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Syntheses and Pharmacological Activities of 2-Heterocyclic Substituted 4(3*H*)-Quinazolinone Derivatives

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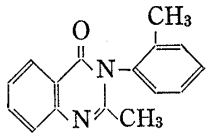
The preparation of a series of 2-pyridyl-4(3*H*)-quinazolinones is described. Some of them showed a hypnotic action in mice when given orally. Studies on the structure-activity relationship demonstrated that 2-pyridyl, 3-pyridyl, and 4-pyridyl substitution at 2 position of quinazolinone ring, and *o*-, *m*-, and *p*-substitution of the aromatic ring at 3 position are suitable for manifestation of hypnotic activity. The order of potency of activities produced by the difference in the position of substitution of substituents at 2 and 3 position decreased in the order of 4-pyridyl, *o*-tolyl>3-pyridyl, *o*-tolyl>2-pyridyl, *o*-tolyl. The anthranilates of these 4(3*H*)-quinazolinones were inactive. A maximum hypnotic effect accompanied with other potent pharmacological properties was observed in 2-(4-pyridyl)-3-*o*-tolyl-4(3*H*)-quinazolinone (**14**), the potency of which was equal to or stronger than Methaqualone in mice.

Diverse biological activities have been found in compounds having a quinazolinone ring system.[2] A large number of 4(3*H*)-quinazolinones, in particular those possessing 2-alkyl-3-aryl,[3] 2-alkyl-3-alkyl,[4] and 2-alkyl-3-amino[5] substitutions, have been prepared and evaluated for pharmacological activities, but, 2-heterocyclic substituted derivatives have received relatively limited attention.[6]

It is well known that quinazolinone derivatives show a central nervous system activity and one of the most active compounds is 2-methyl-3-*o*-tolyl-4(3*H*)-quinazolinone (Methaqualone), a well-known potent hypnotic.



methaqualone

In the previous paper,[7] the present authors reported the convenient synthetic method to obtain 2-heterocyclic substituted 4(3*H*)-quinazolinones under the modified Willgerodt-Kindler reaction conditions. In our preliminary experiments, it was found that 2-(2-pyridyl)-3-aryl-4(3*H*)-quinazolinones possess hypnotic and anticonvulsant activities to some extent in mice. In order to obtain a more detailed structure-activity relationship, the above finding led us to continue studies on a series of 2,3-disubstituted 4(3*H*)-quinazolinones.

The present paper deals with the syntheses and a gist of pharmacological activities of such compounds, substituted with 2-pyridyl, 3-pyridyl, or 4-pyridyl at 2 position (Table I).

Syntheses

To obtain the corresponding 2-(2-pyridyl)- and 2-(4-pyridyl)-3-aryl-4(3*H*)-quinazolinones in one step, the modified Willgerodt-Kindler reaction was utilized in these cases (Chart 1,

1) Location: *Oe-hon-machi, Kumamoto.*
2) W.L.F. Armarego, *Adv. Heterocycl. Chem.*, **1**, 253 (1963).
3) *a*) M.L. Gujral, K.N. Sacreen, and R.P. Kohli, *Indian J. Med. Res.*, **45**, 207 (1957); *b*) C. Bianci and A. David, *J. Pharm. Pharmacol.*, **12**, 501 (1960); *c*) S. Rani, S. Gupta, and K.S. Narang, *J. Indian Chem. Soc.*, **30**, 331 (1953).
4) A. Buzas and C. Hoffman, *Bull. Soc. Chim. France*, **26**, 1889 (1959).
5) *a*) S. Petersen, H. Herlinger, E. Tietze, and W. Stiefken, *Angew. Chem.*, **74**, 855 (1962); *b*) S. Somasekhra, V.S. Dighe, P.R. Mankad, and F.A. Mukherjee, *Indian J. Chem.*, **2**, 369 (1964).
6) K.-H. Boltz, H.-D. Dell, H. Lehwald, D. Lorenz, and M. Rüberg-Schweer, *Arzneimittelforsch.*, **13**, 688 (1963).
7) T. Hisano, T. Nishi, and M. Ichikawa, *Yakugaku Zasshi*, **92**, 582 (1972).

method A),[7] and the compounds (**1**—**8**, **13**—**18**, and **24**) (Table I) were prepared by this procedure. The condensation usually occurred under the experimental condition of heating without a solvent at 190—200° for 8 hr the equivalent amount of 2-picoline or 4-picoline, corresponding aromatic amine, and anthranilic acid in the presence of three-fold amount of sulfur.

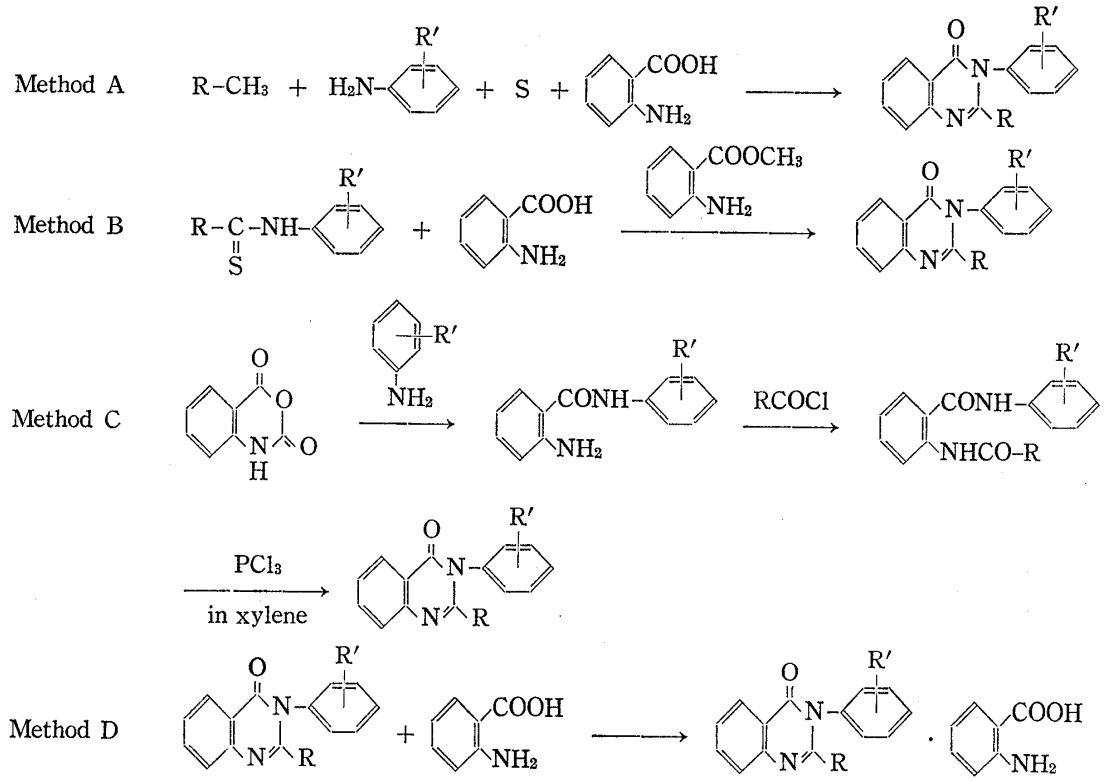
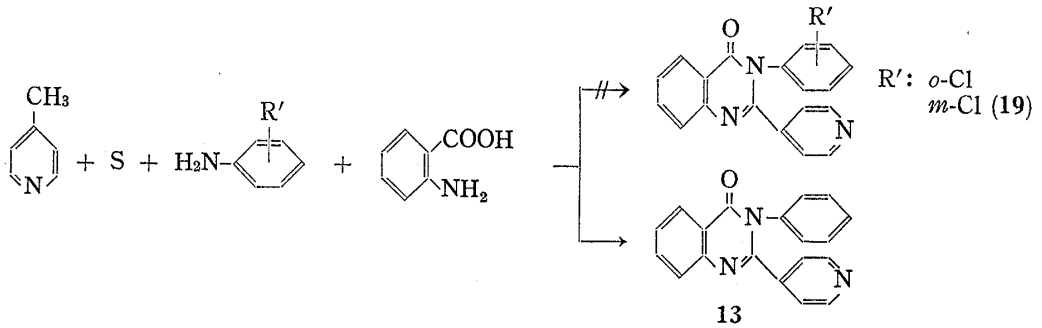


Chart 1. Synthetic Method for 2-Pyridyl-3-aryl-4(3*H*)-quinazolinones

Most of the products were readily pruified by recrystallization or chromatography on alumina.

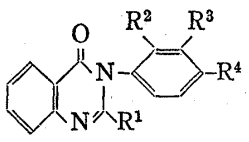
The compounds (**9**—**12**) were prepared in a moderate yield from anthranilic acid with an excess of the corresponding thioanilides in the presence of methyl anthranilate (Chart 1, method B).[8]

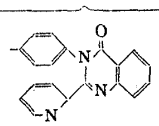
Attempts to obtain 2-(4-pyridyl)-3-(*o*- or *m*-chlorophenyl)-4(3*H*)-quinazolinone using 4-picoline with *o*- or *m*-chloroaniline as the aromatic amine under the modified Willgerodt-Kindler reaction condition (Chart 1, method A) resulted in the formation of a dechlorinated compound instead of the expected chloro-substituted compounds, producing 2-(4-pyridyl)-3-phenyl-4(3*H*)-quinazolinone (**13**) in both cases. This product was identified by the mixed melting point determination with an authentic sample and by elemental analyses. The reason for this result has not been clarified.



8) T. Hisano and M. Ichikawa, *Chem. Pharm. Bull.* (Tokyo), **19**, 2625 (1971).

TABLE I. 2-Pyridyl-3-aryl-4(3*H*)-quinazolinones



Compd. No.	R^1	R^2	R^3	R^4	mp[a] (°C)	Appearance (Recrystn. solvent)	Formula	Method	Yield (%)	Analysis (%) Calcd. (Found) C	H	N
1		H	H	H	162[b]	colorless prisms (petr. benzin)	$C_{19}H_{13}ON_3$	A	36.7[c]	76.25 (76.23)	4.35 (4.51)	14.05 (13.83)
2		CH_3	H	H	154[d]	colorless needles (petr. benzin–benzene)	$C_{20}H_{15}ON_3$	A	35.2[c]	76.66 (76.64)	4.83 (4.72)	13.41 (13.39)
3		H	CH_3	H	134[e]	colorless needles (petr. benzin–benzene)	$C_{20}H_{15}ON_3$	A	37.5[c]	76.66 (76.61)	4.83 (4.63)	13.41 (13.42)
4		H	H	CH_3	194	colorless needles (petr. benzin–benzene)	$C_{20}H_{15}ON_3$	A	43.5[c]	76.66 (76.75)	4.83 (4.83)	13.41 (13.38)
5		OCH_3	H	H	163	colorless needles (petr. benzin–benzene)	$C_{20}H_{15}O_2N_3$	A	38.6[c]	72.95 (72.98)	4.56 (4.51)	12.77 (12.59)
6		H	H	OCH_3	219[f]	colorless prisms (petr. benzin)	$C_{20}H_{15}O_2N_3$	A	42.3[c]	72.95 (73.01)	4.56 (4.63)	12.77 (12.95)
7		H	H	OC_2H_5	167	colorless prisms (petr. benzin)	$C_{21}H_{17}O_2N_3$	A	44.5[c]	73.47 (73.40)	4.96 (5.11)	12.24 (12.34)
8		H	H	$CO_2C_2H_5$	190	colorless needles (petr. benzin)	$C_{22}H_{17}O_3N_3$	A	22.3[c]	71.16 (71.30)	4.58 (4.32)	11.32 (11.56)
9					182	colorless prisms (petr. benzin–benzene)	$C_{18}H_{12}ON_4$	B	18.3[g]	71.99 (72.28)	4.03 (4.27)	18.67 (18.58)
10		H	H	H	142	colorless prisms (petr. benzin–benzene)	$C_{20}H_{15}ON_3$	B	33.5[g]	76.66 (76.82)	4.83 (4.89)	13.41 (12.95)
11		H	H	H	166	colorless prisms (petr. benzin–benzene)	$C_{20}H_{15}ON_3$	B	36.7[g]	76.66 (76.45)	4.83 (4.68)	13.41 (12.98)
12					281	colorless prisms (petr. benzin–benzene)	$C_{32}H_{20}O_2N_6$	B	26.0[g]	73.85 (73.60)	3.85 (3.55)	16.15 (16.40)
13		H	H	H	159	colorless prisms (petr. benzin–benzene)	$C_{19}H_{13}ON_3$	A	44.3[c]	76.25 (76.41)	4.35 (4.21)	14.05 (13.87)
14		CH_3	H	H	174[h]	colorless prisms (petr. benzin–benzene)	$C_{20}H_{15}ON_3$	A	30.3[c]	76.66 (76.54)	4.83 (4.60)	13.41 (13.22)
15		H	CH_3	H	173	colorless prisms (petr. benzin)	$C_{20}H_{15}ON_3$	A	33.5[c]	76.66 (76.44)	4.83 (4.68)	13.41 (13.50)
16		H	H	CH_3	233	colorless pillars (petr. benzin–benzene)	$C_{20}H_{15}ON_3$	A	43.1[c]	76.66 (76.55)	4.83 (4.70)	13.41 (13.48)
17		H	H	OCH_3	172	colorless needles (petr. benzin–benzene)	$C_{20}H_{15}O_2N_3$	A	28.1[c]	72.95 (72.77)	4.56 (4.45)	12.77 (12.61)
18		H	H	OC_2H_5	156	colorless needles (petr. benzin–benzene)	$C_{21}H_{17}O_2N_3$	A	35.0[c]	73.47 (73.45)	4.96 (4.88)	12.24 (12.41)
19		H	Cl	H	179	colorless prisms (petr. benzin–benzene)	$C_{19}H_{12}ON_3Cl$	C	20.1[i]	68.37 (68.24)	3.63 (3.57)	12.59 (12.41)
20		CH_3	H	H	156	colorless prisms (petr. benzin–benzene)	$C_{20}H_{15}ON_3$	C	22.5[i]	76.66 (76.72)	4.83 (4.70)	13.41 (13.45)
21		H	CF_3	H	183	colorless prisms (petr. benzin–benzene)	$C_{20}H_{12}ON_3F_3$	C	19.5[i]	65.40 (65.64)	3.29 (2.91)	11.44 (11.59)
22		H	Cl	H	224	colorless prisms (petr. benzin–benzene)	$C_{19}H_{12}ON_3Cl$	C	16.8[i]	68.37 (68.67)	3.63 (3.57)	12.59 (12.73)
23		CH_3	CH_3	H	153	colorless prisms (petr. benzin–benzene)	$C_{21}H_{17}ON_3$	C	23.2[i]	77.04 (77.12)	5.23 (5.16)	12.84 (12.70)
24		H	H	H	189	colorless needles (petr. benzin)	$C_{23}H_{15}ON_3$	A	41.0[c]	79.08 (78.92)	4.30 (4.41)	12.03 (11.98)
MTQ	CH_3	CH_3	H	H	115							

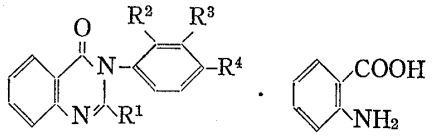
a) All melting points are uncorrected. *b*) reported,[6] 153° *c*) Calcd. on the basis of methylpyridine *d*) reported,[6] 153° *e*) reported,[6] 133°
f) reported,[6] 212° *g*) Calcd. on the basis of anthranilic acid *h*) reported,[6] 166° *i*) Calcd. on the basis of isatotic anhydride

Therefore, 2-(4-pyridyl)-3-(*m*-chlorophenyl)-4(3*H*)-quinazolinone (**19**) was prepared by another procedure. **19** was readily prepared by heating isatoic anhydride with *m*-chloroaniline (Chart 1, method C) to give 2-amino-N-(*m*-chlorophenyl)benzamide which was then isonicotinoylated and cyclized with phosphorus trichloride (Chart 1, method C).[9]

In the synthesis of 2-(3-pyridyl) derivatives, 3-picoline cannot be used in the modified Willgerodt-Kindler reaction, since the methyl group in pyridine ring at 3 position does not react under that procedure condition. 2-(3-Pyridyl)-3-aryl-4(3*H*)-quinazolinones (**20—23**) were also prepared by method C (Chart 1).

The anthranilates of quinazolinones were obtained in a good yield by refluxing anthranilic acid and appropriate 4(3*H*)-quinazolinone in the presence of ethanol for 1 hr (Chart 1, method D). Compounds **25—30** were obtained in this way.

Table II. Anthranilates of 4(3*H*)-Quinazolinones



Compd. No.	R^1	R^2	R^3	R^4	mp[a] (°C)	Appearance (Recrystn. solvent)	Formula	Method	Yield (%)	Analysis (%) Calcd. (Found) C	H	N
25		H	H	H	260	colorless needles (EtOH)	$C_{19}H_{13}ON_3 \cdot C_7H_7O_2N$	D	89.5	71.56 (71.66)	4.59 (4.70)	12.84 (13.07)
26		H	H	CH_3	243	colorless needles (EtOH)	$C_{20}H_{15}ON_3 \cdot C_7H_7O_2N$	D	88.9	72.00 (72.11)	4.89 (5.07)	12.44 (12.66)
27		H	H	OCH_3	260	colorless needles (EtOH)	$C_{20}H_{15}O_2N_3 \cdot C_7H_7O_2N$	D	93.0	69.53 (69.90)	4.72 (5.10)	12.02 (11.91)
28		H	H	OC_2H_5	236	colorless needles (EtOH)	$C_{21}H_{17}O_2N_3 \cdot C_7H_7O_2N$	D	88.6	69.94 (70.21)	5.01 (5.30)	11.69 (11.50)
29		H	H	H	249	colorless prisms (EtOH)	$C_{19}H_{13}ON_3 \cdot C_7H_7O_2N$	D	92.0	71.56 (71.43)	4.59 (4.52)	12.84 (12.84)
30		H	H	H	264	colorless needles (EtOH)	$C_{20}H_{15}ON_3 \cdot C_7H_7O_2N$	D	84.6	72.20 (72.26)	4.89 (5.34)	12.44 (12.19)

a) All melting points are uncorrected.

Pharmacology

Materials——Test Compounds: Thirty compounds used for the present study were synthesized as described above. The compounds shown in Tables I and II are sparingly soluble in water, and were suspended in water with the aid of 0.5% carboxymethylcellulose solution and the suspensions were given to mice orally or intraperitoneally. Methaqualone, supplied by Eisai Co., Ltd, Tokyo, was used as a reference drug.

Animal: Male mice of ddY strain weighing 18—20 g were used for the experiments.

Methods——The following eight experiments were selected as the first screening methods.

Gross Observation: A group of 5 mice was used for each test compound. Each of three graded doses such as 200, 500, and 1000 mg/kg of the test compounds was given intra-

9) S. Hayao, H.J. Havera, and W.G. Strycker, *J. Med. Chem.*, **1969**, 936.

peritoneally to each group of mice. The behavior and toxic signs were observed in detail for the next 120 min. The results thus obtained were useful as criteria for screening of pharmacological activities.

1. Acute Toxicity and LD_{50}: Ten to 12 groups of 7 mice were used. Five or six graded doses of the test compounds were administered orally or intraperitoneally. LD_{50} and its fiducial limits were calculated by the Litchfield-Wilcoxon method[10] from the lethality within 72 hr ($p=0.05$).

2. Effect on Motor Activity: A group of 9 mice was used for each test compound. Motor activity was measured by using a revolving wheel cage; frequency of rotation of the cage was counted and used as an indicator of spontaneous motor activity. Counting began 15 min after oral administration of a test compound, and it was carried out every 15 min for 90 min. The results were compared with those of control groups.

3. Effect on Muscle Tone: Muscular weakness due to the test compounds was examined by the method of Courvoisier.[11] When a normal mouse is hung with its forepaws on to a wire, which is stretched horizontally at 30 cm high, it can grip the wire with one or both hindpaws within 5 sec. Abolishment or delay of the response was regarded as an indication of muscular weakness. A group of 7 mice was used for each test compound.

4. Hypnotic Effect: A test compound was given to a group of 10 mice and time needed for recovery from complete loss of righting reflex was determined as sleeping time. A complete loss of the reflex for more than 2 min was regarded as positive hypnotic effect.

5. Prolongation of Hexobarbital Sleeping Time: An intraperitoneal dose (70 mg/kg) of hexobarbital sodium was given to a group of 10 mice for each test compound and an individual sleeping time was determined as in 4. Ten min after oral administration of the test compounds, the same dose of hexobarbital was given and sleeping time was measured again in just the same manner as in 4.

6. Anticonvulsant Effect: Ten min after oral administration of the test compounds to a group of 10 mice, 100 mg/kg of Pentetrazol was given intraperitoneally. This dose of the convulsant is able to induce tonic extention followed by death without fail. The number of animals which were able to survive for 30 min after the test drug was checked.

7. Effect on Body Temperature: The rectal temperature of mice were measured by thermometer (thermister) before and at appropriate time intervals (15 or 30 min) after oral administration of the test compounds. A group of 10 mice was used for each test compound and the experiment was carried out under an ambient temperature of $23.5°\pm1°$ and relative humidity of 58%.

In all the experiments 1 to 7, Methaqualone was used as a reference drug.

Result

1. Acute Toxicity and LD_{50}

Six out of 30 compounds tested showed a distinct activity, and LD_{50} and its fiducial limits of the active compounds, (**1**, **2**, **13**, **14**, **15**, and **20**), are shown in Table III in comparison with those of Methaqualone.

In an oral dose of 100 or 200 mg/kg, all the compounds caused a remarkable decrease in spontaneous motility and ataxia in 2—3 min, and the compound (**14**) abolished the righting reflex 10 min after its administration. When a larger dose was given, all the compounds ceased spontaneous movement and caused respiratory paralysis.

10) J.T. Litchfield and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.*, **96**, 99 (1949).
11) S. Courvoisier, R. Durcot, and L. Jolou, "Psychotropic Drugs," Elsevier Publishing Co., Amsterdam, 1957 p. 373.

Table III. Acute Toxicity of Compounds in Mice

Compd. No.	Route	LD_{50} (mg/kg)	Fiducial limit ($p=0.05$)
1	*p.o.*	1000—1500	
	i.p.	401	339— 473
2	*p.o.*	2000<	
	i.p.	580	513— 655
13	*p.o.*	770	497—1194
	i.p.	460	414— 511
14	*p.o.*	595	488— 726
	i.p.	405	348— 472
15	*p.o.*	518	445— 604
	i.p.	390	325— 468
20	*p.o.*	1580	1370—1820
MTQ	*p.o.*	1200	
	i.p.	980	817—1076

2. Effect on Motor Activity

Effect of six compounds and Methaqualone on motor activity of mice are shown in Fig. 1 and Table IV. With an oral dose of 100 mg/kg of the compounds (**1** and **2**), 50 mg/kg of **13** and **17**, and 20 mg/kg of **14** and **20**, a 50% decrease in motor activity occurred, but the decrease seemed to be partly due to the muscle relaxant activity of all the compounds used. On the other hand, there was no effect on the activity with a dose of 100 mg/kg of other compounds.

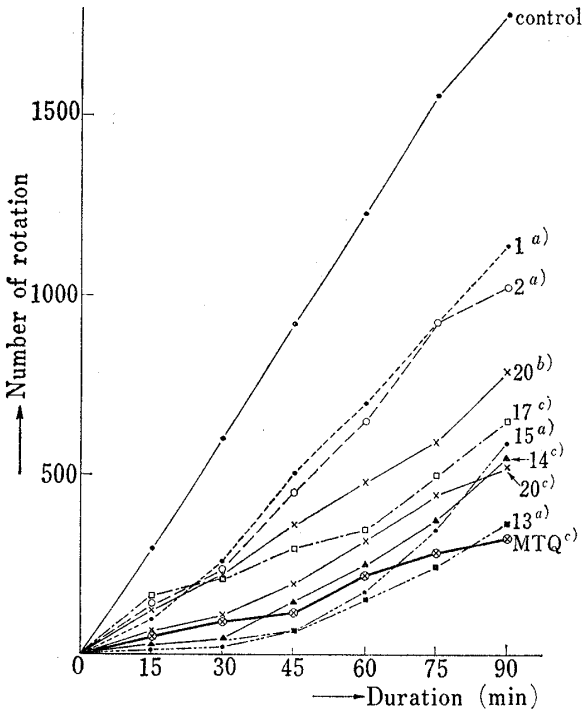


Fig. 1. Effect of Compounds on the Motor Activity in Mice

a) 100 mg/*p.o.* *b*) 20 mg/kg *p.o.* *c*) 50 mg/kg *p.o.*

Table IV. Repression Effect

Compd. No.	Dose (mg/kg) (*p.o.*)	Repression (%)
1	50	39.3
	100	46.8
2	50	35.4
	100	46.9
13	20	19.8
	50	49.7
	100	88.9
14	20	38.9
	50	81.6
15	50	28.3
	100	84.3
16	50	14.0
	100	80.9
17	50	59.5
	100	95.4
18	100	35.6
20	20	60.4
	50	76.5
24	100	15.2
MTQ	20	39.4
	50	83.3
Nitrazepam	10	75.0
Chlordiazepoxide	10	70.0

3. Decreasing Effect on Muscle Tone

The results are shown in Table V. In the case of compounds **1** and **2**, oral dose of more than 100 mg/kg caused a definite though weak effect. The compounds **14** and **15** showed a stronger effect than Methaqualone in an oral dose of 50 mg/kg of each, while all the other compounds did not show any effect.

Table V. Effect of Compounds on Muscular Relaxation in Mice

Compd. No.	Dose (mg/kg) (*p.o.*)	No. of animals	No. of failed animals
1	100	7	2
	200	7	6
2	100	7	2
	200	7	5
13	50	7	1
	100	7	7
14	50	7	6
15	50	7	5
16	50	7	1
17	50	7	3
18	50	7	0
19	50	7	0
20	50	7	1
	100	7	6
MTQ	50	7	3
	100	7	5

4. Hypnotic Effect

The sleeping time of eight compounds and Methaqualone is shown in Table VI. A significant hypnotic effect was demonstrated by 200 mg/kg of compound **13**, 100 mg/kg of **14**, and 200 mg/kg of **20** given orally, while no effect was observed with 200 mg/kg of other compounds. Methaqualone showed a definite hypnotic effect with doses of more than 200 mg/kg.

5. Potentiation Effect on Hexobarbital-induced Sleep

Prolongation of hexobarbital sleeping time by five of the test compounds (**1**, **2**, **13**, **14**, and **20**) and by Methaqualone is shown in Table VII. Sleeping time was significantly prolonged by compounds **1** and **2** with an oral dose of 100 mg/kg and also by compounds (**13**, **14**, and **20**) with such a smaller dose as 20 mg/kg. The potentiation effect by the latter three was approximately equal to that by Methaqualone.

Table VI. Effect of Compounds on Righting Reflex in Mice

Compd. No.	Dose (mg/kg) (*p.o.*)	Sleeping time (min)
1	100	—
2	100	—
13	100	—
	200	29.0
14	50	8.9
	100	55.2
15	200	6.8
17	200	5.2
18	200	3.3
20	200	68.0
MTQ	100	14.9
	200	21.9

Table VII Effect of Compounds on Duration of Sleeping induced by Hexobarbital Sodium in Mice

Compd. No.	Dose (mg/kg) (*p.o.*)	Sleeiping time (min)
Control	—	21.8
1	50	16.6
	100	64.2[a]
2	50	22.0
	100	32.1[b]
13	20	45.9[b]
	50	83.1[a]
14	20	60.5[a]
	50	95.3[a]
20	50	167.0[a]
MTQ	20	36.7[b]
	50	62.9[a]

a) significance: $p<0.01$
b) significance: $p<0.05$

Table VIII. Effect of Compounds on Clonic Convulsion and Tonic Extension induced by Pentetrazol in Mice

Compd. No.	Dose (mg/kg) (*p.o.*)	No. of animals	No. of animals induced C.C.	No. of aminals induced T.E.	Mean time of C.C. (min)	Mean time of T.E. (min)
Control	—	10	10	10	1.8	1.8
1	200	10	10	10	1.7	3.2
2	200	10	10	7	2.6	5.4
13	50	10	10	3	2.6	7.9
	100	10	10	1	11.8	19.7[a]
14	20	10	5	4	1.5	11.7
	50	10	4	0	1.7	—
15	100	10	10	1	1.7	24.2[a]
16	50	10	10	7	1.3	8.1
	100	10	10	4	4.9	9.1
17	100	10	9	6	1.4	12.7[a]
20	50	10	9	2	1.9	3.6
	100	10	9	0	2.0	
MTQ	20	10	8	2	3.4	17.3
	50	10	5	0	3.5	

C.C.: clonic convulsion T.E.: tonic extension
a) significance: $p<0.05$

6. Anticonvulsant Effect

An oral dose of 50 mg/kg of compound (**14**) and Methaqualone was able to inhibit the induction of tonic extension completely, though clonic convulsion occurred. In contrast, compounds (**13**, **15**, **17**, and **20**) were less effective that they could only prolong the duration of clonic and tonic convulsions significantly in a dose of 100 mg/kg.

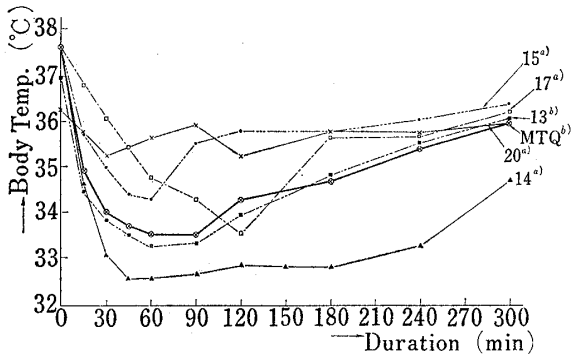


Fig. 2. Time Course of Hypothermic Activity of Compound in Mice
a) 50 mg/kg *p.o.* *b*) 100 mg/kg *p.o.*

7. Effect on Body Temperature

The hypothermic effect of five compounds (**13**, **14**, **15**, **17**, and **20**) and Methaqualone is shown in Fig. 2. The compound (**14**), with an oral dose of 50 mg/kg, remarkably reduced the body temperature of mice and the effect continued for more than 3 hr. Four other compounds and Methaqualone also showed a weak hypothermic effect, though the time course of fall in temperature was similar.

Discussion

In 1957, Gujral and his co-workers[3a] reported that some of the derivatives of 4(3*H*)-quinazolinone exhibited a potent hypnotic action in animals. Since then, a large number of studies on the syntheses and hypnotic activities of 2,3-disubstituted quinazolinones have been carried out, but there have been very few studies on 2-heterocyclic derivatives. 2-Heterocyclic ethenyl-3-aryl-4(3*H*)-quinazolinones, prepared by the condensation of Methaqualone with appropriate compounds having an aldehyde, was reported to have similar but weaker activities and stronger toxicity[6] than Methaqualone.

Grishina[12] referred to the structure-activity relationship of a series of halogen substituted 4(3*H*)-quinazolinones, and stated that methyl group at 2 position is essential for the activity and, in addition, an *o*-chlorophenyl or *o*-bromophenyl group must be present at 3 position.

In connection with the above findings, the present study was carried out for evaluation of pharmacological activities with particular reference to the hypnotic effect of a series of newly synthesized 4(3*H*)-quinazolinones having a pyridyl group (2-, 3-, and 4-) at 2 position of the quinazolinone ring.

Attempts were made to determine whether and, if any, to what kind of the pyridyl group at 2 position and of aryl group at 3 position in the 4(3*H*)-quinazolinone ring might affect the pharmacological effect.

Hypnotic effect and other related pharmacological activities of 30 analogues were investigated and compared with those of Methaqualone, and the following structure-activity relationship was established.

1) The compound (**24**), having a quinolyl substituent at 2 position, is almost inactive. The compounds (**1** and **13**) possessing both pyridyl and phenyl substituents at 2 and 3 position, respectively, show a weak activity. 4-Pyridyl has a stronger potency for activities than 2-pyridyl group at 2 position.

2) There seems to be a tendency of augmentation of pharmacological activities when an *o*-methyl group is introduced into the phenyl substituent at 3 position (*e.g.*, compounds **2**, **14**, and **20**). In contrast, an introduction of a *m*- or *p*-methyl group to the same position (*e.g.*, compounds **3**, **4**, **15**, and **16**) markedly diminished the activities compared to the original compounds (**1** and **3**). The potency of activities produced by the difference in position of methyl group in phenyl ring at 3 position decreases in the order of 4-pyridyl, *o*-tolyl>3-pyridyl, *o*-tolyl>2-pyridyl, *o*-tolyl.

3) Introduction of one of other substituents such as alkoxy, halogen, and so forth to the phenyl group at 3 position decreases the pharmacological activities.

4) The anthranilates of 4(3*H*)-quinazolinone are quite inactive.

5) Substitution of 2 position by a pyridyl group remarkably increases the pharmacological activities and is stronger than at 3 position.

6) It is concluded that a maximum hypnotic activity with some pharmacological properties will be found in structures like 2-(4-pyridyl)-3-*o*-tolyl-4(3*H*)-quinazolinone (**14**), which is equal to or more potent than Methaqualone in mice.

Experimental

Method A. General Method

A mixture of 1.9 g (0.02 mole) of methylpyridine, 0.02 mole of an aromatic amine, 2.7 g (0.02 mole) of anthranilic acid, and 1.9 g (0.06 mole) of sulfur was refluxed at 195—200° for 8 hr. The reaction mixture was cooled, dissolved in 40 ml of $CHCl_3$, and the solution was purified by chromatography (Al_2O_3) using benzene as eluent. The product was recrystallized from petr. benzin (or petr. benzin–benzene) to colorless crystals (**1**—**8**, **13**—**18**, and **24**) in about 30—40% yields (Table I).

2-(2-Pyridyl)-3-phenyl-4(3*H*)-quinazolinone (**1**)——A mixture of 1.9 g (0.02 mole) of 2-picoline, 1.9 g (0.02 mole) of aniline, 2.7 g (0.02 mole) of anthranilic acid, and 1.9 g (0.06 mole) of sulfur was heated at 195—200° for 8 hr. The mixture was cooled, dissolved in 40 ml of $CHCl_3$, and then applied to the top of a column packed with 70 g of Al_2O_3 (300 mesh). The product (**1**) was eluted with benzene. The fraction eluted was evaporated in vacuum. Resulting solid was recrystallized from petr. benzin to 2.1 g (36.7%) of colorless amorphous substance, mp 162° (reported,[8] 153°). *Anal.* Calcd. for $C_{19}H_{13}ON_3$: C, 76.25; H, 4.35; N, 14.05. Found: C, 76.23; H, 4.51; N, 13.83.

Other compounds (**2**—**8**, **13**—**18**, and **24**) were prepared similarly by the above procedure.

12) V.M. Grishina, *Tr. Perm. Farm. Inst.*, **1969**, 9 [*C.A.*, **71**, 20638 (1969)].

Method B. General Method

A mixture of 0.0175 mole of thioanilides,[13] 1.4 g (0.01 mole) of anthranilic acid, and 1.5 g (0.01 mole) of methyl anthranilate was heated at 190—195° for 8 hr. After the reaction had been completed, the reaction mixture was dissolved in 30 ml of $CHCl_3$ and then kept overnight up at below 5°. Separated crystals were filtered by suction, the filtrate was applied to the top of a column packed with 50 g of Al_2O_3 (300 mesh). The product was eluted with $CHCl_3$, was evaporated in vacuum and the resulting solid was recrystallized from benzene–petr. benzin to colorless crystals (**9**—**12**).

2,3-Di(2-pyridyl)-4(3*H*)-quinazolinone (**9**)——A mixture of 3.8 g (0.0175 mole) of 2-thiopicolinoyl-N-(2-pyridyl)amide, mp 83° (reported,[14] 82°) and 1.4 g (0.01 mole) of anthranilic acid was heated with 1.5 g (0.01 mole) of methyl anthranilate, and treated by the general procedure of method B. Colorless prisms 0.55 g (18.3%), mp 182°. IR (KBr): 1678 cm^{-1} ($\nu_{C=O}$). *Anal.* Calcd. for $C_{18}H_{12}ON_4$: C, 71.99; H, 4.03; N, 18.67. Found: C, 72.28; H, 4.27; N, 18.58. Mass Spectrum *m/e*: M^+ 300.

2-[2-(6-Methylpyridyl)]-3-phenyl-4(3*H*)-quinazolinone (**10**)——A mixture of 4.0 g (0.0175 mole) of 6-methyl-2-thiopicolinoylanilide[15] and 1.4 g (0.01 mole) of anthranilic acid was heated with 1.5 g (0.01 mole) of methyl anthranilate, treated by the general procedure of method B, and gave colorless prisms 1.05 g (33.5%), mp 142°. IR (KBr): 1673 cm^{-1} ($\nu_{C=O}$). *Anal.* Calcd. for $C_{20}H_{15}ON_3$: C, 76.68; H, 4.79; N, 13.42. Found: C, 76.82; H, 4.89; N, 12.95.

Other 2-(2-pyridyl) derivatives (**11**—**12**) were prepared by this procedure.

Method C

2-Amino-N-(*m*-chlorophenyl)benzamide——A mixture of 10.0 g (0.0613 mole) of isatoic anhydride and 8.6 g (0.0675 mole) of *m*-chloroaniline was heated at 120° in an oil bath for 4 hr. The product was recrystallized from EtOH to 8.5 g (56.4%) of colorless prisms, mp 130—132°. *Anal.* Calcd. for $C_{13}H_{11}ON_2Cl$: C, 63.31; H, 4.46; N, 11.36. Found: C, 63.20; H, 4.58; N, 11.50. Other N-substituted 2-aminobenzamides were prepared similarly.

2-Nicotinoylamino-N-(*m*-chlorophenyl)benzamide——To a solution of 2.8 g (0.02 mole) of nicotinoyl chloride dissolved in 15 ml of pyridine, a solution of 4.9 g (0.02 mole) of 2-amino-N-(*m*-chlorophenyl)benzamide dissolved in 10 ml of pyridine was added and the mixture was refluxed for 2 hr. After evaporation of the solvent *in vacuo*, water was added to the residue and the mixture was allowed to stand overnight. The separated colorless prisms were collected and recrystallized from EtOH to 2.8 g (39.8%) of colorless prisms, mp 186—188°. *Anal.* Calcd. for $C_{19}H_{14}O_2N_3Cl$: C, 64.88; H, 4.01; N, 11.95. Found: C, 64.75; H, 3.88; N, 11.70.

Other N-substituted 2-nicotinoylaminobenzamide were prepared similarly.

2-(3-Pyridyl)-3-(*m*-chlorophenyl)-4(3*H*)-quinazolinone (**22**)——To a solution of 3.5 g (0.01 mole) of 2-nicotinoylamino-N-(*m*-chlorophenyl)benzamide dissolved in 50 ml of dry xylene, a solution of 0.48 g (0.0035 mole) of PCl_3 in 10 ml of dry xylene was added dropwise and the mixture was refluxed for 4 hr. The coloed reaction mixture was filtered by suction, the filtrate was washed with 5% Na_2CO_3 solution, and the xylene layer was dried and concentrated under vacuum. The crystals obtained were recrystallized from petr. benzin–benzene to 2.5 g (75.1%) of colorless prisms, mp 224°. *Anal.* Calcd. for $C_{19}H_{12}ON_3Cl$: C, 68.37; H, 3.63; N, 12.59. Found: C, 68.67; H, 3.57; N, 12.73.

The compounds **19**—**23** were prepared similarly.

Method D. General Method

Anthranilates of 4(3*H*)-Quinazolinones (**25**—**30**)——A solution of 0.7 g (0.005 mole) of anthranilic acid, 0.005 mole of appropriate 4(3*H*)-quinazolinone, and 20 ml of EtOH was refluxed for 1 hr on a steam bath, and the solvent was evaporated. The resulting residue was recrystallized from EtOH to give anthranilate of 4(3*H*)-quinazolinones as colorless crystals in about 90% yield.

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