_2O. After the reaction mixture was heated for 30 min., 30 cc. of 2*N* HCl was added and the HCl layer was neutralized with K_2CO_3 and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over anhyd. Na_2SO_4, and the $CHCl_3$ was removed under reduced pressure to yield 0.4 g. of the residue. The residue was divided into the benzene soluble and insoluble parts by addition of benzene.

The solvent was evaporated from the benzene soluble part to give 0.2 g. (38%) of an oily substance. Its picrate, m.p. 161~162°, from MeOH, was undepressed on admixture with (IVa) prepared by the Grignard reaction.

The benzene insoluble part was crystallized from benzene to afford 0.08 g. (20%) of orange crystals m.p. 208~209° of (VIII). *Anal.* Calcd. for $C_{16}H_{10}N_4$ (4,4′-biquinazoline): C, 74.40; H, 3.90; N, 21.70. Found: C, 74.32; H, 3.68; N, 21.45.

Reaction of (VII) with Phenylmagnesium Bromide——The Grignard reagent was prepared from 0.65 g. of bromobenzene and 0.12 g. of Mg in 10 cc. of anhyd. Et_2O. After the reaction mixture was refluxed for 2 hr., 30 cc. of 2*N* HCl was added and the HCl layer was neutralized with K_2CO_3. The $CHCl_3$ solution was dried over anhyd. Na_2SO_4 and the $CHCl_3$ removed to obtain the residue. The residue was divided into benzene soluble and insoluble parts by addition of benzene.

The benzene insoluble part was crystallized from benzene to give 0.11 g. (28%) of crystals, m.p. 208~209°. This was undepressed on admixture with (VIII) obtained by reaction of (VII) with isopropylmagnesium bromide.

The structure of uncrystalline substances from the benzene soluble part was not clarified.

Reaction of (VII) with Benzylmagnesium Chloride——(VII) (0.5 g.) was treated with benzylmagnesium chloride (0.5 g. of benzyl chloride and 0.14 g. of Mg in 10 cc. of anhyd. Et_2O) in anhyd. Et_2O by the same method as (I) afforded (VI), yield 0.2 g. (30%).

Its picrate, m.p. 154° from MeOH was undepressed on admixture with (VIa) obtained as above.

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Summary

Grignard reagents reacted as anionoid with 4-quinazolinecarbonitrile (I).

Reaction of (I) with methylmagnesium iodide, ethylmagnesium bromide, isopropylmagnesium bromide, phenylmagnesium bromide, and benzylmagnesium chloride afforded 4-methyl——(II), 4-ethyl——(III), 4-isopropyl——(IV), 4-phenyl——(V), and 4-benzylquinazoline (VI), respectively.

The mechanism for these reactions may be suggested as in Chart 2.

Reactions of 4-chloroquinazoline (VII) with Grignard reagents were carried out in order to compare them with those of (I) using the same reagents.

(VII), with isopropylmagnesium bromide, afforded (IV) and 4,4′-biquinazoline (VIII), with phenylmagnesium bromide, (VIII), and with benzylmagnesium chloride, (VI).

The foregoing results showed that the 4-position in (I) was very reactive to anionoid reagents, and some differences in chemical properties existed between (VIII) and (I).

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