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Studies on biologically Active Halogenated Compounds. II.[1] Chemical Modifications of 6-Amino-2-fluoromethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone and the CNS Depressant Activities of Related Compounds

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A number of derivatives of 6-amino-2-fluoromethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (**15**), a potent muscle relaxant, have been prepared and screened in terms of the loss of righting reflex test and the rotating rod test in mice. Several derivatives with additional fluorine substitution or with repositioning of the fluorine atom exhibited high activities. Other structural modifications included acylation, carbamoylation, and alkoxycarbonylation of the 6-amino group, hydroxylation at the 3-tolyl group, and replacement of the fluorine atom at the 2-fluoromethyl group by oxygen, nitrogen, and sulfur nucleophiles; these modifications all resulted in loss of activity.

Keywords——4-(3*H*)-quinazolinone; 6-aminomethaqualone derivatives; fluorination; CNS depressant activity; structure–activity relationship

In the previous paper in this series[1] we reported the syntheses and CNS depressant activities of some 2-fluoromethyl-3-aryl-4(3*H*)-quinazolinones and showed that the introduction of a fluorine atom into the 2-methyl group of 2-methyl-3-aryl-4(3*H*)-quinazolinones (which are known to have CNS depressant activity) brought about a dramatic reduction of toxicity and/or enhancement of the activity. The most interesting compound is 6-amino-2-fluoromethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (**15**), which exhibits equipotent muscle relaxing activity and markedly reduced toxicity compared to the parent compound, 6-amino-2-methyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (6-aminomethaqualone).[3a,b] We therefore attempted to prepare more potent muscle relaxants by structural modifications of **15** as follows: (1) repositioning of the fluorine atom and additional fluorine substitution, (2) modification of the 6-amino group, (3) hydroxylation at the tolyl group, and (4) replacement of the fluorine atom by oxygen, nitrogen, and sulfur nucleophiles. By repositioning the fluorine atom and introducing additional fluorine substitution, we hoped to modify the physicochemical properties without significantly changing the size of the molecule, possibly resulting in improved therapeutic properties. By modification of the 6-amino group we hoped to facilitate biological transport and to increase the duration of the activity.

As regards modification of the amino group of 6-aminomethaqualone,[3a] Breuer and co-workers have synthesized several short chain acyl derivatives and some miscellaneous derivatives which generally exhibited delayed and lower activity compared with the parent compound. Therefore, our efforts were directed mainly towards acylation with longer acyl groups, carbamoylation, and alkoxycarbonylation of **15**. N-methyl and N,N-dimethyl derivatives of **15** were also prepared in this study. The biotransformation of methaqualone has

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1) For part I, see J. Tani, Y. Yamada, T. Oine, T. Ochiai, R. Ishida, and I. Inoue, *J. Med. Chem.*, **22**, 95 (1979).

2) Location: *16-89 Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan.*

3) *a*) H. Breuer and A. Roesch, *Arzneim.-Forsch.*, **21**, 238 (1971); *b*) E. Roesch, A. Roesch, G. Hofrichter, and G. Schenk, *ibid.*, **21**, 362 (1971).

been extensively studied by Preuss and co-workers.[4] They have identified several hydroxylated quinazolones as metabolites. In the case of 6-aminomethaqualone,[3a] similar metabolites have been isolated and shown to retain a slightly decreased activity. We therefore synthesized some hydroxy derivatives **14c**—**e**, which are possible metabolites of **15**. Replacements of the fluorine atom with nitrogen, oxygen, and sulfur nucleophiles were also attempted.

In this paper we describe the synthesis of such derivatives of 6-amino-2-fluoromethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (**15**) and their pharmacological activities.

Chemistry

The 6-aminoquinazolones **3** and **5** with an additional fluorine atom on the 2-methyl group were prepared as shown in Chart 1. The starting material **1** was easily prepared in two steps *via* catalytic reduction of 2-amino-5-nitrobenz-*o*-toluidide followed by selective monoacetylation[5] of the 5-amino group. The 2-trifluoromethyl derivative **3** was prepared by trifluoroacetylation of **1** with trifluoroacetic anhydride, followed by ring closure with boron trifluoride etherate in boiling acetic acid. Treatment of **2a** with 10% hydrogen chloride in methanol afforded **3** in 52% overall yield from **1**. In the case of **5**, introduction of fluorine atoms was accomplished by the halogen-exchange reaction of the 2-dichloromethyl derivative **2b** with cesium fluoride. Synthesis of 6-amino-2-fluoromethyl-3-(*o*-trifluoromethylphenyl)-4-(3*H*)-quinazolinone (**9a**) was achieved by a series of reactions starting from 2-amino-5-nitrobenz-(*o*-trifluoromethyl)anilide (**6a**). The fluoroacetylation of **6a** ($R^2=CF_3$, $R^3=R^4=H$) was

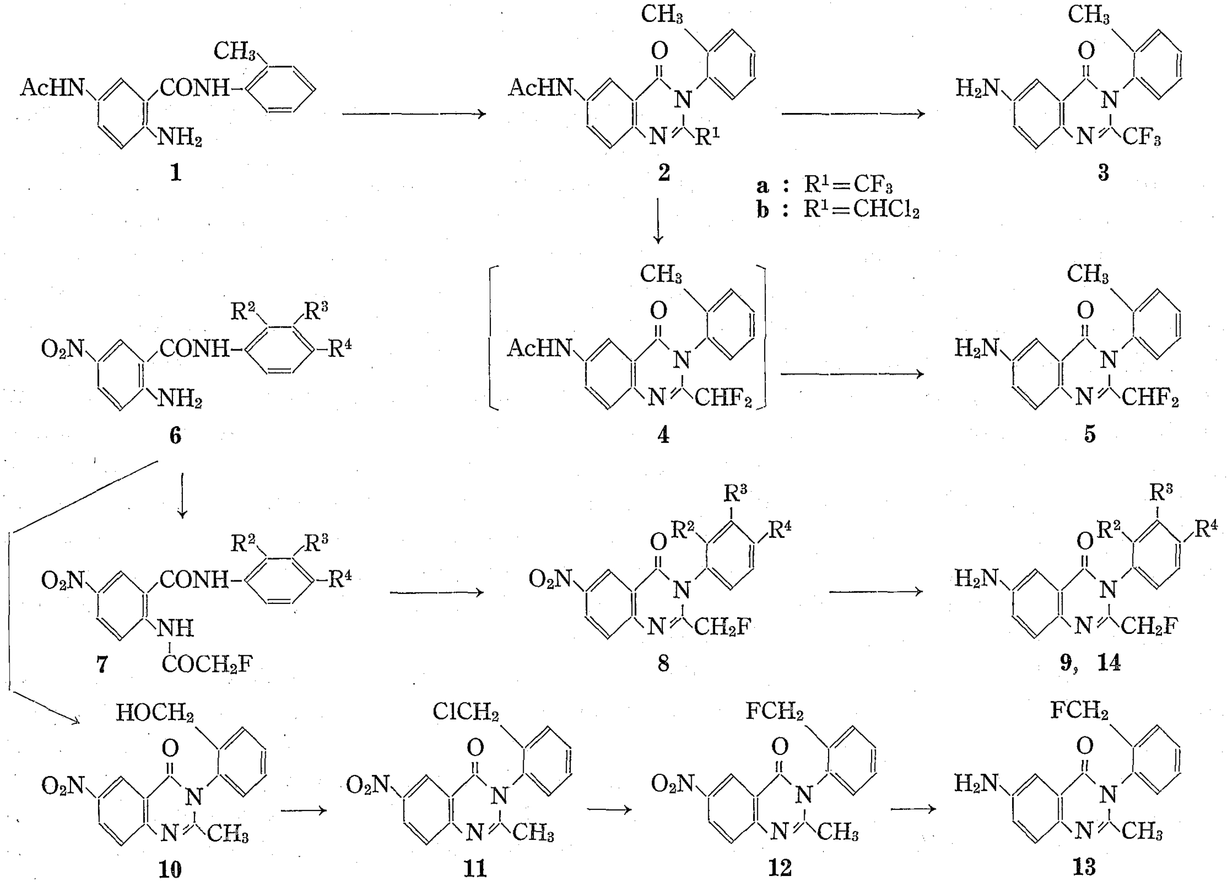

Chart 1

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[4] F.R. Preuss, H. Hoffmann-Pinther, H. Achenbach, and H. Friebolin, *Arzneim.-Forsch.*, **20**, 752 (1970) and references cited therein.

[5] Experimental details were described in the previous paper in this series.

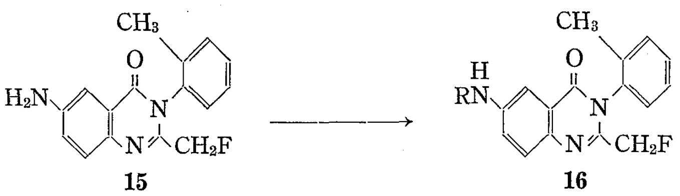


Chart 2

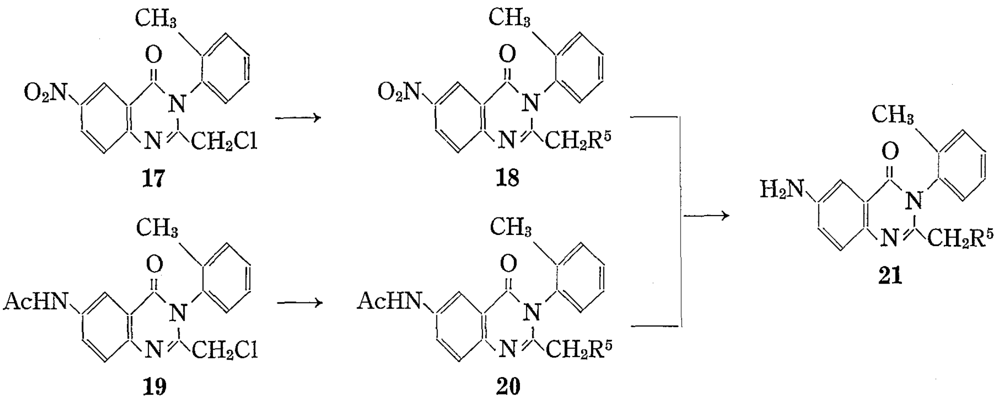
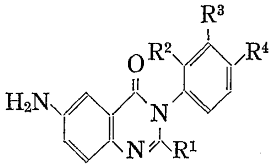


Chart 3

TABLE I. Fluorinated 6-Amino-3-aryl-2-methyl-4(3*H*)-quinazolinones



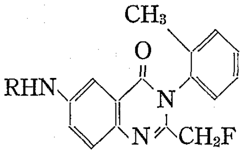
Compd. No.	R^1	R^2	R^3	R^4	Yield (%)	mp (°C)	Recryst. solv.[b)]	Formula	Analysis (%) Calcd. (Found) C	H	N
3	CF_3	CH_3	H	H	84	187—189	—[c)]	$C_{16}H_{12}F_3N_3O$	60.19 (60.09	3.79 3.84	13.16 13.03)
5	CHF_2	CH_3	H	H	42	168—170	A	$C_{16}H_{13}F_2N_3O$	63.78 (63.65	4.35 4.37	13.95 13.85)
9a	CH_2F	CF_3	H	H	70	233—234	B	$C_{16}H_{11}F_4N_3O$	56.98 (57.00	3.29 3.38	12.46 12.40)
9b	CH_2F	CH_5	H	Br	80	193—195	A	$C_{16}H_{13}BrFN_3O$	53.05 (52.71	3.62 3.75	11.60 11.38)
13	CH_3	CH_2F	H	H	58	157—160	A	$C_{16}H_{14}FN_3O$	67.83 (68.03	4.98 5.09	14.83 14.90)
14c	CH_2F	CH_2OH	H	H	50	170—172	C	$C_{16}H_{14}FN_3O_2$	64.20 (64.00	4.70 4.89	14.04 14.29)
14d	CH_2F	CH_3	OH	H	66	282—284[a)]	D	$C_{16}H_{14}FN_3O_2$	64.20 (63.68	4.70 4.91	14.04 13.85)
14e	CH_2F	CH_3	H	OH	66	233—234[a)]	A	$C_{16}H_{14}FN_3O_2$	64.20 (63.94	4.70 4.96	14.04 13.94)

a) Decomposition.
b) A=2-propanol; B=EtOH; C=THF; D=MeOH
c) Not recrystallized.

conducted in tetrahydrofuran in the presence of pyridine to give **7a** in 77% yield. Cyclization was accomplished by treating **7a** with acetic anhydride in boiling acetic acid to afford **8a** in good yield. The nitro group could be reduced selectively with stannous chloride in aqueous methanol below 25°.

The hydroxylated compounds **14c**—**e** were prepared in a similar way, followed by an additional step for removal of the fluoroacetyl group from the fluoroacetoxy group which was formed concomitantly during fluoroacetylation of the amino nitrogen. Cleavage of the fluoroacetoxy group could be easily performed by methanolysis with 10% methanolic hydrogen chloride.

TABLE II. 2-Fluoromethyl-6-(substituted-amino)-3-(*o*-tolyl)-4(3*H*)-quinazolinones (**16**)

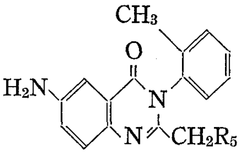


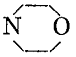
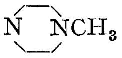
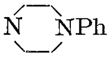
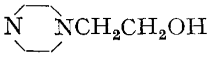
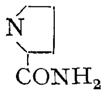
Compd. No.	R	Yield (%)	mp (°C)	Recryst. Solv.[a]	Formula	Analysis (%) Calcd. (Found) C	H	N
16a	HCO	95	255—258	A	$C_{17}H_{14}FN_3O_2$	65.59 (65.67	4.53 4.80	13.50 13.52)
16b	CH_3CO	89	239—241	B	$C_{18}H_{16}FN_3O_2$	66.45 (66.37	4.96 5.09	12.92 12.98)
16c	C_3H_7CO	44	94—98	C	$C_{20}H_{20}FN_3O_2 \cdot H_2O$	64.68 (64.78	5.97 6.21	11.31 11.53)
16d	C_4H_9CO	88	208—210	D	$C_{21}H_{22}FN_3O_2$	68.65 (68.49	6.04 6.44	11.44 11.38)
16e	C_4H_9CO (iso)	66	179—181	D	$C_{21}H_{22}FN_3O_2$	68.65 (68.76	6.04 6.40	11.44 11.62)
16f	C_4H_9CO (*t*)	93	122—125	—[b]	$C_{21}H_{22}FN_3O_2$	68.14 (68.05	7.39 6.98	10.60 10.58)
16g	$C_5H_{11}CO$	93	125—127	E	$C_{22}H_{24}FN_3O_2$	69.27 (69.27	6.34 6.49	11.02 11.04)
16h	$C_9H_{19}CO$	92	80—82	D	$C_{26}H_{32}FN_3O_2$	71.37 (71.29	7.37 7.42	9.60 9.50)
16i	$C_{17}H_{35}CO$	47	98—102	F	$C_{34}H_{48}FN_3O_2$	74.28 (74.40	8.80 8.91	7.64 7.67)
16j	C_2H_5NHCO	29	221—222	A	$C_{19}H_{19}FN_4O_2$	64.39 (64.22	5.40 5.53	15.81 15.81)
16k	C_6H_5NHCO	29	244—246	G	$C_{23}H_{19}FN_4O_2$	68.65 (68.54	4.76 5.04	13.92 13.64)
16l	$C_{18}H_{37}NHCO$	29	116—118	D	$C_{35}H_{51}FN_4O_2$	72.63 (72.96	8.88 9.18	9.68 9.76)
16m	C_2H_5OCO	78	178—180	D	$C_{19}H_{18}FN_3O_3$	64.22 (64.14	5.11 5.33	11.83 11.95)
16n	$C_5H_{11}OCO$	81	177—178	D	$C_{22}H_{24}FN_3O_3$	66.48 (66.62	6.09 6.31	10.57 10.63)
16o	$C_{18}H_{37}OCO$	78	114—116	D	$C_{35}H_{50}FN_3O_3$	72.50 (72.71	8.69 8.76	7.25 7.28)
16p	CH_3	19	208—210	D	$C_{17}H_{16}FN_3O$	68.67 (68.37	5.42 5.95	14.13 14.33)
16q	$(CH_3)_2$	26	180—182	D	$C_{18}H_{18}FN_3O$	69.44 (69.31	5.83 6.03	13.50 13.60)

[a] A=MeOH; B=EtOH; C=EtOH–H_2O; D=2-propanol; E=2-propanol–diisopropyl ether; F=*n*-hexane; G=DMF–EtOH.

[b] Triturated with diisopropyl ether. The analysis data were consistent with calculated values for $C_{21}H_{22}FN_3O_2 \cdot 0.25\,(iso\text{-}C_3H_7)_2O \cdot 0.2H_2O$.

Table III. 6-Amino-2-(substituted-methyl)-3-(*o*-tolyl)-4(3*H*)-quinazolinones (**21**)



Compd. No.	R^5	Method[a]	Yield (%)	mp (°C)	Recryst. solv.[b]	Formula	Analysis (%) Calcd. (Found) C	H	N
21a	$OCOCH_3$	F	66	198—201[c]	—[d]	$C_{18}H_{17}N_3O_3$[f]	60.09 (59.94	5.04 5.07	11.68 11.71)
21b	$OCOC_4H_9$	F	50	229—230[c]	A	$C_{21}H_{23}N_3O_3$[f]	62.76 (63.04	6.02 6.15	10.46 10.56)
21c	$OCOC_{15}H_{31}$	F	63	180—185[c]	B	$C_{32}H_{45}N_3O_3$[f]	69.11 (68.92	8.34 8.37	7.56 7.59)
21d	OCOPh	F	85	176—179	B	$C_{23}H_{19}N_3O_3$	71.67 (71.36	4.97 5.19	10.90 10.75)
21e		F	90	202—203	B	$C_{21}H_{24}N_4O$	72.38 (72.13	6.94 6.87	16.08 16.10)
21f		F	73	136—138[e]	C	[g]	52.54 (52.83	5.16 5.13	10.22 10.38)
21g		F	83	219—221	C	$C_{20}H_{23}N_5O$	68.74 (68.50	6.63 6.81	20.04 19.84)
21h		F	76	175—177	—[d]	$C_{21}H_{25}N_5O$	69.39 (68.67	6.93 6.99	19.27 18.68)
21i		F	82	204—205	B	$C_{26}H_{27}N_5O$	73.38 (72.96	6.40 6.58	16.46 16.21)
21j		F	80	205—207	B	$C_{22}H_{27}N_5O_2$	67.15 (67.06	6.92 7.04	17.80 17.45)
21k	$N(C_2H_5)_2$	G	81	142—144	E	$C_{20}H_{24}N_4O$	71.40 (71.00	7.19 7.11	16.66 16.48)
21l		G	94	153—154[e]	D	[h]	54.13 (54.30	5.30 5.33	10.52 11.01)
21m	$N(CH_2CH_2OCH_3)_2$	G	66	227—230[c]	F	$C_{22}H_{28}N_4O_3$[i]	56.28 (55.99	6.44 6.66	11.94 12.10)
21n	$N(CH_2CH_2OH)_2$	G	89	189—191	B	$C_{20}H_{24}N_3O_3$	65.20 (65.12	6.57 6.58	15.21 15.09)
21o	$NHCH_2CH_2OCH_3$	G	86	161—163	B	$C_{19}H_{22}N_4O_2$	67.43 (67.18	6.55 6.65	16.56 16.34)
21p	$NHCH_2CH_2OH$	G	61	245—248[c]	F	$C_{18}H_{20}N_4O_2$[j]	53.21 (53.65	6.16 5.66	13.79 14.07)
21q	$NHCH_2CO_2H$	H	37	163—165	G	$C_{18}H_{18}N_4O_3$[k]	62.23 (62.29	5.51 5.88	16.13 16.28)
21r		G	76	233—235[c]	A	$C_{21}H_{23}N_5O_2$[l]	51.75 (51.61	5.58 5.84	14.37 14.36)
21s	SPh	G	66	160—165[c]	B	$C_{22}H_{19}N_3OS$[f]	64.45 (64.61	4.92 5.16	10.25 10.20)
21t	SC_2H_5	G	98	108—110[c]	B	$C_{18}H_{19}N_3OS$[m]	59.77 (59.45	6.17 6.40	10.72 10.34)
21u	OC_2H_5	G	86	191—193	B	$C_{18}H_{19}N_3O_2$	69.88 (69.74	6.19 6.30	13.58 13.43)
21v	OCH_2CH_2OH	G	37	131—136	D	$C_{18}H_{19}N_3O_3$[k]	64.65 (64.77	6.03 6.33	12.57 12.30)
21w	OH	G	48	233—235[c]	H	$C_{16}H_{15}N_3O_2$[i]	54.24 (53.77	4.85 5.03	11.87 11.79)

a) See "Experimental." *b*) A=MeOH–Et_2O; B=2-propanol; C=EtOH; D=DMF–EtOH; E=2-propanol–diisopropyl ether; G=EtOH–H_2O; H=10% HCl. *c*) Dec. of HCl-salt. *d*) Not recrystallized. *e*) Dec. of oxalate. *f*) Analyzed as HCl-salt. *g*) $C_{20}H_{22}N_4O_2 \cdot 2C_2H_2O_4 \cdot H_2O$. *h*) $C_{20}H_{22}N_4O \cdot 2C_2H_2O_4 \cdot H_2O$. *i*) Analyzed as 2HCl-salt. *j*) Analyzed as 2HCl-salt·0.5H_2O. *k*) Analyzed as hemihydrate. *l*) Analyzed as 2HCl-salt·2H_2O. *m*) Analyzed as HCl-salt·0.5 iso-C_3H_7OH.

Modifications of the 6-amino group were accomplished by treating **15** with acyl anhydrides, alkyl chloroformates, or alkyl isocyanates. 2-Fluoromethyl-6-methylamino-3-(*o*-tolyl)-4(3*H*)-quinazolinone (**16p**) was prepared by direct methylation of **15** with methyl iodide in the presence of sodium hydrogen carbonate in low yield. The 6-dimethylamino derivative **16q** was obtained *via* usual dimethylation with formic acid-formaldehyde.

Finally, the 6-aminoquinazolone derivatives **21** were prepared as shown in Chart 3. 6-Acetamido-2-chloromethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (**19**) was employed as a common intermediate for the preparation of the 2-alkoxy-, 2-substituted amino-, and 2-alkylthiomethyl derivatives **21k**—**w**. The 2-acyloxymethyl derivatives **21a**—**d** and some of the 2-substituted amino derivatives **21e**—**j** were prepared *via* 2-chloromethyl-6-nitro-3-(*o*-tolyl)-4(3*H*)-quinazolinone (**17**).[1]

Pharmacological Activity

The compounds described above were tested by intraperitoneal administration to mice for CNS depressant activity and acute toxicity according to the procedures described later. The results of loss of righting reflex tests and rotating rod tests, and the acute toxicities of representative derivatives are given in Table IV.

Replacement of one or two hydrogen atoms of the 2-fluoromethyl group of **15** by fluorine resulted in a slight decrease in the rotating rod test activity with almost no change in the

Table IV. Pharmacological Data. ED_{50} Values in Mice

Compd. No.	LD_{50}, mg/kg, *i.p.* (95% CL)[a]	ED_{50}, mg/kg, *i.p.*(95% CL)[a]		$\frac{LD_{50}}{RR, ED_{50}}$	$\frac{LRR, ED_{50}}{RR, ED_{50}}$
		LRR[b]	RR[c]		
15	315.4(265.5—373.8)	35.1(28.7—43.0)	15.6(12.1—20.2)	20.2	2.25
3	305.0(249.0—373.5)	24.9(20.3—30.5)	22.5(17.2—31.1)	13.5	1.10
5	337.5(265.0—429.8)	37.6(19.7—66.1)	24.1(12.4—46.8)	14.0	1.58
9a	249.0(111.6—555.7)	31.6(25.1—38.4)	16.0(11.2—21.9)	15.6	1.98
9b	225.0(168.9—299.9)	18.3(11.4—29.2)	14.0(7.2—27.2)	14.0	1.29
13	82.7(74.1—94.5)	44.9(40.8—49.0)	33.7(25.3—45.0)	2.4	1.33
14c	>300	—[d]	40.7(27.1—61.0)		
14d	>300	—	—		
14e	>300	—	—		
16a	>300	—	—		
16b	>300	—	—		
16c	>300	—	81.6(54.6—128.9)		
16d	>300	—	—		
16j	>300	—	—		
16m	>300	—	—		
21a	100[e]	—	—		
21e	100[e]	—	—		
21k	100[e]	—	—		
21l	150(125.8—179.9)	—	66.6(55.5—79.9)	2.2	
21g	>300	—	—		
21t	100[e]	—	—		
21u	100[e]	—	—		
21w	100[e]	54.3(26.1—98.8)	54.3(26.1—98.8)		
HB-218[f]	95.9(79.0—116.5)	28.1(22.4—34.8)	27.9(23.4—33.1)	3.4	1.01

a) Confidence limits for $p=95\%$.
b) Loss of righting reflux test.
c) Rotating rod test.
d) No action at a dose of half the maximal tolerable dose or 300 mg/kg, *i.p.*
e) Maximal tolerable dose.
f) This notation for 6-aminomethaqualone was used by Breuer.

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6) I.R. Ager, D.R. Harrison, P.D. Kennewell, and J.B. Taylor, *J. Med. Chem.*, **20**, 379 (1977).

acute toxicity. Activity in the loss of righting reflex test was slightly potentiated only in the 2-trifluoromethyl analog **3**. This is in marked contrast with the report[6] that the 2-trifluoromethyl analog of methaqualone is devoid of hypnotic activity. Compound **13** exhibited significant decreases in activity in both tests and a marked increase in acute toxicity. Compounds **9a** and **9b** both exhibited high activity, similar to that of **15**, in the rotating rod test, and even higher activity in the loss of righting reflex test. However, their acute toxicities were also higher. Thus the ratios LD_{50}/ED_{50} in the rotating rod test of these compounds were smaller than that of **15**. Replacement of the fluorine atom of the 2-fluoromethyl group by heteroatom groups generally resulted in loss of activity and enhancement of acute toxicity. The introduction of a hydroxy group at the 3-phenyl group and modification of the 6-amino group caused dramatic decreases in the activities.

The above results show that the size of the 2-substituent has a marked influence on the CNS depressant activity. In addition, it is clear that the 6-amino group is essential for the activity.

Experimental

Chemistry

All melting points are uncorrected. The ^{1}H-nuclear magnetic resonance (^{1}H NMR) spectra were recorded with a Hitachi Perkin-Elmer R20A spectrometer and are reported in parts per million downfield from tetramethylsilane as an internal standard.

6-Acetamido-3-(*o*-tolyl)-2-trifluoromethyl-4(3*H*)-quinazolinone (2a)——Trifluoroacetic anhydride (4.5 g, 21.2 mmol) was added to a solution of 2-amino-5-acetamidobenz-*o*-toluidide (**1**, 3.0 g, 10.6 mmol) in THF (100 ml) at 0°. This mixture was warmed to room temperature and stirred for 3 hr. The reaction mixture was concentrated to dryness *in vacuo*, then the residue was treated with $BF_3\cdot$ether (2.0 g) in AcOH (50 ml) at reflux temperature for 1 hr. The mixture was concentrated to dryness *in vacuo*. The residue was triturated with H_2O and with 2-propanol to give 2.4 g (62.7%) of **2a**: mp 266—268°. Recrystallization from EtOH–DMF afforded an analytical sample as colorless leaflets: mp 267—268°; NMR (DMSO-d_6) δ: 2.10 (s, 3H), 2.17 (s, 3H), 7.46 (s, 4H), 7.90 (d, $J=9$ Hz, 1H), 8.19 (d.d, $J=9$ Hz, $J'=2$ Hz, 1H), 8.60 (d, $J'=2$ Hz, 1H), 10.56 (s, 1H). *Anal.* Calcd. for $C_{18}H_{14}F_3N_3O_2$: C, 59.83; H, 3.90; N, 11.63; F, 15.78. Found: C, 59.64; H, 3.97; N, 11.60; F, 15.50.

6-Amino-3-(*o*-tolyl)-2-trifluoromethyl-4(3*H*)-quinazolinone (3)——A suspension of **2a** (1.5 g) in 15% HCl–MeOH (30 ml) was refluxed for 30 min. The mixture was concentrated to dryness and the residue was mixed with 5% aqueous $NaHCO_3$ solution. The mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was dried and evaporated. Crystallization of the residue from 2-propanol gave 1.1 g of crude product. This was purified by silica gel column chromatography using $CHCl_3$ to give 0.85 g (93%) of **3**: mp 187—189°; NMR ($CDCl_3$) δ: 2.12 (s, 3H), 4.10 (br, 2H), 7.0—7.9 (m, 7H).

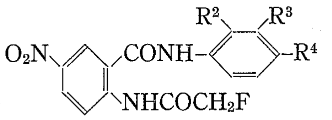
6-Acetamido-2-dichloromethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (2b)——Dichloroacetyl chloride (3.5 g) was added dropwise to a suspension of **1** (3.4 g, 0.012 mol) in AcOH (70 ml) at room temperature. The reaction mixture became clear, and then fresh crystals precipitated. After stirring for 1 hr, a further portion (1.0 g) of dichloroacetyl chloride was added, and the mixture was stirred at room temperature for 1 hr. $BF_3\cdot$ether (3 ml) was added to the reaction mixture. After refluxing for 1 hr, the solvent was removed under reduced pressure and the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried ($MgSO_4$), and concentrated to dryness. The residue was triturated with 2-propanol and the crystals were collected by filtration to give crude **2b** (3.6 g): mp 242—245°. Recrystallization from 2-propanol gave analytically pure **2b** (3.26 g, 72.5%): mp 248—250°; NMR ($CDCl_3$+DMSO-d_6) δ: 2.15 (s, 6H), 6.13 (s, 1H), 7.2—7.6 (m, 4H), 7.83 (d.d, $J=9$ Hz, $J'=2$ Hz, 1H), 8.3—8.55 (m, 2H), 9.80 (s, 1H). *Anal.* Calcd. for $C_{18}H_{15}Cl_2N_3O_2$: C, 57.46; H, 4.02; N, 11.17; Cl, 18.85. Found: C, 57.26; H, 4.27; N, 11.16; Cl, 18.67.

6-Amino-2-difluoromethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (5)——A mixture of **2b** (3.0 g, 8 mmol), CsF (6.0 g), and diethyleneglycol (30 ml) was stirred at 160—165° for 4 hr. A further portion of CsF (2.0 g) was added to the mixture, and stirring was continued at the same temperature for a further 2 hr. After cooling, the reaction mixture was poured into H_2O (150 ml) and extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried ($MgSO_4$), and concentrated to dryness. The residue was treated with 10% HCl–MeOH (40 ml) at room temperature for 4 hr. The reaction mixture was concentrated to dryness and the residue was dissolved in H_2O, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The $CHCl_3$ layer was dried ($MgSO_4$) and concentrated to dryness. The residue (2.4 g) was purified by silica gel column chromatography using C_6H_6–THF (75:25). Appropriate fractions were combined and concentrated under reduced pressure. The residue was triturated with diisopropyl ether and the crystals were collected by filtration to give 1.0 g (42%) of crude **5**. Recrystallization from 2-propanol yielded an analytically pure sample (0.6 g): mp 168—170°; NMR ($CDCl_3$) δ: 2.11 (s, 3H), 4.15 (br. s, 2H), 6.18 (t, $J_{H-F}=53$ Hz, 1H), 6.9—7.8 (m, 7H).

General Procedure for the Preparation of 2-Fluoroacetamido-5-nitrobenzanilide Derivatives (7). A Typical Example: 2-Fluoroacetamido-5-nitrobenz-*o*-trifluoromethylanilide (7a)——A solution of fluoroacetyl chloride (3.5 g, 0.036 mol) in THF (20 ml) was added to a solution of 2-amino-5-nitrobenz-*o*-trifluoromethylanilide (7.9 g, 0.024 mol) and pyridine (3.2 g, 0.4 mol) in THF (100 ml) at 0—5° over a period of 1.5 hr. The reaction mixture was stirred at the same temperature for 1 hr and then at room temperature for another hour. The mixture was concentrated to dryness *in vacuo* and the residue was crystallized with H_2O. Crystals were collected by filtration and washed with 2-propanol (50 ml) to yield 9.1 g of crude product. Recrystallization from EtOH–DMF (10: 1) gave 7.1 g (76.6%) of **7a**: mp 215—217°; NMR (DMSO-d_6) δ: 5.08 (d, $J_{H-F}=47$ Hz, 2H), 7.40—8.00 (m, 4H), 8.35—9.00 (m, 3H), 10.97 (s, 1H), 11.93 (br. d, 1H).

Data for the anilides **7a—e** prepared as described above are listed in Table V.

TABLE V. 2-Fluoroacetamido-5-nitrobenzanilides (7)



Compd. No.	R^2	R^3	R^4	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
7a	CF_3	H	H	77	215—217a)	$C_{16}H_{11}F_4N_3O_4$	49.88 (50.11	2.88 2.91	10.91 11.06)
7b	CH_3	H	Br	76	250—253a)	$C_{16}H_{13}BrFN_3O_4$	46.84 (46.70	3.19 3.27	10.24 10.26)
7c	CH_2OCOCH_2F	H	H	55	208—209b)	$C_{18}H_{15}F_2N_3O_6$	53.07 (53.00	3.71 3.92	10.32 10.75)
7d	CH_3	$OCOCH_2F$	H	82	238—240b)	$C_{18}H_{15}F_2N_3O_6$	53.07 (52.69	3.71 4.09	10.32 10.54)
7e	CH_3	H	$OCOCH_2F$	60	224—226a)	$C_{18}H_{15}F_2N_3O_6$	53.07 (53.02	3.71 3.91	10.32 10.16)

a) Recrystallized from DMF–EtOH.
b) Recrystallized from DMF–2-propanol.

General Procedure for the Preparation of 2-Fluoromethyl-6-nitro-3-(substituted-aryl)-4(3*H*)-quinazolinones (8). A Typical Example: 2-Fluoromethyl-6-nitro-3-(*o*-trifluoromethylphenyl)-4(3*H*)-quinazolinone (8a)——A mixture of **7a** (7.1 g), acetic anhydride (26 ml), and AcOH (40 ml) was refluxed for 5 hr. A further portion (26 ml) of Ac_2O was then added to the reaction mixture. After refluxing overnight, the mixture was concentrated to dryness *in vacuo* and the residual crystals were collected by filtration. The crystals were washed with 2-propanol, dried, and recrystallized from EtOH–DMF (2: 1) to give **8a** (4.1 g, 60.5%) as yellow prisms: mp 217—219°: NMR (DMSO-d_6) δ: 5.15 (d, $J_{H-F}=47$ Hz, 2H), 7.0—8.23 (m, 5H), 8.60—8.96 (m, 2H).

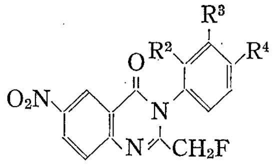
Data for the nitroquinazolinones **8a—e** prepared as described above are listed in Table VI.

General Procedure for the Preparation of 6-Amino-2-fluoromethyl-3-(substituted-aryl)-4(3*H*)-quinazolinones (9 and 14). A Typical Example: 6-Amino-2-fluoromethyl-3-(*o*-trifluoromethylphenyl)-4(3*H*)-quinazolinone (9a)——A solution of $SnCl_2 \cdot 2H_2O$ (9.0 g, 0.04 mol) in conc.HCl (9 ml) was added to a suspension of **8a** (3.67 g, 0.01 mol) in MeOH (100 ml) at 0—5° over a period of 40 min. The mixture was stirred at room temperature overnight and then diluted with H_2O (400 ml). This solution was neutralized with $NaHCO_3$ and extracted with $CHCl_3$ (500 ml). The $CHCl_3$ extract was dried ($MgSO_4$) and concentrated to dryness *in vacuo*. The residual crystals were triturated with 2-propanol and collected by filtration to give a crude product. Recrystallization from EtOH gave **9a** (2.25 g, 70%) as pale yellow prisms: mp 233—234°; NMR (DMSO-d_6) δ: 5.00 (d, $J_{H-F}=48$ Hz, 2H), 5.90 (br.s, 2H), 7.10—8.17 (m, 7H).

Data for the aminoquinazolinones **9a, b** and **14c—e** prepared as described above are listed in Table I.

3-(*o*-Hydroxymethylphenyl)-2-methyl-6-nitro-4(3*H*)-quinazolinone (10)——A mixture of 2-amino-5-nitrobenz-*o*-hydroxymethylanilide (12.6 g) and acetic anhydride (120 ml) was refluxed for 9 hr. The mixture was concentrated to dryness *in vacuo* and the residual crystals were collected by filtration to give a crude product (8.2 g). Recrystallization from EtOH (250 ml) gave 3-(*o*-acetoxymethylphenyl)-2-methyl-6-nitro-4(3*H*)-quinazolinone (6.3 g, 40.6%) as pale yellow leaflets: mp 157—160°; NMR (DMSO-d_6) δ: 1.90 (s, 3H), 2.21 (s, 3H), 4.93 (s, 2H), 7.50—7.75 (m, 4H), 7.87 (d, $J=9$ Hz, 1H), 8.57 (d.d, $J=9$ Hz, $J'=3$ Hz, 1H), 8.80

Table VI. 3-Aryl-2-fluoromethyl-6-nitro-4(3*H*)-quinazolinones (**8**)



Compd. No.	R^2	R^3	R^4	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
8a	CF_3	H	H	61	217—219[a)]	$C_{16}H_9F_4N_3O_3$	52.33 (52.25	2.47 2.51	11.46 11.50)
8b	CH_3	H	Br	71	210—213[a)]	$C_{16}H_{11}BrFN_3O_3$	49.00 (48.78	2.83 3.00	10.72 10.59)
8c	CH_2OCOCH_2F	H	H	75	150—153[b)]	$C_{18}H_{13}F_2N_3O_5$	55.53 (55.67	3.36 3.58	10.79 11.10)
8d	CH_3	$OCOCH_2F$	H	82	191—193[b)]	$C_{18}H_{13}F_2N_3O_5$	55.53 (55.42	3.36 3.62	10.79 10.95)
8e	CH_3	H	$OCOCH_2F$	73	172—175[a)]	$C_{18}H_{13}F_2N_3O_5$	55.53 (55.42	3.36 3.55	10.79 10.70)

a) Recrystallized from DMF–EtOH.
b) Recrystallized from DMF–2-propanol.

(d, $J'=3$ Hz, 1H). *Anal.* Calcd. for $C_{18}H_{15}N_3O_5$: C, 61.19; H, 4.28; N, 11.89. Found: C, 61.09; H, 4.39; N, 11.81.

The above product (3.93 g, 0.011 mol) was treated with 10% HCl–MeOH (150 ml) at room temperature for 5 hr. The solution was concentrated to dryness *in vacuo* and the residue was triturated with MeOH. The crystals were collected by filtration to give crude **10**·HCl (3.5 g); recrystallization from MeOH (25 ml) afforded 2.84 g (73.5%) of **10**·HCl: mp 195—200°; NMR (DMSO-d_6) δ: 2.39 (s, 3H), 4.36 (s, 2H), 7.40—7.80 (m, 4H), 8.04 (d, $J=9$ Hz, 1H), 8.55—8.90 (m, 2H), 9.32 (s, 2H). *Anal.* Calcd. for $C_{16}H_{13}N_3O_4$·HCl: C, 55.26; H, 4.06; N, 12.08. Found: C, 55.68; H, 4.17; N, 12.17.

3-(*o*-Chloromethylphenyl)-2-methyl-6-nitro-4(3*H*)-quinazolinone (**11**)——A solution of $SOCl_2$ (2.86 g, 0.024 mol) in $CHCl_3$ (10 ml) was added to a solution of **10**·HCl (4.16 g, 0.012 mol) and pyridine (1.05 g, 0.013 mol) in $CHCl_3$ (50 ml) at 5—8° over a period of 5 min. The reaction mixture was stirred at room temperature for 3 hr and then concentrated to dryness *in vacuo*. The residue was triturated with cold H_2O and the crystals were collected by filtration. Recrystallization from 2-propanol (20 ml) gave 3.86 g (97%) of **11**·HCl: mp 160—163°; NMR (DMSO-d_6) δ: 2.26 (s, 3H), 4.64 (d, $J=2$ Hz, 2H), 7.50—7.78 (m, 4H), 7.88 (d, $J=9$ Hz, 1H), 8.60 (d.d, $J=9$ Hz, $J'=3$ Hz, 1H), 8.83 (d, $J'=3$ Hz, 1H). This sample was used in the next step without purification.

3-(*o*-Fluoromethylphenyl)-2-methyl-6-nitro-4(3*H*)-quinazolinone (**12**)——A mixture of **11**·HCl (3.5 g, 0.0106 mol), KF (9.1 g, 0.157 mol), and ethyleneglycol (5 ml) was heated at 160—165° for 8 min. After cooling, the reaction mixture was added to H_2O and the precipitate was collected by filtration to give a crude product (3.7 g). Purification by silica gel column chromatography using C_6H_6–THF (8: 2) gave crude **12** (2.0 g), which was shown to be a mixture of **12** and unchanged **11** (2: 1) by NMR spectroscopy. This crude product was again treated with KF (5.0 g) and ethyleneglycol (2.5 ml) at 160—163° for 15 min, and the reaction mixture was worked up as described above to give 1.3 g (39.2%) of **12** as yellow prisms: mp 174—177°; NMR (DMSO-d_6) δ: 2.20 (s, 3H), 5.34 (d, $J_{H-F}=48$ Hz, 2H), 7.50—7.88 (m, 4H), 7.88 (d, $J=9$ Hz, 1H), 8.60 (d.d, $J=9$ Hz, $J'=3$ Hz, 1H), 8.81 (d, $J'=3$ Hz, 1H). *Anal.* Calcd. for $C_{16}H_{12}FN_3O_3$: C, 61.34; H, 3.86; N, 13.41; F, 6.06. Found: C, 61.59; H, 4.00; N, 13.41; F, 5.80.

6-Amino-3-(*o*-fluoromethylphenyl)-2-methyl-4(3*H*)-quinazolinone (**13**)——A solution of $SnCl_2·2H_2O$ (3.5 g, 0.0154 mol) was added to a solution of **12** (1.2 g, 3.8 mmol) in MeOH (35 ml) at 5—7°. After stirring at room temperature for 2.5 hr, the reaction mixture was poured into cold H_2O (150 ml) and neutralized with $NaHCO_3$. The mixture was extracted with $CHCl_3$ (250 ml), dried ($MgSO_4$), and concentrated to dryness *in vacuo*. The residue was subjected to silica gel column chromatography using C_6H_6–THF (8: 2) to afford crude **13**; recrystallization from 2-propanol gave 633 mg (58%) of **13** as yellow prisms: mp 157—160°; NMR (DMSO-d_6) δ: 2.03 (s, 3H), 5.20 (d, $J_{H-F}=48$ Hz, 2H), 5.60 (br.s, 2H), 7.0—7.80 (m, 7H).

General Procedure for the Preparation of 2-Fluoromethyl-3-(*o*-tolyl)-6-(substituted-amino)-4(3*H*)-quinazolinones (16). Typical Examples: (A) 6-Butyrylamino-2-fluoromethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (16c)——A mixture of **15** (2.83 g) and $(C_3H_7CO)_2O$ (2.4 g) was heated at 100° for 20 min. After cooling, the reaction mixture was washed with diisopropyl ether (100 ml) and the residue was triturated with MeOH–H_2O (2: 8). The crystals were collected by filtration to give 2.65 g of crude product. Recrystallization from 50% aqueous EtOH (35 ml) yielded 1.56 g (44%) of **16c** as colorless needles: mp 94—98°; NMR ($CDCl_3$) δ: 0.90 (t, $J=7$ Hz, 3H), 1.3—2.20 (m, 4H), 2.10 (s, 3H), 4.90 (d, $J_{H-F}=47$ Hz, 2H), 7.10—8.60 (m, 7H), 8.94 (s, 1H).

(B) 6-Ethylcarbamoylamino-2-fluoromethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (16j)——A solution of **15** (5.66 g, 0.02 mol) and EtNCO (1.8 g, 0.03 mol) in dioxane (30 ml) was heated at 100° overnight. After cooling, the precipitate was removed by filtration and the filtrate was concentrated to dryness *in vacuo*. The residue was triturated with 2-propanol (30 ml) and the crystals were collected by filtration to give a crude product (2.45 g). Repeated fractional crystallization from 2-propanol yielded 2.05 g (29%) of **16j** as colorless prisms: mp 219—222°. An analytical sample recrystallized from MeOH showed mp 221—222°; NMR ($CDCl_3$) δ: 0.93 (t, $J=7$ Hz, 3H), 2.13 (s, 3H), 2.92 (q, $J=7$ Hz, 2H), 4.90 (d, $J_{H-F}=47$ Hz, 2H), 5.40 (t, $J=7$ Hz, 1H), 7.20—7.95 (m, 6H), 8.36 (s, 1H), 8.56 (d.d, $J=9$ Hz, $J'=2$ Hz, 1H).

(C) 6-Ethoxycarbonylamino-2-fluoromethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (16m)——A solution of ethyl chloroformate (1.21 g, 0.011 mol) in THF (10 ml) was added to a solution of **15** (2.83 g, 0.01 mol) and pyridine (0.88 g, 0.011 mol) in THF (30 ml) at 5° over a period of 30 min. The mixture was stirred at the same temperature for 2 hr, then at room temperature for 1 hr. The reaction mixture was concentrated to dryness *in vacuo* and the residue was triturated with H_2O and diisopropyl ether. Crystals were collected by filtration to give a crude product (3.4 g), which upon recrystallization from 2-propanol (20 ml) yielded 2.77 g (78%) of **16m** as colorless leaflets: mp 178—180°; NMR ($CDCl_3$) δ: 1.06 (t, $J=7$ Hz, 3H), 2.10 (s, 3H), 4.20 (q. $J=7$ Hz, 2H), 4.90 (d, $J_{H-F}=47$ Hz, 2H), 7.10—8.05 (m, 7H), 8.12 (s, 1H).

General Procedure for the Preparation of 6-Nitro-2-(substituted-methyl)-3-(*o*-tolyl)-4(3*H*)-quinazolinones (18). Typical Examples: Method A. 2-Acetoxymethyl-6-nitro-3-(*o*-tolyl)-4(3*H*)-quinazolinone (18a)——A mixture of **17**[1)] (6.6 g, 0.02 mol), KOAc (9.8 g, 0.1 mol), and AcOH (100 ml) was refluxed for 16 hr. The reaction mixture was concentrated to dryness *in vacuo* and the residue was extracted with C_6H_6. The extract was washed with H_2O, dried ($MgSO_4$), and concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography using $CHCl_3$ to give 3.5 g (49.6%) of **18a**: mp 110—113°; NMR ($CDCl_3$) δ: 2.16 (s, 3H), 2.21 (s, 3H), 4.70 (s, 2H), 7.1—9.2 (m, 7H).

Method B. 6-Nitro-2-piperazinomethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (18g)——Piperazine 7.8 g (0.091 mol) was added to a solution of **17** (5 g, 0.015 mol) in THF (50 ml). The mixture was stirred at room temperature for 17 hr then warmed at 50—60° for 5 hr. The mixture was concentrated to dryness *in vacuo* and the residue was crystallized with H_2O. The crystals were collected by filtration, washed with MeOH, and dried to give a crude product (6.0 g): mp 196—200°. Recrystallization from DMF-EtOH (1: 1) gave 3.96 g (70%) of **18g** as colorless needles: mp 201—203°; NMR ($CDCl_3$) δ: 1.57 (s, 1H), 2.19 (s, 3H), 2.1—2.9 (m, 8H), 3.10 (d, $J=14$ Hz, 1H), 3.39 (d, $J=14$ Hz, 1H), 7.1—7.5 (m, 4H), 7.86 (d, $J=9$ Hz, 1H), 8.55 (d.d, $J=9$ Hz, $J'=2$ Hz, 1H), 9.13 (d, $J'=2$ Hz, 1H).

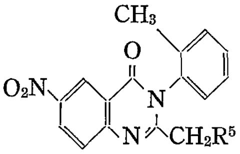
A General Procedure for the Preparation of 6-Acetamido-2-(substituted-methyl)-3-(*o*-tolyl)-4(3*H*)-quinazolinones (20k—v). Typical Examples: Method C. 6-Acetamido-2-diethylaminomethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (20k)——A mixture of **19** (5.5 g, 0.016 mol), Et_2NH (5.5 g, 0.075 mol) and THF (100 ml) was refluxed for 48 hr. The mixture was concentrated to dryness *in vacuo* and the residue was triturated with H_2O. The crystals were collected by filtration to yield 6.5 g of crude product: mp 170—173°. Recrystallization from C_6H_6 (100 ml) gave 4.7 g (88%) of **20k** as colorless fine needles: mp 185—187°; NMR ($CDCl_3$) δ: 0.76 (t, $J=7$ Hz, 6H), 1.63 (s, 3H), 2.11 (s, 3H), 2.36 (q, $J=7$ Hz, 4H), 3.16 (d, $J=14$ Hz, 1H), 3.43 (d, $J=14$ Hz, 1H), 7.1—7.5 (m, 4H), 7.74 (d, $J=10$ Hz, 1H), 8.13 (d, $J'=3$ Hz, 1H), 8.58 (d.d, $J=10$ Hz, $J'=3$ Hz, 1H), 9.20 (br.s, 1H).

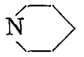
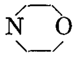
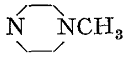
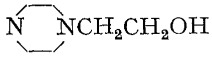
Method D. 6-Acetamido-2-ethoxymethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (20u)——Compound **19** (3.42 g, 0.01 mol) was added to a solution of NaOEt (0.01 mol) in EtOH (50 ml), and the mixture was stirred at room temperature for 90 hr. After removal of the solvent, the residue was dissolved in $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried ($MgSO_4$), and concentrated to dryness *in vacuo*. The residue was purified by silica gel column chromatography using $CHCl_3$ to give 1.6 g (45.7%) of **20u**: mp 184—187°. Recrystallization from 2-propanol afforded an analytically pure sample: mp 188—190°; NMR ($CDCl_3$) δ: 1.07 (t, $J=7$ Hz, 3H), 1.25 (s, 3H), 2.00 (s, 3H), 3.27 (q, $J=7$ Hz, 2H), 4.06 (s, 2H), 7.1—8.7 (m, 7H), 9.03 (s, 1H).

Method E. 6-Acetamido-2-phenylthiomethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (20s)——NaH (55% oil dispersion, 0.6 g, 0.014 mol) and **19** (4.11 g, 0.012 mol) were added to a solution of thiophenol (1.5 g, 0.014 mol) in THF (90 ml) at room temperature. The reaction mixture was stirred at the same temperature for 2 hr. The mixture was concentrated to dryness *in vacuo* and the residue was triturated with H_2O. The crystals were collected by filtration to yield a crude product (5.2 g): mp 230—233°. Recrystallization from DMF–EtOH gave **20s** (4.0 g, 80%): mp 236—237°; NMR (DMSO-d_6) δ: 2.10 (s, 3H), 2.21 (s, 3H), 3.91 (s, 2H), 7.27 (s, 5H), 7.42 (s, 4H), 7.66 (d, $J=10$ Hz, 1H), 8.06 (d.d, $J=10$ Hz, $J'=3$ Hz, 1H), 8.49 (d, $J'=3$ Hz, 1H), 10.35 (br.s, 1H).

General Procedure for the Preparation of 6-Amino-2-(substituted-methyl)-3-(*o*-tolyl)-4(3*H*)-quinazolinones (21a—w). Typical Examples: Method F. 2-Acetoxymethyl-6-amino-3-(*o*-tolyl)-4(3*H*)-quinazolinone (21a)——A solution of **18a** (2.0 g) in AcOH (50 ml) was hydrogenated in an atmosphere of hydrogen (3.6 kg/cm^2)

Table VII. 6-Nitro-2-(substituted-methyl)-3-(*o*-tolyl)-4(3*H*)-quinazolinones (**18**)



Compd. No.	R^5	Method[a]	Yield (%)	mp (°C)	Recryst. solv.[b]	Formula	Analysis (%) Calcd. (Found) C	H	N
18a	$OCOCH_3$	A	50	110—113	—[c]	$C_{18}H_{15}N_3O_5$	61.19 (61.14	4.28 4.49	11.89 11.85)
18b	$OCOC_4H_9$	A	78	90—93	A	$C_{21}H_{21}N_3O_5$	63.79 (63.85	5.35 5.50	10.63 10.60)
18c	$OCOC_{15}H_{31}$	A	60	81—83	A	$C_{32}H_{43}N_3O_5$	69.92 (69.96	7.89 8.05	7.65 7.62)
18d	OCOPh	A	82	Oil		[d]			
18e	 N	B	90	207—209[e]	B	$C_{21}H_{22}N_4O_3$	66.45 (66.57	5.86 5.98	14.81 14.74)
18f	 N O	B	86	225—227[e]	B	$C_{20}H_{20}N_4O_4$	63.15 (63.16	5.30 5.41	14.73 14.81)
18g	 N NH	B	70	201—203	B	$C_{20}H_{21}N_5O_3$	63.31 (62.93	5.58 5.75	18.46 18.38)
18h	 N NCH3	B	76	210—212	B	$C_{21}H_{23}N_5O_3$	64.11 (63.94	5.89 5.96	17.80 17.97)
18i	 N NPh	B	94	189—191	B	$C_{26}H_{25}N_5O_3$	68.55 (68.56	5.53 5.68	15.38 15.37)
18j	 N NCH2CH2OH	B	82	176—178	C	$C_{22}H_{25}N_5O_4$	62.40 (62.36	5.95 6.03	16.54 16.37)

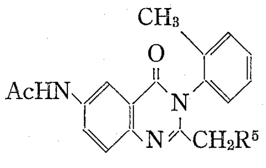
a) See "Experimental."
b) A=2-propanol; B=DMF–EtOH; C=EtOH.
c) Not recrystallized.
d) Not analyzed.
e) Dec.

in the presence of 5% Pd-charcoal for 2.5 hr. After removal of the catalyst by filtration, the filtrate was concentrated to dryness *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with aqueous $NaHCO_3$ solution and with H_2O, then dried ($MgSO_4$), and concentrated to dryness *in vacuo*. The residual oil was applied to a silica gel column, eluting with $CHCl_3$. The main fractions which contained the target compound were combined and evaporated to give an oil. Upon trituration with a mixture of diisopropyl ether and 2-propanol this oil afforded 1.2 g (65.5%) of **21a** as pale brown prisms: mp 100—103° (dec.); NMR ($CDCl_3$) δ: 2.03 (s, 3H), 2.15 (s, 3H), 3.5—4.3 (br., 2H), 4.65 (s, 2H), 7.0—7.5 (m, 7H). Elemental analysis was done with **21a**·HCl: mp 198—201° (dec.).

Method G. 6-Amino-2-phenylthiomethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (21s)——A mixture of **20s** (4.0 g) and 10% HCl–MeOH (60 ml) was stirred at room temperature overnight. The reaction mixture was concentrated to dryness *in vacuo* and the residue was dissolved in H_2O. After neutralization with K_2CO_3, the mixture was extracted with $CHCl_3$. The $CHCl_3$ layer was dried ($MgSO_4$) and concentrated to dryness *in vacuo*. The residual oil was crystallized as the hydrochloride to give **21s**·HCl (2.6 g, 66%): mp 160—165° (sintered at 110° and decomposed at the mp); NMR (DMSO-d_6) δ: 2.10 (s, 3H), 3.9 (s, 2H), 6.8—7.5 (br., 2H), 7.26 (s, 5H), 7.42 (s, 4H), 7.6—7.9 (m, 3H).

Method H. 6-Amino-2-carboxymethylaminomethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (21q)——A mixture of **20q** (3.1 g) and 10% HCl–MeOH (60 ml) was stirred at room temperature overnight. The reaction mixture was concentrated to dryness *in vacuo* and the residue was dissolved in H_2O. The aqueous solution was neutralized with NaOAc and extracted with $CHCl_3$. The $CHCl_3$ layer was concentrated to dryness and the residual oil was treated with KOH (1.5 g) in 10% aqueous MeOH (20 ml) at room temperature for 3 hr. After neutralization with 10% hydrochloric acid, the mixture was concentrated *in vacuo*. The residue was taken up in 10% aqueous NaOH and passed through a column of cation exchange resin (SK-IB, H^+ form). After washing with H_2O, the column was eluted with 5% aqueous ammonia. Concentration of the eluent *in vacuo*, followed by filtration with 2-propanol yielded crude **21q** (1.1 g). Recrystallization from aqueous EtOH gave 0.98 g (37.5%) of **21q** as brownish yellow prisms: mp 170—173° (dec.); NMR (DMSO-d_6) δ: 2.01

Table VIII. 6-Acetamido-2-(substituted-methyl)-3-(*o*-tolyl)-4(3*H*)-quinolinones (21)



Compd. No.	R^5	Method[a]	Yield (%)	mp (°C)	Recryst. solv.[b]	Formula	Analysis (%) Calcd. (Found) C	H	N
20k	$N(C_2H_5)_2$	C	88	185—187	A	$C_{22}H_{26}N_4O_2$	69.81 (69.73	6.92 6.83	14.81 14.51)
20l		C	91	215—218	B	$C_{22}H_{24}N_4O_2$	70.18 (70.09	6.43 6.50	14.88 14.83)
20m	$N(CH_2CH_2OCH_3)_2$	C	71	Oil	—	[c]			
20n	$N(CH_2CH_2OH)_2$	C	80	175—177	C	$C_{22}H_{26}N_4O_4$	64.37 (64.06	6.39 6.44	13.65 13.53)
20o	$NHCH_2CH_2OCH_3$	C	95	182—185	C	$C_{21}H_{24}N_4O_3$	66.30 (65.88	6.36 6.44	14.73 14.50)
20p	$NHCH_2CH_2OH$	C	—[d]	—	—				
20q	$NHCH_2CO_2CH_3$	C	55	172—173	C	$C_{21}H_{22}N_4O_4$	63.94 (63.66	5.62 5.71	14.21 14.05)
20r	 CONH$_2$	C	—[d]	—	—				
20s	SPh	E	80	236—237	D	$C_{24}H_{21}N_3O_2S$	69.38 (69.02	5.10 5.25	10.12 10.08)
20t	SC_2H_5	E	86	177—179	C	$C_{20}H_{21}N_3O_2S$	65.38 (65.20	5.76 5.91	11.44 11.36)
20u	OC_2H_5	D	46	188—190	C	$C_{20}H_{21}N_3O_3$	68.36 (68.11	6.02 6.05	11.96 11.88)
20v	OCH_2CH_2OH	D	—[d]	—	—				

a) See "Experimental."
b) A=benzene; B=EtOH; C=2-propanol; D=DMF-EtOH.
c) Not analyzed.
d) Not isolated.

(s, 3H), 3.23 (s, 2H), 3.20 (d, *J*=16 Hz, 1H), 3.56 (d, *J*=16 Hz, 1H), 4.90 (br., 5H: exchangeable proton in D_2O), 7.0—7.7 (m, 7H).

2-Fluoromethyl-6-methylamino-3-(*o*-tolyl)-4(3*H*)-quinazolinone (16p)——A mixture of **15** (100 g, 0.353 mol), CH_3I (63.5 g, 0.45 mol), $NaHCO_3$ (42 g, 0.50 mol), and THF (1.5 l) was stirred at room temperature for 3 days. The mixture was concentrated *in vacuo* and the residue was extracted with $CHCl_3$. The $CHCl_3$ layer was washed with H_2O, dried ($MgSO_4$), and concentrated to dryness *in vacuo*. The residue was purified by silica gel chromatography with $CHCl_3$ to give a crude product (22.8 g). Recrystallization from 2-propanol afforded 19.5 g (18.5%) of **16p** as pale yellow prisms: mp 208—210°; NMR ($CDCl_3$) δ: 2.13 (s, 3H), 2.88 (s, 3H), 4.84 (d, $J_{H-F}=47$ Hz, 2H), 4.0—4.5 (br., 1H), 6.9—7.8 (m, 7H).

6-Dimethylamino-2-fluoromethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (16q)——A mixture of **15** (2.83 g, 0.01 mol), 37% aqueous formaldehyde (1.63 g, 0.02 mol), and 98% formic acid (1.41 g, 0.03 mol) was heated at 80° for 30 min. The mixture was taken up in $CHCl_3$ and washed with 5% aqueous $NaHCO_3$ solution. The $CHCl_3$ layer was dried ($MgSO_4$) and concentrated *in vacuo* to give a syrup. The syrup was purified by column chromatography using silica gel (solv.: $CHCl_3$) to afford 0.8 g (25.7%) of **16q**; mp 179—183°. The recrystallized sample showed mp 180—183°; NMR ($CDCl_3$) δ: 2.15 (s, 3H), 3.10 (s, 6H), 4.94 (d, $J_{H-F}=47$ Hz, 2H), 7.1—7.8 (m, 7H).

6-Amino-2-hydroxymethyl-3-(*o*-tolyl)-4(3*H*)-quinazolinone (21w)——A suspension of **21a** (2.5 g) in 10% HCl–MeOH (30 ml) was stirred at room temperature overnight. The reaction mixture became clear and then fresh crystals precipitated out. The crystals were collected by filtration to yield 2.2 g of crude product. Recrystallization from 10% HCl (5 ml) gave 1.55 g (48%) of pure **21w**·2HCl as colorless prisms: mp 233—235° (dec.); NMR (D_2O) δ: 2.21 (s, 3H), 4.35 (d, *J*=18 Hz, 1H), 4.76 (d, *J*=18 Hz, 1H), 7.2—8.5 (7H, m).

Pharmacology

Male ddk-strain mice weighing 18—22 g were used for all studies reported here. The test compounds were suspended in 0.5% CMC solution.

Acute Toxicity

The test compounds were administered to groups of 6 mice in increasing doses. The animals were observed for 72 hr and the lethality after that time was used for determining the LD_{50} value.

Righting Reflex Test

Groups of 6 mice were injected intraperitoneally with the test compounds. After 15, 30, 60, 90, and 120 min each animals was placed gently on its back on a desk. When the animal remained on its back for more than 20 sec, the reflex was considered lost. The ED_{50} value was estimated from the number of mice which had lost the reflex by this criterion.

Rotating Rod Test

Groups of 6 mice were injected intraperitoneally with the test compounds. After 30 min the mice were placed for 1 min on a rotating rod (3.5 cm in diameter, 14 rpm.). The ED_{50} value was estimated from the number of mice which fell off the rod twice during the test.

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