On the Reaction of 1-Chloroisoquinoline and 4-Chloroquinazoline with Several Ketone Carbanions

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Ketone carbanion reacted as nucleophilic reagent with 1-chloroisoquinoline (II) and 4-chloroquinazoline (III).

The reaction of II in the presence of sodium amide with acetophenone, propiophenone, acetone, 3-pentanone, 2-butanone, 2-pentanone, 3-methyl-2-butanone, 4-methyl-2-pentanone, and cyclopentanone respectively afforded 2-(1-isoquinolinyl)acetophenone (B-1), 2-(1-isoquinolinyl)propiophenone (B-2), 1-(1-isoquinolinyl)-2-propanone (B-3), 2-(1-isoquinolinyl)-3-pentanone (B-4), 2-(1-isoquinolinyl)-2-butanone (B-5), 1-(1-isoquinolinyl)-2-pentanone (B-6), 1-(1-isoquinolinyl)-3-methyl-2-butanone (B-7), 1-(1-isoquinolinyl)-4-methyl-2-pentanone (B-8) and 2-(1-isoquinolinyl)cyclohexanone (B-9).

Similarly, the reaction of III with acetophenone, 2-methylpropiophenone, acetone, and cyclopentanone afforded respectively 2-(4-quinazolinyl)acetophenone (C-1), 2-(4-quinazolinyl)-2-methylpropiophenone (C-2), 1-(4-quinazolinyl)-2-propanone (C-3), and 2-(4-quinazolinyl)cyclopentanone (C-6). The reaction with propiophenone and 3-pentanone gave 4-ethylquinazoline (D-1), with butyrophenone and cyclohexanone respectively afforded 4-propylquinazoline (D-2) and 4-quinazolinehexanoic acid (D-3). The reaction with 2-butanone gave 1-(4-quinazolinyl)-2-butanone (C-4) and D-1, with 2-pentanone afforded 1-(4-quinazolinyl)-2-pentanone (C-5) and D-2.

It was thereby concluded that the reaction of II and III with ketone carbanion formed the carbon–carbon bond accompanied with the elimination of chloro ion.

It has been well known that the chloro group located in α- or γ-position against the ring nitrogen of benzazine and benzodiazine has been replaced by varieties of nucleophilic reagents. However no study had been published on the reactions between those chlorocompounds and ketone carbanions as nucleophilic reagents except that of 1-chlorophthalazine (I) with several ketone carbanions reported by E. Oishi[2] afforded the compounds of the type A.

Chart 1

Chart 2
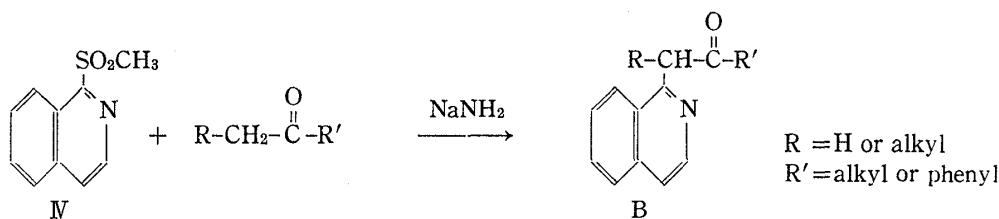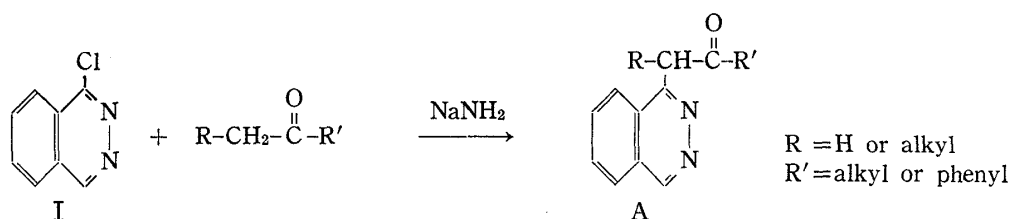
1) Location: *160, Oshika, Shizuoka.*
2) E. Oishi, *Yakugaku Zasshi*, **89**, 959 (1969).

In this paper we carried out the reactions of 1-chloroisoquinoline (II) and 4-chloroquina-zoline (III) with several ketones in the presence of sodium amide and succeeded in finding the formation of carbon–carbon bond accompanied with the elimination of chloro ion.

Reaction of 1-Chloroisoquinoline (II) with Ketones in the Presence of Sodium Amide

E. Hayashi, Y. Tamura[3] showed that the reaction between 1-(methylsulfonyl)isoquino-line (IV) and several ketones in the presence of sodium amide resulted in the formation of corresponding (1-isoquinolinyl)alkyl alkyl (or phenyl) ketones (B) involving the accompanying with elimination of methanesulfinate ion.

They explained this reactivity due to the overlapping of inductive and mesomeric electron–withdrawal from the 1-position by methylsulfonyl group, the neighbouring ring nitrogen and the fused benzene ring. As a similar electoronic effects should be expected on the 1-position of II, the reactions of II with several ketone carbanions were made in order to compare with that of IV.

Sources of carbanions used in these reactions were following ketones:
  (a) aromatic ketones
      i: acetophenone, ii: propiophenone

$$R\text{-}CH_2\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}R' \; + \; \overset{\cdot\cdot}{N}H_2 \; \rightleftharpoons \; R\text{-}\overset{\cdot\cdot}{C}H\text{-}\overset{\overset{\displaystyle O}{\|}}{C}\text{-}R' \; + \; NH_3$$
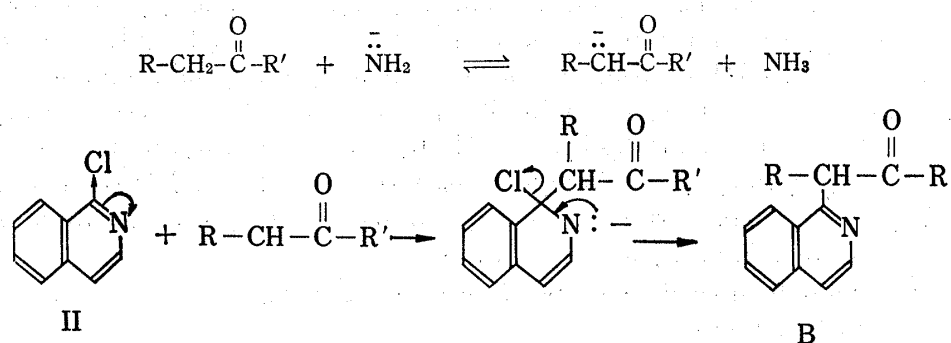

Chart 3

TABLE I. The Reaction of II with Ketone Carbanions

Ketones	React. temp. (°C)	React. time (hr)	React. products R ![isoquinolinyl]	Yield (%)	Melting point (°C)
$CH_3COC_6H_5$	55	2	$-CH_2COC_6H_5$	B-1 17.0	85— 86
$CH_3CH_2COC_6H_5$	reflx.	2	$-CH(CH_3)COC_6H_5$	B-2 2.6	141—142
CH_3COCH_3	reflx.	2	$-CH_2COCH_3$	B-3 31.8	201[a]
$C_2H_5COC_2H_5$	reflx.	2	$-CH(CH_3)COC_2H_5$	B-4 21.5	166—167[a]
$CH_3COC_2H_5$	reflx.	1	$-CH_2COC_2H_5$	B-5 24.6	165—166[a]
$CH_3COCH_2CH_2CH_3$	reflx.	2	$-CH_2COC_3H_7$	B-6 9.4	187—188[a]
$CH_3COCH(CH_3)_2$	reflx.	2	$-CH_2COCH(CH_3)_2$	B-7 3.5	190—191[a]
$CH_3COCH_2CH(CH_3)_2$	reflx.	2	$-CH_2COCH_2CH(CH_3)_2$	B-8 15.0	45— 46
![cyclohexanone]	reflx.	1	![product]	B-9 5.4	136—138

reflx.=reflux   a) melting point of picrate

3) E. Hayashi and Y. Tamura, *Yakugaku Zasshi*, **90**, 594 (1970).

(b) symmetric aliphatic ketones

iii: acetone, iv: 3-pentanone

(c) asymmetric aliphatic ketones

v: 2-butanone, vi: 2-pentanone, vii: 3-methyl-2-butanone,

viii: 4-methyl-2-pentanone

(d) cyclic ketone

ix: cyclohexanone

The reactions with those ketones, a,b,c, and d, proceeded as similar as that of IV and gave corresponding B as shown in Table I.

In the case of the reactions with c it may be expected to form two carbanions from the equilibrium between c and amide ion. One is a carbanion of the primary carbon atom at the α-position of carbonyl group and another is that of the secondary or tertiary carbon atom. However these reactions only resulted in formation of the compounds combined with the former carbanions and we could not isolate the reaction products from the later carbanions.

The Reactions of 4-Chloroquinazoline (III) with Ketones in the Presence of Sodium Amide

T. Higashino[4] reported that the reactions of 4-quinazolinecarbonitrile (V) with several ketones in the presence of 50% sodium hydroxide solution as a base catalyst at ordinary temperature afforded corresponding 4-quinazolinylmethyl alkyl (or phenyl) ketones represented by the formula of type C and 4-alkylquinazoline (type D). And he also showed that the application of acetone to III resulted in the formation of 4(3H)-quinazolinone (VI) instead of the formation of expected 1-(4-quinazolinyl)-2-propanone (C-3). It seems to suppose that the formation of VI may be due to hydrosis of III by attacking of hydroxide ion. Therefore in order to avoid the hydrolysis and to expect the formation of C and D the reactions of III with several ketones must be carried out in anhydrous media by use of sodium amide as a base catalyst instead of sodium hydroxide solution.

Sources of carbanions used in these reaction were following ketones:

(a) aromatic ketones

i: acetophenone, ii: propiophenone, iii: butyrophenone,

iv: 2-methylpropiophenone

(b) symmetric aliphatic ketones

v: acetone, vi: 3-pentanone

(c) asymmetric aliphatic ketones

vii: 2-butanone, viii: 2-pentanone

(d) cyclic ketones

ix: cyclopentanone, x: cyclohexanone

Chart 4
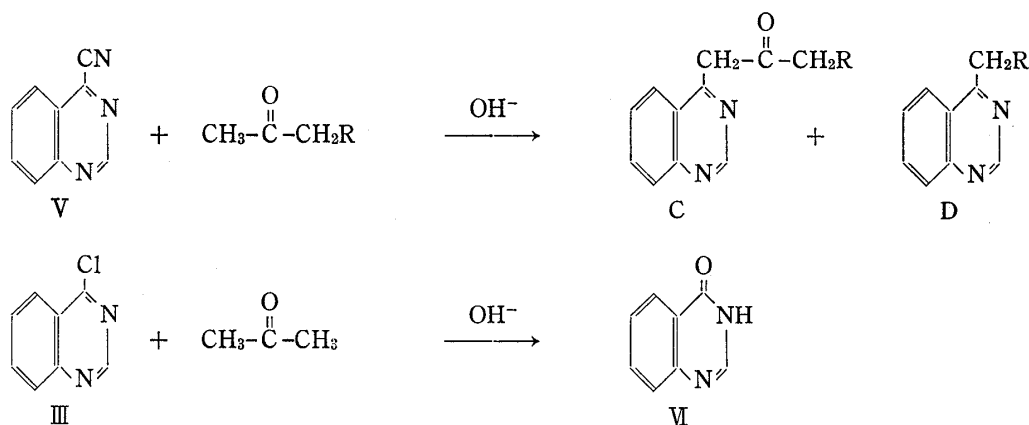
4) T. Higashino, *Chem. Pharm. Bull.* (Tokyo), **10**, 1048 (1962).

TABLE II. The Reaction of III with Ketone Carbanions

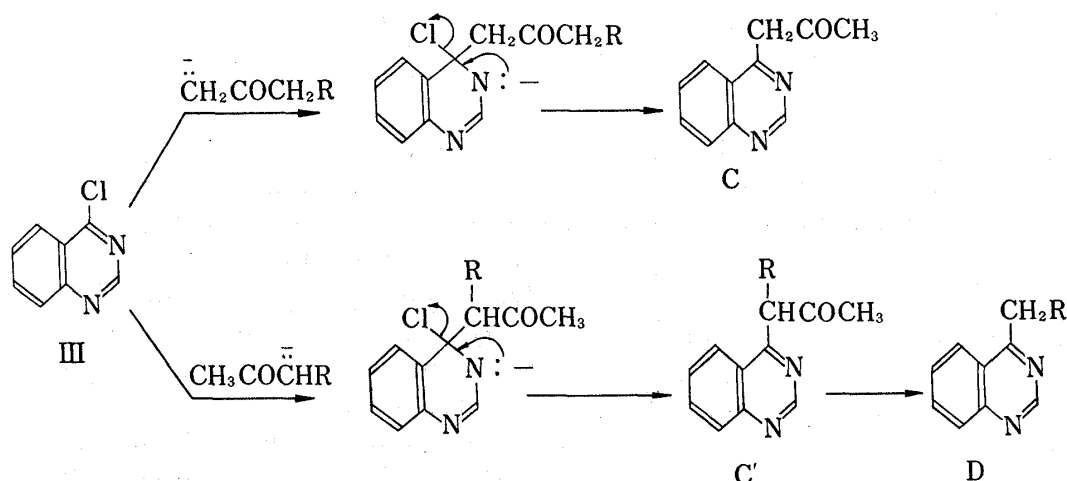| Ketones	C R=		D R=	
$CH_3COC_6H_5$	$-CH_2COC_6H_5$	C-1		
$C_2H_5COC_6H_5$			$-C_2H_5$	D-1
$C_3H_7COC_6H_5$			$-C_3H_7$	D-2
$(CH_3)_2CHCOC_6H_5$	$-C(CH_3)_2COC_6H_5$	C-2		
CH_3COCH_3	$-CH_2COCH_3$	C-3		
$C_2H_5COC_2H_5$			$-C_2H_5$	D-1
$CH_3COC_2H_5$	$-CH_2COC_2H_5$	C-4	$-C_2H_5$	D-1
$CH_3COC_3H_7$	$-CH_2COC_3H_7$	C-5	$-C_3H_7$	D-2
☐>=O	O=<☐	C-6		
◇>=O			$-(CH_2)_5COOH$	D-3

Chart 5

The reactions of III with these ketones, a, b, c, and d, smoothly progressed as similar as that of V in the presence of sodium hydroxide solution and resulted in the formation of corresponding C and D as shown in Table II and Chart 5.

C-1, C-3, C-4, C-6, D-1 and D-3 so obtained were identified by admixture with corresponding authentic specimen[4] or its picrate prepared by another route from V.

Identity of C-2 was established by correspondence of its analytical values to $C_{18}H_{16}ON_2$ and the presence of marked absorption bands due to the geminal methyl group ($\tau=8.06$ and 8.22, singlet) and to the proton of the 2-position in quinazoline molecule ($\tau=1.52$, singlet) in its nuclear magnetic resonance (NMR) spectrum.

TABLE III. IR Spectra of C-1, C-3 and C-5

Compounds	IR ν_{max}^{KBr} cm^{-1} (C=O)
C-1	1612
C-3	1618
C-5	1620

The structure of C-5 should be presumed to be 1-(4-quinazolinyl)-2-pentanone through correspondence of its analytical values to $C_{13}H_{14}ON_2$ and by comparison of its infrared (IR) and ultraviolet (UV) spectra with those of C-3 as shown in Table III and IV.

TABLE IV. UV Spectra of C-1, C-3, C-5 and C-2

Compounds	UV λ_{max}^{EtOH} mμ (log ε)										
C-1	220		264	290	296[a]				374[a]	392	413
	(4.39)		(3.87)	(3.96)	(3.94)				(4.29)	(4.55)	(4.56)
C-3	218	243	251	275[a]	285		340[a]	356	373	393	
	(4.43)	(3.47)	(3.51)	(3.93)	(4.08)		(3.91)	(4.20)	(4.42)	(4.35)	
C-5	218	244	252	278[a]	285		340[a]	360	375	395	
	(4.41)	(3.48)	(3.49)	(3.93)	(4.03)		(3.84)	(4.14)	(4.34)	(4.26)	
C-2	220	243				300	311				
	(4.65)	(4.12)				(3.54)	(3.56)				

a) shoulder

D-2 corresponding the analytical values of its picrate to $C_{17}H_{15}O_7N_5$ showed the absorption peaks approximate to those of 4-methylquinazoline (VII) or D-1 in its UV spectrum as shown in Table V. So D-2 should be postulated to be 4-propylquinazoline.

TABLE V. UV Spectra of 4-Alkylquinazoline (D)

Compounds	UV λ_{max}^{EtOH} mμ (log ε)									
VII	222.5	(4.69)	270 (3.51)	280 (3.45)[a]	305 (3.46)	311 (3.43)[a]
D-1	223	(4.62)	270 (3.47)	280 (3.42)[a]	305 (3.42)	311 (3.41)[a]
D-2	223	(4.64)	270 (3.50)	280 (3.45)[a]	305 (3.46)	312 (3.43)[a]

a) shoulder

The foregoing experimental results showed that when III combined with the primary carbon atom in the α-position of the carbonyl group the reaction product (C) was not affected by hydrolysis during the after treatment of the reaction mixture, but when it did with the secondary carbon atom D was formed via intermediate products represented by the formula of type C' in Chart 5 except the case of the reactions with 2-methylpropiophenone and cyclopentanone.
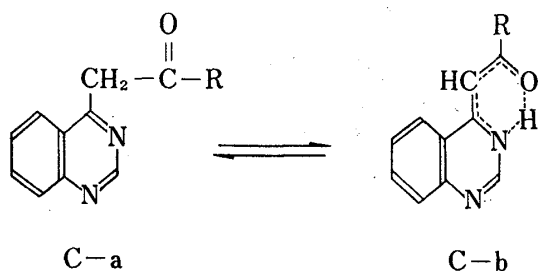
C-1, C-3, C-4 and C-5 formed by combining with the primary carbon atom in the α-position of carbonyl group will exist to be one form or the other of two tautomeric isomers, C-a and C-b, as shown in Chart 6.

Chart 6

In general, it is known that the conjugate chelation effect induces the carbonyl absorption to a low frequency shift in IR absorption band such as any structures represented by the type of $-\overset{X-H}{\underset{|}{C}}=\overset{Y}{C}-\overset{\|}{C}-$, in which X and Y can act as electron donors or acceptors.[5] Similarly, it might be assumed that low frequencies shifts of carbonyl absorption bands in these compounds in contrast with normal carbonyl vibrations were contributed to the conjugate chelation effect (see Table III). Also it might be seemed that low frequency shifts and decreasing intensities of the secondary amine streching bands attribute to conjugate chelation effect to result in the elimination of NH bands of the materials.

UV spectra also comfirmed the above conjugate chelation because it was shown that longer wave length shifts of long–wavelength absorption bands of these compounds in the contrast with that of C-2 which could not exist as the conjugate chelation form attributed to increasing of conjugated double bonds system as shown in Table IV.

5) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," Methun Co., Ltd. (London), 1958, p. 142.

Moreover, NMR technique is often a powerful tool to clarify the keto-enol equilibrium.[6] In NMR spectra of these compounds the strong desielding of internal hydrogen bonding in conjugate chelation were well recognized at range -4——-5 (τ) as very broading band which equivalent just to one proton in their integration and were easily removed by D_2O exchange. And each spectrum of these compounds also showed one olefinic proton as a sharp singlet at range 3——4 (τ). Usually the proton of the 2-position of quinazoline molecule resonances at low magnetic field at range 0.5——1.5 (τ)[7] as a sharp singlet. However in each of these compounds it could not be found at this field but could be done at higher magnetic field than that as shown in Table VI. It might be considered that this higher magnetic field shift was due to the decreasing a anistropy of aromatic ring current effect by a collapse of aromaticity of the pyrimidine portion in quinazoline molecule.

From above spectropheotometric data it was well concluded that these compounds should be existed as enol form constituting a conjugate chelation system.

Table VI. NMR Spectra of VII, C-1, C-2 and C-3 in $CDCl_3$

Compounds	NMR (τ)				
	Chelating H	Aromatic H	2-H	Conjugate olefinic H	–CH$_3$
VII	—	1.67—2.63 (m)	0.74 (S)	—	7.02 (S)
C-1	-5.2 (b)	1.80—2.90 (m)	2.48 (S)	3.28 (S)	—
C-2	—	1.50—2.90 (m)	1.25 (S)	—	8.06 (S), 8.22 (S)
C-3	-4.5 (b)	1.95—2.80 (m)	2.40 (S)	4.00 (S)	7.77 (S)

b: broading, m: multiplet, s: singlet

Experimental[8]

UV spectra were measured in 99.5% EtOH on a Hitachi Spectrophotometer Model ESP-2U.

IR spectra were recorded with a Hitachi Spectrophotometer Model EPI-G2.

NMR spectra were measured at 60 Mc and 23° C on a Japan Electron Optics Lab. Spectrophotometer Model JNM-C-60H. Tetramethylsilane was used as internal standard.

Reaction of II with Ketones in the Presence of NaNH$_2$——General Method: A solution of 1.5 ml of ketone dissolved in 10 ml of anhyd. benzene was gradually added to a mixture of 0.5 g of NaNH$_2$ and 0.5 g of II in 10 ml of anhyd. benzene with vigorous stirring. The reaction was continued under the condition shown in Table I. The reaction mixture was neutralized by dil. AcOH. The benzene layer was then washed with H$_2$O and dried over anhyd. Na$_2$SO$_4$. The benzene solution was passed through a column of alumina to remove impurities.

So obatined 2-(1-isoquinolinyl)acetophenone (B-1), 2-(1-isoquinolinyl)propiophenone (B-2), 1-(1-isoquinolinyl)-4-methyl-2-pentanone (B-8), 2-(1-isoquinolinyl)cyclohexanone (B-9), 1-(1-isoquinolinyl)-2-propanone (B-3), 2-(1-isoquinolinyl)-3-pentanone (B-4), 1-(1-isoquinolinyl)-2-butanone (B-5), 1-(1-isoquinolinyl)-2-pentanone (B-6) and 1-(1-isoquinolinyl)-3-methyl-2-butanone (B-7) was undepressed on admixture with corresponding specimen or its picrate prepared from another route,[3] respectively.

Reaction of III with Acetophenone——A solution of 3.0 ml of acetophenone dissolved in 5 ml of anhyd. benzene was gradually added to a mixture of 1.0 g of III, 1.0 g of NaNH$_2$ and 10 ml of anhyd. benzene with vigorous stirring under cooling with a mixture of ice and H$_2$O. The exothermic reaction took place. After addition of acetophenone the stirring was continued for 1 hr. The reaction mixture was poured onto an excess of ice-H$_2$O mixture, neutralized by dil. AcOH and then extracted with CHCl$_3$. The CHCl$_3$ solution was then extracted with 2N HCl. The separated the crystals of hydrochloride of 2-(4-quinazolinyl)aceto-phenone (C-1) were collected by suction and neutralized by K$_2$CO$_3$ solution. Recrystallization of crude C-1 from a mixture of petr. ether and benzene gave yellow needles, mp 160—161°, in 26.5% yield (0.4 g).

Reaction of III with Acetone——A solution of 2.0 ml of acetone dissolved in 4.0 ml of anhyd. benzene was gradually added to a mixture of 1.0 g of NaNH$_2$, 1.0 g of III and 10 ml of anhyd. benzene with vigorous

6) S. J. Rhoads, *J. Org. Chem.*, **31**, 171 (1966).
7) A. R. Katritzky, R. E. Reavill and F. J. Swinbourne, *J. Chem. Soc.* (B), **1966**, 351.
8) All melting points were not corrected.

stirring under cooling with a mixture of ice and H_2O. After addition of acetone the stirring was continued for 0.5 hr. The reaction mixture was poured onto an excess of ice–H_2O mixture, neutralized by dil. AcOH and then extracted with $CHCl_3$. The $CHCl_3$ solution was extracted with 2N HCl. The separated crystals by neutralization of the HCl layer with anhyd. K_2CO_3 were recrystallized from MeOH to give 1-(4-quinazolinyl)acetone (C-3) as yellow needles, mp 121—122° in 88.5% yield (1.0 g).

Reaction of III with 2-Methylpropiophenone——A mixture of 1.0 g of III, 1.0 g of $NaNH_2$, 2.0 g of 2-methylpropiophenone and 10 ml of anhyd. benzene was vigorously stirred for 2 hr at room temperature. The reaction mixture was poured onto an excess of ice–H_2O mixture and extracted with benzene. After evaporation of benzene from the extracte an excess of 2-methylpropiophenone was removed by steam distillation. The oily residue was again dissolved with benzene, dried over anhyd. Na_2SO_4 and passed through a column of alumina to remove impurities. Recrystallization from petr. ether afforded colorless plate, mp 100—105°, in 23.8% yield (0.4 g). *Anal.* Calcd. for $C_{18}H_{16}ON_2$ (2-(4-quinazolinyl)-2-methylpropiophenone): C, 78.23; H, 5.84; N, 10.14. Found: C, 78.40; H, 5.94; N, 10.23.

Reaction of III with Propiophenone——To a mixture of 1.0 g of III, 1.0 g of $NaNH_2$ and 10 ml of anhyd. benzene, 3.0 ml of propiophenone was gradually added with vigorous stirring under cooling with a mixture of ice and H_2O. The stirring was continued for 1.5 hr. The reaction mixture was poured onto excess of ice–H_2O mixture, neutralized by dil. AcOH, extracted with $CHCl_3$. The $CHCl_3$ layer was extracted with 2N HCl and the extracte was neutralized by K_2CO_3 to separate oily substance which was again dissolved with $CHCl_3$. After drying over anhyd. Na_2SO_4 the $CHCl_3$ solution was passed through a column of alumina to remove impurities. Evaporation of $CHCl_3$ afforded 4-ethylquinazoline (D-1) as oily substance in 37.5% yield (0.36 g) and its picrate from MeOH showed mp 170—171°.

Reaction of III with Butyrophenone——The reaction used 1.0 g of III, 1.0 g of $NaNH_2$ and 3.0 ml of butyrophenone in 10 ml of anhyd. benzene, according as same treatment as the reaction of III with propiophenone, afforded 4-propylquinazoline as oily substance in 29.5% yield (0.31 g) and its picrate showed mp 165—167° from MeOH. *Anal.* Calcd. for $C_{17}H_{15}O_7N_5$ (4-propylquinazoline picrate): C, 50.87; H, 3.77; N, 17.54. Found: C, 50.91; H, 3.95; N, 17.74.

Reaction of III with 3-Pentanone——According as same treatment as the reaction of III with propiophenone, the reaction used 1.0 g of III, 1.0 g of $NaNH_2$ and 3.0 ml of 3-pentanone in 10 ml of anhyd. benzene afforded D-2 in 72.9% yield (0.71 g).

Reaction of III with Cyclopentanone——According as same treatment as the reaction of III with propiophenone, the reaction used 0.5 g of III, 0.5 g of $NaNH_2$ and 1.5 ml of cyclopentanone in 6 ml of anhyd. benzene afforded 2-(4-quinazolinyl)cyclopentanone (C-6) as orange needles in 19.4% yield (0.25 g), mp 154—155° from petr. ether.

Reaction of III with 2-Pentanone——To a mixture of 1.0 g of III, 1.0 g of $NaNH_2$ and 10 ml of anhyd. benzene, 3.0 ml of 2-pentanone was gradually added with vigorous stirring under cooling with a mixture of ice and H_2O. The stirring was continued for 0.5 hr. The reaction mixture was poured onto an excess of ice–H_2O mixture, neutralized by dil. AcOH and extracted with $CHCl_3$. The $CHCl_3$ layer was extracted with 2N HCl and the HCl layer was then neutralized by anhyd. K_2CO_3 to separate an brown oily substance which was dissolved in $CHCl_3$. After drying over anhyd. Na_2SO_4 the $CHCl_3$ solution was passed through a column of alumina to separate the reaction mixture. From the first fraction D-2 as a oil was obtained in 20.9% yield (0.22 g) and its picrate from MeOH showed mp 165—167°.

From the second fraction 1-(4-quinazolinyl)-2-pentanone (C-5) as yellow needles from petr. ether, mp 75°, was obtained in 15.4% yield (0.2 g). *Anal.* Calcd. for $C_{13}H_{14}ON_2$ (1-(4-quinazolinyl)-2-pentanone): C, 72.87; H, 6.59; N, 13.08. Found: C, 72.52; H, 6.18; N, 12.74.

Reaction of III with 2-Butanone——According as same treatment as the reaction of III with 2-pentanone, the reaction used 1.0 g of III, 0.5 g of $NaNH_2$, 1.5 ml of 2-butanone in 10 ml of anhyd. benzene afforded D-1 as a oil in 83.3% yield (0.8 g) from the first fraction and 1-(4-quinazolinyl)-2-butanone (C-4) as yellow needles from petr. ether, mp 111—112°, in poor yield (trace) from the second fraction.

Reaction of III with Cyclohexanone——To a mixture of 1.0 g of III, 1.0 g of $NaNH_2$ and 10 ml of anhyd. benzene, 3.0 ml of cyclohexanone was gradually added with vigorous stirring under cooling with a mixture of ice and H_2O. The stirring was continued for 0.5 hr. The reaction mixture was poured onto an excess of ice–H_2O mixture, neutralized by dil. AcOH and extracted with $CHCl_3$. The $CHCl_3$ solution was then extracted with 2N HCl and the HCl layer was neutralized and basified by an excess of K_2CO_3. By neutralization of K_2CO_3 layer by AcOH 4-quinazolinehexanoic acid (D-3) began to separate out. Recrystallization from a mixture of petr. ether and benzene afforded white needles, mp 100—101°, in 6.8% yield (0.1 g).