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The Transformation of 3,4-Dihydro-4-quinazolinylmethyl Alkyl Ketones into Quinolines

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Both the reactions of 3,4-dihydro-4-quinazolinylmethyl alkyl ketones (**4**) with active methylene compounds or ketones (NuH) without a catalyst and in the presence of alumina as a catalyst were carried out, and resulted in the transformation of **4** into quinolines (**3**).

Thus 2-(3,4-dihydro-4-quinazolinyl)acetophenone (**4a**), 2-(3,4-dihydro-4-quinazolinyl)-cyclohexanone (**4b**), and 1-(3,4-dihydro-4-quinazolinyl)-2-propanone (**4c**) reacted with diethyl malonate (NuH-2), phenylacetonitrile (NuH-3), acetophenone (NuH-4), cyclopentanone (NuH-5), and cyclohexanone (NuH-6) without catalyst to give 2-phenylquinoline (**3b**), 1,2,3,4-tetrahydroacridine (**3c**), and 2-methylquinoline (**3d**), respectively, together with the dissociation product, quinazoline (**1a**), although the yield of **3** was very poor. Alumina as a catalyst accelerated these reactions to give **3** in moderate yield. Even the reaction with chloroform (NuH-7) and ethyl orthoformate (NuH-8) gave **3** in good yield. The phenyl and methyl groups substituted at the 2-position prevented **4** from transforming into **3** in both the reactions without a catalyst and in the presence of alumina.

A similar transformation was also found between 4,5-dihydro-5-hydroxy-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-malononitrile (**5**) and NuH in the presence of alumina, and resulted in the formation of 6-amino-1-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carbonitrile (**8**).

The possible mechanism of the reaction was discussed.

Keywords——dihydroquinazolinylmethyl alkyl ketones; quinolines; dihydropyrazolopyrimidinemalononitrile; pyrazolopyridine; ring transformation; dissociation; mechanism

Since it has been reported that quinazoline (**1a**)[2a)] and its 3-oxide (**2**),[2b,c)] on treatment with active methylene compounds or ketones (NuH) without catalyst or solvent, were transformed into quinolines (**3**), the generality of this transformation has been shown by its application to many kinds of the condensed pyrimidines such as pyrido[2,3-*d*]pyrimidine,[2d,e)] 1-methyl- or 1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine,[2f,g)] purine,[3a)] pteridine,[3b)] and 3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine.[3c)] For example, **1a** reacted with malononitrile (NuH-1) to give 2-amino-3-quinolinecarbonitrile (**3a**),[2a)] and **2** and acetophenone (NuH-4) gave 2-phenylquinoline (**3b**).[2b)]

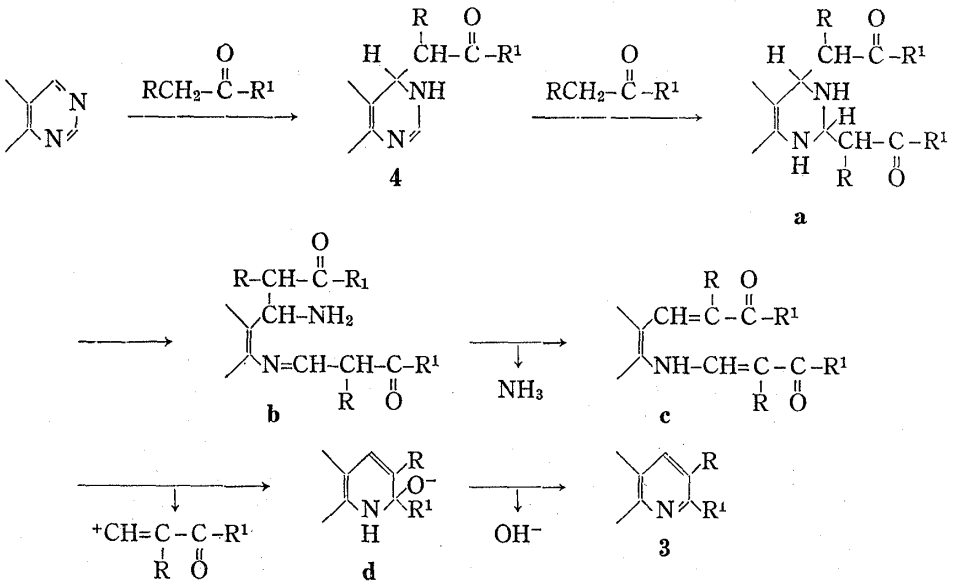
The two possible mechanisms of the transformation have been presented as shown in Chart 1; path A, involving addition–ring opening between the 2- and 3-positions–ring closure, by Higashino, *et al.*,[2)] and path B, involving addition–ring opening between the 3- and 4-positions–ring closure, by Albert, *et al.*,[3)] both the mechanisms indicated that the dihydro-compounds such as 3,4-dihydro-4-quinazolinylmethyl alkyl ketones (**4**) would be the precursors of the ring opened intermediate.

1) Location: *2-2-1 Oshika, Shizuoka-shi.*

2) *a*) T. Higashino, H. Ito, and E. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **20**, 1544 (1972); *b*) T. Higashino, Y. Nagano, and E. Hayashi, *ibid.*, **21**, 1943 (1973); *c*) T. Higashino, K. Suzuki, and E. Hayashi, *ibid.*, **23**, 746 (1975); *d*) T. Higashino and E. Hayashi, *ibid.*, **21**, 2643 (1973); *e*) T. Higashino, K. Suzuki, and E. Hayashi, *ibid.*, **23**, 2939 (1975); *f*) T. Higashino, Y. Iwai, and E. Hayashi, *ibid.*, **25**, 535 (1977); *g*) *Idem*, *ibid.*, **24**, 3120 (1976).

3) *a*) A. Albert and W. Pendergast, *J. Chem. Soc.* Perkin I, **1973**, 1794; *b*) A. Albert and H. Mizuno, *ibid.*, 1973, 1615; *c*) A. Albert and W. Pendergast, *ibid.*, **1973**, 1620.

path A



path B

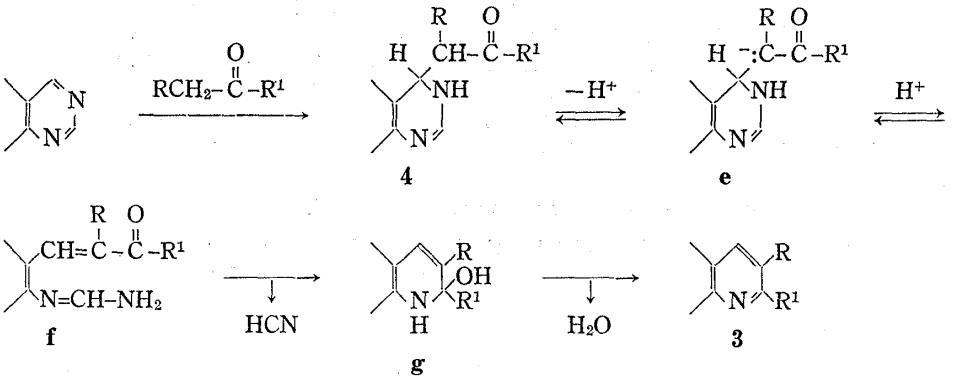


Chart 1

	R^1	R^2
1		
1a	–H	–H
1b	$-C_6H_5$	–H
1c	$-CH_3$	–H
1d	–H	$-C_6H_5$
1e	–H	$-CH_3$

2

	R	R^1	R^2
3			
3a	–CN	$-NH_2$	–H
3b	–H	$-C_6H_5$	–H
3c	$-(CH_2)_4-$		–H
3d	–H	$-CH_3$	–H
3e	–CN	$-NH_2$	$-C_6H_5$
3f	–CN	$-NH_2$	$-CH_3$
3g	$-C_6H_5$	$-NH_2$	–H

	R	R^1	R^2
4			
4a	–H	$-C_6H_5$	–H
4b	$-(CH_2)_4-$		–H
4c	–H	$-CH_3$	–H
4d	–H	$-C_6H_5$	$-C_6H_5$
4e	$-(CH_2)_4-$		$-C_6H_5$
4f	–H	$-C_6H_5$	$-CH_3$
4g	$-(CH_2)_4-$		$-CH_3$

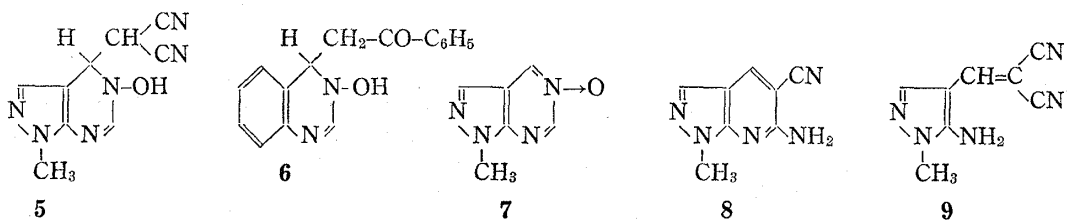


Chart 2

In the present work the transformation of **4** as the dihydro-compounds into **3** with NuH without catalyst and that in the presence of alumina as a catalyst were examined together with the effects of the substituents. The dihydro-compounds **4b** to **4g** except for **4a**[4] were prepared by the reaction of **1** with the corresponding ketones in 4 N sulfuric acid. Their structures were indicated by elemental analyses and confirmed by nuclear magnetic resonance (NMR) and infrared (IR) spectra.

Behavior of 4 to Heating, Base, and Acid

When a solution of **4** (**4a** to **4c**) dissolved in benzene in a sealed tube was heated at 120°, the dissociation occurred to form its constituents, **1a** and the corresponding ketones. The same dissociation was also found in the reaction with methoxide ion at room temperature, while a solution of **4** in 4 N sulfuric acid at 80° did not give any product and recovered **4** in good yield. These facts showed that heating, base, and acid did not cause **4** to transform into **3**.

Reaction of 4 with NuH without Catalyst

NuH used in this section was as follows; NuH-1, diethyl malonate (NuH-2), phenylacetonitrile (NuH-3), NuH-4, cyclopentanone (NuH-5), and cyclohexanone (NuH-6). The molar ratio of **4** and NuH was set at 1: 1.2. A suitable time and temperature for each case was shown in Table I.

The dihydro-compounds, **4a**, **4b**, and **4c**, when fused with NuH without solvent and catalyst, gave **3b**,[5] **3c**,[6] and **3d**[5] respectively, together with **1a**, even if the yields were poor. These poor yields might be caused by the occurring of the concerted reaction with the dissociation and the transformation of **4**.

On the other hand the application of this reaction to 2-substituted dihydro-compounds (**4d** to **4f**) resulted in the formation of none of **3** (**3b** and **3c**) and gave only the dissociation

Table I. Reaction of 4 with NuH without Catalyst

NuH	Reaction time 4 (hr)		Reaction temp. (°C)	Transformation product 3 %		Dissociation product 1 %		Recovery %
NuH-2	**4a**	21	130—140	**3b**	21.9	**1a**	6.9	15.1
NuH-3	**4a**	20	135—140	**3b**	8.7	**1a**	51.9	11.2
NuH-4	**4a**	5	130—140	**3b**	6.5	**1a**	48.2	14.5
NuH-6	**4a**	21	130—140	**3b**	10.2	**1a**	69.4	8.0
NuH-2	**4b**	6	90—100	**3c**	7.2	**1a**	13.9	50.2
NuH-3	**4b**	8	110—120	**3c**	2.5	**1a**	22.3	22.7
NuH-4	**4b**	12	125—135	**3c**	4.5	**1a**	34.4	7.6
NuH-5	**4b**	14	125—135	**3c**	10.4	**1a**	30.5	5.6
NuH-6	**4b**	7	120—130	**3c**	14.4	**1a**	13.6	20.9
NuH-2	**4c**	24	120—130	**3d**	7.5	**1a**	7.0	46.8
NuH-3	**4c**	13	120—130	**3d**	7.7	**1a**	14.9	41.5
NuH-4	**4c**	21	120—130	**3d**	5.9	**1a**	5.9	40.6
NuH-5	**4c**	17	100—110	**3d**	11.9	**1a**	—	45.6
NuH-6	**4c**	15	100—110	**3d**	7.1	**1a**	—	42.3
NuH-4	**4d**	10	110—120	**3b**	—	**1b**	70.1	—
NuH-6	**4d**	11	120—130	**3b**	—	**1b**	62.2	—
NuH-4	**4e**	14	120—130	**3c**	—	**1b**	90.6	—
NuH-6	**4e**	7	120—130	**3c**	—	**1b**	67.2	—
NuH-4	**4f**	12	140—145	**3b**	—	**1c**	18.7	—

4) T. Higashino and E. Hayashi, *Chem. Pharm. Bull.* (Tokyo), **12**, 1111 (1964).
5) O. Doebner and W.v. Miller, *Chem. Ber.*, **16**, 1665, 2465 (1883).
6) W. Borshe, *Chem. Ber.*, **41**, 2206 (1908).

product (**1b** and **1c**) as shown in Table I. These facts showed that the phenyl and methyl groups substituted at the 2-position prevented **4** from transforming into **3**. And these facts agreed well with the facts that 2-phenylquinazoline (**1b**)[7] prevented its transformation with NuH-1 and NuH-3 into **3a** and **3g**, but the reaction of 4-phenyl- (**1d**)[8] and 4-methylquinoline (**1e**)[8] with NuH-1 gave 4-phenyl- (**3e**)[9] and 4-methyl-2-amino-3-quinolinecarbonitrile (**3f**),[10] respectively.

Reaction of 4 with NuH in the Presence of Catalyst

The dihydro–compounds (**4a** to **4c**) were reacted with chloroform (NuH-7) in the presence of alumina as a catalyst under the mild condition to give the corresponding **3** (**3b** to **3d**) as shown in Table II. The reaction with NuH-4, NuH-6, and ethyl orthoformate (NuH-8) instead of NuH-7 also gave the corresponding **3** (**3b** to **3d**). But in the presence of silica gel, amberite IRA-410, potassium or sodium carbonate, and barium hydroxide instead of alumina, **4a** and NuH-7 did not give **3b** and resulted only in recovering the starting material or in yielding the dissociation product (**1a**). The reaction between **4a** and methanol in the presence of alumina did not afford any reaction product resulting in recovery of the starting materials (**4a**).

But the phenyl or methyl groups substituted at the 2-position prevented **4** (**4d** to **4f**) from transforming with NuH-7 in the presence of alumina to give none of the corresponding **3** (**3b** and **3c**) and to recover the starting material. This proves the hindered reaction of 2-substituted dihydro–compounds with NuH without catalyst mentioned in the preceding section.

Table II. Reaction of 4 with NuH in the Presence of Catalyst

NuH	4	Catalyst	Reaction time (hr)	Reaction temp. (°C)	Transformation product 3%		Dissociation product 1%		Recovery %
NuH-7	**4a**	Al_2O_3	20	Room temp.	**3b**	90.2	**1a**	5.3	—
NuH-7	**4b**	Al_2O_3	24	50—55	**3c**	30.8	**1a**	9.8	—
NuH-7	**4c**	Al_2O_3	24	50—55	**3d**	37.4	**1a**	5.2	—
NuH-8	**4a**	Al_2O_3	26	60—65	**3b**	20.2	**1a**	24.5	24.6
NuH-8	**4b**	Al_2O_3	24	70—80	**3c**	9.7	**1a**	16.8	20.8
NuH-8	**4c**	Al_2O_3	30	70—80	**3d**	53.8	**1a**	9.6	—
NuH-4	**4a**	Al_2O_3	20	50—60	**3b**	82.1	**1a**	6.1	—
NuH-4	**4b**	Al_2O_3	20	70—75	**3c**	16.8	**1a**	37.4	—
NuH-4	**4c**	Al_2O_3	21	70—80	**3d**	37.4	**1a**	2.9	—
NuH-6	**4a**	Al_2O_3	19	50—60	**3b**	33.8	**1a**	6.3	25.0
NuH-6	**4b**	Al_2O_3	17	70—75	**3c**	11.4	**1a**	11.0	—
NuH-6	**4c**	Al_2O_3	21	70—75	**3d**	32.5	**1a**	12.2	—
NuH-7	**4a**	SiO_2	41	Room temp.	**3b**	—	**1a**	—	77.7
NuH-7	**4a**	IRA-410	23	Room temp.	**3b**	—	**1a**	—	83.0
NuH-7	**4a**	K_2CO_3	23	Room temp.	**3b**	—	**1a**	82.1	8.6
NuH-7	**4a**	Na_2CO_3	23	Room temp.	**3b**	—	**1a**	83.6	5.1
NuH-7	**4a**	$Ba(OH)_2$	23	Refluxing	**3b**	—	**1a**	86.6	3.6
NuH-7	**4d**	Al_2O_3	24	Room temp.	**3b**	—	**1b**	—	89.3
NuH-7	**4e**	Al_2O_3	24	Room temp.	**3c**	—	**1b**	—	81.9
NuH-7	**4f**	Al_2O_3	24	Room temp.	**3b**	—	**1c**	—	82.7
NuH-7	**4g**	Al_2O_3	24	Room temp.	**3c**	—	**1c**	—	93.3
MeOH	**4a**	Al_2O_3	24	Room temp.	**3b**	—	**1a**	—	95.7

7) M. T. Bogert and F. D. Nabenhauer, *J. Am. Chem. Soc.*, **46**, 1702 (1924).
8) T. Higashino, *Chem. Pharm. Bull.* (Tokyo), **10**, 1043 (1962).
9) E. Campaique and G. Randau, *J. Heterocycl. Chem.*, **1971**, 111.
10) H. Junek and W. Wilfinger, *Monatsh. Chem.*, **101**, 1123 (1970).

Reaction of 4,5-Dihydro-5-hydroxy-1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-malononitrile (5) with NuH in the Presence of Alumina

Because any dihydro–compounds of **2** such as 2-(3,4-dihydro-3-hydroxy-4-quinazolinyl)-acetophenone (**6**) could be hardly prepared, their transformation into **3** could not be examined. In this section we examined the transformation of **5**, instead of **6**, prepared from 1-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidine 5-oxide (**7**) and NuH-1,[2f] into 6-amino-1-methyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carbonitrile (**8**)[2f] in the presence of alumina.

The behavior of **5** to heating and acid was parallel to that of **4**. Thus the heating gave the dissociation product **7** and NuH-1, and the acid formed (5-amino-1-methyl-1*H*-pyrazol-4-ylmethylene)malononitrile (**9**).[2f] The dihydro–compound, **5**, also reacted with NuH-4, NuH-7, and NuH-8 in the presence of alumina to give **8** as shown in Table III. From these facts it becomes clear that the mechanism of the transformation of the condensed pyrimidine N-oxide with NuH is similar to that of the condensed pyrimidines.

Table III. Reaction of **5** with NuH in the Presence of Al_2O_3

NuH	Reaction time (hr)	Reaction temp. (°C)	Transformation product (8) %
NuH-4	15	50—60	3.3
NuH-7	40	Room temp.	41.7
NuH-8	24	60—70	31.0

Mechanism

The transformation of **4** needs NuH as a reagent, and is accelerated by a catalytic action of alumina. Path B indicates that the carbanion (**e**), induced by the abstract of the hydrogen from the methylene group of **4**, is the cause of the ring opening between the 3- and 4-positions. If it is supposed that the abstract of the hydrogen is not affected by any substituent at the 2-position, **4d** to **4f** give the ring transformation product (**3b** and **3c**). But these dihydro–compounds did not give any of **3**, showing path B may be not appropriate for the mechanism. In path A if it is supposed that the addition of NuH or a carbanion, derived from NuH and alumina, across the 1- and 2-positions of **4** is affected by any substituent at the 2-position, **4d** to **4f** do not give any of **3**. In fact the reaction of these compounds with NuH or with NuH in the presence of alumina did not give any of **3**.

Consequently, it can be said that path A is preferable to path B for the transformation mechanism, based on the results of this study as well as for the reasons described in the previous papers.[2]

Experimental[11]

IR spectra were recorded on a Jasco Grating Infrared Spectrophotometer Model IRA-1. NMR spectra were measured at 60 Mc and 23° on a Hitachi High Resolution NMR Spectrometer Model R-24 using tetramethylsilane as an internal standard.

2-(3,4-Dihydro-4-quinazolinyl)cyclohexanone (4b)——A mixture of 600 mg of **1a** and 900 mg of NuH-6 in 3.0 ml of 4 N H_2SO_4 was heated at 70—75° for 8 hr, and the reaction mixture was allowed to stand overnight at room temperature. After removing NuH-6 by the extraction with benzene, the H_2SO_4 layer was neutralized with K_2CO_3, and extracted with $CHCl_3$. After drying over anhyd. Na_2SO_4, the $CHCl_3$ extract was passed through a column of silica gel. The elution with MeOH gave **4b**, mp 44—45° as pale yellow needles from petr. ether, in 82.6% yield (869 mg). IR ν_{max}^{KBr} cm^{-1}: 3180 (NH), 1740 (C=O). NMR (in $CDCl_3$) ppm: 6.37—7.32 (5H, multiplet, aromatic H), 5.48 (1H, broad singlet, NH), 5.21 (1H, multiplet, 4-H), 0.70—3.30 (9H, multiplet, –CO–$(CH_2)_4$–CH–). *Anal.* Calcd. for $C_{14}H_{16}N_2O$: C, 73.65; H, 7.06; N, 12.27. Found: C, 73.59; H, 7.05; N, 11.89.

11) All melting points were not corrected.

1-(3,4-Dihydro-4-quinazolinyl)-2-propanone (4c)——A mixture of 1040 mg of **1a** and 696 mg of acetone in 2.0 ml of 4 N H_2SO_4 was heated at 70—75° for 8 hr. The isolation procedure was carried out in the same fashion as for the preparation of **4b**. The elution with benzene–$CHCl_3$ (1: 1) recovered **1a**, mp 48—48.5° from petr. ether, in 16.4% yield (170 mg). The elution with MeOH gave **4c**, pale yellow oil, in 44.6% yield (671 mg). Its 2,4-dinitrophenylhydrazone monosulfate showed mp 222—224° (dec.). IR ν_{max}^{neat} cm^{-1}: 3300 (NH), 1680 (C=O). *Anal.* Calcd. for $C_{17}H_{18}N_6O_8S$ (2,4-dinitrophenylhydrazone monosulfate): C, 43.77; H, 3.98; N, 18.02. Found: C, 43.63; H, 4.10; N, 17.75.

3,4-Dihydro-2-phenyl-4-quinazolinylmethyl Alkyl Ketone (4d and 4e)——A mixture of 500 mg of **1b** and 700 mg of ketone (NuH-4 and NuH-6) in 3.0 ml of 4 N H_2SO_4 was heated at 75—80° for 8 hr. After allowing to stand overnight at room temperature, the reaction mixture was extracted with benzene, and the H_2SO_4 layer was neutralized with K_2CO_3. The separated crystals were recrystallized from benzene–petr. ether to give 3,4-dihydro-2-phenyl-4-quinazolinylmethyl alkyl ketone (**4d** and **4e**).

Thus, the reaction with NuH-4 gave 4d, mp 155—156°, in 77.7% yield (615 mg). IR ν_{max}^{KBr} cm^{-1}: 3350 (NH), 1680 (C=O). NMR (in $CDCl_3$) ppm: 6.65—8.00 (14H, multiplet, aromatic H), 6.55 (1H, broad singlet NH), 5.33 (1H, quartet, $J_{ax}=9$ Hz, $J_{bx}=3$ Hz, 4-H), 3.90 (1H, quartet, $J_{ab}=13.5$ Hz, $\overset{*}{C}H_x-\underset{H_b}{\overset{H_a}{C}}-CO-$), 3.18 (1H, quartet, $\overset{*}{C}H_x-\underset{H_b}{\overset{H_a}{C}}-CO$). *Anal.* Calcd. for $C_{22}H_{18}N_2O$: C, 80.90; H, 5.56; N, 8.58. Found: C, 80.84; H, 5.56; N, 8.31.

The reaction with NuH-6 gave **4e**, mp 145—146°, in 48.3% yield (356 mg). IR ν_{max}^{KBr} cm^{-1}: 3400 (NH), 1690 (C=O). NMR (in $CDCl_3$) ppm: 6.67—7.87 (9H, multiplet, aromatic H), 6.05 (1H, broad singlet, NH), 5.41 (1H, multiplet, 4-H), 1.00—3.00 (9H, multiplet, $CH-(CH_2)_4-CO$). *Anal.* Calcd. for $C_{20}H_{20}N_2O$: C, 78.92; H, 6.62; N, 9.20. Found: C, 78.65; H, 6.58; N, 8.96.

3,4-Dihydro-2-methyl-4-quinazolinylmethyl Alkyl Ketone (4f and 4g)——A mixture of 550 mg of **1c** and 770 mg of ketone (NuH-4 and NuH-6) in 3.0 ml of 4 N H_2SO_4 was heated at 75—80° for 12 hr. The isolation procedure was carried out in the same fashion as for the preparation of **4b**. The elution with MeOH gave 3,4-dihydro-2-methyl-4-quinazolinylmethyl alkyl ketone (**4f** and **4g**).

Thus, the reaction with NuH-4 gave **4f**, mp 216—217° (dec.) as white prisms from benzene–MeOH, in 41.5% yield (476 mg). IR ν_{max}^{KBr} cm^{-1}: 3170 (NH), 1685 (C=O). NMR (in $CDCl_3$) ppm: 7.00—8.00 (9H, multiplet, aromatic H), 6.00 (5H, broad singlet, NH and $2H_2O$), 5.40 (1H, multiplet, 4-H), 3.20—4.20 (2H, multiplet, $\overset{*}{C}H-\underline{CH_2}-CO$), 2.33 (3H, singlet, CH_3). *Anal.* Calcd. for $C_{17}H_{16}N_2O\cdot 2H_2O$: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.80; H, 6.79; N, 9.50.

The reaction with NuH-6 gave **4g**, as pale yellow oil, in 47.2% yield (436 mg). Its 2,4-dinitrophenylhydrazone monosulfate showed mp 230—235° (dec.). *Anal.* Calcd. for $C_{21}H_{24}N_6O_8S\cdot H_2O$: C, 46.83; H, 4.82; N, 15.60. Found: C, 46.89; H, 4.82, N, 15.92.

Behavior of 4 to Heating——A mixture of **4** (**4a** to **4c**) and 5.0 ml of benzene in a sealed tube was heated at 120° for 20 hr. After cooling the reaction mixture was chromatographed on a column of silica gel. The elution with benzene gave ketone. The yield of NuH-4 from **4a** was 3.4% (4 mg) and that of NuH-6 from **4b** was 13.4% (13 mg). The elution with benzene–$CHCl_3$ (1: 1) gave **1a**. The yields from **4a**, **4b**, and **4c** were 18.3% (23.8 mg), 64.8% (84.2 mg); and 4.6% (6.0 mg), respectively.

The elution with MeOH recovered **4**. The recoveries of **4a** and **4c** were 80.2% and 78.6%, respectively.

Behavior of 4 to Base——To a solution of 25 mg of Na dissolved in 5.0 ml of MeOH, 0.5 mmol of **4** (**4a** to **4c**) was added and the mixture was allowed to stand at room temperature for 45 hr. The residue obtained by removing MeOH was dissolved in 5.0 ml of 2 N HCl and extracted with benzene. After drying over Na_2SO_4, the benzene extract was chromatographed on a column of silica gel. The elution with benzene gave the corresponding ketone (NuH-4 and NuH-6).

The HCl extract was neutralized with K_2CO_3 and extracted with $CHCl_3$. After drying over Na_2SO_4, the extract was chromatographed on a column of silica gel. The elution with benzene–$CHCl_3$ (1: 1) gave **1a**, and that with $CHCl_3$ and MeOH recovered 4.

The yields of **1a** from **4a**, **4b**, and **4c** were 88.4%, 24.7%, and 40.0%, respectively. The recoveries of **4a**, **4b**, and **4c** were 4.1%, 34.3%, and 43.0%, respectively.

Behavior of 4 to Acid——A solution of 1.0 mmol of **4** (**4a** to **4c**) dissolved in 3.0 ml of 4 N H_2SO_4 was heated at 80° for 12 hr. The reaction mixture was neutralized with 10% NaOH, and extracted with $CHCl_3$. After drying over Na_2SO_4, the extract was chromatographed on a column of silica gel by changing eluate as follows; benzene, benzene–$CHCl_3$ (1: 1), $CHCl_3$, and MeOH.

The elution with $CHCl_3$ and MeOH recovered **4**; **4a** in 63.0% (158 mg), **4b** in 89.9% (205 mg), and **4c** in 62.9% yield (118 mg).

Reaction of 4 with NuH without Catalyst——i) A mixture of 1.0 mmol of **4** (**4a** to **4c**) and 1.2 mmol of NuH was heated under the condition described in Table I. The reaction mixture was extracted with 2 N HCl, and the HCl extract was washed with benzene. The HCl extract was neutralized with K_2CO_3 and

extracted with $CHCl_3$. After drying over Na_2SO_4, the extract was chromatographed on a column of silica gel by changing eluate as follows; benzene, benzene–$CHCl_3$ (1: 1), $CHCl_3$, and MeOH.

The elution with benzene gave 3 (**3b** to **3d**), that with benzene–$CHCl_3$ afforded **1a**, and that with $CHCl_3$ and MeOH recovered 4 (**4a** to **4c**). The yields of **3b** and **1a** from **4a**, **3c** and **1a** from **4b**, and **3d** and **1a** from **4c** were shown in Table I.

ii) A mixture of 1.0 mmol of 4 (**4d** to **4f**) and 1.2 mmol of NuH (NuH-4 and NuH-6) was heated under the condition described in Table I. The isolation procedure was carried in the same fashion as for i) described above. The elution with benzene from the reaction of **4d** and **4e** gave **1b**, and that from **4f** afforded **1c**. The yields of **1b** and **1c** were listed in Table I.

Reaction of 1b with NuH-1 and NuH-3——A mixture of 412 mg of **1b** (2.0 mmol) and 4.0 mmol of NuH (NuH-1 and NuH-3) was heated under the following condition; in the case of the reaction with NuH-1 the reaction time and temperature were 0.6 hr and 75—80°, and with NuH-3 they were 4.5 hr and 190—195°. After cooling, the separated crystals were recrystallized from petr. ether to recover **1b**. The yields from the reaction with NuH-1 and NuH-3 were 78.6% (323 mg) and 70.6% (291 mg), respectively.

Reaction of 1d and 1e with NuH-1——A mixture of 1.0 mmol of **1d** and 3.0 mmol of NuH-1 was heated at 75—80° for 0.5 hr. After cooling, the separated crystals were recrystallized from benzene to give **3e**, mp 241° as pale yellow needles, in 15.7% yield (38 mg).

A mixture of 1.0 mmol of **1e** and 3.0 mmol of NuH-1 was treated by the same fashion as for the reaction of **1d** described above to give **3f**, mp 313—315° (dec.) as yellow needles from MeOH, in 9.3% yield (17 mg).

Reaction of 4 with NuH-7 in the Presence of Al_2O_3——i) A mixture of 1.0 mmol of 4 (**4a** to **4c**), 5.0 ml of NuH-7, and 2000 mg of Al_2O_3 was stirred under the condition described in Table II. After removing Al_2O_3 by suction, the reaction mixture was chromatographed on a column of silica gel by changing eluate as follows; benzene, benzene–$CHCl_3$ (1: 1), $CHCl_3$, and MeOH. The elution with benzene–$CHCl_3$ gave 3 (**3b** to **3d**). Thus, **4a** gave **3b**, **4b** gave **3c**, and **4c** gave **3d**. The elution with $CHCl_3$ gave **1a**. The yields of these compounds were shown in Table II.

ii) A mixture of 1.0 mmol of 4 (**4d** to **4g**), 5.0 ml of NuH-7, and 2000 mg of Al_2O_3 was stirred at room temperature for 24 hr. After removing Al_2O_3 by suction and evaporating of NuH-7 it recovered 4 (**4d** to **4g**). The yield of 4 were listed in Table II.

Behavior of 5 to Heating——A mixture of 250 mg of 5 (1.16 mmol) and 50 ml of benzene in a sealed tube was heated at 100—110° for 3 hr. After cooling, the separated crystals were recrystallized from MeOH to recover **5** in 23.3% yield (50.8 mg). The benzene filtrate was concentrated and chromatographed on a column of silica gel by changing eluate as follows; benzene, benzene–$CHCl_3$ (1: 1), $CHCl_3$, and MeOH. The elution with benzene gave NuH-1 in 22.1% yield (12.6 mg), and that with MeOH gave $7^{2f)}$, mp 187—189° as yellow needles from MeOH, in 18.0% yield (23.4 mg).

Behavior of 5 to Acid——A solution of 216 mg of 5 (1.0 mmol) dissolved in 5.0 ml of 4 N H_2SO_4 was heated at 70—80° for 25 min. After cooling, the reaction mixture was neutralized with K_2CO_3 to separate crystals which were recrystallized from MeOH to give **9**, mp 239—240° as yellow needles from MeOH, in 45.6% yield (79 mg).

Reaction of 5 with NuH-7 in the Presence of Al_2O_3——A mixture of 300 mg of 5 (1.39 mmol), 60 ml of NuH-7, and 8000 mg of Al_2O_3 was stirred under the condition described in Table III. After removing Al_2O_3 by suction, the reaction mixture was concentrated to separate the crystals which were recrystallized from MeOH to give **8**, mp 252—253° as yellow needles, in 41.7% yield (100 mg).

Reaction of 5 with NuH-8 in the Presence of Al_2O_3——A mixture of 324 mg of **5** (1.5 mmol), 25 ml of NuH-8, and 3000 mg of Al_2O_3 was stirred under the condition described in Table III. After removing Al_2O_3, the reaction mixture was concentrated, and th resulted residue was dissolved in benzene. The benzene solution was extracted with 2 N HCl, and the HCl extract was neutralized with K_2CO_3 to separate **8** in 31.0% yield (80.6 mg).

Reaction of 5 with NuH-4 in the Presence of Al_2O_3——A mixture of 324 mg of **5** (1.5 mmol), 15 ml of NuH-4, and 3000 mg of Al_2O_3 was stirred under the condition described in Table III. After removing Al_2O_3 by suction, the reaction mixture was dissolved in benzene and extracted with 4 N HCl. The HCl extract was neutralized with K_2CO_3 and extracted with $CHCl_3$. After drying over Na_2SO_4, the $CHCl_3$ extract was concentrated and chromatographed on a column of silica gel by changing eluate as follows; benzene, benzene–$CHCl_3$ (1: 1), $CHCl_3$, and MeOH. The elution with benzene–$CHCl_3$ gave **8** in 3.3% yield (8.6 mg).

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